

Low dose metronomic weekly Docetaxelin previously treated patients with non-small cell lung cancer

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Abstract: Background: Low dose metronomic chemotherapy (LDM) involves administering cytotoxic drugs on a daily or weekly basis at low doses without a long interval of interruption which can modulate the cancer microenvironment and disrupt tumor-associated vascular angiogenesis. The aim of this study is to evaluate the toxicity and efficacy of low dose weekly metronomic docetaxel in previously treated patients with non-small cell lung cancer (NSCLC). **Patients and methods:** Twenty three (23) patients were treated at Tanta University Hospital, Clinical Oncology Department. Patients received weekly 15 mg/m² of docetaxel intravenously. **Results:** The median age was 59 years. The median number of cycles administered was 15 (range: 5–37). No patients achieved CR; 2 patients showed PR (8.7%); 10 patients had SD (43.5%) with clinical benefit (52.2%) and 11(47.8%) patients showed progressive disease. The median OS time was 10.5 months. The one year survival rate was 43.5%. The median progression-free survival time (PFS) was 4.5 months ranged from 1.5-14 months (95% CI: 2.7–6.3) and the one year PFS rate was 13%. Low dose metronomic docetaxel was well tolerated where no patients experienced grade 4 toxicities and only 2 (8.7%) patients had grade 3 anemia. No patients had high grade (3-4) non-haematological toxicities. **Conclusion:** This study suggested that metronomic low dose weekly Docetaxel was well tolerated and active in patients with previously treated NSCLC. Thus, further investigation of this LDM regimen with larger number of patients is warranted.

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Key words: NSCLC, Low dose metronomic chemotherapy, Taxotere.

1. Introduction

Conventional chemotherapy with high doses of a cytotoxic agents followed by a 3-4 weeks rest period is important to balance the drug's toxic effects on the tumor and on the host. However, recent studies have demonstrated a rapid chemotherapy resistance in certain patient populations after an initial response. ⁽¹⁾Also, conventional chemotherapy drugs have been associated with many toxic adverse effects that often impair quality of life and limit continuation of therapy. ⁽²⁾

A metronomic chemotherapy is characterized by frequent (dose-dense) chemotherapy administration with no interruptions without using the maximal tolerated dose (MTD), no administration of hematopoietic growth factors, preference for oral drugs with low incidence of treatment related toxicity. ⁽³⁾

The progress of chemotherapy over the past few decades has resulted in survival benefit for patients with advanced non-small cell lung cancer (NSCLC) who have poor prognosis and the use of low-dose metronomic (LDM) chemotherapy might have an antitumor effects. Docetaxel has been recognized as an active drug that can exhibit metronomic activity both in vitro and in vivo. ^(4, 5, 6)

Yokoi et al. (2012) evaluated the toxicity and efficacy of LDM chemotherapy with weekly docetaxel in patients with non-small cell lung cancer (NSCLC).

Twenty-seven patients received 15 mg/m² of docetaxel on a weekly basis. Their results indicate that metronomic docetaxel was well tolerated and active in patients with NSCLC. ⁽⁷⁾

Joshi et al. (2013) evaluated patients with recurrent and advanced NSCLC were treated with weekly paclitaxel at 80 mg/m². They concluded that weekly low-dose continuous metronomic-type scheduling of paclitaxel is safe and effective for those patients. ⁽⁸⁾

2. Patients and methods:

This study was carried out at Clinical Oncology Department, Tanta University Hospital, between May 2013 and November 2015. Twenty three (23) patients with histologically or cytologically diagnosed NSCLC (clinical stage IIIB or IV at the time of enrollment). Inclusion criteria were: Performance Status (PS) 0–1 according to Eastern Cooperative Oncology Group (ECOG), patients had previously received at least one regimen of platinum based systemic chemotherapy with previous paclitaxel use allowed, adequate baseline bone marrow function (absolute neutrophil count \geq 1500/ml, platelet count \geq 100.000/ml and haemoglobin \geq 8 gm/dl), adequate renal function (creatinine \leq 1.5 mg/dl), adequate baseline hepatic function (serum bilirubin \leq 2.0 mg/d, transaminase aspartate aminotransferase, alanine transaminase \leq 2.0 the upper limit of normal level).

Docetaxel was administered intravenously (15 mg/m²) diluted with 5% glucose (250 mL) over 60 minutes each week without interval. Treatment was continued as long as there is no disease progression or unacceptable toxicity (e.g., grade 3 or worse hematological/ non-hematological toxicity, not appetite loss, constipation, and nausea/vomiting). Treatment response was evaluated using chest CT scan every 8 weeks during the treatment period and when indicated.

Statistical analysis:

Version 21 of SPSS software was used. The OS was defined as the time from the start of the LDM chemotherapy to the time of death from any cause or to the date of last visit. At same time, PFS was estimated from date of start of metronomic chemotherapy till the date of progression and/or change of therapy due to any reason (e.g. toxicity, patient request) or death. Treatment-related adverse effects were evaluated using National Cancer Institute Common Toxicity Criteria, version 2.0.9. ⁽⁹⁾ Objective tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0.10 ⁽¹⁰⁾. The OS was estimated with the Kaplan–Meier product method.

