Leukemia Cancer

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Abstract: Cancer is the cells that grow out of control. Cancer cells can also invade other tissues. Growing out of control and invading other tissues are what makes a cell a cancer cell. Involved in more than 100 diseases, the cancer can cause serious illness and death. Normally, the cells become cancer cells because of DNA damage. This material is a literature collection of the researches on the leukemia cancer.
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1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

Literatures

Alonzo, T. A., N. L. Kobrinsky, et al. (2002). "Impact of granulocyte colony-stimulating factor use during induction for acute myelogenous leukemia in children: a report from the Children's Cancer Group." J Pediatr Hematol Oncol **24**(8): 627-35.

PURPOSE: To determine whether granulocyte colony-stimulating factor (G-CSF) administered during acute myelogenous leukemia (AML) induction affects hematopoietic and nonhematopoietic toxicity, length and outcome of induction therapy, event-free survival, overall survival, and prognostic significance of the day 7 bone marrow. PATIENTS AND METHODS: In Children's Cancer Group study 2891, patients were given intensively timed induction with G-CSF (n = 254) after accrual for the regimen without G-CSF (n = 258) was met. RESULTS: Time to neutropenic recovery after induction courses 1 and 2 was significantly shorter for patients who received G-CSF. Times to platelet recovery were similar regardless of G-CSF use. Effects on incidence of grades 3 and 4 toxicities, infections, or fatal infections were not observed. Use of G-CSF reduced the median length of induction by 9 days and hospital stay by 6 days. Induction remission rates, overall survival, and event-free survival were similar with and without G-CSF. Day 7 bone marrow was prognostic of better long-term outcome. Patients with hypercellular day 7 marrow who received G-CSF had a higher remission rate and event-free survival than patients who did not receive G-CSF. CONCLUSIONS: The incidence of severe toxic event and infection, induction remission rate, overall survival, and event-free survival were comparable regardless of G-CSF use. Use of G-CSF decreased neutropenia duration, hospital stay, and length of induction. Patients with hypercellular day 7 bone marrow who received G-CSF had an induction remission rate and event-free survival superior to those of patients who did not receive G-CSF.

Baldus, C. D., S. M. Tanner, et al. (2003). "BAALC expression predicts clinical outcome of de novo acute myeloid leukemia patients with normal cytogenetics: a Cancer and Leukemia Group B Study." Blood **102**(5): 1613-8.

Cytogenetic aberrations are important prognostic factors in acute myeloid leukemia (AML). Of adults with de novo AML, 45% lack cytogenetic abnormalities, and identification of predictive molecular markers might improve therapy. We studied the prognostic impact of BAALC (Brain And Acute Leukemia, Cytoplasmic), a novel gene involved in leukemia, in 86 de novo AML patients with normal cytogenetics who were uniformly treated on Cancer and Leukemia Group B 9621. BAALC expression was determined by comparative real-time reverse transcriptase-polymerase chain reaction in pretreatment blood samples, and patients were dichotomized at BAALC's median expression into low and high expressers. Low expressers had higher white counts (P =.03) and more frequent French-American-British M5 morphology (P =.007). Compared to low expressers, high BAALC expressers showed significantly inferior overall survival (OS; median, 1.7 vs 5.8 years, P =.02), event-free survival (EFS; median, 0.8 vs 4.9 years, P =.03), and disease-free survival (DFS; median, 1.4 vs 7.3 years, P =.03). Multivariable analysis confirmed high BAALC

expression as an independent risk factor. For high BAALC expressers the hazard ratio of an event for OS, EFS, and DFS was respectively 2.7, 2.6, and 2.2. We conclude that high BAALC expression predicts an adverse prognosis and may define an important risk factor in AML with normal cytogenetics.

Balduzzi, A. and M. Castiglione-Gertsch (2005). "Leukemia risk after adjuvant treatment of early breast cancer." Womens Health (Lond Engl) **1**(1): 73-85.

Modern cancer treatment has substantially increased the survival and curability of patients with various malignancies. Therefore, favorable prognosis mandates for the evaluation of long-term complications of treatment. Since the late 1970s, adjuvant combination chemotherapy for operable breast cancer has come into widespread use. Several recent studies have estimated the risk of acute myeloid leukemia associated with these regimens. The purpose of this analysis is to discuss the risk of leukemia after early breast cancer therapy, the types of leukemia, and the relationship between the risk of leukemia and treatment with different cytotoxic agents (alkylating agents, antimetabolities, topoisomerase II inhibitors, dose-dense therapy, high-dose therapy and growth factor use) and radiotherapy.

Bamberger, A. M., I. Thuneke, et al. (1998). "Differential regulation of the human 'leukemia inhibitory factor' (LIF) promoter in T47D and MDA-MB 231 breast cancer cells." Breast Cancer Res Treat **47**(2): 153-61.

Leukemia inhibitory factor (LIF) is a pleiotropic inflammatory cytokine. A potential role for LIF in the pathogenesis of human breast cancer was recently indicated by the finding that LIF is produced by MDA-MB 231 breast cancer cells and that it stimulates proliferation of the T47D and MCF-7 breast cancer cell lines. Despite its role as a possible therapeutic target in breast cancer, the transcriptional regulation of the LIF gene in breast cancer cells has not been investigated so far. In this context, we investigated the regulation of the human LIF promoter (human LIF666-luciferase) by ovarian steroids in transient transfection assays in MDA-MB 231 and T47D cells. Since the MDA-MB 231 cells are devoid of both estrogen (ER) and progesterone (PR) receptors, these cells were co-transfected with the respective receptor expression vector. Estradiol induced no stimulation in either T47D or ER-transfected MDA-MB 231 cells. Treatment with the progesterone agonist MPA (medroxy-progesterone acetate) resulted in induction of LIF transcription in PR-transfectant MDA-MB 231 cells, while it had no effect in T47D cells. Both PR isoforms (PR-B and PR-A) were effective in inducing the LIF promoter in MDA-MB 231 cells, and this effect was inhibited by the progestin antagonist RU 486. The stimulatory effect of MPA was maintained on deletion constructs (h274LIF-Luc, h148LIF-Luc and h82LIF-Luc), indicating that 82 bp are sufficient to mediate this effect. Our results indicate that the LIF promoter is transcriptionally active in human breast cancer cells and its activity can be modulated by progestins and anti-progestins in cells expressing the LIF protein, which might have therapeutic implications.

Barry, E., D. J. DeAngelo, et al. (2007). "Favorable outcome for adolescents with acute lymphoblastic leukemia treated on Dana-Farber Cancer Institute Acute Lymphoblastic Leukemia Consortium Protocols." J Clin Oncol **25**(7): 813-9.

PURPOSE: Historically, adolescents with acute lymphoblastic leukemia (ALL) have had inferior outcomes when compared with younger children. Adolescents were more likely to present at diagnosis with biologically higher risk disease (T-cell phenotype and absence of the TEL-AML1 fusion) and more likely to experience treatment-related complications than younger children. However, the 5-year EFS for older adolescents was 78% +/- 6%, which is superior to published outcomes for similarly aged patients treated with other pediatric and adult ALL regimens. Based on this experience, we currently are piloting our regimen in patients aged 18 to 50 years.

Bartlett, N. L., G. R. Petroni, et al. (2001). "Dose-escalated cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide (CHOPE) chemotherapy for patients with diffuse lymphoma: Cancer and Leukemia Group B studies 8852 and 8854." Cancer **92**(2): 207-17.

BACKGROUND: To address the feasibility and outcome of moderate dose intensification with granulocyte-colony stimulating factor (G-CSF) for patients with aggressive non-Hodgkin lymphoma (NHL), the Cancer and Leukemia Group B (CALGB) conducted two studies evaluating dose-escalated cyclophosphamide and etoposide in the cyclophosphamide, doxorubicin, vincristine, prednisone, etoposide (CHOPE) regimen. METHODS: Eligibility criteria included histologically documented, diffuse small cleaved, diffuse mixed, diffuse large cell, or immunoblastic lymphoma, Stage III--IV or bulky Stage II disease, and an ECOG performance status of 0--1. CALGB 8852, a group-wide study, accrued 227 patients: 120 patients in the pilot study to determine the maximum tolerated dose (MTD) without G-CSF and 107 in the pilot study of dose-escalated CHOPE with G-CSF. CALGB 8854, a limited-institution, Phase I study, enrolled 38 patients and determined the MTD of CHOPE with G-CSF to

be used in CALGB 8852. The MTD in both studies was defined as the dose at which 50% of patients had 1) Grade 4 neutropenia or thrombocytopenia lasting 7 days or more, or 2) Grade 3--4 hemorrhage or nonhematologic toxicity (excluding alopecia, nausea, and emesis), or 3) were prevented from receiving 100% of drug on Day 22. RESULTS: The MTD of CHOPE without G-CSF was cyclophosphamide 1000 mg/m(2) on Day 1 and etoposide 100 mg/m(2) on Days 1--3 with doxorubicin 50 mg/m(2) on Day 1, vincristine 1.4 mg/m(2) (maximum, 2 mg) on Day 1, and prednisone 100 mg on Days 1--5. With the addition of G-CSF at 200 microg/m(2) on Days 5--19, the MTD was cyclophosphamide 1500 mg/m(2) and etoposide 160 mg/m(2) on Days 1-3 with standard doses of doxorubicin, vincristine, and prednisone. Increasing the dose of G-CSF from 200 microg/m(2) to 400 microg/m(2) did not allow for further dose escalation. The primary toxicity in all cohorts was neutropenia. Four toxic deaths occurred on CALGB 8852. The 5-year failure free survival (FFS) and overall survival (OS) rates for eligible patients on CALGB 8852 were 31% (95% confidence interval [95%CI], 23--39) and 48% (95%CI, 40--57), respectively. The 5-year FFS and OS rates for eligible patients on CALGB 8854 were 34% (95%CI, 17--52) and 51% (95%CI, 33--70), respectively. CONCLUSIONS: Moderate dose escalation with G-CSF is feasible. However, response and survival rates of patients who receive dose-escalated CHOPE, even with the addition of G-CSF, appear similar to the rates reported with standard-dose CHOP.

Bauduer, F., L. Ducout, et al. (2002). "Chronic myeloid leukemia as a secondary neoplasm after anti-cancer radiotherapy: a report of three cases and a brief review of the literature." Leuk Lymphoma **43**(5): 1057-60.

Chemotherapy-related acute leukemias or myelodysplasias are well-recognized entities. On the other hand, little is known about the possible occurrence of secondary chronic myeloid leukemia (CML) after radiotherapy, albeit accidental irradiation represents a classical predisposing factor for this disease. We report here three cases of Philadelphia-positive CML appearing one to 25 years after breast or uterine cervix cancer radiotherapy. One patient had also received chemotherapy. Clinical and biological characteristics of these cases did not significantly differ from those of de novo CMLs. A brief review of the literature is made about this possible peculiar entity. Large registries appear warranted to assess the real risk of developing CML after anti-cancer radiotherapy.

Blum, K. A., J. L. Johnson, et al. (2007). "Single agent bortezomib in the treatment of relapsed and refractory Hodgkin lymphoma: cancer and leukemia Group B protocol 50206." Leuk Lymphoma **48**(7): 1313-9.

Constitutive activation of nuclear factor-kappaB (NF-kappaB) has been described in patient-derived Reed - Sternberg cells and Hodgkin lymphoma (HL) cell lines and contributes to the proliferation and survival of HL. Therapeutic inhibition of the proteasome with bortezomib may inhibit over-expression of nuclear NF-kappaB by preventing degradation of IkappaB, which sequesters NF-kappaB in the cytoplasm. To evaluate this hypothesis, the Cancer and Leukemia Group B (CALGB) conducted a multi-institutional phase II trial of single agent bortezomib in patients with relapsed or refractory classical HL. Thirty patients received bortezomib 1.3 mg/m(2) on days 1, 4, 8, 11 and every 21 days for a median of 2 cycles (range, 1 - 8). Patients were heavily pre-treated with a median of four prior therapies, and 83% were previously transplanted. No responses were observed, 9 patients had stable disease, and 21 progressed. The median progression-free and overall survivals were 1.4 months [95% CI, (1.28, 1.91)] and 14.8 months [95% CI (11.2, 22.3)], respectively. Grade 3 - 4 adverse events, primarily thrombocytopenia, occurred in 15 patients. Therefore, although well tolerated, 1.3 mg/m(2) bortezomib administered biweekly has no single agent activity in relapsed/refractory classical HL.

Bogart, J. A., J. E. Herndon, 2nd, et al. (2004). "70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small-cell lung cancer: analysis of Cancer and Leukemia Group B study 39808." Int J Radiat Oncol Biol Phys **59**(2): 460-8.

PURPOSE: To prospectively evaluate the feasibility of delivering 70 Gy once-daily thoracic radiotherapy (TRT), concurrent with chemotherapy, in the treatment of limited-stage small-cell lung cancer (L-SCLC). MATERIALS AND METHODS: Eligible patients received two cycles of induction paclitaxel (175 mg/m(2) on Day 1) and topotecan (1 mg/m(2) on Days 1-5) with granulocyte colony stimulating factor support, followed by three cycles of carboplatin (area under the curve = 5 on Day 1) and etoposide (100 mg/m(2) on Days 1-3). TRT (70 Gy, 2 Gy/fx/7 weeks) was initiated with the first cycle of carboplatin and etoposide. Prophylactic cranial irradiation was offered to patients achieving a complete response or good partial response. RESULTS: Ninety percent of patients (57 of 63) proceeded to protocol TRT. There was one treatment-related fatality. Nonhematologic Grade 3/4 toxicities affecting more than 10% of patients, during or after TRT, were dysphagia

(16%/5%) and febrile neutropenia (12%/4%). The response rate to all therapy was 92% and the median overall survival is 22.4 months (95% confidence interval 16.1, infinity). Twenty-eight patients remain alive with a median follow-up of 24.7 months. CONCLUSION: 70 Gy once-daily TRT can be delivered safely in the cooperative group setting for patients with L-SCLC. Initial efficacy data are encouraging. The hypothesis that high-dose once-daily TRT results in comparable or improved survival compared with twice-daily accelerated TRT warrants testing in a Phase III trial.

Bok, R. A., S. Halabi, et al. (2001). "Vascular endothelial growth factor and basic fibroblast growth factor urine levels as predictors of outcome in hormone-refractory prostate cancer patients: a cancer and leukemia group B study." Cancer Res **61**(6): 2533-6.

Better prognostic markers are needed for hormone-refractory prostate cancer (HRPC) patients. No single biochemical or clinical parameter can reliably predict patient response to therapy or rapidity of disease progression. Peptide factors involved in major cancer growth pathways, such as tumor angiogenesis, are attractive candidates as markers of low- and high-risk HRPC patients. We analyzed prospectively collected urine specimens from 100 of 390 HRPC patients undergoing therapy with the growth factor antagonist suramin as part of CALGB 9480. Levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) were assessed from day 1 of therapy (D1) and day 29 (D29) urine samples from this subset of 100 randomly selected patients. Growth factor levels were determined by standardized ELISA microtiter plate assays from a commercial (bFGF) or proprietary (VEGF) source. Pretreatment urine VEGF levels were predictive of survival. In univariate analysis, patients whose baseline urine VEGF level was < or =28 pg/ml (the median level) had an average survival of 17 months; those with baseline VEGF >28 pg/ml had a significantly shorter survival of 10 months (P = 0.024). This difference corresponded to a 60% increased risk of dying for the higher urine VEGF patients (hazard ratio, 1.62; P = 0.03) and remained significant in multivariate analysis (hazard ratio, 1.72, P = 0.02). No significant correlations between urine bFGF level or change in bFGF levels and survival were found. These results support the notion that certain peptide growth factor-mediated, mitogenic pathways are important in HRPC and that their levels can predict outcome.

Brassesco, M. S., M. L. Camparoto, et al. (2004). "Analysis of ETV6/RUNX1 fusions for evaluating the late effects of cancer therapy in ALL (acute lymphoblastic leukemia) cured patients." Cytogenet Genome Res **104**(1-4): 346-51.

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in childhood. The improvements of therapies have increased the number of long-term survivors. However, an increased incidence of secondary neoplasias has been observed in this cohort. Our purpose was to evaluate the late effects of cancer therapy in cured patients previously treated for ALL, considering previous reports on the occurrence of gene fusions as putative markers of chromosomal instability. Twelve ALL patients (aged 5 to 16 years) and twelve healthy subjects (aged 18 to 22 years) were studied for the presence of ETV6/RUNX1 (TEL/AML1) translocations, which were detected by FISH (fluorescence in situ hybridization). The blood samples were collected months or years after completion of the therapy, and the frequencies of gene fusions in lymphocytes were compared with those obtained retrospectively for bone marrow samples at the time of diagnosis, and also for the control group. It was demonstrated that ETV6/RUNX1 gene fusion was a frequent event (0.59-1.84/100 cells) in peripheral blood lymphocytes from normal individuals and the ALL patients who underwent chemotherapy showed significantly (P = 0.0043) increased frequencies (0.62-3.96/100 cells) of the rearrangement when compared with the control groups (patients at diagnosis and healthy subjects). However, a significant difference was not found between the groups of patients at diagnosis and healthy subjects, when the two patients who were positive for the rearrangement were excluded. Therefore, increased frequencies of ETV6/RUNX1 fusions in ALL cured patients indicate the influence of previous exposure to anti-cancer drugs, and they may represent an important genetic marker for estimating the risk of relapse, or development of secondary neoplasias.

Briasoulis, E., E. Tzouvara, et al. (2003). "Biphenotypic acute leukemia following intensive adjuvant chemotherapy for breast cancer: case report and review of the literature." Breast J **9**(3): 241-5.

The risk of secondary leukemia in breast cancer patients who receive adjuvant chemotherapy is an open question. We describe the case a 38-year-old woman who developed acute leukemia 18 months after completion of intense adjuvant chemotherapy with prophylactic granulocyte colony-stimulating factor (G-CSF) support and chest wall irradiation. The diagnosis of biphenotypic T-cell acute myeloid leukemia (AML) was based on morphologic and immunophenotypic criteria. Chromosomal analysis of blasts revealed multiple trisomies and tetrasomies.

The patient failed to respond to induction and salvage chemotherapy and died 4 months later. This case of acute leukemia occurred in a cohort of 65 high-risk breast cancer patients who were given intense adjuvant chemotherapy during the last 5 years in our hospital. This is the first case reported in the literature of acute leukemia following intense adjuvant chemotherapy with continuous prophylactic G-CSF, which is an actively investigated therapeutic strategy. Vigilance and investigation are needed to determine the leukemogenic potential of intense adjuvant chemotherapy plus radiotherapy in breast cancer patients. A brief review of the literature that deals with acute leukemia that develops after adjuvant chemotherapy for breast cancer and with secondary biphenotypic acute leukemia is presented.

Cave, H., J. van der Werff ten Bosch, et al. (1998). "Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia. European Organization for Research and Treatment of Cancer--Childhood Leukemia Cooperative Group." N Engl J Med **339**(9): 591-8.

BACKGROUND AND METHODS: The implications of the detection of residual disease after treatment of acute lymphoblastic leukemia (ALL) are unclear. We conducted a prospective study at 11 centers to determine the predictive value of the presence or absence of detectable residual disease at several points in time during the first six months after complete remission of childhood ALL had been induced. Junctional sequences of T-cell-receptor or immunoglobulin gene rearrangements were used as clonal markers of leukemic cells. Residual disease was quantitated with a competitive polymerase-chain-reaction (PCR) assay. Of 246 patients enrolled at diagnosis and treated with a uniform chemotherapy protocol, 178 were monitored for residual disease with one clone-specific probe (in 74 percent) or more than one probe (in 26 percent). The median follow-up period was 38 months. RESULTS: The presence or absence and level of residual leukemia were significantly correlated with the risk of early relapse at each of the times studied (P<0.001). PCR measurements identified patients at high risk for relapse after the completion of induction therapy (those with > or =10(-2) residual blasts) or at later time points (those with > or =10(-3) residual blasts). Multivariate analysis showed that as compared with immunophenotype, age, risk group (standard or very high risk), and white-cell count at diagnosis, the presence or absence and level of residual disease were the most powerful independent prognostic factors. CONCLUSIONS: Residual leukemia after induction of a remission is a powerful prognostic factor in childhood ALL. Detection of residual disease by PCR should be used to identify patients at risk for relapse and should be taken into account in considering alternative treatment.

Chang, H. R., T. L. Cheng, et al. (2006). "Genetic and cellular characterizations of human TCF4 with microsatellite instability in colon cancer and leukemia cell lines." Cancer Lett **233**(1): 165-71.

