

Rechallenge pemetrexed-based chemotherapy provides an option for initially benefited patients with advanced lung adenocarcinoma

Jia-Ni Wang¹, Quan-Hui Qiao², Xing-Sheng Hu¹, Yu-Tao Liu¹, Zhi-Jie Wang¹, Jian-Chun Duan¹, Yu Feng¹, Hao-Hua Zhu¹

¹Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China;

²Department of Medical Oncology, Gongyi People's Hospital, Gongyi, Henan 451200, China.

To the Editor: Pemetrexed plus platinum (cisplatin or carboplatin) chemotherapy doublets are widely recommended as the standard first-line treatment for non-small cell lung cancer (NSCLC) with no identified genetic mutations.^[1] However, their efficiency has been confirmed with a median survival of approximately 10.2 to 13.0 months and a 5-year survival rate of 13% to 15%. Initial chemotherapy with pemetrexed has been confirmed as an effective regimen for advanced lung adenocarcinoma without specific genetic biomarker predicting the benefit of pemetrexed efficacy.^[2] Patients treated with pemetrexed-based regimens can also receive a single agent as maintenance treatment after the induction chemotherapy. In addition, pemetrexed has shown an excellent patient tolerance and safety profile in previous studies. Previous reports suggested that rechallenge with pemetrexed with or without maintenance regimens for acquired resistance of tyrosine kinase inhibitors might be a feasible option in specific subgroup of NSCLC patients. One possible explanation is that clones of pemetrexed-sensitive tumor cells may still survive following the pemetrexed rechallenge. Since the absence of standard multiline treatment in advanced NSCLC, we hypothesized a benefit from rechallenge with pemetrexed alone or combination regimens. This study focused on the efficacy and safety of rechallenge pemetrexed-based regimens in patients with locally advanced or metastatic lung adenocarcinoma, who had achieved beneficial response from first-line pemetrexed platinum chemotherapy.

Our retrospective study evaluated clinical data from 34 pemetrexed rechallenge patients with advanced lung adenocarcinoma who had a beneficial response after first-line pemetrexed platinum regimens between January 2012 and December 2017. Eligible inclusion criteria were limited to (i) confirmation of informed consent for chemotherapy, (ii) pathological diagnosis and radiograph-

ic examination confirmed local advanced or metastatic non-squamous NSCLC (IIIB–IV stage), (iii) receiving pemetrexed rechallenge as second or further-line chemotherapy (at least two cycles) before study enrollment, (iv) experiencing therapeutic benefit (stable disease [SD] or partial response [PR]) from initial first-line pemetrexed platinum regimens, and (v) completeness of full medical records. Exclusion criteria included histological squamous lung cancer, or receiving the curative effect of disease progression, or lost to follow up.

We followed patients from initial enrollment and subsequently every two to three cycles until death or withdrawal of consent or study cutoff. We conducted descriptive analyses of progression-free survival (PFS) and overall survival (OS) as effectiveness endpoints. The response data included complete response (CR), PR, SD, and progressive disease, according to Response Evaluation Criteria in Solid Tumors (Version 1.1). The objective response rate was considered as CR + PR and the disease control rate (DCR) was defined as CR + PR + SD. The toxicity evaluation was based on the National Cancer Institute-Common Toxicity Criteria for Adverse Events (Version 4.0). The study was approved by the Independent Ethics Committee of the National Cancer Center/Cancer Hospital (No. 2018101511114902). All patients signed written informed consent before each chemotherapy treatment. The Statistical Package for the Social Sciences software (Version 22.0; IBM Corp., Armonk, NY, USA) was selected to statistically analyze the data. The Kaplan-Meier method was used to estimate the median OS and PFS, followed by the log-rank test to determine statistical significance. Multivariate Cox analyses were used to assess potential independent effects of baseline characteristics. All statistical tests were

Jia-Ni Wang and Quan-Hui Qiao contributed equally to this work.

