Journal of Cancer Research & Therapy

Khosravi A et al., J Cancer Res Ther 2015, 3(1):1-7
http://dx.doi.org/10.14312/2052-4994.2015-1

NobleResearch
An Open Access Publisher
www.nobleresearch.org

Original research

Open Access

Comparing docetaxel with gemcitabine as second-line chemotherapy in patients with advanced non-small cell lung cancer: A single institute randomized phase II study

Khosravi Adnan[1], Esfahani-Monfared Zahra[1], Karimi Shirin[2], Emami Habib[3] and Khodadad Kian[4,*]

[1] Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Mycobacteriology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3] Nursing and Respiratory Health Management Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4] Tobacco Prevention and Control Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Background: Platinum-based doublet chemotherapy is the backbone of treatment in advanced non-small cell lung cancer (NSCLC) however second-line treatment options are controversial particularly in patients with borderline performance status (PS) of 2. The aim of this study was to compare efficacy and toxicity of weekly docetaxel versus gemcitabine in this clinical setting. *Patients and methods:* A total of 70 patients with advanced (stage IIIB, IV) NSCLC entered this single institute study. Cases of this study had experienced disease progression after the first-line platinum-based doublet chemotherapy, with PS 0- 2 in "Eastern Cooperative Oncology Group" scale. They were randomly assigned by stratified blocks to receive docetaxel 35 mg/m^2 (Arm A, n=34) or gemcitabine 1000 mg/m^2 (Arm B, n=36) days 1, 8 and 15 every three weeks, for up to six cycles. Primary end point was progression free survival (PFS) and secondary end points were objective response rate, disease control rate, median overall survival (OS) and toxicity. Dose modification was permitted upon clinician's discretion for each individual patient. *Results:* Median of PFS was 2.03 months in arm A and 2.63 months in arm B (HR= 1.279; 95% CI: 0.710-2.304, P= 0.551). Although median OS for arm A was numerically greater (9.2 months) than arm B (8.3 months) it was statistically non-significant (HR= 1.384; 95% CI: 0.632 to 2.809, P= 0.59). Objective response was higher in Arm B than that in Arm A (P= 0.20) but disease control rates were statistically different in both arms (P= 0.034). Statistically significant differences in term of leukopenia was seen in arm B (P= 0.013). *Conclusion:* This study, with limited number of cases, indicates that in advanced NSCLC, weekly docetaxel and gemcitabine are reasonable second-line treatment options with statistically similar effectiveness in terms of PFS and median OS with manageable toxicities in patients with PS 0-2.

Keywords: docetaxel; gemcitabine; platinum-based doublet chemotherapy; non-small cell lung cancer

Background

Lung cancer is known as an important health problem in the world. According to IARC (International Agency for Research on Cancer) report, 1.8 million new cases were estimated in 2012, and lung cancer was responsible for nearly one in five cancer-related deaths worldwide (1.59 million deaths, 19.4% of the total) [1]. In Iran, approximately 3252 patients die of this disease annually. Also, lung cancer age-standardized rate (ASR) is 7.09 in males and 3.38 in females [2]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases and the majority of patients are diagnosed with advanced stages [3]. In advanced NSCLC that is not associated with epidermal growth factor receptor tyrosine

***Corresponding author:** Dr. Kian Khodadad, MD, National Research Institute of Tuberculosis and Lung Disease, Shahid Bahonar Ave., Darabad, Tehran 19556, Iran. Tel./ Fax: +98 (21) 26109946; Email: kiankhodadad@yahoo.com

Received 16 October 2014 *Revised* 6 December 2014 *Accepted* 17 December 2014 *Published* 26 December 2014

Citation: Khosravi A, Esfahani-Monfared Z, Karimi SH, Emami H, Khodadad K. Comparing docetaxel with gemcitabine as second-line chemotherapy in patients with advanced non-small cell lung cancer: A single institute randomized phase II study. J Cancer Res Ther. 2015; 3(1):1-7. doi:10.14312/2052-4994.2015-1

kinase (EGFR TK) activating mutations or anaplastic lymphoma kinase (ALK) rearrangement, combination chemotherapy is the backbone of systemic therapy. This regimen consists of a platinum (carboplatin or cisplatin) along with a taxane [4], docetaxel [5], paclitaxel [6, 7], gemcitabine [8], vinorelbine [9] or pemetrexed [10] (in non-squamous histology). Adding targeted agents (i.e. bevacizumab, cetuximab) [6] to chemotherapy protocols in some subsets of patients may improve treatment outcomes.

