

Original Research Article

Pemetrexed in third and fourth line chemotherapy for non-squamous non-small cell lung cancer

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Abstract

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Lung cancer is responsible for the highest mortality caused by malignant solid tumors. Chemotherapy remain one of the most important modality of treatment. This retrospective study analyzed the records of 42 patients treatment with pemetrexed, used in second, third and fourth line chemotherapy for advanced non-squamous non-small cell cancer (NSCLC). Kaplan Meier curve was used for calculation of overall survival. The median overall survival in the second-line was 10 months and in third- and fourth-line was 6.5 months. We discuss the similar study with pemetrexed in mono-chemotherapy or combination, study with similar results. Also, we make a reference to the new therapy with best results but with much higher cost and effective only for a part of patients. This result and other results presented in similar studies encourage us to recommend pemetrexed in the third and fourth line chemotherapy for well-selected patients.

Keywords: Chemotherapy, lung cancer, Non-small cell lung cancer, pemetrexed, third line chemotherapy

INTRODUCTION

Lung cancer determines the highest mortality by cancer in Europe, accounting for approximately 20% of all cancer deaths and for the loss of 3.2 million disability-adjusted life-years annually in Europe. An important number of cases of lung cancer occur among the patients under 60-years-old (about a quarter of cases). At this time, seven out of eight patients die within 5 years after diagnosis. However, recent discoveries in the biology of lung cancer promise new more efficient therapies (<http://www.erswhitebook.org/chapters/lung-cancer/>). The situation is similar in United States, where lung cancer is also the leading cause of cancer-related mortality (<https://siteman.wustl.edu/ncipdq/cdr0000062932/>).

Platinum-based chemotherapy remains the standard first-line treatment for aNSCLC. Somehow a standard for second-line chemotherapy for aNSCLC is represented by docetaxel or pemetrexed. The third-line and fourth-line of chemotherapy are poorly defined.

In 2009, the only proven third-line agent was Erlotinib,

based on the same trial that led to the drug's approval in second-line therapy, and there are no drugs that have a proven benefit either for survival or for improved QOL after that. At the present time, immunotherapy with check inhibitors demonstrated an improvement in survival when they were used in second line therapy, but the trend is to move this therapy in the first line (Gregory and Dhaval, 2016; Roxanne, 2015).

Some physicians have, however, a pessimistic approach. Peter Wise, a former consultant physician at Charing Cross Hospital and Imperial College School of Medicine, London, published a very pessimistic opinion regarding unethical use of expensive therapy prolonging survival only with a few weeks or months (Zosia, 2016). In this respect, the American Society of Clinical Oncology (ASCO) Cancer Research Committee considers that a relative improvement in median OS of at least 20% (3-4 months) is regarded to define a clinically meaningful improvement in the outcome of NSCLC patients (Klaus

et al., 2016).

The existing possibilities for chemotherapy in second-line for advanced NSCLC in 2009 were represented by three agents: docetaxel, erlotinib and pemetrexed. These three drugs show that they can modestly prolong survival when the disease progressed after the first-line chemotherapy. At that time, there was only one proven third-line agent (Tarceva - Erlotinib), based on the same trial that led to the drug's approval in second-line therapy (BR21) (Pennell, 2009; Shepherd et al., 2005).

Aims

This study tries to demonstrate that in particular cases pemetrexed could be a treatment option for advanced non-small cell lung cancer (NSCLC) with non-squamous histology in second-line, third-line and fourth-line chemotherapy, taking in consideration that the new drugs are very expensive and we didn't explore sufficiently chemotherapy with actual best supportive care.

METHODS

Twenty-six patients (Group A) were evaluated retrospectively after the second-line treatment with pemetrexed (P), and 16 patients (Group B) were evaluated after third and fourth line. The evaluation was performed by using the written data from the medical records of the Institute of Oncology from Bucharest. The enrollment was done successively using the first data of presentation of the patients in institute for the treatment in the first line. The criteria of selections were:

- age between 18 to 80 years old;
- the administration of second line, third line or fourth line of chemotherapy;
- existing imaging data evaluation of response after two or three cycles of chemotherapy;
- existing data about the main toxicity;
- use of erlotinib in the first or second line was permitted;
- palliative radiotherapy for mediastinal compression, bone pain, hemoptysis was also permitted.

Overall survival was calculated for patients included in each line of therapy using the Kaplan Meier curve. The toxicity was appreciated using the WHO criteria.

