



The role of continuous maintenance therapy with pemetrexed in non-squamous non-small cell advanced lung cancer: A prospective cohort study in Vietnam

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Article History

Received: 06 April 2020

Reviewed: 06/April/2020 to 09/May/2020

Accepted: 10 May 2020

E-publication: 16 May 2020

P-Publication: July - August 2020

Citation

Nguyen Thi Thai Hoa, Nguyen Tien Chung, Huynh Quang Huy. The role of continuous maintenance therapy with pemetrexed in non-squamous non-small cell advanced lung cancer: A prospective cohort study in Vietnam. *Medical Science*, 2020, 24(104), 1930-1935

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General Note



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ABSTRACT

Aims: To evaluate overall survival (OS) and progression-free survival (PFS) of patients with advanced-stage non-squamous non-small-cell lung cancer who were treated with pemetrexed as maintenance therapy after first-line treatment by pemetrexed-cisplatin. **Method:** Fifty-one patients with advanced Non-squamous Non-small-cell Lung cancer underwent first-line combination chemotherapy. When initial disease control had been achieved, these patients were received Pemetrexed as continuous maintenance (500mg/m², on day 1 of the 21-day cycle) at National Cancer Hospital. The primary endpoint of this study was overall survival. **Results:** Median OS was 16.1 months; Median PFS was 7.8 months. Patients having a partial response to first-line treatment have median OS was 22.8 months, median PFS 9.8 months. Group of patients having a stable disease to first-line treatment has median OS was 13.6 months, median PFS 6.6 months. **Conclusion:** Our finding shows that pemetrexed maintenance therapy was effective in prolonging OS, PFS in patients with advanced non-squamous non-small-cell lung cancer after treatment with pemetrexed-cisplatin.

Keywords: maintenance, pemetrexed, non-small cell lung

1. INTRODUCTION

According to Globocan 2018, for both sexes, lung cancer ranked first in terms of incidence and mortality (Bray et al., 2018). The disease generally develops in men, middle-aged, with a history of smoking (Nguyen Thi Hoai Nga, 2008, Bray et al., 2018). Lung cancer is categorized into two histological groups: small cell lung cancer, which accounts for 10-15%, and non-small cell lung cancer (80-85%). The majority of lung cancer patients are diagnosed at an advanced stage, which means the disease has invaded, spread, and cannot be cured. The main aims of treatment for those patients are controlling symptoms and improving quality of life. Palliative chemotherapy in advanced lung cancer with platinum (Cisplatin, Carboplatin) based combined with one of the agents such as taxane, gemcitabine, vinorelbine, pemetrexed has shown efficacy in improving overall survival and quality of life, compared to palliative care alone (Baxevanos et al., 2018). The role of maintenance therapy with pemetrexed in non-small cell lung cancer, non-squamous, the advanced stage had been proven in many studies. Studies that maintained pemetrexed in patients with non-small cell lung cancer, non-squamous, advanced stage showed significant improvement in terms of progression-free survival and overall survival (Gridelli et al., 2013, Minami et al., 2015). However, in Vietnam, there has not been any studies evaluating the efficacy of this treatment strategy. Thus, we conducted this study with the primary objective is to evaluate the overall survival in patients with non-small cell lung cancer, non-squamous, continuous maintenance therapy after first line of pemetrexed – cisplatin; and the secondary objective is to evaluate the progression-free survival of this group of patients.

2. MATERIALS AND METHODS

Study population

Fifty-one advanced stage non-small cell lung cancer patients who were maintained by Pemetrexed after first-line treatment of Pemetrexed-Cisplatin at National Cancer hospital from 2015 to 2019 were prospectively analyzed. This study was approved by The Ethical Committee of the hospital under the approval number of 03022015-NCH. Informed consent was obtained from all patients.

Inclusion criteria: 1) Patients with non-small cell lung cancer (NSCLC) stage IV; 2) Histological diagnosis was adenocarcinoma; 3) Wild type or unknown EGFR or ALK mutations; 4) Performance status (PS) $\leq$ 1; 5) Had been treated with 4-6 cycles of Pemetrexed-cisplatin with complete/partial response or stable disease; 6) Maintained with Pemetrexed until progression or intolerance; 7) Hematology and biochemistry parameters were adequate for chemotherapy.

Exclusion criteria: Other histological type, brain metastasis, loss of follow-up information.

Treatment protocol

We performed a clinical intervention without controls.

- Regimen: Pemetrexed dose of 500mg/m² IV day 1, Q21; folic acid and vitamin B12 supplement during treatment, patients were continuously maintained until progression or appearance of unacceptable side effects.
- During the treatment, clinical, subclinical features and responses to the treatment were documented. PFS is defined as the duration of starting treatment until progression or death due to any reasons.

