EUROPEAN STANDARD CLINICAL PRACTICE RECOMMENDATIONS FOR CHILDREN AND ADOLESCENTS WITH PRIMARY AND RELAPSED OSTEOSARCOMA

INTRODUCTORY PAGES

- EUROPEAN STANDARD CLINICAL PRACTICE RECOMMENDATIONS FOR CHILDREN AND ADOLESCENTS WITH PRIMARY AND RELAPSED OSTEOSARCOMA
- European standard-of-care guidelines for osteosarcoma
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This document contains guidance for the treatment of primary localized as well as metastatic and relapsed osteosarcoma, including diagnostics, treatment and supportive care. This guidance document assumes the availability of essential facilities, supportive care, medicines and expertise to provide care for the intensive and complex treatments.

This document provides state-of-the-art work-up and management suggestions, including technical guidance on imaging, pathology, and suggestions for further biological examinations. In the absence of current ongoing phase III trials, it aims to provide a consensus document which might be considered standard-of-care and act as a comparator for future phase III trials in childhood and adolescent osteosarcoma.

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1. INTRODUCTION

Osteosarcoma is a malignant tumor arising from primitive mesenchymal bone precursor cells. Production of osteoid and/or bone matrix and the proliferation of malignant mesenchymal tumor cells are key histopathological features (1, 2). Osteosarcoma is the most common primary high-grade sarcoma of the skeleton with three predominant variants: conventional, telangiectatic and small-cell osteosarcoma. Separate entities are high-grade surface osteosarcoma, secondary osteosarcoma, periosteal osteosarcoma, parosteal osteosarcoma and low-grade central osteosarcoma (1, 2).

In 2021, a comprehensive clinical practice guideline on bone sarcomas was published by the European Society for Medical Oncology (ESMO) in collaboration with ERN PaedCan (European Reference Network for Paediatric Oncology), GENTURIS (genetic tumor risk syndromes) and EURACAN (European Network for Rare Adult Solid Cancer) representatives (3). The ESMO-PaedCan-GENTURIS-EURACAN clinical practice guideline was an important update on current therapeutic strategies. In the present document, we describe detailed clinical practice guidance for the treatment of children and adolescents with osteosarcoma, based on most recent published evidence, as part of the European Standard Clinical Practice (ESCP) project. The ESCP project is a collaboration between ERN PaedCan and SIOP Europe's Clinical Trial Groups aiming to develop approved clinical recommendations reflecting current best practice for each common childhood cancer type.

We provide background on the different histological subtypes, clinical subgroups (e.g. metastatic vs. non-metastatic, resectable vs. non-resectable), and discuss the outcomes of the most recent clinical trials. We provide therapeutic guidance for treatment-naïve as well as for relapsed/refractory osteosarcoma. For optimal management as well as for the prospect of continuously improving the understanding of the disease even outside the setting of clinical trials, it is important to define minimal investigations. We will reflect on optimal pathological, radiological and surgical work-up, response assessment and follow-up.

In conclusion, we aim to provide detailed guidance for optimal management of children and adolescents with osteosarcoma.

2. METHODOLOGY

This ESCP guideline has been drafted by RE and NH in accordance with ESMO's standard operating procedures for Clinical Practice Guidelines development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). SB and LK have supervised the development of the draft version. Recommended interventions and regimens are intended to correspond to 'standard' approaches, according to current consensus among the European expert multidisciplinary sarcoma community. Experts involved in the finalization of this guidance document were recruited from the recently established FOSTER ('Fight OsteoSarcoma Through European Research') consortium.

Algorithms accompany the text, covering the main presentations of the disease, are meant to guide the user throughout the text. The relevant literature has been selected by the authors. Levels of evidence and grades of recommendation have been applied using the system shown in Table 1. Statements without grading were considered justified standard clinical practice by the experts.

Table 1. Levels of evidence and grades of recommendation

Levels of evidence	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended

C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs…), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

3. BACKGROUND

3.1 Presentation, diagnosis and initial work-up

Currently, the World Health Organization (WHO) describes conventional osteosarcoma (OS NOS, ICD-O scoring: 9180/3) as an intramedullary high-grade sarcoma in which the tumor cells produce bone. Telangiectatic and small cell osteosarcoma are mentioned as histologic subtypes. Conventional osteosarcoma can be further subdivided according to the predominant matrix, being either osteoblastic, chondroblastic or fibroblastic, but bone formation is required to make the diagnosis. Specific osteosarcoma entities comprise low-grade central osteosarcoma (LGCOS, ICD-O scoring: 9187/3), parosteal osteosarcoma (ICD-O scoring: 9192/3), periosteal osteosarcoma (ICD-O scoring: 9193/3) and high-grade surface osteosarcoma (ICD-O 9194/3) (1, 2). The IICC-investigators (International Incidence of Childhood Cancer) recently reported that bone sarcomas constitute approximately 4.7% and 7.8% of all cancers in children (0-14 years) and adolescents (15 – 19 years), respectively (4). The total estimated number of cases per year in Europe across all age groups is 1135 with a peak incidence of 0.5 cases per 100.000 (standard error < 0.1) between 15 – 24 years (5).

The *etiology* of osteosarcoma is unknown. The incidence of osteosarcoma is increased in children and adolescents with certain cancer predisposition syndromes who harbor, for example, pathogenic variants in *TP53* (as in Li-Fraumeni syndrome) and *RB1* (hereditary retinoblastoma) or in genes encoding DNA helicases like *RECQL4* (Rothmund-Thomson type II syndrome), *WRN* (Werner syndrome) and *BLM* (Bloom syndrome) as well as variants in genes encoding for ribosomal proteins like *RPS19* or *RPL5* (Diamond-Blackfan anemia) (6-8). More recently, in a study which involved 1244 patients with high-grade osteosarcoma, the knowledge on variants in cancer predisposition genes in relation to high-grade osteosarcoma has been significantly extended, and rare pathogenic variants were found to be enriched in DNA repair genes like *BRCA1*, *BRCA2*, *RAD51*, *ATM*, etc. (9). This indicates that failures in the maintenance of genome integrity play an important role in the pathogenesis of this malignancy. Other factors related to the pathogenesis include genotoxic therapies, most importantly radiotherapy (10) and growth/hormonal factors (7). Interestingly, females have an earlier puberty growth spurt than males, this coincides with the peak in high-grade osteosarcoma incidence (6). Moreover, there might be a slightly increased risk of osteosarcoma in children treated with recombinant human growth hormone (11).

Clinically, children and adolescents with osteosarcoma present with localized swelling, pain, and limitations of joint movement due to local expansion of, and tissue destruction by, the tumor. The metaphyses of the long bones proximally and distally of the knee are the most frequent tumor locations in up to two thirds of the patients. This localization is followed by the proximal humerus and, less frequently, the axial skeleton (12, 13). Children are most commonly diagnosed during adolescence (incidence 4.4 cases per million individuals), with a higher prevalence in boys (approx. ratio 1.3:1) (14-18).

In case of suspected diagnosis of a bone sarcoma, imaging of the probable primary tumor site starts with conventional radiography in at least two planes. A combination of bone destruction and osteoid formation is suggestive of osteosarcoma with a typical, but not specific, phenomenon of a “Codman triangle”, which can arise due to a lift of the periosteum (19, 20). In case of a suspected bone tumor, an MRI covering the whole anatomical compartment and the adjacent joints is indicated to evaluate the primary tumor (size), its relationship with surrounding tissues, the presence of skip lesions (i.e. additional osteosarcoma foci within the same bone, stage III tumors) and the relationship to joints, which are all essential to guide the later surgical treatment approach possibilities (e.g. limb-sparing techniques vs. amputation). MRI is the modality of choice due to the superior delineation of soft-tissues as well as intra-osseous extension and should include T1, T2, fat sat and post-contrast sequences. A CT scan may be of added value in uncommon sites like the skull (19, 21-26). Diffusion weighted imaging (DWI) and dynamic contrast enhanced (DCE) imaging sequences are often part of an oncological MRI acquisition, aiming to predict tumor response to preoperative chemotherapy. Currently, however, no evidence supports its use in clinical decision making (27-30).

The site for a *biopsy,* either core needle or open, incisional biopsy, should be selected based on the imaging results and discussed and planned in collaboration with an orthopedic surgeon and/or experienced dedicated interventional radiologist. The biopsy site and procedure must be performed in such a way that the entire biopsy tract can later be excised during definitive surgery. It is recommended to perform the biopsy in a center of expertise as this leads to fewer local relapses and better outcomes (31-33).

Pathological diagnosis should be performed according to the WHO 2020 guidelines (1-3). The identification of neoplastic bone formation seen on hematoxylin/eosin staining is to the defining feature of the histopathological diagnosis. A permeative growth pattern of the tumor is usually identified, with replacement of bone marrow and destruction of pre-existing trabecula. Typically, the tumor cells demonstrate severe anaplasia and pleomorphism, with abundant atypical mitotic figures present. Immunohistochemistry is usually not helpful (1, 2). In cases of diagnostic uncertainty, DNA methylation and copy number profiling can support the diagnosis, but cannot replace the defining morphologic features (34). Genetically, osteosarcomas are diverse and harbor variation high degree of inter- and intratumoral heterogeneity. There are generally multiple structural aberrations caused by chromoanagenesis as well as localized hypermutation patterns (kataegis). The most frequent mutation affects the TP53 gene, including translocations of intron one, as well as RB1 (35); as such osteosarcomas show the highest genomic instability among pediatric cancers. To date, no treatment-stratifying genetic biomarkers have been identified.

In confirmed high-grade osteosarcoma, *staging* should include a high-resolution chest CT to evaluate for pulmonary metastatic disease, as high-grade osteosarcoma primarily metastasizes to the lungs and surgery of pulmonary lesions is essential for curative treatment (36, 37). Studies have shown chest CT to be superior to conventional radiographs for the diagnosis of pulmonary metastases, mainly in detecting smaller nodules (19, 38, 39). Despite superior detection, studies comparing CT imaging to open thoracotomies have demonstrated that CT still misses an important number of metastatic lesions (40, 41). The question whether surgery of these sub-centimeter lesions in oligometastatic disease impacts survival remains open (41). Concerning the definition of imaging-classified lung metastases, studies have shown no specific criteria, neither size nor characteristics, can clearly diagnose nodules to be benign or malignant (39, 42, 43). The EURAMOS-1 investigators have arbitrarily defined “certain” pulmonary metastases as one or more pulmonary/pleural nodule(s) of 1 cm or larger; or three or more nodules of 0.5 cm or larger maximum diameter. Fewer or smaller lesions are defined as “indeterminate” but should be considered “possible” metastatic disease and pathological assessment is advised particularly if these lesions persist on chest CT after neoadjuvant chemotherapy (44).

In high-grade osteosarcoma, metastases to the bone or (extremely unusual) to other tissues are rare (37). Nevertheless, staging should also include a body-wide screening for such spread. The current recommended modality is - at least - a bone scintigraphy. However, where available, [18F]2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)-CT or PET-MRI, whole-body (WB) -MRI, are increasingly utilized (45-50). Some studies, retrospective and of limited size, have shown better detection of non-pulmonary metastases by FDG PET-CT as compared to conventional imaging (bone scintigraphy) (49, 51). However, no prospective studies have been performed with sufficient number of patients to show that a higher detecting rate translates to improved survival. Other FDG-PET studies have investigated the prognostic value of standardized uptake values, quantified FDG-PET indices. Potentially, quantified uptake of the primary tumor might be correlated with histologic response or survival (52, 53), but larger prospective studies are needed before recommendations can be made.

In conclusion, staging in osteosarcoma, should include conventional radiographs of the primary tumor, an MRI of the primary tumor (incl. assessment of joints, skip lesions), a chest CT and whole-body imaging. Imaging should be performed closely, and no longer than 28 days, before start of chemotherapy to prevent misclassification of response on neoadjuvant therapy.

Before initiation of chemotherapy, baseline organ function should be evaluated, see supplement 1. With the patient and family side-effects and outline of proposed therapy should be discussed, next to fertility and fertility preservation in line with international guidelines (54, 55).

Diagnostic recommendations - Level of evidence and grade of recommendation		Ref
In case of suspected bone sarcoma, early patient referral to a reference center for diagnostic work-up and management of disease is recommended.	IV, A	(31, 32)
In case of suspected bone sarcoma, plain radiographs and an MRI of the primary tumor (including the whole compartment and adjacent joints) are recommended to be made prior to biopsy.	III, A	(20, 23, 24, 26)
It is recommended to plan and perform a biopsy in collaboration with an oncology-experienced orthopedic surgeon and/or interventional radiologist.	IV, A	(31-33)
Histopathological diagnosis is recommended to be performed according to the WHO 2020 guidelines.		
In confirmed high-grade osteosarcoma, a high-resolution chest CT is recommended for evaluation of pulmonary metastatic disease	III, A	(36-38, 40, 41)
Whole body staging is recommended to screen for non-pulmonary metastases. If available FDG PET-CT, FDG PET-MRI, whole body MRI are recommended modalities, or at least bone scintigraphy.	III, A	(37, 45, 47, 49-51, 56-58)

3.2 Management of primary high-grade, resectable, osteosarcoma

High-grade osteosarcoma is the most common bone sarcoma of childhood, with a peak incidence in adolescence (14-18). A separate entity, high-grade surface osteosarcoma, should be similarly treated as high-grade osteosarcoma (59, 60). The current treatment approach is heavily reliant on combining multi-agent chemotherapy with aggressive surgery. Before the introduction of chemotherapy, where surgery was the only treatment, 80-90% of the patients developed lung metastases in the years after diagnosis, consistent with the hypothesis that pulmonary micrometastases are present at diagnosis in the majority of patients (61, 62). In early multi-institutional trials, a drastic improvement of survival was observed, with 2-year survival rates rising from ~20% to ~65% (62, 63). Over the following decades, study groups such as the North American Children's Oncology Group (COG), the Cooperative Osteosarcoma Study Group (COSS), the European Osteosarcoma Intergroup (EOI), the French Bone Sarcoma group (SFCE and GSF-GETO) and the Scandinavian Sarcoma Group (SSG) have made international collaborative efforts with the aim to improve therapy (64-71). For patients with localized disease, recent prospective clinical trials have achieved five-year event-free- (EFS) and overall survival (OS) rates of 60% and 70-80%, respectively. Patients with known primary metastatic disease perform considerably worse with 5-year EFS rates of ~30% and 5-year OS of ~45% (44, 64, 65, 71, 72). Unfortunately, treatment intensification by addition of more chemotherapeutic agents did not yield improved survival in the investigational arms of the latest randomized clinical phase III trials (64, 65).

The most common current treatment approach for high-grade osteosarcoma combines neoadjuvant multi-agent chemotherapy followed by aggressive surgery, aiming for complete resection with wide margins (including re-resection in case of intralesional resection), and adjuvant chemotherapy. A combination of three drugs seems superior in terms of efficacy and/or toxicity as compared to regimens containing either 2 (73), 4 (74), or 5 drugs (64, 75). The EURAMOS-1 trial has been the largest international phase III trial where the standard arm including methotrexate, doxorubicin and cisplatin (MAP) (65) (based on the COG INT-0133 trial (76, 77)) was non-inferior to investigational arms. In addition to the EURAMOS-1 standard arm, other regimens have shown efficacy. These include the French Sarcome/OS2006 approach, including methotrexate, ifosfamide and etoposide. This study aimed to investigate an alternative regimen to MAP with the aim to limit long-term toxicities of doxorubicin and cisplatin (71). Furthermore, the efficacy of other combination regimes omitting methotrexate, such as the St. Jude OS99 (78) and the API-AI regimen (79) might provide alternatives in case of methotrexate-intolerability or contraindications. The results of these studies and studies investigating muramyl tripeptide will be presented and discussed.

EURAMOS -1

EURAMOS-1 was an open-label, international, randomized, phase III, controlled trial. The trial included children and adults below the age of 40 with high-grade resectable non-metastatic and metastatic osteosarcoma of the extremity or axial skeleton including those arising as second malignancies between 2005 and 2011. Following neoadjuvant chemotherapy, the histologic response of the primary tumor was stratifying for different randomizations. Poor histological response was defined as 10% or more vital tumor present at histological assessment. The standard preoperative treatment was MAP and after evaluation of histologic response two randomizations were performed. In case of good histologic response, the addition of Interferon alfa-2b, based on the previously observed anti-osteosarcoma activity of alpha interferons against osteosarcoma (80) and, in case of poor histologic response, the adjuvant treatment augmentation with ifosfamide at 2.8 g/m^2, combined with etoposide at 100 mg/m^2 per day, on days 1 to 5, MAP-IE, was investigated. 716 patients with a good histologic response showed no statistically significant survival benefit of adding Interferon alfa-2b maintenance to standard postoperative chemotherapy (65). However, a considerable proportion of patients never started Interferon alfa-2b or stopped prematurely. 618 patients with a poor histologic response showed no survival benefit of the addition of ifosfamide and etoposide to postoperative chemotherapy despite an increase in toxicity (64). Post-analyses of the full cohort, n=2186, with 93% of patients with a conventional osteosarcoma and a median age of 14 years, were published sequentially with a median follow-up of 54 months (44). For the full registration cohort, 5-year EFS was 54% (95% CI: 52 – 56%) and 5-year OS was 71% (95% CI: 68 – 73%). In patients with localized disease 5-year EFS and OS were 60% (95% CI: 57 – 62%) and 76% (95% CI: 74 – 78%), respectively. In patients with metastatic disease, 5-year EFS and OS rates were 28% (95% CI: 23-33%) and 45% (95% CI: 39 – 50%), respectively. The most common event was the detection of new metastases (53% of events). In non-metastatic patients who achieved complete surgical remission 3 to 6 months after diagnosis, the 5-year EFS and OS were 64% and 79%, respectively (44). Acute toxicities led to dose reductions in 58% of all patients treated with MAP and 86% experienced a grade 4/5 toxicity. Most important acute non-hematological toxicities were electrolyte disturbances, acute kidney injury and raised bilirubin. Left ventricular cardiac dysfunction grade 1/2 was identified in 15% of patients and hearing problems in 25% of patients (64). Long term toxicity data is currently not available of the EURAMOS study.