It has been reported that the mutational inactivation of the adenomatous polyposis coli (APC) and beta-catenin genes play important roles in colorectal carcinogenesis. However, alteration of the components in the Wnt signaling pathway in colorectal cancer (CRC) with microsatellite instability (MSI) has been elucidated. To define the precise role of the Wnt signaling components in CRC and leukemia cell lines with MSI, mutational analyses of the T cell factor 4 (TCF4) genes were performed. Here we describe for the first time a TCF4 MSI+ phenotype in leukemia cell lines except in colon cancer cell lines. Moreover, we found that these cell lines exhibited deletion and insertion of 1-2A in an (A)9 repeat so as to result in (A)7, (A)8, (A)10 and (A)11 repeat, respectively. To characterize the cellular function of these special TCF4 mutant clones, transient transfection and fluorescent microscopy were analyzed and the results revealed that the TCF4 frameshift gene products all localized in nuclei. Surprisingly, these TCF4 frameshift mutants lost transcriptional activity with beta-catenin and down-regulate the target gene expression. These results delineate a novel role for MSI+TCF4 in leukemia and colon cancer progression.

Chow, E. J., D. L. Friedman, et al. (2008). "Timing of menarche among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study." Pediatr Blood Cancer **50**(4): 854-8.

BACKGROUND: The objective of this study was to determine risk factors associated with abnormal timing of menarche among survivors of childhood acute lymphoblastic leukemia (ALL). PROCEDURE: Self-reported age of menarche was determined among 949 female ALL survivors participating in the Childhood Cancer Survivor Study (CCSS), a cohort of 5-year survivors of common pediatric cancers diagnosed from 1970 to 1986, and compared with 1,128 siblings. RESULTS: The majority of survivors (92%) and siblings (97%) reported menarche between the ages of 10 and 16. Survivors treated with chemotherapy alone, including those exposed to alkylating agents, experienced menarche at a similar rate to siblings. However, compared to chemotherapy alone, cranial radiotherapy was associated with early menarche (age < 10; OR

6.2, 95% CI 2.1, 18.5) while craniospinal radiotherapy was associated with both early (OR 8.6, 95% CI 1.9, 38.6) and late (age > 16; OR 4.8, 95% CI 1.4, 16.7) menarche. There were no differences in effect between <20 and >/=20 Gy radiotherapy doses. In multivariable analysis, younger age at diagnosis was an independent risk factor for early menarche. CONCLUSIONS: Few female childhood ALL survivors experienced menarche outside of the normal range. Alkylating agent exposure was not associated with abnormal timing. However, those exposed to cranial and craniospinal radiotherapy, especially at a young age, should be monitored closely for abnormal timing of menarche.

Citron, M. L., D. A. Berry, et al. (2003). "Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741." J Clin Oncol **21**(8): 1431-9.

PURPOSE: Using a 2 x 2 factorial design, we studied the adjuvant chemotherapy of women with axillary node-positive breast cancer to compare sequential doxorubicin (A), paclitaxel (T), and cyclophosphamide (C) with concurrent doxorubicin and cyclophosphamide (AC) followed by paclitaxel (T) for disease-free (DFS) and overall survival (OS); to determine whether the dose density of the agents improves DFS and OS; and to compare toxicities. PATIENTS AND METHODS: A total of 2,005 female patients were randomly assigned to receive one of the following regimens: (I) sequential A x 4 (doses) --> T x 4 --> C x 4 with doses every 3 weeks, (II) sequential A x 4 --> T x 4 --> C x 4 every 2 weeks with filgrastim, (III) concurrent AC x 4 --> T x 4 every 3 weeks, or (IV) concurrent AC x 4 --> T x 4 every 2 weeks with filgrastim. RESULTS: A protocol-specified analysis was performed at a median follow-up of 36 months: 315 patients had experienced relapse or died, compared with 515 expected treatment failures. Dose-dense treatment improved the primary end point, DFS (risk ratio [RR] = 0.74; P =.010), and OS (RR = 0.69; P =.013). Four-year DFS was 82% for the dose-dense regimens and 75% for the others. There was no difference in either DFS or OS between the concurrent and sequential schedules. There was no interaction between density and sequence. Severe neutropenia was less frequent in patients who received the dose-dense regimens. CONCLUSION: Dose density improves clinical outcomes significantly, despite the lower than expected number of events at this time. Sequential chemotherapy is as effective as concurrent chemotherapy.

Damiani, D., M. Tiribelli, et al. (2006). "The prognostic value of P-glycoprotein (ABCB) and breast cancer resistance protein (ABCG2) in adults with de novo acute myeloid leukemia with normal karyotype." Haematologica **91**(6): 825-8.

Multidrug resistance is a major cause of treatment failure in acute myeloid leukemia (AML). P-glycoprotein (PGP) over-expression has an unfavorable prognostic significance, while the role of breast cancer resistance protein (BCRP) is less clear, especially in AML patients with a normal karyotype. We studied 73 consecutive AML patients with a normal karyotype. BCRP was over-expressed in 24 patients (33%) and was significantly co-expressed with PGP (13/24 vs 11/49, p=0.006) and with CD56. Only PGP, along with age and CD34, affected the achievement of complete remission (p=0.02), while BCRP-positive cases showed an increased risk of relapse (p=0.005) and a shorter disease-free survival (p=0.027). BCRP over-expression did not influence the achievement of remission, but significantly affected the duration of complete remissions. BCRP may, therefore, be regarded as a prognostic factor in patients with normal karyotype AML, for the design of risk-adapted post-remission therapy.

Davies, S. M., L. L. Robison, et al. (2000). "Glutathione S-transferase polymorphisms in children with myeloid leukemia: a Children's Cancer Group study." Cancer Epidemiol Biomarkers Prev **9**(6): 563-6.

GSTM1 and GSTT1 are polymorphic genes. Absence of enzyme activity is due to homozygous inherited deletion of the gene, reducing detoxification of carcinogens such as epoxides and alkylating agents and potentially increasing cancer risk. We hypothesized that GST null genotype would increase risk of acute myeloid leukemia and myelodysplasia (AML/MDS) in children. DNA was extracted from bone marrow slides of 292 AML/MDS patients. PCR amplification was used to assign GSTM1 and GSTT1 genotypes for cases and controls. Given that the frequency of the null genotype varies by ethnicity and that the majority of the cases were Caucasian, analyses were restricted to 232 white (non-Hispanic) cases and 153 Caucasian non cancer controls. The frequency of GSTM1 null was significantly increased in AML/MDS cases compared with controls [64 versus 47%; odds ratio (OR), 2.0 [95% confidence interval (CI), 1.3-3.1]; P = 0.001], whereas the frequency of GSTT1 null genotype in AML/MDS cases was not statistically different from controls. AML comprises biologically distinct subtypes, and a test for homogeneity revealed a statistically significant difference among subtypes (P = 0.04; df, 8) for GSTM1 only. In particular, there was an increased

frequency of GSTM1 null genotypes in French-American-British groups M3 [82%; n = 22; OR, 5.1 (95% CI, 1.6-21.3)] and M4 [72%; n = 53; OR, 2.9 (95% CI, 1.4-6.0)]. We conclude that the GSTM1 null genotype is a significant risk factor for childhood AML, particularly French-American-British groups M3 and M4. This may indicate an important role for exogenous carcinogens in the etiology of childhood AML.

Dhingra, K., A. Sahin, et al. (1998). "Expression of leukemia inhibitory factor and its receptor in breast cancer: a potential autocrine and paracrine growth regulatory mechanism." Breast Cancer Res Treat **48**(2): 165-74.

Leukemia inhibitory factor (LIF) is a pluripotent cytokine which has a diverse array of effects on hematopoietic and epithelial cells. Depending on the nature of the target cells, these effects can be growth-stimulatory or growth-inhibitory. Receptors for leukemia inhibitory factor (LIFR) have been identified on a variety of hematopoietic and epithelial cells. We have recently demonstrated in vitro growth stimulation of human breast cancer cells, both primary tumors and cultured cell lines, by LIF. To begin to understand the in vivo relevance of these observations, we investigated the expression of LIF and LIFR in human breast cancer specimens. Specimens from 50 cases were immunostained with mouse monoclonal antibodies D62.3 and M1 (to stain for LIF and LIFR, respectively). LIF expression was observed in 78% of the specimens and correlated with favorable biological features, i.e. low S-phase fraction (SPF) (P = 0.001) and diploidy (P = 0.08). LIFR expression was observed in 80% of the tumors and correlated with the presence of estrogen receptor (ER) (P = 0.04) and diploidy (P = 0.07). Coexpression of LIF and LIFR was associated with diploidy (P = 0.02) and low SPF (P = 0.05). LIF staining was primarily cytoplasmic whereas LIFR staining was cytoplasmic in the majority of cases and membranous in a minority of cases. The presence of LIFR in the primary tumor specimens correlated with the growth stimulation of tumor cells (derived from the same specimens) by exogenous LIF in methylcellulose colony assays. The findings support a widespread but probably complex role for LIF and LIFR in breast tumor growth regulation which should be investigated in greater detail in larger cohorts of tumors.

DiGiovanna, M. P., D. F. Stern, et al. (2008). "Influence of activation state of ErbB-2 (HER-2) on response to adjuvant cyclophosphamide, doxorubicin, and fluorouracil for stage II, node-positive breast cancer: study 8541 from the Cancer and Leukemia Group B." J Clin Oncol **26**(14): 2364-72.

PURPOSE: ErbB-2 (human epidermal growth factor receptor 2) overexpression may be predictive of relative resistance and/or sensitivity to specific chemotherapeutic agents. Results from a previous study from the Cancer and Leukemia Group B (CALGB 8541) demonstrated an interaction between ErbB-2 and increasing dose of adjuvant cyclophosphamide, doxorubicin, and fluorouracil (CAF) chemotherapy. Other studies have suggested that evaluation of the phosphorylated/activated form of ErbB-2 might be more precise in defining the impact of ErbB-2 in breast cancer. We have evaluated tumor tissue sections from CALGB 8541 patients to determine whether the interaction of ErbB-2 with CAF dose is dependent on ErbB-2 activation state, and whether phosphorylated ErbB-2 is an adverse prognostic factor in patients treated with CAF. PATIENTS AND METHODS: Patients were randomly assigned to one of three dosing regimens of CAF. Paraffin samples from 992 of 1,572 patients who participated in CALGB 8541 were available. Of the 570 tumors with any staining for ErbB-2, 488 had tissue available for assay for phosphorylated ErbB-2, which was performed by immunohistochemistry. RESULTS: Of 910 total assessable cases, 112 of 488 ErbB-2-positive cases (23%) stained positively for phosphorylated ErbB-2. The previously described interaction of dosing regimen of CAF with ErbB-2 was not dependent on phosphorylation status of ErbB-2. CONCLUSION: Monitoring phosphorylation of ErbB-2 with an antiphospho-ErbB-2 antibody did not add further precision to identifying those patients most likely to benefit from increased dose of anthracycline-based adjuvant chemotherapy. Favorable outcomes are observed in ErbB-2-overexpressing patients treated with high-dose CAF regardless of ErbB-2 phosphorylation state.

Ding, Q., X. He, et al. (2007). "Myeloid cell leukemia-1 inversely correlates with glycogen synthase kinase-3beta activity and associates with poor prognosis in human breast cancer." Cancer Res **67**(10): 4564-71.

Myeloid cell leukemia-1 (Mcl-1), an antiapoptotic Bcl-2 family member, is overexpressed in many types of human cancer and associates with cell immortalization, malignant transformation, and chemoresistance. Glycogen synthase kinase-3beta (GSK-3beta), a key component of the Wnt signaling pathway, is involved in multiple physiologic processes such as protein synthesis, tumorigenesis, and apoptosis. Here, we report that expression of Mcl-1 was correlated with phosphorylated GSK-3beta (p-GSK-3beta) at Ser(9) (an inactivated form of GSK-3beta) in multiple cancer cell lines and primary human

cancer samples. In addition, Mcl-1 was strikingly linked with poor prognosis of human breast cancer, in which the high level of Mcl-1 was related to high tumor grade and poor survival of breast cancer patients. Furthermore, we found that activation of GSK-3beta could down-regulate Mcl-1 and was required for proteasome-mediated Mcl-1 degradation. Under some physiologic conditions, such as UV irradiation, anticancer drug treatment, and inhibition of growth factor pathways, Mcl-1 was down-regulated through activation of GSK-3beta. Our results indicate that Mcl-1 stabilization by GSK-3beta inactivation could be involved in tumorigenesis and serve as a useful prognostic marker for human breast cancer.

Dusenbery, K. E., W. B. Howells, et al. (2003). "Extramedullary leukemia in children with newly diagnosed acute myeloid leukemia: a report from the Children's Cancer Group." J Pediatr Hematol Oncol **25**(10): 760-8.

OBJECTIVES: To describe features of patients with acute myeloid leukemia presenting with extramedullary leukemic tumors (EML). METHODS: Among 1,832 patients entered on Children's Cancer Group's chemotherapy trials with acute myeloid leukemia, 199 patients had EML, defined as any leukemic collection outside the bone marrow cavity. Three patient groups were denoted: group 1 (n=109) with EML involving skin (with or without other sites of EML), group 2 (n=90) with EML in sites other than skin, and group 3 (n=1,633) without EML. RESULTS: The incidence of EML was 10.9%. Group 1 patients tended to be younger, had higher white blood cell counts, were more often CNS positive, had FAB M4 or M5 subtypes, and possessed more abnormalities of chromosome 11 than group 3 patients. Group 2 patients were younger, more often had the FAB M2 subtype, and had a higher incidence of t(8;21)(q22;q22) abnormality than group 3, but had similar white blood cell counts and incidence of CNS positivity at diagnosis. For group 1 the 5-year event-free survival was 26%, significantly worse than for group 3 at 29%. Event-free survival was better for group 2 patients (5-year estimate 46%), which remained a favorable prognostic factor by multivariate analysis. The authors retrospectively determined whether 118 (59%) of the EML patients received localized radiotherapy to the site of EML: 42 did and 76 did not. There were no differences in estimated event-free survival between patients who did and did not receive radiotherapy. CONCLUSIONS: Non-skin (group 2) EML appeared to be an independent favorable prognostic factor. Localized radiotherapy to the site of EML at the end of induction chemotherapy did not improve outcome.

Edelman, M. J., D. Watson, et al. (2008). "Eicosanoid modulation in advanced lung cancer: cyclooxygenase-2 expression is a positive predictive factor for celecoxib + chemotherapy--Cancer and Leukemia Group B Trial 30203." J Clin Oncol **26**(6): 848-55.

PURPOSE: Increased expression of eicosanoids in cancer has been associated with adverse prognosis. We performed a randomized phase II trial to test the hypothesis that inhibitors of two eicosanoid pathways (cyclooxygenase-2 [COX-2], celecoxib and 5-lipoxygenase [5-LOX], zileuton) added to chemotherapy would improve outcome in advanced non-small-cell lung cancer (NSCLC). PATIENTS AND METHODS: Patients with advanced NSCLC, a performance status of 0 to 2, and no prior therapy were eligible. All patients received carboplatin area under the curve (AUC) 5.5 mg/mL x min day 1 + gemcitabine (1,000 mg/m(2)) days 1 and 8. Patients were randomly assigned to: (a) zileuton 600 mg PO qid, (b) celecoxib 400 mg PO bid, or (c) celecoxib and zileuton at the same doses. Immunohistochemical staining for COX-2 and 5-LOX was performed without knowledge of outcomes. RESULTS: One hundred forty patients were entered and 134 were eligible and treated. There was no survival difference between the arms. COX-2 expression was a negative prognostic marker for overall survival (OS; hazard ratio [HR] = 2.51, P = .019 for index >or= 4; HR = 4.16, P = .005 for index = 9) for patients not receiving celecoxib. Patients with increased COX-2 expression (index >or= 4), receiving celecoxib had better survival than did COX-2-expressing patients not receiving drug (HR = .342, P = .005 for OS; HR = .294, P = .002 for failure-free survival). Multivariate analysis confirmed the interaction of COX-2 and celecoxib on survival. 5-LOX expression was neither prognostic nor predictive. CONCLUSION: This study failed to demonstrate the value of dual eicosanoid inhibition or benefit from either agent alone in addition to chemotherapy. However, a prospectively defined subset analysis suggests an advantage for celecoxib and chemotherapy for patients with moderate to high COX-2 expression.

Falanga, A., R. Consonni, et al. (1998). "Cancer procoagulant and tissue factor are differently modulated by all-trans-retinoic acid in acute promyelocytic leukemia cells." Blood **92**(1): 143-51.

All-trans-retinoic acid (ATRA) downregulates the expression of two cellular procoagulants, tissue factor (TF) and cancer procoagulant (CP), in human promyelocytic leukemia cells. To evaluate whether or not changes of the procoagulant activities (PCAs) may share mechanisms with the ATRA-induced cyto-differentiation process,

we have characterized the effect of ATRA on the TF and CP expression by NB4 cells, an ATRA maturation-inducible cell line, and two NB4-derived cell lines resistant to ATRA-induced maturation, the NB4. 306 and NB4.007/6 cells. Next, we evaluated the effect on the PCAs of the NB4 parental cells of three synthetic retinoid analogues, ie: AM580 (selective for the retinoic acid receptor [RAR] alpha), capable to induce the granulocytic differentiation of NB4 cells; and CD2019 (selective for RARbeta) and CD437 (selective for RARgamma), both lacking this capability. Cells were treated with either ATRA or the analogues (10(-6) to 10(-8) mol/L) for 96 hours. The effect on cell differentiation was evaluated by morphologic changes, cell proliferation, nitro blue tetrazolium reduction assay, and flow cytometry analysis of the CD33 and CD11b surface-antigen expression. PCA was first measured in 20 mmol/L Veronal Buffer cell extracts by the one-stage clotting assay of normal and FVII-deficient plasmas. Further TF and CP have been characterized and quantified in cell-sample preparations by chromogenic and immunological assays. In the first series of experiments, ATRA downregulates both TF and CP in NB4 parental cells, as expected. However, in the differentiation-resistant cell lines, it induced a significant loss of TF but had little or no effect on CP. In a second series of experiments, in the NB4 parental cells, the RARalpha agonist (AM580) induced cell maturation and reduced 91% CP expression, whereas CD437 and CD2019 had no cyto-differentiating effects and did not affect CP levels. On the other hand, in the same cells the TF expression was reduced by ATRA and AM580, but also by the RARbeta agonist CD2019, which did not induce cell maturation. These data indicate that in NB4 cells, ATRA modulation of CP occurs in parallel with signs of cell differentiation, while the regulation of TF appears to be at least in part independent from these processes, and involves both alpha and beta nuclear retinoid receptors.

Farag, S. S., K. J. Archer, et al. (2006). "Pretreatment cytogenetics add to other prognostic factors predicting complete remission and long-term outcome in patients 60 years of age or older with acute myeloid leukemia: results from Cancer and Leukemia Group B 8461." Blood **108**(1): 63-73.

We investigated the relative prognostic significance of cytogenetics in 635 adult acute myeloid leukemia (AML) patients 60 years of age or older treated on front-line protocols. Classification trees and tree-structured survival analysis (TSSA) were used to identify important cytogenetic groups, and their prognostic significance was then assessed in multivariable analysis (MVA). Overall, 48.5% achieved complete remission (CR); 6.6% survived at 5 years. Complex karyotypes with at least 3 abnormalities (complex > or = 3) and a group including "rare aberrations" predicted lower CR rates (25% and 30%) versus other patients (56%). Compared with complex > or = 3, the odds of CR were significantly higher for noncomplex karyotypes without rare aberrations on MVA. Cytogenetically, complex > or = 5 predicted inferior disease-free survival on TSSA, remaining significant on MVA together with white blood cell count (WBC), sex, and age. For survival, complex > or = 5, rare aberrations, and core-binding factor (CBF) abnormalities were prognostic (P < .001), with 5-year survivals of 0%, 0%, and 19.4%, respectively, and 7.5% for remaining patients. Together with WBC, marrow blasts, sex, and age, the cytogenetic groups remained significant on MVA. In conclusion, pretreatment cytogenetics adds to other prognostic factors in older AML patients. Patients with complex > or = 5 appear to benefit minimally from current treatment and are better suited for investigational therapy or supportive care.

Farag, S. S., K. J. Archer, et al. (2002). "Isolated trisomy of chromosomes 8, 11, 13 and 21 is an adverse prognostic factor in adults with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B 8461." Int J Oncol **21**(5): 1041-51.

