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Opinion

Immuno-oncology Medicines' Paradoxical function in Osteosarcoma

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ABSTRACT

Osteosarcoma is a bone tumour that is extremely rare. Multi-agent chemotherapy and full surgical resection are used to treat the cancer. The chance of recurrence is substantial, even when multi-agent treatment is used. Since the 1980s, survival rates for patients with osteosarcoma have remained unchanged. There has been interest in adding immunotherapies to upfront curative purpose chemotherapy, such as mifamurtide (a macrophage activator) and interferon, based on biologic justification. However, the outcomes have been underwhelming thus far. Checkpoint inhibitors alone have not been shown to be useful in the metastatic scenario.

Keywords: PDL1, Systemic treatment, Immunotherapy, Osteosarcoma

INTRODUCTION

Primary sarcomas of the bone are uncommon, severe tumours that often necessitate multimodal treatment. The most prevalent subtypes are osteosarcoma, Ewing Sarcoma, and chondrosarcoma. Based on a national retrospective registry, the incidence rate per 100,000 person years for osteosarcoma, 0.16 for chondrosarcoma, and 0.15 for Ewing Sarcoma in the Netherlands has been reported as 0.27 for osteosarcoma, 0.16 for chondrosarcoma, and 0.15 for Ewing Sarcoma. The focus of our discussion will be on osteosarcoma. Children and young people are disproportionately affected by osteosarcoma. The conventional treatment for resectable osteosarcoma patients is multi-agent chemotherapy with Cisplatin (C)-Doxorubicin (D) +/- High Dosage Methotrexate (HD-MTX) (MAP), followed by oncologic resection. Rare bone tumours, such as osteosarcoma, should be treated in specialised sarcoma centres, according to many guidelines. Patients with metastatic osteosarcoma continue to have dismal results, which have remained basically constant since the introduction of cytotoxic chemotherapy over three decades ago.

After showing considerable increases in both survival and quality of life for patients in clinical trials, strategies like checkpoint inhibition and cellular therapy are now frequently used treatments for certain cancer types. Given the efficacy of immunotherapy in treating a variety of cancers, there has been a lot of interest in looking into it for osteosarcoma. Tumor Associated Macrophages (TAM) make up a considerable portion of the osteosarcoma immune milieu as compared to epithelial tumours. TAMs can have varied effects on tumour development depending on their polarisation. Because of their functions in angiogenesis and the generation of immunosuppressive cytokines, M2-polarised TAMs have been shown to promote tumour growth. Patients with tumours expressing activated M1-polarised macrophages were less likely to acquire metastatic disease, according to tissue microarrays prepared from osteosarcoma samples upon diagnosis. Furthermore, increased macrophage infiltration was linked to a better overall survival rate. used pre-treatment samples from patients who did and did not develop metastases to undertake genome-wide mRNA expression analysis. A large number of genes were differently expressed, including overexpression of genes involved in macrophage activity in tumours from patients who did not develop metastases. In the group, the expression of two macrophage-associated genes, CD14 and HLA-DRA, was independently linked to metastasis-free survival.

Muramyl Tripeptide Ethanolamine (MTP-PE), a synthetic derivative of muramyl dipeptide, is the active ingredient in Mifamurtide (MDP). MDP is found in the cell walls of bacteria and has a function in the cell wall's immunological potentiating activity. MDP has been proven to activate monocytes and macrophages in vitro and in vivo. This is assumed to be due to nuclear factor activation and secretion of various downstream pro-inflammatory cytokines via the Nucleotide-binding Oligomerization Domain (Nod) 2. MTP-PE is contained in liposomes, which are taken up selectively by macrophages and incorporated into the phospholipid bilayer. MTP-PE is released as the bilayer breaks down, causing an inflammatory response similar to MDP. Mifamurtide has been demonstrated to have anti-tumour efficacy in vitro by activating macrophages, causing direct cytotoxicity, and releasing tumoricidal substances.

CAR-T cell treatment includes genetically modifying T cells taken from patients to produce a chimeric antigen receptor that

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recognises a tumor-specific antigen. When the CAR-T cells are reintroduced into the patient, they are able to target tumour cells that express the antigen. Up to 60% of osteosarcomas express the Human Epidermal Growth Factor Receptor 2 (HER2). However, the amount of expression is minimal, and HER2 monoclonal antibodies such trastuzumab have little anti-osteosarcoma activity. The use of HER2-expressing CAR-T cells for osteosarcoma has sparked a lot of attention as a way to overcome this.Ganglioside GD2 is expressed in the majority of primary and metastatic osteosarcomas. When injected alone, GD2 expressing CAR-T cells were successful at killing GD2 positive osteosarcoma cell lines in vitro, but demonstrated a limited anti-tumour effect in an in vivo osteosarcoma xenograft mice mode Despite this, there are a number of ongoing trials using GD2 to investigate cellular treatment, including the phase I GD2-CAR PERSIST and VEGAS trials, both of which have completed accrual, and another phase I trial that is presently enrolling. The results will be anxiously awaited in order to guide future study.

The genetic intricacy of these tumours has been proven by recent whole genome sequencing work on osteosarcoma tissues. Multiple genes, including MYC, CCNE1, RAD21, VEGFA, AURKB, CDK4, TP53, RB1, and PTEN, were altered, but no obvious hallmark or sub-grouping of patients emerged. It was, however, possible to categorise individuals based on Somatic Copy Number Alteration (SCNA) and then match existing medicines to SCNAs.

CONCLUSION

Immunotherapies for osteosarcoma have had mixed results in early investigations. Interpretation of large studies with considerable patient dropout or little follow-up data is one of the issues. According to the research, immuno-oncology medications alone are unlikely to have a major impact on the outcomes of osteosarcoma patients. Improved outcomes may be seen in rationally designed translational trials that address osteosarcoma heterogeneity.