



Pemetrexed-Carboplatin as first-line treatment in elderly patients with stage IV adenocarcinoma lung cancer

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General Note



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ASBTRACT

Introduction: In Vietnam, 60-70% of lung cancer is diagnosed at the metastatic stage. Platinum-based doublet chemotherapy plays an important role at this stage. This study aims to describe the clinical, subclinical features and evaluate the overall response rate (ORR), disease control rate (DCR), and side effects of treatment using Pemetrexed-Carboplatin regimen for elderly patients with

stage IV adenocarcinoma lung cancer. *Methods:* A single-arm intervention was conducted on 37 patients in Vietnam National Cancer Hospital from January 2017 to June 2019. All patients were intravenously treated with pemetrexed 500 mg/m² on day 1 followed by intravenously carboplatin area under the curve (AUC) 5 on day 1; every 3 weeks. *Results:* The mean age was 67 ± 4,1 (60-74); male/female ratio = 2.7/1. The smoking rate was 66.2%; 78% of patients had comorbidity; 56.8% of patients suffered from cardiovascular diseases. The overall response rate (ORR) was 35.1%, and disease control rate (DCR) was 59.5%. The common side effects were at grade 1 or 2, no drug-related death. *Conclusion:* The Pemetrexed-Carboplatin regimen treating elderly patients with stage IV lung adenocarcinoma has the same response rate and tolerance similar to other age groups.

Keywords: non-small cell lung cancer, adenocarcinoma, pemetrexed, carboplatin, elderly.

1. INTRODUCTION

According to Globocan 2018, in Vietnam, lung cancer ranked second among males and third among females in terms of incidence, the second among males and the first among females in terms of mortality (Bray et al., 2018). Lung cancer is categorized into two histological groups: non-small cell lung cancer (NSCLC), which accounts for about 80-85% and small cell lung cancer (10-15%) (Zappa et al., 2016). Since most lung cancer in Vietnam is diagnosed at the metastatic stage, treatment options are primarily systemic therapies (Pham et al., 2019). While targeted therapies require sensitive gene mutations, immunotherapy indications are not widely applied and cost very high. Chemotherapy still plays an important role in this stage. Towards non-squamous NSCLC, the Platinum combined with Pemetrexed regimen was associated with prolonged overall survival and lesser toxicity, compared to Platinum – Gemcitabine combination (Scagliotti et al., 2008, Gronberg et al., 2009, Ito et al., 2019). Treatment of NSCLC in elderly patients is more difficult when compared to younger patients due to other coexisting diseases such as chronic obstructive pulmonary disease, diabetes, cerebrovascular diseases, cardiovascular, and osteoporosis. Memory loss is one of the causes of late medical diagnosis and treatment in elderly (Hutchins, 1999). Also, elderly patients need more drugs and are more likely to electrolyte and water disorders.

Regarding treatments for elderly patients, combining of pemetrexed and carboplatin has been proven to be an excellent regimen for elderly patients with stage IV adenocarcinoma lung cancer (Gridelli, 2014). In elderly patients, treatments with combined regimens should be considered between risks and benefits. However, there have not been many studies in Vietnam and over the world evaluating the result of Pemetrexed-Carboplatin regimen in elderly patients with advanced NSCLC. Therefore, we conducted this study with two objectives: 1) To assess the response of Pemetrexed-Carboplatin regimen in elderly patients with adenocarcinoma stage IV lung cancer; 2) To assess the side effects of the treatment.

2. MATERIALS AND METHODS

Study population

We prospectively analyzed thirty-seven patients who were treated at Vietnam National Cancer Hospital between January 2017 and June 2019.

Inclusion criteria were: 1) Stage IV, measurable adenocarcinoma lung cancer; 2) No driver mutation; 3) Performance status: Eastern Cooperative Oncology Group (ECOG) 0 and 1 (Prigerson et al., 2015); 4) over than 60 years old; 4) Hepato and renal function was stable

Exclusion criteria: brain metastasis at diagnosis, combined immunotherapy.

