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Commentary

New therapeutic strategies for malignant pleural mesothelioma

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ABSTRACT

Malignant pleural mesothelioma (MPM) is a rare and aggressive malignant disease affecting the mesothelium, commonly associated to asbestos exposure. Therapeutic actions are limited due to the late stage at which most patients are diagnosed and the intrinsic chemo-resistance of the tumor. The recommended systemic therapy for MPM is cisplatin/pemetrexed regimen with a mean overall survival of about 12 months and a median progression free survival of less than 6 months. Considering that the incidence of this tumor is expected to increase in the next decade and that its prognosis is poor, novel therapeutic approaches are urgently needed. For some tumors, such as lung cancer and breast cancer, druggable oncogenic alterations have been identified and targeted therapy is an important option for these patients. For MPM, clinical guidelines do not recommend biological targeted therapy, mainly because of poor target definition or inappropriate trial design. Further studies are required for a full comprehension of the molecular pathogenesis of MPM and for the development of new target agents. This review updates pre-clinical and clinical data on the efficacy of targeted therapy and immune checkpoint inhibition in the treatment of mesothelioma. Finally, future perspectives in this deadly disease are also discussed.

1. Introduction

Malignant pleural mesothelioma (MPM) is an aggressive malignant disease affecting the surface mesothelium of the pleural cavity, primarily associated with exposure to asbestos fibers. Despite the rarity of this disease, MPM incidence is increasing worldwide, and it is estimated to peak around the next 15 years [1]. The production and the use of asbestos is forbidden in most of the industrialized countries, but in many developing countries it is still currently used and approximately 125 million people are believed to be exposed in the workplace. Based on the World Health Organization (WHO 1994–2008), age-adjusted mortality rate (AAMR) was 4.9 per million population, with an increase of 5.4% per year [2]. Considering the long latency of tumor development (30–40 years) and the late stage at which most patients are diagnosed, radical surgery is only applicable to a very few early stage fit patients and its benefit is still controversial [3].

At present the only recommended systemic therapy for MPM, based on the phase III EMPHACIS trial [4], is platinum/antifolate regimen that has extended the median overall survival (OS) of MPM patients to approximately 1 year with a median progression free survival (PFS) of less than 6 months. Due to the high chemo-resistance of the disease, systemic treatment results in only short-term regression and local tumors relapse rapidly. The management of MPM patients remains controversial. Currently, a multimodal treatment regimen of chemotherapy, surgery, and radiotherapy provides the best long-term results; however, even after such an aggressive approach, the prognosis remains poor, with mean patient survival time of just over one year. Based on the increasing incidence and on the poor prognosis, additional studies concerning the molecular pathogenesis of MPM are required to develop new therapeutic strategies.

There are three major histological types of mesothelioma. The epithelioid type, characterized by square-shaped cells with visible nucleus, is the most common (50–70%) and tends to have a much more favorable prognosis; the sarcomatoid type (10–20%) with elongated and spindle-shaped cells is the most aggressive one; the biphasic type is a mixture of epithelial cells and sarcomatoid cells (20–35%).

Abbreviations: AE, adverse event; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; EGFR, epidermal growth factor receptor; FAK, focal adhesion kinase; IGFR, insulin growth factor receptor; MPM, malignant pleural mesothelioma; MTD, maximum tolerated dose; mTOR, mammalian target of rapamycin; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressive disease; PFS, progression free survival; PD-1, programmed death 1; PDL-1, programmed death ligand 1; PI3K, phosphatidylinositol 3-kinase; PR, partial response; RB, retinoblastoma; RT, radiotherapy; RTK, receptor tyrosine kinase; SD, stable disease; TKI, tyrosine kinase inhibitor; TNFα, tumor necrosis factor-alpha; VEGFR, vascular endothelial growth factor receptor.

