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Under the Magnifying Glass: Searching for The Evidence of Pemetrexed in Nonsquamous Nonsmall Cell Lung Cancer

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Platinum-based doublet chemotherapy has been the backbone of the treatment of advanced nonsmall cell lung cancer (NSCLC) before the advent of targeted therapy and immune checkpoint inhibitors. For patients without targetable mutations and ineligible or unaffordable for immunotherapy, chemotherapy remains the treatment of choice.[1,2] Histology-based selection of chemotherapy brought pemetrexed–platinum combination for nonsquamous subtype to the center stage; however, this paradigm shift was based only on a subgroup analysis of a phase-3 randomized trial with noninferiority design.[3] Subsequent trials, PRONOUNCE and point break restricted to nonsquamous histology only, could not demonstrate clear superiority of pemetrexed based combination; however, the addition of bevacizumab in one or both treatment arms might have influenced the results.[4,5]

Point beak trial compared pemetrexed–carboplatin–bevacizumab and paclitaxel–carboplatin–bevacizumab with progression-free survival (PFS), significantly better in the pemetrexed arm with similar overall survival (OS).[4] PRONOUNCE trial demonstrated that pemetrexed–carboplatin resulted in numerically improved PFS; however, it was not superior to paclitaxel carboplatin bevacizumab in terms of PFS and OS which might have been masked by the effect of bevacizumab in comparator arm.[5] Use of bevacizumab in first-line advanced NSCLC has shown PFS and OS benefit when combined with taxane and nontaxane based regimens.[6–9]

Ease of administration and better nonhematological safety profile are certainly a few advantages of pemetrexed–platinum combination over other regimens; however, cost issues remain a concern. The superiority of pemetrexed–platinum was never demonstrated in patients with advanced nonsquamous NSCLC in chemotherapy alone comparisons.

Recently, we have published the results of a randomized control trial comparing pemetrexed–carboplatin with paclitaxel (weekly)–carboplatin in advanced nonsquamous NSCLC in the June 2021 issue of *Oncology*.[10]

This was a single-center, open-labeled randomized trial. It was powered to detect superiority of pemetrexed–carboplatin over paclitaxel–carboplatin by 15% in terms of 6-month PFS rates (primary outcome) and a total of 182 events were required for the same. Patients with known driver mutation positive status were excluded; however, we included the patients in whom the mutation results were awaited. Paclitaxel was given in a weekly manner due to the inclusion of patients with the Eastern Cooperative Oncology Group Performance status (ECOG PS) 2.[11] Patients aged 18 to 65 years with ECOG PS 0 to 2 were randomized into one of the study arms, experimental arm, pemetrexed 500 mg/m^2 and carboplatin area under curve (AUC) of 5 every 3 weeks for four cycles, or control arm, paclitaxel 80 mg/m^2 on days 1, 8, and 15 with carboplatin AUC of 5 on day 1 at every 4 weeks for four cycles. Responding patients in both arms were allowed to receive maintenance pemetrexed 500 mg/m^2 every 3 weekly until disease progression or intolerance. The primary endpoint was 6-month PFS rate and secondary endpoints were objective response rates, disease control rates, overall OS, and toxicities.

This study was terminated early because of slow accrual and change in the standard of care for advanced NSCLC during the trial period; however, almost 76% of the required

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events had already occurred at the time of data analysis. Between April 2016 and January 2019, a total of 171 patients were randomized. Finally, 83 patients in the pemetrexed arm and 81 in the paclitaxel arm were included in the analysis. Baseline characteristics were well matched among both the study arms including the number of patients subsequently detected to have driver mutations. ECOG PS 2 constituted up to 28% and 26% in pemetrexed and paclitaxel arms, respectively. Brain metastases were present in 19.28% and 19.75% of patients in each treatment arm, respectively.