Nearly all patients who receive first-line chemotherapy finally experience relapse of the disease. Many of them have a good performance status and are suitable candidates for second-line chemotherapy. Choosing optimal chemotherapy protocol depends on multiple factors such as tolerability profile, histologic subtype, cost and patients preference. There are several options for second-line systemic therapy but among them, monotherapy with docetaxel [11, 12], pemetrexed [13, 14], (in nonsquamous NSCLC) and erlotinib [15] have been approved in disease recurrence/progression following prior chemotherapy. Gemcitabine has also been studied as second-line therapy but has not approved in this setting [16, 17]. This study was conducted to compare clinical benefits and toxicities of weekly docetaxel and gemcitabine in patients with recurrent/progressive advanced NSCLC who had been treated with platinum-doublet chemotherapy as the first-line therapy and have a borderline performance status.

Patients and methods

Study design

This phase II, randomized, single blind, controlled, single institute study was performed to compare intravenous (IV) docetaxel with gemcitabine in patients with locally advanced or metastatic NSCLC previously exposed to a platinum-containing regimen. The primary end point was progression free survival (PFS) and secondary end points included response rate and overall survival (OS). Patients were allowed to enter the study 30 days after the prior chemotherapy with full recovery from all toxic effects. Informed written consent was obtained prior to participation in the study based on the ethics and scientific committees of Shahid Beheshti Medical University, and the study was conducted in compliance with the Helsinki declaration.

Eligibility criteria

Eligible patients had to meet the following criteria: aged over 18 years, with histologically confirmed NSCLC, initially at stage IIIB and IV (according to AJCC, 6th edition) [18] with recurrence/progression after the previous doublet-platinum based chemotherapy regimen. They had a performance status (PS) of 2 in the Eastern Cooperative Oncology Group performance status scale. Other eligibility criteria were as follows: at least one uni-dimensionally measurable or assessable disease, adequate bone marrow reserve, serum creatinine less than or equal to 1.5 mg/dL or a calculated creatinine clearance greater than or equal to 60 mL/min, bilirubin level less than or equal to 2.0 mg/dL, AST less than or equal to twice the institutional upper limits of normal, or less than or equal to four times the institutional upper limits of normal if the patient had liver metastasis. Patients with significant or uncontrolled cardiac, metabolic or infectious diseases as well as patient with symptomatic brain metastasis were excluded. Previous treatment with docetaxel or gemcitabine was also permitted.

Treatment plan

Patients were randomly assigned in a 1:1 ratio to receive docetaxel 35 mg/m^2 (Arm A, n=34) in an hour infusion or gemcitabine 1000 mg/m^2 (Arm B, n=36) in 100 ml 5% dextrose which was administered over 30 min. in on days 1, 8 and 15 of a 28-day cycle. Dexamethasone (8 mg) twice daily was given the day before and after docetaxel infusion and also 30 min. before chemotherapy. In the absence of progressive disease or intolerable toxicity, the patients were treated for a minimum of four cycles. Patients who achieved a complete or partial response (CR or PR) could receive two additional cycles of therapy, for a maximum of 6 cycles. Presence of progressive disease, intolerable and serious side effect or patients refusal would lead to treatment discontinuation. Chemotherapy with docetaxel was discontinued if the patient experienced a significant hypersensitivity reaction or unacceptable toxicity (e.g., fluid retention, neurologic side effects of WHO grade 3 to 4, severe skin reactions, or serious organ toxicity).

All patients had a complete blood cell (CBC) count and biochemistry study, at baseline and prior to each therapy. Notably, in this real world study the dosage of cytotoxic agents was permitted to be adjusted by clinicians discretion based on adverse events in the course of treatment for each individual. Dose modification and concomitant granulocyte-colony stimulating factor (G-CSF) were allowed during the course of treatment with respect to the grade of neutropenia. The dose of cytotoxic agents was attenuated by 25% if patients experienced neutropenia at 1,000-1,500/dL and/or platelets 75,000-100,000/dL. If neutrophil or platelet count were less than 1,000/dL and 75,000/dL, respectively chemotherapy was postponed. Chemotherapy was delayed for a maximum of two weeks until recovery if the granulocyte count was $< 1{,}000\ /\mu$l or the platelet count was $< 50{,}000/\mu$l. Gemcitabine administration would be delayed if bilirubin levels were >2 mg/dL.

