

Bone sarcoma: success through interdisciplinary collaboration

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Abstract

Purpose: Osteosarcoma and Ewing sarcoma are the most frequent malignant bone tumours of childhood and adolescence. This review summarizes the oncologist's view of these diseases and their treatment.

Methods: A non-systematic literature review was performed, the personal impressions and experience of the authors is described.

Results: Local therapy and chemotherapy, each on their own, will not cure patients with malignant bone sarcomas. Together, they present a highly efficacious combination. While the most effective drugs were defined decades ago, progress since then has been limited. It is hoped that substances shown to be active in relapsed disease will be forwarded into even more efficacious frontline treatments. Good palliative therapy is necessary when cure is no longer an option.

Conclusion: Close interdisciplinary collaboration is the key to successful treatment of bone sarcomas in paediatric patients.

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Introduction

Osteosarcoma and Ewing sarcoma are the classic example of what is feasible only by close interdisciplinary collaboration. The (orthopaedic) surgeon alone cannot cure the affected patient, neither can the radiotherapist. The (paediatric) oncologist alone cannot cure the patient. Together with other disciplines such as pathology, radiology, thoracic surgery and others, however, they can turn the majority of affected patients into long-term, disease-free survivors who are able to lead a productive life. This paper will review the essence of this collaboration and will highlight the oncologist's role.

Epidemiology and natural disease course

High-grade osteosarcoma of bone is a typical malignancy of adolescents and young adults. Male children, adolescents and young adults are affected more frequently than female. The primary tumour typically arises in the metaphysis of a long bone, most frequently the femur. Metastases usually involve the lung, less frequently other bones, only rarely other sites. They are present in a minority of patients at diagnosis, but will arise in almost all with local therapy only.^{1,2} Rare variants may be less malignant and treatable by surgery alone. An exact diagnosis by an experienced bone sarcoma reference pathologist is essential.³

All Ewing sarcomas are fully malignant, there are no low-grade variants. This is also a typical disease of adolescence. About half of all cases involve the body trunk, half the extremities. Male children, adolescents and young adults are again affected slightly more often than female. Metastases involve the lungs and distant bones equally, other organs less commonly.^{4,5} Again, diagnosis by reference pathology centre is strongly recommended.³ Ewing sarcoma is characterized by specific genetic alterations, translocations involving the EWSR-gene with a member of the ETS-family, most often FLI1.⁶ Molecular biology should be a routine part of every workup for a suspected Ewing sarcoma. It may be the only chance to distinguish this diagnosis from other tumours such as CIC-DUX4, BCOR-CCNB3 or other, rarer translocations. The distinction between Ewing sarcoma and the so-called Ewing-like sarcomas is essential, as the different tumour types may also be treated differently.⁷

The strong tendency for metastases has major therapeutic implications for both bone cancers: even the most sophisticated operative procedure of the primary alone will not save the patient! Major improvements of the up to then dismal prognosis of both sarcomas occurred only some 45 years ago when adjuvant (postoperative) and a little later neoadjuvant (preoperative) multidrug chemotherapy was added to surgery. Multiple prospective trials and registries have then shown disease-free survival rates of some 50% to 80%, depending on the patients who were included.^{1,2,4,5}

Local therapy: from the oncologist's view

Surgical removal of the primary osteosarcoma and any primary metastases remains a prerequisite for cure in 2021. The type of surgery used does not affect cure rate if the principles of a 'wide' resection⁸ are followed. This means that the tumour and a surrounding, unviolated cuff of normal tissue must be removed *en bloc*. Metastases are operated using this same principle. The surgeon may be aided by the oncologist, as tumours devitalized by preoperative chemotherapy tend to have a lower local recurrence rate.⁹ If wide margins are not achieved, local recurrence and a dismal prognosis are heralded.¹⁰ Modern radiotherapy techniques such as proton therapy may save the occasional patient when complete surgery is not an option.^{11,12} However, complete surgery must remain the first choice in all cases.

In Ewing sarcoma, radiotherapy may also be very effective. Adequate surgery, however, seems to be even more efficacious,¹³ leading to a shift in preferences. Nowadays, operable Ewing sarcomas are usually operated, while radiotherapy remains a viable option for inoperable sites. The same surgical principles as for osteosarcoma must be followed. Radiotherapy may be added after surgery.¹⁴

The discussion about how large the cuff of normal tissue surrounding must be is ongoing for both sarcomas. Fascia probably present a certain barrier to tumour extension. It must be highlighted that everything must go in a correct manner, starting with the biopsy, as any operative errors will lead to local recurrences and often death.^{10,15}

Chemotherapy: why, when, and how

Chemotherapy is always a part of curative therapy for high-grade osteosarcoma and for Ewing sarcoma. In osteosarcoma, four agents have emerged as the most efficacious: Doxorubicin (adriamycin), high-dose methotrexate, cisplatin and ifosfamide. Protocols using at least three of these were found clearly superior to others.¹⁶ Multiple other agents have been tested, none has gained universal acceptance. In Ewing sarcoma, doxorubicin, ifosfamide or

cyclophosphamide, etoposide, vincristine and actinomycin D are heralded as the most efficacious.^{4,5}

Doxorubicin was first introduced into therapy in the 1970s.^{17,18} It may be the most active agent of them all.¹⁹ A major concern is its potential for cardiotoxicity. Attempts to reduce this life-threatening side effect include limiting its cumulative dose, avoiding high peak drug-levels, and coadministration of the cardioprotectant dexrazoxane.²⁰ Analogues have so far not demonstrated equivalence.