After a median follow-up of 17 months, 6-month PFS rates were 47.45% and 48.64% in pemetrexed and paclitaxel arms, respectively ($p = 0.88$). Median PFS was 5.67 months (95% confidence interval [CI]: 3.73–7.3) in the pemetrexed arm and 5.03 months (95% CI: 2.63–7.43) in the paclitaxel arm (hazard ratio [HR] = 1.13; 95% CI: 0.81–1.59; $p = 0.44$). Objective response rates were significantly higher in the paclitaxel group (30% vs. 15.79%; $p = 0.04$); however, clinical benefit rates (complete response + partial response + stable disease) were similar in both treatment groups (58.7% vs. 60.53%; $p = 0.81$). Median OS in the pemetrexed arm was 14.83 months (95% CI: 9.5–18.73), while 11.3 months (95% CI: 8.3–19.7) in the paclitaxel arm. The difference was not statistically significant (HR = 1.19, 95% CI: 0.8–1.78; $p = 0.37$). Four cycles of chemotherapy could be completed in 61% of patients in the pemetrexed arm and 52% in the paclitaxel arm. The most common reason for discontinuation of chemotherapy was progressive disease. Both the chemotherapy regimens were well tolerated. Toxicity profile was not much different, except for alopecia and peripheral neuropathy, as expected, which were higher in the paclitaxel arm.

Overall, this study failed to demonstrate the superiority of pemetrexed–carboplatin combination over paclitaxel (weekly)–carboplatin in advanced nonsquamous NSCLC and thus, further challenges the current practice change which was based solely on a subgroup analysis of a noninferiority study. Although this study was terminated early, at 75% maturity in terms of the number of events, there was no difference in PFS. It was highly unlikely to detect a difference even if the study would have completed its planned sample size. This study is particularly relevant in the Indian context, since a large majority of patients are still treated primarily with chemotherapy, owing to drug availability issues and cost constraints. The incorporation of patients with ECOG PS 2 (almost one-fourth of total patients) in this study correlates well with the real-world scenario, especially in developing countries such as India. Interestingly, higher objective response rates were seen with paclitaxel (weekly)–carboplatin combination, making it a suitable regimen for patients with heavy disease burden. Belani et al have also shown better objective response rates with weekly paclitaxel over standard 3 weekly paclitaxel based regimen, and similar to our study, no difference in survival outcomes.[11] Weekly paclitaxel regimen has been preferred particularly for the elderly population.[12] Major studies comparing pemetrexed–platinum combination with other regimens are summarized in ►**Table 1**. Quality of life assessment and cost-effectiveness analysis would have added to the relevance of this study.

Table 1 Landmark phase-III studies comparing pemetrexed–platinum combination and nonpemetrexed–platinum combination chemotherapies in nonsquamous NSCLC

Study	Type of study	Treatment arms	ORR	mPFS	mOS	Conclusion
Scagliotti et al[3]	Phase-III study Advanced-stage NSCLC (histology specific subgroup analysis)	Gemcitabine cisplatin vs. pemetrexed cisplatin	28.2 vs. 30.6%	4.7 vs. 5.3 months (HR = 0.9; 95% CI: 0.79–1.02)	10.4 vs. 11.8 (HR = 1.23; 95% CI: 1.00–1.51; $p = 0.05$)	Pemetrexed cisplatin is superior to gemcitabine cisplatin in a subset with nonsquamous NSCLC
Patel et al[4] POINT BREAK	Phase-III study Stage-IIIB/IV nonsquamous NSCLC	Pemetrexed carboplatin + bevacizumab vs. paclitaxel carboplatin + bevacizumab	34.1 vs. 33%	6 vs. 5.6 months (HR = 0.83; 95% CI: 0.71–0.96; $p = 0.012$)	12.6 vs. 13.4 months (HR = 1.00; 95% CI: 0.86–1.16; $p = 0.949$)	Pemetrexed carboplatin bevacizumab improved PFS in comparison to paclitaxel carboplatin bevacizumab
Zinner et al[5] PRONOUNCE trial	Phase-III study Stage-IV nonsquamous NSCLC	Pemetrexed carboplatin vs. paclitaxel carboplatin bevacizumab	23.6 vs. 27.4% ($p = 0.414$)	4.44 vs. 5.49 months (HR = 1.06; 95% CI: 0.84–1.35; $p = 0.610$)	10.5 vs. 11.7 months (HR = 1.07; 95% CI: 0.83–1.36; $p = 0.615$)	Pemetrexed carboplatin is not superior in PFS, OS or response rate

Abbreviations: CI, confidence interval; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, nonsmall cell lung cancer; ORR, objective response rate; OS, overall survival.

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Selection of a chemotherapy regimen should be based on the patient's clinical profile, disease burden, and acceptable toxicity pattern.

Conflict of Interest
None declared.

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