

Recent Advances in Cancer Chemotherapy

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Abstract: Conventional anticancer therapies are deficient in the management of patients. This has led to the need for alternative techniques developed to target tumour cells. Recent therapies intended to replace conventional methods include photodynamic therapy, human alpha-lactalbumin made lethal to tumor cells, gene therapy, telomerase therapy, hyperthermia therapy, complementary and alternative therapy, diet therapy, insulin potentiating therapy and bacterial treatment. However, these therapies are controversial due to lack of evidence, efficacy, feasibility, availability, specificity and selectivity. As a result, cancer still remains as one of the diseases with extremely high mortality and as such, adjunct and neoadjuvant cancer chemotherapy remains the main hope for cancer treatment. There is need to focus future research on the development of more potent and less toxic cancer chemotherapeutic agents from the vast array of natural and synthetic compounds so as to improve health, prolong life and reduce the high mortality associated with this epidemic.

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1. Introduction

Cancer is characterized by abnormal, uncontrolled and invasive growth of cells. These cells may spread to other parts of the body, and this is called metastasis. Although conventional anticancer therapies, consisting of surgical resection, radiotherapy and chemotherapy, are effective in the management of many patients but for about half of cancer sufferers these are ineffective, so alternative techniques are being developed to target their tumours (Hirsch, 2006). Experimental cancer treatments are medical therapies intended or claimed to treat cancer by improving, supplementing or replacing conventional methods. These include photodynamic therapy, HAMLET (human alpha-lactalbumin made lethal to tumor cells), gene therapy, telomerase therapy, hyperthermia therapy, complementary and alternative therapy, diet therapy, insulin potentiating therapy and bacterial treatment (Jain *et al.*, 2001) But many of these therapies are controversial due to lack of evidence, efficacy, feasibility, availability, specificity and selectivity. Chemotherapy refers to the treatment of cancer with cytotoxic antineoplastic drugs (Ray and Koczwara, 2003).

Antineoplastic Chemotherapeutic Agents

Alkylating Agents

Alkylating agents kill cells by covalently binding hydrocarbons, or alkyl groups, to a cell's DNA. This causes DNA cross-links and strand breaks that result

in either apoptosis (programmed cell death) or cell necrosis. Rapidly dividing cells are most susceptible to DNA alkylation, but alkylation can also occur in quiescent cells. Because there is some kill achieved in quiescent cells, some of the effects of alkylating agents are nonphase specific (Huitema *et al.*, 2000).

Chlorambucil.

It is a member of Alkylating drugs that attack DNA of cancerous cells and kill them. Great numbers of conjugates have been designed in order to make Chlorambucil more effective and less harmful. A couple of reports have suggested that accumulation and uptake of Polyamine compounds and amino acid transporters increase in cancer tissues (Nishiyama and Eguchi, 2009). Connecting an amine amino acid (Asparagine) to Chlorambucil was carried out in order to create a novel and efficient anticancer conjugate. After purifying the product and performing some quality control tests, its anti-cancer effects on HT1080 cell line was evaluated (Nishiyama and Eguchi., 2009). MTT, apoptosis, necrosis and abnormality tests was conducted to check its toxic properties. Finally, it was evaluated if Chlorambucil affects blood hemolysis rate and blood clotting factors or not. It was observed that not only does Chlorambucil-Asparagine conjugate has anticancer property, but also it is capable of killing the half of the cancerous cells in lower concentrations compared to Chlorambucil (Nishiyama and Eguchi, 2009).

Hydralazine

Hydralazine is a non-nucleoside analog that inhibits DNA methylation and reactivates the expression of tumor suppressor genes. This activity is synergized when used in combination with valproic acid. A phase I study has evaluated the tolerability and the effects of hydralazine upon DNA methylation and gene reactivation in patients with untreated cervical cancer (Temkin *et al.*, 2010). Hydralazine was well-tolerated. Toxicities were mild, with nausea, dizziness, fatigue, headache and palpitations among the most common. Overall, 70% of the pretreatment samples and all patients had at least one methylated gene. Gene expression analysis showed only 12 informative cases, of which 9 (75%) re-expressed the gene. There was no change in the methylation status of H19 and clone1.2 or in global DNA methylation. However, results relating to OS, DFS and ORRs were not reported in this trial (Temkin *et al.*, 2010). Worthy of mention, another pilot study, which evaluated the combination of hydralazine with magnesium valproate and radiation therapy in 22 untreated patients with cervical cancer, showed promising results (CR 100%, 48 month estimated OS 67%) (Temkin *et al.*, 2010).

Platinum Salts

Platinum compounds cause intrastrand and interstrand cross-linkages in DNA that ultimately result in cell apoptosis most readily in cells that are actively replicating, and are thus relatively cell-phase specific. The platinum compounds currently approved for use in the United States are cisplatin, carboplatin, and oxaliplatin (Hirsch, 2006).

Oxaliplatin

Oxaliplatin, is a new platinum analogue with great promise in multiple cancers. Phase II studies have shown its potential in gastric cancer therapy when combined with 5-FU and folinic acid (Louvét *et al.*, 2002).