Isolated trisomy is a relatively common cytogenetic abnormality in acute myeloid leukemia (AML), but with uncertain prognostic significance. We studied a large cohort of newly diagnosed de novo AML patients karyotyped on CALGB 8461 from 1984-1999, where trisomy was the sole abnormality. The common isolated trisomies (IT(C)), +8, +11, +13 and +21, comprised 90% of all sole trisomies. The outcome of 101 IT(C) patients was compared to that of 976 with normal and "poor risk" cytogenetics. The overall survival (OS) for IT(C) patients was unsatisfactory with 10% [95% confidence interval (CI), 3-17%] alive at 5 years. Repeated cycles of I/HDAC intensification did not improve outcome. However, SCT significantly improved relapse-free survival (RFS). Among IT(C) patients <60 years in first remission, only 1 of 7 receiving SCT relapsed, compared to 16 of 19 patients treated with chemotherapy only. The prognosis of IT(C) was dependent on SCT. For non-transplanted patients, the 5-year OS for IT(C) was 5% (95% CI, 0-11%), compared to 20% (95% CI, 16-23%) for 640 normal cytogenetics patients. IT(C) was an independent adverse prognostic factor for OS in non-transplanted patients. In those receiving SCT, however, the 5-year OS for IT(C) patients (69%, 95% CI, 32-100%) was not different to that of transplanted normal cytogenetics patients (60%, 95% CI, 38-81%). We conclude that in de novo adult AML patients not

receiving SCT, IT(C) appears to independently predict a poor outcome that may be improved with SCT in first remission. Prospective studies are required to confirm this hypothesis.

Florin, T. A., G. E. Fryer, et al. (2007). "Physical inactivity in adult survivors of childhood acute lymphoblastic leukemia: a report from the childhood cancer survivor study." Cancer Epidemiol Biomarkers Prev **16**(7): 1356-63.

PURPOSE: To determine if adult survivors of childhood acute lymphoblastic leukemia (ALL) are less active (and more inactive) than the general population and to identify modifying factors. PATIENTS AND METHODS: Physical activity was assessed by self-report in 2,648 adult survivors of the Childhood Cancer Survivor Study. Participants in the Behavioral Risk Factor Surveillance System (BRFSS) survey administered through the Centers for Disease Control and Prevention (CDC) were used as a comparison group. RESULTS: Survivors had a mean age of 28.7 years (range, 18.0-44.0 years) and were a mean of 23.1 years from their cancer diagnosis (range, 16.0-33.8 years). In multivariate models, ALL survivors were more likely to not meet CDC recommendations for physical activity [odds ratio (OR), 1.44; 95% confidence interval (95% CI), 1.32-1.57] and more likely to be inactive (OR, 1.74; 95% CI, 1.56-1.94) in comparison with the BRFSS general population. Survivors treated with >20-Gy cranial radiotherapy were at particular risk. Compared with BRFSS participants and adjusted for age, race, and ethnicity, survivors were more likely to not meet CDC recommendations (females: OR, 2.07, 95% CI, 1.67-2.56; males: OR, 1.43, 95% CI, 1.16-1.76) and more likely to be inactive (females: OR, 1.86; 95% CI, 1.50-2.31; males: OR, 1.84; 95% CI, 1.45-2.32). CONCLUSIONS: Long-term survivors of childhood ALL are less likely to meet physical activity recommendations and more likely to report no leisure-time physical activity in the past month. This level of inactivity likely further increases their risk of cardiovascular disease, osteoporosis, and all-cause mortality.

Fujioka, Y., T. Taira, et al. (2001). "MM-1, a c-Myc-binding protein, is a candidate for a tumor suppressor in leukemia/lymphoma and tongue cancer." J Biol Chem **276**(48): 45137-44.

The c-myc oncogene product (c-Myc) is a transcription factor that dimerizes with Max and recognizes the E-box sequence, and it plays key functions in cell proliferation, differentiation, and apoptosis. We previously showed that MM-1 bound to myc box II within the transactivation domain of c-Myc and repressed the E-box-dependent transcriptional activity of c-Myc. Here we report that MM-1 showed features of a tumor suppressor. In an EST data base search for cDNAs homologous to MM-1, we found a frequent substitution of amino acid 157 of MM-1, from alanine to arginine (A157R), and the substitution was observed more in tumor cells than in normal cells. A survey of the A157R mutation of MM-1 in 57 cultured cancer cells and 90 tissues from cancer patients showed that the A157R was present in about 50-60% of leukemia/lymphoma cells and in more than 75% of squamous cell carcinoma of tongue cancer. Although both the A157R and the wild-type MM-1 bound to c-Myc, only A157R lost the activities to repress both the E-box-dependent transcriptional activity of c-Myc and the myc/ras cooperative transforming activity in rat 3Y1 cells. Furthermore, the wild-type MM-1, but not A157R, arrested the growth of 3Y1 cells. The human MM-1 gene was mapped at chromosome 12q12-12q13, where many chromosome abnormalities in cancer cells have been reported. The results suggest that MM-1 is a novel candidate for a tumor suppressor that controls the transcriptional activity of c-Myc.

Gamis, A. S., W. G. Woods, et al. (2003). "Increased age at diagnosis has a significantly negative effect on outcome in children with Down syndrome and acute myeloid leukemia: a report from the Children's Cancer Group Study 2891." J Clin Oncol **21**(18): 3415-22.

PURPOSE: To determine the outcome of children with Down syndrome (DS) and acute myeloid leukemia (AML) receiving standard timing chemotherapy without bone marrow transplantation (BMT), with determination of prognostic factors. PATIENTS AND METHODS: Children with DS and newly diagnosed AML or myelodysplasia were prospectively enrolled on Children's Cancer Group study 2891 (N = 161) and treated uniformly with four standard timing induction courses of dexamethasone, cytarabine arabinoside, 6-thioguanine, etoposide, daunorubicin (DCTER) followed by intensively timed high-dose cytarabine. RESULTS: Children with DS were significantly younger at diagnosis than those without (median age, 1.8 v 7.5 years, respectively; P <.001), with more megakaryocytic leukemia (70% v 6%; P <.001). Higher complete remission rates (91%) were achieved in children with DS than among those without DS (75%; P <.001). Equivalent grade 3 to 4 toxicity (29% v 30%; P =.84) was seen, though children with DS had greater pulmonary toxicity (P <.01) during induction and mucositis during intensification (P =.12). Children with DS had significantly better 8-year event-free survival (EFS; 77% v 21% standard and 40% intensive induction; P <.0001). Multivariate analysis in children with DS revealed that only age at diagnosis of 2 years or older

was a risk factor for greater relapse risk (odds ratio, 4.9; P =.006) and worse survival. Children between ages 0 to 2 years (n = 94) had a 6-year EFS of 86%; those from 2 to 4 years (n = 58), 70%; and those older than 4 years (n = 9), 28%. Remission failures were the primary reason for worse 6-year EFSs (1% in those 0 to 2 years v 14% if >2 years; P =.002). CONCLUSION: Outcome for children with DS and AML is excellent with standard induction therapy, but declines with increasing age.

Garcia, B. H., 2nd, A. Hargrave, et al. (2007). "Antibody microarray analysis of inflammatory mediator release by human leukemia T-cells and human non small cell lung cancer cells." J Biomol Tech **18**(4): 245-51.

Cytokines and chemokines are responsible for regulating inflammation and the immune response. Cytokine and chemokine release is typically measured by quantitative enzyme-linked immunosorbant assay (ELISA) or Western blot analysis. To expedite the analysis of samples for multiple cytokines/chemokines, we have developed slide-based Thermo Scientific ExcelArray Antibody Sandwich Microarrays. Each slide consists of 16 subarrays (wells), each printed with 12 specific antibodies in triplicate and positive and negative control elements. This 16-well format allows for the analysis of 10 test samples using a six-point standard curve. The array architecture is based on the "sandwich" ELISA, in which an analyte protein is sandwiched between an immobilized capture antibody and a biotinylated detection antibody, using streptavidin-linked Thermo Scientific DyLight 649 Dye for quantitation. The observed sensitivity of this assay was <10 pg/mL. In our experiments, the Jurkat cell line was used as a model for human T-cell leukemia, and the A549 cell line was used as a model for human non-small cell lung cancer. To evoke a cytokine/chemokine response, cells were stimulated with tumor necrosis factor alpha (TNFalpha), phorbol-12-myristate-13-acetate (PMA, TPA), and phytohemagglutinin (PHA). Cell supernatants derived from both untreated and stimulated cells were analyzed on four different arrays (Inflammation I, Inflammation II, Angiogenesis, and Chemotaxis), enabling the quantitation of 41 unique analytes. Stimulated cells showed an increase in the expression level of many of the test analytes, including IL-8, TNF-alpha, and MIP-1alpha, compared to the non-treated controls. Our experiments clearly demonstrate the utility of antibody microarray analysis of cell-culture supernatants for the profiling of cellular inflammatory mediator release.

George, D. J., S. Halabi, et al. (2001). "Prognostic significance of plasma vascular endothelial growth factor levels in patients with hormone-refractory prostate cancer treated on Cancer and Leukemia Group B 9480." Clin Cancer Res **7**(7): 1932-6.

PURPOSE: Plasma vascular endothelial growth factor (VEGF) levels are significantly elevated in patients with hormone-refractory prostate cancer (HRPC) compared with patients with localized disease and have been associated with disease progression in other cancer patient populations. Therefore, we measured VEGF levels in plasma prospectively collected from patients enrolled in Cancer and Leukemia Group B 9480, an intergroup study of suramin in patients with HRPC, to determine whether these levels had prognostic significance. EXPERIMENTAL DESIGN: Pretreatment plasma was collected from patients with HRPC enrolled in Cancer and Leukemia Group B 9480. In a subset of samples representative of the entire cohort, plasma VEGF levels were determined in duplicate using a Quantiglo chemiluminescent ELISA kit (R&D Systems, Minneapolis, MN). Statistical analyses were performed to determine the correlation between pretreatment plasma VEGF levels and time of overall survival. The proportional hazards model was used to assess the prognostic significance of various cut points in multivariate models. RESULTS: Plasma VEGF levels in this population ranged from 4-885 pg/ml, with a median level of 83 pg/ml. As a continuous variable, plasma VEGF levels inversely correlated with survival time (P = 0.002). Using various exploratory cut points, plasma VEGF levels appeared to correlate with survival. In multivariate models in which other prognostic factors (serum prostate-specific antigen, alkaline phosphatase, evidence of measurable disease, and hemoglobin) were included, plasma VEGF levels were significant at various cut points tested. CONCLUSION: Although these data are exploratory and need to be confirmed in an independent data set, they suggest that VEGF may have clinical significance in patients with HRPC.

Govindan, R., R. A. Kratzke, et al. (2005). "Gefitinib in patients with malignant mesothelioma: a phase II study by the Cancer and Leukemia Group B." Clin Cancer Res **11**(6): 2300-4.

PURPOSE: The Cancer and Leukemia Group B conducted a phase II study of gefitinib, an inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase, in patients with previously untreated malignant mesothelioma. EXPERIMENTAL DESIGN: Eligible patients had unresectable pleural or peritoneal mesothelioma, measurable disease, no prior therapy, and performance status 0-1 by Cancer and Leukemia Group B criteria. Gefitinib (500 mg p.o.) was administered once a day for 21 days. Patients underwent restaging after every two cycles. Therapy

was continued until disease progression or unacceptable toxicity. RESULTS: The most common grade 3 toxicities were diarrhea (16%) and nausea (12%). Of 43 patients enrolled, 1 patient (2%) had a complete response, 1 patient (2%) had a partial response, 21 (49%) had stable disease lasting two to eight cycles, 15 (35%) had progressive disease, and 5 (12%) had early deaths. One-year survival was 32% [95% confidence interval (CI), 21-50%]. Median survival and failure-free survival were 6.8% (95% CI, 3.5-10.3) and 2.6 months (95% CI, 1.5-4.0), respectively. The 3-month failure-free survival was 40% (95% CI, 25-56%). EGFR expression score by immunohistochemistry done in 28 patients was categorized as low (EGFR 1+ or 2+) or high (EGFR 3+) expression: 97% had EGFR overexpression (2+ or 3+). The median and 3-month failure-free survival were 3.6 months and 40% for those patients with low EGFR expression compared with 8.1 and 40% for those with high EGFR expression. CONCLUSIONS: Although 97% of patients with mesothelioma had EGFR overexpression, gefitinib was not active in malignant mesothelioma. EGFR expression does not correlate with failure-free survival.

Guibal, F. C., M. Alberich-Jorda, et al. (2009). "Identification of a myeloid committed progenitor as the cancer-initiating cell in acute promyelocytic leukemia." Blood **114**(27): 5415-25.

Acute promyelocytic leukemia (APL) is characterized by a block in differentiation and accumulation of promyelocytes in the bone marrow and blood. The majority of APL patients harbor the t(15:17) translocation leading to expression of the fusion protein promyelocytic-retinoic acid receptor alpha. Treatment with retinoic acid leads to degradation of promyelocytic-retinoic acid receptor alpha protein and disappearance of leukemic cells; however, 30% of APL patients relapse after treatment. One potential mechanism for relapse is the persistence of cancer "stem" cells in hematopoietic organs after treatment. Using a novel sorting strategy we developed to isolate murine myeloid cells at distinct stages of differentiation, we identified a population of committed myeloid cells (CD34(+), c-kit(+), FcgammaRIII/II(+), Gr1(int)) that accumulates in the spleen and bone marrow in a murine model of APL. We observed that these cells are capable of efficiently generating leukemia in recipient mice, demonstrating that this population represents the APL cancer-initiating cell. These cells down-regulate the transcription factor CCAAT/enhancer binding protein alpha (C/EBPalpha) possibly through a methylation-dependent mechanism, indicating that C/EBPalpha deregulation contributes to transformation of APL cancer-initiating cells. Our findings provide further understanding of the biology of APL by demonstrating that a committed transformed progenitor can initiate and propagate the disease.

Guidi, A. J., D. A. Berry, et al. (2002). "Association of angiogenesis and disease outcome in node-positive breast cancer patients treated with adjuvant cyclophosphamide, doxorubicin, and fluorouracil: a Cancer and Leukemia Group B correlative science study from protocols 8541/8869." J Clin Oncol **20**(3): 732-42.

PURPOSE: Increased microvessel density (MVD), a reflection of tumor angiogenesis, is associated with diminished relapse-free and overall survival (OS) in several subsets of breast cancer patients. However, the utility of this assay in node-positive patients treated with adjuvant cyclophosphamide, doxorubicin, and fluorouracil (CAF) has not been well studied. PATIENTS AND METHODS: Immunostaining for factor VIII-related antigen was performed on tissue sections from a subset of node-positive patients who received one of three dose/schedule regimens of CAF during participation in Cancer and Leukemia Group B protocol 8541. Sections from 577 cancers exhibited acceptable tumor and immunostaining quality and were included in the study. Each section was examined quantitatively for MVD as well as non-quantitatively by scoring the presence or absence of a prominent vascular pattern. RESULTS: MVD counts were not associated with relapse-free or OS in univariate analysis. The presence of a prominent plexiform vascular pattern was correlated with decreased OS (P =.0085) in univariate analysis, but this pattern was not an independent prognostic indicator of survival in multivariate analysis. No apparent clinically important interactions between measures of angiogenesis, other prognostic factors, administration of tamoxifen, and chemotherapy dose were observed. CONCLUSION: Assessment of angiogenesis does not provide useful information regarding prognosis in node-positive breast cancer patients treated with adjuvant CAF, nor do these measures predict which patients will benefit from dose intensification or addition of tamoxifen.

Gunawardana, D. H., R. L. Basser, et al. (2003). "A phase I study of recombinant human leukemia inhibitory factor in patients with advanced cancer." Clin Cancer Res **9**(6): 2056-65.

PURPOSE: Leukemia inhibitory factor (LIF) is a pleiotropic molecule of the interleukin 6 family of cytokines. We aimed to examine the safety, pharmacokinetics, and biological effects of recombinant human LIF (rhLIF, emfilermin) in patients with advanced cancer. EXPERIMENTAL

DESIGN: In stage 1 of the study, 34 patients received rhLIF or placebo (3:1 ratio) at doses of 0.25-16.0 micro g/kg/day or 4.0 micro g/kg three times daily for 7 days. In stage 2, 40 patients received rhLIF or placebo, either once daily for 14 days commencing the day after chemotherapy (0.25-8.0 micro g/kg/day) or for 7 days commencing the day before chemotherapy (4.0 micro g/kg three times daily). The chemotherapy was cisplatin 75 mg/m(2) and paclitaxel 135 mg/m(2). RESULTS: In stage 1, platelet counts increased in most patients, including those who received placebo. Blood progenitor cells increased in response to rhLIF. In stage 2, platelet recovery to baseline levels was earlier for patients receiving higher doses of rhLIF (>/=4.0 micro g/kg/day; P = 0.02). The neutrophil nadir after chemotherapy was less severe in patients receiving >/=4.0 micro g/kg/day of rhLIF. In stages 1 and 2, increases in C reactive protein were seen at higher doses. Several patients developed evidence of autonomic dysfunction, in particular impotence and episodic hypotension. The dose-limiting toxicities were hypotension and rigors. Pharmacokinetic studies demonstrated a short half-life (1-5 h) independent of dose. CONCLUSIONS: We demonstrated a biological effect of rhLIF on blood progenitor cells, C reactive protein levels, and hemopoietic recovery after chemotherapy.

Halabi, S., N. J. Vogelzang, et al. (2006). "Clinical outcomes by age in men with hormone refractory prostate cancer: a pooled analysis of 8 Cancer and Leukemia Group B (CALGB) studies." J Urol **176**(1): 81-6.

PURPOSE: We determined if age is a prognostic factor of clinical outcomes, specifically overall survival, disease-free survival and progression-free survival in men with hormone refractory prostate cancer. MATERIALS AND METHODS: Data from 8 multi-institutional trials performed by Cancer and Leukemia Group B were combined. Eligible patients had progressive adenocarcinoma of the prostate after androgen ablation, Eastern Cooperative Oncology Group performance status 0 to 2, and adequate hematological, renal and hepatic function. The proportional hazards model stratified by study was used to assess the prognostic importance of age for predicting clinical outcomes. RESULTS: Of 1,194 men 132 (11%) were 50 to 60 years old and 120 (10%) were 80 to 89 years old. Median survival was 12.2 months (95% CI 10.6 to 13.8) in men 50 to 59 years old, 15.9 months (95% CI 14.2 to 17.6) in men 60 to 69 years old, 15.6 months (95% CI 13.8 to 16.9) in men 70 to 79 years old and 8.9 months (95% CI 6.6 to 12.1) in men 80 to 89 years old. Compared to 70 to 79-year-old men the HR for death in octogenarians was 1.3 (95% CI 1.0 to 1.6, p = 0.015). Furthermore, the HR for prostate cancer death in octogenarians was 1.3 (95% CI 1.1 to 1.7, p = 0.010) and in 50 to 59-year-old men it was 1.3 (95% CI 1.0 to 1.6, p = 0.042) compared to men 70 to 79 years old. Black men were at lower risk for death than white men (HR 0.77, 95 CI% 0.65 to 0.92, p = 0.004). CONCLUSIONS: Octogenarians and white men are at increased risk for death compared to other men with hormone refractory prostate cancer.

Hayes, D. F., H. Yamauchi, et al. (2001). "Circulating HER-2/erbB-2/c-neu (HER-2) extracellular domain as a prognostic factor in patients with metastatic breast cancer: Cancer and Leukemia Group B Study 8662." Clin Cancer Res **7**(9): 2703-11.

PURPOSE: The HER-2/erbB-2/c-neu (HER-2) proto-oncogene is a M(r) 185,000 transmembrane tyrosine kinase that is amplified and/or overexpressed by 20-40% of breast cancers. HER-2 has been associated with worse prognosis and resistance or sensitivity to specific treatment. We evaluated circulating levels of extracellular domain of HER-2 (ECD/HER-2) in metastatic breast cancer patients and investigated the prognostic and predictive significance of circulating HER-2 levels regarding endocrine therapy or chemotherapy. EXPERIMENTAL DESIGN: Plasma samples from 242 patients were assayed for circulating ECD/HER-2 levels, using a sandwich enzyme immunoassay. ECD/HER-2 was correlated with clinical data gathered from these patients while they were participating in prospective Cancer and Leukemia Group B (CALGB) therapeutic protocols for metastatic breast cancer. RESULTS: Eighty-nine (37%) of 242 patients had elevated ECD/HER-2 levels (> or =10.5 ng/ml). ECD/HER-2 was significantly associated with tumor burden, progesterone receptor levels, and presence of visceral metastases. Patients with elevated pretreatment levels had a significantly shorter OS but not time-to-progression than did those with ECD/HER-2 levels <10.5 ng/ml in univariate analysis. In univariate but not multivariate subset analyses, among patients treated with endocrine therapy (megestrol acetate), elevated initial ECD/HER-2 was associated with worse OS compared with nonelevated patients. However, among patients treated with chemotherapy (mainly anthracycline-containing regimens), OS did not differ significantly.

Heath, J. A., P. G. Steinherz, et al. (2003). "Human granulocyte colony-stimulating factor in children with high-risk acute lymphoblastic leukemia: a Children's Cancer Group Study." J Clin Oncol **21**(8): 1612-7.

