Angiogenesis in mesothelioma

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Discussion and future perspectives

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Malignant mesothelioma is a tumour arising from the mesothelial lining of the pleura, peritoneum, pericardium and tunica vaginalis. Pleural mesothelioma is the most common of these, accounting for approximately 90% of the disease.

The association between mesothelioma and asbestos exposure is well established and is confirmed in more than 80% of cases. In rare cases germline BAP1 mutations give rise to a tumour predisposition syndrome with increased risk of developing melanoma, mesotheliomas and renal cell carcinomas.

Malignant pleural mesothelioma (MPM) is notoriously refractory to different treatment modalities. There are several treatment options though, that in general do not lead to a curation. These involve in selected cases surgery alone; surgery in combination with chemotherapy and/or radiotherapy or chemotherapy alone. Several kinds of biologicals and immunotherapies have been or are currently under investigation. Until recently, chemotherapy was considered to be the standard treatment for patients with mesothelioma. Two large phase 3 studies have shown that the combination of cisplatin with an antifolate drug (pemetrexed or raltitrexed) significantly improved both response rate and median overall survival compared with cisplatin alone with a survival benefit of 2.8 months in the first-line setting.[1, 2] More recently, it was shown that the addition of bevacizumab to cisplatin and pemetrexed was of benefit in a randomised phase 3 trial (MAPS).[3] The primary outcome, overall survival, was significantly better for the group of patients randomised to the bevacizumab arm. In both arms, a much better median overall survival was observed compared to the historic data, with 16.1 month for cisplatin pemetrexed alone and 18.8 months for the experimental arm. However, an OS benefit of 2.7 months with a HR of 0.77 (p=0.01) was not enough to fulfil the required criteria for a general acceptance in the European countries. Therefore, this drug combination was not registered in the Netherlands as the new standard of care. Very recently, on October 2, 2020, the Food and Drug Administration approved the combination of nivolumab plus ipilimumab as first-line treatment for adult patients with unresectable malignant pleural mesothelioma, a major breakthrough. Hopefully, the rest of the world will follow soon. Efficacy was investigated in CHECKMATE-743 (NCT02899299), a randomised, open-label trial in patients with unresectable malignant pleural mesothelioma and no prior anticancer therapy. Patients were randomised to receive either nivolumab and ipilimumab for up to 2 years (n=303) or 6 cycles of combination chemotherapy with cisplatin or carboplatin plus pemetrexed (n=302). The trial demonstrated a statistically

significant improvement in overall survival (OS) for patients treated with nivolumab plus ipilimumab compared with those who received chemotherapy. Median OS was 18.1 months versus 14.1 months (HR 0.74; p=0.002). There was a larger magnitude of benefit found in the non-epithelioid subgroup. Median OS was 18.7 months for epithelioid patients (HR 0.86; 95% CI 0.69–1.08) and 18.1 months for non-epithelioid patients (HR 0.46; 95% CI 0.31–0.68) with the dual immunotherapy combination compared to 16.5 months and 8.8 months, respectively.

Despite the development of many other trials with different compounds in the recent years, no other approved treatments have been identified to date yet.

There is evidence that suggests that neoangiogenesis is an important factor in the development and progression of mesothelioma. In preclinical models vascular endothelial growth factor (VEGF) increased proliferation of mesothelioma and antibodies against VEGF and its receptor inhibited mesothelioma growth.[4] A two-to three fold higher serum levels of VEGF has been observed in patients with mesothelioma, compared to other malignancies or healthy volunteers. This suggests an autocrine growth effect of the tumour. Furthermore, a higher microvessel density (MVD) has been observed in mesothelioma biopsies compared to other malignancies. A high MVD was independently related to poor survival, even when adjusted for other known prognostic factors such as histological subtype and age.[4, 5] These observations led to the testing of several kinds of antiangiogenic drugs in mesothelioma, used as a monotherapy or in combination with chemotherapy and made this category of drugs the base of this thesis.