3. Results:

Twenty three (23) patients were evaluated in this study from May 2013 to November 2015. All patients were treated at Tanta University Hospital, Clinical Oncology Department. Table (1) showed the patients' characteristics. The median age was 59 years (range: 46–71). Nineteen patients (82.6%) were males and 5 patients (17.4%) were females. Adenocarcinoma and squamous cell carcinoma were presented in 15 (65.2%) and 8 patients (34.8%), respectively. Stage IIIB presented in 8 patients (34.8%), while 15 patients (65.2%) had stage IV disease. The performance status (PS) according to Eastern Cooperative Oncology Group (ECOG) was 1 in 6 patients (26.1%) and 2 in 17 patients (73.9%). Eighteen patients received chemotherapy alone and 5 patients received concomitant chemotherapy and thoracic irradiation (CCRT). Seven patients received one chemotherapy regimen and 16 patients received two regimens. The median number of cycles administered was 15 (range: 5–37). Treatment was discontinued in patients developed disease progression, unacceptable toxicity, deterioration of PS, and/or patient refusal to continue the treatment. These patients offered the best supportive care.

Characters		No (%)
Age (years)	Median	59
	Range	46-71
	Mean ±SD	59.09±6.9
Gender	Male	19 (82.6%)
	Female	4 (17.4%)
Performance Status (ECOG)	1	6 (26.1%)
	2	17 (73.9%)
Pathology	Adenocarcinoma	15 (65.2%)
	SCC	8 (34.8%)
Tumor Stage	IIIB	8 (34.8%)
	IV	15 (65.2%)
Previous Treatment	Chemotherapy	18 (78.3%)
	CCRT	5 (21.7%)
No. of prior CTh regimens	1	7 (30.4%)
	2	16 (69.6%)
No. of administered cycles	Total	411
	Median	15
	Range	5-37
SSC: Squamous cell carcinoma; CCRT: Concurrent chemo-radiation therapy		

Table (2) showed the treatment response where no patients achieved CR; 2 patients showed PR (8.7%); 10 patients had SD (43.5%); and 11 patients (47.8%) showed progressive disease. Seventeen patients died, and 6 patients were still alive at end of the study.

The Kaplan–Meier survival curve of OS is shown in Figure 1. The median OS time was 10.5 months (95% CI: 8.2–12.8). The one year survival rate was 43.5%. The median progression-free survival time (PFS) was 4.5 months ranged from 1.5–14 months (95% CI: 2.7–

6.3). The one year PFS rate was 13%. At the end of the study, 19 (82.6%) patients had disease progression while 4 (17.4%) patients were free of progressive disease (2 patients with SD and 2 patients with PR). Regarding treatment related haematological toxicities, table (3) showed that low dose metronomic docetaxel

was well tolerated where no patients experienced grade 4 toxicities and only 2 (8.7%) patients had grade 3 anemia. No patients had high grade (3-4) non haematological toxicities (nausea, vomiting, diarrhea, hepatic, renal, and neurotoxicity).

Response	No (%)
Complete Response	0 (0%)
Partial Response (PR)	2 (8.7%)
Stable Disease (SD)	10 (43.5%)
Progressive Disease (PD)	11 (47.8%)

Toxicity	Grade I No (%)	Grade II No (%)	Grade III No (%)	Grade IV No (%)
Anemia	14 (60.9%)	7 (30.4%)	2 (8.7%)	-
Neutropenia	2 (8.7%)	3 (13.1%)	-	-
Thrombocytopenia	2 (8.7%)	3 (13.1%)	-	-
Nausea	5 (21.7%)	1 (4.3%)	-	-
Vomiting	4 (17.4%)	1 (4.3%)	-	-
Diarrhea	3 (13.1%)	1 (4.3%)	-	-
Hepatic	13 (56.5%)	2 (8.7%)	-	-
Renal	3 (13.1%)	1 (4.3%)	-	-
Neuropathy	4 (17.4%)	1 (4.3%)	-	-

