Preliminary results of continuation maintenance treatment of advanced non-squamous non small cell lung cancer patients after prior induction chemotherapy– A Single-Arm Phase II Study

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Abstract: Purpose: The present work aimed to study the efficacy and toxicity of continuation maintenance treatment with pemetrexed (Alimta) in patients showing disease control after four cycles of treatment with cisplatin plus pemetrexed in advanced non-squamous non small cell lung cancer (NSCLC). **Methods:** The work was done at April 2013 and April 2015, 16subjects with pathologically proven stage III/IV, non squamous NSCLC, in Clinical Oncology Department, Tanta University Hospital and Tanta Insurance Hospital who had received prior four cycles of induction with cisplatin at dose of 75mg/m^{2}in addition to pemetrexed at dose of 500mg/m^2 every 21 days without disease progression were enrolled. Patients received continuation maintenance treatment with pemetrexed (500mg/m2, every 21 days).The primary endpoints of the study were the overall survival (OS) and progression-free survival (PFS). Secondary end point was the safety profile. **Results:** A total of 64 chemotherapy cycles of continuation maintenance pemetrexed were given. The median number of cycles was 4 cycles, ranged between 2-30 cycles for the patients represented in the study. Only two subjects from 64 were given only two cycles owing to rapid advancement of the disease. The estimated median PFS and OS were 7.5 and 17 months, respectively. The side effects were manageable with 1 patient only (6.25%) suffered from Grade 3 anemia and another 1 patient (6.25%) suffered from Grade 4 neutropenia. Grade 3/4 non-hematologic toxicity was not documented. All patients received full doses of pemetrexed throughout the study. There was no treatment-related death. **Conclusion**: Using the continuation maintenance regimen with pemetrexed preceded by four cycles of induction with cisplatin plus pemetrexed for patients selected for a maintenance strategy represents an obvious treatment advance with an acceptable clinical profile for patients with non-squamous NSCLC patients.
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Key words: Non-squamous non small cell lung cancer, pemetrexed, continuation maintenance

1. Introduction:

Non small cell lung tumor is a worldwide oncological problem, as it always presented in advanced stage, platinum based chemotherapy is the main line of treatment **(1)**. Several efforts have been done to improve the response rate and the survival of NSCL patients, pemetrexed (Alimta) have been used in nonsquamous NSCL and have shown improvement in the treatment response and the survival with less toxicity **(2,3).**

Pemetrexed have been used with combination with cisplatinum or with gemcitabine-cisplatinum, both showed improvement in survival and tolerability **(4).**

Other efforts focused on the prolongation of tumer response by administrating well tolerated maintenance therapy for who have not progressed on the first line treatment **(5).**

Maintenance therapy is used until disease progression or unacceptable toxicity with specific focus on improving the overall survival and progression free survival **(6).**

Pemetrexed showed efficacy as maintenance therapy in nonsquamous NSCL patients who treated with pemetrexed cisplatin combination as first line therapy or with cisplatinum combination other than pemetrexed **(7).**

The administration of pemetrexed as a maintenance after first line pemetrexed cisplatinum shows efficacy in tolerability with advantage of continuing of well tolerated therapy with less toxicity used as first line **(8).**

2. Patients and Methods

Patient eligibility criteria

Between April 2013 and April 2015, 16patients with pathologically proven stage III/IV, non squamous NSCLC, in Clinical Oncology Department, Tanta University Hospital and Tanta Insurance Hospital were enrolled. Patients were followed up until May 2016. Eligible patients received prior induction chemotherapy that included 4 cycles of pemetrexed plus cisplatin without disease progression**.**

Patients fulfilled the following criteria:- age between 18-70 years, Eastern Cooperative Oncology

Group (ECOG) performance status (PS) of ≤ 2, adequate bone marrow reserve (WBC count ≥3.5 x 10^9/L, ANC count≥1.5 x10^9/L, platelets ≥100 x 10^9/L, and hemoglobin ≥10 g/dL), adequate renal function (measured creatinine clearance ≥ 60 mL/min) and adequate liver function (transaminases less than 2 x upper normal limit, and serum bilirubin concentrations below 1.5 mg/dL). Patients with CNS metastases were eligible if the metastases were stable and successfully treated with local therapy (that is, stable treated metastases), and the patient was off corticosteroids for at least 4 weeks.