3. RESULTS

Fifty-one patients with advanced non-squamous non-small-cell Lung cancer underwent first-line combination chemotherapy. The mean age was 56.8 (range: 26 – 75). The male/female ratio was 4.1/1. Most of the cases were histologically defined as adenocarcinoma (Table 1). The total number of cycles was 403. The mean value was 7.9 ± 4.6 . The min number of cycles was 2, while the max number of cycles was 21 (Table 2).

Table 1 Study population's features

Features	n = 51
Age (Mean)	56.8 (26 – 75)
Sex	
Male	41 (80.3%)
Female	10 (19.7%)
Performance status (PS)	
0	17 (33.3%)
1	34 (66.7%)
Histology	
Adenocarcinoma	49 (96.1%)
Large cell carcinoma	2 (3.9%)
Number of cycles in first-line treatment	
4 cycles	46 (90.2%)
6 cycles	5 (9.8%)
First-line treatment response	
Partial	24 (47.1%)
Stable	27 (52.9%)

Table 2 Number of maintenance cycles

Cycles	Number
Total	403
Mean	7.9
Standard deviation	4.6
Min	2
Max	21

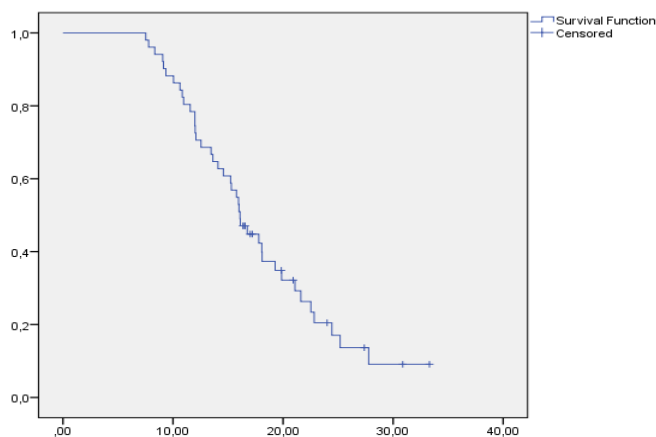


Figure 1 Overall survival

At the end of the study, there were 40/51 patients died, accounted for 78.4%, 11/51 (21.6%) were alive. Median OS was 16.1 months. OS at 12 month, 18 month, 24 month was 72.5 %, 31.4%, 13.7%, respectively (Figure 1). Group of patients having a partial response to first-line treatment: median OS was 22.8 months. OS at 12 month, 18 month, 24 month were 87.5%, 58.3% and 29.2%, respectively (Figure 2).

Median PFS was 7.8 months (4.2 – 19.1 months). Min PFS was 4.2 months, and max PFS was 19.1 months (Figure 3). In the group of patients having the response to first-line treatment, median PFS was 9,8 months, while in the group of stable patients, PFS was 6,6 months. The difference was statistically significant with $p=0,001$ (Figure 4).