The French OS 2006 study

The French OS 2006-study was a multicenter national study for patients with high-grade osteosarcoma which included a phase III randomized trial investigating the impact on outcome of adding zoledronate to the standard treatment (NCT00470223) (71). First results showed no added benefit of zoledronate (72). The study also aimed to identify an alternative to MAP, which would then result in similar survival but less long-term cardiotoxicity (doxorubicin) and ototoxicity (cisplatin) (81) in a sub-cohort of young patients with high-grade osteosarcoma. The neoadjuvant chemotherapy in patients aged <18 years (and also in a selected group of 55 patients aged between 18 and 25 years) consisted of 7 courses of high-dose methotrexate (HD-MTX) (vs. 4 courses in EURAMOS-1), and two courses of etoposide and ifosfamide (M-EI) followed by surgery. Postoperative chemotherapy consisted of M-EI in patients with good histologic response and M-AP in patients with poor histologic response, limiting the exposure to cisplatin and doxorubicin of patients with good prognostic markers. All adults above 25 years of age were treated with a combination of doxorubicin, cisplatin and ifosfamide (API-AI). For patients aged 18 and 25 years, centers decided at the start of the study which regimen would be used, i.e. between the methotrexate based M-EI or the API-AI regimen.

Between 2007 and 2014, 522 patients were enrolled. Safety and efficacy were reported for all patients up to 25 years of age treated according to the M-EI regimen. 409 patients were analyzed with a median follow-up of 4.8 years. Reported 5-year EFS was 56% (95% CI, 51-62%) and 5-year OS 71% (66-76%). After 14 weeks neoadjuvant M-EI (vs 10 weeks EURAMOS-1) 73% of these young patients (up to 25 years vs up to 40 years EURAMOS-1) achieved good histologic responses (71). The outcomes of a total of 187 young patients with localized completely resected high-grade osteosarcoma with good histologic response treated with M-EI were reported (71). The median follow-up for this cohort was 4.8 years. Whereas cardiotoxicity and ototoxicity can be avoided via the M-EI treatment, other toxicities like gonadotoxicity and nephrotoxicity (renal Fanconi syndrome) potentially caused by high doses of ifosfamide (cumulative dose of 60 g/m^2) need to be considered and carefully monitored for. Furthermore, the use of etoposide in younger patients with high-grade osteosarcoma (cumulative dose 1.2 g/m^2), especially in the context of cancer predisposition syndromes, should be monitored as etoposide might increase the risk for secondary leukemia (9). Long-term outcome and toxicity data from M-EI should be monitored and are currently being analyzed in OS2006 trial. M-EI may be a treatment to be considered for individuals who will not tolerate doxorubicin or cisplatin. Furthermore, 106 patients were treated with API-AI. The median age was 30.2 years, with only 40 patients between 18 – 25 years of age. The median follow-up was 4.8 years (range 0.2-8.1). 5-year EFS and OS of 46% (95% CI: 36 -56%) and 57% (95%CI: 47 – 67%), respectively, were reported (79, 82).

The St. Jude OS99

The OS99 protocol may be considered in young patients suspected not to tolerate HD-MTX. This St. Jude Children's Research Hospital protocol, from North America, included patients under the age of 25 years with a non-metastatic, resectable, high-grade osteosarcoma into a single center protocol between 1999 and 2006. It combined ifosfamide, doxorubicin and carboplatin. 72 patients were enrolled with a median age of 13.4 years. The median follow-up was 5.1 years with a 5-year EFS of 66.7% ± 7.0% and 5-year OS of 78.9% ± 6.3, respectively (78).

Table 2. Number of patients in study and cumulative chemotherapy dose for each treatment protocol

	Number	Doxorubicin	Cisplatin	Methotrexate	Etoposide	Ifosfamide	Carboplatin
EURAMOS-1 (GHR)[1]	716	450 mg/m^2	480 mg/m^2	144 g/m^2			
EURAMOS-1 (PHR)[2]	618	450 mg/m^2	480 mg/m^2	144 g/m^2	1500 mg/m^2	60 g/m^2	
OS 2006 (GHR/L/R)[3]	212			228 g/m^2	1200 mg/m^2	60 g/m^2	
OS 2006 (PHR/M+/U)[3]	164	375 mg/m^2	600 mg/m^2	144 g/m^2	600 mg/m^2	24 g/m^2	
OS 2006 API-AI (GHR)[4]	106*	420 mg/m^2	500 mg/m^2			54 g/m^2	
OS 2006 API-AI (PHR/M+/U)[4]		300 mg/m^2	300 mg/m^2		1500 mg/m^2	90 g/m^2	
St Jude OS99	72	375 mg/m^2				63,6 g/m^2	8* AUC 8 mg/ml x min
ISG/OS-2	194	420 mg/m^2	600 mg/m^2	120 g/m^2		60 g/m^2	

1 RCT randomizing the addition of Interferon alfa-2b

2 RCT randomizing the addition of ifosfamide and etoposide

3 RCT randomizing the addition of zoledronate

4 106 patients were included in the analysis of the OS 2006 API-AI regime

GHR: good histological response; PHR: poor histological response; L: localized; R: resectable; M+: metastatic disease; U: unresectable disease

Mifamurtide

Mifamurtide, a liposomal formulation of muramyl triphosphate phosphatidylethanolamine, L-MTP-PE, is an immunostimulatory drug. It has been investigated as an addition to standard adjuvant chemotherapy in high-grade osteosarcoma patients. The hypothesis of the immunomodulatory effect is based on the rare phenomenon of regression of tumors after infections, where activation of the immune system might add to the eradication of micrometastases (74, 83-85). Most commonly reported acute side effects are chills, fever, fatigue, nausea, tachycardia and headache with mild to moderate CTCAE grade (86).

The INT-0133 trial was a randomized phase III trial in patients with high-grade localized osteosarcoma. The aim was to investigate the potential added value of ifosfamide and the addition of liposomal mifamurtide to MAP in a two-by-two factorial design. 677 patients below the age of 30 years were included. In a first analysis, there was no added value of the addition of ifosfamide, with a 3-year EFS rate of 68% in the group that received a combination of mifamurtide and MAP (with methotrexate up to 20 g/m^2 per cycle) and a rate of 78% for those who received mifamurtide combined with MAP and ifosfamide (9 g/m^2 per cycle). An interaction between ifosfamide and mifamurtide and no significant benefit for mifamurtide were reported (76). Subsequently, with different analysis cut-off points (i.e., 6-years OS), the investigators reported improved overall survival rates in patients who were randomized to receive mifamurtide (77). The results of this trial, however, were confounded by a possible interaction between ifosfamide and mifamurtide. Currently, it remains questionable if mifamurtide can really help to improve outcomes in patients with high-grade osteosarcoma (83, 87, 88). Therefore, the US Food and Drug Administration (FDA) did not approve the drug. Mifamurtide, however, received marketing authorization in the EU by the EMA for patients aged 2–30 years with newly diagnosed, nonmetastatic osteosarcoma (83).

The ISG/OS-2 trial was a single-arm phase II trial for patients with non-metastatic osteosarcoma of the extremities < 40 years, with a median age of 14 years. All patients received MAP for induction chemotherapy. Patients with ABCB1/P-glycoprotein expression received adjuvant mifamurtide. Furthermore, in ABCB1/P-glycoprotein positive patients with a poor histological response to neoadjuvant chemotherapy, mifamurtide was combined with four consecutive cycles of high-dose ifosfamide. The EFS was compared to historical series (89, 90) and considered superior. Reported 5-year EFS rate was 69.8% (90% CI, 62.2%-76.2%). The impact of ifosfamide on EFS, which was added in the case of ABCB1/P-glycoprotein positivity and a poor histological response to preoperative chemotherapy, remains unknown, nor is it clear whether the interaction with mifamurtide was synergic (91).

Surgery

Surgery of the primary tumor and metastatic lesions with wide resection margins is essential if treatment is to be with curative intent (92-95). In non-metastatic osteosarcoma the timing of surgical resection of the primary tumor is preferably planned around neo-adjuvant chemotherapy, but can be performed at diagnosis. One randomized trial, including 100 patients, showed no differences in survival nor potential for limb salvage between direct surgery and surgery after 10 weeks of neoadjuvant chemotherapy (96). However, neoadjuvant chemotherapy provides the possibility for assessment of pathologic response to chemotherapy and provide for optimal planning of surgery. Additionally good tumor response to chemotherapy provides for optimal surgical margins, as it will allow for less invasive surgery (97). In non-metastatic tumors of the extremity, limbs salvage procedures can often be performed with adequate and free surgical margins (95). When wide margins can be expected, amputation does not provide any survival benefit over limb sparing surgery (98, 99).

The optimal surgical approach for lung metastases is part of ongoing discussion. Historically, thoracotomy with palpation of the lung was advised. With the availability of high resolution CT scans smaller lung metastases are more likely to be identified by imaging. There might therefore potentially be a role for minimally-invasive surgical techniques in oligo-metastatic disease. Up to one third of the surgeons approach oligo-metastatic disease by video-assisted thoracoscopy (100). However, no prospective trials have yet been performed. A retrospective analysis of 202 pediatric patients (thoracotomy (n = 154) or thoracoscopy (n = 48)) showed no difference in event-free and pulmonary-relapse free survival between both techniques. The findings, however, are limited by significant selection bias (41). A prospective trial comparing thoracotomy versus thoracoscopy by the COG is currently ongoing in upfront and relapsed/refractory osteosarcoma.

Prognostic factors / risk stratification

In multiple trials prognostic factors associated with a poor prognosis were analyzed. Metastatic disease, inadequate surgical margins, non-extremity osteosarcoma, proximal osteosarcoma, male gender, older age, a large tumor volume (with the cut-off

mostly being > 8 cm or ≥1/3 of the involved bone diameter) and a poor histological response after neoadjuvant chemotherapy (poor histological response defined as ≥10% viable malignant cells in the resected primary tumor) were consistently associated with poor outcomes (44, 64, 65, 71, 72, 101-103). Ilcisin et al. developed risk groups at diagnosis based on 3069 patients less than 50 years of age registered in the Surveillance, Epidemiology, and End Results (SEER) database, where metastatic disease, axial tumor localization and tumor size were important variables for risk stratification in people < 39 years of age, see figure 1. Unfortunately, incomplete data and the inclusion of adult patients limits the applicability in childhood osteosarcoma (104).

Staging systems

International staging systems, like those of the American Joint Committee on Cancer (AJCC), the Enneking Musculoskeletal Tumor Society (MSTS), and the Vanderbilt Osteosarcoma staging system all seem to perform similarly well (105-107).

Discussion

Combined with tumor surgery, intensive chemotherapy has led to approximately 70% 5-year survival rates for patients with resectable high-grade osteosarcoma. Large-scale clinical trials have unfortunately not resulted in significantly improved survival rates over the last four decades. Based on current available evidence, the MAP regimen from the EURAMOS-1 trial could be considered the standard of care in osteosarcoma. The French M-EI approach reported similar outcomes in a far smaller group of patients (64, 65, 71, 108). While analyses of both long-term outcomes and toxicities of M-EI are still ongoing (gonadotoxicity, nephrotoxicity and induction of secondary leukemia/MDS), M-EI might be an alternative for patients with pre-existing hearing loss or cardiac disease. Future studies should thus aim to improve both survival, in particular for patients with poor risk markers, and decrease chemotherapy induced organ toxicities. As such, M-EI might be an alternative in patients where auditory and cardiac toxicities want to be avoided. In case of contraindications to methotrexate the St. Jude OS99 (78) or the API-AI regimen (79) might be an option, or in patients where methotrexate toxicity want to be avoided.

Current standard systemic therapy is a 3-drug chemotherapy regimen (3, 75, 109). Similar outcomes have been reported with 4-drug regimens, and poorer outcomes with 2-drug regimens (75, 110). Very few patients (< 10%) may survive with ablative surgery alone (61, 62) and only up to 50% treated with 2-drug regimens (73, 74). Stratification and treatment intensification according to currently known prognostic factors have not overcome the observed prognostic stagnation. It remains essential to establish novel stratification strategies in order to identify those patients eligible for dose reductions (and therefore reductions of chemotherapy induced organ toxicities) and to introduce novel therapies for those patients known to have poor prognostic features. A subtlety worth mentioning is that a gap between intended and received chemotherapy intensity seems to be associated with poorer survival (111). Furthermore, insight into chemotherapy resistance and pharmacogenomics will hopefully allow for more individually tailored chemotherapy regimens in the future (74, 112, 113).

The use of mifamurtide is a matter of ongoing debate among clinical and regulatory experts. The European Commission has granted marketing authorization to mifamurtide combined with postoperative chemotherapy in localized osteosarcomas but not in patients with metastatic disease, while the FDA has denied this authorization (83, 86). Unfortunately, a definitive prospective randomized trial comparing MAP versus MAP with mifamurtide was not supported by industry. Trials like the current French Sarcome-13/OS2016 randomized phase II trial (NCT03643133) and the ISG/OS-2 single-arm trial (NCT01459484, NCT04383288) (91) were not designed to address the question of the added value of mifamurtide to MAP. Further prospective, randomized trials would definitely be required to better define the potential benefits vs. none of mifamurtide against osteosarcoma.

Recommendations for high-grade, resectable, osteosarcoma - Level of evidence and grade of recommendation		Ref
• Patients with high-grade osteosarcoma should be treated with three-drug chemotherapy in combination with aggressive surgery aiming for wide resection margins.	I, A	(62-65, 71, 74, 76, 77)
• Patients with primary resectable metastatic high-grade osteosarcoma should be treated following the same principles as non-metastatic osteosarcoma plus complete surgical resection of all metastatic sites.	I, A	(62-65, 71, 74, 76, 77)
• Surgery of the primary tumor and metastatic lesions with wide resection margins is essential if treatment is to be with curative intent.	III, A	(92-95)
• The MAP regimen (methotrexate, cisplatin and doxorubicin) could be considered a standard for current osteosarcoma treatment.	I, A	(64, 65, 76, 77)

• The M-EI regimen (methotrexate, ifosfamide and etoposide) might pose an alternative to the MAP regimen in patients with a contra-indication for cisplatin or doxorubicin.	III, B	(71, 81)
• In case of a contra-indication to methotrexate, the St. Jude OS99 and the API-AI regimens provide reasonable alternative treatment approaches.	III, C	(78, 79, 114)
• Due to lack of clear evidence for a benefit of additional mifamurtide, this is not a part of current standard treatment.	II, C	(76, 77, 83, 115, 116)

3.3 Management of primary high-grade, unresectable, osteosarcoma

As described for the management of resectable osteosarcoma, aggressive surgery aiming for wide margins of the primary tumor and complete metastasectomy are the cornerstones of curative treatment. Therefore, osteosarcoma for which complete resection of either the primary tumor or metastases is not feasible is particularly challenging. This includes synchronous multifocal osteosarcoma (117).

At first, it is crucial to evaluate whether there might be any possibility to transform a non-resectable primary or metastatic osteosarcoma lesion into a resectable one via chemotherapy. It is up to debate whether neoadjuvant chemotherapy, as recommended for resectable osteosarcoma, can increase resectability in terms of tumor reduction (96, 118-120). However, delineation of the tumor's boundaries might be improved in patients whose tumors have a good response to chemotherapy (121, 122). Whereas patients with chemosensitive tumors can benefit from neoadjuvant chemotherapy, the situation can become detrimental in patients who have tumors that do not respond (121). In some case reports, improved resectability has been described following high-dose radiotherapy (123, 124).

In case of definitively unresectable localized or oligo-metastatic osteosarcoma, intensive radiotherapy, with doses of 70 gray (Gy) or higher, is recommended for local therapy, whereas debulking surgery does not appear to confer a survival benefit and should only be considered to improve quality of life (for example primary tumor resection in case of pain) (125, 126). Evidence is based on non-randomized studies with limited patient numbers, where heavy-ion and proton beam therapy are considered to be the modalities of choice, and sometimes are combined (125, 127-131). In series describing the treatment of unresectable osteosarcoma, with very high-dose radiotherapy being used as an alternative to achieve local control, 5-year OS of 67% was reported as encouraging result (125, 131, 132). However, current evidence only includes case-series. As this group is often excluded from trials, the evidence grade for this guidance in children and adolescent with unresectable osteosarcoma is low. A recent review summarized the current North American and European radiotherapy treatment in osteosarcoma (133). In case of multi-metastatic osteosarcoma, widely disseminated disease, treatment is often not curative. Case series describe longer symptom control with radiotherapy to metastatic sites, often 40 Gy or higher, in symptomatic patients (134). In those cases hypofractioned or stereotactic radiotherapy could be considered(135, 136) We consider the use of chemotherapy, radiotherapy and (palliative) surgery to be useful with focus on quality of life and balanced on individual basis.