Toxicity and response evaluation

After the initial two cycles, response was assessed according to "Response Evaluation Criteria in Solid Tumors" (RECIST) criteria [19]. Objective response was comprised of CR + PR. Combination of CR, PR and stable disease (SD) was defined as “disease control” rate. Patients were evaluated after every cycle for any response based on physical examination and chest X-ray. Chest CT scan was requested after every 2 cycles and/or at the termination

of protocol. After completion of therapy, patients were monitored at 8 weekly intervals until disease progression or death. The OS was calculated for all patients who died, from the date of registration to the date of death. Otherwise, the patient who was confirmed to be alive, was censored until the last day. PFS was calculated from the date of registration to the date of progression or death.

All patients who received at least one cycle were assessed for safety, toxicity assessment was based on "common terminology criteria for adverse events (CTCAE)" version 3.0 [20] criteria for withdrawal from study were unacceptable toxicity as determined by the treating physician in consultation with the study coordinator, a delay in treatment greater than 2 weeks, requirement for palliative radiotherapy, or patient refusal.

Statistical analysis

This study was designed to enroll a total of 70 patients. The sample size was determined based on a significance level of 5% for alpha to test the hypothesis if two treatment arms were equal in term of response rate, PFS and toxicity. For testing the differences in categorical variables between the two arms, the Chi-square test or Fisher's exact test was used. The difference in quantitative variables of both groups was compared by the Student's t-test or non-parametric Mann-Whitney test. Kaplan Meier's survival curves were obtained and the log-rank test was used to assess the significance of differences for PFS and OS between the two study groups. COX-PH regression model was used to estimate hazard ratios and their 95% CIs (confidence intervals). The analysis was "intention to treat" and includes` all randomized patient regardless of subsequent withdrawal from treatment or deviation from the protocol. All analysis was performed by SPSS version 16.

Results

From August 2007 to January 2010, a total of 70 eligible patients were randomly assigned in one of the two arms (Figure 1). There was no deviation from assigned treatment in our trial and also, no exclusion occurred after randomisation. The age range of patients was between 24 and 85 years with the mean of 55.50 ± 13.46. Patient's characteristics in both arms at baseline are shown in Table 1. There was no significant difference in

Table 1 Demographic characteristics of patients in both study arms.

		Arm A	***Arm B***	***Total***	***P-value***
Age					
	Mean ± SD	58.50±15.19	52.67±11.08	55.50±13.46	
	Median	57.5	51	55	0.07
	Range	24-84	32-85	24-85	
Stage					
	IIIB	10(29.4%)	9(25%)	19(24.4%)	0.678
	IV	24(70.6%)	27(75%)	51(72.9%)	
Histology					
	Adenocarcinoma	21(61.8%)	19(52.8%)	40(57.1%)	
	Squamous cell	7(20.6%)	6(16.7%)	13(18.6%)	
	Mixed NSCLC	1(2.9%)	1(2.8%)	2(2.9%)	0.621
	Undifferentiated NSCLC	5(14.7%)	9(25%)	14(20%)	
	Large cell	0(0%)	1(2.8%)	1(1.4%)	
Sex					
	Female	13(38.2%)	13(36.1%)	26(37.1%)	0.854
	Male	21 (61.8%)	23(63.9%)	44(62.9%)	
Smoking status					
	Yes	12(35.3%)	13(36.1%)	25(35.7%)	0.906
	No	22(64.7%)	23(63.9%)	45(64.3%)	
First-line chemotherapy					
	Gemcitabine + cisplatin	12(38.2%)	5(13.8%)	17(24.2%)	
	Gemcitabine + carboplatin	1(2.9%)	0	1(1.4%)	
	Docetaxel + cisplatin	6(17.6%)	11(30.5%)	17(24.2%)	0.077
	Paclitaxel + carboplatin	4(11.7%)	11(30.5%)	15(21.4%)	
	Etoposide + cisplatin	2(5.8%)	3(8.3%)	5(7.1%)	
	Others	9(26.4%)	6(16.6%)	15(21.4%)	