Along the use of the antiangiogenic drugs thalidomide and axitinib in this thesis, we also explored new response measurements in mesothelioma patients. Since the outcome overall survival is not always reliable in small (non-randomised) trials, image-based response assessment is often used as a surrogate for the efficacy of a treatment in patients. For that reason, the most relevant response classification criteria would be those that correlate the radiologic assessment with overall survival of individual patients. In the past, the original Response Evaluation Criteria in Solid Tumors (RECIST) classification categorised progressive disease (PD) as an increase in the bidimensional measurement of 25% or more and a partial response (PR) as a bidimensional measurement decrease of 50%.[6] Later on, these two-dimensional measurements were converted to one-dimensional measurements using an assumption of spherical volume geometry, leading to the current RECIST classification criteria.[7, 8] However, mesothelioma is a malignancy of the pleural lining that is separating the lungs and the thoracic wall and therefore is usual an

aspherical disease. Furthermore, the thickening of the pleura may often be subtle and therefore not reproducible and the surface of the tumour is often large.

These facts casted some doubt on the applicability of these criteria on mesothelioma and this lead to the modified RECIST guidelines, which calls for 2 linear measurements of tumour thickness to be summed from each of three axial sections, primarily in computed tomography (CT) scans.[9, 10] In the past, theoretical geometric models were developed and these indicated that if the definition of stable disease (SD) were broader it would more closely approximate the corresponding volume changes seen in tumours of spherical morphology.[11] In an attempt to improve this scoring system, a study was performed focussing on the growth changes of the tumour in time.[12] Changing the different response category thresholds to -64% (PR) and +50% (PD) and applying them to best response or first follow up scan resulted in an improved correlation with patient survival. The question whether these optimised modified RECIST criteria would hold in another cohort was not confirmed yet.

The aim of this thesis was to improve progression free survival and overall survival in mesothelioma patients with antiangiogenic drugs and increase the understanding of the mechanism action of VEGF inhibitors in humans. Furthermore, the reliability of the newly proposed optimised modified RECIST criteria were tested in an independent mesothelioma cohort.

In **chapter 2**, we conducted a systematic review of the current literature at that time for the activity and toxicity of second-line treatment. The results were presented according to the class of drugs: chemotherapy and targeted or biological agents.

In **chapter 3** we show the results of a large, open-label phase 3 maintenance study that randomised between thalidomide versus active supportive care after first-line chemotherapy in 222 mesothelioma patients.[13] The study was performed in 8 Dutch and 4 Australian centers. Thalidomide is an oral drug and has an excellent bioavailability. Besides immunomodulatory and anti-inflammatory properties, it also inhibits angiogenesis. It was not until 2009 that it was shown that thalidomide blocked the filopodial outgrowth of endothelial cells and that proliferation and migration and forming of vascular tubes was prevented.[14] This explained the serious congenital birth defects observed in the late fifties in pregnant woman who used the drug as a non-barbiturate with sedative and anti-emetic activity. In our study, we could not show any benefit in the time to progression when thalidomide maintenance therapy was given. The median time to progression in the thalidomide group was 3.6 months compared to 3.5 months in the control

arm (HR 0.95; 95% CI 0.73–1.20; p=0.72). The median overall survival was also not different with 10.6 months in the thalidomide arm and 12.9 months in the control arm (HR 1.2; 95% CI 0.9–1.6; p=0.21).

The study also included a voluntary biomarker research part. Serum samples were collected prospectively in 73 patients, which were tested for VEGF, bFGF, IL6, Cyfra 21.1 and SMRP expression. The demographic profiles of patients with and without biomarker samples were comparable. Of these markers, only IL6 and Cyfra 21.1 were prognostic for survival, irrespective of treatment with thalidomide. Patients with both reduced baseline interleukin 6 and Cyfra 21.1 values had improved prognosis, with a median overall survival of 17.1 months (95% CI 13.4–24.5) compared to 7.6 months (6.7–12.2) for patients with an increased baseline interleukin 6 and Cyfra 21.1. Although SMRP seems to be a promising tumour marker in mesothelioma,[15] there was no association found with survival in this cohort. A possible reason for the absence of prognostic value may be found in the time of measurement and the eligibility criteria of the patients. Samples were taken after completion of the first-line treatment and only in patients who had not progressed. Since SMRP is suggested to be associated with the status (volume) of disease, as it performs better in advanced disease, the possible value of SMRP as a prognostic marker could have been underestimated in our study.