PURPOSE: To investigate the effect of granulocyte colony-stimulating factor (G-CSF) on hematopoietic toxicities, supportive care requirements,

time to complete intensive therapy, and event-free survival (EFS) and overall survival (OS) in children with high-risk acute lymphoblastic leukemia (HR-ALL). PATIENTS AND METHODS: A total of 287 children with HR-ALL were randomly assigned to intensive chemotherapy regimens (New York I [NY I] or NY II) as part of the Children's Cancer Group (CCG)-1901 protocol. The induction phases consisted of five drugs (vincristine, prednisone, l-asparaginase, daunorubicin, and cyclophosphamide). Initial consolidation comprised six-agent chemotherapy combined with 18 Gy of total-brain irradiation. Patients were randomly assigned to receive G-CSF (5 microg/kg/day) during either induction or initial consolidation. A crossover study analysis was done on the 259 patients who completed both phases of therapy. RESULTS: The mean time to neutrophil recovery (>/= 0.5 x 109/L) was reduced with G-CSF (16.7 v 19.1 days, P =.0003); however, patients who received G-CSF did not have significantly reduced episodes of febrile neutropenia (149 v 164, P =.41), positive blood cultures (57 v 61, P =.66), or serious infections (75 v 79, P =.62). Hospitalization (14.0 v 13.9 days, P =.87) and induction therapy completion times (NY I, 30.3 v 31.3 days, P =.11; NY II, 33.4 v 32.3 days, P =.40) were not significantly altered. There were no differences in 6-year EFS (P =.24) or OS (P =.54) between patients receiving or not receiving G-CSF on CCG-1901, NY I and NY II. CONCLUSION: Children with high-risk ALL do not appear to benefit from prophylactic G-CSF.

Heerema, N. A., J. B. Nachman, et al. (2004). "Deletion of 7p or monosomy 7 in pediatric acute lymphoblastic leukemia is an adverse prognostic factor: a report from the Children's Cancer Group." Leukemia **18**(5): 939-47.

Monosomy 7 or deletions of 7q are associated with many myeloid disorders; however, the significance of such abnormalities in childhood acute lymphoblastic leukemia (ALL) is unknown. Among 1880 children with ALL, 75 (4%) had losses involving chromosome 7, 16 (21%) with monosomy 7, 41 (55%) with losses of 7p (del(7p)), 16 (21%) with losses of 7q (del(7q)), and two (3%) with losses involving both arms. Patients with losses involving chromosome 7 were more likely to be > or =10 years old, National Cancer Institute (NCI) poor risk, and hypodiploid than patients lacking this abnormality. Patients with or without these abnormalities had similar early response to induction therapy. Event-free survival (EFS) and survival for patients with monosomy 7 (P<0.0001 and P=0.0007, respectively) or del(7p) (P<0.0001 and P=0.0001, respectively), but not of patients with del(7q), were significantly worse than those of patients lacking these abnormalities. The poorer EFS was maintained after adjustment for a Philadelphia (Ph) chromosome, NCI risk status, ploidy, or an abnormal 9p. However, the impact on survival was not maintained for monosomy 7 after adjustment for a Ph. These results indicate that the critical region of loss of chromosome 7 in pediatric ALL may be on the p-arm.

Heerema, N. A., J. B. Nachman, et al. (1999). "Hypodiploidy with less than 45 chromosomes confers adverse risk in childhood acute lymphoblastic leukemia: a report from the children's cancer group." Blood **94**(12): 4036-45.

We have determined the prognostic significance of hypodiploidy (<46 chromosomes) in a large cohort of children with acute lymphoblastic leukemia (ALL) treated by the Children's Cancer Group. Among 1,880 patients, 110 (5.8%) had hypodiploid karyotypes: 87 had 45 chromosomes, 15 had 33 to 44 chromosomes, none had 29 to 32 chromosomes, and 8 had 24 to 28 chromosomes (near-haploidy). Six-year event-free survival (EFS) estimates for patients with 45 chromosomes, 33 to 44 chromosomes, or 24 to 28 chromosomes were 65% (standard deviation [SD], 8%), 40% (SD, 18%), and 25% (SD, 22%), respectively (log rank, P =.002; test for trend, P =.0009). The combined hypodiploid group had worse outcome than nonhypodiploid patients, with 6-year EFS of 58% (SD, 7%) and 76% (SD, 2%), respectively (P <.0001).

Heerema, N. A., H. N. Sather, et al. (1999). "Cytogenetic studies of infant acute lymphoblastic leukemia: poor prognosis of infants with t(4;11) - a report of the Children's Cancer Group." Leukemia **13**(5): 679-86.

Infants less than 1 year of age at diagnosis of acute lymphoblastic leukemia (ALL) have a poor prognosis, which has been attributed primarily to a breakpoint in chromosomal band 11q23 or the MLL gene. Most infants with an 11q23 breakpoint have a t(4;11)(q21 ;q23). We studied the cytogenetics of the leukemia cells of 56 infants on CCG-1883, a single-arm clinical treatment protocol for infant ALL. Twenty-one patients had t(4;11)(q21;q23), seven had other rearrangements with breakpoints in 11q23 (other 11q23), 16 had normal chromosomes, two had t(1;19)(q32;p13), one had >50 chromosomes, and nine had non-recurring structural abnormalities.

Heerema, N. A., H. N. Sather, et al. (1998). "Frequency and clinical significance of cytogenetic abnormalities in pediatric T-lineage acute lymphoblastic leukemia: a report from the Children's Cancer Group." J Clin Oncol **16**(4): 1270-8.

PURPOSE: Nonrandom chromosomal translocations are frequently observed in pediatric

patients with acute lymphoblastic leukemia (ALL). Specific translocations, such as t(4;11) and t(9;22), identify subgroups of B-lineage ALL patients who have an increased risk of treatment failure. The current study was conducted to determine the prognostic significance of chromosomal translocations in T-lineage ALL patients. MATERIALS AND METHODS: The study included 169 children with newly diagnosed T-lineage ALL enrolled between 1988 and 1995 on risk-adjusted protocols of the Children's Cancer Group (CCG) who had centrally reviewed cytogenetics data. Outcome analyses used standard life-table methods. RESULTS: Presenting features for the current cohort were similar to those of concurrently enrolled patients for whom cytogenetic data were not accepted on central review. The majority of patients (80.5%) were assigned to CCG protocols for high-risk ALL and 86.4% had pseudodiploid (n = 80) or normal diploid (n = 66) karyotypes; modal chromosome number was not a significant prognostic factor. Overall, 103 of 169 (61%) patients had an abnormal karyotype, including 31 with del(6q), 29 with 14q11 breakpoints, 15 with del(9p), 11 with trisomy 8, nine with 11q23 breakpoints, nine with 14q32 translocations, and eight with 7q32-q36 breakpoints.

Heerema, N. A., H. N. Sather, et al. (2000). "Prognostic significance of cytogenetic abnormalities of chromosome arm 12p in childhood acute lymphoblastic leukemia: a report from the Children's Cancer Group." Cancer **88**(8): 1945-54.

BACKGROUND: The authors have determined the prognostic significance of cytogenetically detectable 12p abnormalities, which are frequent in children with acute lymphoblastic leukemia (ALL), in a large cohort of patients treated on risk-adjusted protocols of the Children's Cancer Group (CCG). There was no difference in EFS for the 12 patients with a dic(9;12) compared with patients lacking an abnormal 12p. CONCLUSIONS: These data suggest that although a cytogenetically detectable 12p aberration is a favorable risk factor for children with ALL and pseudodiploidy, it is not prognostic for the overall group of pediatric ALL patients treated with contemporary therapies of the CCG.

Heerema, N. A., H. N. Sather, et al. (1999). "Association of chromosome arm 9p abnormalities with adverse risk in childhood acute lymphoblastic leukemia: A report from the Children's Cancer Group." Blood **94**(5): 1537-44.

Cytogenetic abnormalities of chromosome arm 9p occur frequently in children with acute lymphoblastic leukemia (ALL). We analyzed 201 such cases (11%) in 1,839 children with newly diagnosed ALL treated between 1989 and 1995 on risk-adjusted protocols of the Children's Cancer Group (CCG). The majority of patients (131; 65%) with a 9p abnormality were classified as higher risk. Nearly all patients had complex karyotypes; most cases had deletions of 9p, add/der(9p), a dicentric involving chromosome arm 9p, and/or balanced translocations and inversions involving 9p.

Heinonen, K., K. Mrozek, et al. (1998). "Clinical characteristics of patients with de novo acute myeloid leukaemia and isolated trisomy 11: a Cancer and Leukemia Group B study." Br J Haematol **101**(3): 513-20.

Isolated trisomy 11 is the third most common sole trisomy in de novo acute myeloid leukaemia (AML). However, only 49 cases have been published, and for only a fraction of these cases has full description of clinical and haematological features been provided. As a result, little is known about the clinical characteristics of de novo AML patients with solitary trisomy 11. We have identified 13 patients (0.9%) with isolated trisomy 11 among a total of 1496 consecutive adult patients successfully karyotyped as part of a prospective Cancer and Leukemia Group B (CALGB) cytogenetic study (CALGB 8461). Nine patients (69%) were over the age of 60 (range 29-73 years). Eight patients (62%) were diagnosed with AML of FAB M2 subtype, three patients (23%) had FAB M1 AML and one patient each had AML of FAB M0 and M7, respectively. Seven patients (54%) had high, >100 x 10(9)/l, platelet counts (median 102 x 10(9)/l; range 17-207 x 10(9)/l). All patients received CALGB induction therapy with standard doses of cytarabine and daunorubicin. Six patients (46%) achieved a complete remission (CR).

Heinrich, M. C., K. Owzar, et al. (2008). "Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group." J Clin Oncol **26**(33): 5360-7.

PURPOSE: Imatinib mesylate is standard treatment for patients who have advanced gastrointestinal stromal tumor (GIST), but not all patients benefit equally. In previous studies, GIST genotype correlated with treatment outcome and optimal imatinib dosing. We confirmed the favorable impact of KIT exon 11 genotype when compared with KIT exon 9 and wild-type genotype for patients with advanced GIST who are treated with imatinib.

Hemminki, K., P. Kyyronen, et al. (1999). "Parental age as a risk factor of childhood leukemia and brain cancer in offspring." Epidemiology **10**(3): 271-5.

We use here the Swedish Family-Cancer Database to analyze the time trends in childhood leukemia and brain cancer between 1960 and 1994 and the effect of parental age on childhood leukemia and brain cancer of some 1500 cases each. The database includes all persons born in Sweden after 1940 with their biological parents, over 6 million individuals, whose cancers were retrieved from the Swedish Cancer Registry from years 1958-1994. Incidence in cancer increased from 1960 to 1994; low grade astrocytoma accounted for most of the increase, whereas high grade astrocytoma has not increased in incidence.

Hershman, D., A. I. Neugut, et al. (2007). "Acute myeloid leukemia or myelodysplastic syndrome following use of granulocyte colony-stimulating factors during breast cancer adjuvant chemotherapy." J Natl Cancer Inst **99**(3): 196-205.

BACKGROUND: Recently, increasing numbers of women receiving adjuvant chemotherapy for breast cancer have also received granulocyte colony-stimulating factors (G-CSFs) or granulocyte-macrophage colony-stimulating factors (GM-CSFs). Although these growth factors support chemotherapy, their long-term safety has not been evaluated. We studied the association between G-CSF use and incidence of leukemia in a population-based sample of breast cancer patients. The use of G-CSF was associated with a doubling in the risk of subsequent AML or MDS among the population that we studied, although the absolute risk remained low. Even if this association is confirmed, the benefits of G-CSF may still outweigh the risks. Meanwhile, however, G-CSF use should not be assumed to be risk free.

Hohn, O., H. Krause, et al. (2009). "Lack of evidence for xenotropic murine leukemia virus-related virus(XMRV) in German prostate cancer patients." Retrovirology **6**: 92.

BACKGROUND: A novel gammaretrovirus named xenotropic murine leukemia virus-related virus (XMRV) has been recently identified and found to have a prevalence of 40% in prostate tumor samples from American patients carrying a homozygous R462Q mutation in the RNaseL gene. This mutation impairs the function of the innate antiviral type I interferon pathway and is a known susceptibility factor for prostate cancer. Here, we attempt to measure the prevalence of XMRV in prostate cancer cases in Germany and determine whether an analogous association with the R462Q polymorphism exists. RESULTS: 589 prostate tumor samples were genotyped by real-time PCR with regard to the RNaseL mutation. DNA and RNA samples from these patients were screened for the presence of XMRV-specific gag sequences using a highly sensitive nested PCR and RT-PCR approach. Furthermore, 146 sera samples from prostate tumor patients were tested for XMRV Gag and Env antibodies using a newly developed ELISA assay.

Hong, D., R. Gupta, et al. (2008). "Initiating and cancer-propagating cells in TEL-AML1-associated childhood leukemia." Science **319**(5861): 336-9.

Understanding cancer pathogenesis requires knowledge of not only the specific contributory genetic mutations but also the cellular framework in which they arise and function. Here we explore the clonal evolution of a form of childhood precursor-B cell acute lymphoblastic leukemia that is characterized by a chromosomal translocation generating a TEL-AML1 fusion gene. We identify a cell compartment in leukemic children that can propagate leukemia when transplanted in mice. By studying a monochorionic twin pair, one preleukemic and one with frank leukemia, we establish the lineal relationship between these "cancer-propagating" cells and the preleukemic cell in which the TEL-AML1 fusion first arises or has functional impact. Analysis of TEL-AML1-transduced cord blood cells suggests that TEL-AML1 functions as a first-hit mutation by endowing this preleukemic cell with altered self-renewal and survival properties.

Humphrey, P. A., S. Halabi, et al. (2006). "Prognostic significance of plasma scatter factor/hepatocyte growth factor levels in patients with metastatic hormone- refractory prostate cancer: results from cancer and leukemia group B 150005/9480." Clin Genitourin Cancer **4**(4): 269-74.

BACKGROUND: Scatter factor, also known as hepatocyte growth factor (SF/HGF), is a polypeptide growth factor thought to be important in the growth and spread of prostatic carcinoma. PATIENTS AND METHODS: Scatter factor/HGF levels in pretreatment plasma samples from 171 men with metastatic hormone-refractory prostate cancer enrolled in CALGB 9480 were quantified by solid-phase, enzyme-linked immunosorbent assay. RESULTS: The Cox proportional hazards model was used to assess the prognostic importance of SF/HGF with adjustment for established prognostic factors. Median SF/HGF was 991 pg/mL (range, 212-2733 pg/mL).

Hutchinson, R. J., P. S. Gaynon, et al. (2003). "Intensification of therapy for children with lower-risk acute lymphoblastic leukemia: long-term follow-up of

patients treated on Children's Cancer Group Trial 1881." J Clin Oncol **21**(9): 1790-7.

PURPOSE: From December 1988 through December 1992, the Children's Cancer Group (CCG) conducted a randomized trial (CCG-1881) designed to evaluate the impact of adding a single delayed intensification phase of therapy to standard therapy for patients with newly diagnosed low-risk acute lymphoblastic leukemia (ALL). PATIENTS AND METHODS: Patients (n = 778) with newly diagnosed ALL, 2 to 9 years of age at diagnosis with an initial WBC count less than 10,000/microL, were eligible for this protocol. All patients received induction, consolidation, and interim maintenance phases of therapy over the first 16 weeks. At week 16, patients remaining in remission were randomly assigned to receive or not receive a single 7-week delayed intensification (DI) phase of therapy. Maintenance therapy was given in lieu of or after DI, with total duration of therapy approximately 3 years for boys and 2 years for girls. RESULTS: Patients randomized to receive DI experienced fewer relapse events in all categories. Kaplan-Meier life-table estimates for continuous complete remission (CCR) at 7 years for the randomized regimens were 77% (SE, 2.4%) for the standard regimen and 83% (SE, 2.7%) for the DI regimen (P =.072). The only prognostic factor of significance post-randomization in this selected low-risk population was the day 14 marrow response (P =.0001). CONCLUSION: The addition of a single DI phase of therapy was well tolerated and augmented 7-year CCR by 6% (SE of the difference, 3.3%), resulting in 26% fewer adverse events. Overall survival for eligible patients at 7 years is 90% (SE, 1.2%).

Iwai, T., S. Yokota, et al. (1999). "Internal tandem duplication of the FLT3 gene and clinical evaluation in childhood acute myeloid leukemia. The Children's Cancer and Leukemia Study Group, Japan." Leukemia **13**(1): 38-43.

We analyzed tandem duplication in the juxtamembrane (JM) domain of the FLT3 (FMS-like tyrosine kinase 3/FLK2, CD135) gene in 94 children with acute myeloid leukemia (AML) and evaluated its correlation with clinical features. Longer polymerase chain reaction (PCR) products were observed in five patients; 1/3 of M0, 119 of M1, 1/39 of M2, 1/9 of M3 and 1/12 of M5. The sequence analyses of abnormal PCR products showed that all the abnormal products were derived from tandem duplications involving the JM domain and that all the lengthened sequences were in-frame as we previously reported. Statistical analyses revealed a significantly lower incidence of the tandem duplication in childhood AML patients than in adult patients ($P < 0.05$), and significantly shorter disease-free survival in patients with mutant FLT3 than in patients with wild-type FLT3 ($P < 0.05$). Our results suggest that the tandem duplication in the JM domain of the FLT3 gene is not a frequent phenomenon but might be a factor of poor prognosis in childhood patients with AML.

Kim, T. K., J. S. Lee, et al. (2007). "Direct transcriptional activation of promyelocytic leukemia protein by IFN regulatory factor 3 induces the p53-dependent growth inhibition of cancer cells." Cancer Res **67**(23): 11133-40.

IFN regulatory factor 3 (IRF3) is a transcriptional factor that plays a crucial role in activation of innate immunity and inflammation in response to viral infection, and is also involved in p53-dependent inhibition of cell growth. Although functional activation of IRF3 by viral infection is relatively well documented, the biological role and regulatory mechanism underlying cell growth inhibition by IRF3 are poorly understood. Here, we show a novel regulatory pathway connecting IRF3-promyelocytic leukemia protein (PML)-p53 in primary and cancer cell lines. Overexpression of IRF3 induces p53-dependent cell growth inhibition in cancer cell lines with normal p53 activity. In addition, doxycycline-induced expression of IRF3 in U87MG cells inhibits tumor growth in nude mice in vivo.

Kosty, M. P., J. E. Herndon, 2nd, et al. (2001). "High-dose doxorubicin, dexrazoxane, and GM-CSF in malignant mesothelioma: a phase II study-Cancer and Leukemia Group B 9631." Lung Cancer **34**(2): 289-95.

Doxorubicin is the most widely studied agent for the treatment of malignant mesothelioma. In conventional doses, the response rate is approximately 17%. Higher dose doxorubicin has been successfully employed in other tumor types. Dexrazoxane has been demonstrated to reduce the cardiac toxicity associated with long term, chronic use of doxorubicin. Based upon phase I data generated by the Cancer and Leukemia Group B (CALGB) indicating that doxorubicin at a dose of 120 mg/m(2) when combined with dexrazoxane and GM-CSF could be safely administered, the CALGB undertook a phase II study of high-dose doxorubicin in patients with malignant mesothelioma. Toxicity was excessive, necessitating protocol modification and ultimately protocol termination. There were no objective responses observed. We conclude that high-dose doxorubicin administered with dexrazoxane is unacceptably toxic in this patient population.

Langer, C., M. D. Radmacher, et al. (2008). "High BAALC expression associates with other molecular

prognostic markers, poor outcome, and a distinct gene-expression signature in cytogenetically normal patients younger than 60 years with acute myeloid leukemia: a Cancer and Leukemia Group B (CALGB) study." Blood **111**(11): 5371-9.

BAALC expression is considered an independent prognostic factor in cytogenetically normal acute myeloid leukemia (CN-AML), but has yet to be investigated together with multiple other established prognostic molecular markers in CN-AML. We analyzed BAALC expression in 172 primary CN-AML patients younger than 60 years of age, treated similarly on CALGB protocols. High BAALC expression was associated with FLT3-ITD (P = .04), wild-type NPM1 (P < .001), mutated CEBPA (P = .003), MLL-PTD (P = .009), absent FLT3-TKD (P = .005), and high ERG expression (P = .05). In multivariable analysis, high BAALC expression independently predicted lower complete remission rates (P = .04) when adjusting for ERG expression and age, and shorter survival (P = .04) when adjusting for FLT3-ITD, NPM1, CEBPA, and white blood cell count. A gene-expression signature of 312 probe sets differentiating high from low BAALC expressers was identified.

Le Deley, M. C., F. Suzan, et al. (2007). "Anthracyclines, mitoxantrone, radiotherapy, and granulocyte colony-stimulating factor: risk factors for leukemia and myelodysplastic syndrome after breast cancer." J Clin Oncol **25**(3): 292-300.