Patients were ineligible for this study if they had second malignancy, or patients who were pregnant or have dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent were excluded from this study. Also, patients suffering from concurrent serious, uncontrolled medical illness (e.g. persistent immune-compromised states, uncontrolled infection, and clinically significant cardiac disease), extensive symptomatic visceral disease and current central nervous system metastases, were not eligible.

Design of the Study

This study is a prospective single-arm phase II study. The Ethics Committee in Faculty of Medicine, Tanta University, granted protocol approval and all patients signed an informed consent before the initiation of any treatment.

Treatment Plan and Dose Medication

Eligible patients for the maintenance phase of the study displaying disease control after four cycles of induction with cisplatin (75mg/m2) plus pemetrexed (500mg/m2) every 21 days in advanced non-squamous non small cell lung cancer (NSCLC).After documented radio-graphical confirmation of partial or complete tumor response or stable disease, patients received pemetrexed maintenance therapy (500 mg/m² day 1 of a 21-day cycle) plus best supportive care.

Maintenance intravenous pemetrexed began 7 days or less from the date of inclusion and 21–42 days from day 1 of the last cycle of induction therapy. During the study, all patients received folic acid, vitamin B12, and prophylactic dexamet has one.

Maintenance intravenous pemetrexed is discontinued in case of disease progression or major toxicities.

Adequate hematological and within normal range organ functions were insured every cycle. Adverse events were monitored throughout the study. A complete resolution of hematologic and non-hematologic toxicity was required except for alopecia and fatigue. If toxicities did not resolve, then a 1- 2 weeks delay were allowed.

2. Patient assessment

Assessment of clinical benefit

A tumor response assessment was performed after every three cycles of treatment. Pre- and on-treatment monitoring consisted of medical history, assessment of performance status, body weight and vital signs, physical and neurological examination, laboratory analyses, CT-scan of the chest, abdomen and pelvis, bone scan, MRI or CT scan of the brain if indicated. Criteria of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were based on the standard definitions according to RECIST 1.0 criteria **(9),** with the disease control rate, including complete response, partial response and stable disease.

Assessment of toxicity

Patients were assessed for adverse events at each site with clinical and laboratory evaluations every 3 weeks and cardiac monitoring, by ECHO, every 12 weeks. Toxicity grading was based on the common terminology criteria for adverse events (NCI-CTC, version 3.0. **(10)**

Primary and secondary endpoints

The primary endpoints of the study were overall survival and progression-free survival. Secondary end point was the safety profile.

Statistical analyses

Overall-survival (OS) rates were calculated from the date of start of intravenous pemetrexed maintenance therapy to the time of the last follow-up visit or death using the Kaplan-Meier method **(11)** with SPSS [Statistical package] (version 12.0). Progression-free survival (PFS) was the time elapsed from the date of initiation of intravenous pemetrexed maintenance therapy to the date of first evidence of disease progression or death in the absence of disease progression. Kaplan Meier method **(11)**] is used for estimating survival. The 95% confidence intervals (95% CIs) were calculated with the exact method. All *P* values were two-tailed; a value of 0.05 was considered significant.

3. Results

Patient characteristics

Between April 2013 and April 2015, 16 patients with pathologically proven stage III/IV, non squamous NSCLC, in Clinical Oncology Department, Tanta University Hospital and Tanta Insurance Hospital were enrolled. Eligible patients received prior induction chemotherapy that included 4 cycles of pemetrexed plus cisplatin without disease progression**.** After documented radio-graphical confirmation of disease control, patients received pemetrexed maintenance therapy (500 mg/m² day 1) cycle every 21 days plus best supportive care.

The patients characteristics were illustrated in table 1.