High-dose methotrexate entered medical therapy at about the same time as doxorubicin.²¹ Ultra-high doses are required for its efficaciousness and extensive accompanying supportive measures are mandatory. Largely devoid of late effects, it carries the risk for a stop of renal elimination and ensuing severe acute toxicity. This can only be countered by high doses of the antidote, leucovorin and measures to hasten excretion of the drug. In recent years, glucarpidase (carboxypeptidase G2), an enzyme which cleaves methotrexate into less toxic metabolites, has been added to the therapeutic armamentarium for such cases.²²

In osteosarcoma, cisplatin's intra-arterial administration directly into the vessel nourishing the tumour was not shown more efficacious than administering it via the traditional intra-venous route.²³ Important toxicities include renal impairment and hearing loss. The genetic make-up of an individual may influence this largely irreversible toxicity.²⁴ Administration of the drug over a longer period of time in order to lower peak-levels may be beneficial.

Ifosfamide was the last active agent to be introduced against osteosarcoma and is also active against Ewing sarcoma.²⁵ Its analogue's cyclophosphamide's activity seems to be somewhat lower and largely limited to Ewing sarcoma.²⁶ Ifosfamide toxicities include haemorrhagic cystitis, making the concomitant administration of the uroprotector sodium-2-mercaptoethane sulfonate (Mesna) mandatory, and renal electrolyte wasting. The latter becomes more common with increasing cumulative ifosfamide doses.^{27,28}

The epipodophyllotoxin etoposide (VP16) is a part of frontline therapy against Ewing sarcoma and part of some protocols for recurrent osteosarcoma. While other late effects are rare, it carries the risk of early secondary acute myeloid leukemias.²⁹ The drug is, therefore, not given without some hesitation.

The vinca-alkaloid vincristine and the antitumour antibiotic actinomycin D are both associated with acute toxicities, but largely devoid of severe late effects. Both are active against Ewing sarcoma and may be combined with other agents.³⁰ They must be administered strictly intravenously, as they are strong vesicants.

Whilst preoperative, neoadjuvant therapy is part of basically all modern treatment protocols in both sarcoma,^{2,4} it probably does not increase cure rates above those achievable with postoperative, adjuvant therapy

alone. However, it allows time to prepare for optimal surgery and allows assessment of the histological response to the preoperative regimen. This response has emerged as one of the strongest prognostic factors in osteosarcoma³¹ and Ewing sarcoma.³² Unfortunately, attempts to improve the outcome of poor responders by postoperative treatment adaptations have proven completely unsuccessful in osteosarcoma. Most notably, the world's largest ever osteosarcoma trial, EURAMOS-1, failed to show any effect of adding high-dose etoposide and ifosfamide to the poor response regimen.³³

In Ewing sarcoma, the situation is more complex and certain subgroups may benefit from postoperative alterations for poor responders. High-dose chemotherapy plus stem cell rescue benefitted patients with localized disease but a poor response to preoperative chemotherapy in the EURO-E.W.I.N.G.99 trial.³⁴ Using a conventional backbone of vincristine, ifosfamide, doxorubicin and etoposide (VIDE), the trial showed the benefit of adding a single course of busulfan/melphalan high-dose treatment for poor responders. In the same EURO-E.W.I.N.G.99 study, patients with lung metastases did not benefit from high-dose chemotherapy compared with pulmonary irradiation.³⁵

The Children's Oncology Group, representing North America's paediatric oncologists, used a different backbone chemotherapy, vincristine, doxorubicin, and cyclophosphamide (VDC). The success rate of this regimen could be improved by adding ifosfamide and etoposide (VDC/IE).³⁶ They improved the cure rate further by interval compression aided by granulocyte colony stimulating factor,³⁷ but not by further dose-escalation.³⁸ Regimens based on Europe's VIDE and America's interval-compressed VDC/IE were compared in the prospective EURO-E.W.I.N.G.2012 study. Interval compressed VDC/IE emerged as more efficacious and less toxic and is considered the new standard.³⁹

Over the decades, multiple additional trials have been performed by many institutions or cooperative groups. The interested reader is referred to recent reviews.^{2,4,5,40}

What to do in case of recurrence

Approximately 20% to 50% of bone sarcoma patients, depending on selection criteria, will develop recurrences. In osteosarcoma, these may be local or metastatic, with the lung being by far the most commonly affected organ, followed by distant bones.⁴¹ In Ewing sarcoma, the organs at risk are the lungs and bones at approximately even proportions, less frequently others.⁴²