Oxaliplatin is a third-generation platinum agent having synergistic activity with 5-FU. It is active against first- and second-line colorectal cancer (Diaz-Rubio *et al.*, 1998) and, in combination with 5-FU/LV, it was shown to be superior to 5-FU/LV alone in terms of response rate and time to progression in two randomized studies (De Gramont *et al.*, 2000). The infusional 5-FU/LV/oxaliplatin combination was approved by the U.S. Food and Drug Administration in August 2002 for the treatment of patients with metastatic colorectal cancer whose disease had recurred or progressed during or within 6 months of completing first-line therapy with combination 5-FU/LV/irinotecan. The approval was based on a pivotal trial with an interim analysis of 59 patients, showing response rates of 0%, 1%, and 9% for

infusional 5-FU/LV, oxaliplatin alone, and 5-FU/LV/oxaliplatin, respectively. The median time to progression in the combination arm was 2 months longer than that in the infusional 5-FU/LV arm and 3 months longer than that seen with oxaliplatin alone (Oxaliplatin, 2003). A comparison between the 5-FU/LV/oxaliplatin and 5-FU/LV/irinotecan regimens was presented to the American Society of Clinical Oncology (ASCO) as part of the N9741 study, indicating that the first regimen had a more favorable toxicity profile and led to a higher response rate (40% versus 30%), longer time to progression (8.8 versus 6.9 months), and longer survival time (19.1 versus 14.8 months) than the second regimen (Goldberg, 2003).

Cisplatin

A three arm Phase III study [Japan Clinical Oncology Group (JCOG) 9912 comparing continuous infusion 5-FU, S-1 monotherapy, and CPT-11/cisplatin with the primary end point of OS showed that S-1 monotherapy seemed superior to continuous 5-FU and almost comparable with CPT-11/cisplatin combination, with significantly less incidence of grade 3, 4 toxicity than CPT-11/cisplatin (Boku, 2008). The SPIRITS trial comparing S-1 monotherapy with S-1/cisplatin combination demonstrated that S-1/cisplatin combination significantly improved OS (11 vs.13 months; HR 0.774; 95% CI 0.610-0.980; P=0.0366) and PFS (4 vs.6 months; HR 0.57; 95% CI 0.437-0.734; P=0.0001) at a median follow-up of 34.6 months (Koizumin *et al.*, 2008). The phase III First-Line Advanced Gastric Cancer (FLAGS) trial, designed to compare CF with S-1/cisplatin, is currently in progress in North and South America, Australia, and Europe (Lenz *et al.*, 2007). The incorporation of biological agents, such as bevacizumab and cetuximab, into combination regimens is another innovative approach, and the best partner of these agents is now under intense investigation.

Carboplatin

(Sagent, Schaumburg, Illinois, United States), a platinum-based drug, has previously been reported to induce PSA reduction of 50% in patients with prostate cancer that progressed after docetaxel chemotherapy (Ross *et al.*, 2008). Everolimus, an mTOR inhibitor, in addition to platinum-based chemotherapy, demonstrated increased antitumor effects and surmounting of resistance to chemotherapy (Fury *et al.*, 2012). In this regard, a Phase II study was conducted to evaluate the efficacy of combination therapy using carboplatin and everolimus in metastatic prostate cancer patients. In this study, the combination of carboplatin and everolimus showed no

pharmacokinetic interaction, and the median overall survival was 12.5 months in metastatic CRPC patients who progressed under docetaxel-based chemotherapy (Vaishampayan *et al.*, 2015).

Antimetabolites

Antimetabolites are agents that are structurally related to and compete with physiologic molecules in the formation of cellular macromolecules. The resultant macromolecules that incorporate antimetabolites into their framework lack the functionality of the normal corresponding cellular component. Most antimetabolites used in cancer chemotherapy affect DNA or ribonucleic acid (RNA) synthesis, and this is usually by either replacing a nucleotide (e.g., 6-mercaptopurine) or depressing nucleotide synthesis (e.g., methotrexate and 5-fluorouracil). DNA or RNA that incorporates nonphysiologic, antimetabolite nucleotides results in the formation of truncated cellular proteins, and ultimately apoptotic cell death. Antimetabolites are considered the most versatile drug class in chemotherapy (Kummar *et al.*, 2006) and they are used to treat a disparate group of tumors that includes lymphocytic leukemia, breast cancer, gastrointestinal (GI) adenocarcinomas, squamous cell carcinoma, and HCC (Ray and Koczwara, 2003).

Gemcitabine

Until recently, chemotherapy for gastrointestinal and pancreatic cancers was based on 5-fluorouracil (5-FU) and on modulation of 5-FU with leucovorin (LV) (Eduardo *et al.*, 2010). Gemcitabine has emerged as the cornerstone of current chemotherapy for gastrointestinal and pancreatic cancer based on the results of a randomized trial comparing it with the conventional 5-FU in patients with advanced unresectable disease (Burriss *et al.*, 1997). In that trial, the primary end point was clinical benefit response, derived from measuring three common debilitating signs or symptoms: pain, functional impairment, and weight loss. Clinical benefit response was experienced by 23.8% of patients in the gemcitabine arm of the trial, compared with 4.8% in the 5-FU arm ($p = 0.0022$). Survival and objective response were secondary end points. Gemcitabine showed only a slightly longer, but statistically significant, median survival time compared with 5-FU (5.65 months versus 4.41 months; $p = 0.0025$). Of note, the objective response rates for patients with measurable disease were not significantly different (5.4% and 0% for gemcitabine and 5-FU, respectively). Gemcitabine has also shown activity in pancreatic cancer refractory to 5-FU and seems to produce a similar clinical benefit response when it is used as first-line therapy (Rothenberg *et al.*, 1996). A randomized trial

comparing gemcitabine alone with gemcitabine in combination with 5-FU showed no significant difference in survival, although there was a trend in favor of the combination (5.4 months versus 6.7 months; $p = 0.09$) and a significantly longer progression-free survival time in the combination arm (2.2 months versus 3.4 months; $p = 0.022$) (Berlin *et al.*, 2002).