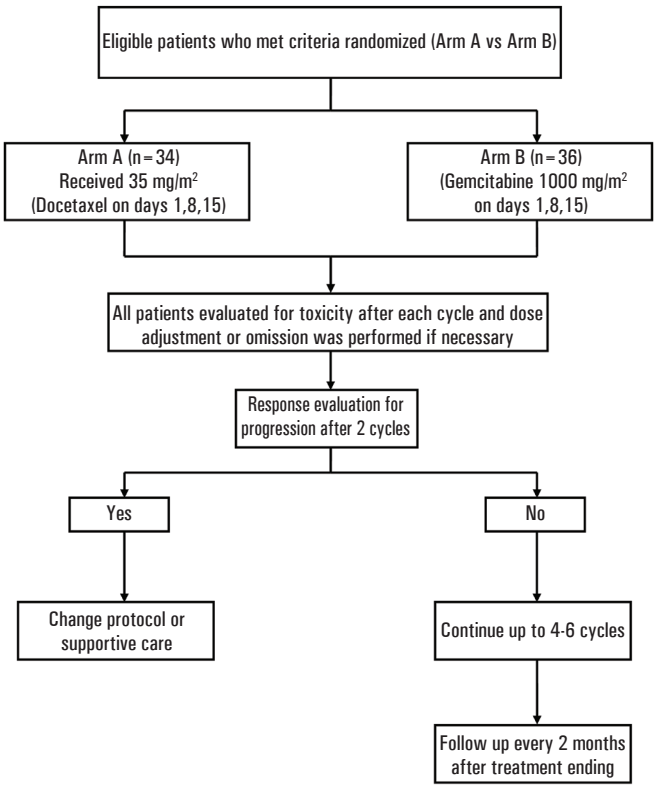

Figure 1 Diagram of the study and clinical trial flow chart. A total of 70 patients received study treatment consisting of at least one dose of docetaxel (Arm A; n = 34) or gemcitabine (Arm B; n = 36).

any of the characteristics listed between the two groups including age, gender, stage and histologic subtype. Mean administered cycles in arm A was 2.15 (1-6) versus 2.62 (1-6) in arm B (P=0.146). Dose modification during the course of treatment was more common in gemcitabine arm compared to that in docetaxel arm (13 vs 1 patients, P=0.003). Three patients in arm A and 4 patients in arm B were treated with chest radiation therapy prior to second-line therapy.

Response and survival

Although median overall survival for docetaxel arm was numerically longer (9.2 months) than that for gemcitabine arm (8.3 months) but it was not statistically significant (P= 0.59) (Figures 2 and 3). Objective response rate was non-statistically higher in gemcitabine arm (arm A = 5.8%, arm B =16.6%, P=0.20). Disease control rate was statistically different. (Arm A = 38.2%, Arm B = 66.6%, P=0.034) (Table 2).

All surviving patients had a minimum follow-up time of 12 months from September 2007 to December 2011. Fifty patients (21.4%) were lost to follow-up. The median follow-up of 10 months; 7 (10%) patients in docetaxel arm and 5 (7%) patients in gemcitabine arm were alive (P= 0.33). Post protocol third-line chemotherapy was administered in 29 and 28 patients in arm A and B, respectively (P= 0.787). During the study no patient received any targeted agent in any lines of therapy.

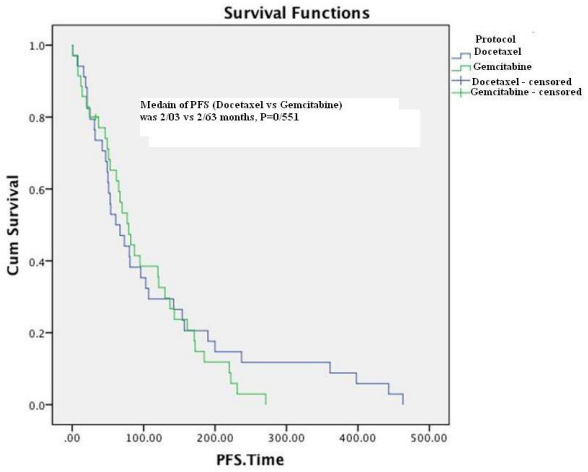

Figure 2 Progression free survival (PFS) in intention to treatment population docetaxel Vs gemcitabine. Kaplan-Meier survival curve from onset of recurrence for the effect of single agent second-line chemotherapy on progression free survival. Non-significant shortened PFS was observed between two groups, (P=0.551).