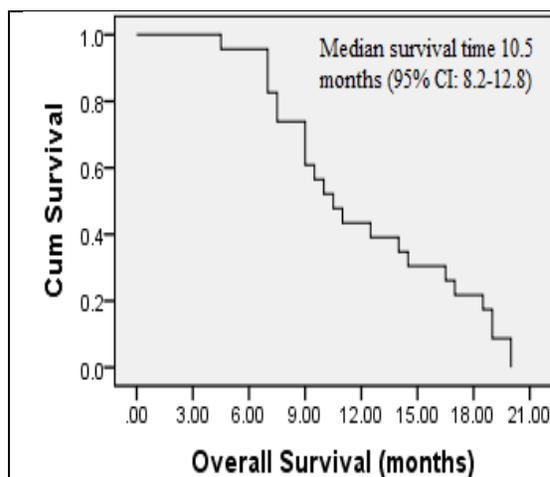


Fig (1): Overall survival for all patients

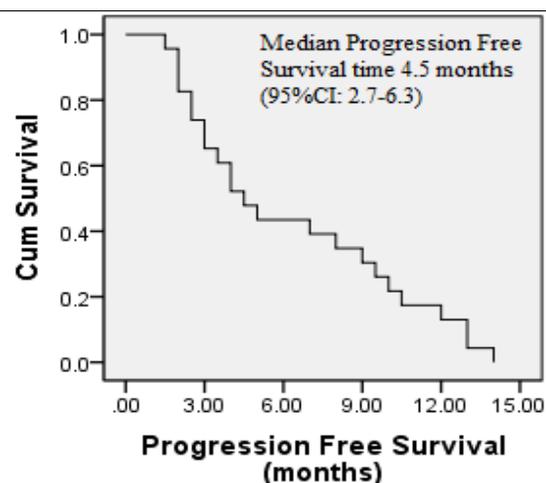


Fig (2): Progression free survival for all patients

4. Discussion:

Low dose metronomic chemotherapy is an emerging form of chemotherapy with distinct mechanisms of action from conventional chemotherapy (e.g., antiangiogenesis). Although developed to overcome resistance to conventional chemotherapy, metronomic chemotherapy is subject to resistance on its own. Metronomic chemotherapy may

overcome chemotherapy resistance and control tumors with low side effects.⁽¹¹⁻¹⁵⁾

Docetaxel as a metronomic chemotherapy has also been shown to decrease the micro vessel density of tumors and inhibit the mobilization of circulating endothelial precursors. Thus, these findings have been the basis for several clinical studies on the use of LDM chemotherapy for NSCLC treatment.^(16, 17)

Among 23 patients were evaluated in our study, No patients achieved CR; 2(8.7%) patients showed PR; 10 (43.5%) patients had SD; and 11(47.8%) patients showed progressive disease. Seventeen patients died, and 6 patients were still alive at end of the study. The median OS time was 10.5 months (95% CI: 8.2–12.8) and the one year survival rate was 43.5%. The median progression-free survival time (PFS) was 4.5 months ranged from 1.5-14 months (95% CI: 2.7–6.3). The one year PFS rate was 13%. At the end of the study, 19 (82.6%) patients had disease progression while 4 (17.4%) patients were free of progressive disease (2 patients with SD and 2 patients with PR).

Regarding treatment related haematological toxicities, the low dose metronomic docetaxel was well tolerated where no patients experienced grade 4 toxicities and only 2 (8.7%) patients had grade 3 anemia. No patients had high grade (3-4) non haematological toxicities (nausea, vomiting, diarrhea, hepatic, renal, and neurotoxicity).

Joshi et al. (2013) evaluated the administration of weekly paclitaxel in relapsed and refractory NSCLC or in patients not eligible for platinum-based chemotherapy. The complete remission was (2.7%), partial remission (32.4%), stable disease (32.4%), and progressive disease (27%). The median PFS was four months, and the estimated median OS was seven months. Paclitaxel was well tolerated. The most frequent grade 3 toxicities included anemia in 8%, neutropenia in 5.4%, and sensory neuropathy in 8%. They concluded that low dose continuous weekly paclitaxel is safe and effective in recurrent and refractory NSCLC. ⁽⁸⁾

Yokoi et al. (2012) evaluated LDM chemotherapy with weekly low-dose docetaxel for previously treated twenty-seven patients diagnosed with non-small cell lung cancer (NSCLC). Patients received 15 mg/m² of docetaxel intravenously weekly without interval. Eleven patients were stage IIIB, and 16 patients were stage IV. The performance status was 0 or 1 according to eastern Cooperative Oncology Group. There was no severe hematological adverse effect (neutropenia and/or thrombocytopenia). One patient (3.7%) showed complete remission, one patient (3.7%) showed partial response, 12 patients (44.4%) had stable disease and 13 patients (48.1%) had progressive disease. The median survival time was 16.4 months and one year survival rate was 58.8%. The median progression free survival time was 6.5 months. Their results suggested that metronomic docetaxel was active and well tolerated in patients with NSCLC. ⁽⁷⁾

Gorn *et al.* (2008) studied 21 patients with stage IV disease NSCLC to evaluate the use of docetaxel and oral trofosamide as a metronomic second line treatment of patients with metastatic non-small cell

lung cancer (NSCLC). Patients received docetaxel 25 mg/m² on days 1, 8, and 15 every 4 weeks plus trofosamide 50 mg per day. The overall response rate was 19%, median overall survival was 6.9 months, the median progression-free survival 2.9 months, the one year survival rate was 28.6%, and the 2-year survival rate 7.1%. No grade IV toxicity was observed. They suggested that, the combination of docetaxel and trofosamide as a metronomic regimen is active and well tolerable in patients with metastatic NSCLC. ⁽¹⁶⁾

Conclusion:

This study suggested that in patients with previously treated NSCLC, metronomic low dose weekly Docetaxel showed activity and was well tolerated. Thus, LDM regimen may be considered as an alternative choice in those patients. Further investigation with larger number of patients is warranted.

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