Recently, preliminary results of three randomized trials of gemcitabine combinations were reported (Heineman *et al.*, 2003). The combination of gemcitabine and cisplatin showed a benefit over gemcitabine alone for both progression-free survival and overall survival (5.4 months versus 2.8 months and 8.3 months versus 6.0 months, respectively) in patients with metastatic or locally advanced disease (Heineman *et al.*, 2003). Gemcitabine plus irinotecan showed a superior response rate over gemcitabine alone (16.1% versus 4.4%, $p < 0.001$); however, this did not translate into an improvement in long-term outcome in terms of either time to progression or overall survival (Rocha-lima *et al.*, 2003). A trial comparing the combination of gemcitabine and oxaliplatin with gemcitabine alone showed that the combination produced a better clinical response rate (25.8% versus 16.1%, $p = 0.03$) and rate of clinical improvement (39.3% versus 28.4%, $p = 0.05$) and showed an advantage in time to disease progression (25 weeks versus 16 weeks, $p = 0.05$), compared with gemcitabine alone in patients with both locally advanced and metastatic pancreatic cancer; patients with locally advanced disease and those with metastatic disease both responded the same to the two treatments (Louvet *et al.*, 2003). For all patients who achieved a response, median survival was approximately 41 weeks, irrespective of treatment. Gemcitabine is the new standard of care in ovarian, pancreatic and other cancers, offering a slightly better overall survival than 5-FU. Current gemcitabine- or 5-FU-containing combinations may result in longer survival times than those seen with single-agent therapy; however, results to date remain preliminary.

5-Flourouracil

While chemotherapy for gastric cancer is largely palliative, several studies have shown a survival benefit for chemotherapy over best supportive care (Vanhoefler *et al.*, 2000), with 5-FU being the mainstay of chemotherapeutic regimens (Cullinan *et al.*, 1985). Several investigators have attempted to improve on the relatively low response rates and poor survival using 5-FU alone by combining 5-FU with other agents. However, these attempts have been largely unsuccessful (Cullinan *et al.*, 1985). Although several combination regimens showed remarkable response rates in phase II trials, as with many other

tumor types, the results in well-controlled randomized trials have been far less impressive (Vanhoefer *et al.*, 2000). For example, in a randomized multicenter trial by Vanhoefer *et al.*, three standard regimens were compared in 399 patients with advanced unresectable gastric cancer. The regimen 5-FU, doxorubicin, and sequential high-dose methotrexate (FAMTX) produced response rates of 30%–60% and median survival times of 7–9 months in prior phase II trials; the regimen etoposide, LV (folinic acid), and 5-FU (ELF) yielded response rates of 27%–53% and median survival times of 7.1–11.5 months in prior phase II trials; and the regimen of infusional 5-FU and cisplatin (FUP) yielded response rates of 41% and 43% and median survival times of 10.6 months and 9 months in two large phase II trials (Vanhoefer *et al.*, 2000). When these regimens were compared in a large randomized trial, however, response rates for FAMTX, ELF, and FUP were 12%, 9%, and 20%, respectively, and median survival times were 6.7 months, 7.2 months, and 7.2 months, respectively (Vanhoefer *et al.*, 2000). More promising results have been accomplished using epirubicin, cisplatin, and infusional 5-FU (ECF). In a randomized trial of ECF compared with FAMTX, ECF rendered a significant benefit over FAMTX in both response rate (46% versus 21%, $p = 0.00003$) and median survival time (8.7 months versus 6.1 months, $p = 0.0005$) (Waters *et al.*, 1990). Regimens not containing 5-FU have also been examined in gastric cancer. In a phase II trial by Wang *et al.*, the combination of etoposide, doxorubicin, and carboplatin produced a response rate of 49%, including a 7% complete response rate (Wang *et al.*, 2002). Swiss investigators showed that a regimen combining cisplatin, doxorubicin, and etoposide produced a response rate of 34% with tolerable toxicities (Roth *et al.*, 1998). Ridwelski *et al.* demonstrated a response rate of 37.2% with a combination of docetaxel and cisplatin (Ridwelski *et al.*, 2001). 5-FU, often modulated with LV, is the most widely used agent for the treatment of colorectal cancer, both in the adjuvant and in the advanced disease settings (Rougier *et al.*, 1998). Adjuvant chemotherapy with 5-FU regimens clearly improves disease-free survival and overall survival times in patients with surgically resected stage III (and subpopulations of stage II) colon cancer and in patients with advanced disease (Rougier *et al.*, 1998). Despite this, objective response rates with LV-modulated 5-FU in two recently published large randomized trials of first-line metastatic colon cancer were 15.5% and 21%, leaving substantial room for improvement (Saltz *et al.*, 2000). Most studies comparing CI with bolus administration are in favor of CI in relation to response rate and, probably, time to progression, although overall survival is not clearly

better (Leichman *et al.*, 1995). An additional step toward improving upon 5-FU-based therapy is the oral fluoropyrimidine prodrug capecitabine. When compared with standard 5-FU/LV in a phase III randomized trial, capecitabine showed a significantly greater response rate as assessed by the individual investigators (24.8% versus 15.5%; $p = 0.005$), but no significant differences in progression-free or overall survival times, or in response rates as assessed by an independent review committee (Hoff *et al.*, 2001).

