

## The Role of Immunotherapy in Malignant Mesothelioma

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Received date: March 6, 2018; Accepted date: March 12, 2018; Published date: March 17, 2018

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### Abstract

Malignant mesothelioma is an aggressive form of cancer affecting the pleura and the serous membranes. Asbestos exposure is the most important factor contributing to the development of malignant mesothelioma. Malignant pleural mesothelioma in general has poor prognosis with studies suggesting that without treatment the median survival is between 4 to 12 months. Unfortunately, there are not many therapeutic interventions that can be offered to patients with malignant mesothelioma. In recent years, another approach that centers on the cancer immune response has shown promising results in managing certain types of tumors including malignant mesothelioma. In addition, to Pembrolizumab there are other immunotherapy agents currently under investigation for the potential future treatment options for patients with malignant mesothelioma. The new approaches using immunotherapy to manage patients with malignant pleural mesothelioma are encouraging. However, more evidence is still required before immunotherapy becomes acceptable form of treatment for malignant pleural mesothelioma.

**Keywords:** Malignant mesothelioma; Immunotherapy

### Introduction

Malignant mesothelioma is an aggressive form of cancer affecting the pleura and the serous membranes [1,2]. Asbestos exposure is the most important factor contributing to the development of malignant mesothelioma [3]. The epidemiological studies suggested that both the cumulative exposure and the time since the first exposure to asbestos remain detrimental risk factors for development of malignant mesothelioma [4]. The epidemiological studies indeed reported on a long latency period of around 20 to 40 years between the exposure to asbestos and the disease manifestation [5,6]. Malignant pleural mesothelioma in general has poor prognosis with studies suggesting that without treatment the median survival is between 4 to 12 months [7]. Overall, the median life expectancy in patients with malignant pleural mesothelioma in the UK has been reported between 12 to 21 months [8]. Unfortunately, there are not many therapeutic interventions that can be offered to patients with malignant mesothelioma. As based on the recent guidelines recommendations, surgical intervention may only be appropriate for consideration in a relatively small proportion of patients with malignant mesothelioma [5,7]. In fact, in many patients the only intervention would be surgical or medical thoracoscopy, which is aimed to provide histological confirmation, drain the pleural effusion and allow for the pleurodesis to be performed [9,10]. A recent MesoVATS study showed that there was no difference in overall survival between patients with malignant mesothelioma undergoing medical pleurodesis or surgical Video-assisted thoracoscopic surgery (VATS) partial pleurectomy with the former having shorter hospital stay and fewer complications [9]. A proportion of patients mainly those with good performance status may be offered systemic treatment in the form of chemotherapy. The studies showed that this palliative chemotherapy approach might result in a median increase in survival in malignant mesothelioma in order of around 3 months [11]. The current approach to chemotherapy involves

the use of Cisplatin and folate drug analogues [7,12]. A recommended combination of Pemetrexed and Cisplatin has been used as the first line chemotherapy for patients with malignant mesothelioma. Other agents that can be used for management of malignant mesothelioma include Gemcitabine, Carboplatin, Vinorelbine and Doxorubicin [13-15]. Carboplatin, which is a platinum based drug like Cisplatin and can also be used in combination with Pemetrexed for treatment of malignant mesothelioma [16,17]. Gemcitabine can be used as a second line chemotherapy or if Cisplatin or Carboplatin are not tolerated [16,18]. Another option may be to consider a re-treatment with Pemetrexed based chemotherapy [19]. Vinorelbine can be used as a second line treatment, if patients relapse, and it was shown to have 16% response with overall survival of 9.6 months [7,20]. Doxorubicin can also be used as a second line treatment of malignant mesothelioma for recurrence with studies showing 16% response and a median survival for those with response of 16.7 months [7,20]. There are studies that assessed other agents such as tyrosine kinase inhibitor Axitinib in combination with Cisplatin and Pemetrexed but unfortunately did not show any clinical benefits [21]. In another study, Amatuximab, which is a chimeric monoclonal antibody to mesothelin, a cell surface glycoprotein highly expressed in malignant pleural mesothelioma, in combination with Pemetrexed and Cisplatin was assessed in patients with malignant mesothelioma and was shown to be well tolerated but the progression free survival was no different with historical data with median overall survival of 14.8 months [22].