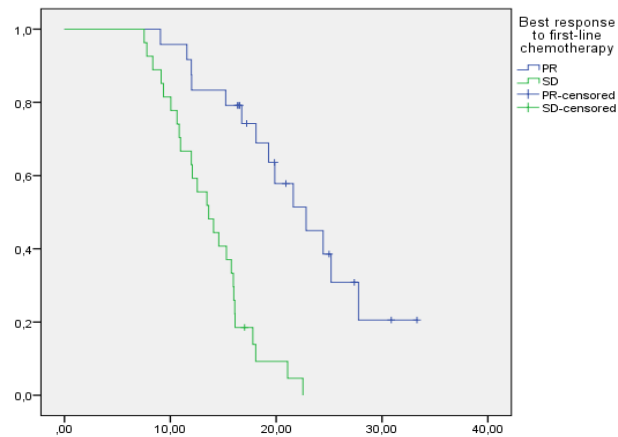


Figure 2 Overall survival by first-line response status

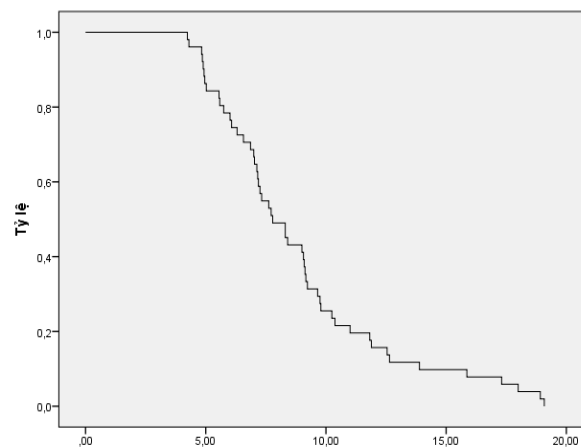


Figure 3 Progression free survival

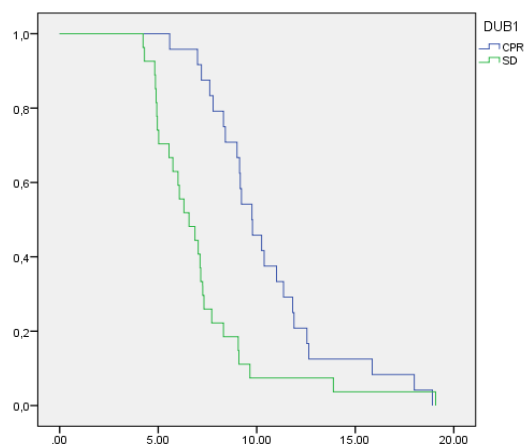


Figure 4 Progression-free survival by first-line response status

4. DISCUSSION

At the end of the study, 11/51 patients were alive. Mean OS in this study was 16.6 ± 0.8 months, and median OS was 16 months, OS at 12 months, 18 months, and 24 months were 72.5%, 31.4%, and 13.7%, respectively. OS in our study is similar to other studies of pemetrexed maintenance. In the Paramount trial (2013), median OS in pemetrexed maintenance arm was 16.9 months (95%: 15.8 – 19 months), OS at 12 months, 24 months (from switching maintenance therapy) were 58% and 32%, respectively. Also, in this trial, in patients received palliative care alone without pemetrexed maintenance therapy, OS was only 14 months (95%CI: 12.9-15.5 months), OS at 12 months, 24 months were 45%, and 21%, respectively (Paz-Ares et al., 2012). According to Ciuleanu et al. (2009), in pemetrexed maintenance arm, median OS was 16.5 months (range: 15.1-19.1 months), while median OS was only 13.9 months in patients without pemetrexed maintenance (range 12.2- 15.4 months) (Ciuleanu et al., 2009).

By reviewing some large studies of first-line chemotherapy with pemetrexed- platinum followed by palliative care and follow up, we have learned that OS in maintenance therapy is significantly higher than OS in single first-line chemotherapy. Scagliotti et al. (2008) conducted a phase III study with a large sample size to compare overall survival in 1,725 stage IIIB or IV NSCLC patients with good performance status (PS = 0 or 1). Median OS was 11.8 months in patient groups of adenocarcinoma and large cell carcinoma (Scagliotti et al., 2008). According to Novello et al. (2016), who studied 85 non-squamous, advanced NSCLC patients with first-line pemetrexed and cisplatin, median OS was 10.38 months (Novello et al., 2017). In the study of Scagliotti et al. (2014), patients maintaining pemetrexed had statistically significantly higher OS than patients in JMDB study with single first-line treatment (16.9 months vs. 14.2 months, $p=0.003$, HR=0.75) (Scagliotti et al., 2014).

Median PFS in our study was 7.8 months, and this result is similar to other pemetrexed maintenance studies in non-squamous advanced NSCLC. In the Paramount trial, 359 patients with non-squamous advanced NSCLC, PS=0.1 achieved disease control after first-line pemetrexed-cisplatin treatment followed by pemetrexed maintenance, PFS was 6.9 months (Paz-Ares et al., 2012, Gridelli et al., 2013). The JMEN trial, which investigated 441 NSCLC patients at advanced stage being treated by pemetrexed maintenance after achieving disease control with pemetrexed-platinum, PFS was 7.7 months (Ciuleanu et al., 2009). In Okamoto et al. trial, 60 non-squamous advanced NSCLC patients who were maintained by pemetrexed after pemetrexed-carboplatin doublet chemotherapy had PFS 7.5 months (Okamoto et al., 2013). These studies once again demonstrated the efficacy of maintaining pemetrexed in prolonging progression-free survival, compared to palliative care alone.

During analyzing the relationship between overall survival and response to first-line chemotherapy, we found that in the group having the response to first-line treatment, median OS was 22.8 months, while in patients with stable disease after first-line therapy, median OS was 13.6 months. The difference was statically significant. We explain that in patients with response to first-line treatment, their tumors shrank better, reduced symptoms, improved quality of life, and thus prolonged overall survival. On the other hand, patients with response to first-line treatment were expected to have better response and tolerance, compared to the group of stable disease.

5. CONCLUSION

Our finding shows that pemetrexed maintenance therapy was effective in prolonging OS, PFS in patients with advanced non-squamous non-small-cell lung cancer after treatment pemetrexed- cisplatin. Further studies are strongly recommended in the field with a larger sample size and long-term follow-up to ascertain conclusions drawn from this study.

Abbreviations

OS:	overall survival;
PFS:	progression-free survival;
NSCLC:	non-small cell lung cancer;
PS:	Performance status.

Author contributions

All participated in the study design, data collection, and literature search. Data was analyzed by NTH. NTH and HQT wrote the paper. All authors read and approved the final manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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