Immune checkpoint inhibitors in mesothelioma

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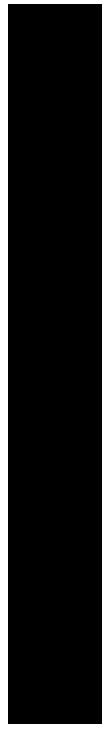

PART I

Mesothelioma treatment

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Chapter 2

Optimal therapy of advanced stage mesothelioma

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Introduction

Malignant pleural mesothelioma (MPM) is a cancer of the pleural cavity. It has a well-documented causal relation with (occupational) asbestos exposure (1). The latency time between exposure and presentation of the malignancy varies from less than 20 to more than 50 years. It is estimated that approximately 43,000 people will die from this disease worldwide (2). The survival of patients with MPM is poor, with a 5-year survival rate in Europe of 7.2% according to the age-standardized relative survival data from the Eurocare-5 study (3).

The Eurocare-5 data also point out that the prognosis of MPM has only shown a slight improvement over the last decades. The poor survival data of the general popu- lation contrast with the median overall survival estimates from study populations, which range from 7 to 8 months to 16 months for untreated cases (4, 5). This emphasizes the selection of patients within the studies, and has implications for patient selection for chemotherapeutic treatment in general practice. One should beware for a certain therapeutic nihilism based on these data.

The low incidence of mesothelioma has impaired the realization of larger randomized studies for many years. Mainly, based on patient series and retrospective analysis of single center data, surgery is a possible therapy in MPM, being embedded in a multimodality protocol with chemotherapy and radiotherapy. Surgery by itself does not seem to be of benefit for the patient (6). There is an ongoing discussion whether extrapleural pneumonectomy or extended pleurectomy/decortication is the procedure of choice.

Radiation therapy has been implemented in multimodality studies. The routine use of hemithorax irradiation as part of a trimodality regime with neoadjuvant chemotherapy and extrapleural pneumonectomy was recently debated by a randomized trial, showing that hemithorax irradiation (median dose 55.9 Gy) did not significantly improve the median locoregional relapse-free survival from surgery (7). The use of radiotherapy is primarily confined to palliation of local pain or tumor invasion. Pain relief was achieved in more than 50% of the patients in a 189-patients study (8).

Optimization of the therapy in the patient with advanced MPM

Chemotherapy in first line

It took more than 10 years before further progress was made in the first line setting after the initial studies showed that cisplatin combined with antifolate improved survival of the non-surgical patients with MPM (9, 10). The most promising data to date is the additional

effect of bevacizumab to the standard of care in patients who were amenable for a treatment with chemotherapy and an anti-vascular agent (5).

The French intergroup study reported a 2.7-month gain in OS from 16.1 months in the control group to 18.8 months in the bevacizumab group, which was a statistically significant difference (HR 0.77 (0.62–0.95); p = 0.0167). In this study, the median overall survival in the control group was considerably better than the OS reported in the earlier registration studies. This is most likely an effect of the inclusion criteria: better PS, better selection of patients without cardiovascular diseases or a country specific effect. So far, the results of this study have not led to a change of the standard approach in most countries except France.

In this perspective it should be noted that the phase II study randomizing MPM-patients who had a first line therapy with gemcitabine-cisplatin failed to show any improvement in PFS or OS when bevacizumab or placebo was added to this regimen (11). Whether this is a consequence of differences in specific drug-drug interactions or not still remains to be resolved.

Nintedanib, oral, triple angiokinase inhibitor of VEGFR, PDGFR, and FGFR, has been investigated in a phase II study randomizing patients who received first line pemetrexed-cisplatin between nintedanib or placebo. Recently, preliminary data were reported on the additional effect of nintedanib added to cisplatin/pemetrexed. The PFS significantly increased from 5.7 to 9.4 months (HR 0.56 (0.34–0.91) p = 0.017), which was promising enough to proceed to a phase III study (12, 13).

Maintenance therapy

Both the bevacizumab and the nintedanib trial mentioned above are examples of continuation maintenance therapy in mesothelioma. Continuation treatment with pemetrexed is feasible, as described in an observational study by Van den Bogaert et al. (14). The study design does not allow to conclude whether the better PFS and OS in patients who had maintenance treatment, compared to those who had not, was due to patient selection or the actual therapy.