Recommendations for high-grade, unresectable, osteosarcoma - Level of evidence and grade of recommendation		Ref
• Diagnostic work up and staging is similar to resectable osteosarcoma.	III, A	(20, 23, 24, 26)
• Neoadjuvant chemotherapy and radiotherapy can be considered in an attempt to achieve resectable disease.	IV, B	(123, 124)
• High-dose radiotherapy can be considered as local therapy in definitively unresectable local or oligo-metastatic disease. Chemotherapy, as recommended for resectable osteosarcoma, should be administered if the approach is curative.	IV, B	(125, 127-130)
• In multi-metastatic unresectable osteosarcoma therapies considered should be balanced with quality of life.		

3.4 Management of relapsed or refractory high-grade osteosarcoma

Relapsed/refractory osteosarcoma remains a major challenge, occurring in around one third of the patients (44, 64, 65). Most patients in this cohort present with metastatic disease, with lung metastases in up to 80%. The overall survival of patients with relapsed/refractory osteosarcoma remains poor. 5-year overall-survival hovers below 30%, in subgroups ranging from 13% to 57%. Achieving a second surgical remission strongly improves the chance for survival. Not achieving this milestone is associated with an extremely poor prognosis, ranging from 0 to 8% 5-year OS (137-141).

The management depends on the localization of the relapse (local vs metastatic), the time of the relapse, the number of metastases, and the metastatic sites. Early relapses (in most studies defined ≤ 18 months) have a worse prognosis than late relapses (138, 139, 142-146). Survival of patients with two or less lesions at relapse is better as compared to disseminated relapse (137, 139). Next to the inability to reach a second surgical remission, relapses shortly after therapy or relapses including bone metastases have a very poor survival (137, 139, 141). When treating relapsed/refractory osteosarcoma, the chance to cure has to be balanced with the toxicity of curatively intended treatment, which is important when discussing with patients as part of advanced care planning (147, 148).

Aggressive surgery should be performed where feasible, including re-surgery in case of subsequent relapses (36). Complete removal of all lesions, including locally relapsed/refractory osteosarcoma (10-20% of relapses) or osseous metastases should be attempted (149). In case of any inoperable lesions or in case of preference for non-thoracotomic approaches in multi-repetitive relapsed patients or as part of palliative treatment, stereotactic RT (134, 150, 151) or thermo-ablation including radiofrequency or microwave (152, 153) might be alternatives for local control of pulmonary lesions.

The benefit of chemotherapy or radiotherapy in relapsed osteosarcoma remains debatable, as randomized controlled clinical trials in this situation are lacking. The optimal systemic treatment approach for relapsed osteosarcoma therefore remains ill-defined. Retrospective analyses showed either no improved outcome with chemotherapy added to surgery (137, 146, 154-156) or demonstrated a moderately improved outcome (56, 139, 157-160). Regarding the choice of second-line systemic therapy, exposure to previous agents frequently precludes the use of anthracyclines and cisplatin. Ifosfamide or cyclophosphamide, often combined with etoposide or carboplatin, are best studied (138, 139, 161-163). Conflicting results are published concerning the combination of gemcitabine with docetaxel (164-167). In current expert view, ifosfamide (9 to 14 g/m^2/cycle) with or without etoposide (300 to 500 mg/m^2/cycle), are the most often used second-line chemotherapy regimens.

No new agents have been evaluated in phase III trials in relapsed/refractory osteosarcoma. Phase II trials with tyrosine kinase inhibitors (TKIs) have demonstrated some clinical efficacy of such agents, including regorafenib (median PFS of 3.6 months vs 1.7 months in controls (168) and 8 week PFS of 65% versus 0% in controls (169)), sorafenib (4 month PFS of 46% (170)), cabozantinib (4 month PFS of 71% (171)), apatinib (4 month PFS of 57% and 6 month PFS of 37% (172)), and lenvatinib (4 month PFS of 33%) (173). In search of improved efficacy, such TKIs have been combined with everolimus (174)) or chemotherapy (173, 175). The use of different trial designs with different endpoints in predominantly single arm studies prohibits direct cross trial comparisons. TKIs could, however, be considered as alternatives/additives to chemotherapy, ideally to be given in the context of a phase III trial (168-170, 174). Next to TKIs, COG has identified immunotherapies targeting B7-H3, CD47-SRIPα inhibitors, telaglenastat, and epigenetic modifiers as agents of future interest (176). These need to be evaluated in carefully designed trials, using optimal endpoints, addressing the difficulties of generally used response markers in osteosarcoma (66, 177).

In summary, relapsed/refractory osteosarcoma is challenging to treat. Surgery aiming for a renewed surgical remission of all tumor-sites is essential for a curative intent. It is highly recommended to include affected patients into clinical trials. Chemotherapy, most often ifosfamide ± etoposide or other combinations dependent on previously given therapies (e.g., IE or CE after MAP or AP after M-EI), is recommended to be considered in the absence of accessible clinical trials in patients with early local or metastatic relapses.

Recommendations for high-grade, refractory or relapsed, osteosarcoma - Level of evidence and grade of recommendation		Ref
• Surgery and, if necessary, re-surgery are strongly recommended in resectable, relapsed/refractory osteosarcoma.	II, A	(36, 137-139)
• Chemotherapy might be considered in multi-metastatic, unresectable relapses or in early relapses.	III, B	(138, 139, 146, 158-160)
• Chemotherapy or experimental therapies should be preferably given in the context of osteosarcoma-specific clinical trials.	V, B	(66, 177)
• Tyrosine kinase inhibitors (sorafenib, regorafenib, cabozantinib, lenvatinib, apatinib) have demonstrated some efficacy in small phase II trials and might be of added value. They require further studies	III, B	(168-172, 174)
• In unresectable disease or in multi-repetitive relapsed patients, high dose radiotherapy or radio-frequency ablation might be considered in order to achieve local and/or metastatic control.	IV, B	(134, 150-153)

3.5 Craniofacial osteosarcoma

Craniofacial osteosarcoma is a rare subset of osteosarcoma (approx. 5%). Dedicated randomized trials are lacking. The peak incidence of this specific disease is reported to be between ages 30 and 40 years (178). In the COSS study, which mainly caters to pediatric centers, the median age was only 19.7 years (179). A Dutch study reported two peaks in incidence, one in the 2nd and one in the 5th decade of life (180).

Craniofacial osteosarcoma is most frequently sporadic, but can also be associated with a tumor predisposition syndrome (e.g., hereditary retinoblastoma, Li-Fraumeni syndrome) (181, 182). It can also rarely occur as a malignant transformation from fibrous dysplasia (183, 184), or secondary in patients previously given oncogenic therapies, in particular radiotherapy for cancers like retinoblastoma or rhabdomyosarcoma of the head-and-neck region (180, 182, 185-188). The majority of studies are retrospective. Craniofacial osteosarcoma most commonly affects the jaws. Extragnathic craniofacial osteosarcoma is a negative predictive factor (179, 189, 190). Craniofacial osteosarcoma has a lower propensity to metastasize than its extremity counterpart, but it is generally more difficult to obtain permanent local tumor control (191).

The standard-of-therapeutic care is largely identical to extra-axial osteosarcoma. Chemotherapy, as described above, together with complete surgery has been considered efficacious (192-197), also in the case of craniofacial osteosarcoma secondary to retinoblastoma treatment (186). However, non-response to chemotherapy with the risk of local progression during neoadjuvant chemotherapy is a concern (197, 198). Primary surgery, followed by adjuvant chemotherapy, might be preferred in selected patients. This seems particularly advisable if resectability is of concern, especially in older patients (199). Inoperability and incomplete resection are more frequent than in extra-axial osteosarcoma, thus radiotherapy has to be considered. Heavy-ions have a higher biological efficacy and seem to be better confined to the target volume (131, 189, 191, 200, 201). In craniofacial osteosarcoma some locations seem to have a lower tendency to metastasize. Therefore, for some patients systemic treatment might be discussed to be omitted. Examples of patients eligible for expert discussion are patients with an osteosarcoma of the jaw (202) or craniofacial osteosarcoma associated with a tumor predisposition syndrome.

Recommendations for craniofacial osteosarcoma - Level of evidence and grade of recommendation		Ref
• In general, use the same diagnostic procedures (including staging) and treatment modalities as for other high-grade osteosarcoma	IV, A	(192-196)
• Consider primary surgery instead of neoadjuvant chemotherapy even in case of resectability, thereby omitting the risks of associated with potential tumor progression and, consequently, unresectability. This might be particularly wise in older patients,	IV, B	(199)
• Favor proton/heavy-ion radiotherapy over photon therapy for the management of unresectable/incompletely resected craniofacial osteosarcoma	V, B	(131, 189, 191, 200, 201)

3.6 Management of low grade and intermediate grade osteosarcoma

Low-grade osteosarcoma is an important differential diagnosis of high-grade osteosarcoma. Low-grade osteosarcomas encompass low-grade central osteosarcoma (LGCOS; ICD-O 9187/3), which account for 1-2% of osteosarcomas and parosteal osteosarcoma (ICD-O 9192/3), which account for about 4% of osteosarcomas. Low-grade osteosarcoma has a peak incidence in the third decade of life, amplification of 12q13-q15 involving *MDM2* and *CDK4* is often observed. While low-grade osteosarcoma can be cured by surgery alone, this must be with wide margins to prevent both local recurrence and dedifferentiation into high-grade osteosarcoma (203). Parosteal low-grade osteosarcoma can be radiographically difficult to distinguish from high-grade osteosarcoma, hence, careful histopathological work-up is mandatory (204). Given its malignant nature and the risk of local recurrence with dedifferentiation into high-grade osteosarcoma, it is important not to misdiagnose low-grade osteosarcoma as benign bone tumors or fibrous dysplasia. Otherwise, this might lead to suboptimal management (205, 206).

In up to 25% of low-grade osteosarcoma, a clinical challenge is posed by foci of dedifferentiation. Here, one retrospective study suggested that low-grade osteosarcoma with up to 50% of high-grade dedifferentiation might be treated by surgery alone (207). This was corroborated by Norwegian registry data which indicated 5-year overall survival rates >90% when treatment was surgery alone (208). Low-grade osteosarcoma with >50% high-grade dedifferentiation might be treated with adjuvant high-grade osteosarcoma-type chemotherapy (see above). The benefit of such an approach is at present unclear, as metastatic relapse rates similar to those observed in exclusively surgically treated patients have been observed (207-211).

Periosteal osteosarcoma (ICD-O 9193/3) is an intermediate grade bone-forming sarcoma. It typically affects the diaphyses of the femur or tibia. Periosteal osteosarcoma accounts for 2% of all osteosarcomas. It has its peak incidence in the

second decade of life (1). Marrow involvement is rare and may predict a more aggressive behavior. Wide surgical excision is essential. Chemotherapy is not routinely recommended (3).

Recommendations for low-grade and intermediate grade osteosarcoma - Level of evidence and grade of recommendation		Ref
• Diagnostic work-up, including staging, and follow-up should be the same as for high-grade osteosarcoma	V, B	(207-212)
• Surgery, with wide margins, is the treatment of choice	IV, A	(207-211)

3.7 Osteosarcoma and tumor predisposition syndromes

Germline predisposition can nowadays be identified in at least 8% or more of childhood cancers (213-216). Recent guidelines have suggested evaluation for pediatric tumor predisposition syndromes (modified Jongmans criteria) if a patient present with dysmorphic traits, has ≥ 2 malignancies (e.g. secondary, bilateral, multifocal, metachronous), if there is a positive family history (≥ 2 malignancies occurred in family members before age 18 years, including index patient; parent or sibling with current or history of cancer before age 45 years; ≥ 2 first or second degree relatives in the same parental lineage with cancer before age 45 years; or when the parents of the child with cancer are consanguineous), in case of excessive toxicity of cancer therapy or when genetic tumor analyses reveal defect suggesting germline predisposition (215, 217). We refer to specific guidelines for post-therapy follow-up e.g. (218).

Osteosarcoma is overrepresented among pediatric cancers with known germline predisposition. Approximately 10% of patients with osteosarcoma harbor germline mutations of *TP53* and potentially over 25% of patients harbor any germline pathogenic or likely pathogenic mutations in cancer-susceptibility genes (9), making osteosarcoma an index malignancy that should raise suspicion for tumor predisposition. Li-Fraumeni syndrome, hereditary retinoblastoma and possibly Alpha-thalassemia x-linked intellectual disability syndrome (219) as well as Diamond-Blackfan anemia (220) are examples of tumor predisposition syndromes presenting with osteosarcoma. Defects in different members of the RECQL gene family of helicases are also predisposing factors for osteosarcoma development: Werner syndrome, Bloom syndrome, Rothmund-Thompson syndrome and RAPADILINO syndrome are the best characterized tumor of such predisposition syndromes (221-223).

The risk of radio- and chemotherapy-induced secondary cancers is of considerable concern in osteosarcoma patients with germline tumor predisposition (224, 225). With - possibly - the exception of the antimetabolites methotrexate and, infrequently administered, gemcitabine and the microtubule toxin docetaxel, most osteosarcoma-directed chemotherapeutic drugs are directly genotoxic. The combination of docetaxel and gemcitabine has not been evaluated in the upfront treatment of osteosarcoma and can therefore not be recommended. There is certainly a need for clinical trials that evaluate the efficacy of non-genotoxic therapies for patients with germline predisposition.

Recommendation tumor-predisposition syndromes in osteosarcoma - Level of evidence and grade of recommendation		Ref
• Consider hereditarity in all osteosarcoma cases Consider referral for genetic counselling, in line with (inter)national guidelines, for potential cancer predisposition syndromes in case of clinical suspicion, a positive family history, or when genetic tumor analysis reveals a defect suggesting germline predisposition	V, A	(215-217)
• Take into consideration potentially increased toxicity and secondary cancers with genotoxic treatment (e.g. chemotherapy and radiation therapy)	V, B	(224)

3.8 Supportive care

We refer to local practice, national recommendations, and international guidelines for general aspects of supportive care in pediatric oncology (226-228). Due to osteosarcoma biology and chemotherapeutic treatment at maximum tolerated doses, several aspects of supportive care warrant a more detailed discussion.

Pain management incl. in case of pathological fractures

Local pain at diagnosis due to swelling, infiltrative growth or, in rare cases, pathologic fractures can cause significant pain. In the latter case, brace or cast immobilization can be employed (229). Apart from osteosarcoma directed therapy, effective pain medication should be provided according to institutional guidance, which should account for interactions with chemotherapy.

Supportive therapy during chemotherapy

Methotrexate

High-dose methotrexate (HD-MTX, 12 g/m^2) therapy requires the capacity of rapid MTX plasma concentration measurements. Major HD-MTX toxicities are often mediated by reduced drug-excretion and include acute kidney injury (AKI), severe myelosuppression, hepatotoxicity, mucositis, and CNS toxicity (230). The latter might require supportive intensive care (231). MTX toxicities to the bone-marrow and mucous membranes are thought to be mediated by MTX's mode of action as an inhibitor of dihydrofolate reductase. Its nephrotoxicity is mainly thought to be mediated by MTX-precipitation in the renal tubules and by direct tubular toxicity. MTX is mainly excreted via the kidneys, hence, MTX-induced AKI can be life-threatening due to reduced MTX clearance and prolonged systemic MTX exposure (232, 233).

To prevent MTX-mediated AKI, hyperhydration (e.g., 3L/m^2/24 hours) and urine alkalization (urinary pH must be >7 before start of MTX infusion to increase MTX solubility) are essential. Non-renal toxicities can be prevented by antagonizing MTX with the antidote leucovorin, commonly initiated 24 hours after the MTX-infusion. Leucovorin mitigates the risk of toxicity of HD-MTX by bypassing dihydrofolate reductase and restarts the intracellular folate cycle. As long as renal excretion of methotrexate is not impaired, leucovorin rescue is sufficient to prevent life-threatening toxicities (234, 235).

Risk factors for the development of delayed MTX-clearance include: impaired, pre-existing renal function; volume depletion due to fluid loss (vomiting, diarrhea), adrenal insufficiency or renal salt wasting; third spacing (ascites, pleural effusion, edema); and drugs decreasing the renal methotrexate clearance (234). If methotrexate-excretion is severely delayed, the standard daily dose of leucovorin has to be adjusted to prevent major toxicities or even death (234, 235).

If severe MTX related AKI is suspected, the use of glucarpidase should be considered. Glucarpidase is a carboxypeptidase that cleaves extracellular MTX to the soluble products deoxyaminomethylpteroic acid and glutamate. It can thereby rapidly decrease MTX serum-concentrations. Glucarpidase can lower MTX serum-concentration by 90%–95% within minutes of its administration. The catalytic effect persists for 48–72 hours (236, 237). MTX toxicity and delayed MTX excretion can pose significant and immediate threats to any patient receiving HD-MTX. Guidance has been published for the handling of toxicity and the use of glucarpidase (234, 237, 238). Use of glucarpidase in patients of any age is always at the discretion of the treating physician. The following guidance on its potential indications was provided In the EURAMOS-1 protocol: (a) plasma MTX concentrations ≥10µmol/L 48 hours after MTX administration; or (b) rise in creatinine of 100% or more within 24 hours of MTX.

