Abstract

We provide here a brief review of emerging therapeutic options for metastatic osteosarcomas in the second- and later-line treatment context, favoring clinical outcome data from high-level (preferably randomized or meta-analytic) studies. In the challenging second and later-line setting, we identified and discussed outcome data for four promising agents: pirarubicin, SLIT cisplatin, ridaforolimus, and pazopanib, one of which - SLIT cisplatin - appears to have some specialized benefit in pulmonary-metastatic osteosarcoma. Collectively, this brief clinical review of emerging agents in the two classes of chemotherapy and biological therapies suggests that there are many promising interventions available in current clinical practice, and these can be supplemented from the growing number of innovative clinical trials in progress, or pending.

Osteosarcoma is one of three major types of bone: osteosarcomas, from osteoblast lineage; chondrosarcomas, from cartilage; and primitive neuroectodermal tumors, also called Ewing’s sarcoma. Osteosarcoma is characterized by the production of malignant osteoid or bone produced by malignant spindle cells, and exhibits a primary peak of incidence during adolescence, and a somewhat smaller secondary peak in elder age (median 60 years), and are associated with intense osteoblast proliferation, exposure to ionizing radiation and family history. Although rare, they are nonetheless the most common malignant tumor of bone, accounting for 35% of bone cancer. The most common conventional osteosarcomas are divided primarily into chondroblastic, fibroblastic, and osteoblastic variants, based on the predominant type of matrix produced by the malignant cells, with other more rare forms. Although all osteosarcomas have a challenging prognosis, there are small classes (<10%) of low-grade central, periosteal, and especially parosteal osteosarcomas which are more indolent, and hence associated with better outcomes. In this brief selective review are special focus is on metastatic osteosarcomas, and wherever possible we address interventions with particular promise in the later (second and subsequent) line therapeutic settings.
CHEMOTHERAPIES

L-MTP-PE/Mifamurtide
Liposomal muramyl tripeptide phosphatidyl ethanolamine (L-MTP-PE) [aka mifamurtide (Mepact)], the first new agent approved for the treatment of nonmetastatic osteosarcoma in over 3 decades, was found in a recent randomized trial [1] when combined with ifosfamide to significantly improve the 6-year overall survival of patients with primary osteosarcoma from 70% to 78%. For specifically metastatic osteosarcoma, a recent trial at MD Anderson of L-MTP-PE (NCT00631631) in the metastatic setting has completed but results have not yet been reported, and we would conclude that although promising, without direct metastatic osteosarcoma outcome data, L-MTP-PE remains investigational. A nonrandomized, patient-access protocol [2] assessed efficacy outcomes from the immunomodulator MIFAMURTIDE (Mepact), and although these first results are suggestive of significant impact of mifamurtide on metastatic/recurrent osteosarcoma patient outcomes, we must await more robust randomized data to adopt into clinical practice.

SLIT Cisplatin
Sustained release lipid inhalation targeting (SLIT) Cisplatin is a novel sustained-release inhalation-route formulation of cisplatin, thereby allowing for the targeting of the lungs with little systemic exposure. An open-label, phase IB/IIA trial [3] confirmed the safety and efficacy of SLIT cisplatin in in heavily pre-treated patients with lung-metastatic osteosarcoma who have already received multiple cycles of therapy. Results are promising, with 2 of 14 patients being pulmonary disease free one year after initiation of therapy, and with the agent (SLIT cisplatin) showing exceptional tolerability and near-zero toxicity, while improving survival from 40 to 53%. We would conclude that SLIT cisplatin is especially attractive for osteosarcoma patients with pulmonary metastases.

Pirarubicin
A retrospective study [4] compared the efficacy of anthracycline PIRARUBICIN-based chemotherapy with gemcitabine–docetaxel combination regimens as a second-line treatment for relapsed and refractory osteosarcoma. Patients on pirarubicin-based chemotherapy had a response rate of 25.0 % compared to just 13.0 % in the gemcitabine–docetaxel group. Moreover, the median OS was longer in the pirarubicin-based chemotherapy group (14.0 vs. 9.0 months), especially in the pirarubicin–ifosfamide subgroup (14.0 months) and the pirarubicin-cisplatin (15.0 months) subgroup. These are promising results, and if confirmed in prospective trials, pirarubicin (THP) may prove to be a new and significantly effective agent for the second-line treatment of relapsed and refractory osteosarcoma.

BIOLICAL THERAPIES

Sorafenib
The kinase inhibitor sorafenib (Nexavar) demonstrated activity in terms of progression-free survival at 4 months and median OS of 7 months, but with some unprecedented long-lasting responses [5], yielding a clinical benefit rate/CBR (complete (CR + partial (PR) response + stable disease (SD)) to nearly one of three patients with progressive disease at enrollment; note that all patients were progressing at baseline after receiving standard therapy plus one or two additional lines, thus representing a particularly challenging population.

