Chapter

Current Mesothelioma Treatment and Future Perspectives

Danijela Štrbac, Katja Goričar, Viljem Kovač and Vita Dolžan

Abstract

The established treatments in malignant mesothelioma are based on trimodality approach including surgery, radiation and chemotherapy. Such approach has proved to clinically benefit mesothelioma patients, however the current treatments seem to have reached a limit regarding the survival and disease control. One approach to overcome the limitations of current treatments is focused on finding appropriate serum or genetic biomarkers that could support personalized medicine and improve outcomes with established treatment modalities in mesothelioma patients. The other approach is exploiting better understanding of molecular and genetic characteristics of mesothelioma to search for new treatment modalities. Immunotherapy with anti PD-1, PD-L1 and CTLA-4 agents is a new frontier in mesothelioma treatment. As in many solid tumors, CAR-T cell therapy is emerging from the field of hematological malignancies. Immunomodulatory approaches seem to be a new perspective in treatment of malignant mesothelioma. This chapter aims to explore possible new therapeutic approaches in mesothelioma.

Keywords: mesothelioma treatment, genetic biomarkers, patient based therapy, gene therapy, immunomodulation

1. Introduction: trimodality approach to mesothelioma treatment

The established treatments in mesothelioma are based on trimodality approach including surgery, radiation and chemotherapy. Such concept for MM was introduced in the late 1990s by Sugarbaker et al. It was proposed that the treatment of mesothelioma should start with extrapleural pneumonectomy (EPP) and followed by chemoradiation [1]. A study of 120 patients concluded that a 40% survival rate was feasible in patients with epithelial histology and negative nodes. A need for a more precise staging and more effective management strategies was stated [1].

Two and a half decades after the trimodality approach was introduced, little has changed in the treatment of mesothelioma. According to the National Comprehensive Cancer Network (NCCN) guidelines, in stages I to III of surgically operable mesothelioma, a chemotherapy regimen of pemetrexed with cisplatin or carboplatin is proposed in either preoperative or postoperative setting. For patients who received the entire trimodality approach, a median survival of 20 to 29 months has been reported [2, 3].

However, the majority of mesothelioma patients are diagnosed in advanced stages, are inoperable and/or have a poor performance (WHO performance status (PS) of 2 or above). Treatment with systemic chemotherapy significantly improves survival of MM patients and patients are usually treated with a platinum agent in

combination with either pemetrexed or gemcitabine [4, 5]. Studies have shown that both chemotherapy regimens have comparable results [4, 6, 7]. The only FDA approved treatment for advanced stages of mesothelioma is pemeterexed/cisplatin with possible options of vinorelbine or gemcitabine.

The combination with pemetrexed has become standard treatment in various clinical guidelines such as the NCCN, the European Society of Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) [3, 8, 9]. In a Slovenian clinical study, gemcitabine in a prolonged infusion with cisplatin was shown as one of the most successful systemic treatments [4, 6]. Although current treatments clinically benefit mesothelioma patients, they seem to have reached a limit regarding the survival and disease control. One approach to overcome the limitations of current treatments is focused on finding appropriate serum or genetic biomarkers that could support personalized medicine and improve outcomes with established treatment modalities in mesothelioma patients [10].

A deeper understanding of tumor biology has also enabled the development of target drugs. These drugs target and inhibit the molecular signaling pathways along which a tumor develops, grows, and spreads. Several target drugs have been tested in the treatment of MM in the last few years, but so far no targeted treatment has shown sufficient results to allow patients to be treated outside of clinical trials. Slovenian researchers also participated in one of these clinical trials with target drugs, focusing on bortezomib and cisplatin treatment [11]. The addition of bevacizumab to gemcitabine and cisplatin or pemetrexed and cisplatin has shown slightly better results. An addition of bevacizumab to the pemetrexed/cisplatin doublet has increased overall survival for up to 2.7 months, but it is suitable only for patients that do not have bleeding tendencies or a risk of thrombosis. Bevacizumab treatment has shown sufficiently promising results that it has come into routine use in the United States [12].

