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Immune checkpoint therapy of mesothelioma: Pre-clinical bases and clinical evidences

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ABSTRACT

Treatment with immune-checkpoint blocking monoclonal antibody (mAb) is demonstrating a significant efficacy in different tumor types.

Here, we discuss the impact of this promising approach in malignant mesothelioma (MM), a still dreadful disease in which medical treatment has been set on platinum based chemotherapy for decades with unsatisfactory results.

1. Standard treatment for malignant mesothelioma (MM)

Malignant mesothelioma (MM) patients have a highly dismal prognosis and MM aetiology is mostly related to previous asbestos exposure. The incidence of MM has already peaked in the United States whereas it is still increasing in European countries; the worldwide incidence is expected to peak between 2015 and 2030 [1].

Due to its pattern of growth, pleural MM is generally diagnosed at a late stage; therefore, only a minority of patients is amenable to radical surgery. A complete resection is theoretically unattainable; therefore surgery has been implemented mainly within the context of multimodality treatments. Two main surgical procedures have been proposed: extrapleural pneumonectomy (EPP) with removal of the pleura, the entire lung, pericardium and diaphragm, and pleurectomy/decortication (P/D) that is a more limited resection in which the lung is spared and the pleura is removed to a variable extent [2]. EPP was considered for a long time as the optimal procedure for pleural MM, with a reported prolonged survival in selected patients with epithelioid histology, absence of lymph-nodal involvement and maximal cyto-reduction [3]. However, EPP compared to chemotherapy alone in the randomized MARS trial, it offered no survival gain, with even a detrimental effect on overall survival (OS) and quality of life (QoL) [4]. P/D has been proposed as a less aggressive procedure, with several retrospective series reporting a reduction in peri-operative mortality and morbidity and better survival outcome as compared to EPP [5,6]. P/D may vary widely in its extent, ranging from a merely palliative procedure to an extended resection comprising removal of visceral and parietal pleura and possibly of diaphragm and/or pericardium [2]. In the Meso-VATS trial, partial video-thoracoscopy assisted P/D was compared to talc pleurodesis in 175 pleural MM patients. No difference was observed in 1-year OS between the two study arms; P/D led to a modest advantage in QoL and pleural effusion control, at the expense of higher costs and morbidity, and of a longer hospitalization [7]. The ongoing MARS2 trial is comparing extended P/D versus no P/D in pleural MM patients; the results are eagerly awaited to hopefully draw final conclusions on the role of surgery in pleural MM, after decades of debates and uncertainties [8].

Several retrospective analyses on surgical series have clearly shown that loco-regional recurrences remain the main site of failure in pleural MM patients [5,9]. These observations have led to the development of radiotherapy (RT) studies, the most recent using techniques of Intensity-Modulated RT (IMRT) after either EPP

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[10] or PD [11,12]. However, use of post-operative RT on the pleural bed after EPP did not result in improved loco-regional control or OS in the randomized Phase II SAKK-17/04 trial [13]. Studies of IMRT after lung-sparing procedures are ongoing, although the potential benefit in local control and OS must be balanced with the risk of severe lung toxicity, impairment of pulmonary function, and QoL [12]. However, two teams recently published promising data of large single-centre series when optimizing local control of the disease, with both an operative mortality rate $\leq$3% [14,15].

Chemotherapy remains the standard of care for most patients with MM [16]. The combination of cisplatin and pemetrexed has been set as the reference regimen for nearly 15 years [17]. In patients unfit to receive cisplatin, several phase II studies [18] and a large expanded access program [19] have shown that the association of carboplatin and pemetrexed can provide similar results. Unfortunately, nearly all MM patients progress during or after first-line chemotherapy, and there are no standard options or registered drugs in the second- and further-line setting [20]. Single agent chemotherapy with vinorelbine or gemcitabine has limited activity [21]. In the selected subset of patients achieving a prolonged benefit from first-line pemetrexed-platinum treatment, re-challenge with a pemetrexed-based regimen is a valid option [22]. A number of small phase II studies and a few phase III trials with several targeted therapies have failed to improve patient outcome in this setting [23].

Overall, new treatment options in MM are eagerly awaited. Several research lines are being pursued, among them, inhibition of angiogenesis, and immunotherapy seem the most promising approaches.

