Progression Free Survival Analysis of Metastatic Non-Small Cell Lung Cancer In Patients Treated with First Line Chemotherapy Regimens

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Abstract

Background: Lung cancer is the 1st cause of cancer-related death in both men and women in Iraq.

Objectives: Analyze the progression-free survival of stage IV metastatic Non-Small Cell Lung Cancer (NSCLC) of Iraqi Patients who were treated with first-line chemotherapy regimens.

Method: Stage IV metastatic non-small cell lung cancer of patients was followed up between September 2018 to November 2019 in Iraqi patients who were divided into two groups according to the chemotherapy regimen of treatment: 169 received first-line platinum-based chemotherapy without maintenance treatment and 54 received first-line platinum-based chemotherapy with maintenance Pemetrexed drug.

Results and conclusion: Patients in this study their mean of age 61.6 years, the male has a higher incidence than a female that was 76% and 24% respectively. Adenocarcinoma histology was the most common subtype with 57.7% and squamous accounts for 42.3%. In patients who received first-line platinum-based regimen without maintenance treatment, the mean of Progression-Free Survival (PFS) was 6.3 months and the median was 5.5 months. Median PFS correlation with adenocarcinoma histology was 5 months and squamous cell carcinoma histology was 6.5 months. In patients who received an induction platinum-based regimen and followed by maintenance Pemetrexed, the mean of PFS was 5.5 months and the median of PFS was 5 months.

Keywords: Progression , Survival Analysis ,Non-Small Cell

Introduction:

INCIDENCE AND EPIDEMIOLOGY : According to World Health Organization (WHO), lung cancer is 2nd most common malignancy, accounting for 14.2% of all cancer deaths, and it is the 1st cause of cancer-related death in both men and women in Iraq [1].

PATHOLOGY: Lung cancers are classified into Small cells (15%) and Non-Small cell lung cancer NSCLCs (85%). Histologic subtype now has an influence on treatment selection [2]. Adenocarcinoma account for 40-50% of all NSCLCs, are more likely to be peripherally located than squamous cell or small cell cancer and tends to metastasize frequently. Squamous cell cancers account for approximately 25-30% of all NSCLCs [3],[4]. The treatment strategy should take into account factors such as histology, molecular pathology, age, performance status (PS). Systemic therapy usually should be offered to all stage IV patients with PS 0–2. [5] .

Progression-free survival (PFS) : The United States Food and Drug Administration (FDA) was defined the PFS as the time elapsed between treatment initiation and tumor progression or death from any cause, with censoring of patients who are lost to follow-up [7,8].

Aim of this study : The aim of this study to analyze the progression-free survival of stage IV metastatic Non-Small Cell Lung Cancer (NSCLC) of Iraqi Patients who were treated with first-line chemotherapy regimens.

Patients And Methods:

In this survival analytic study, patients in Oncology Teaching Hospital, National Cancer Center, and Al-Diwaniyah Teaching Hospital who fulfill in inclusion criteria followed up between September 2018 to November 2019. Those centers picked because of was teaching and tertiary centers.

Information of patients was collected in form of Patients' age and gender, Date of diagnosis and initiation treatment with chemotherapy, Tumor histology, site of metastatic disease, and Patient phone number and close relative.

Eligibility Criteria: Stage IV Non-Small Cell Lung Cancer (NSCLC): patients staging according to the American Joint Committee on Cancer staging manual (AJCC) the seventh edition [9], was selected after Cytological or histologic confirmation in the form of Fine Needle Aspiration (FNA), Malignant cytology in pleural effusion and Bronchoscopic biopsy.

The treatment of Chemotherapy: naïve patients who received first-line platinum-based chemotherapy according to their tumor histological type were divided into two groups according to the chemotherapy regimen of treatment:

Group one: 169 patients who have received the first-line platinum based chemotherapy at least two cycles up to six cycles every three weeks without maintenance therapy: All those patients received Carboplatin (AUC 5 mg)

min/ml iv with Pemetrexed 500 mg/m2 iv (adenocarcinoma histology) [10], or Carboplatin (AUC 5 mg) min/ml iv with Day 1, and 8 Gemcitabine 1000 mg/m2 iv (adenocarcinoma and squamous histology) [11], or Carboplatin (AUC 5 mg) min/ml iv with paclitaxel 200 mg/m2 iv (adenocarcinoma and squamous histology) [12] .All regimens repeated every (three) weeks for at least (two) cycles up to (six) cycles.

Group two: 54 patients who have received first-line chemotherapy up to six cycles every three weeks without progression then followed by maintenance therapy and all of them are adenocarcinoma histology. They received Carboplatin (AUC 5 mg) min/ml iv and Pemetrexed 500 mg/m2 iv every (three) weeks for (six) cycles then continue on maintenance on Pemetrexed 500 mg/m2 iv every (three) weeks until disease progression or unacceptable adverse effects [6] .