The alliance for clinical trials in oncology is performing a randomized phase II trial in the USA to determine whether pemetrexed maintenance after 4 cycles of chemotherapy for malignant mesothelioma has a better progression-free survival than observation only. The study is ongoing but not recruiting any patients and results are expected. (NCT01085630).

Switch maintenance with thalidomide, a drug with anti-angiogenic properties, in patients who did not progress on the standard first line chemotherapy, did not result in improved PFS or OS in a 222 patient randomized phase III study (15). Currently, a randomized phase II switch maintenance study with gemcitabine, which has antitumor activity as shown in several phase II studies, is accruing patients (NVALT19, Netherlands Trial Register NTR4132). The command study compared the impact of the focal adhesion kinase inhibitor defactinib in patients with MPM. Unfortunately, the study has been terminated prematurely due to ineffectiveness (16). The full data are now being awaited shortly.

Chemotherapy in second line

Twenty-five to 30% of patients are refractory to first line chemotherapy, and most patients will have a recurrence of disease within 6 months. All these patients are possible candidates for second line treatment. Over the last three decades, different drugs have been tested in second or third line. Unfortunately, until now there is no therapeutic modality with a proven clinical benefit. Patients in a good performance status should therefore be advised to participate in clinical trials (6).

In an ideal situation, the outcome of chemotherapy could be predicted for each individual patient, but so far, all techniques have failed to do so. The NCI developed a platform with a series of cell lines where responses as well as the corresponding genome sequence are provided (the NCI60 platform). This was further explored in wide analyses to correlate drug responses to the genetic profile (17). Correlations were observed between particular drugs and the cell's genetic makeup, yet it is hard to translate this into clinical practice. How that translates to primary tumor tissue or real patient treatment is now being investigated in patients with MPM (18). In Fig. 1, it is shown how such an approach can be done in the lab using fresh pleural fluid, extracted from patients with MPM.

A difference in the metabolic state of the cancer cell is another approach of selecting patients for a specific treatment. The sarcomatoid subtype of MPM seems to lack an enzyme arginine succinate synthetase 1 (ASS1) (19). These cells are unable to generate arginine for the metabolic processes and fully depend on its availability in the bloodstream. When pegylated arginine deiminase (ADI-PEG) is administered in these cases, arginine will catalytically degrade and apoptosis will be the result when ASS1 levels are low. The initial study proved this concept to be important (20). The sarcomatoid type of MPM accounts for only 20% of all cases, which will make this approach possible in the minority of patients.

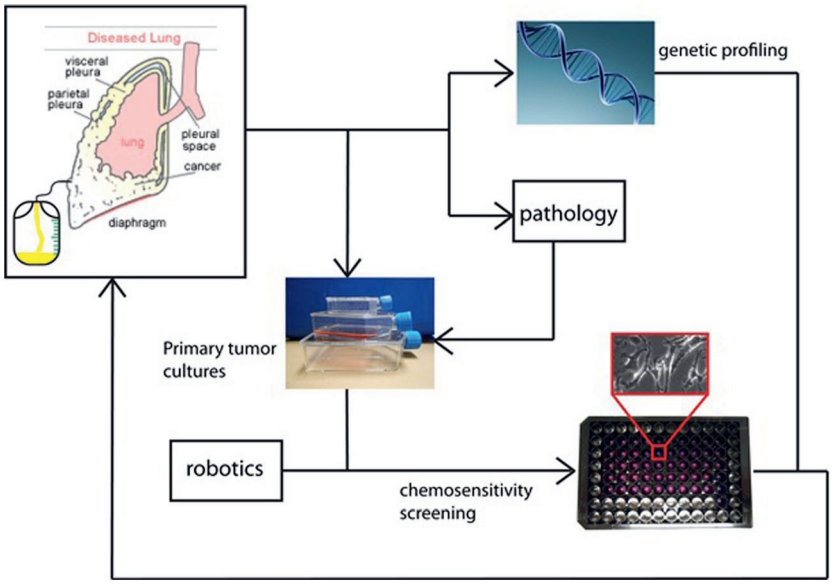

Figure 1 Pleural fluid is collected from patients with a MPM. In the cases where tumor cells are shed, these can be cultured and tested to different doses and types of chemotherapy. The best results of the exposure can be used to select the most promising treatment for the patient, or when resistance is seen with all known drugs other avenues can be chosen.