PURPOSE: To determine the risk factors for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) after breast cancer. PATIENTS AND METHODS: We conducted a case-control study among women treated for breast cancer between 1985 and 2001 in French general hospitals, cancer centers, or clinics. We included 182 AML and MDS patients and 534 matched controls. This large case-control study demonstrates that the risk of AML/MDS is much higher with mitoxantrone-based chemotherapy than with anthracyclines-based chemotherapy in a population of women recently treated for breast cancer. The risk of AML/MDS associated with mitoxantrone must be kept in mind when using this drug to treat diseases other than breast cancer (eg, prostate cancer or multiple sclerosis). In addition, our study suggests the need to monitor the long-term effects of G-CSF therapy.

Levine, E. G., S. Halabi, et al. (2002). "Higher doses of mitoxantrone among men with hormone-refractory prostate carcinoma: a Cancer and Leukemia Group B study." Cancer **94**(3): 665-72.

Mitoxantrone in combination with a low-dose glucocorticoid has been shown to produce more favorable outcomes among men with hormone-refractory prostate carcinoma than glucocorticoid alone. Therefore, the authors sought to determine the safety and activity of higher doses of mitoxantrone in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) and a glucocorticoid in preparation for a possible Phase III trial comparing standard to dose-escalated mitoxantrone. METHODS: This Phase II trial enrolled 45 patients from October 1996 to March 1998. Twenty-one patients without pelvic irradiation (Arm I) received 21 mg/m(2) of mitoxantrone every 3 weeks, and 24 patients who had received pelvic irradiation (Arm II) were given 17 mg/m(2) on the same schedule. All patients received 40 mg of hydrocortisone in divided doses daily and GM-CSF at 500 microg/daily for a minimum of 10 days per cycle beginning on the third day of the cycle. In Arm I, 33% of assessable patients achieved a partial response, 50% had a > or = 50% decline in their PSA, and 35% had a > or = 75% decline in PSA values. The comparable numbers in Arm II were 24%, 48%, and 35%, respectively. The median survival times were 12 months in Arm I and 14 months in Arm II. Treatment had to be discontinued in 13% of patients because of thrombocytopenia. No other significant toxicities were encountered. Higher doses of mitoxantrone (17 and 21 mg/m(2)) were associated with activity comparable to many estramustine combinations and generally were well tolerated. However, because the degree and frequency of thrombocytopenia were greater than that observed with standard dose mitoxantrone (12-14 mg/m(2)), and because the median survival is apparently comparable to standard dose mitoxantrone, this approach to HRPC cannot be recommended for Phase III testing.

Levy, A. S., H. N. Sather, et al. (2003). "Reduced folate carrier and dihydrofolate reductase expression in acute lymphocytic leukemia may predict outcome: a Children's Cancer Group Study." J Pediatr Hematol Oncol **25**(9): 688-95.

PURPOSE: Methotrexate is a major component of current treatment regimens for children with acute lymphocytic leukemia (ALL). Potential mechanisms of methotrexate resistance include impaired drug uptake, decreased drug retention, and dihydrofolate reductase (DHFR) amplification. The purpose of this study was to assess whether reduced folate carrier (RFC) and DHFR expression in untreated leukemic blasts correlated with outcome. METHODS: Quantitative real-time RT-PCR was used to measure RFC and DHFR mRNA expression in leukemic blasts from 40 newly diagnosed patients with ALL obtained in a blinded fashion from Children's Cancer Group studies. RESULTS: Low RFC expression at diagnosis correlated significantly

with an unfavorable event free survival. Surprisingly, low, not high, DHFR expression correlated significantly with an unfavorable event-free survival. Proliferative cell nuclear antigen (PCNA) expression demonstrated a weak inverse relationship between sample PCNA and DHFR or RFC expression, suggesting that DHFR and RFC expression may be markers for factors other than drug resistance. CONCLUSIONS: These results suggest that impaired transport may be an important mechanism of intrinsic methotrexate resistance in ALL, and DHFR expression also may be an important prognostic factor in ALL. Additional studies are necessary to clarify the mechanism for the correlation of low DHFR expression with poor outcome.

Likui, W., L. Qun, et al. (2009). "Prognostic role of myeloid cell leukemia-1 protein (Mcl-1) expression in human gastric cancer." J Surg Oncol **100**(5): 396-400.

BACKGROUND: Myeloid cell leukemia-1 protein (Mcl-1), an anti-apoptotic member of Bcl-2 family, has been reported to be correlated with tumor progression. The purpose of this study was to establish the prognostic value of Mcl-1 expression in human gastric cancer. Mcl-1 is highly upregulated in gastric cancer and high Mcl-1 expression is correlated with a poor prognosis in gastric cancer patients. Thus, Mcl-1 can be utilized as an independent prognostic factor.

Loh, M. L., M. G. Reynolds, et al. (2004). "PTPN11 mutations in pediatric patients with acute myeloid leukemia: results from the Children's Cancer Group." Leukemia **18**(11): 1831-4.

The PTPN11 gene encodes SHP-2, a nonreceptor protein tyrosine phosphatase that relays signals from activated growth factor receptors to p21(ras) (Ras) and other signaling molecules. Somatic PTPN11 mutations are common in patients with juvenile myelomonocytic leukemia (JMML) and have been reported in some other hematologic malignancies. We analyzed specimens from 278 pediatric patients with acute myelogenous leukemia (AML) who were enrolled on Children's Cancer Group trials 2941 and 2961 for PTPN11 mutations. Missense mutations of PTPN11 were detected in 11 (4%) of these samples.

Marcucci, G., C. D. Baldus, et al. (2005). "Overexpression of the ETS-related gene, ERG, predicts a worse outcome in acute myeloid leukemia with normal karyotype: a Cancer and Leukemia Group B study." J Clin Oncol **23**(36): 9234-42.

PURPOSE: To test the prognostic significance of ETS-related gene (ERG) expression in cytogenetically normal primary acute myeloid leukemia (AML). PATIENTS AND METHODS: Pretreatment blood samples from 84 cytogenetically normal AML patients aged less than 60 years, who were characterized for BAALC expression, FLT3 internal tandem duplication (ITD), and MLL partial tandem duplication (PTD) and uniformly treated on Cancer and Leukemia Group B 9621 protocol, were analyzed for ERG expression by real-time reverse transcriptase polymerase chain reaction. Patients were divided into quartiles according to ERG levels and were compared for clinical outcome. High-density oligonucleotide arrays were used to identify genes differentially expressed between high and low ERG expressers. RESULTS: With a median follow-up of 5.7 years, patients with the upper 25% of ERG expression values had a worse cumulative incidence of relapse (CIR; $P < .001$) and overall survival (OS; $P = .011$) than the remaining patients. In a multivariable analysis, high ERG expression ($P < .001$) and the presence of MLL PTD ($P = .027$) predicted worse CIR. With regard to OS, an interaction was observed between expression of ERG and BAALC ($P = .013$), with ERG overexpression predicting shorter survival only in low BAALC expressers ($P = .002$). ERG overexpression in AML patients with normal cytogenetics predicts an adverse clinical outcome and seems to be associated with a specific molecular signature.

Marcucci, G., K. Maharry, et al. (2007). "High expression levels of the ETS-related gene, ERG, predict adverse outcome and improve molecular risk-based classification of cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B Study." J Clin Oncol **25**(22): 3337-43.

PURPOSE: To validate ERG overexpression as an adverse predictor and assess its prognostic value in the context of other molecular markers in cytogenetically normal (CN) -acute myeloid leukemia (AML). PATIENTS AND METHODS: Seventy-six adult patients with primary CN-AML, younger than 60 years and treated on Cancer and Leukemia Group B (CALGB) trial 19808, were evaluated for ERG expression by quantitative reverse transcriptase polymerase chain reaction. They were then combined with 72 patients enrolled onto CALGB 9621 for analyses that included other molecular markers. RESULTS: Similar to patients enrolled onto CALGB 9621, high ERG expressers on CALGB 19808 had fewer complete remissions (CRs; $P = .03$) and worse event-free survival (EFS; $P = .016$) than low ERG expressers. In the combined set, high expressers ($n = 55$) had fewer CRs ($P = .004$) and shorter EFS ($P < .001$) than low expressers ($n = 93$). High ERG predicted failure to achieve CR ($P = .004$) after adjusting for BAALC expression ($P = .04$) and age ($P = .008$), and EFS ($P = .004$) after adjusting for FLT3

internal tandem duplication (ITD; P < .001). Among patients without FLT3-ITD (FLT3-ITD negative), only high ERG predicted shorter EFS (P = .001). Among NPM1-mutated (NPM1 positive) patients, high ERG predicted shorter EFS (P = .003), after adjusting for FLT3-ITD (P < .001).

Marcucci, G., K. Mrozek, et al. (2005). "Prognostic factors and outcome of core binding factor acute myeloid leukemia patients with t(8;21) differ from those of patients with inv(16): a Cancer and Leukemia Group B study." J Clin Oncol **23**(24): 5705-17.

PURPOSE: Because both t(8;21) and inv(16) disrupt core binding factor (CBF) in acute myeloid leukemia (AML) and confer relatively favorable prognoses, these cytogenetic groups are often treated similarly. Recent studies, however, have shown different gene profiling for the two groups, underscoring potential biologic differences. Therefore, we sought to determine whether these two cytogenetic groups should also be considered separate entities from a clinical standpoint. PATIENTS AND METHODS: We analyzed 144 consecutive adults with t(8;21) and 168 with inv(16) treated on Cancer and Leukemia Group B front-line studies. We compared pretreatment features, probability of achieving complete remission (CR), overall survival (OS) and cumulative incidence of relapse (CIR) between the two groups. RESULTS: With a median follow-up of 6.4 years, for CBF AML as a whole, the CR rate was 88%, 5-year OS was 50% and CIR was 53%. After adjusting for covariates, patients with t(8;21) had shorter OS (hazard ratio [HR] = 1.5; P = .045) and survival after first relapse (HR = 1.7; P = .009) than patients with inv(16).

Matsuo, K., K. Kiura, et al. (2006). "Clustered incidence of acute promyelocytic leukemia during gefitinib treatment for non-small-cell lung cancer: experience at a single institution." Am J Hematol **81**(5): 349-54.

Although gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, has been shown a significant activity for recurrent non-small-cell lung cancer (NSCLC), its long-term adverse effect with its continuous usage has hitherto not been clearly elucidated. Subjects were 108 consecutive NSCLC cases who were treated with gefitinib between November 2001 and December 2004 at our single institution. A crude incidence rate ratio was calculated by ratio of crude incidence rate in our subject to population-based incident rate of all leukemia (ICD: C91-95) in the same region. The 95% confidence intervals (CIs) were calculated based upon a Poisson distribution. Three cases of acute promyelocytic leukemia (APL) occurred during gefitinib treatment, and these patients' past treatment histories are presented herein. No other malignancy was identified. All of the cases were diagnosed at the stage of mild-to-moderate cytopenia, especially thrombocytopenia, without disseminated intravascular coagulation.

Matsuzaki, A., Y. Nagatoshi, et al. (2005). "Prognostic factors for relapsed childhood acute lymphoblastic leukemia: impact of allogeneic stem cell transplantation--a report from the Kyushu-Yamaguchi Children's Cancer Study Group." Pediatr Blood Cancer **45**(2): 111-20.

BACKGROUND: The treatment results of childhood acute lymphoblastic leukemia (ALL) with a first relapse were retrospectively analyzed to determine prognostic factors. In particular, an attempt was made to clarify whether stem cell transplantation (SCT) had any advantages over chemotherapy. PROCEDURES: Of the 407 children with ALL diagnosed between 1984 and 1996, 117 suffered from a relapse before December 1999. The patients were treated differently according to the protocols of each institution. The potential prognostic factors examined were: the time of initial diagnosis, gender, immunophenotype of leukemic blasts and the NCI-risk classification at initial diagnosis, the site of relapse, the time of relapse (early: within 18 months after diagnosis, intermediate: other than either early or late relapse, late: later than 6 months after the discontinuation of front-line chemotherapy), and the treatment after relapse (chemotherapy alone and SCT). RESULTS: A second complete remission (CR2) was achieved in 90 patients (77%) and thirty of them maintained CR2, thus resulting in an event-free survival rate (EFS) of 25.1% and an overall survival rate of 26.1%.

Meloni, G., A. Proia, et al. (2000). "Acute myeloid leukemia and lung cancer occurring in a chronic lymphocytic leukemia patient treated with fludarabine and autologous peripheral blood stem-cell transplantation." Ann Oncol **11**(11): 1493-5.

An increased incidence of different malignancies associated to chronic lymphocytic leukemia (CLL) has been reported. The association of CLL and acute leukemia is a rare event described in < 1% of CLL, the type of acute leukemia being either from the lymphoid or more often from the myeloid lineage. The coexistence of acute myeloid leukemia (AML) and CLL in the same patient has been occasionally reported. Most of these cases have been associated with the administration of chemotherapy or radiotherapy for CLL, suggesting that the former may be a secondary leukemia. On the other hand, CLL could precede, but could also be diagnosed at the same, or delayed time as AML, suggesting the

presence of other leukemogenic factors. We describe the exceptional development of AML and lung cancer in a patient with previously diagnosed CLL in minimal residual disease status after fludarabine treatment followed by autologous peripheral blood stem-cell transplantation.

Meyerhardt, J. A., D. Niedzwiecki, et al. (2008). "Impact of body mass index and weight change after treatment on cancer recurrence and survival in patients with stage III colon cancer: findings from Cancer and Leukemia Group B 89803." J Clin Oncol **26**(25): 4109-15.

PURPOSE: Obesity is a risk factor for the development of colon cancer. However, the influence of body mass index (BMI) on the outcome of patients with established colon cancer remains uncertain. Moreover, the impact of change in body habitus after diagnosis has not been studied. PATIENTS AND METHODS: We conducted a prospective, observational study of 1,053 patients who had stage III colon cancer and who were enrolled on a randomized trial of adjuvant chemotherapy. Patients reported on height and weight during and 6 months after adjuvant chemotherapy. Patients were observed for cancer recurrence or death. RESULTS: In this cohort of patients with stage III cancer, 35% of patients were overweight (BMI, 25 to 29.9 kg/m(2)), and 34% were obese (BMI >or= 30 kg/m(2)). Increased BMI was not significantly associated with a higher risk of colon cancer recurrence or death (P trend = .54). Compared with normal-weight patients (BMI, 21 to 24.9 kg/m(2)), the multivariate hazard ratio for disease-free survival was 1.00 (95% CI, 0.72 to 1.40) for patients with class I obesity (BMI, 30 to 34.9 kg/m(2)) and 1.24 (95% CI, 0.84 to 1.83) for those with class II to III obesity (BMI >or= 35 kg/m(2)) after analysis was adjusted for tumor-related prognostic factors, physical activity, tobacco history, performance status, age, and sex. Similarly, after analysis was controlled for BMI, weight change (either loss or gain) during the time period between ongoing adjuvant therapy and 6 months after completion of therapy did not significantly impact on cancer recurrence and/or mortality. CONCLUSION: Neither BMI nor weight change was significantly associated with an increased risk of cancer recurrence and death in patients with colon cancer.

Millot, F., S. Suciu, et al. (2001). "Value of high-dose cytarabine during interval therapy of a Berlin-Frankfurt-Munster-based protocol in increased-risk children with acute lymphoblastic leukemia and lymphoblastic lymphoma: results of the European Organization for Research and Treatment of Cancer 58881 randomized phase III trial." J Clin Oncol **19**(7): 1935-42.

PURPOSE: The European Organization for Research and Treatment of Cancer 58881 study was designed to test in a prospective multicentric randomized trial the value of high-dose (HD) intravenous (IV) cytarabine (Ara-C) added to HD IV methotrexate (MTX) to reduce the incidence of CNS and systemic relapses in children with increased-risk acute lymphoblastic leukemia (ALL) or stage III and IV lymphoblastic lymphoma treated with a Berlin-Frankfurt-Munster (BFM)-based regimen. PATIENTS AND METHODS: After completion of induction-consolidation phase, children with increased-risk (risk factor > 0.8 or T-lineage) ALL or stage III and IV lymphoblastic lymphoma were randomized to receive four courses of HD MTX (5 g/m(2) over 24 hours every 2 weeks) and four intrathecal administrations of MTX (Arm A) or the same treatment schedule with additional HD IV Ara-C (1 g/m(2) in bolus injection 12 and 24 hours after the start of each MTX infusion) (Arm B). RESULTS: Between January 1990 and January 1996, 653 patients with ALL (593 patients) or lymphoblastic lymphoma (60 patients) were randomized: 323 were assigned to Arm A (without Ara-C) and 330 to Arm B (with Ara-C). A total of 190 events (177 relapses and 13 deaths without relapse) were reported, and the median follow up was 6.5 years (range, 2 to 10 years). The incidence rates of CNS relapse were similar in both arms whether isolated (5.6% and 3.3%, respectively) or combined (5.3% and 4.6%, respectively). The estimated 6-year disease-free survival (DFS) rate was similar (log-rank P =.67) in the two treatment groups: 70.4% (SE = 2.6%) in Arm A and 71.0% (SE = 2.5%) in Arm B. The 6-year DFS rate was similar for ALL and LL patients: 70.2% (SE = 1.9%) versus 76.3% (SE = 5.6%). CONCLUSION: Prevention of CNS relapse was satisfactorily achieved with HD IV MTX and intrathecal injections of MTX in children with increased-risk ALL or stage III and IV lymphoblastic lymphoma treated with our BFM-based treatment protocol in which cranial irradiation was omitted. Disappointingly, with the dose schedule used in this protocol, HD Ara-C added to HD MTX, although well tolerated, failed to further decrease the incidence of CNS relapse or to improve the overall DFS.

Mori, T., A. Manabe, et al. (2001). "Allogeneic bone marrow transplantation in first remission rescues children with Philadelphia chromosome-positive acute lymphoblastic leukemia: Tokyo Children's Cancer Study Group (TCCSG) studies L89-12 and L92-13." Med Pediatr Oncol **37**(5): 426-31.

BACKGROUND: The prognosis of Philadelphia chromosome-positive acute

lymphoblastic leukemia (Ph(+) ALL) is generally poor and reports from large studies are scarce. We evaluated the efficacy of allogeneic bone marrow transplantation (allo-BMT) for children with this type of leukemia. PROCEDURE: The chemotherapy regimens consisted of an induction phase and very intensive consolidation followed by a reinduction phase and late intensification treatment. The selection of treatment modalities such as chemotherapy, allo-BMT, or autologous transplantation was made by each institute. The principal endpoint was the outcome of children with Ph(+) ALL according to the treatment options. RESULTS: Thirty-two patients (4.3%) were diagnosed as Ph(+) ALL out of the 741 cases of ALL consecutively enrolled in two protocols of the Tokyo Children's Cancer Study Group (TCCSG) from 1989 to 1994. Thirty patients (93.8%) were induced into complete remission (CR). Of these 30 patients, eight children electively received allo-BMT in the first CR. Six of these patients are in continuous remission at a median follow-up of 58 (range 48-105) months after the diagnosis. One patient died following recurrence and another patient died of graft vs. host disease. Three patients treated with autologous BMT or peripheral blood stem cell transplantation in the first CR experienced a subsequent relapse. In the remaining 19 patients, 13 patients were treated with very high-risk chemotherapy alone and all relapsed within 28 months. One patient was excluded from the analysis because he was treated with standard-risk chemotherapy until relapse. The other five patients were also excluded from the analysis because Philadelphia chromosome was not detected until they relapsed. None of the relapsed patients survived in spite of treatment including allo-BMT. In multivariate analysis, only allo-BMT remained as an independent factor for good prognosis. CONCLUSIONS: The only way to cure children with Ph(+) ALL was allo-BMT in this study and its outcome seemed promising.

Mrozek, K., T. W. Prior, et al. (2001). "Comparison of cytogenetic and molecular genetic detection of t(8;21) and inv(16) in a prospective series of adults with de novo acute myeloid leukemia: a Cancer and Leukemia Group B Study." J Clin Oncol **19**(9): 2482-92.