Among the novel treatment approaches, immunotherapy is becoming the most promising, especially with immune checkpoint inhibitors such as inhibitors of programmed cell death 1 (PD-1, *PDCD1*) and programmed cell death 1 ligand 1 (PD-L1, *CD274*) [13]. Based on the results of clinical trials, it is currently estimated that 20–25% of patients with MM may benefit from treatment with immune checkpoint inhibitors [14].

Subsequent treatment lines are less effective in mesothelioma. Novel second line treatment approaches include immunotherapy with PD-1 inhibitors, such as pembrolizumab or nivolumab. Nivolumab can be used in a combination with CTLA-4 inhibitor, ipilimumab [15, 16]. However, if immunotherapy is not accessible or has a high toxicity such as pneumonitis, a chemotherapy regimen with gemcitabine or vinorelbine is a valid option.

The aim of this chapter is to explore possible new therapeutic approaches in mesothelioma.

2. Biomarker guided chemotherapy treatment in malignant mesothelioma

Research of biomarkers in malignant mesothelioma has been ongoing for the last twenty years. Predictive and prognostic biomarkers are also needed to support the treatment and follow up of patients with MM [17]. It has been shown that apart from clinical characteristics such as C-reactive protein or tumor stage, serum and genetic markers may be associated with treatment outcome in MM [10, 18–29]. Traditional research in mesothelioma biomarkers involves soluble molecules, such as mesothelin, fibulin and survivin [18, 20, 30], but novel serum biomarkers for

disease risk, diagnosis and treatment are also emerging [31]. Mesothelin is the only clinically validated biomarker in the diagnosis of mesothelioma. However, there are no predictive biomarkers that would allow patient stratification and a more personalized treatment approach. Studies have shown that patient stratification based on genetic biomarkers could improve chemotherapy outcome, but these approaches are not routinely used in the clinic yet [32, 33]. It is becoming more and more widely accepted that pharmacogenomics is enabling personalized medicine by testing for genetic variability in drug metabolizing enzymes, transporters, and drug targets thus accounting for interindividual variability in drug levels (pharmacokinetics), drug response (pharmacodynamics) and adverse events. Using pharmacogenomics approach, the treatment of malignant mesothelioma could perhaps be tailored also to individual's genetic make-up, thereby promising safer and also more effective drug treatment [34–38].

2.1 Pharmacogenomics of cisplatin treatment

Cytotoxic activity of cisplatin and other platinum analogues is based on their ability to covalently bind to DNA, form intrastrand DNA adducts or interstrand cross-links, and lead to replication and transcription arrest. DNA adducts are recognized and repaired by nucleotide excision repair (NER) mechanisms. Genetic variability in NER genes such as ERCC excision repair 2 (*ERCC2*) and ERCC excision repair 1 (*ERCC1*) was associated with malignant mesothelioma treatment outcomes [23, 39]. In particular, *ERCC1* rs3212986 (c.*197G > T) wild-type genotype was significantly associated with better progression-free survival (PFS), but also with increased odds of treatment-related toxicities. The risk for cisplatin toxicity was also increased in patients with wild type genotype of *ERCC2* rs1799793 (p.Asn312Asp) polymorphism [23].

Interstrand crosslinks are among the most detrimental forms of DNA damage because both DNA strands are affected. As translesion DNA polymerases are needed to bypass these crosslinks and restore one of the two DNA strands in order for repair mechanisms to proceed, they may also contribute to response to cisplatin treatment [40]. Studies have shown that disruption or suppression of expression of two genes participating in translesion repair, *REV3L* and *REV1* modifies sensitivity to cisplatin [41, 42]. Similarly, *REV3L* polymorphisms rs465646 (c.*461C > T) and rs462779 (p. Thr1224Ile) were significantly associated with longer overall survival in MM patients treated with cisplatin based doublet chemotherapy, while *REV1* rs3087403 (p. Val138Met) allele and *REV1* TGT haplotype were associated with increased risk for leukopenia and neutropenia [43].