In a multicenter randomized phase 2 clinical trial, 68 out of 201 patients with newly diagnosed or recurrent MPM were identified with a ASS1 deficiency. The administration of weekly ADI-PEG20 i.m. plus best supportive care (BSC) was compared with BSC alone. The primary endpoint PFS was determined in this patient population with a follow-up of up to 38 months. With a randomization of 2:1, 44 patients completed 2 × 4-week cycles and were compared to the 22 patients receiving only best supportive care. No partial or complete responses were observed, and the PFS in the active treatment arm was 3.2 months compared to 2.0 months for the control arm. These figures met the predefined statistical endpoint with a HR of 0.56 to 0.60 for patients treated without or with prior cisplatin containing therapy. A clear relationship was observed for the patients who had a higher (975%) depletion of ASS1 and the PFS (19). Currently this treatment is now tested in a phase III multicenter study.

Immunotherapy

Cancer immunotherapy has emerged in the last decade as the most promising new cancer treatment approach. Immune checkpoints are crucial for the maintenance of self-tolerance, but the expression of immune checkpoint proteins can be dysregulated in

tumor cells as a major mechanism of immune resistance. Thus, in recent years, checkpoint inhibitors have emerged as primary agents in clinical testing to manipulate antitumor immunity (21).

Recent data suggest a moderate expression of PD-L1 in mesotheliomas, in particular, the sarcomatoid subtype. Cedrés et al. analyzed tumor samples from 119 chemotherapy naïve patients with MPM. The data were collected between January 2000 and April 2014. In 77 samples, with adequate tumor tissue, IHC analysis of PD-L1 was performed, giving 16 (20.8%) positive and 61 (79.2%) negative results. All patients presented TILs (tumor infiltrating lymphocytes) in the tumor specimen, without any predominant cell line. The univariate analysis demonstrated a correlation between PD-L1 expression and histology: in the non-epithelioid histology group a significantly higher rate of patients was PD-L1 positive, compared to the epithelioid MPM group (respectively: 9/24 pts., 37.5% vs 7/53pts, 13.2%; $p = 0.033$). Moreover, PD-L1 expression was associated with outcome, with PD-L1 positive patients having a shorter survival (22).

Similar results were achieved in another case series including patients diagnosed with MPM between 1987 and 2003 at the Mayo Clinic of Rochester, Minnesota (23). Forty-two (40%) out of the 106 patients who were considered eligible expressed PD-L1 (i.e., PD-L1 expression ≥5% cells). PD-L1 expression was cytoplasmic in 18 patients (43%), membranous in 10 patients (24%) and both cytoplasmic and membranous in 14 patients (33%). All the sarcomatoid MPMs were found to be PD-L1-positive, except for one single case. Moreover, patients in the PD-L1 positive cohort were characterized by a significantly shorter survival compared to PD-L1 negative MPMs (median OS: 5 months, range 2–9.5; vs 14.5 m, range 9.25–19; $p < 0.0001$) and the results were confirmed in the multivariate analysis (risk ratio for PD-L1 expression: 1.71, 95% CI 1.03–2.78; $p = 0.04$) (23). Among patients with epithelioid MPM, PD-L1 positive patients showed a trend toward a worse prognosis compared to PD-L1 negative ones, although not statistically significant (23).

Single agent treatment with PD-1 or CTLA-4 IO blocking drugs have been tested in MPM. For both pembrolizumab and nivolumab promising data have been reported. Unfortunately a large phase III study with tremelimumab (anti CTLA-4) was negative after initial promising data (24).

At the 16th World Conference Lung Cancer in Vienna results of one phase 1 and two phase 2 studies with single agent PD-1 blockers were reported (25–28). In line with other tumor types, a response percentage of around 25% was observed, occasionally with long-term survivors.