Treatment protocol

Patients were collected to a single-arm intervention who received pemetrexed 500 mg/m² intravenously on day 1 followed by intravenously carboplatin area under the curve (AUC) 5 on day 1; every 3 weeks. Patients were provided folic acid, vitamin B₁₂, or dexamethasone as required by the protocol.

Evaluation

Patients were evaluated the response after 2 cycles based on RECIST 1.1 (Eisenhauer et al., 2009). The duration of response and side effects based on CTCEA 3.0 (Zhang et al., 2016) were also analyzed.

Ethical consideration

Institutional review board of Vietnam National Cancer Hospital approved this prospective study under the reference number of 263/VNCH. Informed consent of patients was obtained.

3. RESULTS

Between January 2017 and June 2019, a total of 37 patients were enrolled in the study. The characteristics of the patients are shown in Table 1. The patients' mean age was 67 ± 4.1 (range: 60-74), 73% were male, 62.2% were smokers, and 78.4% had coexisting morbidities. No patient achieved complete response; the objective response rate was 35.1%; the disease control rate was 59.5%. Ten patients progressed after 2-3 first cycles (Table 2). No statistically significant differences between age groups in disease control rate (Table 3).

Table 1 Baseline characteristics of patients

Characteristics	All patients (n=37)
Mean age (year)	67 ± 4.1 (60-74)
Male, n (%)	27 (73)
Male/Female ratio	2.7/1
Smoking history, n (%)	23 (62.2)
Comorbidities, n (%)	29 (78.4)
Cardiovascular diseases, n (%)	21 (56.8)

Table 2 Response based on RECIST

Treatment response	All patients (n=37)
Mean treatment cycles	4.2
Complete response, n (%)	0 (0.0)
Objective response rate (ORR), n (%)	13 (35.1)
Disease control rate (DCR), n (%)	22 (59.5)

The principal adverse events observed in the 37 enrolled patients are shown in Figure 1 and Figure 2. Leukopenia was noted in 13 patients (35.1%), hypohemoglobin in 9 (23.3%), neutropenia in 10 (27%), and thrombocytopenia in 5 (13.5%). Non-hematologic toxicity included nausea in 37 patients (100%), vomiting in 37 (100%), allergy in 37 (100%), and liver enzyme elevations in 37 (100%). There were no treatment-related deaths.

