The PARAMOUNT trial: implications for maintenance therapy in lung cancer patients

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“...the PARAMOUNT study is a unique cornerstone trial opening the door on a further strategic approach for the treatment of nonsquamous non-small-cell lung cancer patients.”

The maintenance strategic approach has been extensively investigated in hematologic malignancies and then in solid tumors. Among thoracic cancers, small-cell lung cancer has been the setting for several clinical trials of maintenance treatment. The most recent systematic review pooled the available trials evaluating maintenance therapy in small-cell lung cancer, producing a thorough picture of efficacy related to different pharmacological strategies. Despite an overall survival (OS) advantage reported for maintenance chemotherapy and interferon treatment, the results are not clinically relevant [1,2,101]. Maintenance therapy has only recently been accepted as a treatment strategy for advanced non-small-cell lung cancer (NSCLC) with the main goal of prolonging a favorable clinical state after induction first-line platinum-based combination chemotherapy in respect of an adequate tolerability and without impairing quality of life (QoL). This renewed interest has been raised with the availability of active and tolerable new drugs. Among these, pemetrexed, a new cytotoxic agent, is a potent inhibitor of thymidylate synthase and other folate-dependent enzymes. Based on its mechanism of action, pemetrexed

was the first chemotherapeutic to be studied as a targeted agent. In fact, due to the evidence of the differential expression of thymidylate synthase between adenocarcinoma and squamous NSCLC, pemetrexed reported an increased efficacy in nonsquamous histology, and thus it is now registered only for the treatment of this histotype worldwide [3,4]. With adequate vitamin supplementation, pemetrexed was shown to be active and well tolerated, with grade ≥ 3 toxicities, when administered as a single agent, not exceeding 5–10% [5].

First, pemetrexed was tested as switch maintenance within the randomized Phase III trial JMEN. Advanced NSCLC patients of any histology not progressing after four cycles of platinum-based doublets, not including pemetrexed, were randomized to pemetrexed or placebo. Pemetrexed showed a statistically better progression-free survival (PFS) and OS than placebo, which were more significant for nonsquamous histology [6]. These results led to the design of the PARAMOUNT study, a double-blind, multicenter, Phase III, randomized, placebo-controlled trial. The primary end point was PFS, chosen because this measure is not

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affected by second-line treatments. Advanced nonsquamous NSCLC patients who did not progress to four cycles of induction cisplatin (75 mg/m²) plus pemetrexed (500 mg/m²) combination were randomized (2:1 ratio) to continuation maintenance pemetrexed (500 mg/m² on day 1 of a 21-day cycle) plus best supportive care (n = 359) or placebo plus best supportive care (n = 180) until disease progression. Vitamin supplementation was administered starting from the induction phase in both arms.

Did the PARAMOUNT study reach the primary end point? Patients receiving pemetrexed experienced a significant reduction in the risk of disease progression over the placebo group (hazard ratio [HR]: 0.62; 95% CI: 0.49–0.79; $p < 0.0001$). The median PFS, measured starting from randomization, was 4.1 months for pemetrexed and 2.8 months for placebo. The disease control rate, comprising patients with response or stable disease, was 71.8% in the pemetrexed arm and 59.6% in the placebo arm ($p = 0.009$) [7].

“Pemetrexed showed a statistically better progression-free survival and overall survival than placebo...”

Did the PARAMOUNT study also demonstrate an OS advantage for continuation of maintenance pemetrexed? The use of pemetrexed resulted in a statistically significant 22% reduction in risk of death (HR from randomization: 0.78; 95% CI: 0.64–0.96; $p = 0.0195$) with a median OS of 13.9 versus 11.0 months, respectively. The HR was the same when measured from the beginning of induction with a median OS of 16.9 versus 14.0 months, respectively [8]. All these benefits were reported in patients with both stable and responsive cancer to induction chemotherapy. Overall, continuation maintenance pemetrexed showed an impressive OS advantage of approximately 3 months in nonsquamous NSCLC patients. In a recent and small study involving 30 patients with advanced NSCLC, surveyed before and after two and four cycles of chemotherapy, at baseline, 67% considered maintenance chemotherapy worthwhile for a survival benefit of exactly 3 months [9].

How did the PARAMOUNT study influence patients' compliance? Grade 3–4 hematologic adverse events were more common in the pemetrexed group (9%) than in the placebo group

(<1%; $p < 0.0001$) as were grade 3–5 non-hematologic toxicities which were reported in 9 and 4% of patients, respectively ($p = 0.08$). In addition, QoL was evaluated through the standardized EuroQol 5-dimensional scale (EQ-5D). These data demonstrated that patients can tolerate long-term use of continuation maintenance pemetrexed without worsening the QoL [10].