RESULTS

In the second-line, third-line and fourth-line chemotherapy groups, the characteristic of patients were similar (age, stage of disease, histology). The median age for patients treated in second line with pemetrexed was 57-years-old and 62 years-old for those treated in third and fourth line. The difference was in the number of males and women in the two lots. In the lot treated in second-line, this number

was equal, but in the group treated in third- and fourth-line chemotherapy, there were 3 times more men than women.

Other characteristics of patients and the main results in survival for the two groups can be observed in tables 1-4 and in Figure 1 and 2.

Table1. Baseline characteristics of 26 patients treated with pemetrexed in second line chemotherapy

• **Total number of patients included: 26**

- **Sex:**
 - Male 13 (50%)
 - female 13 (50%)
- **age (years):** 57 (37 – 80)
- **Stage:**
 - IIIB 3 (11.5%)
 - IV 23 (88.5%)

Table 2. First line chemotherapy for NSCLC used in Institute of Oncology Bucharest for this lot of patients

- First line treatment:
 - Paclitaxel+ Carboplatin
 - Paclitaxel+ Carboplatin + Bevacizumab (small number of patients because patients must wait for approval from the National Insurance Commission)
 - Docetaxel+Carboplatin
 - Carboplatin +Vinorelbine
 - Alimta+Cisplatin (small number of patients because patients must wait for approval from the National Insurance Commission)
 - Gem+Cis
 - Other
- Average number of cycles: 4 (2 – 8)

Table3. Baseline characteristic of patients treated with Pemetrexed in third and fourth line chemotherapy

Number of patients treated in third and fourth line with pemetrexed: 16 (12 in third line, 4 in fourth line)

- **Sex**
 - Men 12 (75%)
 - Women 4 (25%)
- **Age (years):** 62 (31 – 80)
- **Stage of disease**
 - IIIB 4
 - IV 12

Table 4. Side effects:

- Hematologic side effects:
 - Mild anemia in 3 case
 - Leucopenia 2 cases
- Nonhematologic side effects:
 - GPT elevation 2 cases
 - Creatinin elevation 1 case
 - LDH elevation 1 case
- Others: dizziness (1), fatigue (1), lack of appetite (2)

Median OS – 10 months

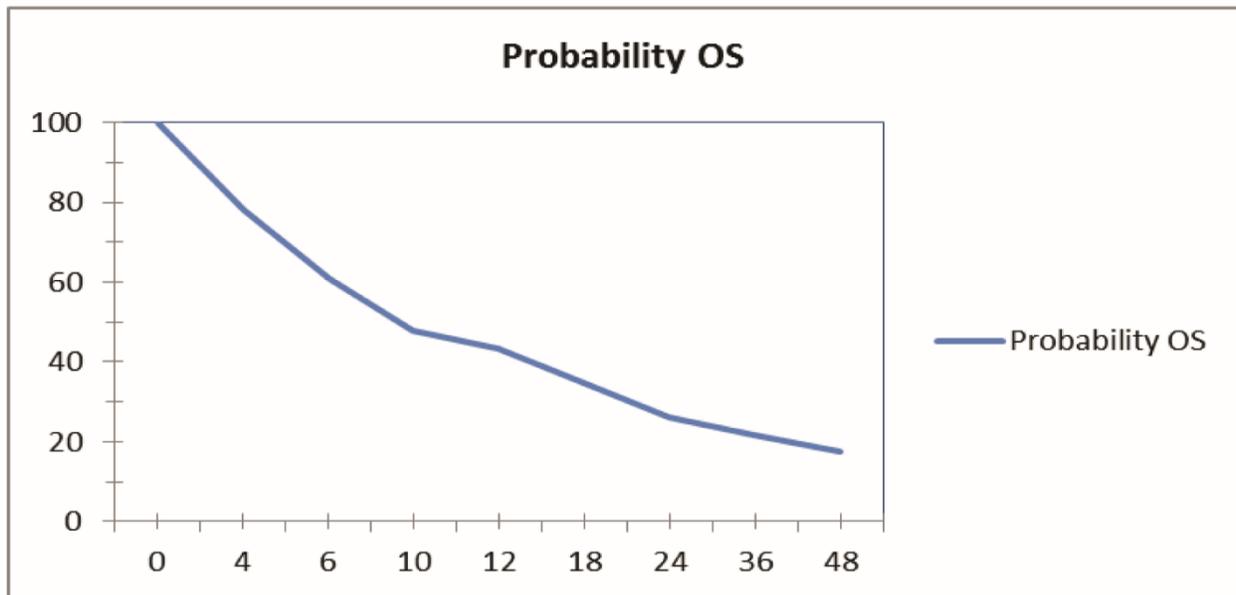


Figure 1. Median overall survival of patients treated with pemetrexed in second line