The negative outcome of the NVALT 5 study is in line with 2 other large randomised studies that studied (continuous) maintenance treatment with an antiangiogenic compound after first-line chemotherapy.

A randomised, double blind, placebo controlled phase 2 trial tested the combination of cisplatin-gemcitabine with bevacizumab or placebo.[16] Bevacizumab is a monoclonal antibody that binds to VEGF-A, thereby disrupting the VEGF pathway. One hundred and eight eligible patients were treated with gemcitabine and cisplatin in the standard dose and randomised to bevacizumab or placebo in a 1 to 1 ratio. The median PFS and OS were not significantly different: 6.9 vs 6.0 months and 15.6 vs 14.7 months respectively.

The second study was the LUME-Meso trial.[17] Patients with epithelial subtype MPM were randomised to nintedanib, 200 mg twice daily, or placebo in combination with cisplatin pemetrexed for up to six cycles, followed by nintedanib or placebo maintenance. Nintedanib is a multitargeted angiokinase inhibitor, with activity against VEGF 1, 2 and 3, PDGFR and FGF receptors, among others. It was hypothesised that this multitargeted approach could enhance efficacy. Unfortunately, the encouraging findings of the phase 2 part of this phase 2/3 trial

could not be confirmed. The primary endpoint PFS was not met. Median OS at the interim analysis for nintedanib versus placebo was 14.4 versus 16.1 months (HR [95% CI] 1.12 [0.79–1.58]; p=0.538). The study was discontinued as per the study protocol.

The large open label, randomised phase 2/3 study that added bevacizumab to cisplatin and pemetrexed in chemo naïve patients (MAPS) is the only study that did show a beneficial effect.[3] A total of 448 patients were treated with up to 6 cycles of standard treatment pemetrexed and cisplatin and were randomised between bevacizumab (15 mg/kg) or chemotherapy alone. Subsequent maintenance bevacizumab was permitted. Not only PFS, but also OS increased significantly in the experimental arm. The effect was modest: median 18.8 months versus 16.1 months (HR 0.77, 95% CI 0.62–0.95).

The reason why the MAPS study was positive in contrast to the study with gemcitabine, may be related to the backbone of the treatment. Subsequent studies have shown that adding bevacizumab to a gemcitabine backbone does not improve survival in either pancreatic or lung cancer[18, 19] and preclinical data suggest a negative interaction between bevacizumab and gemcitabine.[20] Some cytotoxic agents can stimulate angiogenesis and tumour regrowth by mobilizing circulating progenitors from bone marrow. This seems not to be the case for gemcitabine. VEGF inhibitors may augment the cytotoxic effect of some chemotherapy regimen by blunting this effect. According to this hypothesis, for optimal activity, bevacizumab should be combined with agents that can rapidly induce these pro-angiogenic cells.

In **chapter 4** we discuss the additional effect of the VEGF TKI axitinib, a potent oral inhibitor of mainly the tyrosine kinase receptors for VEGF, to cisplatin and pemetrexed combining clinical and translational outcomes in a small randomised phase 2 study. Response evaluation was not only achieved by a CT-scan, but a second thoracoscopy after three courses of systemic therapy was performed to study intra-tumour changes. Based on the mechanism of action of axitinib, we focused on the changes in vascularisation in the paired intraindividual tumour biopsy samples.

Since axitinib was not previously tested in mesothelioma with this chemotherapy regimen, the study design included a lead in period of 6 patients to test the feasibility of the combination. In total, twenty patients received chemotherapy and axitinib and 11 patients chemotherapy alone.

We demonstrated that performing a second thoracoscopy in a patient after initial treatment was successful. Following our study, this model has been used successfully in other mesothelioma studies that focused on immunotherapy in our group.[21, 22]

The clinical outcome of the study was negative. Although the partial response rate was higher in the axitinib group, 36% versus 18%, this did not translate to a longer progression free survival. The median OS was 18.9 months (95% CI 11.2–NA) in the axitinib group and 18.5 months (95% CI 13.7–NA) in the chemotherapy-only group (p=0.78). These results are quite long for both groups, but can be explained by a selection bias. Patients in this study had to have a good performance status to be candidates for a pleurectomy during the second thoracoscopy.

