Immune checkpoint inhibitors in mesothelioma

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IV

PART IV

10

Chapter 10

Discussion

Discussion and future perspective

After almost 20 years of chemotherapy as standard of care chemotherapy for malignant pleural mesothelioma (MPM), the treatment changed to immune checkpoint inhibitors (ICI) administration during the course of this thesis. After the INITIATE phase II trial, described in this thesis (chapter 3), the randomized phase 3 trial of nivolumab plus ipilimumab versus platinum plus pemetrexed chemotherapy demonstrated an impressive overall survival benefit for ICI treatment (mOS 18.1 months vs 14.1 months; HR 0.74; p=0.0020) (1). Now, nivolumab plus ipilimumab is considered the standard of care for treatment-naïve unresectable MPM. Thereby, the INITIATE paper in this thesis contributed to a better treatment for mesothelioma.

Although CheckMate 743 showed a survival benefit, unfortunately some people performed worse with ICI treatment. A similar PFS between the two treatment arms exists (median 6.8 months versus 7.2 months; HR 1.00 (95% CI 0.82–1.21), but a clear inferior PFS for ICI treatment in the first 6 months is seen, with marked crossing of PFS curves. Less clear, but this crossing is also seen in OS curves. A proportion of patients have progressive disease when treated with ICIs compared to chemotherapy. Finally, the benefit of ICI treatment is mainly seen in non-epithelioid subtype (1).

Patients failing the ICI therapy may have primary resistant tumors for ICI treatment, have rapidly progressive disease which requires a fast(er) working agent (added) or have hyperprogression. Therefore it is of utmost importance to select patients that will benefit. This is actually an unmet need in all cancers treated with ICIs, so far a useful predictive biomarker has not been established.

A prognostic biomarker is a clinical or biological characteristic that provides information about the patients overall cancer outcome, regardless of therapy. On the other hand, a predictive biomarker provides information on the probability of response to a particular therapy. Usually this biomarker is measured before start of treatment, but sometimes a biomarker can be measured early during treatment. A predictive biomarker can be a target for therapy, for example as seen in EGFR mutated lung cancer.

In reality, all biomarkers will have some degree of prognostic value, and some degree of predictive value. For example PD-L1 expression on tumor cells in lung cancer, but also in MPM, does have prognostic value; it has been associated with poor prognosis (2-7). PD-L1 suppresses T cell activation and as a result, the tumor is able to escape anti-tumor immune response. But PD-L1 expression is also predictive of response to PD-1 checkpoint inhibitors in NSCLC. Tumors with higher PD-L1 expression usually respond better to IO treatment (8-10).

In MPM a few phase II studies have been performed on evaluating predictive effect of PD-L1 expression on antiPD-(L)1 treatment, with conflicting results(11-14). In the larger phase III trial evaluating nivolumab, PD-L1 expression was not predictive of response for either overall survival or progression free survival (15).

Our INITIATE trial with nivolumab plus ipilimumab showed that PD-L1 expression was significantly associated with clinical benefit (i.e. partial response or stable disease for > 6 months, p = 0.037). But in the larger phase III Checkmate743 trial PD-L1 expression did not show a correlation with outcome (1).

All studies used different antibodies (22C3, SP-263, 28-8, E1L3N) for the PD-L1 staining; used different cut-off points (> 1%, > 5%, > 50%) and had different timing of examining the PD-L1 expression (archival, before chemotherapy, pre-treatment). Even when taking this into account, PD-L1 expression alone can probably not be used as a predictive biomarker.

Dissecting complete mechanisms by which tumor-infiltrating immune cells participate in the development of a systemic antitumor response are still under exploration. The relationship between the tumor, tumor-infiltrating immune cells, the host, and the antitumor effects of ICI is complicated. Comprehensive studies with large sample size are needed. However, so far, this type of research is still lacking, in many tumor types but especially in mesothelioma. Over the last years lots of interesting research has been published on this subject, gaining more and more knowledge.

