VIEWPOINT

Is There Room for Second-Line Treatment of Pleural Malignant Mesothelioma?

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Malignant pleural mesothelioma (MPM) is characterized by a bad prognosis and modest activity of systemic treatment. Currently, there is no clear agreement on the clinical role of second-line chemotherapy in patients with MPM; nevertheless, early case study reports including some pretreated patients had provided evidence that additional responses are possible with the use of further chemotherapy[1] after the failure of first-line treatment.

Unfortunately, the evidence supporting the efficacy of second-line treatment in this setting is globally weak. A randomized phase 3 trial, enrolling 243 patients, compared pemetrexed plus best supportive care vs best supportive care alone in patients previously treated with a first-line regimen not including pemetrexed. When this study was published, however, the use of pemetrexed in combination with cisplatin had been already accepted as standard first-line treatment. The study showed a statistically significant increase in objective response rate, disease control rate, and time to progression for pemetrexed, but without significant benefit in overall survival.[2] Whether the benefit in other end points, in the absence of difference in survival, could be considered sufficient to recommend second-line pemetrexed for clinical practice is debatable. In any case, the trial recruited patients who were pemetrexed naive, which greatly reduces the current applicability of these results, with pemetrexed being part of first-line treatment in the majority of patients now. Can we consider the external validity of these results useful for clinical practice? Probably not.

Even when we consider the shift from pemetrexed to other chemotherapy drugs, like vinorelbine, their use as second-line treatment is based on small, nonrandomized series. Following previous experience in the first-line setting,[3] weekly vinorelbine was tested within a single-center phase 2 open-label study in 63 patients with previous exposure to chemotherapy. Like all the single-arm trials, the results obtained in this series of patients are at strong risk of being conditioned by selection bias: median interval between the end of the first-line chemotherapy and the start of the weekly second-line vinorelbine was 6 months, most patients had a good performance status, all were classified as low risk according to the European Organization for Research and Treatment of Cancer prognostic score, and median age of this highly selected population was 59 years. A total of 10 partial responses (16%) were observed, and a further 43 patients (68%) had stable disease defined as no evidence of progression for 6 months. Median overall survival was 9.6 months. However, can we trust in the reproducibility of these results in unselected patients, with a shorter treatment-free interval, older age, and worse performance status? Probably not.

Similarly, rechallenge with platinum-pemetrexed chemotherapy is sometimes considered in patients who have obtained a long progression-free interval, but the evidence supporting this strategy is again weak. This strategy is probably more supported by the analogy with the rechallenge in other solid tumors where platinum-based therapy is used, rather than by data specifically produced in patients with MPM. In this specific setting, the rechallenge has been explored by Ceresoli et al,[4] describing the outcome of patients who had obtained prolonged progression-free survival (PFS) (greater than 3 months) with the previous first-line treatment. Thirty-one patients were included in the study, but there was heterogeneity in the treatment adopted: 15 patients had a rechallenge with single-agent pemetrexed alone, while 16 had a real rechallenge with both drugs. One patient experienced a complete response, whereas a partial response was achieved in 5 patients, producing a modest overall objective response rate of 19%, and an overall disease control rate of 48%. Is this evidence sufficient to consider rechallenge with pemetrexed-based chemotherapy as a second-line treatment option in patients with MPM? Probably not.

Considering this absence of robust evidence supporting the use of second-line treatment in clinical practice, what is the position of existing guidelines? National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines seem to support the use of second-line treatment. In fact, although specifying that limited data are available to guide the choice, NCCN guidelines state that "second-line chemotherapy options include pemetrexed (if not administered as first-line therapy), vinorelbine, or gemcitabine, and data suggest that rechallenging with pemetrexed is effective if patients had a good response to first-line pemetrexed."[5] Moving from the United States to Europe, current guidelines of the European Society of Medical Oncology, published in 2015, state that, given the absence of standard second-line or further-line therapy, it is recommended that patients who are in good clinical condition at disease progression after first-line treatment should be enrolled into clinical trials.[6] There is no explicit recommendation for patients outside the opportunity of clinical trials, although the statement that "single agent vinorelbine has shown useful activity in phase II trials" implies that, although not standard, second-line treatment can be considered in clinical practice. Italian experts participating in the Third Italian Consensus Conference for MPM stated that, in patients progressing after a first-line pemetrexed-based regimen, there is no standard second-line therapy, and patients should be encouraged to participate in clini-

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cal trials.[7] However, the next recommendation in the same document emphasizes that, outside clinical trials, single-agent chemotherapy could be a possible option for palliation, although the panel was not unanimous about this recommendation.

What shall we do in clinical practice? Of course, patients should be adequately informed to contribute to the decision. Sharing the information with them openly and explaining that even best supportive care, without further active treatment, would be an acceptable treatment option should be a must-do.

Patients should be encouraged to participate in trials, but clinical trials should be better designed. There is a huge variety of ongoing trials at the moment. The oncologic community should be firm and clear on what we want from an interventional trial conducted in the second-line setting. First, trials should be randomized. We acknowledge that observational or retrospective studies are helpful to produce hypothesis-generating evidence, but in this setting, like in the majority of clinical settings, they will never change practice. Furthermore, given the heterogeneity in prognosis and the difficulty of interpreting a single-arm experience without a comparator arm, we believe that a control arm is needed to correctly interpret the outcome of patients treated with the experimental drug. For instance, if we consider the randomized phase 2 trial testing the addition of bevacizumab to cisplatin and gemcitabine as first-line treatment of patients with MPM, the experimental treatment produced a median progression-free survival of 6.9 months and a median overall survival of 15.6 months.[8] These results, if produced within a single-arm trial, would have been probably judged as promising. Unfortunately, the outcome of patients assigned to the control arm of the same trial was superimposable, without any significant difference between the groups. Probably, the same would happen in the second-line setting, considering that the heterogeneity in prognosis and the risk of selection bias can be even higher than in patients eligible for first-line treatment. Given the absence of treatments of proven efficacy, placebo is acceptable for patients assigned to the control arm, although we understand that the presence of an arm without active treatment can reduce the acceptability of the trial.

Patients enrolled in the trials should be well balanced according to existing prognostic scores. Particularly, patients should be stratified based on the duration of disease control obtained with first-line chemotherapy. This is a prognostic factor, but could be also an intriguing predictive marker for second-line chemotherapy, representing what is routinely called "platinum sensitivity."

Patients with MPM who had responded to platinum-based chemotherapy and have a PFS greater than 6 months might have a more responsive cancer, while patients with very short PFS have rather aggressive mesothelioma, unlikely responsive to further treatment. For instance, there are trials exploring immunotherapy in this setting, either in set up or recruiting at the moment, such as the Confirm trial (pembrolizumab, clinicaltrials.gov identifier NCT02083484) and the BIB296 (tremelimumab and durvalumab, clinicaltrials.gov identifier NCT02588131). As far as we know, neither of them has a PFS stratification like the one we have proposed. It should be considered that an imbalance in accrual between the treatment arms will have a potentially negative impact on the final trial results.

In conclusion, we think that, at the moment, the real benefit associated with the administration of further active treatment to patients with MPM whose first-line treatment has failed is uncertain at best. Of course, this should not imply a nihilistic vision. On the contrary, clinical research is vital to obtain progress in this setting, and well-designed clinical trials are strongly needed.

ARTICLE INFORMATION

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