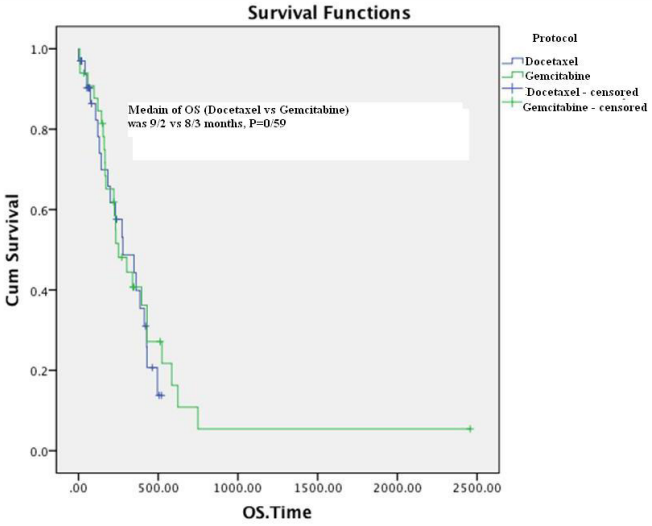

Figure 3 Overall survival (OS) in docetaxel Vs gemcitabine arm. Kaplan-Meier survival curve for overall survival (OS) in docetaxel vs gemcitabine arms. Non-significant differences was observed between two groups, (P=0.59).

Table 2 Response to treatment in two study arms.

	CR	*PR*	*SD*	*Prog*	*NA*
Arm A (docetaxel)	0	5.8% (n=2)	32.4% (n=11)	41.1% (n=14)	20.5% (n=7)
Arm B (gemcitabine)	5.5% (n=2)	11.1% (n=4)	50% (n=18)	22.2% (n=8)	11.1% (n=4)

Abbreviation: CR = complete response; PR = partial response; SD = stable disease; Prog = progressive disease; NA = not available.

Toxicity

All patients in both arms were assessable for toxicity. Important toxicities have been outlined in Table 3. Significant leukopenia was seen in Arm B (P=0.013). Neuropathy was more common in docetaxel arm. In contrast, nausea and vomiting, as well as neutropenia were more frequent in gemcitabine arm but not statistically significant (Table 3). No patient developed

febrile neutropenia or significant renal toxicity in this study. No death related to drug toxicity was reported.

Table 3 Major toxicity profile in two study arms.

*Side effect***	*Arm A (n=34)*	*Arm B (n=36)*	*Overall (n=70)*	*P value*
Neurotoxicity				
Grade 0	29(85.2%)	32(88.8%)	61(87.1%)	
Grade1	2(5.8%)	3(8.3%)	5(7.1%)	
Grade 2	3(8.8%)	1(2.7%)	4(5.7%)	0.932
Grade 3	0	0	0	
Grade 4	0	0	0	
Constipation				
Grade 0	32(94.1%)	31(86.1%)	63(90%)	
Grade1	2(5.9%)	5(14.7%)	7(10%)	
Grade 2	0	0	0	0.264
Grade 3	0	0	0	
Grade 4	0	0	0	
Nausea				
Grade 0	29(85.2%)	31(86.1%)	60(85.7%)	
Grade1	4(11.7%)	3(8.3%)	7(10%)	
Grade 2	1(2.9%)	1(2.7%)	2(2.8%)	0.653
Grade 3	0	1(2.7%)	1(1.5%)	
Grade 4	0	0	0	
Diarrhea				
Grade 0	32(94.1%)	34(94.4%)	66(94.2%)	
Grade1	2(5.9%)	2(5.6%)	4(5.8%)	
Grade 2	0	0	0	0.522
Grade 3	0	0	0	
Grade 4	0	0	0	
Mucositis				
Grade 0	33(97.1)	36(100%)	69(98.5%)	
Grade1	1(2.9)	0	1(1.5%)	
Grade 2	0	0	0	-
Grade 3	0	0	0	
Grade 4	0	0	0	
Leukopenia				
Grade 0	33(97.1%)	30(83.3%)	63(90%)	
Grade1	0	1(2.7%)	1(1.5%)	
Grade 2	1(2.9%)	5(13.8%)	6(7.5%)	0.013*
Grade 3	0	0	0	
Grade 4	0	0	0	
Neutropenia				
Grade 0	34(100%)	28(77.7%)	62(88.5%)	
Grade1	0	5(13.8%)	5(7.1%)	
Grade 2	0	3(8.3%)	3(4.2%)	0.75
Grade 3	0	0	0	
Grade 4	0	0	0	
Anemia				
Grade 0	30(88.3%)	33(91.6%)	63(90%)	
Grade1	3(8.8%)	2(5.6%)	5(7.1%)	
Grade 2	1(2.9%)	1(2.7%)	2(2.8%)	0.246
Grade 3	0	0	0	
Grade 4	0	0	0	
Thrombocytopenia				
Grade 0	33(97.1%)	34(94.4%)	67(95.7%)	
Grade1	0	1(2.7%)	1(1.5%)	
Grade 2	1(2.9%)	1(2.7%)	2(2.8%)	0.163
Grade 3	0	0	0	
Grade 4	0	0	0	