PURPOSE: To prospectively compare cytogenetics and reverse transcriptase-polymerase chain reaction (RT-PCR) for detection of t(8;21)(q22;q22) and inv(16)(p13q22)/t(16;16)(p13;q22), aberrations characteristic of core-binding factor (CBF) acute myeloid leukemia (AML), in 284 adults newly diagnosed with primary AML. PATIENTS AND METHODS: Cytogenetic analyses were performed at local laboratories, with results reviewed centrally. RT-PCR for AML1/ETO and CBFbeta/MYH11 was performed centrally. RESULTS: CBF AML was ultimately identified in 48 patients: 21 had t(8;21) or its variant and AML1/ETO, and 27 had inv(16)/t(16;16), CBFbeta/MYH11, or both. Initial cytogenetic and RT-PCR analyses correctly classified 95.7% and 96.1% of patients, respectively (P =.83). Initial cytogenetic results were considered to be false-negative in three AML1/ETO-positive patients with unique variants of t(8;21), and in three CBFbeta/MYH11-positive patients with, respectively, an isolated +22; del(16)(q22),+22; and a normal karyotype. The latter three patients were later confirmed to have inv(16)/t(16;16) cytogenetically. Only one of 124 patients reported initially as cytogenetically normal was ultimately RT-PCR-positive. There was no false-positive cytogenetic result. Initial RT-PCR was falsely negative in two patients with inv(16) and falsely positive for AML1/ETO in two and for CBFbeta/MYH11 in another two patients. Two patients with del(16)(q22) were found to be CBFbeta/MYH11-negative. M4Eo marrow morphology was a good predictor of the presence of inv(16)/t(16;16). CONCLUSION: Patients with t(8;21) or inv(16) can be successfully identified in prospective multi-institutional clinical trials. Both cytogenetics and RT-PCR detect most such patients, although each method has limitations. RT-PCR is required when the cytogenetic study fails; it is also required to determine whether patients with suspected variants of t(8;21), del(16)(q22), or +22 represent CBF AML. RT-PCR should not replace cytogenetics and should not be used as the only diagnostic test for detection of CBF AML because of the possibility of obtaining false-positive or false-negative results.

Neubauer, A., K. Maharry, et al. (2008). "Patients with acute myeloid leukemia and RAS mutations benefit most from postremission high-dose cytarabine: a Cancer and Leukemia Group B study." J Clin Oncol **26**(28): 4603-9.

PURPOSE: RAS mutations occur in 12% to 27% of patients with acute myeloid leukemia (AML) and enhance sensitivity to cytarabine in vitro. We examined whether RAS mutations impact response to cytarabine in vivo. PATIENTS AND METHODS: One hundred eighty-five patients with AML achieving complete remission on Cancer and Leukemia Group B study 8525 and randomly assigned to one of three doses of cytarabine postremission were screened for RAS mutations. We assessed the impact of cytarabine dose on cumulative incidence of relapse (CIR) of patients with (mutRAS) and without (wild-type; wtRAS) RAS mutations. RESULTS: Thirty-four patients (18%) had RAS mutations. With 12.9 years median follow-up, the 10-year CIR was similar for mutRAS and wtRAS patients (65% v 73%; P = .31).

However, mutRAS patients receiving high-dose cytarabine consolidation (HDAC; 3 g/m(2) every 12 hours on days 1, 3, and 5 or 400 mg/m(2)/d x 5 days) had the lowest 10-year CIR, 45%, compared with 68% for wtRAS patients receiving HDAC and 80% and 100%, respectively, for wtRAS and mutRAS patients receiving low-dose cytarabine (LDAC; 100 mg/m(2)/d x 5 days; overall comparison, P < .001). Multivariable analysis revealed an interaction of cytarabine dose and RAS status (P = .06). After adjusting for this interaction and cytogenetics (core binding factor [CBF] AML v non-CBF AML), wtRAS patients receiving HDAC had lower relapse risk than wtRAS patients receiving LDAC (hazard ratio [HR] = 0.67; P = .04); however, mutRAS patients receiving HDAC had greater reduction in relapse risk (HR = 0.28; P = .002) compared with mutRAS patients treated with LDAC. CONCLUSION: AML patients carrying mutRAS benefit from higher cytarabine doses more than wtRAS patients. This seems to be the first example of an activating oncogene mutation favorably modifying response to higher drug doses in AML.

Niell, H. B., J. E. Herndon, 2nd, et al. (2005). "Randomized phase III intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte colony-stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B Trial 9732." J Clin Oncol **23**(16): 3752-9.

PURPOSE: To determine, in a randomized comparison, whether the addition of paclitaxel to etoposide and cisplatin improves the time to progression and overall survival in patients with extensive small-cell lung cancer (SCLC) compared with standard etoposide and cisplatin and to compare the regimens' toxicity. PATIENTS AND METHODS: Eligible patients (N=587) with untreated extensive SCLC were randomly assigned to receive either cisplatin 80 mg/m2 on day 1 and etoposide 80 mg/m2 on days 1 through 3 administered every 3 weeks for six cycles (EP) or cisplatin 80 mg/m2 on day 1, paclitaxel 175 mg/m2 over 4 hours on day 1, and etoposide 80 mg/m2 on days 1 to 3 followed by recombinant human granulocyte colony-stimulating factor on days 4 to 18 administered every 3 weeks for six cycles (PET). RESULTS: Reporting of demographics, response, and survival included 565 patients, of whom 282 were randomly assigned to receive EP and 283 were assigned to receive PET. Overall response rates were 68% for the EP arm and 75% for the PET arm. Median failure-free survival time was 5.9 months for the EP arm and 6 months for the PET arm (P = .179). Median overall survival time was 9.9 months for patients on EP and 10.6 months for patients on PET (P = .169). Toxic deaths occurred in 2.4% of the patients on EP and 6.5% of patients on PET. CONCLUSION: PET did not improve the time to progression or survival in patients with extensive SCLC compared with EP alone and was associated with unacceptable toxicity.

Oh, W. K., S. Halabi, et al. (2003). "A phase II study of estramustine, docetaxel, and carboplatin with granulocyte-colony-stimulating factor support in patients with hormone-refractory prostate carcinoma: Cancer and Leukemia Group B 99813." Cancer **98**(12): 2592-8.

BACKGROUND: The authors determined the safety and efficacy of estramustine, docetaxel, and carboplatin with granulocyte-colony-stimulating factor (G-CSF) support in patients with hormone-refractory prostate carcinoma. METHODS: In the current multicenter, cooperative group study, patients with advanced prostate carcinoma whose disease progressed despite androgen deprivation therapy were treated with a combination of oral estramustine(240 mg three times per day for 5 days), 70 mg/m2 of docetaxel, and carboplatin at a dose of (area under the curve) 5. G-CSF was used to minimize the neutropenia associated with this regimen. Each cycle was repeated every 21 days. RESULTS: Forty patients were treated with a median of 7 cycles of therapy. Of the 34 evaluable patients with elevated pretreatment prostate-specific antigen (PSA) levels, 23 (68%) had a > or = 50% decline in PSA and 20 (59%) had a > or = 75% decline. Twenty-one patients had measurable disease, with 1 complete response (5%) and 10 partial responses (47%), for an overall measurable response rate of 52% (95% confidence interval [95% CI], 30-74%). The most common Grade 3 or Grade 4 toxicities (according to the National Cancer Institute Common Toxicity Criteria) included neutropenia in 23% of patients, thrombocytopenia in 13%, and fatigue in 13%. Febrile neutropenia occurred in 1 patient (3%). The overall median time to disease progression was 8.1 months (95% CI, 6-10 months) and the overall survival period was 19 months (95% CI, 13-26 months). CONCLUSIONS: The combination of estramustine, docetaxel, and carboplatin with G-CSF support was found to have significant clinical activity with an acceptable toxicity profile in patients with progressive hormone-refractory prostate carcinoma.

Oki, Y., H. M. Kantarjian, et al. (2006). "Adult acute megakaryocytic leukemia: an analysis of 37 patients treated at M.D. Anderson Cancer Center." Blood **107**(3): 880-4.

To characterize acute megakaryocytic leukemia (FAB M7 AML), we identified 37 patients with M7 AML treated at M.D. Anderson Cancer

Center between 1987 and 2003 and compared them with 1800 patients with non-M7, non-M3 AML treated during the same period. The median age of the M7 AML group was 56 years (range, 21-78 years); 22 patients (59%) had an antecedent hematologic disorder or myelodysplastic syndrome or both, and 7 patients (19%) had previously received chemotherapy for other malignancies. Extensive bone marrow fibrosis was found in 23 patients (62%). Poor cytogenetic characteristics were observed in 49% of patients with M7 AML versus 33% of others (P < .001). Complete remission rates were 43% with M7 AML and 57% with non-M7 AML (P = .089). Median overall survival (OS) was 23 and 38 weeks, respectively (P = .006). Median disease-free survivals were 23 versus 52 weeks, respectively (P < .001). By multivariate analysis, M7 AML was an independent adverse prognostic factor for OS, independent of other factors including cytogenetic abnormalities (hazard ratio 1.51, P = .049). These results confirm the poor prognosis of M7 AML and indicate that other biologic characteristics beyond cytogenetic abnormalities likely play a role in this disease.

Paschka, P., G. Marcucci, et al. (2006). "Adverse prognostic significance of KIT mutations in adult acute myeloid leukemia with inv(16) and t(8;21): a Cancer and Leukemia Group B Study." J Clin Oncol **24**(24): 3904-11.

PURPOSE: To analyze the prognostic impact of mutated KIT (mutKIT) in core-binding factor acute myeloid leukemia (AML) with inv(16)(p13q22) and t(8;21)(q22;q22). PATIENTS AND METHODS: Sixty-one adults with inv(16) and 49 adults with t(8;21), assigned to postremission therapy with repetitive cycles of higher dose cytarabine were analyzed for mutKIT in exon 17 (mutKIT17) and 8 (mutKIT8) by denaturing high-performance liquid chromatography and direct sequencing at diagnosis. The median follow-up was 5.3 years. RESULTS: Among patients with inv(16), 29.5% had mutKIT (16% with mutKIT17 and 13% with sole mutKIT8). Among patients with t(8;21), 22% had mutKIT (18% with mutKIT17 and 4% with sole mutKIT8). Complete remission rates of patients with mutKIT and wild-type KIT (wtKIT) were similar in both cytogenetic groups. In inv(16), the cumulative incidence of relapse (CIR) was higher for patients with mutKIT (P = .05; 5-year CIR, 56% v 29%) and those with mutKIT17 (P = .002; 5-year CIR, 80% v 29%) compared with wtKIT patients. Once data were adjusted for sex, mutKIT predicted worse overall survival (OS). In t(8;21), mutKIT predicted higher CIR (P = .017; 5-year CIR, 70% v 36%), but did not influence OS. CONCLUSION: We report for the first time that mutKIT, and particularly mutKIT17, confer higher relapse risk, and both mutKIT17 and mutKIT8 appear to adversely affect OS in AML with inv(16). We also confirm the adverse impact of mutKIT on relapse risk in t(8;21) AML. We suggest that patients with core-binding factor AML should be screened for mutKIT at diagnosis for both prognostic and therapeutic purposes, given that activated KIT potentially can be targeted with novel tyrosine kinase inhibitors.

Patt, D. A., Z. Duan, et al. (2007). "Acute myeloid leukemia after adjuvant breast cancer therapy in older women: understanding risk." J Clin Oncol **25**(25): 3871-6.

PURPOSE: The purpose of this study was to determine the risk of developing acute myeloid leukemia (AML) after adjuvant chemotherapy for breast cancer in older women. PATIENTS AND METHODS: Data from the Surveillance, Epidemiology, and End Results-Medicare linked database were used for women diagnosed with nonmetastatic breast cancer from 1992 to 2002. The primary end point was a claim with an inpatient or outpatient diagnosis of AML (International Classification of Diseases ninth revision, codes 205 to 208), comparing patients treated with and without adjuvant chemotherapy, and by differing chemotherapy regimens. The cumulative hazard of AML was estimated using the Kaplan-Meier method. Cox proportional hazards models were used to determine factors independently associated with the development of AML. RESULTS: In this observational study, there were 64,715 patients: 10,130 received adjuvant chemotherapy and 54,585 did not. The median patient age was 75.6 years (range, 66 to 104 years). The mean follow-up was 54.8 months (range, 13 to 144 months). The absolute risk of developing AML at 10 years after any adjuvant chemotherapy for breast cancer was 1.8% versus 1.2% for women who had not received chemotherapy. The adjusted hazard ratio for AML with adjuvant chemotherapy versus none was 1.53 (95% CI, 1.14 to 2.06). Granulocyte colony-stimulating factor (G-CSF) within the first year of diagnosis did not convey a significantly increased risk of AML (hazard ratio, 1.14; 95% CI, 0.67 to 1.92). CONCLUSION: There is a small but real increase in AML after adjuvant chemotherapy for breast cancer in older women. This study may underestimate the true incidence because myelodysplastic syndrome cannot be identified through claims. G-CSF use within the first year of diagnosis does not convey an increased risk of AML in older women.

Perrillat, F., J. Clavel, et al. (2001). "Family cancer history and risk of childhood acute leukemia (France)." Cancer Causes Control **12**(10): 935-41.

OBJECTIVE: A case-control study was carried out to investigate the role of a family history of solid tumor or hematologic neoplasm in the etiology of childhood acute leukemia. METHODS: Family cancer history in first- and second-degree relatives was compared in 279 incident cases (242 cases of acute lymphocytic leukemia and 37 of acute myeloid leukemia) and 285 controls. Recruitment was stratified by age, gender, hospital, area of residence, and ethnic origin. Odds ratios (OR) were estimated using an unconditional regression model taking into account the stratification variables, socioeconomic status, and familial structure. RESULTS: A significant association between childhood acute leukemia and a family history of hematologic neoplasm (OR = 2.7, confidence interval (CI) = 1.1-6.9) was found. This association was particularly clear-cut when the cases were restricted to acute myeloid leukemia (OR = 13.3, CI = 2.5-70.9). Childhood acute leukemia was associated with a family history of solid tumor (OR = 1.5, CI = 1.0-2.2), and elevated odds ratios were observed for family history of gastrointestinal cancer and melanoma. Those results are most unlikely to be explained by socioeconomic status and familial structure, which were very similar for the cases and controls. Differential misclassification is also unlikely for the first-degree relatives, even though it is difficult to rule it out for the second-degree relatives' history. CONCLUSION: The present study supports the hypothesis that a family history of cancer may be a risk factor for childhood acute leukemia.

Perrotti, D. and P. Neviani (2007). "From mRNA metabolism to cancer therapy: chronic myelogenous leukemia shows the way." Clin Cancer Res **13**(6): 1638-42.

Altered mRNA metabolism is a feature of many cancers including blast crisis chronic myelogenous leukemia. Indeed, loss of function of many tumor suppressors regulating cell proliferation, survival, and differentiation results from aberrant mRNA processing, nuclear export, and/or translation. Here, we summarize the effects of increased BCR/ABL oncogenic activity on the expression and function of RNA binding proteins (e.g., FUS, hnRNP A1, hnRNP E2, hnRNP K, and La/SSB) with posttranscriptional and translational regulatory activities and their importance for the phenotype of BCR/ABL-transformed hematopoietic progenitors. We also provide evidence that these studies not only advance our understanding on the molecular mechanisms contributing to tumor/leukemia emergence, maintenance, and/or progression but they also serve for the identification of novel molecular targets useful for the development of alternative therapies for imatinib-resistant and blast crisis chronic myelogenous leukemia and, perhaps, for other cancers characterized by similar alterations in the mRNA metabolism.

Peterson, B. A., J. Johnson, et al. (2007). "High dose CHOP: a phase II study of initial treatment in aggressive non-Hodgkin lymphoma. Cancer and Leukemia Group B 9351." Leuk Lymphoma **48**(5): 870-80.

Cyclophosphamide and doxorubicin, two important drugs in the treatment of lymphoma, exhibit a relationship between dose and fractional cell kill, and because of their toxicity profiles, they are candidates for significant dose escalation. We performed a phase II trial to determine the response rate, toxicity, and feasibility of escalated doses of both drugs as part of high dose CHOP in diffuse aggressive lymphoma. Patients who had advanced, previously untreated diffuse aggressive lymphomas (IWF E-H) and an International Prognostic Index of intermediate to high risk were eligible. Treatment was cyclophosphamide 2 gm/m(2)/day intravenously on Days 1 and 2 (total cycle dose 4 gm/m(2)), doxorubicin 35 mg/m(2)/day as a continuous infusion on Days 1 and 2 (total 70 mg/m(2)), vincristine 1.4 mg/m(2) (maximum 2 mg) on Day 1 and prednisone 100 mg/day orally on Days 1 - 5 repeated every 3 weeks for a total of four cycles. G-CSF, prophylactic antibiotics, and mesna were provided. A total of 99 patients were enrolled; 98 received therapy. Major toxicities were Grade 4 neutropenia and thrombocytopenia occurring in 97% and 92%, respectively. Serious infections occurred in 53%. Treatment-related mortality was 2%. The overall response rate is 85%, and two-year failure free and overall survival are 39% and 64%, respectively. Persistent or relapsed lymphoma was the overwhelming cause of death. Six patients have developed AML or MDS. In view of the substantial toxicity accompanying high dose CHOP, the observed outcome suggests that its efficacy is not sufficient to make further study feasible.

Pitini, V., C. Arrigo, et al. (2008). "Erlotinib in a patient with acute myelogenous leukemia and concomitant non-small-cell lung cancer." J Clin Oncol **26**(21): 3645-6.

Qiu, Y., Y. Tomita, et al. (2007). "Pre-B-cell leukemia transcription factor 1 regulates expression of valosin-containing protein, a gene involved in cancer growth." Am J Pathol **170**(1): 152-9.

Valosin-containing protein (VCP) is involved in a wide variety of cellular functions. Our previous studies showed that the enhanced expression of VCP in cancer cells correlated with invasion and metastasis of cancers. Here, the regulatory mechanism for VCP transcription was investigated. Luciferase reporter constructs containing serially deleted 5'-flanking region of the VCP gene were transfected into MCF7 mammary carcinoma cell line, in which VCP was abundantly expressed. The deletion and mutation at the two binding motifs for pre-B-cell leukemia transcription factor 1 (PBX1) reduced the luciferase activity, indicating that these two PBX1 motifs mediated the transactivation of the VCP gene. Chromatin immunoprecipitation assay showed the binding of PBX-1 to the 5'-flanking region of the VCP gene. The knockdown of PBX1 by siRNA decreased the expression level of VCP. VCP is reported to maintain cell viability after the treatment of tumor necrosis factor-alpha. The viability of tumor necrosis factor-alpha-treated cells was significantly reduced in PBX1 knockdown MCF7. These findings indicate that PBX1 plays a crucial role in VCP expression and function and that the PBX-VCP pathway might be important for cell survival under cytokine stress.

Ren, L. N., Q. F. Li, et al. (2009). "Endocrine glands-derived vascular endothelial growth factor protects pancreatic cancer cells from apoptosis via upregulation of the myeloid cell leukemia-1 protein." Biochem Biophys Res Commun **386**(1): 35-9.

Endocrine glands-derived vascular endothelial growth factor (EG-VEGF, also termed as Prok1)--a novel cytokine that selectively acts on the endothelial cells of endocrine glands--was recently reported to be involved in the regulation of tumor cell growth and survival. However, its roles in the regulation of pancreatic cancer progression remain unclear. In this report, we investigated the suppressive effects of EG-VEGF on pancreatic cancer cell apoptosis and the relevant mechanisms. By using reverse-transcriptase polymerase chain reaction (RT-PCR) we found that the Mia PaCa II cells of the pancreatic cancer cell line express the mRNAs of both EG-VEGF (Prok1) and its receptors. EG-VEGF protects pancreatic cancer cells from apoptosis through upregulation of myeloid cell leukemia-1 (Mcl-1), an anti-apoptotic protein of the bcl-2 family. Treatment of pancreatic cancer cells with EG-VEGF results in the rapid phosphorylation of mitogen-activated protein kinase (MAPK), STAT3, and AKT, which are involved in the upregulation of Mcl-1 expression. EG-VEGF (Prok1) protects Mia PaCa II cells from apoptosis through G protein-coupled receptor (GPR)-induced activation of multiple signal pathways, and hence can be a novel target for pancreatic cancer therapy.

Rincon, M., G. Broadwater, et al. (2006). "Interleukin-6, multidrug resistance protein-1 expression and response to paclitaxel in women with metastatic breast cancer: results of cancer and leukemia group B trial 159806." Breast Cancer Res Treat **100**(3): 301-8.

Several reports have suggested that breast cancer patients with elevated serum levels of interleukin-6 (IL-6) have a worse prognosis than patients with lower levels. We have studied IL-6 in breast cancer cell lines and have shown that autocrine production of IL-6 can confer multi-drug resistance in vitro by inducing multidrug resistance gene-1 transcription with subsequent overexpression of P-glycoprotein (PGP). Both IL-6 and PGP expression can be measured in malignant cells using immunohistochemical (IHC) techniques. We hypothesized that patients whose tumors expressed higher amounts of IL-6 or PGP would be less likely to respond to paclitaxel, an agent affected by the PGP pathway. If so, then IL-6 could serve as a predictive factor for paclitaxel sensitivity. Both IL-6 and PGP expression were measured in patients treated in a randomized trial that compared three doses of single agent paclitaxel (175, 210, and 250 mg/m(2) over 3 h every 3 weeks) in 469 women with metastatic breast cancer (CALGB 9342). No difference in complete and partial response was found among the three treatment arms. Tissue blocks in this trial were analyzed for IL-6 (154 patients) and PGP (149 patients) in paraffin-embedded sections from tumor samples; clinical characteristics of these patients were similar to the total sample of 469 patients. There were no significant differences among IL-6 or PGP scores whether measured as continuous or dichotomous variables, or by other scoring, and response to paclitaxel. In multivariate analysis neither IL-6 nor PGP was a significant predictor of time to progression or overall survival. IHC expression of IL-6 and PGP levels in tumor cells is not a predictive marker for response to paclitaxel in women with metastatic breast cancer.