Correspondence to: Prof. Xing-Sheng Hu, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17 Panjiayuan Nanli, Chaoyang District, Beijing 100021, China
E-Mail: huxingsheng66@163.com

Copyright © 2021 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2021;134(17)

Received: 19-11-2020 Edited by: Li-Shao Guo

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.1097/CM9.0000000000001511

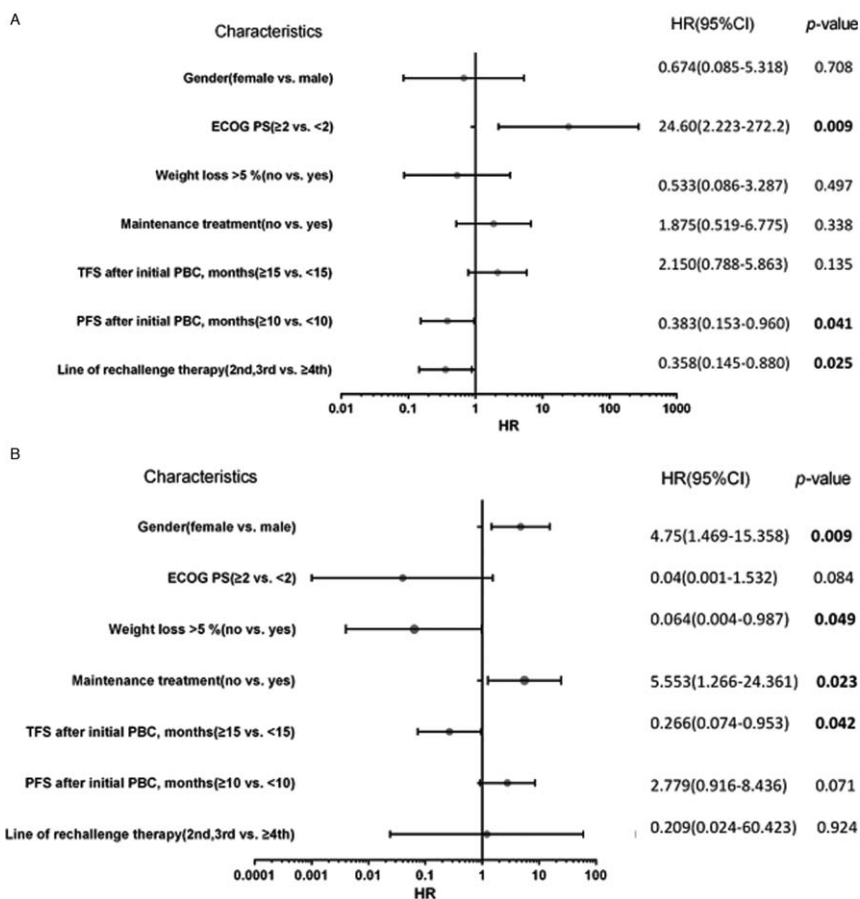


Figure 1: Multivariate Cox analyses for PFS (A) and OS (B) after pemetrexed rechallenge. CI: Confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: Hazard ratio; OS: Overall survival; PBC: Pemetrexed-based chemotherapy; PFS: Progression-free survival; TFS: Treatment-free survival.

considered statistically significant with two-sided and $P < 0.05$.

Between January 2012 and December 2017, 34 Chinese patients received pemetrexed rechallenge in our department, with 13 (38%) males and 21 (62%) females, and 23 patients were non-smokers (68%). The median age of 34 patients was 58 years, ranging from 36 to 79 years. All patients were diagnosed with adenocarcinoma. The final cutoff day for this study cohort was July 31, 2018. All patients presented with IIIb/IV stage diagnosis according to the tumor/node/metastasis Classification of Malignant Tumors (Seventh Edition). Of the enrolled patients, 56% had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1 and 44% had an ECOG PS of 2 to 3. At baseline, 19 patients (56%) had a history of comorbidity. All the above patients were taking concomitant medications (eg, anticoagulant and anti-hypertensive drugs). The epidermal growth factor receptor gene mutation (exons 19 and 21) rate was 35% ($n = 12$), in which one case (3%) had the T790M mutation, and four cases were *EML4-ALK* gene fusion positive (12%). The enrolled patients received pemetrexed and platinum doublets (cisplatin 75 mg/m², carboplatin with an area under the curve of 4–5, or nedaplatin 80 mg/m²) with a median number of five cycles in first-line therapy and 16 patients (48%) underwent pemetrexed maintenance