Ridaforolimus
The selective mTOR inhibitor RIDAFOROLIMUS has been studied in a international, randomized, double-blind, placebo-controlled phase III maintenance trial [6] finding that single-agent ridaforolimus improved PFS in heavily pretreated advanced sarcomas including osteosarcoma, with 28.8% of patients achieving clinical benefit (objective response or stable disease), and a median PFS of 15.3 weeks and median OS of 40 weeks (RECIST confirmed response rate was 1.9%, with four patients achieving confirmed PR (two with osteosarcoma). This has been strongly confirmed in the more recent large randomized placebo-controlled phase III trial [7] which evaluated the mTOR inhibitor ridaforolimus in patients with metastatic sarcoma who experienced benefit with prior chemotherapy, with a modest, although significant, improvement in PFS; thus ridaforolimus administration reduced the risk of progression or death by 28% in patients with advanced soft tissue and bone sarcomas after benefit from immediately prior cytotoxic chemotherapy. Note however that the absolute magnitude of this statistically significant improvement in disease control was nonetheless small, yet ridaforolimus administration did reduce the risk of progression or death by 28% in patients with advanced soft tissue and bone sarcomas after benefit from immediately prior cytotoxic chemotherapy. Note that survival data from the SUCCEED (Sarcoma Multi-Center Clinical Evaluation of the Efficacy of Ridaforolimus) trial (NCT00538239) has now completed although final results have not yet been reported, but preliminary results presented at ASCO 2011 [8] found that PFS was 17.7 weeks in
the ridaforolimus group compared to 14.6 weeks in the placebo group, and although at 15 months, OS was not statistically different between the two groups, it did show a trend toward ridaforolimus (93.3 weeks vs. 83.4 weeks). As a practical footnote, we note that in March of 2012, ridaforolimus was reviewed by the FDA Oncologic Advisory Committee, the Committee voting against approval based on marginal benefit in PFS, lack of survival benefit, and poor tolerability and serious safety issues for a drug that would be used in a maintenance setting. This was followed in November of 2012, by Merck’s withdrawal of its marketing authorization application from the European Medicines Agency, so there appears to be no further investigational activity at this time.

**Pazopanib**

Pazopanib (Votrient), a multi-targeted receptor TKI (tyrosine kinase inhibitor), has been studied in STS (soft tissue sarcomas), most recently with the publication of the results of the multicenter, randomized placebo-controlled phase III PALETTE trial [9] in patients with metastatic STS who had failed prior therapy. Pazopanib increased median PFS by almost three-fold, from 1.6 months for the placebo arm to 4.6 months. The secondary OS endpoint was 12.5 (pazopanib) compared to 10.7 months in placebo arm. Although osteosarcoma patients were not included in this report, single-agent pazopanib activity in patients with chemoresistant sarcomas does suggest that this class of agents may have a role in treating a wide spectrum of sarcomas.

**Trabectedin**

Multiple trials of trabectedin (Yondelis) [10-14], including a retrospective pooled analysis of five phase II trials [15], many in specialized STS populations, have found strong efficacy results and acceptable tolerability for the marine tunicate anticaner agent trabectedin (Yondelis). PFS ranged between 1.9 - 3.3 months, and OS between 9.2 - 13.9 months, although these are ranges across disparate tumor subtypes.

**Methodology Of The Review**

A search of the PUBMED, Cochrane Library / Cochrane Register of Controlled Trials, MEDLINE, EMBASE, AMED (Allied and Complimentary Medicine Database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), PsycINFO, ISI Web of Science (WoS), BIOSIS, LILACS (Latin American and Caribbean Health Sciences Literature), ASSIA (Applied Social Sciences Index and Abstracts), SCEH (NHS Evidence Specialist Collection for Ethnicity and Health) and SCIRUS databases was conducted without language or date restrictions, and updated again current as of date of publication, with systematic reviews and meta-analyses extracted separately. Search was expanded in parallel to include just-in-time (JIT) medical feed sources as returned from Terkko (provided by the National Library of Health Sciences - Terkko at the University of Helsinki). A further "broad-spectrum" science search using SCIRUS (410+ million entry database) was then deployed for resources not otherwise included. Unpublished studies were located via contextual search, and relevant dissertations were located via NTLTD (Networked Digital Library of Theses and Dissertations) and OpenThesis. Sources in languages foreign to this reviewer were translated by language translation software.

**References**


8. Chawla SP, Blay J, Ray-Coquard IL, et al. Results of the phase III, placebo-controlled trial (SUCCEED) evaluating the mTOR inhibitor ridaforolimus (R) as maintenance therapy in advanced sarcoma patients (pts) following clinical benefit from prior standard cytotoxic chemotherapy (CT). J Clin Oncol 2011; 29(suppl): abstract 10005.


