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Role of Immuno-Oncology Drugs in Osteosarcoma Treatment

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Mini Review

The standard treatment for resectable osteosarcoma patients is generally cisplatin (C) -doxorubicin (D) +/- high-dose methotrexate (HD-MTX) (MAP) multidrug chemotherapy followed by oncological resection [1]. The outcomes of patients with metastatic osteosarcoma remain poor, with little change since the introduction of cytotoxic chemotherapy more than 30 years ago [2]. In the latest large EURAMOS-1 study, patients with localized osteosarcoma had a 5-year event-free survival (EFS) of 60% and a 5-year overall survival (OS) of 76%. At the time of publication, patients with metastatic disease had poor 5-year EFS ad OS of 28% and 45%, respectively [3]. Certain patients are often diagnosed at the height of their lives. There is an urgent need to identify new treatments. The field of cancer immunotherapy has evolved rapidly over the past few decades, from stimulating the host's immune response to inhibiting the immunosuppressive properties of tumors. Strategies such as checkpoint inhibition and cell therapy are currently commonly used treatments for certain types of cancer and are significant in both patient survival and quality of life in clinical trials. Improvements can be seen [4]. Given the success of immunotherapy in several types of cancer, there is a keen interest in exploring immunotherapy in osteosarcoma. Compared to epithelial tumors, tumor-associated macrophages (TAMs) make up a significant portion of the immune microenvironment of osteosarcoma.

M2 polarized TAM has been reported to promote tumor growth by its role in angiogenesis and the production of immunosuppressive cytokines. On the other hand, M1 polarized TAM produces inflammatory cytokines and is considered an antitumor. Tissue microarrays developed from osteosarcoma specimens at diagnosis show that patients with tumors expressing activated M1 polarized macrophages are less likely to develop metastases [5]. In addition, higher macrophage infiltration was significantly associated with improved overall survival. Budding hetal. Pretreatment biopsies of patients with and without metastases performed genome-wide mRNA expression profiling [6]. A significant number of genes were expressed differently. Tumors from patients who did not develop metastases showed upregulation of genes involved in macrophage function. Expression of the two macrophage-related genes CD14 and HLA-DRA in tumor specimens is independently associated with metastasis-free survival within the cohort [6]. Importantly, by comparing the expression of macrophage-related genes in tumor specimens and osteosarcoma cell lines, the lack of macrophage activating genes in osteosarcoma cell lines is due to macrophage functional signaling and hematopoiesis within the osteosarcoma microenvironment. It suggests that it is caused by cells [6]. This work forms the basis for exploring macrophage activation as a therapeutic strategy for patients with osteosarcoma. Immunotumor drugs alone are unlikely to have a significant impact on the outcome of patients with osteosarcoma. The improved results may be in rational translation studies to investigate heterogeneity between osteosarcomas.

The bisphosphonate zoledronic acid inhibits bone resorption by suppressing osteoclast differentiation, and also exerts anti-cancer activities through incompletely defined pathways [7]. Zoledronic acid is approved to treat bone metastases from solid tumors. It was first trialed as an additive to chemotherapy to assess toxicity and feasibility in metastatic osteosarcoma patients in 2013 [8]. The authors found that it was safe to administer alongside chemotherapy, but any clinical benefits were difficult to define due to the small number of patients in the trial [9]. A subsequent trial conducted in a similar fashion with 318 patients, including 55 with metastases at diagnosis, found no clinical benefit for patients who received zoledronic acid and chemotherapy versus chemotherapy alone [10].

Stem Cell Rescue

Many osteosarcoma patients initially respond to chemotherapy, but a challenge in maintaining remission is balancing efficacy with the myelosuppressive activity of these treatments [11]. Autologous stem cell rescue combined with high-dose chemotherapy is an alternative treatment protocol for patients unlikely to respond to standard chemotherapy [12]. Several trials have been conducted over the past two decades using stem cell rescue to enable higher doses of treatment to be administered to patients with metastatic osteosarcoma. Unfortunately, survival rates remained unchanged compared to standard treatment protocols, and patients experienced more severe toxicities as a consequence of the increased chemotherapy doses.