Rini, B. I., S. Halabi, et al. (2004). "Cancer and Leukemia Group B 90206: A randomized phase III trial of interferon-alpha or interferon-alpha plus anti-vascular endothelial growth factor antibody (bevacizumab) in metastatic renal cell carcinoma." Clin Cancer Res **10**(8): 2584-6.

The majority of sporadic clear cell renal cell carcinoma (RCC) is characterized by loss of heterozygosity of the von Hippel-Lindau (VHL) tumor suppressor gene and somatic inactivation of the remaining VHL allele. The resulting VHL gene silencing leads to induction of hypoxia-regulated

genes including vascular endothelial growth factor (VEGF). Thus, therapeutic inhibition of VEGF holds promise for treatment of this historically refractory malignancy. An antibody to VEGF (bevacizumab, Avastin) has demonstrated a significant prolongation of time to disease progression compared with placebo in patients with metastatic RCC. Interferon-alpha (IFN-alpha) is a standard initial cytokine therapy in RCC with a modest response rate and a survival advantage demonstrated in randomized trials. We hypothesized that the addition of anti-VEGF therapy to IFN-alpha would prolong survival in untreated metastatic RCC patients. A Phase III trial is now being conducted randomizing untreated, metastatic clear cell RCC patients to IFN-alpha alone or IFN-alpha plus Avastin.

Roman-Gomez, J., A. Jimenez-Velasco, et al. (2007). "Poor prognosis in acute lymphoblastic leukemia may relate to promoter hypermethylation of cancer-related genes." Leuk Lymphoma **48**(7): 1269-82.

The hallmark of acute lymphoblastic leukemia (ALL) is a progressive appearance of malignant cell behavior that is triggered by the evolution of altered gene function. ALL has traditionally been viewed as a genetic disease; however, epigenetic defects also play an important role. DNA promoter methylation has gained increasing recognition as an important mechanism for transcriptional silencing of tumor-suppressor genes. Hypermethylation may contribute to the pathogenesis of leukemias providing an alternative route to gene mutation. We have reported that gene methylation in ALL cells is the most important way to inactivate cancer-related genes in this disease. In fact, this epigenetic event can help to inactivate tumor-suppressive apoptotic or growth-arresting responses and has prognostic impact in B- and T-ALL. The presence in individual tumors of multiple genes simultaneously methylated is an independent factor of poor prognosis in both childhood and adult ALL in terms of disease-free survival and overall survival. Moreover, methylation status is able to redefine the prognosis of selected ALL groups with well-established prognostic features.

Roman-Gomez, J., A. Jimenez-Velasco, et al. (2004). "Promoter hypermethylation of cancer-related genes: a strong independent prognostic factor in acute lymphoblastic leukemia." Blood **104**(8): 2492-8.

Promoter hypermethylation plays an important role in the inactivation of cancer-related genes. This abnormality occurs early in leukemogenesis and seems to be associated with poor prognosis in acute lymphoblastic leukemia (ALL). To determine the extent of hypermethylation in ALL, we analyzed the methylation status of the CDH1, p73, p16, p15, p57, NES-1, DKK-3, CDH13, p14, TMS-1, APAF-1, DAPK, PARKIN, LATS-1, and PTEN genes in 251 consecutive ALL patients. A total of 77.3% of samples had at least 1 gene methylated, whereas 35.9% of cases had 4 or more genes methylated. Clinical features and complete remission rate did not differ among patients without methylated genes, patients with 1 to 3 methylated genes (methylated group A), or patients with more than 3 methylated genes (methylated group B). Estimated disease-free survival (DFS) and overall survival (OS) at 11 years were 75.5% and 66.1%, respectively, for the nonmethylated group; 37.2% and 45.5% for methylated group A; and 9.4% and 7.8% for methylated group B ($P < .0001$ and $P = .0004$, respectively). Multivariate analysis demonstrated that the methylation profile was an independent prognostic factor in predicting DFS ($P < .0001$) and OS ($P = .003$). Our results suggest that the methylation profile may be a potential new biomarker of risk prediction in ALL.

Schafer, H. S., H. Becker, et al. (2008). "Granulocytic sarcoma of Core-binding Factor (CBF) acute myeloid leukemia mimicking pancreatic cancer." Leuk Res **32**(9): 1472-5.

Granulocytic sarcoma mimicking a synchronous second primary neoplasm (SPN) constitutes a diagnostic and therapeutic challenge particularly in elderly patients. We report on a 75-year-old female presenting with a Core-binding Factor (CBF) AML of M4eo subtype. The patient also had jaundice, highly elevated bilirubin, lipase, alkaline phosphatase (AP), CA 19-9, and a pancreatic mass highly suspicious of infiltrating pancreatic carcinoma. However, a biopsy demonstrated granulocytic sarcoma. Since the patient had no comorbidities and had been in excellent performance status until the diagnosis of AML, induction chemotherapy was initiated, with subsequent normalization of bilirubin, CA 19-9, lipase and AP. Complete hematologic remission of AML was attained and the pancreatic mass could not be detected anymore. Retrospective analysis of the c-kit protooncogene did not disclose activating mutations of exons 8 or 17. Following one consolidation treatment, the patient remained in excellent health until relapse occurred 7 months later and she succumbed to AML. In conclusion, AML can rarely mimic the clinical picture of pancreatic cancer. The initially good response of this CBF leukemia highlights the principal usefulness of aggressive induction chemotherapy also in older AML patients, if they are carefully selected not only according to biological risk factors such as cytogenetics, but also to

"host factors" (good performance status, lack of comorbidities, etc.).

Schollkopf, C., D. Rosendahl, et al. (2007). "Risk of second cancer after chronic lymphocytic leukemia." Int J Cancer **121**(1): 151-6.

Smoking is not considered a risk factor for chronic lymphocytic leukemia (CLL) yet increased lung cancer risk has been reported for these patients. Little data exist on the temporal variation in lung cancer risk after CLL, or its histological composition. We investigated the occurrence of second cancers in a large cohort of CLL patients with particular emphasis on lung cancer and its major subtypes. We followed all patients diagnosed with CLL in Denmark in the period 1943-2003 (n = 12,373) for the occurrence of second cancers. The relative risk was expressed as the standardized incidence ratio (SIR), i.e. the ratio of observed to expected number of cancers, based on incidence rates for the Danish population. During follow-up 1,105 cancers occurred among the CLL patients (SIR = 1.59 (95% CI 1.50-1.69)). SIR for all cancers combined remained elevated more than 10 years after CLL (SIR = 1.80 (1.56-2.08)). Lung cancer occurred in 141 patients (SIR = 1.61 (1.37-1.90)). The relative risk of lung cancer did not vary by gender, or time of follow-up, but was higher in younger (SIR(<60 years) = 2.22 (1.62-3.06)) than in older (SIR(70-79 years) = 1.21 (0.88-1.68)) age-groups. Elevated risks were observed for adenocarcinoma (SIR = 2.20 (1.57-3.08)) and squamous cell carcinoma (SIR = 1.52 (1.06-2.17)) of the lung. We speculate that shared genetic risk factors may explain the accumulation of lung and other cancers in CLL patients.

Seedhouse, C. H., M. Grundy, et al. (2007). "Sequential influences of leukemia-specific and genetic factors on p-glycoprotein expression in blasts from 817 patients entered into the National Cancer Research Network acute myeloid leukemia 14 and 15 trials." Clin Cancer Res **13**(23): 7059-66.

PURPOSE: P-glycoprotein (Pgp) is a major prognostic factor for chemotherapy failure in acute myeloid leukemia (AML). This study compared the influence of genetic and leukemia-specific factors on Pgp. EXPERIMENTAL DESIGN: Eight hundred and seventeen samples were studied prospectively for Pgp protein expression and function and G1199A, G2677T, and C3435T polymorphisms in the encoding gene ABCB1. RESULTS: Age, low WBC count, high bcl-2, secondary AML and myelodysplastic syndrome, and adverse cytogenetics all correlated strongly with high Pgp (MRK16) protein expression. However, ABCB1 3435TT homozygosity was negatively correlated with Pgp. Pgp protein is only expressed in 41% of samples such that the negative effect of the polymorphism was not seen at baseline Pgp levels but was marked in the upper 41% of samples (MRK16 Deltamean fluorescence intensity of 75th centile sample = 9 units for TT variant samples and 26 units for CC/CT; P = 0.003). However, no association was found between genetic factors and Pgp function using rhodamine 123 accumulation. CONCLUSIONS: The genetic polymorphism 3435TT (which results in unstable mRNA) has a significant effect on Pgp expression, but this is only seen in approximately 40% of cases in which mRNA and protein are detectable. Moreover, leukemia-specific factors, such as low WBC count and poor risk cytogenetics, have a much greater effect than genetic polymorphisms on Pgp expression in AML blasts.

Seidman, A. D., D. Berry, et al. (2008). "Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840." J Clin Oncol **26**(10): 1642-9.

PURPOSE: Phase II trials suggested that weekly paclitaxel might be more effective and less toxic than every-3-weeks administration for metastatic breast cancer (MBC). Cancer and Leukemia Group B (CALGB) protocol 9840 was initiated to address this question. Subsequently trastuzumab was demonstrated to improve outcomes of paclitaxel therapy for human epidermal growth factor receptor-2 (HER-2)-positive patients, and was therefore incorporated. Because inhibition of HER-family signaling had potential efficacy even without HER-2 overexpression, we randomly assigned for trastuzumab in this population. PATIENTS AND METHODS: Patients were randomly assigned to paclitaxel 175 mg/m(2) every 3 weeks or 80 mg/m(2) weekly. After the first 171 patients, all HER-2-positive patients received trastuzumab; HER-2 nonoverexpressors were randomly assigned for trastuzumab, in addition to paclitaxel schedule. A total of 577 patients were treated on 9840. An additional 158 patients were included in analyses, for combined sample of 735. The primary end point was response rate (RR); secondary end points were time to progression (TTP), overall survival, and toxicity. Primary comparisons were between weekly versus every-3-weeks paclitaxel, and trastuzumab versus no trastuzumab in HER-2 nonoverexpressors. RESULTS: In the combined sample, weekly paclitaxel was superior to every-3-weeks administration: RR (42% v 29%, unadjusted odds ratio [OR] = 1.75; P = .0004), TTP (median, 9 v 5 months; adjusted HR = 1.43; P < .0001), and

survival (median, 24 v 12 months; adjusted HR = 1.28; P = .0092). For HER-2 nonoverexpressors, trastuzumab did not improve efficacy. Grade 3 neuropathy was more common with weekly dosing (24% v 12%; P = .0003). CONCLUSION: Weekly paclitaxel is more effective than every-3-weeks administration for MBC. Trastuzumab did not improve efficacy for HER-2 nonoverexpressors. Neurotoxicity is a treatment-limiting toxicity for weekly paclitaxel.

Selvakumar, E. and T. C. Hsieh (2008). "Regulation of cell cycle transition and induction of apoptosis in HL-60 leukemia cells by lipoic acid: role in cancer prevention and therapy." J Hematol Oncol **1**: 4.

BACKGROUND: Lipoic acid (LA), a potent antioxidant, has been used as a dietary supplement to prevent and treat many diseases, including stroke, diabetes, neurodegenerative and hepatic disorders. Recently, potent anti-tumorigenic effects induced by LA were also reported and evident as assayed by suppression of cell proliferation and induction of apoptosis in malignant cells. However, the mechanism by which LA elicits its chemopreventive effects remains unclear. METHODS AND RESULTS: Herein, we investigated whether LA elicits its anti-tumor effects by inducing cell cycle arrest and cell death in human promyelocytic HL-60 cells. The results showed that LA inhibits both cell growth and viability in a time- and dose-dependent manner. Disruption of the G1/S and G2/M phases of cell cycle progression accompanied by the induction of apoptosis was also observed following LA treatment. Cell cycle arrest by LA was correlated with dose-dependent down regulation of Rb phosphorylation, likely via suppression of E2F-dependent cell cycle progression with an accompanying inhibition of cyclin E/cdk2 and cyclin B1/cdk1 levels. Evidence supporting the induction of apoptosis by LA was based on the appearance of sub-G1 peak in flow cytometry analysis and the cleavage of poly(ADP-ribose) polymerase (PARP) from its native 112-kDa form to the 89-kDa truncated product in immunoblot assays. Apoptosis elicited by LA was preceded by diminution in the expression of anti-apoptotic protein bcl-2 and increased expression of apoptogenic protein bax, and also the release and translocation of apoptosis inducing factor AIF and cytochrome c from the mitochondria to the nucleus, without altering the subcellular distribution of the caspases. CONCLUSION: This study provides evidence that LA induces multiple cell cycle checkpoint arrest and caspase-independent cell death in HL-60 cells, in support of its efficacious potential as a chemopreventive agent.

Sievers, E. L., B. J. Lange, et al. (2003). "Immunophenotypic evidence of leukemia after induction therapy predicts relapse: results from a prospective Children's Cancer Group study of 252 patients with acute myeloid leukemia." Blood **101**(9): 3398-406.

Approximately 40% of children with acute myeloid leukemia (AML) who respond to initial therapy subsequently relapse. Multidimensional flow cytometry employing a standardized panel of monoclonal antibodies enables the detection of small numbers of occult leukemic cells that persist during therapy using technology adaptable by most clinical laboratories. We performed a prospective, blinded evaluation of bone marrow specimens obtained from 252 pediatric patients with de novo AML to determine whether detection of occult leukemia defined as more than or equal to 0.5% blasts with aberrant surface antigen expression as determined by flow cytometry was predictive of subsequent relapse. Occult leukemia was detected in 41 (16%) of the 252 patients who responded to initial induction therapy. In time-dependent multivariate analyses that controlled for allogeneic marrow transplantation, variable intervals between sample submission, age, sex, white blood cell count at diagnosis, presence of splenomegaly or hepatomegaly, and presence of more than 15% blasts in the marrow after the first course of induction, patients harboring occult leukemia were 4.8 times more likely to relapse (95% confidence interval [CI] = 2.8 to 8.4, P <.0001) and 3.1 times more likely to die (95% CI; 1.9 to 5.1, P <.0001) than those lacking leukemia detectable by flow cytometry. In this analysis, flow cytometric evidence of leukemia after the initiation of therapy emerged as the most powerful independent prognostic factor associated with poor outcome. Among patients in whom a marrow sample was available for analysis at the end of consolidation therapy, overall survival at 3 years was 41% versus 69% for patients with and without occult leukemia, respectively (P =.0058).

Small, E. J., S. Halabi, et al. (2003). "Overview of bladder cancer trials in the Cancer and Leukemia Group B." Cancer **97**(8 Suppl): 2090-8.

The Cancer and Leukemia Group B (CALGB) Genitourinary Committee has developed a broad range of clinical trials across most stages of bladder cancer. Recurrence rates of superficial bladder cancer after transurethral resection range from 50-70%. Although adjuvant bacillus Calmette-Guerin reduces the risk of disease recurrence or progression, only 30% of patients have long-term disease-free survival. Because the development of novel secondline agents is needed, the CALGB is evaluating the utility of intravesicle gemcitabine as well as an

oral proapoptotic agent (CP-461). In patients with locally advanced disease with an increased risk of disease recurrence after cystectomy, a randomized trial of conventional chemotherapy versus sequential dose-dense therapy is under development. The gemcitabine/cisplatin combination has become a commonly used regimen for the treatment of advanced transitional cell carcinoma (TCC). The CALGB is undertaking a Phase II study that incorporates a fixed dose rate gemcitabine infusion in this regimen, together with a selective epidermal growth factor receptor tyrosine kinase inhibitor, Iressa (Astra Zeneca, Wilmington, DE). In patients with renal insufficiency, a regimen of carboplatin, gemcitabine, and Iressa is planned. Novel agents, including arsenic trioxide and trastuzumab (Herceptin; Genentech, Inc., South San Francisco, CA), are being evaluated as secondline therapy in patients with advanced TCC who have disease progression after frontline therapy.

Smith, R. E. (2003). "Risk for the development of treatment-related acute myelocytic leukemia and myelodysplastic syndrome among patients with breast cancer: review of the literature and the National Surgical Adjuvant Breast and Bowel Project experience." Clin Breast Cancer **4**(4): 273-9.

Regimens of adjuvant chemotherapy for early-stage breast cancer commonly include alkylating agents and anthracyclines. These agents have been associated with treatment-related acute myelocytic leukemia (AML) or myelodysplastic syndrome (MDS). This article reviews the medical literature concerning the incidence, causes, and natural history of treatment-related AML/MDS, with emphasis on the association of these factors with alkylating agents, topoisomerase inhibitors, growth factors, and radiation treatment. Data from 6 completed adjuvant National Surgical Adjuvant Breast and Bowel Project trials that tested regimens containing doxorubicin and cyclophosphamide were reviewed to characterize the incidence of treatment-related AML/MDS. The regimens differed in cyclophosphamide intensity, cumulative cyclophosphamide dose, and the presence or absence of mandated prophylactic support with growth factor and ciprofloxacin. Rates were compared across regimens, by patient age, and by treatment with or without adjuvant in-breast radiation therapy (RT). The relative risk (RR) for the development of treatment-related AML/MDS was greater for patients undergoing the more-intense regimens than for those undergoing standard AC (doxorubicin/cyclophosphamide) regimens (RR, 6.16; P<0.0001). Risk correlated more closely with dose intensity than with cumulative dose, and the data suggested that granulocyte colony-stimulating factor (G-CSF) dose may also be independently correlated with increased risk. Patients who received in-breast RT experienced more secondary AML/MDS than those who did not (RR, 2.38; P=0.006). Patients treated with AC with intensified doses of cyclophosphamide requiring G-CSF support had increased rates of treatment-related AML/MDS, even though the incidence was slight relative to breast cancer relapse. In-breast RT appeared to be associated with an increased risk of AML/MDS.

Smith, R. E., J. Bryant, et al. (2003). "Acute myeloid leukemia and myelodysplastic syndrome after doxorubicin-cyclophosphamide adjuvant therapy for operable breast cancer: the National Surgical Adjuvant Breast and Bowel Project Experience." J Clin Oncol **21**(7): 1195-204.

PURPOSE: We reviewed data from all adjuvant NSABP breast cancer trials that tested regimens containing both doxorubicin (A) and cyclophosphamide (C) to characterize the incidence of subsequent acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). MATERIALS AND METHODS: Six complete NSABP trials have investigated AC regimens (B-15, B-16, B-18, B-22, B-23, and B-25). Six distinct AC regimens have been tested and are distinguished by differences in cyclophosphamide intensity and cumulative dose and by the presence or absence of mandated prophylactic support with growth factor and ciprofloxacin. In all regimens, A was given at 60 mg/m(2) q 21 days x 4. C was given as follows: 600 mg/m(2) q 21 days x 4 ("standard AC"); 1,200 mg(2) q 21 days x 2; 1,200 mg/m(2) q 21 days x 4; 2,400 mg/m(2) q 21 days x 2; and 2,400 mg/m(2) q 21 days x 4. Occurrence of AML/MDS was summarized by incidence per 1,000 patient-years at risk and by cumulative incidence. Rates were compared across regimens, by age, and by treatment with or without breast radiotherapy. RESULTS: The incidence of AML/MDS was sharply elevated in the more intense regimens. In patients receiving two or four cycles of C at 2,400 mg/m(2) with granulocyte colony-stimulating factor (G-CSF) support, cumulative incidence of AML/MDS at 5 years was 1.01% (95% confidence interval [CI], 0.63% to 1.62%), compared with 0.21% (95% CI, 0.11% to 0.41%) for patients treated with standard AC. Patients who received breast radiotherapy experienced more secondary AML/MDS than those who did not (RR = 2.38, P=.006), and the data indicated that G-CSF does may possibly also be independently correlated with increased risk. CONCLUSION: AC regimens employing intensified doses of cyclophosphamide requiring G-CSF support were characterized by increased rates of subsequent AML/MDS, although the incidence of AML/MDS was small relative to that of breast cancer relapse.

Breast radiotherapy appeared to be associated with an increased risk of AML/MDS.

Stinchcombe, T. E., L. Hodgson, et al. (2009). "Treatment outcomes of different prognostic groups of patients on cancer and leukemia group B trial 39801: induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for unresectable stage III non-small cell lung cancer." J Thorac Oncol **4**(9): 1117-25.