Fluoropyrimidines

A meta-analysis study reported that UFT, a combination of uracil and tegafur (1-[2-tetrahydrofuran-5-yl]-5-fluorouracil) in a fixed molar ratio of 4:1, was an effective drug for adjuvant chemotherapy of NSCLC (Hamada *et al.*, 2005). UFT is a prodrug of the antimetabolite 5-FU, whose active metabolite, 5-fluorodeoxyuridine monophosphate, suppresses the conversion of deoxyuridine monophosphate to deoxythymidine monophosphate by forming a stable covalent ternary complex with TS. A recent clinical study in 173 patients with resectable NSCLC revealed that TS status ($P = 0.01$) was a significant prognostic factor in patients with stage II–III NSCLC. Furthermore, in patients with stage II–III NSCLC, the survival of UFT-treated patients with TS-negative tumors was significantly better (Huang *et al.*, 2005). Therefore, the synergistic activity of the vinorelbine–UFT schedule against *in vitro* and *in vivo* models of NSCLC may be attributed to increased chemosensitivity to UFT caused by vinorelbine-induced suppression of TS (thymidilate synthase) (Matsumoto *et al.*, 2004).

Natural Products

Natural products are chemotherapeutic agents derived from plants, fungi, or bacteria; these agents are diverse in their mechanisms of action. The two major categories of natural products are plant alkaloids and antineoplastic antibiotics. *Plant alkaloids* such as vincristine, vinblastine, and paclitaxel inhibit the movement of microtubules, which form the cytoskeletal framework of a cell that allows intracellular transport of cellular components. Plant alkaloids exert their greatest effect during the mitotic phase of cell replication; however, because microtubules form the framework that allows intracellular transport in both quiescent and actively replicating cells, plant alkaloids are relatively nonphase specific (Ray and Koczwara, 2003).

Plant alkaloids are used extensively in systemic chemotherapy for a variety of neoplasms (e.g., leukemias, lymphomas, myeloma, breast, ovarian, brain, a wide range of childhood malignancies), and

often in combination with other drug classes (Rowinsky and Tolcher, 2005).

Antineoplastic antibiotics such as doxorubicin and mitomycin C are extracted from various species of the *Streptomyces* genus, which is a type of actinobacteria commonly found in soil and decaying vegetation. Interestingly, many non-antitumoral antibiotics such as vancomycin and amphotericin B are also derived from species of *Streptomyces*. Doxorubicin and mitomycin C are both used in the IR suite in hepatic intraarterial chemotherapy regimens, and a third antineoplastic antibiotic, bleomycin, is commonly used in pleurodesis (Ray and Koczwara, 2003).

Bacteria as tumoricidal drug -combination bacteriolytic therapy (COBALT).

Clostridium novyi-NT spores and other attenuated bacteria organisms were administered in combination with conventional chemotherapeutic agents like dolastatin-10, mitomycin C, vinorelbine and docetaxel. This strategy known as combination bacteriolytic therapy (COBALT) (Luo *et al.*, 1999). *Bacillus Calmette-Guerin* (BCG), the most successful bacterial agent so far is used specifically for the treatment of superficial bladder cancer. VNP20009, a derivative strain of *Salmonella typhimurium* has now been developed for use in cancer treatment (Luo *et al.*, 1999). Deletion of two of its genes - *msb B* and *pur I* - resulted in its complete attenuation (by preventing toxic shock in animal hosts) and dependence on external sources of purine for survival. This dependence renders the organism incapable of replicating in normal tissue such as the liver or spleen, but still capable of growing in tumours where purine is available. This vector showed long-lasting efficacy against a broad range of experimental tumors and was even able to target metastatic lesions (Luo *et al.*, 1999). One advantage of using *Salmonella* instead of *Clostridium* or *Bifidobacterium* is its ability to grow in both aerobic and anaerobic conditions, indicating its usefulness against small tumors. VNP20009 has been investigated successfully in Phase 1 clinical trials in cancer patients. It is also likely that other live, attenuated bacteria, such as *Clostridia* and *Bifidobacterium*, will be evaluated in human clinical trials in the future. New strains of bacteria being investigated as anticancer agents are: *Salmonella choleraesuis*, *Vibrio cholerae*, *Listeria monocytogenes* and even *Escherichia coli* (Bermudes *et al.*, 2002).

Trabectedin

Trabectedin is a novel, marine-derived, anticancer compound that selectively inhibits the transcription of several genes, particularly those encoding the multidrug resistance protein 1, heat

shock protein 70, and the cyclin-dependent kinase inhibitor p21WAF1/Cip1, contributing to the induction of programmed cell death (Friedman *et al.*, 2002). Using MTT assay, Pousseur *et al.* (Preusser *et al.*, 2012) observed strong antineoplastic activity of trabectedin on the series of 19 meningioma samples, 9 of them benign. However, cytotoxic activity was significantly reduced in cells derived from low-grade versus high-grade tumours despite comparable proliferation rates of the respective primary cell cultures. The cytotoxic effect was characterized by distinct cell cycle arrest, down-regulation of multiple cyclins, deregulated expression of cell death-regulatory genes, and massive apoptosis induction (Preusser *et al.*, 2012).

Paclitaxel

Paclitaxel has been incorporated into polychemotherapy regimens for relapsed and refractory GCTs based on the strength of demonstrated in vitro synergy with cisplatin (Sandler *et al.*, 1998) and single-agent activity. The most robust data for paclitaxel in relapsed GCTs evaluate the use of TIP.