treatment with a median number of six cycles after initial induction chemotherapy. Ten patients (29%) received the pemetrexed rechallenge as second-line regimen and 24 patients (71%) as third or further-line treatment. Four of the median cycles were adopted (range: 2–8 cycles) in the pemetrexed rechallenge treatment. The rechallenge regimens consisted of pemetrexed carboplatin (11 cases, 32%), pemetrexed cisplatin (nine cases, 26%), pemetrexed nedaplatin (two cases, 6%), pemetrexed taxane (four cases, 12%), and pemetrexed alone (eight cases, 24%). Thirteen patients (38%) received bevacizumab with pemetrexed rechallenge therapy. Eight patients underwent pemetrexed maintenance for a median number of four cycles (range: 1–12). All patients received oral folic acid at 400 μ g per day, beginning 7 to 10 days before the first cycle and continuing until 30 days after the last treatment and a vitamin B12 injection (1 mg) every three cycles. The median PFS (PFS1) and treatment-free survival (TFS) after initial pemetrexed-based treatment were 12.7 months (range: 2.3–48.6 months) and 15.5 months (range: 0.0–71.0 months), respectively. Baseline clinical characteristics of eligible patients and treatment stratification are shown in Supplementary Table 1, <http://links.lww.com/CMJ/A551>.

After a median of 30.8 months' follow-up, the DCR rate was 82% for pemetrexed rechallenge. Median PFS for

pemetrexed rechallenged was 9.35 months (0.9–44.2 months). Median OS was 42.2 months (15.3–87.1 months). There were no significant differences in the PFS and OS between the various rechallenged regimens ($P=0.465$ and $P=0.564$, respectively). The significant prognostic factors for prolonging PFS after pemetrexed rechallenged were PFS1 (≥ 10 vs. < 10 months, hazard ratio [HR], 0.383; $P=0.041$) and line of rechallenged (second/third vs. \geq fourth, HR, 0.358; $P=0.025$) [Supplementary Figure 1, <http://links.lww.com/CM9/A551>].

The relationship between baseline characteristics and effectiveness was explored via univariate and multivariate Cox analyses, as shown in Supplementary Table 2, <http://links.lww.com/CM9/A551>. The significant ($P < 0.05$) prognostic baseline factors for prolonging PFS after pemetrexed rechallenged were previous initial PFS (≥ 10 vs. < 10 months, HR, 0.383; 95% confidence interval [CI], 0.153–0.960; $P=0.041$) and line of rechallenged therapy (second/third vs. \geq fourth, HR, 0.358; 95% CI, 0.145–0.880; $P=0.025$) [Figure 1A]. It is noteworthy that initial maintenance treatment (HR, 5.553; 95% CI, 1.266–24.361; $P=0.023$) and TFS after initial pemetrexed (≥ 15 vs. < 15 months, HR, 0.266; 95% CI, 0.074–0.953; $P=0.042$) were indicated as significant beneficial prognostic factors for OS [Figure 1B]. Overall, the pemetrexed-based rechallenged treatment was well tolerated. Combination regimens were assessed with more severe hematologic toxicities and gastrointestinal adverse effects, compared with single pemetrexed agent.