The same surgical principles as described apply to recurrences, be they local or metastatic. Again, all sites

of recurrent osteosarcoma must be removed with wide or radical margins to enable long-term survival.^{41,43} Only a small minority will become long-term survivors of recurrent Ewing sarcoma.^{5,42} Local therapy following the guidelines for primary disease plus a variety of systemic approaches may be attempted.^{5,44}

In recurrent osteosarcoma, the debate about whether to use second-line systemic therapy or to rely on surgery alone is still open. Most investigators agree that solitary recurrences arising more than three years after initial diagnosis can be treated by surgery alone. Other recurrences may benefit from second line chemotherapy,^{41,43} albeit to a much smaller degree than during primary therapy. The optimal drugs are yet to be well defined. Most oncologists would agree to administer any of the clearly efficacious drugs not given during primary treatment. Further options, some but not all supported by phase II trials, include high-dose ifosfamide, carboplatin/etoposide or gemcitabine/docetaxel.

In Ewing sarcoma, the optimal systemic treatment of relapse has also not been defined. A major step forward to filling this void is the ongoing pan-European rEECur study.^{45,46} There, various chemotherapy regimens are tested for their efficacy in a multi-arm, multi-step design. First results have shown gemcitabine/docetaxel,⁴⁵ then irinotecan/temozolomide⁴⁶ to be less efficacious than topotecan/cyclophosphamide or high-dose ifosfamide. The trial is ongoing and other arms may be added.

Multiple non-chemotherapeutic drugs have also been tested in phase II trials, most notably tyrosine-kinase inhibitors.^{44,47,48} A major hurdle in the testing of any new osteosarcoma agent – not true for Ewing sarcoma – is that the tumour's osteoid matrix prevents shrinkage even when the agent in question kills all osteosarcoma cells. Hence, innovative ways to measure a drug's efficaciousness must be sought and found.⁴⁹ Methods used recently to try to define a drug's activity include, for example, randomized comparisons of the time to progression.^{47,48} It remains to be seen if any of the investigated agents will be able to increase cure rates.

What to do when complete surgery and cure are no longer options

An osteosarcoma patient's disease becomes palliative the moment that any lesion is no longer amenable to complete surgery. Extrapulmonary lesions become more and more frequent as the disease progresses, be it as metastases in their own right, by implantation during previous surgeries or as extrapulmonary extension of pulmonary lesions.⁴³ In Ewing sarcoma, treatment can also become palliative at any time of disease progression. Palliative therapy usu-

ally involves caring for young people with inoperable lung metastases in osteosarcoma, caring for young people with inoperable lung or bone disease in Ewing sarcoma, and problems arising thereof. Therapeutic approaches can still be aimed at prolonging life, accepting that cure is no longer an option. The same drugs as mentioned above, particularly if not used previously, may still be active. Treatments, however, tend to become less efficacious with increasing lines of therapy. Their side effects must be weighed against their often limited efficaciousness.

With time, the therapeutic focus must shift towards palliation, as inoperable metastases often herald progression and death.³¹ Potential problems caused by the tumour and its metastases must be known and anticipated. Pain must be taken very seriously and treated accordingly. Appropriate medical steps include a liberal prescribing practice of opioids.⁵⁰ A welcome side effect is that opioids also tend to reduce the drive to breathe and can, therefore, be beneficial in case of progressive lung metastases. Other problems vary by the site of metastatic involvement. Examples include seizures caused by brain compression, pathological fractures of affected bone and even spinal paralysis due to vertebral involvement. Severe pain caused by metastatic organ involvement may be present. The treating physician should consider the use of radiotherapy for selected lesions. While rarely curative in the long run, radiotherapy may temporarily arrest tumour cell growth and reduce selected symptoms.⁵¹ As both osteosarcoma and Ewing sarcoma are tumours often affecting adolescents and young adults, age-appropriate end-of-life communication has to be provided to these patients and their families.⁵²

Outlook into the future

Osteosarcoma and Ewing sarcoma remain incurable for surgeons (or radiotherapists) or oncologists alone, while the majority of affected young patients can be made free of disease if the disciplines work together throughout therapy. The past decades have seen major operative improvements, both related to tumour removal and to reconstruction. Unfortunately, medical therapy has been met with comparatively limited progress, despite numerous attempts to find more efficacious treatments. It is hoped that new, especially targeted drugs, added to standard chemotherapy will be able to break this stalemate. Close collaboration between surgical and non-surgical specialists will remain essential to achieve progress. Only then can the ultimate goal of bone sarcoma therapy be reached: one day, nobody should have to die from these cancers.

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ETHICAL STATEMENT

Ethical approval: This research involved a review of the pertinent literature only. No humans or animals were used. No Institutional Review Board/Ethics Committee was involved in this literature review.

Informed consent: There were no research subjects, hence no informed consent was obtained.

ICMJE CONFLICT OF INTEREST STATEMENT

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AUTHOR CONTRIBUTIONS

SHN: Writing and completion of the manuscript, Read and approved the final version for submission

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