TIP was evaluated in a phase I/II dose escalation trial with paclitaxel 175–250 mg/m² (30 patients) as second-line therapy by the Memorial Sloan-Kettering group (Motzer *et al.*, 2000), which demonstrated complete response rates in 23 (77%) patients undergoing chemotherapy alone, with durable response rates in 22 (73%). The phase II study (Kondagunta *et al.*, 2005) of 46 patients with paclitaxel at 250 mg/m² over 24 hours demonstrated complete response in 70% of patients undergoing chemotherapy alone, with durable response rates in 30 (65%). Both of these cohorts selected patients with favorable prognostic features, including gonadal primary tumors, prior treatment limited to a single line of platinum-based chemotherapy, and either a complete response or partial response with negative tumor markers (PRm) to first-line treatment. TIP with paclitaxel at 250 mg/m² over 24 hours resulted in moderately severe toxicity with grade 3 neutropenic fever with or without sepsis in 48% cases, 1 (2%) death due to neutropenic sepsis, and grade 4 or 5 renal toxicity in 3 patients (7%). In attempts to limit the toxicity of TIP, 2 trials have evaluated the regimen with an alternate paclitaxel schedule of 175 mg/m² over 3 hours. A UK Medical Research Council (MRC) trial (Mead *et al.*, 2005) evaluated 43 patients with both favorable-risk (n¼26) and unfavorable-risk (n¼17) disease, demonstrating lower rates of overall complete response in 8 patients (19%), of whom 7 (27%) had favorable-risk disease, with durable response rates in 36% at 1 year. The MRC trial had comparable hematologic toxicity with 70% grade 3/4

neutropenia and 28% febrile neutropenia. The efficacy of paclitaxel in the salvage setting has prompted its inclusion within trials of intensified first-line regimens for IGCCC intermediate- and poor-risk patients before first relapse. TIP has promising efficacy in the first-line setting for intermediate- and poor-risk disease (Feldman *et al.*, 2013), and a randomized phase II trial comparing TIP and BEP is currently recruiting subjects.

Magnesium valproate/valproic acid

The magnesium salt of valproic acid (2-propylpentanoic acid) has antiepileptic and potential antineoplastic activities. According to the U.S. National Institutes of Health and others, valproic acid appears to have wide implications in the treatment of various cancers (Isenberg *et al.*, 2007), through its activity as a histone deacetylase inhibitor, inducing tumor cell differentiation, apoptosis, and growth arrest (Atmaca *et al.*, 2007). Valproic acid has found clinical use as an anticonvulsant and mood-stabilizing drug, primarily in the treatment of epilepsy, bipolar disorder and, less commonly, major depression. It is also used to treat migraine headaches and schizophrenia. It exerts an antiepileptic effect, most likely by inhibiting enzymes that catabolize the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) catabolism, thereby increasing concentrations of GABA in the central nervous system (CNS). In cervical cancer, it has been evaluated combined with epirubicin in patients with metastatic disease (anthracycline-resistant) (Munster *et al.*, 2005). Moreover, it has been tested in combination with chemoradiation (Chavez-blanco *et al.*, 2005) and with hydralazine and radiation therapy (Candelara *et al.*, 2010) in an untreated population. These results provide evidence that magnesium valproate, at doses between 20 mg and 40 mg/kg, inhibits deacetylase activity and hyperacetylates histones in tumor tissues (Chavez-blanco *et al.*, 2005). Its clinical efficacy, along with a demethylating agent plus chemotherapy or radiation, is currently being tested in phase II studies (Chavez-blanco *et al.*, 2005).

Cetuximab.

Cetuximab (Erbix; Merck KGa A, Darmstadt, Germany) is an immunoglobulin G1 monoclonal antibody that binds the epidermal growth factor receptor (EGFR) with high affinity, which competitively blocks ligand binding, inhibits tyrosine kinase activation, and results in receptor down regulation. Addition of cetuximab to chemotherapies has shown a good tolerability and safety profile with further efficacy recorded in clinical trials in advanced colorectal cancer (CRC) and head and neck squamous cell carcinoma. As far as advanced cervical cancer is

concerned, cetuximab has been evaluated as monotherapy (Santin *et al.*, 2011), in combination with cisplatin (Farley *et al.*, 2011), and in combination with topotecan and cisplatin (Kurtz *et al.*, 2009). Five patients (14.3%; two-sided 90% CI, 5.8% to 30%) survived without progression for at least 6 months; all of them harbored tumors with squamous cell histology. Additionally, the GINECO trial, evaluated the combination of cetuximab with topotecan and cisplatin in patients with advanced cervical cancer. However, this study was stopped early due to excessive toxicity; 28% of patients died during the treatment, including 3 deaths related to treatment toxicity (infection, febrile neutropenia and pulmonary embolism) (Santin *et al.*, 2011).

Matuzumab.

Matuzumab (EMD72000, Merck) is a humanized antibody that competitively inhibits natural ligand binding to the EGF receptor with abrogation of EGFR downstream signaling. In a phase II Trial (Blohmer *et al.*, 2005), matuzumab showed promising results in patients with cervical cancer progressing after treatment with platinum-based chemotherapy. Among 38 evaluated patients, best responses in the preliminary analysis were 2 PR and 9 SD (Blohmer *et al.*, 2005). Matuzumab-related grade 3 and 4 adverse events included elevated γ -GT (2.44%), hepatotoxicity (2.44%), diarrhea (2.44%), fainting and thrombocytopenia (2.44%), anorexia and lethargy (2.44%), abdominal pain (4.88%), skin peeling/dryness (2.44%), and pancreatitis (2.44%). (Blohmer *et al.*, 2005).