Cisplatin

Cisplatin is directly toxic to the (proximal) renal tubule which actively imports cisplatin (239-241). Tubular damage can lead to a Fanconi-like syndrome, characterized by a loss of reabsorption capabilities and resulting in losses of sodium, potassium, magnesium, calcium, glucose, bicarbonate (renal tubular acidosis) and protein (242-244). Cisplatin-associated nephrotoxicity can be reduced by an adequate prehydration and by prolonged cisplatin infusion rates (245, 246). As cisplatin-induced hypomagnesaemia can increase nephrotoxic effects, magnesium supplementation during and immediately following cisplatin administration is recommended (247-251). Furthermore, concomitant use of other nephrotoxic agents (e.g. aminoglycosides, acyclovir) should be avoided (252).

Ototoxicity is another major concern related to cisplatin-based chemotherapy. Due to different grading scales reported rates vary. Rates range from acute grade 1/2 toxicity in 25% in EURAMOS-1 (64) to 40% in an institutional review of osteosarcoma patients (253), which is in similar range to the 45% reported in other solid tumors treated with cisplatin-based chemotherapy (254). Due to concerns of reduced cisplatin efficacy (that have so far not been assessed sufficiently in osteosarcoma), prophylactic administration of the otoprotective sodium thiosulfate can currently not be recommended in the disease (255-258). In cases of accidental cisplatin overdose or drug-related acute kidney failure, however, plasmapheresis along with sodium thiosulfate can be considered (259-261).

Doxorubicin

Doxorubicin administration, particularly when in combination with cisplatin, is highly myelosuppressive. Febrile neutropenia as well as mucositis are common. Recombinant G-CSF (filgrastim) or pegylated filgrastim is recommended following an AP course if patients were suffering from non-catheter associated neutropenic sepsis or prolonged hospitalization due to neutropenic fever (>7 days) after a previous AP course. Recombinant G-CSF to mitigate/shorten severe episodes of mucositis can be considered in patients who suffered from severe mucositis after previous AP courses (262).

In order to monitor cardiotoxicity, echocardiography should be performed at baseline and prior to each doxorubicin course (at least with cumulative doses of >225 mg/m^2) (263). To reduce cardiotoxicity, prolonged continuous infusion of doxorubicin of 6 hours or longer are advised based on adult data, with need for more studies in children (264). The EMA decided in 2017 that the cardioprotectant dexrazoxane could be given to patients younger than 18 years who were planned to receive more than 300 mg/m^2 doxorubicin. In a recent meta-analysis, including 5 pediatric randomized clinical trials a reduction in cardiotoxicity was described with no evidence of effect on chemotherapy efficacy (265). Current international supportive care guidelines made a moderate recommendation that in patients receiving 250 mg/m^2 or more doxorubicin the benefits of dexrazoxane outweigh the risk (266). Dexrazoxane, if considered, should be given intravenously 30 minutes prior to doxorubicin, starting with its very first dose (267). In patients with renal impairment (GFR < 40 mL/min*1.73 m^2), dexrazoxane doses should be reduced by 50%. If dexrazoxane is not used pre-emptively, it should be considered if the LVEF shows a confirmed reduction of >10% within the normal range or if the FS shows a similar fall.

Ifosfamide

Just like cisplatin, ifosfamide can cause renal tubular damage. The drug-metabolite chloroacetaldehyde is thought to be responsible (268-270). Kidney damage might be reduced by prolonged infusions and by adequate intravenous hydration. Urothelial damage leading to hemorrhagic cystitis is due to the ifosfamide metabolite acrolein. It has to be prevented by administering the antioxidant sodium 2-mercaptoethane sulfonate (MESNA) (271). Ifosfamide can also cause encephalopathy, clinically spanning from confusion to coma (272). The most important intervention is stopping further ifosfamide administration. Administration of methylene blue (methylthioninium) has been described as an effective antidote in case series (273-276). Expert consensus in ESMO-EONS-EANO clinical practice guideline do not recommended the routine use of methylene blue in the prevention or treatment of ifosfamide induced central neurotoxicity, based on the very limited data available (277). Since methylene blue administration can cause hemolytic crises in patients with genetic hemolytic anemia, screening for glucose-6-phosphate dehydrogenase (G6PD) deficiency is advised to be considered prior to ifosfamide in populations with a high incidence of G6PD deficiency (278).

Recommendations on supportive care in osteosarcoma - Level of evidence and grade of recommendation		Ref
• Adhere to general local, national and international guidelines		
• Treat pathological fractures conservatively	IV, B	(229)
• High-dose MTX should only be administered at experienced centers, and glucarpidase should be available rapidly	V, A	(234, 237, 238).
• Combinations of MTX (and cisplatin, ifosfamide) with concomitant nephrotoxic medication should be avoided	IV, B	(252)
• Consider supplementation of magnesium with cisplatin therapy	II, A	(247-251)
• Cardiotoxicity should be monitored with echocardiography at base-line and at least following cumulative doxorubicin doses >225 mg/m^2	V, B	(263)
• To prevent cardiotoxicity, dexrazoxane can be considered with expected cumulative doxorubicin dose higher than 250 mg/m2, either starting with the first administration of doxorubicin or after fall in left ventricular function	I, B	(265-267)
• During ifosfamide treatment, MESNA supplementation to prevent hemorrhagic cystitis is mandatory	II, A	(271)
• Methylene blue can be considered to treat severe ifosfamide-induced neurotoxicity	V, D	(273)

3.9 Response assessment and long-term follow-up

Imaging response evaluation on therapy

In frontline therapy, pre-operative imaging is essential to guide surgery and to assess radiologic response. In localized disease, MRI of the primary tumor and X-ray or CT of the chest is recommended to be performed preoperatively. In metastatic disease, appropriate imaging of the metastatic site(s) is mandatory. In pulmonary metastatic disease or indeterminate pulmonary nodules this includes a preoperative chest CT. Due to its calcified matrix, complete or partial imaging-response to preoperative chemotherapy is rarely seen in osteosarcoma (279). The definition of progressive disease, prior to surgery, measured as a one-dimensional increase of more than 20% according to RECIST 1.1, is associated with poor survival (280). It is recommended to classify progressive disease in the context of clinical features of progression, such as increased pain, inflammatory signs, rising alkaline phosphatase, as increases in tumor size might also be a reflection of delay between staging and start of therapy or a result of hemorrhagic/necrotic changes reflecting response to therapy (pseudoprogression). Furthermore, re-staging should be performed (chest CT and whole body imaging) in case of local progression to evaluate potential metastatic progression.

Various studies have investigated the potential predictive value of functional quantitative imaging indices in FDG-PET, diffusion-weighted MRI and dynamic contrast-enhanced MRI (52, 281-289). Although promising, all of these quantitative measurements require larger prospective studies for validation. These need to address both the prognostic value for survival and the additive value over histologic response.

In patients with either localized or metastatic disease who achieved complete surgical remission, further imaging is focused on potential disease recurrences. After surgery, the primary tumor site can be followed using conventional radiographs, with added value of CT or MRI in case of a suspected local relapse. In case of prostheses or surgery including osteosyntheses, specific CT or MR protocols are advised (290). Of note, it has to be checked with the manufacturer whether an MRI is still possible. Certain length-adaptable prostheses might be damaged by such a procedure. Chest radiographs are recommended for follow-up of pulmonary metastases with a chest CT at end of therapy. MRI is recommended for the follow-up of unresectable bone metastases. In patients with bone metastases achieving surgical remission, bone-scintigraphy(291), FDG PET imaging (292), or WB-MRI might be considered at the end of therapy.

In patients with either localized or metastatic disease where surgical remission cannot be achieved, response assessment might support decision making. No studies have systematically investigated the value of functional imaging like FDG-PET to guide local treatment in these patients.

Pathology

To evaluate the (surgical) resection status, tumor margins should be assessed in conformity with the MSTS system or the margin distance method. Wide resections are essential to reduce local recurrence risks (92, 293). The response to preoperative chemotherapy is assessed histologically. Therefore, a section through the largest diameter of the tumor has to be completely embedded and histologically evaluated for residual viable tumor. Less than 10% viable tumor cells (or > 90% response) (necrosis, fibrosis and calcification) are considered a good response to neoadjuvant treatment (294), which correlates with a favorable survival (44, 71, 91).

Follow-up after therapy

Apart from diagnosing and managing toxicities known to affect quality-of-life (ototoxicity, cardiotoxicity, nephrotoxicity, secondary malignancies) (263, 295{Armenian, 2015 #27, 296) and the function after (reconstructive) surgery, the main goal of surveillance is the detection of disease recurrences. There is a lack of prospective studies investigating the optimal follow-up schedule. Generally, imaging is recommended to be performed at least up to 10 years after primary or relapsed disease, with more frequent screening in the first years post therapy. In cases of doubt and particularly with suspected disease recurrences, a complete restaging is strongly recommended and a biopsy considered.

In patients achieving complete surgical remission, regular radiographs of the primary tumor are recommended. For screening of recurrent pulmonary disease, EURAMOS-1 advised chest radiographs for non-metastatic patients, whereas the COG imaging guidelines favor the use of chest CT (19). No randomized studies investigating whether the use of chest CT leads to better post-recurrence survival rate in osteosarcoma are available. In non-metastatic high-grade bone sarcoma (n= 352, disease type and treatment not further specified) a randomized study did show that chest radiography as an imaging modality did not lead to

worsened 3-year survival and was not inferior to CT scan in terms of detecting pulmonary metastasis (297). Researchers from the Rizzoli Institute reported better outcomes in patients who developed lung metastases when the metastases were detected via CT-scans (N=112 patients; 5-year post-relapse survival (PRS) 49%), when compared to patients whose metastases were detected via chest x-ray (N=119; 5-year PRS 30%) in a retrospective study (298). The recommended surveillance frequencies after completion of chemotherapy are: every 2-3 months for the first 2 years, every six months for years 3-5, every 6-12 months thereafter (3). We recommend to perform chest radiographs and conventional radiographs of the primary tumor in primary non-metastatic patients that achieved complete surgical remission status on therapy. Awaiting future studies, chest CT in follow remains of debate and should be performed according to institutional practice. In line with the EURAMOS-1 protocol, we recommend to perform chest CT in primary pulmonary metastatic patients that achieved complete surgical remission status on therapy every 6 months for a minimum of 2 years. In case residual disease at end of therapy, imaging should include the site of residual disease (no specific recommendations for modalities). In case of relapsed disease, we recommend to start the surveillance over again, starting every 2-3 months for the first 2 years.

3.10 Future perspective

Outcomes for patients with osteosarcoma have not improved during the last decades. This might partially be explained by the heterogeneous and complex biology of osteosarcoma. Ongoing preclinical and clinical research needs to elucidate patient-specific aspects of osteosarcoma biology and immunology to foster rational development of urgently needed novel therapeutic approaches. Progress requires international collaboration due to the limited number of patients per country. Within an international consortium, translational research should complement clinical evaluation of new therapies in frontline and relapsed/refractory disease. The role of maintenance therapy, the optimal backbone in relapsed osteosarcoma, the potential of multi-tyrosine kinase inhibitors, be it in upfront or relapse therapy, as well as the role of immunotherapy are some important questions to addressed. The development of oncological treatment should be accompanied by research in supportive care to optimize oncological efficacy while at the time minimizing acute and long-term toxicities.

3.11 Conclusion

These guidelines provide the current standard-of-care in frontline, refractory and relapsed osteosarcoma, with a focus on but not limited to high-grade osteosarcoma. Treatment at specialized centers that can guarantee optimal work-up, chemotherapy delivery, surgery, and supportive care is essential to achieve best oncological outcome and manage treatment-related complications.

4. PATIENT GROUP

This document applies to the following patients:

- Newly diagnosed patients with a high-grade osteosarcoma of the extremity or axial skeleton, either localized or metastatic, including those arising as secondary malignancies
- Patients with a progressive or recurrent high-grade osteosarcoma
- Children and adolescents

Specific modifications may be required for patients with:

- Underlying chromosomal breakage syndrome
- Previous malignancy or previous chemotherapy
- Pre-existing disease prohibiting standard therapy
- During pregnancy or lactation

For specific conditions only recommendations are provided in the background section. No further specific guidance is provided for:

- Low grade osteosarcoma
- Juxtacortical (periosteal, parosteal) osteosarcoma
- Craniofacial osteosarcoma

5. DIAGNOSIS AND STAGING

Diagnostic recommendations - Level of evidence and grade of recommendation		Ref
In case of suspected bone sarcoma, early patient referral to a reference center for diagnostic work-up and management of disease is recommended.	IV, A	(31, 32)
In case of suspected bone sarcoma, plain radiographs and an MRI of the primary tumor (including the whole compartment and adjacent joints) are recommended to be made prior to biopsy.	III, A	(20, 23, 24, 26)
It is recommended to plan and perform a biopsy in collaboration with an oncology-experienced orthopedic surgeon and/or interventional radiologist.	IV, A	(31-33)
Histopathological diagnosis is recommended to be performed according to the WHO 2020 guidelines.		
In confirmed high-grade osteosarcoma, a high-resolution chest CT is recommended for evaluation of pulmonary metastatic disease	III, A	(36-38, 40, 41)
Whole body staging is recommended to screen for non-pulmonary metastases. If available FDG PET-CT, FDG PET-MRI, whole body MRI are recommended modalities, or at least bone scintigraphy.	III, A	(37, 45, 47, 49-51, 56-58)

Imaging of the primary tumor is advised.

For definitive diagnosis of osteosarcoma, a histologic diagnosis by core needle or open biopsy, is essential. The biopsy should be taken in a center with expertise in sarcoma, where the biopsy route is in accordance with the planned surgery by the orthopedic surgeon.

Staging should be performed preferably within 14 days before initiation of treatment, with a maximum of 30 days

Assessment of the primary tumor

- Plain radiograph in two planes
- MRI of the primary site, including, at least, entire involved bone and adjacent joints

Minimal technical quality recommendations and standardized reports can be found in appendix B.

MRI is preferred over CT because of the most detailed characterization of the tumor, tumor extension, skip lesion detection, and the relation to the surrounding tissues. At least one sequence (for example coronal T1) should cover the entire involved bone and adjacent joints for the identification of skip lesions. The field of view of the other sequences can be focused on the tumor and its relation to the nearest joint. MRI should be performed with the use of gadolinium and include T1, T2 (preferably with fat-suppression) and T1 post-gadolinium sequences with fat-suppression. Axial and coronal images are strongly recommended for the identification of intra-medullar tumor extension and the diagnosis of skip lesions (25, 299). If feasible, diffusion weighted imaging and perfusion studies can be added to the conventional MRI sequences. The report of the primary tumor should include description and localization of the tumor, the maximal diameter (assessed according to RECIST 1.1), the relationship of the tumor with surrounding tissues, i.e. the relationship to joints, nerves and vessels, and the presence of skip lesions.

Skip metastases were initially defined as synchronous smaller foci of tumor occurring in the same bone anatomically separated from the primary lesion or as synchronous smaller foci of tumor on the opposing side of a joint (300, 301). However, as skip metastases in the same bone have a more favorable prognosis than trans-articular metastases (23), the latter should be regarded as distant bone metastases. The American Joint Committee on Cancer (AJCC) classification system considers skip metastases as stage III tumors, and trans-articular bone metastases as stage IV disease (302).

Assessment of metastatic disease

- High-resolution chest CT
- FDG PET-CT / MRI or whole body MRI (if available); or at minimum a bone scintigraphy

Minimal technical quality recommendations and standardized reports can be found in appendix B.

Chest CT should be acquired on maximal inspiration. The ideal slice thickness is 1.0 – 1.5 mm. FDG PET-CT / MRI should be acquired according to current EANM guidelines (303, 304). The field-of-view should include the whole body. If FDG PET-CT or FDG PET-MRI is not available, bone scintigraphy may be an alternative and should be acquired according to the current EANM guideline (305).

Definition of lung metastases

Lung metastases are diagnosed using chest CT. Minimum criteria determined by chest CT scanning are 3 or more lesions, which are ≥ 5 mm in maximum diameter or a single lesion ≥ 1 cm. These patients will be classified as having “certain” pulmonary metastases. Scans of patients registered as having metastatic disease with fewer or smaller lesions will be classified as “possible” metastatic disease. In case of possible metastatic disease pathological assessment is advised, particularly if these lesions persist on chest CT after neoadjuvant chemotherapy.

Definition of bone metastases

Bone metastases are diagnosed using bone scans, or if available FDG PET-CT/MRI or WB-MRI. Bone metastases are identified by increased, non-physiological, tracer uptake confirmed by abnormalities on the MRI, CT or conventional radiographs. In case of doubt, histological confirmation is necessary.

<u>Baseline assessment of organ function</u>

1. Complete history and detailed physical examination including performance status
2. Full blood count, differential white count and AB0 typing
3. Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, LD, bilirubin)
4. Measurement of glomerular filtration rate (GFR) and tubular function (urine phosphate and creatinine)
5. Urine analysis (dip stick) for blood, protein and glucose
6. Pregnancy test for girls/female adolescents with signs of puberty
7. Echocardiogram and ECG, evaluating left ventricular ejection fraction (LVEF) or fractional shortening (FS)

8. Audiogram
9. Fertility preservation (according to Childhood Cancer Guideline Harmonization Group (54, 55))*:
    a. General information recommended to each patient and their parents, caregivers.
    b. In general MAP provides a low risk for infertility with a cyclophosphamide-equivalent dose of 0.
    c. Male: Sperm storage is recommended for male patients of reproductive age.
    d. Female: In post-pubertal girls, there is a moderate recommendation for oocyte or embryo cryopreservation, only for patients at high risk of cancer recurrence

*in protocols which use high-dose ifosfamide, fertility preservation is much more important than with MAP based regimens

Classification

Staging is important for optimal assessment of either localized or metastatic disease. Classification of staging can be performed according either the American Joint Committee on Cancer (AJCC), the Enneking Musculoskeletal Tumor Society (MSTS) or the Vanderbilt Osteosarcoma staging system (105-107), see appendix A.