Monitoring and Response assessment:

- Monitoring and response assessment was done with Computerized Tomography Scan (CT scan) of known sites of disease with or without contrast (when clinically indicated) as fellow:
  1. After the first two cycles, then every 2–4 cycles of chemotherapy.
  2. New or emergent clinical complain that suspected further metastasis.
- Progression concluded to have occurred based on :
  1. The appearance of one or more new lesions documented by CT scan report.
  2. Clear, unequivocal increase in single or multiple lesions that was documented by previous CT scan reports.
  3. Deterioration of the symptoms and signs of disease are not manifest on radiological assessments.

Statistical Analysis PFS was calculated and correlated with histology types and chemotherapy regimens then compare the results with trails that recommend the use of these regimens. International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) version 24 software was applied for the statistical analysis of our data.

Table 1: Summarization of NSCLC patient's data

Total No. of patients	**223**		
Age in years	Range	30-83 year	
	Mean	61.6 year	
Gender	Male	170	76%
	Female	53	24%
Tumor histology	Adenocarcinoma	128	57.7%
	Squamous cell carcinoma	95	42.3%

Results And Discussion:

This is a survival analytic study of 223 patients diagnosed with NSCLC, their age range from 30 to 83 with a mean age of 61.6 years, which was accordant with other Iraqi studies [13, 14], besides to another study from India 2013 [15]. While in western countries the mean age at the period of diagnosis was 70 years [16]. The relationship between cancer incidence and age is explained by the extended exposure to different carcinogens like tobacco smoke, asbestos, air pollutions, and other types of chemicals or radiations [17].

The study showed that males have a higher incidence than females 76% and 24% respectively, the results were comparable to other Iraqi studies in which males represent (72.3%) of the total number, while females represent (27.7%) [18].

Our study showed adenocarcinoma was the most common subtype with 57.7% and squamous account 42.3%. It is comparable to Iraqi prior studies which showed also increase adenocarcinoma incidence than Squamous Cell Carcinoma [19]. A study in the kingdom of Saudi Arabia also revealed a higher incidence of adenocarcinoma[20]. On the other hand, these findings were differing with the findings recorded by Abbass, S. F., Hussein A. et al who described that the common type of lung cancer was squamous cell carcinoma [21]

Table 2: Statistic values of PFS period in months for NSCLC patients

PFS (in months)	**Patients treated without maintenance Pemetrexed**	**Patients treated with maintenance Pemetrexed**
Range	3-14	3-10
Mean ± SD*	6.3 ± 2.58	5.5 ± 1.99
Median	5.5	5

*SD= Standard Deviation

Table 3: Statistic values PFS in months in Squamous Cell Carcinoma and Adenocarcinoma of NSCLC patients without maintenance Pemetrexed.

PFS in months	Squamous Cell Carcinoma	Adenocarcinoma
No. of patients	95	74
Percentage	56.2%	43.8%
Mean ± SD	7.03 ± 2.7	5.4 ± 2.1
median	6.5	5
Range	3-14	3-13