** Toxicity assessment was based on "Common Terminology Criteria for Adverse Events" (CTCAE) version 3.0.

Discussion

This study was conducted to evaluate the effectiveness of weekly docetaxel versus gemcitabine in real world practice as the second-line therapy. The present study demonstrated that significant higher disease control rate and possibility of achieving numerically (but non-significant) objective response rate with gemcitabine second-line chemotherapy and considerable longevity of median OS in docetaxel arm. Both regimens had very manageable toxicity with no difference in the incidence of major side effects. This is when both arms are relatively identical in terms of patients' age, gender ratio, and histologic subtypes. Second-line systemic therapies might improve survival of patients with advanced NSCLC with recurrent/progressive disease after the first-line treatment with doublet platinum based chemotherapy compared with best supportive care [21, 22].

There are several agents available for second-line treatment and in standard practice; clinicians are required to carefully choose the optimal option with respect to histologic subtype of tumor, EGFR and ALK status, as well as patient's performance status and preference. The "National Comprehensive Cancer Network" (NCCN) has considered docetaxel, pemetrexed and erlotinib as standard second-line treatment options [23]. However, several attempts in the world aim to improve the outcome in clinical trials with combination therapy or maintenance therapy (continuation or switch) [24–27].

Unfortunately, most patients at the time of disease recurrence/progression after first-line combination chemotherapy are minimally frail. Thus, monotherapy with a cytotoxic agent with weekly schedule is a much tolerable regimen for most of them in comparison to 3-weekly regimens. Docetaxel with every three-week schedule causes significant toxicity such as grade 3 to 4 neutropenia in 40% to 60% of patients and its side effects may deteriorate the physical well-being of patients [12]. Weekly docetaxel has been experienced in phase II studies in breast [28], prostate [29] and NSCLC [30] and its related toxicity is more manageable [31]. The response rate to weekly docetaxel in second and higher lines of therapy in advanced NSCLC is 10%-24 % [32, 33]. Result of this study with respect to response rate is similar to Shepherd et al. [11] that reported 6% partial responses.

Single agent gemcitabine, as second-line therapy in advanced NSCLC is an effective therapy in terms of symptom control and improvement of quality of life in comparison to best supportive care alone [34–36]. However, this cytotoxic agent has received no approval from Food and Drug Administration (FDA) for this setting. Response rate in Arm B is similar to Crinò et al. [16] study with about 16% response rate.

In this study, primary end point was PFS because few studies report significant differences in OS with chemotherapy in advanced NSCLC. Additionally, PFS is not influenced by other lines of therapy. Also, in many studies and in our study PFS was prolonged but it was not statistically significant. It should be considered that statistical significance in relation to clinical significance needs more attention and sample size plays an important role to reach clinically significant result [37]. PFS results in our study were partially similar to the other studies with single agent second-line chemotherapy with docetaxel and gemcitabine [11, 38]. Our patients showed less sever toxicity in both arm compared with the other studies [11, 17, 39].