Biopsy

The diagnosis of high-grade osteosarcoma must be verified histologically before initiation of chemotherapy. In order to ensure appropriate biopsy techniques and an appropriate evaluation of the obtained material, it is strongly recommended that biopsies should only be performed in specialized sarcoma centers, together with an orthopedic surgeon / experienced dedicated interventional radiologist. Either core-needle or open biopsy may be performed. The biopsy specimen should be forwarded without prior fixation and needs to be assessed by an expert or reference pathologist for bone tumor pathology.

Tissue processing

All tissue, whether from a biopsy, or resection of a suspected bone tumor should be processed in a manner that allows molecular studies to be undertaken successfully. Decalcification can be detrimental to nucleic acid; therefore, freezing samples or viable freezing is preferred. Next to freezing, fixation of non-calcified portions of the tumor in buffered formalin alone before paraffin embedding is encouraged, to facilitate modern technologies (e.g. next-generation sequencing) that facilitate diagnosis. Decalcification in ethylenediaminetetraacetic acid (EDTA) is preferred over harsher acidic reagents.

Histopathological diagnosis according to the WHO 2020 guideline (306)

According to the WHO classification, the identification of neoplastic bone formation is the defining feature for the diagnosis of osteosarcoma. The tumor grows in a permeative pattern; replacing the marrow space and encasing and destroying pre-existing trabeculae, it fills and expands haversian systems within cortical bone. The neoplastic cells typically demonstrate severe anaplasia and pleomorphism, and they may be fusiform, plasmacytoid, or epithelioid. Neoplastic cells can become small and normalized in appearance (mimicking benign osteocytes) when surrounded by bone matrix. Mitotic activity is usually brisk, and abundant atypical mitotic figures are often present, which are useful in the differential diagnosis of benign mimics of osteosarcoma. No minimum quantity of bone formation is required; any amount is sufficient to render the diagnosis. Characteristically, the bone is intimately associated with the tumor cells; varies in quantity; is woven in architecture; and is deposited as primitive, disorganized trabeculae that may produce fine (filigree) or coarse lace-like patterns, or as broad, large sheets of compact bone formed by coalescing trabeculae.

Bone matrix is eosinophilic on H&E-stained sections if unmineralized and basophilic/purple if mineralized, and it may have a pagetoid appearance imparted by haphazardly deposited cement lines. Distinguishing unmineralized matrix (osteoid) from other eosinophilic extracellular materials such as collagen or compacted fibrin matrices may be difficult and subjective. Collagen tends to be less glassy and more fibrillar, and it is frequently deposited in broad aggregates or elongated fibrils compressed between lesional cells. Immunohistochemistry is not useful in the diagnosis of osteosarcoma.

Cytology is not clinically relevant.

No specific diagnostic molecular pathology tests are available. Methylation and copy number profiling might be considered in ambiguous cases, particularly if only little tissue has been obtained during biopsy, but is usually not required and cannot be used for the diagnosis without the appropriate (morphological) context.

6. ASSESSMENTS ON MAP BASED CHEMOTHERAPY

Overview of imaging assessments

	Diagnosis	Pre 2nd MAP	Pre-surgery	Post-surgery	Pre 5th MAP	End of treatment
Site / Week	1	6	8 - 11	12	21	30 – 32
Primary tumor						
Radiographs	x			x[1]		x
MRI	x	(x)[2]	x	(x)[3]		(x)[3]
Lung, non-metastatic						
Chest CT	x	(x)[2]	x			
Lung radiographs				x	x	x
Lung, metastatic						
Chest CT	x	(x)[2]	x		x	x
Bone metastases						
If readily available FDG PET-CT/MRI or whole-body MRI[4]; or at minimum bone scan	x		x[5]			
MRI of metastatic lesion	x		x			

1. Radiographs of the primary site every 4 months after surgery

2. In case of evident clinical progression of disease

3. MRI of primary tumor site to be considered. MRI should be performed in case of clinical or radiographical suspicion of recurrent disease

4. The latter (FDG PET-MRI or whole-body MRI can be considered especially in patients with tumor predisposition syndromes with DNA repair pathologies, when available

5. Optional to evaluate response to chemotherapy in multi-metastatic patients and support decision making in extensive surgery or optional local therapy

Overview of assessments

	AP	M	M	AP	M	M	Surg	AP	M	M	AP	M	M	A	M	M	A	M	M	EOT
Week	1	4	5	6	9	10	11	12	15	16	17	20	21	22	24	25	26	28	29	
Clinical evaluation[1]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory																				
Full blood count[2]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ABO typing	x																			
Blood chemistry[3]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[4]
Urine analysis (dip stick)	x																			
Urine pH		x	x		x	x			x	x		x	x		x	x		x	x	
Echocardiogram[5] and ECG	x													x			x			x
Audiometry	x							x			x									x
Pregnancy test	x																			
Fertility preservation	x																			

1. Including height, weight and surface area

2. Full blood count and differential white count

3. Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin), including measurement of glomerular filtration rate (GFR)

4. Include measurement of renal tubular function (optional) e.g. tubular phosphate reabsorption

5. Assessment of left ventricular function

7. RESPONSE DEFINITIONS

Disease response evaluation

Complete remission (CR)

• The complete macroscopic excision of all detectable disease, **or**

• The complete macroscopic excision of the primary tumor, together with the disappearance of all previously detected lung metastases, as determined by CT scanning. Complete response of bone metastases must be achieved surgically.

Progressive disease (PD)

Primary Tumor

• An increase of ≥ 20% in any dimension of the primary tumor when assessed radiologically IN ASSOCIATION WITH clinical features of progression such as increased pain, inflammatory signs, rising alkaline phosphatase.[1]

Assessment must be repeated in no less than 3 weeks to be regarded as progressive disease.

Metastases

• An increase of at least 20%, in the sum of the longest diameter (LD) of all predefined metastases, or unequivocal progression of smaller metastases, **or**

• The appearance of any new lesion.[2]

[1.] Disease progression in the early stages of treatment of osteosarcoma may be mimicked e.g. by intratumoral hemorrhage. Therefore, clinical and radiological appearances should be interpreted together before considering early surgery.

[2.] According to RECIST 1.1 guidance (307, 308).

Pathologic response assessment of primary tumor / metastatic lesions

The pathological examination has two objectives:

1) Assessment of resection margins

Measurement in mm, narrowest margin

Response classification: intralesional, marginal, wide, radical

Response classification: R0, R1, R2

2) Assessment of the response to chemotherapy

Response in % viable tumor

Response classification: good histologic response (< 10% viable tumor), poor histologic response (≥ 10% viable tumor)

To provide documentation of the soft tissue margins, the initial gross examination should be performed on the fresh specimen. Measurement of the narrowest resection margin (mm) is of most value. Histological sections should be taken in any area where excision margins appear dubious. The specimen should be prepared by dividing it longitudinally in the plane of maximum tumor diameter, and the whole slab should be divided into blocks for preparation of histological sections (at minimum one full slab including the tumor). A photograph and a diagrammatic map of the specimen should be prepared indicating the site of individual blocks. For quantitating the effects of chemotherapy, only the sections where tumor was present or was thought to have been present should be assessed. Normal adjacent bone and soft tissue areas should not be included in the area quantitated.

The amount of viable tumor is reported as less than 10% of the tumor area in cases showing a good response and greater than or equal to 10% in cases showing a poor response.

8. TREATMENT - PRIMARY HIGH-GRADE OSTEOSARCOMA

Recommendations for high-grade, resectable, osteosarcoma - Level of evidence and grade of recommendation		Ref
Patients with high-grade osteosarcoma should be treated with three-drug chemotherapy in combination with aggressive surgery aiming for wide resection margins.	I, A	(62-65, 71, 74, 76, 77)
Patients with primary resectable metastatic high-grade osteosarcoma should be treated following the same principles as non-metastatic osteosarcoma plus complete surgical resection of all metastatic sites.	I, A	(62-65, 71, 74, 76, 77)
Surgery of the primary tumor and metastatic lesions with wide resection margins is essential if treatment is to be with curative intent.	III, A	(92-95)
The MAP regimen (methotrexate, cisplatin and doxorubicin) could be considered a standard for current osteosarcoma treatment.	I, A	(64, 65, 76, 77)
The M-EI regimen (methotrexate, ifosfamide and etoposide) might pose an alternative to the MAP regimen in patients with a contra-indication for cisplatin or doxorubicin.	III, B	(71, 81)
In case of a contra-indication to methotrexate, the St. Jude OS99 and the API-AI regimens provide reasonable alternative treatment approaches.	III, C	(78, 79, 114)
Due to lack of clear evidence for a benefit of additional mifamurtide, this is not a part of current standard treatment.	II, C	(76, 77, 83, 115, 116)

Recommendations for high-grade, unresectable, osteosarcoma - Level of evidence and grade of recommendation		Ref
• Neoadjuvant chemotherapy and radiotherapy can be considered in an attempt to achieve resectable disease.	IV, B	(123, 124)
• High-dose radiotherapy can be considered as local therapy in definitively unresectable local or oligo-metastatic disease. Chemotherapy, as recommended for resectable osteosarcoma, should be administered if the approach is curative.	IV, B	(125, 127-130)
• In multi-metastatic unresectable osteosarcoma therapies considered should be balanced with quality of life.		

8.1 Chemotherapy

MAP – regimen

Disclaimer: Details for the MAP-regimen as detailed below are based on the specifications of the EURAMOS-1 protocol.

As a rule, drug dosage should be modified as little as possible. If necessary, delay treatment to administer full doses. Decisions regarding the possibility of proceeding with chemotherapy after a delay should be re-evaluated at least every 3-4 days. In the absence of prohibitive toxicity, an attempt to give any omitted chemotherapy should be made after the end of scheduled protocol chemotherapy (i.e., after week 29).

Cycle	1			2				3			4			5			6		
Week	1	4	5	6	9	10	11	12	15	16	17	20	21	22	24	25	26	28	29
							S												
Chemotherapy							U												
Doxorubicin 75 mg/m^2							R												
Cisplatin 120 mg/m^2							G												
Methotrexate 12 g/m^2							E												
							R												
Supportive care							Y												
Anti-emetics[1]																			
Magnesium[2]																			
G-CSF[3]																			
Dexrazoxane[4]																			

[1.] The MASCC/ESMO guidelines (309) report a high emetogenic potential for cisplatin, a moderate emetogenic potential for doxorubicin and a low emetogenic potential for MTX. However, a more recent North American pediatric clinical practice guideline (CPG) for chemotherapy-induced nausea and vomiting (CINV)(310) report high-emetogenic potential for both AP and HD-M courses with 12mg/m^2. The pediatric CPG recommendations include a combination of 5HT3-antagonists, dexamethasone, neurokinin receptor antagonists). Anti-emetics should be continued a minimum of 72 hours after cisplatin.

[2.] Start with Mg supplementation with first cisplatin course and give (intravenously or orally) during each cisplatin course.

[3.] In case of previous non-catheter associated neutropenic sepsis or prolonged hospitalization due to neutropenic fever (>7 days). Next chemotherapy should not be given until a patient has been off G-CSF for 2 days.

[4.] In case of a confirmed 10% fall within the normal range of LVEF or similar fall within the normal range of FS occurs or per national / institutional guidelines.

AP Course

Definition

- A: Doxorubicin (Adriamycin) 75 mg/m^2/course
- P: Cisplatin 120 mg/m^2/course

Timing

- Weeks: 1, 6, 12, 17

Pre-course tests

- Height, weight and body surface area
- Clinical examination
- Full blood count and differential white count
- Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin), including measurement of GFR
- At least before the 5th course of doxorubicin (at cumulative dose of doxorubicin 300 mg/m^2) and at the end of therapy: Left ventricular ejection fraction and fractional shortening (echocardiogram or radionuclide scan).
- Audiometry before at baseline and at least before the 3rd and 4th AP cycle

Minimal requirements

- General clinical condition permitting chemotherapy
- Neutrophils ≥ 0.75 x10^9/L or WBC ≥ 2.0 x10^9/L
- Platelets ≥ 75 x10^9/L
- Bilirubin ≤ 1.25 x ULN
- GFR ≥70 mL/min/1.73m^2
- Cardiac function FS ≥28% or LVEF ≥ 50% at last scheduled assessment
- Hearing < Grade 2 at ≤2 kHz

Administration

Note:	Commence doxorubicin containing cycles at full dose unless previous dose reduction for doxorubicin containing cycles for gastrointestinal or cardiotoxicity. In those circumstances continue A at previous reduced doses
Doxorubicin	48 hour continuous IV infusion = 37.5 mg/m^2/day administered by 48-hour continuous infusion (or 4 hour infusion x 2 days).
Cisplatin	Continuous 72 hour IV infusion (or 4 hour infusion (60 mg/m^2) x 2 days).
Hydration	Sufficient hydration with electrolyte supplementation is mandatory.

M Course

Definition

- M: Methotrexate 12 g/m^2

Timing

- Weeks: 4, 5, 9, 10, 15, 16, 20, 21, 24, 25, 28, 29

Pre-course tests

- Height, weight and surface area
- Clinical examination
- Full blood count and differential white count
- Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin)
- Measurement of GFR either by estimation (e.g., via the Schwartz formula; Schwarzt, Brion et al. 1987) or direct measurement (e.g., radionuclide).
- Urinary pH

Minimal requirements

- General clinical condition permitting chemotherapy including resolving mucositis ≤ grade 1
- No serous effusions or other '3rd space' (abnormal accumulation of fluid into an extracellular and extravascular space)
- Neutrophils ≥ 0.25 x10^9/L or WBC ≥ 1.0 x10^9/L
- Platelets ≥ 50 x10^9/L
- Bilirubin ≤ 1.25 x ULN
- Transaminases may be any value in the absence of other causes of liver dysfunction
- GFR ≥ 70 mL/min/1.73 m^2
- Urinary pH > 7.0 immediately prior to MTX
- Monitoring availability of serum MTX level

Administration

Methotrexate	4-hour infusion.
Hyperhydration	Adequate fluid with electrolytes and bicarbonate must be given to maintain urine output and alkalization. This should be maintained until MTX serum level is considered safe according to institutional practice (generally <0.2 µmol/L).
Urine pH	A urinary pH >7 must be achieved before starting the MTX infusion and maintained until serum level is considered safe according to group practice (generally <0.2 µmol/L). Either oral or intravenous administration of sodiumbicarbonate can be used.

Supportive care

MTX serum levels	Must be taken at 24 hours (and 48 hours from start of MTX, then daily until level is considered safe according to institutional practice (generally < 0.2 µmol/L).
Leucovorin Rescue	This must begin 24 - 28 hours after start of MTX infusion and be continued until serum MTX level is considered safe (< 0.2 µmol/L). The standard daily leucovorin dose of 60 mg/m^2 should be divided into 4 doses given every 6 hours. In case of high MTX levels, see section on methotrexate toxicity management.

8.2 Local therapy

For osteosarcoma, surgery is the local treatment of choice. Complete surgical removal of all affected sites is mandatory whenever feasible. In MAP-backbone protocols like EURAMOS-1 surgery of the primary tumor is scheduled in week 11 after the commencement of chemotherapy, which provides time for surgical counselling and evaluation of response to chemotherapy. In other protocols, like the French OS2006 with M-EI backbone, surgery is scheduled at week 14. There are no contraindications to perform surgery of the primary tumor early. For example, in patients at risk for local tumor progression, early resection might provide the window of opportunity for limb-sparing surgery.

Definitive surgery of the primary tumor

Inappropriate surgery may easily lead to local recurrence and death in otherwise curable patients and to morbidity after insufficient procedures in others (31). Therefore, surgery should always be carried out in an orthopedic sarcoma center by a surgical team familiar with the wide range of surgical reconstructions, including age-specific reconstruction challenges, such as the reconstruction of growing bones (3). Surgery should be performed in a manner which guarantees at minimum wide, clear, margins (106). While it is most often possible to reach such margins without sacrificing the affected limb, mutilating surgery may become necessary if this is not the case. Marginal or intralesional surgery (R1 or R2 resections) should be avoided whenever possible and must be restricted to situations where wide or radical margins are not achievable. Areas where there is suspicion of close margins should be marked on the surgical specimen sent to pathology. In case of intralesional resection re-resection is strongly recommended when anatomically feasible. In case of marginal resection, the possibility for re-resection should be discussed in a multi-disciplinary tumor board. If surgery is not feasible in patients with a marginal resection local radiotherapy should be considered (125, 133).

Pathologic fractures:

In cases of fracture, internal fixation is contraindicated, as with this procedure tumor cells are distributed further into both bone and soft tissues and increases the risk of local recurrence. External fixation within healthy tissue or immobilization using a cast is recommended. There is no need for ablative surgery, if the tumor and affected tissue can be removed completely. Neoadjuvant chemotherapy might help to allow subsequent complete surgical resections. Pathological fractures were associated with poorer outcomes in adult patients, but not in children with osteosarcoma (311).