2.2 Pharmacogenomics of pemetrexed treatment

Only a few studies investigated the influence of genetic polymorphism in the folate metabolic pathways on treatment outcome in MM patients that received antifolate chemotherapeutic pemetrexed [22, 44, 45]. MM patients with at least one polymorphic *MTHFD1* rs2236225 (p.Arg653Gln) allele had a lower response rate and shorter PFS than carriers of two wild-type alleles. Furthermore, polymorphisms in pemetrexed transporter genes, such as *ABCC2* and *SLCO1B1* influenced the risk for toxicity in patients receiving antifolates [22]. Another study investigating 5,10-methylenetetrahydrofolate reductase (*MTHFR*) and *ERCC1* gene polymorphisms failed to prove an association between the selected polymorphisms and treatment outcome, but did show that a 6-base pair insertion/deletion in the 3′ untranslated region of the thymidylate synthase *TS* gene was associated with differences in disease control rate and PFS in MM [44].

2.3 Pharmacogenomics of gemcitabine treatment

Because gemcitabine is frequently used in combination with cisplatin in Slovenian mesothelioma patients, a study investigating pharmacogenomics factors that may influence the response to gemcitabine has also been performed. Deoxycytidine kinase and ribonucleotide reductase M1 (*RRM1*) were investigated as the main metabolic and target enzymes, respectively. The study indicated that the *RRM1* rs1042927 (c.*316C > A) polymorphism significantly decreased overall survival. Two promoter polymorphisms, *RRM1* rs11030918 (c.-524 T > C) and rs12806698 (c.-37C > A), decreased the odds of nausea and vomiting, while the *RRM1* TTCCA haplotype was associated with worse tumor response and worse overall survival [25]. DNA repair gene polymorphisms, particularly *XRCC1* rs25487 (p.Arg399Gln), may also modify the response to gemcitabine/platinum combination chemotherapy and effect overall survival in mesothelioma patients [24].

2.4 Clinical-pharmacogenomic models predicting outcome of malignant mesothelioma treatment

Pharmacogenomic findings motivated further research into developing a clinical-pharmacogenomic model combining clinical and genetic data and an algorithm that would enable treatment stratification in MM. The clinical-pharmacogenomic model that could help predict response to gemcitabine/cisplatin combination and survival of MM patients included C-reactive protein, histological type, performance status, *RRM1* rs1042927, *ERCC2* rs13181, *ERCC1* rs3212986, and *XRCC1* rs25487. The clinical-pharmacogenomic model that could help predict response to pemetrexed/cisplatin combination included C-reactive protein, *MTHFD1* rs2236225, and *ABCC2* rs2273697 [10]. An algorithm for treatment stratification was proposed based on both clinical-pharmacogenomic models, where a more favorable chemotherapy regimen could be recommended in 64.2% of patients: pemetrexed/cisplatin in 35.9% and gemcitabine/cisplatin in 28.3%. The algorithm predicted that 21.4% of patients would respond equally well to both treatments, but 14.5% of patients would probably not respond well to either [10]. The algorithm requires further independent validation, before it could be used in the clinical decision making, but is nevertheless proof that a tailored treatment could be applied in mesothelioma chemotherapy.

3. Future perspectives in the treatment of mesothelioma

3.1 Immunotherapy in mesothelioma

Immunotherapeutic approach is proposed as second line treatment in mesothelioma. It entails three basic immunological targets as either anti-PD-1 (nivolumab, pembrolizumab), anti-PD-L1 (atezolizumab, durvalumab) or anti-CTLA-4 (ipilimumab) or in combination, such as nivolumab/ipilimumab. The most promising trial data come from a combination of ipilimumab and nivolumab with median survival of 15.9 months. However, there is 94% rate of treatment related adverse events with combination immunotherapy [15].