The importance of this study is more prominent in developing countries, where potential toxicities of therapies and their managements are major concerns of clinicians who treat patients with advanced NSCLC with palliative intent. In some parts of these countries specialized centers as well as expertise medical staff and physicians are not available to deal with major chemotherapy toxicities. For this reason, two weekly regimens were chosen for this study which has more manageable toxicities. Combination chemotherapy in second-line setting is associated with significant increase in some toxicity [24, 40]. Besides, the clinicians in this study were permitted to modify dosages according to patients' age, frailty, comorbid conditions, or even their clinical judgment. Moreover, in the most of the developing countries newer cytotoxic agents such as pemetrexed or molecular targeted agents such as erlotinib are not affordable for most of the patients or not fully funded by public health care system as a second-line or maintenance therapy. Bearing all of these in mind, in patients with advanced NSCLC who experience disease progression after platinum-doublet chemotherapy, weekly docetaxel or gemcitabine are the two treatment options in clinical practice, although they are not necessarily optimal therapies in some cases.

A relevant limitation of this study is the difference in first-line treatment schedules among both arms which could have masked the impact of second-line chemotherapy on OS or toxicity.

Conclusion

This study demonstrated that two regimens of weekly docetaxel and gemcitabine are comparable in terms of PFS with manageable toxicities. We propose that effectiveness of different standard chemotherapy regimens (along with biologic agents) be evaluated in the real world setting in developing countries. The results of these studies might be different from the results reported from highly selected patient populations in phase II or III clinical trials, conducted in developed countries. The importance of these issues will be more evident when we consider diversity of treatment facilities, trained staff, financial constrains or even patients socio-cultural level as confounding factors that could have an impact on the selection of systemic treatment in patients with relapsed/progressed NSCLC.

Acknowledgment

Authors of this article take this chance to appreciate all of patients which enrolled and attended in this research. This project supported by a grant from National Institute of Tuberculosis and Lung Disease (NRITLD) (number P25/29/34561).

Conflict of Interests

There was no conflict of interests.

References

[1] International Agency for Research on Cancer. GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012. 2012; Section on Cancer Information. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx (Accessed on Jan 26, 2014).

[2] Islamic Republic of Iran, Ministry of Health and Medical Education, Office of Deputy Minister for Health Center for disease control, cancer office. 2009-2010: pp 17.

[3] SEER Stat Fact Sheets: Lung and Bronchus Cancer. Surveillance Research Program, National Cancer Institute. http://seer.cancer.gov/statfacts/html/lungb.html (Accessed on February 2, 2014).

[4] Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol. 2011; 6(2):244–285.

[5] Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol. 2003; 21(16):3016–3024.

[6] Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006; 355(240):2542–2550.

[7] Langer CJ, Leighton JC, Comis RL, O'Dwyer PJ, McAleer CA, et al. Paclitaxel and carboplatin in combination in the treatment of advanced non-small-cell lung cancer: a phase II toxicity, response, and survival analysis. J Clin Oncol. 1995; 13(8):1860–1870.

[8] Grønberg BH, Bremnes RM, Fløtten O, Amundsen T, Brunsvig PF, et al. Phase III study by the Norwegian lung cancer study group: pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as first-line chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol. 2009; 27(19):3217–3224.

[9] Winton T, Livingston R, Johnson D, Rigas J, Johnston M, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med. 2005; 352(25):2589–2597.

[10] Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008; 26(21):3543–3551.

[11] Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol. 2000; 18(10):2095–2103.

[12] Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol. 2000; 18(12):2354–2362.

[13] Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol. 2004; 22(9):1589–1597.

[14] Pujol JL, Paul S, Chouaki N, Peterson P, Moore P, et al. Survival without common toxicity criteria grade 3/4 toxicity for pemetrexed compared with docetaxel in previously treated patients with advanced non-small cell lung cancer (NSCLC): a risk-benefit analysis. J Thorac Oncol. 2007; 2(5):397–401.

[15] Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005; 353(2):123–132.

[16] Crinò L, Mosconi AM, Scagliotti G, Selvaggi G, Novello S, et al. Gemcitabine as second-line treatment for advanced non-small-cell lung cancer: A phase II trial. J Clin Oncol. 1999; 17(7):2081–2085.

[17] Rosvold E, Langer CJ, Schilder R, Millenson M, Reimet E, et al. Salvage therapy with gemcitabine in advanced non-small cell lung cancer (NSCLC) progressing after prior carboplatin-paclitaxel (abstract 1797). Proc Am Soc Clin Oncol. 1998; 17:467a.

[18] AJCC Cancer Staging Manual 6th edition; Chapter 19; Lung - original pages 167–177. http://www.cancerstaging.org/products/csmanual6ed-4.pdf (Accessed on Feburary 2, 2014).