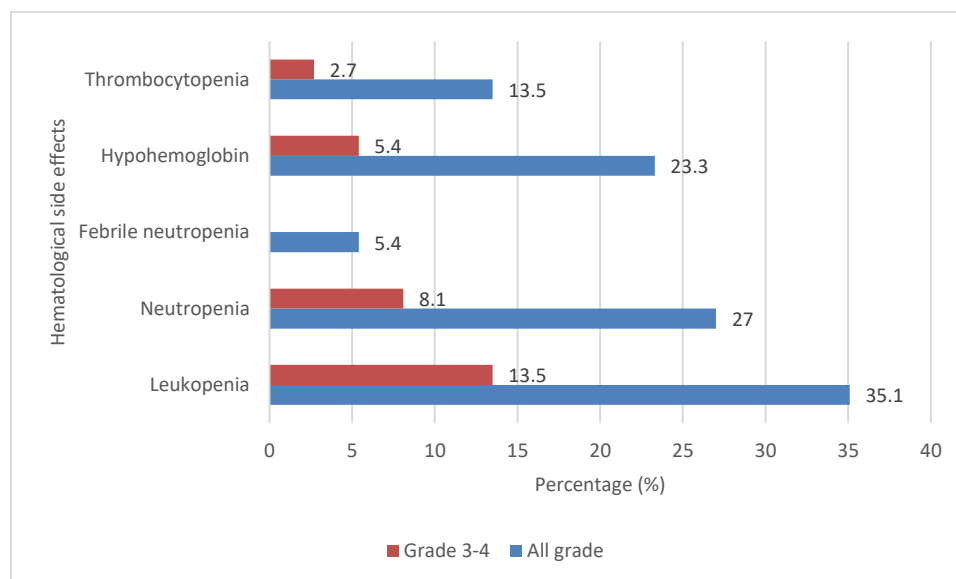
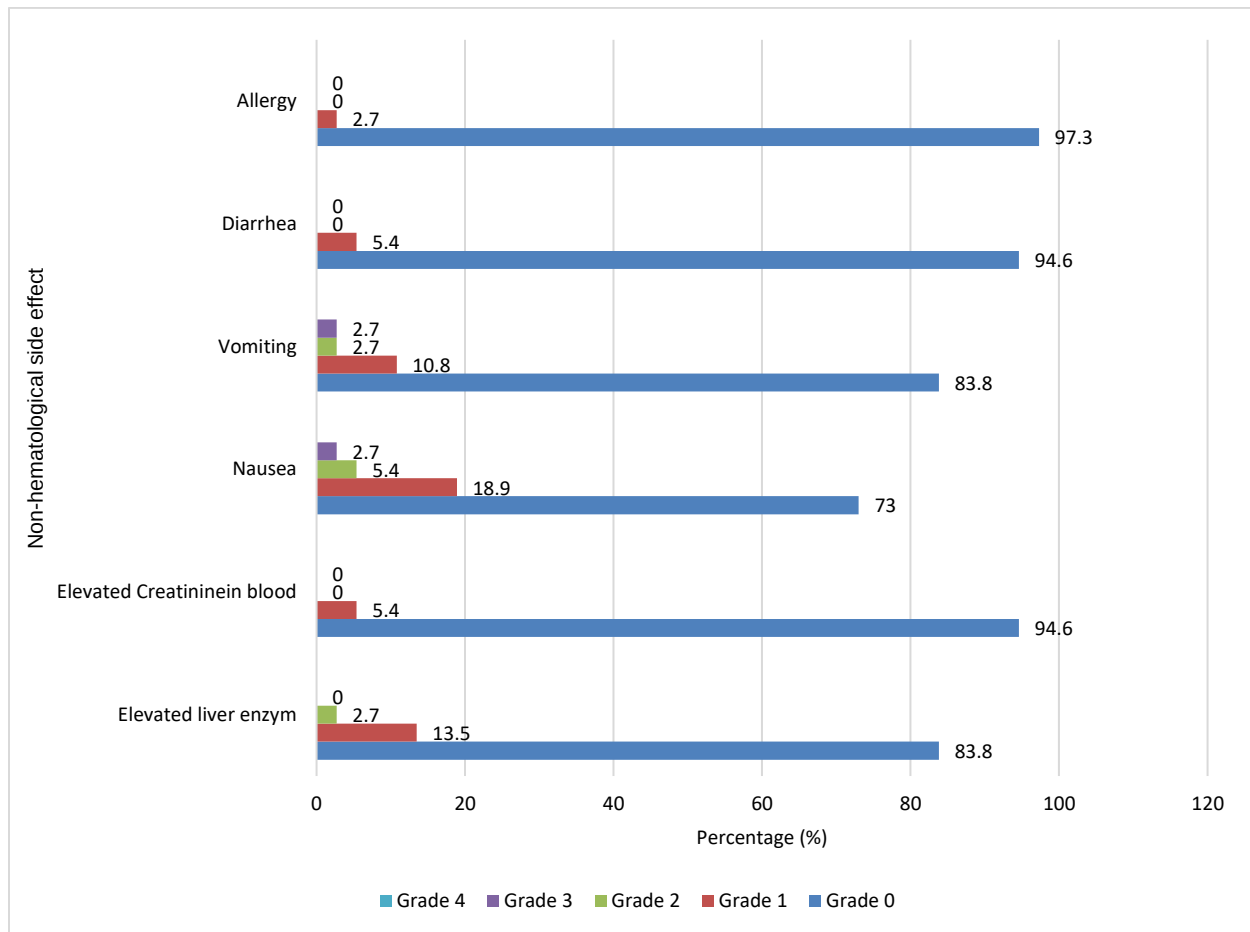


Figure 1 Hematological side effects (n=37)