Angiogenesis is a relevant phenomenon in MM, as shown by preclinical models [24] and by the established negative prognostic value of high serum Vascular Endothelial Growth Factor (VEGF) levels in MM patients [25]. Bevacizumab, an anti-VEGF antibody, has been extensively investigated in the first line setting in combination with chemotherapy [26–29]. In a large randomized Phase III trial in 448 pleural MM cases, patients were randomized to receive bevacizumab in combination with cisplatin/pemetrexed versus the same chemotherapy alone. The addition of bevacizumab improved significantly both progression free survival (PFS) and OS by nearly 2 months [29], However, this regimen is not yet considered a new standard of care in most countries. Nintedanib is another interesting anti-angiogenic agent, targeting VEGF receptors, fibroblast growth factor and platelet-derived growth factor receptors [30]. Nintedanib is being evaluated in a double-blind, randomized Phase II–III trial in addition to standard chemotherapy; the results of the Phase II part of the study have been recently reported: the addition of nintedanib improved PFS and OS, mainly in epithelioid, pleural MM [31]. The Phase III part of the trial is actively recruiting.

2. Immunotherapy of MM

The presence of functionally active, cytotoxic tumor infiltrated lymphocytes (TILs) is a prerequisite for an effective immune activity against cancer [32]. However, in every cancer, there may be a failed immune activation (the so called immune escape of a tumor in the cancer immunoediting) [33], a crucial phenomenon in MM growth. MM pathogenesis includes a prolonged inflammation caused by asbestos fibers, which ultimately affect the immune cell composition of the tumor stroma [34], with a high number of immunosuppressive cells among TILs and a low number of cytotoxic T-cells [35]. One of the most prominent immunosuppressive cell types in MM are tumor associated myeloid cells. It has been shown that the presence of immunosuppressive macrophages (M2) is prognostic in MM [36].

Induction of tumor directed cytotoxic T-cells is a complex mechanism including different crucial steps: recognition of tumor associated antigens by antigen presenting cells (APC), such as dendritic cells (DC), activation of naïve T-cells by APC in the lymph nodes, trafficking of the T-cells towards the tumor site through blood flow, migration into tumor stroma, then tumor cell recognition, and ultimately tumor cell killing by cytotoxic T cells [37]. It is becoming more and more appreciated that *per* tumor type and even over time this immune activation is influenced by the tumor depending on the immune activity. Effective immunotherapy may therefore need knowledge of the immune status of the patient. For instance, PD-1/PD-L1 checkpoint inhibitors can only be effective when there is a cytotoxic T-cell infiltration of the tumor [32].

In most MM patients other immunosuppressive mechanisms may also be activated and this may explain the low number of patients responding to PD-1/PD-L1 checkpoint inhibitors [38]. For instance, the abundant presence of immunosuppressive myeloid cells precludes activation of APC. The most potent APC are DC whose function may be inhibited by immunosuppressive cells such as tumor-associated macrophages type 2 (TAM-2) and regulatory T-cells (Treg) but also by cytokines/chemokines released by the tumor (e.g. VEGF), the tumor stroma (hypoxia, acidosis). Inhibition of this function causes inappropriate cytotoxic T-cell induction. The inactivation of APC is also one of the potential explanations for the failure of the randomized trial DETERMINE assessing tremelimumab versus placebo in relapsing MM [39]. Tremelimumab is an anti-CTLA-4 checkpoint inhibitor; amongst other mechanism of action, activation of the CTLA-4 axis inactivates the APC T-cell interaction. Inactivation of this inhibition potentiates DC-induced T-cell activation increasing the number of cytotoxic T-cells. In metastatic melanoma, single agent CTLA-4 checkpoint inhibitor therapy has been found to increase long-term survival, showing that CTLA-4 is a major immunosuppressive mechanism in these patients. In case of inactive DC, the CTLA-4 axis will not be activated as an immunosuppressive mechanism and CTLA-4 checkpoint inhibitions; therefore, no clinical benefit should be observed. However, also in MM there is activity seen in a minority of patients [40], which again highlights the individual variance present in the mechanism of inhibition of the immune activation. This underscores the diversity of immunosuppressive mechanism(s) in different tumor types.

To induce an effective anti-tumor response in MM, decreasing the immunosuppressive environment seems an attractive option. In murine models, however, it was found that decreasing the number of myeloid cells had limited or no beneficial effect [41–43]. The absence of a beneficial effect can be ascribed to the dual character of the myeloid cells. Myeloid cells may either be immunosuppressive but also have a role in immune activation. Whether myeloid cells become immunosuppressive or immune active is dependent on the local conditions within the tumor. It may therefore be most optimal to skew monocytes towards the immunoactive myeloid cells when entering the tissue.

Among different immunotherapeutic approaches currently under clinical investigation in MM, the most majority is focused on the targeting of mesothelin and immune checkpoint inhibitors.

2.1. Mesothelin targeting strategy

Mesothelin is a cell surface tumor associated antigen and its expression on benign tissue is limited to mesothelial cells of pleura, peritoneum and pericardium. It is highly expressed in many solid tumors including mesothelioma, pancreatic cancer, and ovarian cancer and, with a lesser extent, lung adenocarcinoma [44]. Different compounds can achieve targeting of mesothelin, with distinct mechanisms of action; they include chimeric mAb