EDITORIAL

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What is Currently the Best for Adenocarcinoma without Driver Mutation?

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Since the discovery of driver mutations or actionable alterations in several genes such as epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*), the management paradigms of non-small cell lung cancer (NSCLC) have changed dramatically[1]. However, in global guidelines[2], platinum-based chemotherapy remains a standard of care for patients who do not harbor driver mutations. Among several regimens of platinum doublet chemotherapy, the pemetrexed/cisplatin combination confers better overall survival compared to gemcitabine/cisplatin in patients with adenocarcinoma histology[3]. In the PARAMOUNT study, continuation maintenance therapy with pemetrexed is an effective and well-tolerated treatment for patients with advanced non-squamous NSCLC with good performance status who have not progressed after 4 cycles of pemetrexed/cisplatin[4,5]. Moreover, pemetrexed became one of the most frequently administered cytotoxic chemotherapeutic agents for treating stage IV non-squamous NSCLC[6].

In the article of the last issue of *Tuberculosis and Respiratory Diseases* (TRD), Paik et al.[7] addressed that pemetrexed continuation maintenance treatment is associated with better clinical outcomes in patients with wild-type lung adenocarcinoma, compared to those associated with conventional platinum-based chemotherapy. A total of 114 patients with *EGFR*-negative adenocarcinoma who were treated with platinum doublet chemotherapy were retrospectively enrolled. They compared the survival rates between patients who received pemetrexed maintenance after induction chemotherapy and those who received at least 4 cycles of platinum doublet chemotherapy without maintenance strategy as a first-line treatment. The median progression-free survival (PFS) was significantly higher in the pemetrexed maintenance group than in the conventional group (5.8 months vs. 2.2 months, respectively; p<0.001). Multivariate analyses showed that pemetrexed maintenance chemotherapy was associated with better PFS (hazard ratio, 0.73; 95% confidence interval, 0.15–0.87).

Despite having some limitations, this study had a similar purpose and results as those of the PARAMOUNT trial, in that the study was conducted to demonstrate the benefit of the pemetrexed maintenance strategy. However, this study did not demonstrate overall survival benefits in the pemetrexed maintenance group (22.3 months vs. 16.1 months, p=0.098). This finding seemed to be the result of a retrospective, small sample-sized design. In particular, patients in the conventional chemotherapy group received 4–6 cycles of platinum doublet chemotherapy. If the number of cycles had been operatively restricted to 4, like in well-designed prospective clinical trials, differences in overall survival could have been identified. However, the strength of this study was the reflection of current real-world clinical practice in Korea.

Paik et al.[8] conducted their retrospective study because the previously published phase III clinical trials that proved the clinical benefits of the pemetrexed maintenance strategy enrolled patients regardless of the presence of driving mutations. Moreover, the efficacy of pemetrexed-containing chemotherapy according to *EGFR* mutation status is also controversial[8]. However, recent guidelines have already included pemetrexed continuation after induction chemotherapy for non-squamous type NSCLC treatment following from the results of large-scaled prospective trials[1,2,6]. Therefore, a different approach seems necessary for personalized therapy.

Several molecular biomarkers have been investigated for the predictive marker for pemetrexed, but none have been approved[2,6]. Most retrospective data have suggested that low levels of thymidylate synthase expression may be responsible

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for better sensitivity to pemetrexed, but there have also been reports with inconsistent results[6]. In addition, *ALK* rearrangements are being investigated as a potential predictive biomarker of pemetrexed efficacy[8-11]. Xu et al.[9] demonstrated that *ALK* rearrangements were indeed shown to be associated with low thymidylate synthase messenger RNA expression, and Shaw et al.[10] showed that PFS was not statistically different between patients who were *ALK*-positive and *ALK*-negative.

Paik et al.[7], in the last issue of *TRD*, showed the PFS benefits of pemetrexed continuation maintenance chemotherapy over those of conventional 4- or 6-cycle chemotherapy in patients with *EGFR* wild-type lung adenocarcinoma. This result confirmed that of previously published pivotal studies, which included non-selective patients, and we must now focus our efforts to identify predictive biomarkers of pemetrexed efficacy.

Conflicts of Interest

No potential conflicts of interest relevant to this article have been reported.

References

1. Tan DS, Yom SS, Tsao MS, Pass HI, Kelly K, Peled N, et al. The International Association for the Study of Lung Cancer consensus statement on optimizing management of *EGFR* mutation-positive non-small cell lung cancer: status in 2016. J Thorac Oncol 2016;11:946-63.
2. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman J, Chirieac LR, et al. Non-small cell lung cancer, version 5.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2017;15:504-35.
3. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543-51.
4. Paz-Ares LG, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol 2013;31:2895-902.
5. Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol 2012;13:247-55.
6. Tomasini P, Barlesi F, Mascaux C, Greillier L. Pemetrexed for advanced stage nonsquamous non-small cell lung cancer: latest evidence about its extended use and outcomes. Ther Adv Med Oncol 2016;8:198-208.
7. Paik SS, Hwang IK, Park MJ, Lee SH. Pemetrexed continuation maintenance versus conventional platinum-based doublet chemotherapy in EGFR-negative lung adenocarcinoma: retrospective analysis. Tuberc Respir Dis 2018;81:148-55.
8. Park S, Kim HJ, Choi CM, Lee DH, Kim SW, Lee JS, et al. Predictive factors for a long-term response duration in non-squamous cell lung cancer patients treated with pemetrexed. BMC Cancer 2016;16:417.
9. Xu CW, Wang G, Wang WL, Gao WB, Han CJ, Gao JS, et al. Association between EML4-ALK fusion gene and thymidylate synthase mRNA expression in non-small cell lung cancer tissues. Exp Ther Med 2015;9:2151-4.
10. Shaw AT, Varghese AM, Solomon BJ, Costa DB, Novello S, Mino-Kenudson M, et al. Pemetrexed-based chemotherapy in patients with advanced, ALK-positive non-small cell lung cancer. Ann Oncol 2013;24:59-66.
11. Lee JO, Kim TM, Lee SH, Kim DW, Kim S, Jeon YK, et al. Anaplastic lymphoma kinase translocation: a predictive biomarker of pemetrexed in patients with non-small cell lung cancer. J Thorac Oncol 2011;6:1474-80.