CTLA-4 and PD-1/PD-L1 pathway blockade enhance T cell activity through complementary mechanisms. CTLA-4 inhibition enhances the activity of early stage T cells, leading to enhanced T cell activation and proliferation. PD-1 inhibitors can enhance T cells activity in peripheral tissue, by preventing PD-1 interaction with its ligands. However, many tumors can escape immune-destruction, by PD-L1 and/ or PD-L2 overexpression that can inhibit T cell activity in peripheral tissues.

Preclinical data suggest synergistic effect of CTLA-4 and PD-1 blockade versus these agents alone. Curran et al. described an enhanced rejection of B16 melanoma in mice with the combination therapy rather than with the single agent therapy (rejection of 50% of melanomas in animals with the combination blockade of CTLA-4 and PD-1). Moreover, they showed that the inhibition of a single pathway led to enhanced infiltration of effector T cells in the tumors, but that these T cells accumulated high levels of negative co-receptors that eventually could limit their activity. Blockade of multiple pathways allowed CD4+ and CD8+ to proliferate and carry out their activity within the tumor. This study also demonstrated that the double blockade increases the ratio of effector T cells to regulatory T cells, thus reducing inhibitory signals and promoting inflammation in the tumor microenvironment (29). The efficacy of the combination has recently been confirmed for the treatment of advanced melanoma. These results have led to the start of different phase II studies in MPM. The French intergroup has already completed the randomized study in second line of nivolumab vs. nivolumab plus ipilimumab, and its results are eagerly awaited (NCT02716272) (Table 1).

Table 1. Drugs in development

Drug groups	Positive study	Negative study	Ongoing study
Immunotherapy	Phase II: pembrolizumab (interim analysis) Phase IB: pembrolizumab (Keynote 28) Phase II: nivolumab (NivoMes)	Phase III: tremelimumab	Combination PD-1 and CTLA-4 checkpoint inhibitor
Antibody drug conjugate	Anti-mesothelin. Phase II: anetumab avtansine Phase II: amatuximab		Phase III: amatuximab Phase III: anetumab ravtansine

Antibody drug conjugates

Mesothelin is a tumor antigen that is highly expressed in MPM and other tumors. It can be targeted, and therefore act as a new therapeutic target in MPM. Besides its expression on malignant cells, normal mesothelial cells also show the expression, but these cells are dispensable (30). Several antibody-based therapeutic agents directed at mesothelin are currently under clinical evaluation. Other approaches are vaccine and T cell therapies.

The anti-mesothelin immunotoxins have extensively been studied in the NCI lab. The tested com- pounds were SS1P and RG7787/LMB-100, chimeric anti-mesothelin antibody (amatuximab), mesothelin-directed antibody drug conjugates (anetumab ravtansine, DMOT4039A, BMS-986148), live attenuated Listeria monocytogenes-expressing mesothelin (CRS-207, JNJ-64041757), and chimeric antigen receptor T cell therapies. Two anti-mesothelin drugs are currently in phase III clinical registration trials for malignant mesothelioma; amatuximab and anetumab ravtansine have both shown promising results in the phase II setting (31) (Table 1). The development of the CRS-207 in MPM has not yet matured enough to start randomized studies in MPM (32). It is foreseen that these agents will also be tested in combination with checkpoint inhibitors.

BRCA1-associated protein-1 (BAP1) inactivation

BRCA1-associated protein-1 (BAP1) has a role in DNA repair, control of gene expression through histone modification. It also enhances the progression through the G1-S checkpoint (33). In MPM, BAP1 is inactivated in around 25% of the tumors and can be considered to be a potential target. A number of different mutations have been identified that inhibit the function of BAP1 (34). The role of BAP1 in histone modification is of interest because it could allow histone deacetylase inhibitors (HDAC) to influence the disease. Unfortunately, a large randomized phase 3 trial of the HDAC inhibitor vorinostat in second and third line MPM did not show any activity (16). However, it must be noted that no correlation with BAP1 was made in this study.

Ongoing is a phase II, two-stage trial of tazemetostat. In part 1, patients will be treated regardless of BAP1 status, and in part 2, only patients who are BAP1 deficient (NCT02860286) are included.

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