Immunotherapy

The relatively high levels of infiltrating lymphocytes in osteosarcomas compared to other sarcomas [13, 14] have made them a promising candidate for immunotherapies [15, 16]. One of the earliest trials of sole agent immunotherapy against metastatic osteosarcoma explored the efficacy of inhaled granulocyte macrophage colony stimulating factor (GM-CSF) against recurrent pulmonary metastases [17]. Although the treatment had low toxicity, the authors detected no immunostimulatory effects against pulmonary metastases and no improvement in patient outcome [18].

After encouraging results from treating non-metastatic osteosarcoma patients with the immune modulator liposomal muramyl tripeptide (mifamurtide) [19, 20], addition of this agent to chemotherapy was explored in patients with metastatic disease. Mifamurtide activates macrophages and monocytes to stimulate the production of cytokines, which may result in increased anti-tumor activity of infiltrating immune cells. Metastatic osteosarcoma patients treated with chemotherapy plus mifamurtide took significantly longer to relapse than historical controls who just received chemotherapy. However, in the context of a randomized controlled trial, mifamurtide

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unfortunately did not significantly boost the 5-year survival of metastatic osteosarcoma patients compared to those who received chemotherapy alone, although low participant numbers may have precluded detection of a subtle survival benefit. No subsequent trials of mifamurtide in metastatic osteosarcoma have been conducted, but it has been approved by the European Medicines Agency to treat osteosarcoma patients aged between 2 and 30.

The combination of recombinant interleukin 1α and etoposide, which was documented to provoke anti-tumor activity by lymphoid cells, was trialed in eight patients with relapsed metastatic osteosarcoma. Two had progressive disease and the rest partial or mixed responses. Although the clinical response was modest, the authors interpreted these results as a good outcome considering the poor prognosis typically experienced by patients who relapse with metastatic disease. Unfortunately, the trial was stopped early due to a halt in the production of recombinant interleukin 1α.

A high proportion of osteosarcomas, particularly pulmonary metastases, express programmed cell death protein-1 ligand (PD-L1). This suggests that metastases may be especially sensitive to PD-1 inhibitors such as pembrolizumab several trials have evaluated the efficacy of pembrolizumab against metastatic and advanced osteosarcoma, but only one of 49 evaluable patients across three separate trials had a partial response to treatment. Equally disappointingly, the majority of patients with metastatic disease who participated in trials of PD-1 inhibitors, such as nivolumab, camrelizumab and ipilimumab, experienced progressive disease.

Many osteosarcoma patients have human epidermal growth factor receptor 2 (HER2) positive tumors, which formed the basis of a trial evaluating HER2-specific chimeric antigen receptor modified T-cells (CAR T-cells) against HER2-positive sarcomas. Unfortunately, CAR T-cell therapy was no more effective than PD-1 inhibition with 75% of osteosarcoma patients experiencing progressive disease and the remainder only stable disease. Other immunotherapies that rely on the anti-cancer activity of cytotoxic lymphocytes, such as dendritic and T-cell receptor therapies, have failed to improve the outcome of patients with metastatic osteosarcoma.

Although the previously described immunotherapies failed to improve patient outcomes, a prospective study of metastatic osteosarcoma patients who received MAP in addition to IL-2 and lymphokine activated killer (LAK) cell reinfusion yielded more promising results. Of 27 patients who received LAK cell reinfusion and IL-2, 11 remained alive at the time of publication with an overall survival rate of 45% at 130-month median follow up.

The paucity of better-than-expected survival outcomes in osteosarcoma clinical trials summarized above suggests that a dramatic improvement in outcomes for the majority of metastatic osteosarcoma patients will probably require targeting of a novel process or molecule, distinct from those engaged by agents used in clinical trials to date. Hopefully, ongoing pre-clinical research will uncover such game-changing novel targets. Until/unless those approaches bear fruit, extending lifespans for some osteosarcoma patients may hopefully be realized by assembling a panel of therapies that exhibit efficacy in subsets of patients, coupled with development of biomarker assays to enable tailoring of treatments to individual patients.

Conflict of Interest

None

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