Pemetrexed with or without maintenance has demonstrated promising outcomes in previous reports for NSCLC patients. As reported by the PARAMOUNT study,^[3] selection of a pemetrexed plus cisplatin maintenance treatment is a vital factor for improved effectiveness and reduced side effects for NS-NSCLC patients. Moreover, the AVAPERL trial (MO22089)^[4] confirmed the survival benefits of Bev-containing pemetrexed maintenance treatment after first-line Bev-containing pemetrexed-cisplatin treatment in NSCLC patients. Consistent with these results, our study demonstrated that pemetrexed maintenance is a significant beneficial prognostic factor for rechallenged OS (HR, 5.553; 95% CI, 1.266–24.361; $P=0.023$). Therefore, pemetrexed rechallenged and maintenance is an effective strategy in lung adenocarcinoma patients who received first-line pemetrexed platinum induction chemotherapy. People who had benefited from pemetrexed induction chemotherapy should continue pemetrexed maintenance regimen in the rechallenged period.

As the absence of high-level evidence for a standard multiline treatment for advanced NSCLC, rechallenged with pemetrexed-based chemotherapy could be considered as a promising option for sensitive patients in view of this scenario, aiming to improve quality of life, prolong survival, and alleviate cancer-related symptoms.^[5] However, there is generally very little strong evidence of the

modest benefit of pemetrexed rechallenged regimens. This clinical strategy may be a beneficial option for multiline treatment in patients who had initial better response, which led us to write this paper to share our experience with the medical community.

In conclusion, our results revealed that an effective and well-tolerated strategy with rechallenged pemetrexed-based chemotherapy might be a palliative option for advanced lung adenocarcinoma patients who had shown beneficial response to previous pemetrexed platinum regimens. Therefore, patients with a PFS1 ≥ 10 months, TFS ≥ 15 months, ≤ 3 rd line, and rechallenged maintenance may be selected as benefit subgroups for pemetrexed rechallenged.

Acknowledgements

The author thanks all the participants of this study and gratefully acknowledged the collaboration of all investigators in the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College for their contributions.

Conflicts of interest

None.

References

1. Cortellini A, Gambale E, Cannita K, Brocco D, Parisi A, Napoleoni L, *et al*. Multicentric retrospective analysis of platinum-pemetrexed regimens as first-line therapy in non-squamous non-small cell lung cancer patients: a “snapshot” from clinical practice. *Thorac Cancer* 2018;9:241–252. doi: 10.1111/1759-7714.12570.
2. Guo LH, Zhang MF, Zhang HL, Zhou JY, Cai XH, Long Y, *et al*. Survival benefit and genetic profile of pemetrexed as initial chemotherapy in selected Chinese patients with advanced lung adenocarcinoma. *Front Oncol* 2020;10:1568. doi: 10.3389/fonc.2020.01568.
3. Langer CJ, Paz-Ares LG, Wozniak AJ, Gridelli C, de Marinis F, Pujol JL, *et al*. Safety analyses of pemetrexed-cisplatin and pemetrexed maintenance therapies in patients with advanced non-squamous NSCLC: retrospective analyses from 2 phase III studies. *Clin Lung Cancer* 2017;18:489–496. doi: 10.1016/j.clc.2017.04.003.
4. Barlesi F, Scherpereel A, Gorbunova V, Gervais R, Vikstrom A, Chouaid C, *et al*. Maintenance bevacizumab-pemetrexed after first-line cisplatin-pemetrexed-bevacizumab for advanced nonsquamous non-small-cell lung cancer: updated survival analysis of the AVAPERL (MO22089) randomized phase III trial. *Ann Oncol* 2014;25:1044–1052. doi: 10.1093/annonc/mdu098.
5. Xiao F, Zhang ZR, Wang XW, Liu DR, Guo YQ, Shi B, *et al*. Applying comprehensive histologic assessment and genetic testing to synchronous multifocal lung adenocarcinomas and further survival analysis. *Chin Med J* 2019;132:227–231. doi: 10.1097/cm9.000000000000055.

How to cite this article: Wang JN, Qiao QH, Hu XS, Liu YT, Wang ZJ, Duan JC, Feng Y, Zhu HH. Rechallenged pemetrexed-based chemotherapy provides an option for initially benefited patients with advanced lung adenocarcinoma. *Chin Med J* 2021;134:2119–2121. doi: 10.1097/CM9.0000000000001511