What about costs? To date, only one paper has addressed this issue, which was based on the Chinese health care system, reporting that continuation maintenance with pemetrexed after induction with cisplatin/pemetrexed strategy for patients with advanced nonsquamous NSCLC is not cost-effective [11]. However, these costs should vary due to several influencing factors that may be different among different nations, thus impacting the final results.

In the last few years, the concept of maintenance chemotherapy in NSCLC patients has come under debate due to only modest survival benefits, additional toxicity and QoL concerns, as well as economic considerations. In this context, the PARAMOUNT study showed several strengths that influence current clinical practice. Cisplatin/pemetrexed induction followed by continuation maintenance pemetrexed offers a reliable chance in the treatment paradigm for advanced nonsquamous NSCLC.

However, the PARAMOUNT study suffers from some weaknesses. The median age of patients enrolled in the study was 61 years (however, this is similar to or higher than the median age of other maintenance trials). These patients are quite young considering that, with a median incidence age of 71 years, lung cancer is a disease that is closely linked with the elderly [12]. The median number of cycles of pemetrexed and placebo was four, which means that most patients do not benefit from the treatment. Despite this, the fact that the advantage of pemetrexed was statistically significant highlighted the need to select patients who may have a greater benefit from this approach. Only 4% of patients randomized in the placebo group at progression received pemetrexed. This is unfortunate for these patients because pemetrexed had initially shrunk/stabilized their disease and its administration was stopped by design not owing to failure of activity. In these patients a rechallenge with pemetrexed would be reasonable. After a treatment-free interval, pemetrexed might also provide clinical benefit, while reducing the costs and toxicities of continuous therapy. But this

kind of approach should be considered in an appropriate trial. Although the fact that pemetrexed is an expensive maintenance drug must be taken into account. This may be more or less relevant depending on the health care system of each nation.

Could patients with a performance status of 2, or who are not suitable for cisplatin treatment and for whom carboplatin would be more appropriate, benefit from continuation maintenance pemetrexed? A Phase III randomized trial did not provide any advantage for carboplatin/pemetrexed versus carboplatin/gemcitabine as first-line therapy of any-histology NSCLC but also when only nonsquamous histology was evaluated [13]. However, if cisplatin is contraindicated, considering that carboplatin is slightly inferior to cisplatin [14] and other maintenance trials used carboplatin-based combinations as induction therapy [15], carboplatin/pemetrexed could be a valid alternative in the induction phase.

“This renewed interest [in maintenance treatment of non-small-cell lung cancer] has been raised with the availability of active and tolerable new drugs.”

Some other flaws can be mentioned, which are common to all the maintenance approach trials. First, the relevance of PFS as the primary end point has been questioned, owing to its variable definition across studies and also because it is a measure which depends on the timing of disease restaging. In the PARAMOUNT study this aspect is outweighed by the benefit in survival.

Another fundamental problem is the definition of stable disease for the inclusion of a patient in the maintenance treatment. In fact, these patients can have up to a 20% increase in the size of tumors, and therefore, in reality could have an early disease progression [16]. Moreover, the lesion measurements are operator-dependent and the difference of a few millimeters could change the type of response and consequently the type of therapeutic approach. This question

is relevant particularly for the switch maintenance approach which is the issue of early versus late introduction of second-line proven agents in a slowly progressing population of patients. Thus, the failure to guarantee that patients on the control arm received the experimental agent is a serious design flaw.

In the induction phase of all maintenance trials, four cycles of platinum-based chemotherapy were administered. This choice was based on the fact that most benefit from initial chemotherapy occurred during the first four courses; however, considering that a further tumor shrinkage can be also observed between the fourth and the sixth cycle of chemotherapy, the main guidelines recommend four to six cycles of treatment [17,18]. To date, there is no evidence that administering six cycles of induction platinum-based chemotherapy improves subsequent maintenance therapy. It is possible that the patients able to receive more platinum-based doublets are the same as those who could receive maintenance therapy.

All of these open questions should be addressed in specific well-designed and well-sized randomized Phase III trials.

Two further randomized Phase III studies evaluated continuation maintenance pemetrexed with only preliminary results available [15,19]. In both studies, maintenance pemetrexed was administered in combination with bevacizumab but, contrary to the PARAMOUNT study, versus an active control arm using bevacizumab. Thus, at the moment, no conclusions can be drawn.

Overall, the PARAMOUNT study is a unique cornerstone trial opening the door on a further strategic approach for the treatment of nonsquamous NSCLC patients.

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