Table 3 Disease control rate by age groups

Age groups	Disease control rate n (%)	Progress disease n (%)	Total n (%)
60-70 yr	17 (58.6)	12 (41.4)	29 (100)
> 70 yr	5 (62.5)	3 (37.5)	8 (100)
Total	22 (59.5)	15 (40.5)	37 (100)

**Figure 2** Non-hematological side effect

4. DISCUSSION

This prospective study evaluated the safety and efficacy of pemetrexed in combination with carboplatin as first-line therapy followed by single-agent pemetrexed maintenance therapy in elderly Vietnamese patients (≥ 60 years of age) with stage IV adenocarcinoma lung cancer. This regimen showed good efficacy and tolerability, which were comparable to those reported in previous studies. As shown in Table 1, the mean age was 67 ± 4.1 (60-74), the patient groups of 60-70 years old comprised approximately 80%. In general, both domestic and international studies showed that 30-50% of lung cancer were diagnosed in elderly patients, 70-80% of those aged 60-70 (Scagliotti et al., 2008, Gronberg et al., 2009, Ito et al., 2019). 62.2% of patients had a smoking history; no female was reported. According to a report from Pham Van Thai in 81 patients, the smoking history represented 60%, while in international studies, this rate was about 70% (Scagliotti et al., 2008, Gronberg et al., 2009, Ito et al., 2019). Approximately 73% of patients were treated at least 4 cycles; the mean number of cycles per patient was 4.2. The min was 2, and max was 6. As shown in Table 2, there were 13 patients with partial response (35.1%), 9 patients with stable disease (24.3%), 15 patients had disease progression (40.6%). Thus, the disease control rate (DCR), which included partial response and stable disease was 59.5%. There was no patient having a complete response.

This result is similar to other studies, and overall response rates were about 25-35%, disease control rates were approximately 50-70% depending on studies, without any differences in terms of age and sex (Scagliotti et al., 2008, Gronberg et al., 2009, Ito et al.,

2019). Approximately 73% of patients were treated at least 4 cycles; the mean number of cycles per patient was 4.2. Min was 2, and max was 6. Two patients had to discontinue treatment due to poor tolerance. As shown in Figure 1, leukopenia represented 35.1%, grades 3-4 were about 14%. Neutropenia comprised 27% of patients; grades 3-4 were about 8%. Febrile neutropenia was seen in 2 patients (5.4%). No patient required a blood transfusion. Most side effects related on-hematology were mild. The most common symptom reported was post-chemotherapy nausea, elevated liver enzymes percentage was low, and there was only one patient experienced rash after drug admission. No patients died due to drug toxicity. Thus, the regimen had good tolerance in elderly patients. The incidences of adverse events in our study were comparable to those results in other reports. In the study of Tamiya et al., grade 3 hematologic toxicity was observed in 56% of in Japanese patients and interstitial lung disease (ILD) presented in 2.9% (Tamiya et al., 2016). Our study enrolled patients older than 60 years of age, while Tamiya et al. included patients more than 75 years old. Renal and cardiac toxicity were evaluated in all of our patients, and were not seen during the study. The hematologic and non-hematologic adverse events in our study were similar to those reported in the IFCT 0501 study (Quoix et al., 2011), particularly hair loss, neuropathy, and grade 3-4 hematological toxicities, which suggests that combination of pemetrexed and carboplatin was safer than weekly paclitaxel + carboplatin and more reasonable for elderly patients.

5. CONCLUSION

Our series highlight that pemetrexed plus carboplatin followed by single-agent pemetrexed maintenance therapy was effective and safe in elderly Vietnamese patients (aged ≥ 60 years) with stage IV adenocarcinoma lung cancer. This regimen may be considered first-line chemotherapy in this population.

Abbreviations

ORR: overall response rate, DCR: disease control rate; AUC: area under the curve; NSCLC: non-small cell lung cancer; ECOG: Eastern Cooperative Oncology Group; PS: Performance status; ILD: interstitial lung disease.

Author's contribution

NTTH and PXD contributed equally to this article. NTTH and HQT gave a substantial contribution in acquisition, analysis, and data interpretation. Each author had a part in preparing article for drafting and revising it critically for important intellectual content. Each author gave the final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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

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