Irinotecan,

Irinotecan, a potent topoisomerase I inhibitor, is the latest therapeutic candidate showing potential in gastric cancer. As a single agent, irinotecan produced response rates of 18.4%–43% (Bleiberg, 1999). In combination regimens with 5-FU and cisplatin, particularly in chemotherapy-naïve patients, irinotecan produced response rates up to 59% (Bleiberg, 1999). Despite these impressive results, however, these combination regimens have yet to be rigorously tested in the phase III setting, where previous experience has shown they may produce relatively disappointing results. Until the introduction of irinotecan, there was no standard therapy for patients with metastatic colon cancer who had progressive disease despite 5-FU-based chemotherapy. Various infusional 5-FU regimens had response rates of 5%–30%; however, none showed a clear survival or quality of life benefit over best supportive care (Rouger *et al.*, 1998). Two large randomized trials in the second-line setting, one comparing irinotecan with best supportive care and

the other comparing irinotecan with infusional 5-FU, showed that irinotecan produced a better quality of life than best supportive care and a longer survival time than either best supportive care or infusional 5-FU when used after 5-FU failure (Bleiberg, 1999). Subsequently, irinotecan was moved into the first-line setting in combination with 5-FU. Saltz *et al.* conducted a randomized phase III trial comparing standard weekly bolus LV-modulated 5-FU with irinotecan alone and with a combination of LV-modulated 5-FU and irinotecan (Saltz *et al.*, 2000). The irinotecan/5-FU/LV arm showed a significantly longer median progression-free survival time (7 versus 4.3 months; $p = 0.004$), a significantly longer median overall survival time (14.8 versus 12.6 months; $p = 0.04$), and a significantly higher objective response rate (39% versus 21%; $p < 0.001$) than LV-modulated 5-FU alone.

Biologic Response Modifiers And Hormonal Agents

Biologic response modifiers and hormonal agents include a diverse array of agents used in cancer treatment, and although they are not commonly used in loco-regional therapy. *Monoclonal antibodies* are engineered to bind to receptors that are selectively expressed on the cell surface of some tumor types. Once bound to the tumor cell surface, the antibodies block growth receptor signaling in most cases (e.g., cetuximab and trastuzumab), although some agents work through an immunologic mechanism (e.g., rituximab). Monoclonal antibodies are commonly used in combination regimens used to treat non-Hodgkin lymphoma (rituximab) and metastatic breast cancer (trastuzumab) (cheng *et al.*, 2005)

Docetaxel /Prednisone

In 2004, docetaxel/prednisone was approved as first-line treatment in Castration-resistant prostate cancer. The SWOG-9916 and TAX-327 studies showed increased survival at 2 months compared to placebo/prednisone. (Mukherji *et al.*, 2014). Before docetaxel, abiraterone acetate, a selective inhibitor of CYP17- α -hydroxylase and C17, 20-lyase, which blocks androgen synthesis, showed an increase in progression free survival from 8.3 to 16.5 months and a reduction in the risk of death by 25% versus placebo/prednisone in the COU-AA-302 trial and when associated with prednisone. (Joan *et al.*, 2016). Enzalutamide is an androgen receptor antagonist which also inhibits its translocation to the nucleus and interaction with DNA; in the PREVAIL trial it showed a progression-free survival increase of 14% at 12 months and reduced the risk of death by 29% compared to placebo. (Beer *et al.*, 2014).

Multikinase Inhibitors

Protein kinases are transmembrane proteins that have an intracellular and an extracellular component that are used in cell signaling pathways, which include the pathways involved in cellular proliferation and differentiation. (Ray and Koczwara, 2003).

Pemetrexed

Pemetrexed (Alimta[®]; Eli Lilly & Co.; Indianapolis, IN) is a multitargeted antifolate that inhibits multiple enzymes important in folate metabolism, including thymidylate synthase, dihydrofolate reductase, glycinamide ribonucleotide formyl-transferase, and aminoimidazole carboxamide ribonucleotide formyl-transferase (Shih, *et al.*, 1997). As a single agent given at a dose of 500 mg/m² every 21 days, pemetrexed has demonstrated promising activity in several malignancies, including malignant pleural mesothelioma, non-small cell lung cancer, breast cancer, colorectal cancer, pancreatic cancer, gastric cancer, bladder cancer, cervical cancer, and cancer of the head and neck (Hanauske *et al.*, 2001) Initial clinical experience with pemetrexed was complicated by severe adverse events, including neutropenia, thrombocytopenia, mucositis, diarrhea, and drug-related death (Calvert *et al.*, 2002), due to vitamin B₁₂ and folate pool depletion. These toxicities are significantly reduced by vitamin B₁₂ and folate supplementation (Calvert *et al.*, 2002).

In a phase II trial of 35 patients with pancreatic cancer, pemetrexed showed an objective response rate of 5.7%, disease stabilization in 40% of patients, and a median survival time of 6.5 months, with 28% of patients alive at 1 year (Miller *et al.*, 2000). Combinations of pemetrexed with agents such as gemcitabine and oxaliplatin are under investigation and have shown promising results in several traditionally resistant tumors, such as cholangiocarcinoma, colon cancer, and mesothelioma (Adjei *et al.*, 2000). In a phase II trial, pemetrexed/gemcitabine showed promising survival results (6.6 months, with a 1-year survival rate of 32%) and acceptable toxicities (mainly hematologic, including grade 3/4 neutropenia and grade 3 leukopenia, thrombocytopenia, and anemia) in chemotherapy-naïve patients with pancreatic cancer (Kindler *et al.*, 2002). This led to an ongoing phase III randomized trial comparing pemetrexed with and without gemcitabine in patients with stage II, III, and IV pancreatic cancer (study ID No. NCI-G02-2125). In a phase II trial conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) cooperative group, the pemetrexed/oxaliplatin combination showed activity in advanced colorectal cancer (23% response rate) and was generally well tolerated, with grade 3/4 neutropenia (23%) being the

major toxicity (Atkins *et al.*, 2003). As a 10-minute infusion every 21 days, pemetrexed is easy to administer, and with appropriate folate and vitamin B₁₂ supplementation, it is associated with a very favorable toxicity profile. Overall, pemetrexed shows promising activity in several gastrointestinal malignancies.