Definitive surgery Guidelines

Prior to definitive surgery hematological recovery after chemotherapy is necessary and the following parameters are recommended:

Neutrophils > 1.0 x 10^9/L

Platelets > 80 x 10^9/L

Indications for limb salvage surgery:

1. Tumor resectable with wide (free / R0) margins
2. Reconstruction possible and likely to be successful
3. Patient aware of risks/ benefits of limb salvage

Indications for amputation:

1. Inability to completely resect the tumor without leaving residual disease (R2)
2. Extensive involvement of neurovascular bundle, reconstruction impossible and likely to be unsuccessful
3. Patient preference

There will be many situations where the decision is not easy, in particular when there has been a poor response to chemotherapy, there is extensive soft tissue involvement, and the tumor is adjacent to the main neurovascular bundle.

Reconstruction after limb salvage surgery

There are many types of limb salvage reconstruction available. The principle aim of the surgeon is to completely resect the tumor with wide / R0 margins. This principle should never be sacrificed to make limb salvage reconstruction easier. The patient will want a reconstruction that will function well and have as little complications as possible. In some situations, an amputation may give a better and more predictable result than attempts at reconstruction (e.g. distal tibia).

The following reconstruction options represent standard treatment but are NOT meant to exclude other options:

Distal femur

In most cases use of an endoprosthesis will give a good result. If the tumor involves the knee joint an extra-articular resection should be carried out.

Proximal tibia

Use of an endoprosthesis will work well if the extensor mechanism is reconstructed. A gastrocnemius muscle flap should be part of the soft tissue reconstruction.

Proximal femur

Modular endoprostheses work well. Because of the significant risk of dislocation, a large unipolar or bipolar head is recommended.

Proximal humerus

Reconstructive options include the use of a prosthesis, a fibula graft (vascularised) or a turn down of the clavicle (*claviculo pro humero*).

Pelvis

All surgical reconstructions are high risk and should be carried out at a center with appropriate expertise. Reconstruction of the hip joint can be performed with the use of modular or 3D printed custom prosthesis.

Diaphyseal tumor

When the joints can be spared above and below a tumor in a long bone then a biological reconstruction is preferred – either using an allograft or an autograft (or a combination). Custom implants can also be considered.

Young children with long bone tumors

Extendable endoprostheses have proved useful but have a significant risk of complications. Families must be fully informed about risks/benefits and the inevitability of the need for further surgery. Rotation-plasty should be considered in these cases.

Surgery of pelvic and other axial tumors

Osteosarcomas arising in the axial skeleton (excluding craniofacial bones) that are deemed resectable with curative intent are eligible for surgery. Subsequent surgical management of such tumors may include amputation (fore or hind quarter for shoulder girdle and pelvic tumors) or complex reconstruction. The chosen approach should be anticipated to achieve the safest oncological margin and at least macroscopic resection.

Surgery of metastatic disease

If primary metastases are present, all of these must also be resected completely, regardless of their number and site, if the patient is treated with curative intent. Resection is strongly recommended for patients felt to have definite or possible pulmonary metastases at initial diagnosis. The preferred time-point for surgery of primary metastases may be between protocol weeks 11

and 20, but other dates may be chosen at the discretion of the treating physicians. While retrospective multi-institutional data have demonstrated equivalent survival with open and thoracoscopic pulmonary metastasectomy, the findings are limited by significant selection bias (41). In a recent survey of the American Pediatric Surgical Association, thoracoscopy was the preferred approach of 34% of surgeons for patients with 3 unilateral nodules but only 21% for those with 5 unilateral nodules. However, a prospective randomized comparison between thoracoscopy and thoracotomy would be necessary to find out which technique offers a better change to cure patients with osteosarcoma lung metastases.

Local therapy in non-resectable osteosarcoma

Radiotherapy

Complete surgical resection is the local therapy of choice. However, not all patients have tumors that can be completely resected. Osteosarcoma requires high doses of radiotherapy to be therapeutically active, which are difficult to achieve with conventional techniques, because of the surrounding organs at risk that cannot be properly protected, so that proton and heavy-ion radiotherapy have come into focus. With those particles the dose deposit is made with a sharp gradient that leads in most cases to a better sparing of the organs at risk. Carbon ions have also a higher relative biological effectiveness (RBE), which means that for the same physical dose it creates more DNA damages resulting in more tumor cells death. In a retrospective analysis from St. Jude Children's Research Hospital, curative-intend radiotherapy (median dose 59.4 Gy; range, 40-76 Gy) was given to 28 pediatric patients with osteosarcoma and resulted in 5-year OS of 42.6% (312). In a series of 55 patients treated with a mean radiation dose of 68.4 Gy via protons, the local control rate was 72% and overall survival was 67% at 5 years (125). In 78 patients with inoperable osteosarcoma of the trunk irradiated with a median of 70.4 Gy carbon-ion radiotherapy (CIRT), the 5-year local control rate was reported to be 62% (129). In 26 pediatric patients with unresectable osteosarcoma, the local control rate at 5 years was 62.9% after CIRT, and 5-year overall-survival was 41.7% (127). Combined ion-beam radiotherapy (CIBRT) with protons and carbon ions were recently studied in a phase I/II trial in 20 patients with primary (N = 18), metastatic (N = 3), or recurrent (N = 2) inoperable pelvic (70%) or craniofacial (30%) osteosarcomas. Patients received protons up to 54 Gy and a carbon ion boost of 18 Gy (131). In this small series, CIBRT showed a favorable toxicity profile and promising results particularly for patients with inoperable craniofacial osteosarcoma (131). While the observed results are encouraging, further research is required before such techniques can be considered standard.

8.3 Methotrexate toxicity management

To prevent acute kidney injury, hyperhydration (e.g., 3L/m^2/24 hours) and urine alkalization (to increase MTX solubility urinary pH must be >7 before start of MTX infusion) are essential. Non-renal toxicities can be prevented by antagonizing MTX with leucovorin initiated 24 hours after MTX-infusion.

Risk factors for the development of delayed clearance of MTX are (234):

- Pre-existing impaired renal function
- Volume depletion due to fluid loss (vomiting, diarrhea), adrenal insufficiency or renal salt wasting
- Thirdspacing phenomenon (ascites, pleural effusion, edema)
- Drugs inducing decreased renal methotrexate clearance

If methotrexate-excretion is severely delayed (i.e. methotrexate concentrations of > 20 µmol/L, 2 µmol/L, 0.2 µmol/L at 24 h, 48 h, 72 h, respectively), the standard daily dose of leucovorin has to be adjusted by multiplying it with the patients serum methotrexate concentration divided by the upper limit of serum methotrexate concentration (i.e. methotrexate concentrations of 20 µmol/L, 2 µmol/L, 0.2 µmol/L at 24 h, 48 h, 72 h, respectively). This adjusted daily dose should be divided by 8 and given every 3 hours. When the methotrexate level is below 0.9 µmol/L, give leucovorin in doses of 8 mg/m^2 orally every 6 hours until one dose after the serum level is < 0.1µM or < 0.2 µM.

If severe MTX related acute kidney injury is suspected, use of glucarpidase (CPG2, Voraxaze®) should be considered. Use of CPG2 is always at the discretion of the treating physician in patients of any age. In EURAMOS-1 protocol the following criteria were provided for considering early use of CPG2:

a) plasma MTX concentrations ≥ 10µmol/L 48 hours after MTX administration or b) rise in creatinine of 100% or more within 24 hours of MTX.

8.4 Dose modifications and delays

Dose Modifications for AP

Toxicity	Grade	Action
Myelosuppression	On day 1 of cycle ANC < 0.75 x 10^9/L or WBC < 2.0 x 10^9/L, or platelets < 75 x 10^9/L	Delay and repeat within 3-4 days until criteria are met. Retreat at full dose unless previous dose reduction. For repeated delay (> 7 days) use G-CSF. If delayed > 7 days in spite of G-CSF reduce cisplatin by 25%.
Febrile neutropenia with or without documented infection	All grade 4, consider for grade 3	Add G-CSF. Further episodes despite G-CSF: reduce cisplatin by 25%.
Mucositis Severe abdominal pain Diarrhea Typhlitis	Grade 4 mucositis or typhlitis or repeated Grade 3 mucositis	Delay until resolved & consider the administration of G-CSF for subsequent courses. By severe toxicity or toxicity after administration of G-CSF decrease subsequent doxorubicin to 60 mg/m^2/cycle.
Cardiotoxicity	LVEF < 50% or SF < 28%	Repeat echo or MUGA in one week. If not within normal range, omit further doxorubicin.
Hearing	≥ Grade 2	Discontinue cisplatin if hearing loss extends to 2kHz or lower frequencies.
Renal toxicity	Serum creatinine > 1.5 x baseline or GFR < 70mL/min/1.73 m^2	Delay for one week. If renal function does not improve, omit cisplatin and give doxorubicin alone. Resume cisplatin at future courses if GFR ≥ 70 mL/min/1.73 m^2.
Hepatic toxicity	Raised Bilirubin	Reduce doxorubicin as follows: Concentration % Dose 0 – 21 µmol/L (0 -1.24 mg/dL) 100% 22 – 35 µmol/L (1.25-2.09 mg/dL) 75% 36 – 52 µmol/L (2.1 -3.05 mg/dL) 50% 53 – 86 µmol/L (3.06-5.0 mg/dL) 25% > 87 µmol/L (> 5.0 mg/dL) 0%
Neuropathy	Grade 1 ≥ Grade 2	Reduce cisplatin by 25% for all future courses. Omit cisplatin for all future courses.

Dose modifications for MTX

Note that no dose reductions will apply

Toxicity	Grade	Action
Myelosuppression	On day 1 of cycle ANC < 0.25 x 10^9/L or WBC < 1.0 x 10^9/L, or platelets < 50 x 10^9/L	Delay and repeat within 3-4 days until criteria are met. Delay until recovery according to group practice
Mucositis Severe abdominal pain Diarrhea	Grade 4 mucositis or diarrhea after MTX If persists for >1 week and is present on Day 29 of MAP cycle	Consider leucovorin rescue adjustment. Reminder: exclude drugs interfering with excretion. Omit Day 29 methotrexate (of this cycle only) and proceed to next cycle (or surgery).
Renal Toxicity	GFR <70mL/min/1.73 m^2	Delay until recovery. If renal function does not improve within 1 week, omit MTX and proceed to next possible cycle. If renal function subsequently improves, MTX can be resumed. (Patients receiving A alone, that is weeks 22 or weeks 26 of therapy in EURAMOS-1, may continue with doxorubicin).
Abnormal LFTs	Not MTX induced LFTs elevated Probably MTX induced i.e. up to 3 weeks after MTX Bilirubin > 1.25 x ULN	Delay one week. Give if ALT < 10 x ULN. It is expected that patients receiving high dose Methotrexate will develop hypertransaminasemia and occasionally hyperbilirubinemia. These elevations can last up to two weeks following the methotrexate infusion and will not be considered toxicity requiring discontinuation of the drug. Persistent hyperbilirubinemia for longer than three weeks will result in discontinuation of MTX.

8.5 Supportive care

Recommendations on supportive care in osteosarcoma - Level of evidence and grade of recommendation		Ref
• Adhere to general local, national and international guidelines		
• Treat pathological fractures conservatively	IV, B	(229)
• High-dose MTX should only be administered at experienced centers, and glucarpidase should be available rapidly	V, A	(234, 237, 238).
• Combinations of MTX (and cisplatin, ifosfamide) with concomitant nephrotoxic medication should be avoided	IV, B	(252)
• Consider supplementation of magnesium with cisplatin therapy	II, A	(247-251)
• Cardiotoxicity should be monitored with echocardiography at base-line and at least following cumulative doxorubicin doses >225 mg/m^2	V, B	(263)
• To prevent cardiotoxicity, dexrazoxane can be considered with expected cumulative doxorubicin dose higher than 250 mg/m2, either starting with the first administration of doxorubicin or after fall in left ventricular function	I, B	(265-267)
• During ifosfamide treatment, MESNA supplementation to prevent hemorrhagic cystitis is mandatory	II, A	(271)
• Methylene blue can be considered to treat severe ifosfamide-induced neurotoxicity	V, D	(273)

Venous access

A permanent indwelling central venous access device is recommended.

Antiemetic

All patients must be treated with appropriate antiemetic medication according to international guidelines.

Infectious prophylaxis

Can be performed according to institutional practice. The use of prophylactic antibiotics including Pneumocystis jirovecii prophylaxis or antifungals is not advised

Neutropenic fever

As per institutional practice, broad spectrum antibiotics in consideration of local bacterial resistance. Aminoglycosides should be used with caution, as nephrotoxic chemotherapy is administered to the patients.

G-CSF

Since treatment intensity is important, G-CSF support is preferable to dose reduction and treatment delay. The recommended dose and schedule indicated in the package insert should be used at the discretion of the physician. Chemotherapy should not be given until a patient has been off G-CSF for 2 days.

Anemia and thrombocytopenia

Transfuse to maintain hemoglobin levels according to institutional practice. Erythropoietin is not recommended as standard therapy but may be used at the discretion of the investigator e.g., for patients who refuse transfusion on religious grounds.

Magnesium supplementation

It may be helpful to supplement magnesium beginning with the first cisplatin-containing course and up to approximately three months after completion of chemotherapy. Intravenous magnesium supplementation in the hydration fluids should be considered during administration of cisplatin.

9. PATIENT FOLLOW-UP

The following are guidelines for timing of follow-up visits *from diagnostic biopsy* to ensure consistency in the detection of relapse or progression. The date of relapse will be defined as the date on which evidence of relapse is confirmed, whether radiologically or clinically. Multimodal therapy of osteosarcoma may be associated with permanent alterations of cardiac, renal, auditory, reproductive function, orthopedic problems and other late effects including secondary malignancies. Appropriate additional investigations, including psychosocial and functional assessment, must therefore be performed in order to ensure optimal patient care.

Clinic visits after end of chemotherapy

Years 1-2	every 2-3 months
Years 3-5	every 6 months
Thereafter	every 6-12 months according to local practice

Minimal investigations at follow-up visits

1. Physical examination at each visit
2. Radiographs (2 dimensions) of the primary tumor site at each visit
3. In non-metastatic patients:

    Chest X-ray

Every 3 months	(year 1 -2)
Every 6 months	(year 3-5)
Every 12 months	> 5 years

    Chest CT scan is optional but should always be performed if chest X-ray shows metastasis or is inconclusive.

4. In pulmonary metastatic patients:

    Assessment every 3 months (year 1-2)

Chest X-ray	3 – 9 – 15 – 21 months after end of therapy
Chest CT	6 – 12 – 18 – 24 months after end of therapy

    Chest X-ray

Every 6 months	(year 3-5)
Every 12 months	> 5 years

Chest CT scan should always be performed if chest X-ray shows metastasis or is inconclusive.

Plain X-ray should be performed on clinical suspicion of bone metastases; if inconclusive, supplement with MRI, and/or CT.

If relapse is detected at any site, a complete diagnostic investigation (chest CT scan, FDG PET-CT/MRI or WB-MRI, imaging of primary tumor site) must be undertaken.

Minimal recommended investigations

	Year 1				Year 2				Year 3		Year 4		Year 5		> 5 year
	3	6	9	12	15	18	21	24	30	36	42	48	54	60	
Outpatient visits	x	x	x	x	x	x	x	x	x	x	x	x	x	x	Every 6-12 mo
Primary tumor site															
Radiograph	x	x	x	x	x	x	x	x	x	x	x	x			
Lung – non metastatic patient															
Chest radiograph	x	x	x	x	x	x	x	x	x	x		x		x	Every 12 mo
Lung – metastatic patient															
Chest radiograph	x		x		x		x								
Chest CT		x		x		x		x	x	x		x		x	Every 12 mo
Audiometry[1]								x[1]							
Echocardiogram								x				x			Every 2 years

[1] Advice is yearly until age of 6, every other year for patients 6 – 12 year, and every 5 year for adolescents. Advice to perform 2 years after end of therapy, further frequency depending on age.

10. TREATMENT - REFRACTORY OR RELAPSED HIGH-GRADE OSTEOSARCOMA

Relapsed/refractory osteosarcoma is challenging to treat and no standardized treatment is defined. Factors that can help to tailor therapy are the time point of occurrence, the number of metastatic lesions and previous therapies. Surgery aiming for surgical remission is essential in (multi)relapsed osteosarcoma (138, 139, 313). After achieving a surgical CR2, about 1/3 of patients survive > 5 years (313). If surgery of lung metastases cannot be performed, stereotactic radiotherapy, radiofrequency ablation (RFA) or cryotherapy might be used as alternatives (3, 152, 153). The most commonly used salvage chemotherapy is ifosfamide ± etoposide. However, there is no definitive proof of an improved overall survival after use of chemotherapy in patients who achieve a second complete surgical remission (CSR), but prolonged survival was reported for patients in whom no CSR had been achieved (139, 146). It is highly recommended to include patients with osteosarcoma relapse in innovative clinical trials. In single / oligo- pulmonary metastatic lesions surgery only can be considered as the management of disease.