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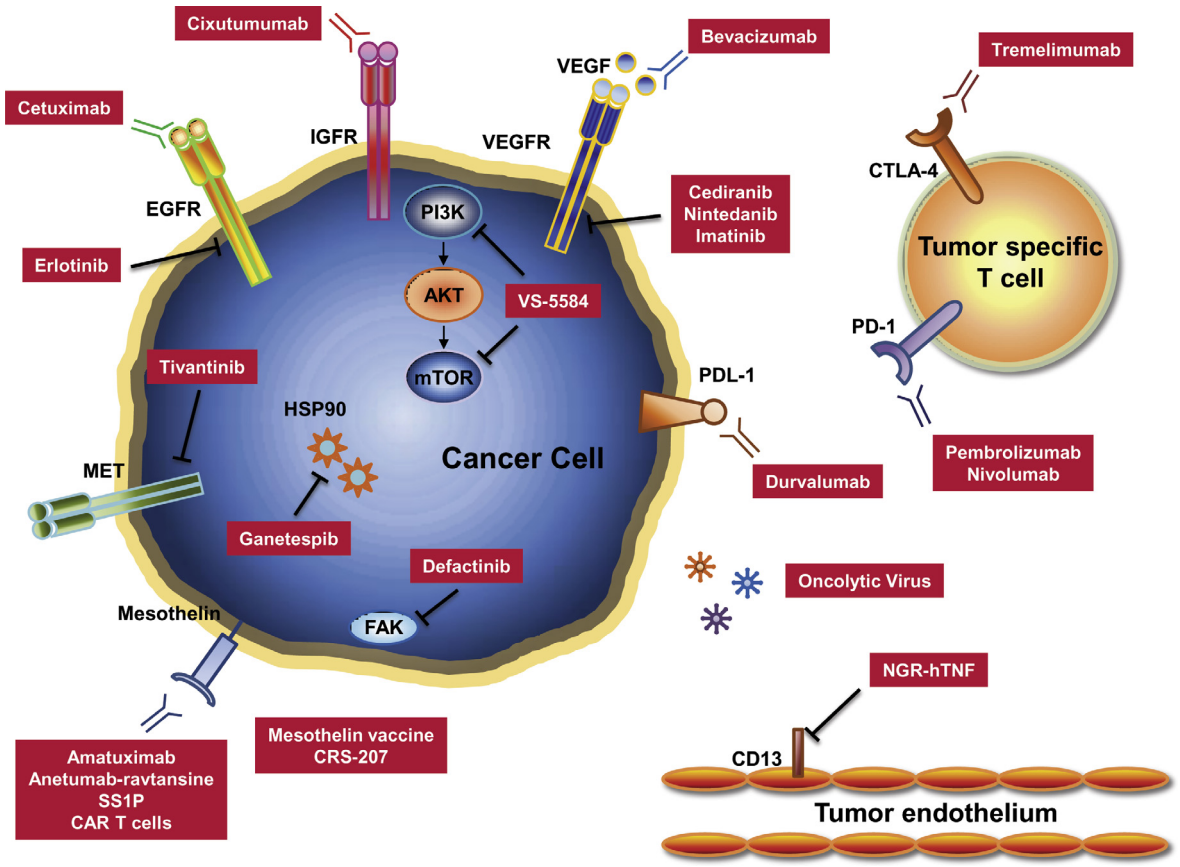

Fig. 1. Molecular targets in MPM and associated inhibitors. Different drugs targeting altered signaling in mesothelioma cancer cells and in surrounding microenvironment under clinical evaluation are shown.

Genetic analyses have identified several genetic and genomic alterations in MPM. The most frequent somatic mutations and copy-number alterations affect *cyclin-dependent kinase inhibitor 2A (CDKN2A/ARF)*, *neurofibromatosis type 2 (NF2)*, *BRCA1-associated protein-1 (BAP-1)* and *Cullin 1* (*CUL1*) genes [5]. The genomic alterations in human MPM that have been previously reported include losses of chromosome arms 1p, 3p, 4q, 6q, 9p, 13q, 14q, 22q and gains of chromosome arms 1q, 5p, 7p, 8q, 17q. In addition, dysregulation in signal transduction pathways, related to cell survival and proliferation, has also been demonstrated [6].

This review updates recent advances and new therapeutic options for the treatment of advanced MPM under pre-clinical and clinical investigation, with particular emphasis to target therapies and immunotherapy (Fig. 1 and Table 1).

2. Systemic chemotherapy and trimodality therapy

Considering the controversial role of surgery the efficacy of surgery is limited and the cytotoxic chemotherapy remains one of the main therapeutic options to prolong survival and improve the quality of life. Since 2003 the systemic treatment of MPM has remained unchanged and the combination chemotherapy with a platin compound and a folate antagonist is still the standard first-line treatment for advanced MPM ineligible for surgery therapy. Two randomized phase III studies [4,7] demonstrated the survival benefit with cisplatin/anti-folate therapy over cisplatin alone. The OS observed with the combinations of cisplatin/pemetrexed and cisplatin/raltitrexed were 12.1 and 11.4 months respectively, significantly higher than the cisplatin monotherapy (9.3 and 8.8 months, respectively). On the basis of these data, the cisplatin/pemetrexed doublet has become the only first-line therapy approved by the US Food and Drug Administration (FDA) for patients with advanced unresectable MPM. Cisplatin is often substituted with carboplatin due to its lower toxicity and results of two phase II studies showed similar activity to cisplatin (time to progression 6.5–7 months and OS 12.7–14 months) [8,9].

At present, a phase II trial comparing four versus six cycles of pemetrexed/platinum in MPM is ongoing with the aim to define the best regimen of chemotherapy (NCT02497053). Another outstanding question is whether the pemetrexed maintenance therapy improves PFS of patients with MPM who have completed an initial therapy. A small study has demonstrated the safety and the feasibility of pemetrexed maintenance in 13 patients [10], and a phase II trial of pemetrexed maintenance versus observation for patients without progression after completion of first-line therapy with pemetrexed and cisplatin/carboplatin is ongoing (NCT01085630).

Several phase II studies indicate that the combination of platinum and gemcitabine is also a reasonable first-line option for the systemic therapy of MPM because of its acceptable toxicity profile, good response rate, and its clinical benefit for patients [11]. Currently, gemcitabine as a first-line therapy is not supported given the lack of phase III studies comparing the two chemotherapy regimens, however gemcitabine in combination with platinum or alone is being used in the clinic as a second-line setting.

Neoadjuvant or adjuvant chemotherapy and adjuvant radiotherapy (RT) are combined with surgery in the trimodality therapy (TMT). Surgery includes pleurectomy/decortication (P/D), extrapleural pneumonectomy (EPP) and extended pleurectomy/decortication (eP/D), that differs from P/D for the resection-reconstruction of the diaphragm. The first study was published in