Mesothelioma research is difficult for a few reasons. Mesothelioma is relatively rare, only about 500 patients in the Netherlands are diagnosed every year. MPM is a heterogenous type of cancer, epithelioid and non-epithelioid subtypes have their own different clinical behavior and response to therapy; making the possible groups for research even smaller. And the larger epithelioid subgroup itself is very heterogeneous. Furthermore patients with MPM are often diagnosed at late stage, which affects the physical condition of the patients negatively; this reduces the number of patients eligible for clinical trials even further.

Another difficulty in clinical trials in MPM is response measurements. Modified RECIST criteria for mesothelioma are used in clinical trials (16, 17), but this is not completely representative for the whole pleural enlargement. Uni-dimensional measurements of tumor thickness perpendicular to the chest wall are measured in 2 sites at 3 different levels on CT scans. Even with a small increase in one diameter, volume increases much more. In the future artificial intelligence techniques for measuring volume of pleural rim could be used. Since MPM is usually slow-growing, radiological stable disease does not always tell something about treatment effect.

Earlier phase II clinical trials, including the INITIATE trial, used disease control (complete response, partial response and stable disease) as primary endpoint. Since it includes stable disease, apparently it does not necessarily measures treatment effect. Different trials showed promising effects in phase II measured by DCR, which did not translate into survival benefit in phase III clinical trials (18-24). Primary endpoint of phase II trials could better be ORR of PFS.

MPM typically has a low tumor mutational burden (TMB), leading to a low neo-antigen burden(25). Based on that, one would not expect a favorable outcome with ICI treatment, since most tumor types having low TMB do not have clinical benefit (26). A possible explanation why responses to ICI treatment are observed may be related to chromosomal rearrangements which serve as neo-antigens. It is hypothesized by Mansfield et al. that the number of alterations actually targeted by T cells, may have a stronger association with ICI response than does TMB. This is based on a mechanism called chromothripsis, a mutational process by which chromosomal rearrangements occur within one or between chromosomes (27). In chapter 9 of this thesis, part of the research in collaboration with Mansfield is published, to determine whether these chromosomal rearrangements are associated with survival benefit in patients from nivolumab and nivolumab plus ipilimumab trial. Junction burden alone was not predictive of overall survival but a significant interaction was seen between junction burden and multiple antigen processing and presentation gene sets. A specific gene set in combination with junction burden was predictive of survival.

Several studies identified a link between T cell infiltration and outcome in patients with mesothelioma, however it is not established that this is a predictor of response to immunotherapy (28-31). Our trial found a correlation of higher numbers of CD4+, CD8+ and FoxP3+ cells in responding patients to therapy. But this was only in a small group of patients.

Gene-expression profiling signatures that identify tumors with a T cell inflamed phenotype show some promising results predicting response to ICI treatment (32). Based on immune gene expression profiles, some trials classified MPMs into different subtypes, different from the histological subtypes. For example, in 3 groups based on immune cell gene expression, forty percent of cases were classified in group 1 (immune desert), the rest were classified in group 2 (higher B-cell and antigen presentation-related gene expression) and group 3 (higher T-cell related gene expression), suggesting that a significant number of MPMs are inflamed tumors (33). In a cohort of 516 MPM patients, groups were analyzed based on presence of T-helper 2 and cytotoxic T-cells. The group with low T-helper 2 cells and high cytotoxic T-cell levels (8.5% of the total group) had the best survival, and on a transcriptional level, upregulation of immune pathways was observed in this group (34).

Another study showed two tumor types based on tumor microenvironment of MPM, the good molecular signature (only 5 patients) had a good radiological response to ICI treatment (35). This suggests an immune based signature in some of the mesotheliomas, with possible clinical relevance. But it needs to be validated in larger cohorts.