Median OS – 6,5 luni

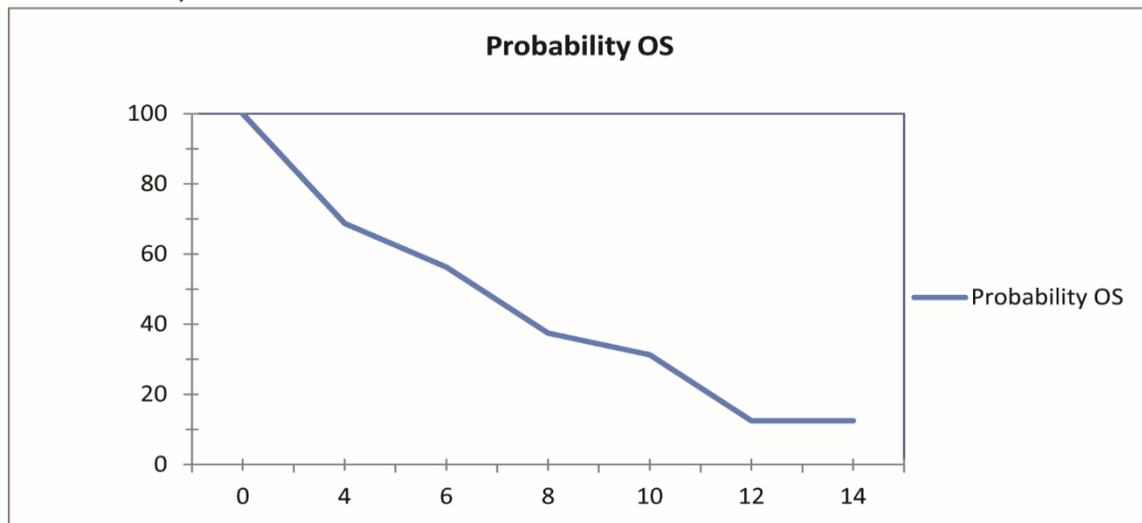


Figure 2. Median overall survival of patients treated with pemetrexed in third and fourth line

DISCUSSIONS

We will discuss predominantly the study which tested pemetrexed in third line, especially the retrospective study. Also, we will discuss about the association of pemetrexed with other drugs in third line and the new trend.

In 2006, Kumar *et al.* recognized the possibility of third-line chemotherapy and beyond for responders to the first-line chemotherapy and good performance status patients. The authors quoted like candidates for third-line

chemotherapy: single-agent gemcitabine, irinotecan, and oral topotecan (Kumar and Wakelee, 2006).

The study published by Song Z *et al.* was a retrospective study which confirmed the small but proved benefit of third-line chemotherapy. The authors found the progression-free survival after third-line therapy to be 2.37 months for all patients and 2.30 months for patients treated with doublet of cytostatics, 2.80 months for single-agent and 2.97 months for EGFR-TKIs arms ($P=0.033$) (Song *et al.*, 2010).

One of the first studies which tested the use of pemetrexed in third-line chemotherapy for advanced NSCLC was a retrospective study of Jong-Mu *et al.* In this study, the medical records of NSCLC patients who received pemetrexed therapy that progressed after systemic therapy were reviewed retrospectively. The authors stratified patients according to clinic-pathologic characteristics to find predictive factors for pemetrexed therapy. The conclusion was that pemetrexed is a suitable third-line treatment option with a good toxicity profile (Jong-Mu *et al.*, 2009).

Adolfo G. Favaretto described in a review published in 2009, in which was stipulated that because pemetrexed had a good toxicity profile, elderly and patients with performance status 3, for which the ASCO guidelines contraindicate any chemotherapy, could benefit from pemetrexed (Weiss *et al.*, 2006; Zinner *et al.*, 2007). Taking into consideration this aspect, we can presume that pemetrexed can be used in the third line therapy, where patients often have a bad performance status (Adolfo, 2009).

Another observational study that refers to pemetrexed in third-line therapy was published in 2014. This study compared pemetrexed alone in third line with pemetrexed plus bevacizumab in third-line chemotherapy for patients with positive EGFR mutation. The conclusion of this study was that “regardless of the order of the first- and second-line chemotherapy and TKI therapy, the pemetrexed plus bevacizumab regimen was superior to the pemetrexed monotherapy as the third-line therapy in patients with advanced EGFR-positive lung adenocarcinoma”. However, the authors recommend further investigation in prospective studies (Zhou *et al.*, 2014).