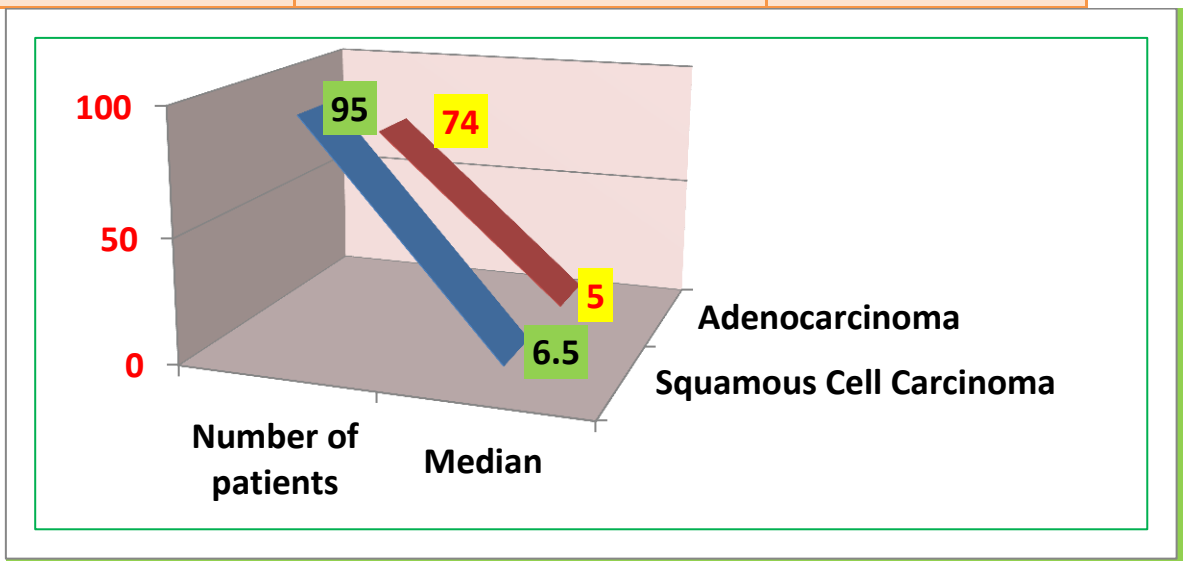

Figure 1: Patients numbers & median PFS period in months of NSCLC patients who were treated without maintenance Pemetrexed according to the histopathology.

Table 4: Statistic values PFS in months for NSCLC patients treated with maintenance Pemetrexed.

Maintenance period in months	
Total patient	54
Mean ± SD	5.5 ± 1.99
Median	5
Range	3-10

Median PFS of NSCLC patients without maintenance Pemetrexed who had Squamous Cell Carcinoma was 6.5 months and adenocarcinoma was 5 months as the result mentioned in table (3) and figure (1). There is a high significance of good PFS with squamous cell carcinoma than adenocarcinoma histopathology with P value (< 0.0005). This was confirmed by a study that

concluded outcome improvement for squamous cell carcinoma over adenocarcinoma [22].

Among our patient's sample chemotherapy doublet regimen is the first-line therapy, which might be chosen by histology, age, comorbidity, and performance status [23]. No main difference in survival was practical among four commonly used protocols; although the protocol of carboplatin and paclitaxel had a lower degree of toxic effects than the other protocols and the most first-line chemotherapy used was Pemetrexed and carboplatin [24].

Fifty-four patients who diagnosed with adenocarcinoma histology take part in our study treated with 4-6 cycles of Pemetrexed and carboplatin protocol of chemotherapy then maintain treatment on Pemetrexed and that depend on phase 3 study with a different design, in which patients with the non-progressive disease after 4 cycles of platinum-based combination therapy randomized to therapy with Pemetrexed or placebo of median progression-free survival was superior with Pemetrexed therapy [25]. The correlation between Pemetrexed and non-Squamous cell carcinoma histology in terms of clinical benefit was also observed in the maintenance setting. A prospective description for this finding is that thymidine synthetase (TS) expression is significantly higher in squamous cell carcinoma than in adenocarcinoma ($p < .0001$) [26], and preclinical data have shown that overexpression of TS correlates with lower sensitivity to Pemetrexed [27,28]. Other probable description for the observed treatment-by-histology interaction might involve the presence or absence of other molecular markers [29, 30].

In the present study regarding a group of patients who received a 4 - 6 cycle first-line platinum-based regimen without maintenance treatment, the mean of PFS was 6.3 months and the median was 5.5 months as the results mentioned in the table (2). Regarding median PFS correlation with adenocarcinoma histology was 5 months and squamous cell carcinoma histology was 6.5 months as the results mentioned in table (3) and figure (1). In Korean patients with advanced non-small-cell lung the median PFS, however, was 6.2 months [31,32].In another Italian study, Median progression-free survival was 6.09 months in patients [33]. It has been substantially suggested that ethnic variations in genetic polymorphisms of genes interrelated to drug activity and metabolism are associated with differential effects on toxicity and outcomes. Also, patient compliance and lifestyle may be related to differing results.

Regarding the other patient's group who not progressed on six inductions platinum-based regimen and followed by maintenance Pemetrexed, the mean of

PFS were mean 5.5 months and median of PFS 5 months as mentioned in table (6) and figure. Regarding Tudor Ciuleanu, Thomas Brodowicz, et al. study Pemetrexed significantly improved PFS that was 4.3 months[6]. In Cohen, Cortazar, Justice, et al. trail was applied in Maryland, USA, the median PFS was 4.0 months [34].

Conclusions:

1. In the present study regarding a group of patients who received first-line platinum-based regimen without maintenance treatment:
   - The median of PFS was 5.5 months.
   - Median PFS of the squamous cell ca. was 6.5 while adenocarcinoma was 5 months.
   - The highest median of PFS periods was with lung metastasis was 7.9 months while the lesser median of PFS with adrenal metastasis was 4.5
2. Patients who received maintenance therapy were:
   - Median PFS was 5 months.
   - The highest median of PFS periods was with pleural effusion metastasis was 9 months and the lesser median with brain metastasis was 3.7 months.

Recommendations

1. In future studies, the assessment of the overall survival of Iraqi patients with NSCLC recommended estimating the quality of treatment and health services.
2. Justify the necessity to promote public awareness educational campaigns to strengthen our national screening among smokers.

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