BACKGROUND: In Cancer and Leukemia Group B 39801, we evaluated whether induction chemotherapy before concurrent chemoradiotherapy would result in improved survival and demonstrated no significant benefit from the addition of induction chemotherapy. The primary objective of this analysis was to dichotomize patients into prognostic groups using factors predictive of survival and to investigate whether induction chemotherapy was beneficial in either prognostic group. PATIENTS AND METHODS: A Cox proportional hazard model was used to assess the impact on survival of the following factors: (>or=70 versus <70 years), gender, race, stage (IIIB versus IIIA), hemoglobin (hgb) (<13 versus >or=13 g/dl), performance status (PS) (1 versus 0), weight loss (>or=5% versus <5%), treatment arm, and the interaction between weight loss and hgb. RESULTS: Factors predictive of decreased survival were weight loss >or=5%, age >or=70 years, PS of 1, and hgb <13 g/dl ($p < 0.05$).

Stinchcombe, T. E., A. M. Mauer, et al. (2008). "Phase II trial of paclitaxel and cisplatin in patients with extensive stage small cell lung cancer: Cancer and Leukemia Group B Trial 9430." J Thorac Oncol **3**(11): 1301-7.

BACKGROUND: Cancer and Leukemia Group B trial 9430 was a randomized phase II trial which investigated the safety and activity of four novel doublets in untreated extensive stage small cell lung cancer. The results of the paclitaxel and cisplatin arm have not been reported. PATIENTS AND METHODS: Patients received paclitaxel 230 mg/m followed by cisplatin 75 mg/m on day 1 every 21 days. All patients received granulocyte colony stimulating factor 5 microg/kg/d beginning on day 3 of each cycle. RESULTS: The patient characteristics of the 34 patients assigned to this treatment arm were: median age 61.5 years (range 41-82), male (76%), performance status 0 (41%), 1 (32%), and 2 (26%). An objective response was observed in 23 patients (68%; 95% confidence interval (CI): 49-83%); 2 complete responses (6%) and 21 partial responses (62%). Median progression-free survival time was 5.6 months (95% CI: 4.8-7.1 month), and median overall survival time was 7.7 months (95% CI: 7.2-12.6 months). The 1-year survival rate observed was 29% (95% CI: 15-45%). Grade 3/4 neutropenia and thrombocytopenia was observed in 5 (15%) and 4 (12%) patients, respectively. Two patients developed febrile neutropenia including one patient who died of neutropenic sepsis. Grade 3/4 nonhematologic observed were: sensory neuropathy in eight patients (24%); and hyperglycemia, malaise and nausea were all observed in four patients (12%). CONCLUSIONS: Cancer and Leukemia Group B will not pursue further investigation of paclitaxel and cisplatin due to the modest activity and the toxicity observed on this trial.

Sutcliffe, M. J., J. J. Shuster, et al. (2005). "High concordance from independent studies by the Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) associating favorable prognosis with combined trisomies 4, 10, and 17 in children with NCI Standard-Risk B-precursor Acute Lymphoblastic Leukemia: a Children's Oncology Group (COG) initiative." Leukemia **19**(5): 734-40.

Chromosome aberrations have a major role in pediatric acute lymphoblastic leukemia (ALL) risk assignment. The Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG) independently assessed the significance of trisomy for chromosomes 4, 10, and 17 in National Cancer Institute (NCI) Standard- and High-Risk ALL. Data from 1582 (CCG) and 3902 (POG) patients were analyzed. Eight-year event-free survivals (EFS) of 91% (CCG) and 89% (POG) ($P < 0.001$) were achieved in patients assigned to NCI Standard Risk whose leukemic cells had simultaneous trisomies 4, 10, and 17. Both groups showed the degree of favorable prognostic importance increased with the actual number of favorable trisomies. POG analyses also demonstrated hyperdiploidy (> or =53 chromosomes) was less of an independently significant prognostic factor in the absence of these key trisomies.

Taplin, M. E., B. Rajeshkumar, et al. (2003). "Androgen receptor mutations in androgen-independent prostate cancer: Cancer and Leukemia Group B Study 9663." J Clin Oncol **21**(14): 2673-8.

PURPOSE: The mechanisms responsible for prostate cancer androgen independence are diverse. Mutations of the androgen receptor (AR) gene that broaden ligand specificity have been implicated. Bone marrow specimens containing prostate tumor were obtained from men undergoing antiandrogen withdrawal for AR sequence analysis and clinical correlation. Materials and METHODS: Eligible men enrolled on a trial of antiandrogen withdrawal had a minimum prostate-specific antigen (PSA) level of 5 ng/dL that was increasing on castration therapy including an antiandrogen. With informed consent,

marrow biopsies were obtained to collect prostate tumor. Additional samples were obtained from men enrolled on chemotherapy trials. AR cDNA or DNA was polymerase chain reaction-amplified, cloned, and sequenced. The AR CAG repeat length was recorded. RESULTS: One hundred eighty-four bone marrow biopsies were obtained, and 48 had prostate tumor detected by light microscopy.

Tomizawa, D., K. Tabuchi, et al. (2007). "Repetitive cycles of high-dose cytarabine are effective for childhood acute myeloid leukemia: long-term outcome of the children with AML treated on two consecutive trials of Tokyo Children's Cancer Study Group." Pediatr Blood Cancer **49**(2): 127-32.

BACKGROUND: Various methods of intensive chemotherapy have contributed to an improved survival in pediatric acute myeloid leukemia (AML). We here report the long-term results of the two consecutive trials of Tokyo Children's Cancer Study Group (TCCSG), incorporating repetitive use of high-dose cytarabine (HD-Ara-C) based combination chemotherapy in post-remission phase. PROCEDURE: A total of 216 eligible children with newly diagnosed AML were treated in the two consecutive multi-center trials of TCCSG, M91-13 and M96-14, from August 1991 to September 1998. In M91-13 trial, patients received eight courses of intensive post-remission chemotherapy, including six HD-Ara-C containing courses, after remission-induction therapy. Autologous hematopoietic stem cell transplantation (HSCT) could be selected by physician's choice, and allogeneic HSCT was allocated if donor was available. In M96-14 trial, the last two HD-Ara-C courses were omitted from the chemotherapy arm. RESULTS: The remission-induction rate was 88.8% and probability of 5-year Overall survival (OS) and event-free survival (EFS) were 62% (56-69% with 95% Confidence intervals (CIs)) and 56% (49-62%), respectively. Treatment-related mortality (TRM) was 7.8%. Among patients without Down syndrome (DS) or acute promyelocytic leukemia (APL), the presence of t(8;21) or inv(16) was a significant good prognostic factor both in the univariate and multivariate analyses. Children with DS (N = 10) and APL (N = 14) also showed a good survival exceeding 70% in 5 years. CONCLUSIONS: These results suggest that repetitive use of HD-Ara-C was effective and safe for childhood AML. However, further optimization of AML therapy is required.

Tong, X., S. Zheng, et al. (2007). "Triptolide inhibits cyclooxygenase-2 and inducible nitric oxide synthase expression in human colon cancer and leukemia cells." Acta Biochim Biophys Sin (Shanghai) **39**(2): 89-95.

Triptolide (TP), a traditional Chinese medicine, has been reported to be effective in the treatment of autoimmune diseases and exerting antineoplastic activity in several human tumor cell lines. This study investigates the antitumor effect of TP in human colon cancer cells (SW114) and myelocytic leukemia (K562), and elucidates the possible molecular mechanism involved. SW114 and K562 cells were treated with different doses of TP (0, 5, 10, 20, or 50 ng/ml). The cell viability was assessed by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT). Results demonstrated that TP inhibited the proliferation of both tumor cell lines in a dose-dependent manner. To further investigate its mechanisms, the products prostaglandin E(2) (PGE(2)) and nitric oxide (NO) were measured by enzyme-linked immunosorbent assay (ELISA). Our data showed that TP strongly inhibited the production of NO and PGE(2). Consistent with these results, the expression of inducible NO synthase (iNOS) and cyclooxygenase-2 (COX-2) was up-regulated both at the mRNA level and the protein expression level, as shown by real-time RT-PCR and Western blotting. These results indicated that the inhibition of the inflammatory factor COX-2 and iNOS activity could be involved in the antitumor mechanisms of TP.

Tsurusawa, M., K. Saeki, et al. (1998). "Bcl-2 expression and prognosis in childhood acute leukemia. Children's Cancer and Leukemia Study Group." Pediatr Hematol Oncol **15**(2): 143-55.

Bcl-2 expression and its prognostic value were evaluated in 42 children with acute leukemia. The Bcl-2 expression of the leukemic blast cells was measured quantitatively by flow cytometry and was further analyzed by the simultaneous immunostaining of Bcl-2 with the surface membrane antigens, DNA, Ki-67 antigen. All of the cases showed a consistent expression of Bcl-2 protein; virtually all leukemic lymphoblasts were Bcl-2 positive. Although the expression of Bcl-2 varied widely from 7 to 80 x 10(3) MESF units, no significant difference was found in the mean value between the patients with acute lymphoblastic leukemia and those with acute myeloblastic leukemia. In more than half of the patients with AML, intraclonal heterogeneity of Bcl-2 expression was observed. The expression of Bcl-2 showed no apparent fluctuations during the different phases of the cell cycle.

Uckun, F. M., J. B. Nachman, et al. (1998). "Clinical significance of Philadelphia chromosome positive pediatric acute lymphoblastic leukemia in the context of contemporary intensive therapies: a report from the Children's Cancer Group." Cancer **83**(9): 2030-9.

BACKGROUND: Children with Philadelphia (Ph) chromosome positive (+) acute lymphoblastic leukemia (ALL) represent a subgroup at very high risk for treatment failure. In this report, the authors assessed the outcome of Ph+ ALL in a large cohort of children treated on contemporary intensive chemotherapy protocols of the Children's Cancer Group (CCG). METHODS: This study included 1322 children enrolled between 1988-1995 on CCG risk-adjusted studies for ALL who had centrally reviewed cytogenetic data. Thirty patients had a t(9;22)(q34;q11) translocation and were referred to as Ph+; 1292 were Ph negative(-). Outcome analyses used standard life table methods. RESULTS: Compared with Ph- ALL patients, Ph+ ALL patients were more likely to be black (P=0.008), age >10 years (P=0.02), and have a leukocyte count > or =50,000/L (P <0.0001). Nearly all Ph+ (96.7%) and Ph (98.3%) patients achieved remission after induction therapy, yet event free survival outcome was significantly worse for Ph+ patients compared with Ph- patients, with 4-year estimates of 20.1% (standard deviation [SD] = 9.1%) and 75.8% (SD =1.2%), respectively (P <0.0001). This difference was maintained among patients regardless of presenting leukocyte count, age, or early response to therapy.

Uckun, F. M., H. N. Sather, et al. (1997). "Clinical features and treatment outcome of children with myeloid antigen positive acute lymphoblastic leukemia: a report from the Children's Cancer Group." Blood **90**(1): 28-35.

Leukemic cells from a significant number of children with acute lymphoblastic leukemia (ALL) express protein antigens characteristic of both lymphoid and myeloid cells, yet the clinical significance of this immunophenotype has remained controversial. In the current study, we have determined relationships between myeloid antigen expression and treatment outcome in a large cohort of children with newly diagnosed ALL. A total of 1,557 children enrolled on risk-adjusted Children's Cancer Group studies were classified as myeloid antigen positive (My+) or myeloid antigen negative (My-) B-lineage ALL (BL) or T-lineage ALL (TL), according to expression of CD7, CD19, CD13, and CD33 antigens on the surface of their leukemic cells. My+ patients in both BL and TL groups were more likely than My- patients to have favorable presenting features.

Uckun, F. M., M. G. Sensel, et al. (1998). "Clinical significance of translocation t(1;19) in childhood acute lymphoblastic leukemia in the context of contemporary therapies: a report from the Children's Cancer Group." J Clin Oncol **16**(2): 527-35.

The nonrandom translocation t(1;19) has been associated with poor outcome in pediatric B-lineage acute lymphoblastic leukemia (ALL). Because most patients treated by contemporary therapies now achieve improved outcomes, we have reassessed the prognostic significance of t(1;19). PATIENTS AND METHODS: Cytogenetic data were accepted for 1,322 children (<21 years old) with newly diagnosed ALL enrolled between 1988 and 1994 on risk-adjusted studies of the Children's Cancer Group (CCG). Forty-seven patients (3.6%) were t(1;19) positive (+); 1,275 (96.4%) were t(1;19) negative (-). Clinical characteristics and treatment outcome were compared using standard methods. RESULTS: Translocation (1;19)+ patients were more likely than t(1;19)- patients to be 10 years of age or greater (P < .001) or CD10+ CD19+ CD34- (P < .0001), or nonwhite (P = .02). Patients with a balanced t(1;19) were less likely to be hyperdiploid than patients with an unbalanced der(19)t(1;19). Event-free survival (EFS) was similar for the overall group of t(1;19)+ and t(1;19)- patients, with 4-year estimates of 69.5% (SD, 6.8%) and 74.8% (SD, 1.3%; P = .48), respectively. However, patients with unbalanced der(19)t(1;19) had significantly better outcomes than patients with balanced t(1;19): 4-year EFS were 80.6% (SD, 7.1%) and 41.7% (SD, 13.5%), respectively (P = .003). These differences were maintained within the individual studies analyses and after exclusion of t(1;19)+ patients whose cells were hyperdiploid with more than 50 chromosomes. CONCLUSION: The overall group of t(1;19)+ patients, as well as the subgroup with an unbalanced der(19)+ (1;19) had outcomes similar to that of t(1;19)- patients, whereas patients with balanced t(1;19) had poorer outcomes. Thus, although the overall prognostic significance of t(1;19) has been obviated by contemporary risk-adjusted protocols, the balanced t(1;19) translocation remains an adverse prognostic factor.

Vincenzi, B., D. Santini, et al. (2009). "Promyelocytic leukemia (PML) gene expression is a prognostic factor in ampullary cancer patients." Ann Oncol **20**(1): 78-83.

BACKGROUND: Promyelocytic leukemia (PML) tumor suppressor gene plays a key role in acute PML pathogenesis but its involvement in pathogenesis and prognosis of solid cancers has not been defined yet. PATIENTS AND METHODS: In all, 62 ampullary adenocarcinoma patients who underwent curative surgery between 1996 and 2005 were included. Expression analysis of PML was carried out by immunohistochemical staining and correlated with disease-free survival (DFS) and overall survival (OS). RESULTS: In 24 tumor specimens (38.7%), PML was classified as absent, in

16 (25.8%) as focally expressed and in 22 (35.5%) as diffusely expressed. By univariate analysis, DFS was significantly influenced by pathological T stage (P=0.03), lymph nodal involvement (P=0.002), and PML expression (P=0.001). DFS in patients without PML expression was 28.0 months versus 45.1 and 75.5 for patients with focal and diffuse expression, respectively. OS in the group of patients without PML expression, with focal expression, and with diffuse expression was 40, 48, and 77 months, respectively (P=0.002). By a multivariate analysis, PML expression was the strongest prognostic factor for DFS (P=0.003) and the only statically significant prognostic factor for OS (P=0.009). CONCLUSIONS: Our preliminary data suggest PML as a novel prognostic tool for ampullary cancer patients.

Wells, R. J., M. T. Adams, et al. (2003). "Mitoxantrone and cytarabine induction, high-dose cytarabine, and etoposide intensification for pediatric patients with relapsed or refractory acute myeloid leukemia: Children's Cancer Group Study 2951." J Clin Oncol **21**(15): 2940-7.

PURPOSE: To evaluate the response rate, survival, and toxicity of mitoxantrone and cytarabine induction, high-dose cytarabine and etoposide intensification, and further consolidation/maintenance therapies, including bone marrow transplantation, in children with relapsed, refractory, or secondary acute myeloid leukemia (AML). To evaluate response to 2-chlorodeoxyadenosine (2-CDA) and etoposide (VP-16) in patients who did not respond to mitoxantrone and cytarabine. Mitoxantrone and cytarabine induction is effective with reasonable toxicity in patients with relapsed/refractory or secondary AML. The cytarabine and etoposide intensification regimen should be abandoned because of toxicity. Patients with relapsed AML with initial remissions longer than 1 year have a relatively good prognosis.

Wen, W. Q., X. O. Shu, et al. (1998). "Family history of cancer and autoimmune disease and risk of leukemia in infancy: a report from the Children's Cancer Group (United States and Canada)." Cancer Causes Control **9**(2): 161-71.

OBJECTIVES: As there are some suggestions that a family history of cancer or autoimmune disease might be associated with an increased risk of leukemia in children, we explored this possibility using data from a matched case-control study conducted by the Children's Cancer Group. METHODS: We compared the family history of cancer and autoimmune diseases of 302 infant leukemia cases (diagnosed within the first 18 months of life) with that of 668 individually matched controls in the United States and Canada. RESULTS: Although not significant, cancer history in parents was found to be associated with an elevated risk of infant leukemia (odds ratio [OR] = 1.4, 95 percent confidence interval [CI] = 0.6-3.6), predominantly acute myeloid leukemia (AML) (OR = 2.2, CI = 0.6-9.0). Cancer history among second-degree relatives was also related to a nonsignificantly elevated risk of AML. Family history of autoimmune diseases, on the other hand, was generally not found to be related to the risk of infant leukemia. CONCLUSION: This study provided no strong evidence that family history of cancer or autoimmune disease is a major risk factor for infant leukemia.

Wetzler, M., R. K. Dodge, et al. (1999). "Prospective karyotype analysis in adult acute lymphoblastic leukemia: the cancer and leukemia Group B experience." Blood **93**(11): 3983-93.

The Cancer and Leukemia Group B (CALGB) has been conducting a prospective cytogenetic companion study (CALGB 8461) to all CALGB treatment protocols for newly diagnosed adults with acute lymphoblastic leukemia (ALL). These protocols underwent a significant change in 1988 when a new intensive chemotherapy program was introduced (CALGB 8811). We asked whether karyotype continued to represent a significant prognostic factor in adult ALL patients after the change. A total of 256 patients had adequate pretreatment cytogenetic analyses: 67 before 1988 and 189 subsequently. The complete remission (CR) rate for the whole group was 80%. Patients with t(9;22), t(4;11), -7, or +8 had significantly lower probabilities of continuous CR and survival at 5 years (.11 and.12) than patients with a normal karyotype (.38 and.37) and patients with miscellaneous cytogenetic abnormalities (.52 and.49; P <.001 for each comparison).

Whitman, S. P., K. J. Archer, et al. (2001). "Absence of the wild-type allele predicts poor prognosis in adult de novo acute myeloid leukemia with normal cytogenetics and the internal tandem duplication of FLT3: a cancer and leukemia group B study." Cancer Res **61**(19): 7233-9.

The FLT3 gene is mutated by an internal tandem duplication (ITD) in 20-25% of adults with acute myeloid leukemia (AML). We studied 82 adults <60 years of age with primary AML and normal cytogenetics, who received uniform high-dose therapy and found FLT3 ITD in 23 (28%) patients. When the 23 FLT3 ITD+ cases were compared with the 59 cases with wild-type (WT) FLT3, disease-free survival (DFS) was inferior (P = 0.03), yet overall survival (OS) was not different (P = 0.14). However, 8 (35%) of 23 FLT3 ITD/+ cases also lacked a FLT3 WT allele

(FLT3(ITD-R)) as determined by PCR and loss of heterozygosity.

Wolf, S., D. Mertens, et al. (2006). "Ala228 variant of trail receptor 1 affecting the ligand binding site is associated with chronic lymphocytic leukemia, mantle cell lymphoma, prostate cancer, head and neck squamous cell carcinoma and bladder cancer." Int J Cancer **118**(7): 1831-5.

Allelic loss of chromosome 8p21-22 is a frequent event in various human cancers including mantle cell lymphoma (MCL), prostate cancer, head and neck squamous cell carcinoma (HNSCC) and bladder cancer. The tumor necrosis factor-related apoptosis inducing ligand (TRAIL) receptors, including TNFRSF10A and TNFRSF10B, are located within this chromosomal region. Since recent studies demonstrate that chronic lymphocytic leukemia (CLL) and prostate cells are TRAIL induced apoptosis, TRAIL-receptors are strong tumor suppressor candidate genes in human cancers exhibiting loss of chromosomal material in 8p21.3. However, no mutation of the TRAIL receptor genes has been reported in CLL, MCL, prostate cancer, HNSCC so far. In this study we analyzed the complete coding region of TNFRSF10A and TNFRSF10B in a series of 32 MCL and 101 CLL samples and detected a single nucleotide polymorphism (SNP) in TNFRSF10A (A683C) with tumor specific allele distribution. We examined allele distribution in 395 samples of different tumor entities (prostate cancer, n = 43; HNSCC, n = 40; bladder cancer, n = 179) and compared them to 137 samples from healthy probands. We found the rare allele of TNFRSF10A is more frequent in CLL, MCL, prostate cancer, bladder cancer and HNSCC. The A683C polymorphism did not cosegregate with other TNFRSF10A polymorphisms previously described. Thus screening for 683A-->C nucleotide exchanges may become important in diagnosis and/or treatment of these malignancies.

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