CONTROVERSIES IN THORACIC ONCOLOGY

Nivolumab Plus Ipilimumab Should Be the Standard of Care for First-Line Unresectable Epithelioid Mesothelioma

Paul Baas, MD, PhD*

The Stone Age

For many years, the standard treatment for malignant pleural mesothelioma (MPM) has been based on chemotherapy agents. In the late twentieth century, cytotoxic drugs were tested mostly in single-arm phase 2 studies and only very modest response rates of 0% to 20% were obtained. The studies were small, and overall survival (OS) data were not impressive. The combination of a platinum compound with an antifolate agent proved to be superior than plat in alone in 2003. But still, the median OS (mOS) was 13 months and the 2-year survival rate was 20%. Inclusion in studies with strict patient selection led to reports with a 15 to 16 months of mOS for the standard of care in the next decade. In general, one can conclude that chemotherapy will not lead to durable responses in median progression-free survival or OS. One of the areas of interest was inhibition of angiogenesis based on the correlation with micro vessel density in MPM. Many approaches with antiangiogenesis drugs alone or in combination with chemotherapy unfortunately failed. Only the addition of bevacizumab to cisplatin/pemetrexed led to an improved survival of 2.8 months, but this was not found for cisplatin plus gemcitabine. Therefore, this combination is not accepted as standard in most countries because of this modest improvement in mOS. It was clear in the past decade that a new approach was needed to free ourselves from this “stone age.”

A New Beginning

In patients with MPM, modulation of the immune system has been the focus of some researchers since the 1990s. One of the first, interesting observations, was the incidental success of intrapleural instillation of bacillus Calmette-Guérin in the 1980s. Pathologic analysis of tumor samples revealed an influx of a variety of immune cells. Immune-modulating drugs available at that time often had serious systemic side effects and precluded further research.

The development of checkpoint inhibitors and the successful outcomes in melanoma and lung cancer urged clinical researchers to test these agents in MPM. Single-agent immuno-oncology (IO) studies revealed that impressive and long-lasting responses could be achieved in some patients, but other studies proved to be negative when tested as a single agent (DETERMINE study with anti–CTLA4). The proof of efficacy of a checkpoint inhibitor (nivolumab) over Besat Supportive Care was given recently by Dr. Dean Fennell in a large, randomized phase 3 study. The data, presented at the World Lung Cancer Conference in 2021, revealed a benefit in overall response rate and OS (9.2 versus 6.6 mo) in second- or third-line treatment of patients with MPM in the United Kingdom. From all these single-arm studies, it can be concluded that there is a subgroup of patients who is sensitive for IO therapies.

The Leap Forward

To improve the outcome of IO in MPM, it was decided to follow the successful developments in melanoma and lung cancer. The combinations of checkpoint inhibitors, tested in single phase 2 settings, revealed promising results. This led to a randomized phase 3 international study that was published in January 2021. In the CheckMate-743 (CM-743) study, patients with all histologic subtypes were randomized between the standard of care (pemetrexed plus cisplatin or carboplatin) for six cycles or the combination of ipilimumab (CTLA4 inhibitor) plus nivolumab (anti–programmed cell death protein-1) for a maximum of 2 years.

The study was positive for the primary end point OS with a gain of 4 months as is illustrated in Figure 1.
There was no difference in overall response rate between the two arms, but when a response was obtained, the duration of response was significantly longer (18.1 versus 14.1 mo, hazard ratio [HR] = 0.74, p = 0.0002).

A striking difference in survival was observed for the nonepithelioid type of MPM. When usually a median OS of 7 to 9 months is expected, the IO combination had a survival gain of a factor of 2 (8.8 versus 16.1 mo, HR = 0.46). Nevertheless, the benefit for the epithelioid type was less expressed, with a benefit of only 2.2 months (18.7 versus 16.5 mo, HR = 0.86). Because of the statistical set-up, it was not allowed to have a formal statistical analysis of the subgroups.