In the translational research part, we showed that axitinib treatment efficiently prevented tumour neoangiogenesis and improved vessel maturation compared to tumour biopsies of patients treated with chemotherapy alone. There was a significant increase in microvessel density in the tumour biopsies after treatment with pemetrexed and cisplatin compared to biopsies before treatment (p<0.0001). In addition, the number of immature blood vessels increased after chemotherapy in this group (p=0.0003). In contrast, in the axitinib group, microvessel density and the number of mature blood vessels remained the same after treatment. Analysis of mRNA expression showed that most of the angiogenic ligands and their receptors (FGF2, PDGFβ and to a lesser extent PGF and their corresponding receptors) were increased after treatment with axitinib. This might reflect a rebound effect caused by stopping axitinib treatment for safety reasons, 5 days before the second thoracoscopy. It is also possible that increased mRNA expression of angiogenic growth factors and their receptors were a compensatory reaction to the inhibition of the VEGF signaling axis by axitinib. The importance of not only controlling VEGF/VEGFR2 signaling, but also of balancing other signaling pathways was underlined by the finding that increased mRNA expression of vascular (PDGFRβ and FLT1/VEGFR1) and lymphatic (FLT4/VEGFR3) growth factor receptors was strongly correlated with worse prognosis; partial regression was only observed in patients with lowest expression levels. These correlations of (lymph)angiogenic factors with clinical outcome suggest that vascular alterations and/or neovessel formation play an important role in mesothelioma. However, we have to keep in mind that this study demonstrated that only reducing MVD and increasing the maturity of blood vessels was not sufficient to obtain better PFS or OS.

In **chapter 5** we focused on the possible implementation of new optimised modified RECIST criteria.

In previous work by Labby et al., 78 mesothelioma patients were analysed comparing the outcome of serial CT scans with survival.[12] The aim of that study was to determine the optimal correlation between response classification and overall survival for MPM patients.

In this study C statistic was used as a determinant for the success of the model. An analysis based on the C statistic is an analysis of the discriminatory value of a test, namely the ability of the test to be able to distinguish between high and low risk people or to make a distinction, compared to mere coincidence. For binary outcomes, the C statistic corresponds to the area under the curve (AUC) of the Receiver Operating Characteristic curve (ROC). The area under the curve indicates the accuracy of the test: 1 is a perfect test and 0.5 is a worthless test which detects as many correct positives as false positives. When the C statistic is higher than 0.7, the models are generally regarded as acceptable and with a C statistic >0.8, highly acceptable.

The optimal response categories were identified by checking all of the possible classification threshold combinations and maximising the resultant concordance (C) value. The cutoff pair that yielded the highest value of C was determined to be the optimum criteria. Changing the different response categories to -64% (PR) and +50% (PD) compared to best response or first follow up scan, resulted in an improved outcome of response classification criteria.[12] To evaluate this recommendation, we conducted a retrospective study in an independent mesothelioma patient cohort, a subset of patients of the NVALT 5 study, using these cut-offs.[23] The results could not confirm the promising results for the initial paper in our patient cohort. While the standard modified RECIST criteria (PR -30% and PD +20%) yielded in this cohort a C statistic of 0.776 with a standard error of 0.057, the Optimised RECIST criteria (PR -64% and PD +50%) yielded a C statistic of 0.737, which was lower than the initially reported C statistics of 0.855.

The differences in outcome of the two mesothelioma studies may be due to the different focus of these trials. The Labby trial evaluated patients treated with chemotherapy in which the PR group seems to be the best represented. The NVALT trial was a randomised maintenance study after first-line chemotherapy and patients were not expect to have a PR on the study drug/active supportive care. Our study had a higher proportion of long survivors, due to the selection criteria. A larger, well-balanced cohort to create new RECIST criteria may result in improvements, giving better tools for how long patients may be treated with the same regimen, to optimise their survival.