Recommendations for high-grade, refractory or relapsed, osteosarcoma - Level of evidence and grade of recommendation		Ref
• Surgery and, if necessary, re-surgery are strongly recommended in resectable, relapsed/refractory osteosarcoma.	II, A	(36, 137-139)
• Chemotherapy might be considered in multi-metastatic, unresectable relapses or in early relapses.	III, B	(138, 139, 146, 158-160)
• Chemotherapy or experimental therapies should be preferably given in the context of osteosarcoma-specific clinical trials.	V, B	(66, 177)
• Tyrosine kinase inhibitors (sorafenib, regorafenib, cabozantinib, lenvatinib, apatinib) have demonstrated some efficacy in small phase II trials and might be of added value. They require further studies	III, B	(168-172, 174)
• In unresectable disease or in multi-repetitive relapsed patients, high dose radiotherapy or radio-frequency ablation might be considered in order to achieve local and/or metastatic control.	IV, B	(134, 150-153)

10.1 Confirmation and restaging

Staging should be performed according to the principals provided for primary disease staging.

Biopsy to confirm progressive or recurrent disease is strongly recommended in case of any uncertainty.

Biopsy of relapsed disease should be strongly encouraged as part of molecular driven studies and molecular driven treatment programs.

Staging disease

Assessment of metastatic disease

- Chest CT
- Bone scan or FDG-PET CT / MRI or WB-MRI
- MRI or CT of the metastatic site(s)

10.2 Chemotherapy

No standard backbone chemotherapy has been defined in relapsed osteosarcoma.

The combination of ifosfamide and etoposide is most commonly used after MAP front-line therapy. The described scheme is based on the EURAMOS-1 IE regimen and Palmerini et al 2020 (163). The scheme below is different to the standard arm of the OLIE study (314), which uses 3000 mg/m2/day ifosfamide for 3 days and etoposide 100 mg/m^2/day for 3 days. Caution must be noted on the use of IE therapy in the context of patients with well-defined cancer predisposition syndromes. Hemorrhagic cystitis due to the ifosfamide metabolite acrolein has to be prevented by administering the antioxidant sodium 2-mercaptoethane sulfonate (MESNA).

Cycle	1			2			3			4			5			6		
Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Chemotherapy																		
Ifosfamide 2800 mg/m^2/day, IV, 5 days	■			■			■			■			■			■		
Etoposide 100 mg/m^2/day, IV, 5 days	■			■			■			■			■			■		
Supportive care																		
Anti-emetics[1]	■			■			■			■			■			■		
Mesna[2]	■			■			■			■			■			■		
G-CSF	■			■			■			■			■			■		

[1.] The MASCC/ESMO guidelines (309) report a moderate emetogenic potential for ifosfamide, and a low emetogenic potential for etoposide. However, a more recent North American pediatric clinical practice guideline (CPG) for chemotherapy-induced nausea and vomiting (CINV) (310) report high-emetogenic potential for the combination (ifosfamide / etoposide). The pediatric CPG recommendations include a combination of 5HT3-antagonists, dexamethasone, neurokinin receptor antagonists). Anti-emetics should be continued a minimum of 72 hours after cisplatin.

[2] Continuous IV infusion (2.8 g/m^2/day x 5) and continuing for a minimum of 12 hours after the final dose of ifosfamide (loading dose allowed)

IE

Course definition

Ifosfamide 14 g/m^2

Etoposide 500 mg/m^2

Course timing

Weeks 1, 4, 7, 10, 13, 16

Pre-course tests

- Height, weight and surface area
- Clinical examination
- Full blood count and differential white count
- Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin)
- Measurement of GFR
- Urine dipstick for blood before and at least once daily during ifosfamide administration
- When indicated: measurement of urinary phosphate re-absorption (TmP/GFR) to assess renal tubular function

Minimum requirements

- General clinical condition permitting chemotherapy
- Neutrophils ≥ 0.75 x10^9/L
- Platelets ≥ 75 x10^9/L
- Bilirubin ≤ 1.25 x ULN
- GFR ≥ 70 mL/min/1.73 m^2
- Urine No hematuria

Administration

Ifosfamide	4-hour IV infusion = 2.8 g/m^2/day x 5
Etoposide	1 hour IV infusion = 100 mg/m^2/day x 5
Mesna	Continuous IV infusion (2.8 g/m^2/day x 5) and continuing for a minimum of 12 hours after the final dose of ifosfamide (loading dose allowed)
Hydration	Adequate hydration throughout ifosfamide infusion and for a minimum of 12 hours after end of ifosfamide infusion.

Supportive care

Encephalopathy	This will occasionally occur and vary in degree from mild agitation to coma and seizures. Risk factors are poor renal function, low albumin and pelvic tumors. See section 10.5 for more details.

10.3 Local therapy

For progressive or recurrent osteosarcoma, surgery is the local treatment of choice. Complete surgical removal of all affected sites is performed whenever feasible, which includes re-resections in case of multiple relapses. There is no specific guidance for timing of surgery.

In unresectable disease, radiofrequency ablation, cryotherapy or stereotactic radiotherapy should be considered to achieve metastatic control.

10.4 Assessments

Baseline assessment of organ function

1. Complete history and detailed physical examination including Lansky/Karnofsky performance status.
2. Full blood count, differential white count and ABO typing.
3. Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, LD, bilirubin)
4. Measurement of glomerular filtration rate (GFR) and tubular function (urine phosphate and creatinine)
5. Urine analysis (dip stick) for blood, protein, and glucose
6. Pregnancy test for girls/female adolescents with signs of puberty
7. Fertility preservation (according to Childhood Cancer Guideline Harmonization Group published (54, 55)):
    a. General information recommended to each patient and their parents, caregivers.
    b. IE (6 courses) poses a high risk for infertility with a cyclophosphamide-equivalent dose of 20.496 mg/m^2.

Overview of imaging assessments

	Restaging	Pre 3rd IE	Pre 5th IE	End of treatment
Site / Week	1	6	12	18
Primary tumor				
Radiographs	x	x[1]	x[1]	x
MRI	x	x[1]	x[1]	x
Metastases				
Chest CT	x	x	x	x
Whole body imaging, bone scan, or if readily available FDG-PET CT/MRI or whole-body MRI	x			
MRI[2]	x[2]			

[1.] In case of local recurrence.

[2.] MRI of affected areas for diagnosis or before planned surgery.

Overview of on-therapy assessments

	IE	IE	IE	IE	IE	IE	EOT
Week	1	4	7	10	13	16	
Clinical evaluation[1]	x	x	x	x	x	x	X
Laboratory							
Full blood count[2]	x	x	x	x	x	x	x
Blood chemistry[3,4]	x	x	x	x	x	x	x[4]
Urine analysis (dip stick)[4]	x						
Pregnancy test	x						
Fertility preservation	x						

1. Including height, weight and surface area.

2. Full blood count and differential white count.

3. Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin), including measurement of glomerular filtration rate (GFR).

4. Include measurement of renal tubular function (optional) e.g. Tubular phosphate reabsorption TmP/GFR.

10.5 Ifosfamide neurological toxicity management

Methylene blue can be considered for patients with severe (mostly defined as grade 3 and 4) neurological toxicity.

Methylene blue is contraindicated in patients with

- Glucose-6-phosphate dehydrogenase deficiency[1]
- Pregnancy & Lactation
- Known sensitivity to the drug
- Severe renal impairment

[1]G6PD deficiency is a heterogeneous disease affecting mainly individuals from malaria endemic areas. More details, including information on G6PD genetic and activity tests, as well as genetic variant classification (classes I–IV), are available at the PharmgKB website (https://www.pharmgkb.org/vip/PA166169539).

Mechanism of action

Whilst the exact mechanisms for Ifosfamide-induced encephalopathy are not known, various metabolic pathways have been suggested. Methylene blue may act by counteracting some of these pathways.

Drug Interactions

No significant drug interactions have been reported with methylene blue.

Dose

Whilst there have been no studies to determine the best dose and scheduling for the treatment of Ifosfamide-induced encephalopathy with methylene blue, suggested is:

Treatment of Ifosfamide-induced encephalopathy:

Adults: 50 mg (5 mL ampule of 1% solution) – 4 hourly

Pediatrics: 1 mg/kg/dose – 4 hourly

Prophylaxis of Ifosfamide-induced encephalopathy:

Adults: 50 mg (5 mL ampule of 1% solution) – 6 hourly

Pediatrics: 1 mg/kg/dose – 6 hourly

Administration

Either as a slow IV bolus – given over several minutes, or in 100 mL normal saline over 15-30 min. The methylene blue should be filtered before use using a 0.45 micron filter.

Side Effects

Potentially life-threatening effects:

• Occasionally: hypotension and cardiac arrhythmias.

Symptomatic Adverse Effects

• IV administration may cause abdominal pain, headache, dizziness, tremors, apprehension, confusion, chest pain, dyspnea, tachycardia, and sweating – however, several of these symptoms are also symptoms of methemoglobinemia for which methylene blue might be considered.

• Nausea, vomiting, diarrhea, and dysuria have been reported with oral administration

• If methylene blue is injected subcutaneously or extravasation occurs, necrotic abscesses may result

• Blue discoloration of urine, stools and saliva.

10.6 IE - Dose modifications and delays

Toxicity	Grade	Action
Myelosuppression	On Day 1 of cycle ANC < 0.75 x 10^9/L Or WBC < 2.0 x10^9/L	Delay and repeat within 3-4 days Retreat at full dose unless previous dose reduction. Consider reduction if cycle is delayed > 7 days in spite of G-CSF (20% dose reduction by omitting the last day of the cycle).
Febrile neutropenia after previous IE	All grade 4 Consider for grade 3	Reduce both drugs by 20% i.e. omit last day of cycle. If a second episode occurs, omit etoposide.
Mucositis, severe abdominal pain, diarrhea, typhlitis	Grade 4 mucositis after previous IE Repeated Grade 3 mucositis	Reduce etoposide by 50%.
Renal Toxicity – glomerular	Serum Creatinine 1.5 x baseline or GFR < 70 mL/min/1.73 m^2	Delay for one week. If renal function does not improve, discontinue ifosfamide, confirm GFR and consider substituting cyclophosphamide and mesna, both 500mg/m^2 x 5 days.
Renal Toxicity – tubular (based on GFR, serum bicarbonate, need for electrolyte replacement, or TmP/GFR)	Grade 1 Grade 2 Grade 3 or 4	No change. Consider reduction of ifosfamide by 20% i.e. omit last day. No further ifosfamide. Consider substituting cyclophosphamide and mesna, both 500 mg/m^2 x 5 days.
Hemorrhage, genitourinary – bladder (Hematuria) - exclude vaginal bleeding and if microscopic, confirm where possible by microscopy	Dipstick positive prior to ifosfamide Microscopic during ifosfamide ≥ 2 occasions ≥ Grade 2	Exclude other causes; double mesna dose +/- increase hydration. Give additional mesna bolus 600 mg/m^2 then continuous infusion at double dose. If persists, discontinue ifosfamide and contact CI. Discontinue ifosfamide, continue double dose mesna and hydration for 24 hours after ifosfamide; consider cystoscopy; contact CI if CTCAE grade 3 or 4
Neurological toxicity – confusion or depressed level of consciousness	Grade 2 Grade 3 Grade 4	No change unless persistent and distressing. Then decrease ifosfamide by 20% (omit last day's dose). If persists, reduce by a further 20%. Stop ifosfamide for this cycle. Decrease next cycle of ifosfamide by 20% (omit last day's dose). If persists, reduce by a further 20%. No further ifosfamide. Consider substituting cyclophosphamide and mesna, both 500 mg/m^2 x 5 days.
Neurological toxicity - seizures	Grade 2 Grade 3	Consider anticonvulsants (benzodiazepines preferred) and/or stopping ifosfamide for this cycle. Continue future cycles at same dose. Stop ifosfamide for this cycle. Consider future cycles at same dose with anticonvulsant coverage.

	Grade 4	No further ifosfamide. Consider substituting cyclophosphamide and mesna, both 500 mg/m^2 x 5 days.
Neurological toxicity – peripheral Neuropathy (exclude other causes)	≥ Grade 2	Omit further ifosfamide. Consider substituting cyclophosphamide and mesna, both 500 mg/m^2 x 5 days.

LIST OF ABBREVIATIONS

AJCC	American Joint Committee on Cancer
AP	Doxorubicin, cisplatin
API-AI	Doxorubicin, cisplatin and ifosfamide
CFOS	Craniofacial osteosarcoma
COG	North American Children's Oncology Group
COSS	The Cooperative Osteosarcoma Study Group
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DWI	Diffusion weighted imaging
DCE	Dynamic contrast enhanced
EANM	European association for nuclear medicine
EDTA	Ethylenediaminetetraacetic acid
EFS	Event-free survival
EOI	The European Osteosarcoma Intergroup
EOT	End of therapy
ESMO	European Society for Medical Oncology
ERN PaedCan	European Reference Network for Paediatric Oncology
EURACAN	European Network for Rare Adult Solid Cancer
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
IE	Ifosfamide and etoposide
IFN-α-2b	Interferon-alpha-2b
FDG PET-CT	18F-FDG (fluorine-18 deoxyglucose) positron emission tomography (PET) imaging
GHR	Good histological response
HGOS	High-grade osteosarcoma
LGOS	Low-grade osteosarcoma
MAP	Methotrexate, doxorubicin and cisplatin
MAPIE	Methotrexate, doxorubicin, cisplatin, ifosfamide and etoposide
MASCC	Multinational association of supportive care in cancer
M-EI	Methotrexate, etoposide and ifosfamide
MSTS	Musculoskeletal tumor society
MTX	Methotrexate
OS	Overall survival
PD	Progressive disease
PHR	Poor histological response
RECIST 1.1	Response evaluation criteria in solid tumors, version 1.1
SSG	The Scandinavian Sarcoma Group
WHO	World Health Organization

APPENDIX A – TUMOR STAGING

Musculoskeletal Tumor Society staging system (MSTS), also known as the Enneking staging

Based on a combination of histologic grade (G), anatomic site (T), and presence or absence of distant metastasis (M). Grade G0 is benign, G1 is low grade and G2 is high grade. T1 where it has basically remained within the bone, T2 where it has extended beyond the bone into other nearby structures. Tumors that have not spread to the lungs, bones, distant lymph nodes or other organs are considered M0, while those that have spread are M1. So, low-grade, localized tumors are stage I; high-grade, localized tumors are stage II and metastatic tumors (regardless of grade) are stage III.

Stage	Site	Distant metastasis	Histologic grade
IA	T1 (intracompartmental)	M0 (no metastasis)	G1 (low)
IB	T2 (extracompartmental)	M0	G1 (low)
IIA	T1	M0	G2 (high)
IIB	T2	M0	G2 (high)
III	T1 or T2	M1 (regional or distant)	G1 or G2

AJCC, TNM staging (105)

The eighth edition of the American Joint Committee on Cancer (AJCC) *AJCC cancer staging manual* stages osteosarcoma arising in the appendicular, truncal, and craniofacial bones based on the presence or absence of distant metastasis, histological grade, and greatest tumor dimension (≤ 8 cm or > 8 cm). Tumors of the pelvic or spinal skeleton are specifically staged based on the anatomical extent of intraosseous invasion or presence of extraosseous invasion.

Stage	Primary tumor extension	Regional lymph node	Distant metastasis	Histologic grade
IA	T1	N0	M0	G1 or GX
IB	T1 or T2	N0	M0	G1 or GX
IIA	T1	N0	M0	G2 or G3
IIB	T2	N0	M0	G2 or G3
III	T3	N0	M0	G2 or G3
IVA	Any T	N0	M1a	Any G
IVB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

Definitions for the primary tumor

Appendicular skeleton, trunk, skull and facial bones

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 Tumor ≤8 cm in greatest dimension
- T2 Tumor >8 cm in greatest dimension
- T3 Discontinuous tumors in the primary bone site (skip metastasis)

Spine

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor

- T1 Tumor confined to one vertebral segment or two adjacent vertebral segments
- T2 Tumor confined to three adjacent vertebral segments
- T3 Tumor confined to four or more adjacent vertebral segments, or any nonadjacent vertebral segments
- T4 Extension into the spinal canal or great vessels
    - T4a Extension into the spinal canal
    - T4b Extension of gross vascular invasion or tumor thrombus in the great vessels

Pelvis

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 Tumor confined to one pelvic segment with no extraosseous extension
    - T1a Tumor ≤8 cm in greatest dimension
    - T1b Tumor >8 cm in greatest dimension
- T2 Tumor confined to one pelvic segment with extraosseous extension or two segments without extraosseous extension
    - T2a Tumor ≤8 cm in greatest dimension
    - T2b Tumor >8 cm in greatest dimension
- T3 Tumor spanning two pelvic segments with extraosseous extension
    - T3a Tumor ≤8 cm in greatest dimension
    - T3b Tumor >8 cm in greatest dimension
- T4 Tumor spanning three pelvic segments or crossing the sacroiliac joint
    - T4a Tumor involves sacroiliac joint and extends medial to the sacral neuroforamen
    - T4b Tumor encasement of external iliac vessels or presence of gross tumor thrombus in major pelvic vessels

Definition of regional lymph node

- NX Regional lymph node cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph nodes metastasis

Definition of distant metastasis

- M0 No distant metastasis
- M1 Distant metastasis
    - M1a Lung
    - M1b Bone or other distant sites

Histologic grade

- GX Grade cannot be assessed
- G1 Well differentiated, low grade
- G2 Moderately differentiated, high grade
- G3 Poorly differentiated, high grade

APPENDIX B – TECHNICAL IMAGING GUIDELINE

Please see the guideline for the appropriate timing of investigations.

Chest CT

Chest CT should be acquired on maximal inspiration. The ideal slice thickness is 1.0 mm.