The Crossing Issue of Survival Curves

One of the issues to address in the use of IO in this setting is that IO does not work for all patients. In Figure 2, it is clear that there is an initial benefit for the chemotherapy arm, albeit small. This observation is also found in other tumor types and represents the group of

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (n = 303)</th>
<th>Chemo (n = 302)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>18.1 (16.8–21.4)</td>
<td>14.1 (12.4–16.2)</td>
</tr>
<tr>
<td>HR (96.6% CI)</td>
<td>0.74 (0.60–0.91)</td>
<td>0.0020</td>
</tr>
</tbody>
</table>

Figure 1. OS curves of the two arms of the CM-743 study. The red line indicates the IPI/NIVO arm; the gray line, the platin/pemetrexed arm; in the blue circle, the crossing of the two curves. Chemo, chemotherapy; CI, confidence interval; CM-743, CheckMate-743; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival.

Figure 2. The OS curves of the epithelioid type and nonepithelioid type are presented for the respective treatments. Indicators are presented for the 12- and 24-month survival percentages. Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival.
patients who have an impaired immune system. One of the most striking observations is that the tail of the survival curves is different when IO therapies are used. Never before we have found significant numbers of patients who were cured with this kind of treatment. Although these data are yet available for the CM-743 study, we are eagerly awaiting to find the 5-year survival curve.

Certain subgroups of tumors are less sensitive for IO treatment or the immune system of patients is not functioning properly. Besides the identification of these patients, one could address this problem by using an approach such as the 9LA study wherein two courses of chemotherapy are combined with the IO combination\(^7\) or by combining a single IO agent with chemotherapy. Studies of this kind are currently underway (DREAM3R study).\(^8\)

**Toxicity: A Limiting Factor?**

Toxicity profiles between chemotherapy and IO therapies are quite different. In general, the overall number of patients experiencing a grade 3 to 4 adverse event is comparable, but the number of serious grade 3 to 4 toxicities or those leading to discontinuation is two and a half-fold higher in the IO combination arm of the CM-743 study. Looking at this in detail, one must take into account the fact that the IO therapy could be given up to 2 years instead of the 12 to 18 weeks with chemotherapy. Chemotherapy simply cannot be given for extended periods and will ultimately lead to unacceptable toxicity. Most of the chemotherapy-induced toxicity is irreversible, such as neurologic, renal, and cardiac dysfunction. In the CM-743 study, the chances of experiencing any (adverse) events were higher in the IO group. Nevertheless, most toxicity is manageable and reversible when patients are treated in centers that are experienced with IO combinations. Further analyses of the CM-743 data revealed that patients treated with the IO combination had no deterioration in quality of life during the treatment but chemotherapy-treated patients did (Fig. 3).\(^9\)

**Are There Subgroups That Should Be Excluded From IO Therapies?**

In the survival analysis of the CM-743 study, a forest plot analysis was constructed in which only two had an indifferent HR. Those with age of more than or equal to 75 years and a programmed death-ligand 1 score of less than 1% had HR of 1. All other subgroups tested (gender, Eastern Cooperative Oncology Group, and subtype) scored better for the IO combination. On the basis of these data and other studies, there is no specific subgroup identified that will reveal a detrimental effect when IO combination is recommended. One of the areas of research which currently has to be addressed is the correlation of IO sensitivity with the pathologic...
subgroups in the epithelioid type of MPM. Although not often reported by pathologists, there are five subtypes that have differences in tumor growth and presentation (subtypes: papillary; tubulopapillary; pleiomorphic; solid, round cell; solid and desmoplastic).10

Conclusions
Both patients and physicians are excited that we finally have a useful addition in the first-line treatment of MPM. The survival benefit of IO therapy is beyond doubt, especially for the nonepithelioid types, and toxicity is manageable. For the epithelioid type, it is clear that further research has to be performed to identify those who might need another, additional, treatment. We do not need to throw away our “old stones” immediately but may add chemotherapy to support the IO treatment.

The great advantage for physicians is that we now can discuss with the patient which treatment is most preferred allowing us to delay the use of chemotherapy with its undesired toxicity. So, there can be no doubt that all patients should first be offered IO therapy for best chance of survival and maintaining quality of life.

The combination of ipilimumab and nivolumab is already approved in the United States by the Food and Drug Administration and in Europe by the European Medicines Agency.

IO therapy is now here to stay.

CRediT Authorship Contribution
Paul Baas: Design, Execution.

References