Therefore, monotherapy approaches have been proposed in second line setting. Pembrolizumab in monotherapy is promising with a 20% partial response rate with a median response duration of one year. Grade 3 or 4 toxicity rate is reported at 20% [46, 47].

These data, however promising, present a high rate of toxicity and rather limited response and survival rates. With analogy to the genetic biomarkers for cytotoxic chemotherapy, further research should be done to determine genetic biomarkers in immunotherapy [48].

3.2 Gene therapy in mesothelioma

The principle of gene therapy is to infiltrate tumor cells and deactivate genes involved in tumor growth and progression. Classical example of gene therapy is to target p53 expression and induce apoptosis in mesothelioma cells. Several clinical trials targeted crucial pathways in mesothelioma cells that would ultimately lead to cell death using oncolytic viruses as vectors. The genes injected in these trials were interleukin-2, interferon α2b, herpes simplex virus thymidine kinase, and interferon β. The response was achieved mostly around the injected site in the pleural cavity, however some clinical response was noted months after injection into tumor site. The direct cell death that was the goal of this gene therapy was limited, however a delayed immune response was proposed since several antibodies were found in patients with response to treatment [49].

While gene therapy with oncolytic viruses as vectors of injection has been tested as monotherapy, combination with chemotherapy has been proposed to achieve a dual effect of local and systemic disease control [50–53].

3.3 CAR-T cells in mesothelioma

Chimeric antigen receptors (CARs) are genetically encoded artificial fusion molecules that can re-program the specificity of peripheral blood polyclonal T-cells against a selected cell surface target. The overall structure of a CAR consists of four domains joined in series, namely: an antigen recognition domain (targeting moiety), a hinge/spacer, a transmembrane element and a signaling endodomain. The CAR ectodomain determines target specificity and, most commonly, contains elements derived from a monoclonal antibody [54].

Unparalleled clinical efficacy has recently been demonstrated using this approach to treat patients with refractory B-cell malignancy, such as lymphomas. Solid tumors were the next to be included in CAR T cell (CAR-T) immunotherapy, but have posed certain toxicity challenges, such as on target off tumor toxicity. A fatal toxicity was noted in human epidermal growth factor receptor 2 (HER-2) CAR-T cells which led to respiratory and multi organ failure with cytokine release syndrome [55].

Also mesothelioma has been studied in the setting of CAR-T therapy. An *in vitro* study of MET receptor tyrosine kinase specific CAR-T cells was designed to target MET expressing mesothelioma cells. The data from the *in vivo* animal models showed that this type of CAR therapy can be safe and effective in MET expressing mesothelioma [56]. A small study reported two patients treated with mesothelin targeting CAR-T cells (CAR-T meso cells). The investigators in this study used a novel approach of mRNA engineered CAR-T cells to overcome the off- tumor on target toxicity. They concluded that the treatment with CAR-T meso cells is feasible in pretreated patients with progressive disease, since they reported partial tumor response [57].

4. Conclusions

The treatment of mesothelioma presents a clinical challenge, especially in the second and further lines of treatment. There is still place for improvement of

current treatment strategies, in particular the response to chemotherapy, by enabling pharmacogenomics based informed selection of patients who would benefit most from a particular treatment regimen. Based on our previous studies, clinical-pharmacogenomic prediction models and algorithms could facilitate treatment stratification and contribute to improved treatment outcome in MM. The future of mesothelioma treatment seems to involve immunologically based treatment with either the already present immunotherapy or the evolving CAR-T therapy. The innovation of the decades old principles of CAR-T cell therapy has proven to be successful in hematological malignancies and mesothelioma seems to be on the forefront of research in solid tumors with such innovations as are the mRNA CAR-T meso cells.

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Conflict of interest

The authors declare no conflict of interest.

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