On-treatment biopsies and PBMCs samples in Nivomes and INITIATE trial were performed at 6 weeks of treatment. At the time of writing the Methods sections for both trials, less was known about tumor microenvironment of mesothelioma and effect of ICI treatment. With current knowledge we would have taken blood samples also earlier on treatment and at time of progression or after a certain time of response. A peak in proliferating cells in other tumor types is seen at 3 weeks of antiPD-1 therapy. It would be interesting to see whether the changes seen in peripheral blood are long lasting or not.

A different timing of the biopsies could have influenced results. In some patients pseudoprogression or hyperprogression to ICI treatment is observed (in 9% in Nivomes trial and in 6% in INITIATE trial). Also it would be informative to take biopsies at progression and beyond, to examine the early changes and duration of these in time. Many patients allowed us to take extra biopsies only for research purposes, but taking even more invasive biopsies would be difficult.

In patients with advanced non-small cell lung cancer (NSCLC), the addition of chemotherapy to immunotherapy in the first-line setting has avoided the crossover of survival curves, thereby reducing the risk of (hyper)progressive disease (36). And evidence exists that chemotherapy can deplete circulating and MPM-infiltrating MDSCs to lift their protumorigenic effect (37, 38). In line with that, combination of chemotherapy plus ICI for MPM showed promising data in two single arm phase 2 trials. In DREAM trial, treatment with durvalumab plus platinum plus pemetrexed in first line demonstrated a PFS at 6 months of 57% and mOS of 18.4 months (39). In PrE0505 trial, presented at ASCO 2020, using the same regimen showed a PFS at 6 months of 69% and mOS of 20.4 months (40). Phase 3 trials combining chemotherapy with ICIs are underway, DREAM3R with the same regimen as DREAM trial (NCT04334759), IND227 trial combining pembrolizumab, platinum and pemetrexed (NCT02784171), and BEAT-Meso trial, randomizing between carboplatin-pemetrexed-bevacizumab and carboplatin-pemetrexed-bevacizumab-atezolizumab (NCT03762018).

Anti-angiogenic agents have been used in different clinical trials in MPM, since angiogenesis plays an important role in MPM. But most trials showed disappointing results in MPM, either being not effective or too toxic. Newer strategies focus on the potential synergistic effects of antiangionesis and immunotherapy. Anti-VEGF has been shown to modulate T cell proliferation, migration and activation (41) and the combination

is now evaluated in clinical trials. The phase III BEAT-meso trial of the ETOP is assessing the combined treatment with atezolizumab, bevacizumab (anti-VEGF antibody) and chemotherapy (NCT03762018). The comparator is not the standard treatment but bevacizumab plus chemotherapy. The combination nivolumab and ramucirumab (anti-VEGFR2 antibody) (NCT03502746) and the combination pembrolizumab and lenvatinib (multikinase inhibitor against VEGF) (NCT04287829) are under investigation in two phase II trials in patients with relapsed mesothelioma.

Other innovative ways to manipulate the immune system are being explored. Genetically engineered T cells called chimeric antigen receptor T (CAR-T) cells have been designed to target mesothelin, an antigen seen in mesothelioma cells. In the first phase I clinical trial these CAR-T cells were delivered intrapleurally in combination with an immune checkpoint inhibitor. A disease control of 60% in 19 patients was seen (42).

Anti-tumor vaccines are in development and are under early phase investigation in combination with checkpoint inhibition (NCT04040231).

Of course many more clinical trials have or are being performed with different kinds of agents, including anti-angiogenic agents, anti-mesothelin, arginine deprivation, cell cycle inhibitors, CAR-T cell, dendritic cell therapy; but it is beyond the scope of this thesis.

In conclusion, malignant pleural mesothelioma is a heterogeneous disease that is almost always lethal. Over the last years progress was made in unraveling the tumor and its microenvironment, in respect to tumor cells, immune cells and its inhibitory receptors, cytokines, genetics and sequencing data. In the (near) future, further steps will be made to improve treatment, probable in a personalized way.

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