### Role of Immunotherapy in Malignant Mesothelioma

In recent years, another approach that centers on the cancer immune response has shown promising results in managing certain types of tumors including malignant mesothelioma. One such strategy would be through the targeted treatments that work on the programmed cell death pathway that incorporates Programmed Death 1 (PD-1) and Programmed Death Ligand 1 (PD-L1), which is an immune check point required for protecting the normal tissue from

the immune attack by inhibiting the T-cell responses [23,24]. Programmed cell death PD-1/PD-L1 pathway has an important role in limiting activity of the T-cells in the peripheral tissues during the inflammatory response to infection and to limit autoimmunity. It has also an important role in tumor pathway and tumor response to the immune system. PD-1 receptor is present on the T lymphocytes and is a negative regulator by inhibiting and preventing overactive immune response. PD-L1 is a cell surface glycoprotein, which is mainly expressed by the antigen presenting cells of the immune system such as the activated T-cells. Thus PD-L1 regulates the cellular response. When PD-L1 binds to its receptor PD-1, it inhibits the proliferation of the activated T-cells. PD-L1 is also expressed by a number of tumors such as non-small cell lung cancer, gastric or colorectal cancers. The PD-L1 has also been shown to be expressed in malignant mesothelioma [25-27]. For example, in a recent report Cedres, et al. revealed that PD-L1 was expressed in 20% of patients with malignant mesothelioma [25]. In this particular study, PD-L1 was more commonly detected in non-epithelioid malignant mesothelioma and was associated with a poorer prognosis. In another study, Nguyen, et al. reported that PD-L1 expression in patients with malignant mesothelioma was in general associated with a shorter survival. This study was a reasonable representation of patients with malignant mesothelioma of whom 84% were male, 72% had epithelioid sub-type and 47% received standard chemotherapy [26]. Tumors that showed more than 1% cell membrane staining of tumor cells were considered positive for PD-L1 expression. The authors found that 72.4% of patients expressed PD-L1. In another recent study, Terra et al reported on a good agreement in PD-L1 expression between the paired primary and secondary malignant mesothelioma lesions obtained at separate time points in 81% of cases and between primary and metastatic lesions in 69% of cases [27]. Therefore in between 19 to 31% of cases studied there was discordance in the PD-L1 expression.

A simplified way of explaining these concepts would be that the PD-L1 is a protein that assists cancer cells including malignant mesothelioma to avoid being detected by the immune system and by doing so it prevents the immune system from destroying malignant mesothelioma cells. Therefore, if malignant mesothelioma cells express the PD-L1 it is more likely to grow unchecked by the immune system hence leading to poorer outcomes and response to treatment. Malignant mesothelioma cells may take advantage of this immune check point by interacting with the PD-1 on the T-cells and blocking its cytolytic activity by inhibition of its proliferation. For this reason, a number of agents have been developed, in the form of monoclonal antibodies, which are targeted to block the PD-1/PD-L1 pathway [23,24]. In fact, this approach is considered to be very promising in the context of improving long-term survival outcomes for a number of cancer types. In general, these agents are called the immune checkpoint inhibitors. Their role has increasingly been assessed in the context of managing malignant mesothelioma. One example of such an agent is Pembrolizumab, which is a highly selective humanised monoclonal IgG4 anti-body directed against the PD-1 receptor on the cell surface [23,24]. Pembrolizumab by binding to the PD-L1 on the tumor cells, blocks the PD-L1 interaction with the PD-1 on the T-cells, which activates these cytotoxic T-cells against the tumor [28]. As a result Pembrolizumab prevents binding and subsequent activation of the PD-L1, which in turn causes activation of the T-cell mediated immune response against the tumor. In a recent multicenter KEYNOTE-028 study, Alley, et al. reported on clinical safety and activity of Pembrolizumab in previously treated 25 patients with advanced PD-L1-positive malignant pleural mesothelioma and good