In the present work the ages of patients were ranged from 51-69 years with an average 60.4 years median age, with 13 (81%) patients were males and 3 (19. %) patients were females. The majority of patients had adenocarcinoma (81%). The stage of disease among patients at diagnosis prior to treatment was stage IV which represent 63% of all cases. Greatest of the diseased subjects (75%) had ECOG show status score of ≥1. As regard to smoking status, 11 of our patients (69%), were smokers. All patients received combination chemotherapy (pemetrexed plus cisplatin) in the induction setting and all patients developed disease control following induction combination chemotherapy (6 [37] %, 9 [56%], and 1 [6%] patients achieved CR, PR and SD, respectively).

Table 1: Patients and tumor Characteristics (N = 16)

Patient Characteristics	No.	%
Sex		
Male	**13**	**81**
Female	**3**	**19**
Age, years		
Median	**60.4**	
Range	**51–69**	
Smoking status		
smokers	**11**	**69**
non-smokers	**5**	**31**
ECOG performance status		
0	**4**	**25**
1	**11**	**69**
2	**1**	**6**
Histopathological type		
Adenocarcinoma	**13**	**81%**
Large cell carcinoma	**2**	**12%**
others	**1**	**6%**
Disease stage		
III B	**6**	**38%**
IV	**10**	**63%**
Response to prior induction chemotherapy		
CR	**6**	**37%**
PR	**9**	**56%**
SD	**1**	**6%**

Treatment Administration

All patients received pemetrexed (500 mg/m2) day 1cycle every 21 days as a continuation maintenance. The total number of chemotherapy cycles were 64.The median number of treatment was 4 cycles of continuation maintenance pemetrexed (range 2-30 cycles). The maintenance pemetrexed was intermittent for up to 2 weeks in the cases showing side effects particularly when greater than Grade 3.

Treatment toxicity:

As demonstrated in table (2) the hematologic and non-hematologic toxicities of the drugs in the patients were determined through using of special software (NCI-CTC, version 3.0) [(2)]. The toxicity of the used drugs were observed in 16 individuals, represented in mild and manageable hematologic and non-hematological symptoms. Neutropenia and anemia (6.25%) were recorded in one patient as a common grade 3-4 hematological toxicities.

Fatigue was the most common side effect, occurred in 56% (9/16) of patients as grade 1/2.There were some other grade 1/2 non-hematologic toxicities, such as diarrhea which occurred in3 patients (19%), nausea/vomiting in 6 patients (37.5%), anorexia in 5 patients (31%), numbness in3 patients (19%),and mucositis in 3 patients (19%).

All patients received full doses of continuation maintenance pemetrexed throughout the study. Interruption of the maintenance therapy for about 2 weeks has been occurred in occasion of occurrence of more than Grade 3 side effects. In our study there were two patients received only2 cycles due to rapid progression of the disease. No one of our patients required hospitalization. There was no treatment-related death.

Table (2): Hematologic and non-hematologic toxicity of continuation maintenance pemetrexed used in the management of the16 patients with non-squamous NSCLC

Toxicity	All Grades No. (%)	Grade 3/4 No. (%)
Non-hematologic Toxicity		
Nausea/vomiting	6(37.5)	
Anorexia	5 (31%)	0.0
Numbness	3 (19%)	0.0
Diarrhea	3 (19%)	0.0
Fatigue	9 (56)	0.0
Mucositis	3 (19%)	0.0
Hematologic Toxicity		
Neutropenia	3 (19)	1 (6.25)
Anemia	4 (25)	1 (6.25)
Thrombocytopenia	2 (13)	2 (5.3%)
febrile neutropenia	0	0

Survival

Median PFS was 7.5 months with its 95% CI 6.90 – 12.59 (Fig. 1). Median OS time was 17 months, with its 95% CI 13.92 – 17.46 (Fig. 2).