Bryostatin

Protein kinase C (PKC) is a family of lipid-dependent membrane-associated enzymes with important roles in cell signaling pathways. Bryostatin 1, a compound derived from the marine invertebrate *Bugula neritina*, has a modulatory effect on PKC-mediated cell biology. It has direct cytotoxic effects on some human cancer cell lines and mediates the *in vitro* cytotoxic effects of several chemotherapeutic agents (Zonder *et al.*, 2001). In a phase II study of patients with advanced colon cancer, bryostatin 1 showed no responses as a single agent (Zonder *et al.*, 2001). However, bryostatin 1 continues to be developed as a response modifier to traditional cytotoxic agents, with active protocols in several tumor types, including gastric cancer in combination with cisplatin (study ID No. NCI-T99-0040) and pancreatic cancer in combination with paclitaxel.

UCN-01

UCN-01 is a PKC inhibitor that, in isolated enzyme assays, can also inhibit cyclin-dependent kinases (CDKs), which are important regulators of cell cycle progression. UCN-01 blocks cell cycle progression and induces apoptosis (Senderowicz, 2000). Initial trials showed some clinical activity in patients with melanoma and lymphoma (Senderowicz, 2000). There are several ongoing trials of UCN-01 in various solid tumors, including two trials in pancreatic cancer, one in combination with 5-FU (study ID No. NCI-5509) and one in combination with gemcitabine.

Flavopiridol

Flavopiridol was the first CDK inhibitor tested in clinical trials. Preclinical features of this drug include the ability to block cell cycle progression, induce apoptosis, promote differentiation, and inhibit angiogenic processes (Senderowicz, 2000). Initial clinical trials with infusional flavopiridol demonstrated activity in some patients with lymphomas and renal, colon, and gastric carcinomas (Senderowicz, 2000). Toxicity was manageable and included mainly diarrhea, which was controlled with appropriate diarrheal prophylaxis, and hypotension. Flavopiridol is being tested in combination chemotherapy trials with several agents including irinotecan, platinum, and docetaxel.

Bevacizumab

Bevacizumab (Avastin®, Genentech) is a humanized antibody that recognizes and neutralizes all major isoforms of VEGF, preventing receptor binding and inhibiting endothelial cell proliferation and vessel formation (Ferrera *et al.*, 2004). Bevacizumab was the first FDA-approved therapy designed to inhibit angiogenesis in patients with advanced colorectal and later non-small lung cancer and renal cancer (Presta *et al.*, 1997). In patients with recurrent metastatic or refractory cervical cancer, bevacizumab has been evaluated as monotherapy, in combination with 5-FU, capecitabine, carboplatin, and with paclitaxel and carboplatin (Takawo *et al.*, 2009), with promising results. Moreover, it has been tested in combination with definitive radiotherapy and cisplatin chemotherapy in untreated patients with locally advanced disease (FIGO Stages IB–IIIB) (Schefer *et al.*, 2010)., another ongoing phase II study is evaluating the combination of bevacizumab with topotecan and cisplatin as first-line treatment for recurrent or persistent cervical cancer. Bevacizumab is now an exciting new candidate for the treatment of colorectal cancer. Trials of several tumor types, including pancreatic and colon cancer, are under way.

Sunitinib malate

Sunitinib malate (SUTENT®; P fizer Inc., New York, NY) is an oral, multi-targeted tyrosine kinase inhibitor of VEGFR-1, -2, and -3, PDGFR- α and - β , and several other related RTKs. It has shown significant activity and has been approved for renal cancer and imatinib-resistant GIST. However, in a phase II study of sunitinib in patients with locally advanced or metastatic cervical carcinoma who had received up to one prior line of chemotherapy for advanced disease, sunitinib had minimal activity and moderate toxicity (Mackay *et al.*, 2010). More specifically, 84% of patients had stable disease (median duration 4.4 months, 2.3–17 months), but no objective response was observed (Mackay *et al.*, 2010).

Pazopanib.

Pazopanib is a potent and selective multi-targeted receptor tyrosine kinase inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- α/β , and c-kit that blocks tumor growth and inhibits angiogenesis. It has been approved for renal cell carcinoma by the FDA (Mackay *et al.*, 2010). A phase II study of pazopanib or lapatinib monotherapy, compared with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical cancer, has demonstrated the benefit of pazopanib. In this trial, patients with measurable Stage IVB persistent/recurrent cervical carcinoma not amenable

to curative therapy, and at least one prior regimen in the metastatic setting, were randomly assigned in a ratio of 1:1:1 to receive pazopanib at 800 mg once daily, lapatinib at 1500 mg once daily, or lapatinib plus pazopanib combination therapy (lapatinib at 1000 mg plus pazopanib at 400 mg once daily or lapatinib at 1500 mg plus pazopanib at 800 mg once daily). Pazopanib improved PFS (hazard ratio, 0.66; 90% CI, 0.48 to 0.91; $p=0.013$) [35]. This study confirms the activity of antiangiogenesis agents in advanced and recurrent cervical cancer and demonstrates the benefit of pazopanib based on the prolonged PFS and favorable toxicity profile (Monk *et al.*, 2010). Anti-EGFR tyrosine kinase inhibitors (TKIs) TKIs are a class of orally available, small molecules that inhibit ATP binding within the TK domain, leading to complete inhibition of EGFR autophosphorylation and signal transduction (Monk *et al.*, 2010).