performance status who had failure of standard therapy [29]. PD-L1 positivity was defined as expression in 1% or more of tumor cells by immunohistochemistry. Patients received Pembrolizumab for up to 2 years or until there was confirmed progression of the disease or unacceptable toxicity. The results showed that 16 (64%) of patients reported a treatment related adverse events with most common being fatigue reported in 24% of patients and arthralgia reported by 20% of patients. In 5 (20%) patients there were more severe grade 3 treatment related adverse events, resulting in 3 (12%) of patients in dose interruption, including rhabdomyolysis in one patient, hypothyroidism in one patient and iridocyclitis in one patient. The effects of treatment with Pembrolizumab in patients with malignant mesothelioma in the KEYNOTE-028 study were encouraging with partial response in 5 (20%) and stable diseases in 13 (25%) of patients respectively. More importantly the response was durable with the median response duration of 12 months. The authors concluded that overall Pembrolizumab was well tolerated and might confer anti-tumor activity in patients with PD-L1 positive malignant pleural mesothelioma.

In addition, to Pembrolizumab there are other immunotherapy agents currently under investigation for the potential future treatment options for patients with malignant mesothelioma [30,31]. Preclinical studies have supported the rationale for current clinical development of agents working on the Cytotoxic T lymphocyte antigen-4 (CTLA-4), which is a protein receptor that down-regulates the immune system and is a key negative regulator of T-cell activation, in the form of anti-CTLA-4 antibodies [32]. Tremelimumab, which is a human monoclonal antibody against CTLA-4, has been tested in the clinical trials as novel therapeutic agents to augment anti-tumor immunity in cancer. Recently, Maio, et al. performed a double-blind, placebo-controlled, phase 2b trial done at 105 study centers across 19 countries in patients with un-resectable pleural or peritoneal malignant mesothelioma who had progressed after one or two previous systemic treatments [33]. The authors reported that the median overall survival in the intention to treat population did not differ between the treatment groups showing 7.7 months in the Tremelimumab group and 7.3 months in the placebo group. Tremelimumab did not significantly prolong overall survival compared with placebo in patients with previously treated malignant mesothelioma. The safety profile of Tremelimumab was consistent with the known safety profile of CTLA-4 inhibitors. In addition, there are ongoing investigations into whether immunotherapy combination regimens can provide greater efficacy than mono-therapies in malignant mesothelioma [30,31,34,35]. In fact, two recent studies MAPS-2 and NIBIT-MESO-1 currently published in an abstract form of which full published results are still awaited were addressing this issue [30,31,34,35]. MAPS-2 study assessed treatment with Nivolumab a human IgG4 anti-PD-1 monoclonal antibody against combination of Nivolumab and Ipilimumab a monoclonal antibody targeting CTLA-4, in previously treated patients with malignant mesothelioma with or without PD-L1 expression [34]. The patients with combined treatments showed better response rates but had more frequent adverse events. In NIBIT-MESO-1 study, which is evaluating Durvalumab anti-PD-L1 monoclonal antibody combined with Tremelimumab as first or second line treatment irrespective of the PD-L1 expression and showed overall response of around 25% and toxicity of around 17.4% [35]. These studies together with other ongoing trials into the role of immunotherapy in malignant mesothelioma will provide hopefully more information into timing, efficacy and toxicity profile of the immunotherapy agents [30,31].

## Conclusion

In conclusion, malignant mesothelioma is a very aggressive form of cancer. The conventional chemotherapy regimens seem to have some survival advantage. The new approaches using immunotherapy to manage patients with malignant pleural mesothelioma are encouraging. However, more evidence is still required before immunotherapy becomes acceptable form of treatment for malignant pleural mesothelioma.

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