In **chapter 6** an up to date review is given of all the studies that were published in recent years, concerning inhibitors of angiogenesis in mesothelioma.

Perspectives

The first landmark study on tumour antiangiogenesis was published in 1971 by Folkman.[24] He stated that the growth of solid neoplasms is always accompanied by neovascularisation. Since then the observation was made that patients with MPM had high circulating VEGF levels, suggesting an autocrine effect of the tumour. It was shown that the tumour itself had a high microvessel density in relation to other tumours and that MVD was independently related to poor survival. These considerations led to the development of many antiangiogenic drugs. Over the last 3 decades, many of these drugs have been tested in clinical trials in MPM patients, as a monotherapy or in combination with chemotherapy, but this did not lead to a break through in the care of MPM patients and sometimes even lead to substantial toxicity. Some of the drugs made it to phase 3 trials, but none of them were registered as a new indication for MPM.

How should we move forward?

We have to keep in mind that mesothelioma is a rare disease. The incidence is low, varying from 2–30/100,000 inhabitants worldwide. In the Netherlands, about 600 new cases are diagnosed each year. Despite of these relatively low numbers, the socio-medical implications are huge and the growing incidence in the developing world is alarming. The need for better treatments are high and we have to keep searching for better drug combinations. With a low incidence disease and large numbers of candidate drugs, small studies need to provide efficiently valuable information. When testing small number of patients, it is of key importance to include a standard treatment arm in the randomisation. This is the most efficient way to quickly gather relative unbiased data for drug-screening purposes. By adding translational research in search for valuable biomarkers we may find signals to better support for the use of a new drug. The fact that we could demonstrate in our axitinib study that only reducing MVD and increasing the maturity of blood vessels was not sufficient to obtain better PFS or OS in patients, favors this statement.

The next step may be combining antiangiogenic therapy with immunotherapy. The aforementioned randomised phase 3 study with nivolumab ipilimumab

versus chemotherapy in the front line setting recently lead to approval by the FDA of the immunotherapy combination (NCT02899299).The results of the large randomised, placebo controlled, phase 3 trial with nivolumab in the salvage setting (NCT03063450) and the randomised phase 3 trial investigating the efficacy of pembrolizumab versus gemcitabine or vinorelbine in relapsed MPM patients (NCT02991482) showed that immunotherapy was better than best supportive care, but not better than chemotherapy.

Why should we combine antiangiogenic therapy with immunotherapy? Angiogenic factors have roles in both blood vessel formation and regulation of the immune system. High levels of VEGF can inhibit dendritic cell functions and VEGF has been shown to directly modulate T-cell proliferation, migration and activation in preclinical studies.[25] It has been suggested that combining antiangiogenic agents with immunotherapy may produce synergistic effects. As an illustration, in the randomised phase 3 study in patients with first-line advanced NSCLC, the addition of bevacizumab and the PD-L1 inhibitor atezolizumab to chemotherapy was more effective than the addition of either agent alone.[26] This hypothesis is now being examined in patients with mesothelioma in several studies. In a phase 1 study also including MPM patients, nintedanib is combined with the PD-1 inhibitor pembrolizumab (NCT02856425) and a phase 2 study is underway evaluating bevacizumab and atezolizumab in MPM patients (NCT03074513). A randomised phase 3 trial comparing atezolizumab plus bevacizumab and standard chemotherapy (carboplatin and pemetrexed) versus bevacizumab and standard chemotherapy as first-line treatment for advanced malignant pleural mesothelioma (NCT03762018) is now recruiting, as well as pembrolizumab plus lenvatinib in second-line and third-line malignant mesothelioma patients (NCT04287829).

In conclusion, malignant pleural mesothelioma remains to be a nearly invariably lethal tumour. Due to the long latency period and the fact that the use of asbestos is not prohibited worldwide, mesothelioma will continue to be a health hazard. Despite all our efforts to improve survival with combinations of surgery, radiotherapy and all kind of drugs, we have barely been able to succeed yet. We should keep in mind that the most effective strategy to decrease the incidence of mesothelioma is to ban the use of asbestos and ensure regulations to disassemble asbestos containing materials all over the world.

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