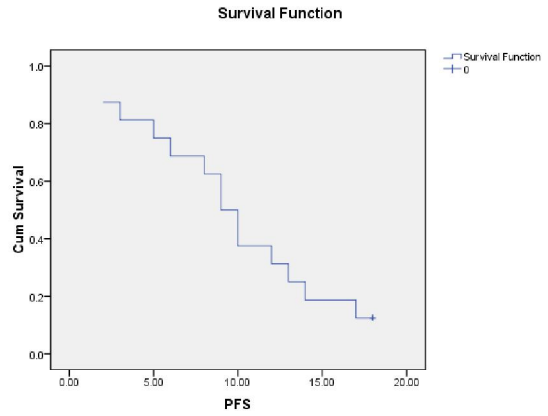

Figure 1: Kaplan–Meier curve of progression-free survival. Median PFS time was 7.5 months

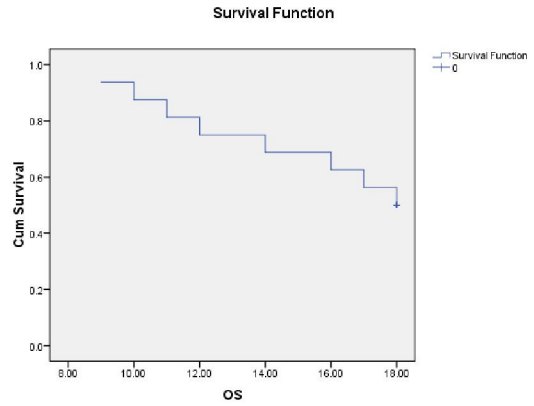

Figure 2: Kaplan–Meier curve of overall survival. Median OS time was 17 months.

4. Discussion

Several studies have demonstrated that most of NSCLC cases presented at the moment of admission and diagnosed as locally progressive stage (stage IIIB) or metastatic disease (stage IV) **(12, 13).**

All the guidelines recommended combinations that contain platinum-based as first-line treatment, recorded a response rate to the treatment of 20–40%, whereas the overall survival rate was averaged 7–12 months **(2, 3, 5).**

Many previous studies dealing with trials for treatment of stage III by applying pemetrexed in addition to standard chemotherapy regimen, or via using of maintenance therapy **(7, 8)**.

By applying of pemetrexed plus cisplatin as a first line of treatment, it was efficacious in the control of non-squamous NSCLC, while, using of a single-agent as maintenance therapy combined with pemetrexed enhanced progression-free survival and overall survival rates post first line of treatment **(13, 14).**

Several studies were carried out several years ago for exploring the role of maintenance chemotherapy in the treatment and control of patients diagnosed as stage III/IV, non squamous NSCLC **(14, 15, 16)**

Because of the high variability of the maintenance therapy regimens. We made this study to investigate the efficacy and tolerability of single-agent maintenance therapy with 500 mg/m^2 pemetrexed, every 3 weeks in 16 patients diagnosed pathologically as stage III/IV, non squamous NSCLC, who had received induction four cycles of with 75mg/m^2 cisplatin combined with 500mg/m^2 pemetrexed every three weeks without disease progression. The principal endpoints of this work were PFS and safety outline. The second end point was OS.

According to the available data, this is considered the first prospective research to evaluate the role of pemetrexed as a maintenance therapy in patients diagnosed pathologically as a stage III/IV, non squamous NSCLC in our country. Our study confirms that pemetrexed was tolerable and didn't increase the incidence of hematologic and non-hematologic toxicity.

In the work the most toxic effects to the present regimen noticed in 16 patients were in the form of mild hematologic and non-hematological toxicities and easily managed. Also, neutropenia and anemia (6.25%) were recorded in one patient who diagnosed in grade 3-4 hematological toxicities.

Fatiguewas the most common side effect, occurred in 56% (9/16) of patients as grade 1/2.There were some other grade 1/2 non-hematologic toxicities, such as diarrhea which occurred in 3 patients (19%), nausea/vomiting in 6 patients (37.5%), anorexia in 5 patients (31%), numbness in3 patients (19%), and mucositis in 3 patients (19%).All patients received500 mg/m2/ day pemetrexed as maintenance continuationfor 1cycle every 21 days. The total number of chemotherapy cycles were 64. The median number of treatment was 4 cycles of continuation maintenance pemetrexed (range 2-30 cycles). The maintenance pemetrexed was intermittent for about 14 days in advanced cases of toxicity of greater than Grade 3 side effects.