Technical

- Slice thickness: Maximal: 1.5 mm
- Matrix size: According to local protocol
- FOV: Adapted to chest size
- kV: According to local protocol
- mAs: According to local protocol
- Patient positioning: Supine
- Level of inspiration: If possible to instruct patient: full inspiration

The report should include technical notes (use of contrast, slice thickness). The presence of any pulmonary or pleural abnormalities (incl. pleural fluid or thickening). The number and location of metastases should be recorded.

MRI

At least one sequence (for example coronal T1) should cover the entire involved bone and adjacent joints for the identification of skip lesions. The field of view of the other sequences can be focused on the tumor and its relation with the nearest joint. MRI should be performed with the use of gadolinium and include T1, T2 (preferably with fat suppression), and T1 post-gadolinium sequences with fat suppression. Axial and coronal images are strongly recommended for the identification of intra-medullar tumor extension and the diagnosis of skip lesions (25, 299). Diffusion weighted imaging and perfusion studies are to be considered.

The following MRI sequences are considered the current clinical standard of care:

- T1-weighted transversal
- T1-weighted sagital/coronal
- Fat-suppressed T2-weighted or STIR (in 2 planes)
- Post gadolinium T1 transversal (fat-suppressed)
- Post gadolinium T1 sag/cor (fat-supressed)

MRI sequences to be considered are:

- Diffusion weighted imaging (DWI) with reconstruction apparent diffusion coefficient (ADC) maps

Dynamic Contrast Enhanced (DCE)

The report of the primary tumor should include description and localization of the tumor, the maximal diameter (assessed according to RECIST 1.1), the intramedullary extent, the relationship of the tumor with surrounding tissues (e.g., vessels, nerves), the relationship to joints and the presence of skip lesions (i.e. additional osteosarcoma foci within the same bone).

Bone scintigraphy

Bone scintigraphy should be acquired according to the current EANM guideline (305).

Technical:

- Patients may eat and drink before the investigation, appropriate hydration is recommended after injection.
- Single-headed or dual-headed gamma camera equipped with a low-energy, high-resolution parallel-hole collimator is recommended.
- Whole-body bone scintigraphy can be accomplished with multiple overlapping (spot) images or with continuous imaging (i.e. whole-body scan) obtained in both anterior and posterior projections.
- Diagnostic sensitivity and specificity of bone scanning can be significantly increased by using SPECT or, if available, SPECT/CT.

- Whole-body bone scintigraphy is routinely used in oncology and other settings. In those cases, limited bone scan or spot views are indicated only where an uptake abnormality or an equivocal finding detected on whole-body image needs to be clarified.

The report should include technical notes (the INN of the radiolabeled bisphosphonate, the injected activity in megabecquerels, the site and time of injection, the time of image acquisition, the scanning protocol used - early phase, late phase, SPECT/CT images -, the different image acquisitions, and the dose–length product and the CT dose index (CTDI) if SPECT/CT is performed). Abnormal tracer uptake (increased, decreased, abnormal pattern, bone findings, soft tissue findings) should be clearly stated.

FDG PET-CT / MRI

FDG PET-CT should be acquired according to current EANM guidelines (303, 304). No current guidelines for FDG PET-MRI are available.

Technical:

- Preparation of the patient according to the guideline is essential for avoid brown adipose tissue activation.
- Administered FDG activities are based and calculated according to the EANM guidelines. Paediatric Guidelines and dose Card recommendations using a 3D mode, adjusted to patient's weight, and adjusted on PET-CT device performances.
- Standard imaging time starts at 60 min post injection, after voiding when possible. Follow up PET-CT scans should be performed on the same device and observe the same scanning interval +/- 10min from baseline.
- Whole-body PET examination from vertex to toes should be performed, including the entire legs and arms. For primary head & neck tumors, a dedicated head and neck PET-CT acquisition should be performed with increased acquisition time of the head & neck region.
- Scan data will be recorded for decay, body weight and injected dose and reconstructed using an iterative algorithm.
- The same FDG dose, acquisition protocol and reconstruction algorithm must be used for baseline and follow-up scans.
- It is recommended to include PET reconstruction according to EARL guidelines.
- Low-dose CT parameters should be adapted to weight and device performances.
- Field of view of CT reconstructions should be adapted to patient size / circumference.

The report should include technical notes (FDG activity, time of administration, serum glucose, preparation, scan range etc) and a quality assessment of the scan (brown adipose tissue activation). The avidity and/or uptake of the primary tumor. The location, extent, and intensity of any abnormal 18F-FDG activity and the relevant CT morphologic findings related to PET abnormalities on CT images should be described. The conclusion should state whether clear metastatic lesions are present and/or the presence of suspicious lesions requiring histological confirmation.

APPENDIX C – THE FRENCH MEI REGIMEN PROTOCOL

Chemotherapy

MEI – regimen

Disclaimer: Details for the regimen as detailed below are based on the specifications of the French OS2006/sarcome-09 protocol.

As a general rule, drug dosage should be modified as little as possible. If necessary, delay treatment to administer full doses. Decisions regarding the possibility of proceeding with chemotherapy after a delay should be re-evaluated at least every 3-4 days. In the absence of prohibitive toxicity, an attempt to give any omitted chemotherapy should be made after the end of scheduled protocol chemotherapy (i.e., after week 21).

Of note, below the MEI regimen is described of the French OS2006/sarcoma-09 protocol. M-EI is given to all patients as neoadjuvant chemotherapy. In patients with localized resected disease with good histological response adjuvant M-EI chemotherapy is given. In patients with poor histological response, metastatic or unresectable disease MAP chemotherapy is given.

Localized, resectable and good histologic response to neoadjuvant chemotherapy

Cycle	Neoadjuvant										1				2				3				4		
Week	**1**	2	3	4	**7**	8	9	**13**	14	15	**16**	17	18	19	**22**	23	24	25	**28**	29	30	31	**34**	35	36
										S															
Chemotherapy										U															
Ifosfamide[1]										R															
Etoposide[2]										G															
Methotrexate[3]										E															
										R															
Supportive care										Y															
Anti-emetics[4]																									
Filgrastim[5] or cardioxane[6]																									

[1] Ifosfamide 3000 mg/m^2/day for 3 days

[2] Etoposide 75 mg/m^2/day for 4 days

[3] Methotrexate 12 g/m^2, 1 day

[4.] The MASCC/ESMO guidelines (309) report a moderate emetogenic potential for ifosfamide, and a low emetogenic potential for etoposide. However, a more recent North American pediatric clinical practice guideline (CPG) for chemotherapy-induced nausea and vomiting (CINV) (310) report high-emetogenic potential for the combination (ifosfamide / etoposide). The MASCC/ESMO guidelines (309) report a low emetogenic potential for MTX. However, a more recent North American pediatric clinical practice guideline (CPG) for chemotherapy-induced nausea and vomiting (CINV)(310) report high-emetogenic potential for HD-M courses with 12mg/m^2. The pediatric CPG recommendations include a combination of 5HT3-antagonists, dexamethasone, neurokinin receptor antagonists). Anti-emetics should be continued a minimum of 72 hours after cisplatin.

[5.] In case of previous non-catheter associated neutropenic sepsis or prolonged hospitalization due to neutropenic fever (>7 days) or per institutional practice

[6.] Cardioxane: In case of a confirmed 10% fall within the normal range of LVEF or similar fall within the normal range of FS occurs or per institutional practice

Metastatic, unresectable or poor histologic response to neoadjuvant chemotherapy

Cycle	Neoadjuvant										1		2	3	4	5
Week	1	2	3	4	7	8	9	12	13	14	16	17	20	23	26	29
										S						
Chemotherapy										U						
Ifosfamide[1]										R						
Etoposide[2]										G						
Methotrexate[3]										E						
Doxorubicin[4]										R						
Cisplatin[5]										Y						
Supportive care																
Anti-emetics[6]																
Magnesium[7]																
Filgrastim[8]																
Cardioxane[9]																

[1] Ifosfamide 3000 mg/m^2/day for 3 days

[2] Etoposide 75 mg/m^2/day for 4 days

[3] Methotrexate 12 g/m^2, 1 day

[4] Doxorubicin 37.5 mg/m^2/day, for 2 days

[5] Cisplatinum 120 mg/m^2, given continuously in 48 hours

[6.] The MASCC/ESMO guidelines (309) report a high emetogenic potential for cisplatin, a moderate emetogenic potential for ifosfamide and doxorubicin, and a low emetogenic potential for MTX and etoposide. However, a more recent North American pediatric clinical practice guideline (CPG) for chemotherapy-induced nausea and vomiting (CINV) (310) report high-emetogenic potential for both AP, IE and HD-M courses with 12mg/m^2. The pediatric CPG recommendations include a combination of 5HT3-antagonists, dexamethasone, neurokinin receptor antagonists). Anti-emetics should be continued a minimum of 72 hours after cisplatin.

[7.] Start with Mg supplementation with first cisplatin course and give (intravenously or orally) during each cisplatin course.

[8.] In case of previous non-catheter associated neutropenic sepsis or prolonged hospitalization due to neutropenic fever (>7 days) or per institutional practice

[9.] In case of a confirmed 10% fall within the normal range of LVEF or similar fall within the normal range of FS occurs or per institutional practice

M Course

Definition

- M: Methotrexate 12 g/m^2

Timing (weeks)

- Neoadjuvant: 1, 2, 3, 7, 8, 12, 13
- Adjuvant (localized resectable disease and GHR): 16, 17, 18, 22, 23, 24, 28, 29, 30, 34, 35, 36
- Adjuvant (metastatic or unresectable or PHR): 16

Pre-course tests

- Height, weight and surface area
- Clinical examination
- Full blood count and differential white count
- Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin)
- Measurement of GFR either by estimation
- Urinary pH

Minimal requirements

- General clinical condition permitting chemotherapy including resolving mucositis ≤ grade 1
- No serous effusions or other '3rd space' (abnormal accumulation of fluid into an extracellular and extravascular space)
- Neutrophils ≥ 0.5 x10^9/L or WBC ≥ 1.0 x10^9/L
- Platelets ≥ 50 x10^9/L
- Bilirubin ≤ 1.25 x ULN
- GFR ≥ 70 mL/min/1.73 m^2
- Urinary pH > 7.0 immediately prior to MTX
- Monitoring availability of serum MTX level

Administration

Methotrexate	4-hour infusion.
Hyperhydration	Adequate fluid with electrolytes and bicarbonate must be given to maintain urine output and alkalization. This should be maintained until MTX serum level is considered safe according to institutional practice (generally <0.2 µmol/L).
Urine pH	A urinary pH >7 must be achieved before starting the MTX infusion and maintained until serum level is considered safe according to group practice (generally <0.2 µmol/L). Oral or intravenous administration of sodiumbicarbonate can be used.

Supportive care

MTX serum levels	To be taken at 24 hours from start of MTX and analyzed if serum creatinine at 24 hours is ≥ 1.5 times increased. Must always be taken and analyzed at 48 hours from start of MTX then daily until level is considered safe according to institutional practice (generally <0.2 µmol/L).
Leucovorin Rescue	This must begin 24 - 28 hours after start of MTX infusion and be continued until serum MTX level is considered safe (<0.2 µmol/L). The standard daily leucovorin dose of 60 mg/m^2 should be divided into 4 doses given every 6 hours. In case of high MTX levels, see section on methotrexate toxicity management. In the French protocol every 6 hours 12 mg/m2 is given.

IE

Course definition

Ifosfamide 9 g/m^2

Etoposide 300 mg/m^2

Timing (weeks)

- Neoadjuvant: 4, 9
- Adjuvant (localized, resectable disease and GHR): 19, 25, 31 (only ifosfamide)
- Adjuvant (metastatic or unresectable or PHR): -

Pre-course tests

- Height, weight and surface area
- Clinical examination
- Full blood count and differential white count
- Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin)
- Measurement of GFR
- Urine dipstick for blood before and at least once daily during ifosfamide administration
- When indicated: measurement of urinary phosphate re-absorption (TmP/GFR) to assess renal tubular function

Minimum requirements

- General clinical condition permitting chemotherapy
- Neutrophils ≥ 0.75 x10^9/L or WBC ≥ 2.0 x10^9/L
- Platelets ≥ 75 x10^9/L
- Bilirubin ≤ 1.25 x ULN
- GFR ≥ 70 mL/min/1.73 m^2
- Urine No hematuria

Administration

Ifosfamide	4 hour IV infusion = 3 g/m^2/day x 3 days
Etoposide	1 hour IV infusion = 75 mg/m^2/day x 4 days
Mesna	Continuous IV infusion (3 g/m^2/day x 3 days) and continuing for a minimum of 12 hours after the final dose of ifosfamide (loading dose allowed)
Hydration	Adequate hydration throughout ifosfamide infusion and for a minimum of 12 hours after end of ifosfamide infusion.

Supportive care

Encephalopathy	This will occasionally occur and vary in degree from mild agitation to coma and seizures. Risk factors are poor renal function, low albumin and pelvic tumors. See section on handling of known adverse events for information on methylene blue and dose modifications for adjustment of subsequent cycles.

AP Course

Definition

- A: Doxorubicin (Adriamycin) 75 mg/m^2
- P: Cisplatin 120 mg/m^2

Timing (weeks)

- Neoadjuvant: -
- Adjuvant (localized resectable disease and GHR): -
- Adjuvant (metastatic or unresectable or PHR): 17, 20, 23, 26, 29

Pre-course tests

- Height, weight and body surface area
- Clinical examination
- Full blood count and differential white count
- Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin), including measurement of GFR
- Before 5th course of doxorubicin (at cumulative dose of doxorubicin 300 mg/m^2) and at end of therapy: Left ventricular ejection fraction and fractional shortening (echocardiogram or radionuclide scan)
- Audiometry before at baseline and at least before 3rd and 5th AP cycle

Minimal requirements

- General clinical condition permitting chemotherapy
- Neutrophils ≥ 0.75 x10^9/L or WBC ≥ 2.0 x10^9/L
- Platelets ≥ 75 x10^9/L
- Bilirubin ≤ 1.25 x ULN
- GFR ≥70 mL/min/1.73m^2
- Cardiac function FS ≥28% or LVEF ≥ 50% at last scheduled assessment
- Hearing < Grade 2 at ≤2 kHz

Administration

Note:	Commence doxorubicin containing cycles at full dose unless previous dose reduction for doxorubicin containing cycles for gastrointestinal or cardiotoxicity. In those circumstances continue A at previous reduced dose Doxorubicin 48-hour continuous IV infusion = 37.5 mg/m^2/day administered by 48-hour continuous infusion.
Cisplatin	Continuous 72-hour IV infusion or 4 hour infusion (60 mg/m^2) x 2 days.
Hydration	Sufficient hydration is mandatory.

Overview of imaging assessments

	Diagnosis	Post 1st IE	Pre-surgery	Post-surgery	Pre IE/MAP	EOT
Site / Week	1	6-7	10 - 14	15	25	33 – 36
Primary tumor						
Radiographs	x	x		x		x
MRI	x	x	x	(x)[1]		(x)[1]
Lung, non-metastatic						
Chest CT	x		x			
Lung radiographs		x		x	x	X
Lung, metastatic						
Chest CT	x	x	x		x	X
Bone metastases						
If readily available FDG PET-CT/MRI or whole-body MRI[2]; or at minimum bone scan	x		X[3]			
MRI of metastatic lesion	x		x			

1. MRI of primary tumor site to be considered. MRI should be performed in case of clinical or radiographical suspicion of recurrent disease

2. The latter (FDG PET-MRI or whole-body MRI can be considered especially in patients with tumor predisposition syndromes with DNA repair pathologies, when available.

3. Can be used to evaluate response to chemotherapy in multi-metastatic patients and support decision making in extensive surgery or optional local therapy.

Assessments (localized disease, resectable and good histologic response)

	M	M	IE	M	IE	M	Surg	M	IE	M	IE	M	I	M	EOT
Week	1	2-3	4	7-8	9	12-13	15	16-17-18	19	22-23-24	25	28-29-30	31	34-35	
Clinical evaluation[1]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory															
Full blood count[2]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ABO typing	x														
Blood chemistry[3]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[4]
Urine analysis (dip stick)	x		x		x				x		x		x		x
Urine pH	x	x		x		x		x		x		x		x	
Pregnancy test	x														
Fertility preservation	x														

1. Including height, weight and surface area.

2. Full blood count and differential white count.

3. Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin), including measurement of glomerular filtration rate (GFR).

4. Include measurement tubular phosphate reabsorption.

Assessments (metastatic or unresectable or PHR)

	M	M	IE	M	IE	M	Surg	M	AP	AP	AP	AP	AP	EOT
Week	1	2-3	4	7-8	9	13-14	15	16	17	20	23	26	29	
Clinical evaluation[1]	x	x	x	x	x	x	x	x	x	x	x	x	X	x
Laboratory														
Full blood count[2]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ABO typing	x													
Blood chemistry[3]	x	x	x	x	x	x	x	x	x	x	x	x	x	x[4]
Urine analysis (dip stick)	x		x		x									x
Urine pH	x	x		x		x		x				x		
ECG	x													
Echocardiogram[5]									x		x	(x)[6]	x	x
Audiometry									x		x	(x)[6]	x	x
Pregnancy test	x													
Fertility preservation	x													

1. Including height, weight and surface area.

2. Full blood count and differential white count.

3. Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin), including measurement of glomerular filtration rate (GFR).

4. Include measurement of tubular phosphate reabsorption.

5. Assessment of left ventricular function.

6. If previous exam was abnormal

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