Gefitinib

Gefitinib (ZD1839, Iressa®, Astra Zeneca Pharmaceuticals) a TKI against EGFR has been approved by the FDA for the treatment of platinum and docetaxel-refractory NSCLC. Gefitinib has also been tested in a phase II study, showing that it has only minimal activity in recurrent disease resistant to standard treatment. However, the observation that 20% of patients treated with gefitinib had stable disease may warrant further investigation. Worthy of mention is that gefitinib was well tolerated, with the most common drug-related adverse events being skin and gastrointestinal toxicities.

Erlotinib

Erlotinib (OSI-774, Tarceva®, Genentech) a TKI against EGFR has been approved by the FDA with gemcitabine as the first-line treatment of pancreatic cancer and in lung cancer. In cervical cancer, it has been evaluated as monotherapy in recurrent squamous cell carcinoma, with negligible results. Moreover, it has been tested in combination with cisplatin and radiotherapy for untreated patients with locally advanced squamous cell cervical cancer, with promising results (Ferreira *et al.*, 2008). In a phase II trial, Ferreira *et al.*, (Ferreira *et al.*, 2008) evaluated the combination of erlotinib, cisplatin and radiotherapy in 37 patients with locally advanced squamous cell cervical cancer (FIGO Stages IIB: 47.8%, IIIA: 4.3% and IIIB: 47.8%). During a median follow-up of 9 (3–25) months, none of the patients progressed; 91.3% of patients presented CR and 8.7% presented partial response (Ferreira *et al.*, 2008). The combination was well-tolerated; significant grade 3 toxicities included diarrhea (12%) and skin rash (20%). Hence, it seems that this combination leads to high CR (91.3%) compared to historical

chemoradiation data (38–75%) and merits further evaluation (Ferreira *et al.*, 2008).

Lapatinib

Lapatinib (GW572016, Tykerb®, Glaxo Smith Kline) is an oral, dual inhibitor of EGFR and HER-2 (Lackay *et al.*, 2006). It has been approved as combination therapy with capecitabine for patients with breast cancer (over expressing HER-2/neu) with prior progression on trastuzumab, an anthracycline and a taxane (Cameron *et al.*, 2008). However, lapatinib has a negligible effect on metastatic cervical cancer; it has been evaluated, as monotherapy and in combination with pazopanib, in a randomized phase II clinical trial in patients with FIGO Stage IVB or recurrent or persistent cervical cancer.

Temsirolimus

Temsirolimus is an mTOR inhibitor (CCI-779, temsirolimus/Torisel®, Wyeth) approved for the treatment of renal-cell carcinoma. A phase I study has evaluated the combination of temsirolimus with topotecan in the treatment of advanced and/or recurrent gynecologic malignancies (Temkin *et al.*, 2010). However, only 2 patients with cervical cancer were included in this trial and detailed data of RR, OS, PFS, efficacy and safety were not reported (Temkin *et al.*, 2010).

Celecoxib

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that directly inhibits the enzyme COX-2. Cervical cancer cell lines treated with celecoxib are more sensitive to radiation induced apoptosis, and this appears to be the result of an increase in the G2M cell cycle arrest and inhibition of sub-lethal radiation damage repair. Celecoxib has been evaluated in combination with definitive chemoradiotherapy in women with locally advanced cervical cancer. Herrera *et al.*, 2007 (Herrera *et al.*, 2007) did not demonstrate any efficacy of celecoxib in addition to CRT, either directly or indirectly, by monitoring tumor biomarkers of response. The recorded response rate of 81% within the first year of treatment is similar to the experience reported with CRT alone, considering that most regimens in advanced cervical cancer achieve pelvic control rates of 70–75% (Herrera *et al.*, 2007).

Entinostat

Entinostat (MS-275), a potent histone deacetylase inhibitor (HDAC) inhibitor, is a synthetic benzamide derivative with potential antineoplastic activity. It exerted growth arrest in PC-3 and LNCaP cells, and induced cell death in DU-145 cells (Eyupoglu *et al.*, 2006). In advanced cervical cancer, entinostat has been evaluated only in one patient in a phase I trial,

with promising results (DFS 10 months). Further trials are more than warranted in this study population.

Imatinib mesylate

Imatinib is a 2-phenylaminopyrimidine derivative that functions as a specific inhibitor of a number of tyrosine kinase enzymes; it is specific for the TK domain in abl (the Abelson proto-oncogene), c-kit and PDGF-R (platelet-derived growth factor receptor). It has demonstrated remarkable clinical efficacy in patients with chronic myeloid leukemia and malignant gastrointestinal stromal tumors. As far as cervical cancer is concerned, Candelaria *et al* (Candelaria *et al.*, 2009) presented a pilot study evaluating imatinib mesylate as second-line treatment of recurrent or metastatic cervical cancer expressing platelet-derived growth factor receptor alpha. Twelve patients were included in the study (Candelaria *et al.*, 2009). All patients expressed the PDGFR-alpha in more than 10% of malignant cells, whereas only 4 coexpressed the PDGFR-beta. No patient showed response (Candelaria *et al.*, 2009). However, despite the lack of activity of single-agent imatinib, further studies in cervical cancer are justified to better define the status of imatinib targets in this tumor and to investigate its activity in combination with cytotoxic drugs.

Conclusion

Cancer still remains as one of the diseases with extremely high mortality. Chemotherapy remains the main hope for cancer treatment including its usage in adjunct and neoadjuvant cancer therapy.

There is need to facilitate further research for the development of more potent and less toxic cancer chemotherapeutic agents from the vast array of natural and synthetic compounds so as to improve health, prolong life and reduce the high mortality associated with cancer.

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