No one of our patients required hospitalization. There was no recorded dead cases due to treatment. Our results were in agreements with that in PARAMOUNT trial**. PARAMOUNT** is a double-blind, phase III randomized trial which evaluate the effectiveness maintenance therapy with single-agent pemetrexedin advanced non-squamous NSCLC. The patients were randomized to treatment with standard induction therapy with pemetrexed-cisplatin followed

by observation plus best supportive care or to standard induction chemotherapy followed by intravenous single-agent pemetrexed maintenance therapy 500 mg/m2 every 3 weeks plus best supportive care. The incidence of drug-related toxicity ore side effects were mild, with grade 3–4anemia neutropenia, and fatigue **(17, 18)**

In our phase 2 study, the patients had a significant improvement in overall survival and progression-free survival. The median OS time was 17 months with its 95% CI (13.92-17.46).The median PFS was 7.5 months with 95% CI (6.90-12.58). In **PARAMOUNT** randomized trial, the progression-free duration was reached an average of 4.1 months (95% CI 3·2–4·6) in cases administered pemetrexed (175 of 359, 49% censored) and it averaged 2.8 months (95% CI 2·6–3·1)in control (placebo group) **(17).**

There are some other protocols have been applied in order to increase the clinical results of patients suffering from NSCLC. In a study which carried out by some investigators for evaluation of the efficacy of bevacizumab (monoclonal antibodyanti-vascular endothelial growth factor (VEGF)) for treatment of NSCLC patients. The two regimens, AVAPERL and PARAMOUNT phase III trial are nearly similar except in case of the PARAMOUNT trial, bevacizumab is added to the treatment protocol **(16).**

In a trial was carried by some authors for evaluating the addition of pemetrxed with or without bevacizumab in addition to the basic regimen of chemotherapy. In this trial, after 4 cycles of treatment with first-line chemotherapy (cisplatin/pemetrexed/bevacizumab), about 67% of the subjects were randomly divided into two treatment groups, one treated with bevacizumab alone and the group was treated with bevacizumab +pemetrexed. The duration of treatments after the maintenance stage was averaged 5 cycles with bevacizumab and 7 cycles with bevacizumab plus pemetrexedtherapy. The first end point was seen, with PFS from randomization time of 7.4 months in the two-drug arm against 3.7 months in the group treated with bevacizumab-alone ($P<$ 0.001). The result of the work was not supported for OS, however the results gained propose a an improvement in OS even it was little in the group treated with bevacizumab plus pemetrexed. With respect to the toxicity or side effects of the regimen used, it is observed that the severe side effects was recorded in the group treated with bevacizumab plus pemetrexed, whereas, the initial statistical analysis revealed to a non-significant variations among the two treated groups in QoL. Following the previous treatments, another treatment was applied on 57% of bevacizumab-alone patients and 39% of bevacizumab plus pemetrexed group **(16).**

Ciuleanu et al. (17), studied the efficacy of switch maintenance therapy with pemetrexed for patients suffering from advanced non-squamous NSCLC after treatment with a regimen of non-pemetrexed-containing platinum doublet. The obtained results concerning with the progression-free survival rate of the maintenance group were comparable to those of **PARAMOUNT**, the progression-free survival period was averaged 4.5 months (95% CI 4.2–5.6).While, in a study done by **Ciuleanuet al. (17)** they showed in the non-squamous NSCLC patientsa significant increase in the overall survival rate **(17)**.

Our results were superior to the previous mentioned results, however our study differs as it is a prospective one arm phase II study which comprised only 16 patients with advanced non-squamous NSCLC.

Conclusion

Depending on the available data, this study is considered the first report of treatment with single-drug pemetrexed as a maintenance treatment following induction treatment with pemetrexed-cisplatin in Egypt. The initial data of our work revealed that, pemetrexed maintenance therapy, for patients with advanced non-squamous NSCLC is a promising regimen in decreasing the incidence of disease progression, with acceptable toxicity profile. Thus, we propose that pemetrexed maintenance therapy an alternative approach with tolerable toxicities for patients with advanced non-squamous NSCLC, however, the experiments still targeted to developthe clinical outcomes more. To achieve this, a multicenter, meta-analysis and a randomized trial include a huge numbers of patientsparticipating in this work are needed in the near future.

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