Another study similar with ours evaluated the clinical outcome of third- and fourth-line chemotherapy for the treatment of advanced NSCLC in consecutive patients who received first-line chemotherapy in the same institution. A global result was that the median survival periods (95% confidence interval [CI]) from the start of first-, second-, third-, and fourth-line chemotherapy until death were 15.3 months. The authors concluded that in their study more than 38% of patients with advanced NSCLC could receive third-line chemotherapy, and it is a need for randomized controlled trials of third-line chemotherapy in patients with advanced NSCLC (Hajime *et al.*, 2012). The possible option for third line chemotherapy has been also highlighted in other studies (Mustafa *et al.*, 2004; Özkan *et al.*, 2006).

Other therapeutic approaches in second-line and third-line therapy

Overall survival was significantly longer with nivolumab than with docetaxel at the time of the interim analysis (minimum follow-up for overall survival: 13.2 months), the median overall survival was 12.2 months (95% confidence

interval [CI], 9.7 to 15.0) with nivolumab and 9.4 months (95% CI, 8.1 to 10.7) with docetaxel, representing a 27% lower risk of death with nivolumab (hazard ratio: 0.73; 96% CI, 0.59 to 0.89; P=0.002). The overall survival rate at 1 year was 51% (95% CI, 45 to 56) with nivolumab and 39% (95% CI, 33 to 45) with docetaxel. These results reveal the fact that the overall survival for some patients could be prolonged with approximately 3 months. We must also take in consideration the toxicity of docetaxel – if it could be reduced, maybe we had other results with docetaxel. But, obviously, is a step forward in NSCLC therapy (Hosseini *et al.*, 2015).

The researchers consider that a new step in the optimization of the treatment of advanced NSCLC is the association between immunotherapy agents (especially inhibitors of PD-1/PD-L1 and TKI). For the moment, the correlation between PD-1/PD-L1 expression and EGFR expression was not elucidated, and needs more evidence to support this combination (Mei *et al.*, 2015).

A study of Zhen Ying Geng and collab. compared 4 groups of patients: the EGFR-TKIs group, the single-agent chemotherapy group, the combination chemotherapy group and the chemo-targeted group. The main parameters compared in this study, partial response, progression-free survival and overall survival, showed no statistically significant difference (Zhen *et al.*, 2013). These results show that chemotherapy remains an important option for selected patients in second-line and third-line therapy.

In the 1st ESMO Consensus Conference in Lung Cancer (Lugano, 2010), the three analyzed options for second-line and third-line chemotherapy showed that more evidence seems to be in third-line therapy for epidermal growth factor receptor inhibitors (Felip *et al.*, 2011).

In a study of researchers from Sevilla (Spain), it was concluded that: “erlotinib/gefitinib and crizotinib, which target EGFR and ALK, are the only recommended agents for third-line therapy in patients with advanced/metastatic NSCLC”. But the authors revealed the fact that in real world, in clinical practice, a variety of chemotherapeutic agents was used in this setting. We need new agents and complementary biomarker analysis to predict the response to these agents and to identify those patients most likely to benefit from them (Jesus Corral *et al.*, 2013).

A total of 33 patients were candidate in third-line chemotherapy or more. The median survival was 23 months for patients treated with more than third-line chemotherapy, compared to 7 months for patients treated with less than second-line chemotherapy. The authors concluded that long-standing chemotherapy is not beneficial to all NSCLC patients. However, patients with a favorable response to first-line chemotherapy tend to receive a higher number and more cycles of chemotherapy than the non-response group. Another conclusion was that multi-line chemotherapy appears to increase survival in

the response group. Further studies are needed to confirm these results (Seh et al., 2010).

CONCLUSIONS

We analyzed patients treated in third-line and fourth-line chemotherapy for NSCLC. We could use this chemotherapy because the third-line and fourth-line treatment in advanced NSCLC is not well defined and for some countries the immunotherapy and other modern therapies are not available. Taking into consideration the ASCO recommendation – “relative improvement in median OS of at least 20% (3-4 months) is regarded to define a clinically meaningful improvement in outcome of NSCLC patients” – we can conclude that pemetrexed reaches this goal. It was proved that patients who had a good response to first-line and second-line chemotherapy have a chance to respond also to the third-line and fourth-line chemotherapy.

Finally, we concluded that for selected patients with advanced non-squamous NSCLC, namely those who responded to first-line and second-line chemotherapy or to erlotinib, pemetrexed can be administered in third-line and fourth-line, with survival benefits and acceptable toxicity. A large study is necessary to confirm the data obtained in this study.

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