[19] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000; 92(3):205–216.

[20] National Cancer Institute (NCI)/National Institute of Health (NIH). Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. https://webapps.ctep.nci.nih.gov/webobjs/ctc/webhelp/welcome_to_ctcae.htm (Accessed on April 30, 2012).

[21] Pfister DG, Johnson DH, Azzoli CG, Sause W, Smith TJ, et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. J Clin Oncol. 2004; 22(2):330–353.

[22] Fossella FV, Lee JS, Hong WK. Management strategies for recurrent non-small cell lung cancer. Semin Oncol. 1997; 24(4):455–462.

[23] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: non-small cell lung cancer. http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (Accessed on February 2, 2014).

[24] Di Maio M, Chiodini P, Georgoulias V, Hatzidaki D, Takeda K, et al. Meta-analysis of single-agent chemotherapy compared with combination chemotherapy as second-line treatment of advanced non-small-cell lung cancer. J Clin Oncol. 2009; 27(11):1836–1843.

[25] Pérol M, Chouaid C, Pérol D, Barlési F, Gervais R, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer J Clin Oncol. 2012; 30(28):3516–3524.

[26] Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczésna A, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2010; 11(6):521–529.

[27] Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet. 2009; 374(9699):1432–1440.

[28] Stemmler J, Mair W, Stauch M ,et al. Weekly docetaxel with or without corticosteroid premedication as first or second-line treatment in patients (pts) with metastatic breast cancer (MBC). Proc Am Soc Clin Oncol. 2002; 21:58a. Abstract 231.

[29] Beer TM, Pierce WC, Lowe BA, Henner WD. Phase II study of weekly docetaxel in symptomatic androgen-independent prostate cancer. Ann Oncol. 2001; 12(9):1273–1279.

[30] Camps C, Massuti B, Jiménez A, Maestu I, Gómez RG, et al. Randomized phase III study of 3-weekly versus weekly docetaxel in pretreated advanced non-small-cell lung cancer: a Spanish Lung Cancer Group trial. Ann Oncol. 2006; 17(3):467–472.

[31] Hainsworth JD. Practical aspects of weekly docetaxel administration schedules. Oncologist. 2004; 9(5): 538–545.

[32] Lilenbaum RC, Schwartz MA, Seigel L, Belette F, Blaustein A, et al. Phase II trial of weekly docetaxel in second-line therapy for nonsmall cell lung carcinoma. Cancer. 2001; 92(8):2158–2163.

[33] Gomez RG, Perez-Segura P, Mendez M. A phase II study of weekly docetaxel in previously treated patients with non-small-cell lung cancer (NSCLC). Proc Am Soc Clin Oncol. 2001; 20:267b.

[34] Sculier JP, Lafitte JJ, Berghmans T, Thiriaux J, Lecomte J, et al. A phase II trial testing gemcitabine as second-line chemotherapy for non small cell lung cancer. The European Lung Cancer Working Party. 101473. Lung Cancer. 2000; 29(1):67–73.

[35] Thatcher N, Anderson H, Betticher DC, Ranson M. Symptomatic benefit from gemcitabine and other chemotherapy in advanced non-small cell lung cancer: changes in performance status and tumour-related symptoms. Anticancer Drugs. 1995; 6:39–48.

[36] Sandler A, Ettinger DS. Gemcitabine: single-agent and combination therapy in non-small cell lung cancer. Oncologists. 1999; 4(3):241–251.

[37] Furburg B, Furberg C. Evaluating clinical research, all that glitters is not gold. 2nd ed. New York: Springer. 2007; pp. 107–108.

[38] Gridelli C, Perrone F, Gallo C, Rossi A, Barletta E, et al. Single-agent gemcitabine as second-line treatment in patients with advanced non small cell lung cancer (NSCLC): a phase II trial. Anticancer Res. 1999; 19(5c):4535–4538.

[39] van Putten JW, Baas P, Codrington H, Kwa HB, Muller M, et al. Activity of single-agent gemcitabine as second-line treatment after previous chemotherapy or radiotherapy in advanced non-small-cell lung cancer. Lung Cancer. 2001; 33(2-3):289–298.

[40] Quoix E, Zalcman G, Oster JP, Westeel V, Pichon E, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet. 2011; 378(9796): 1079–1088.