

Osteosarcoma: Evolution of the strategy pursued by the cooperative German-Austrian-Swiss osteosarcoma study group (COSS)

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The cooperative German-Austrian-Swiss osteosarcoma study group COSS has been performing multicentric studies on the treatment of osteosarcoma since 1977. Meanwhile, most young osteosarcoma patients from these three countries are being entered into the group's studies. While the first protocol, COSS-77, was based on adjuvant chemotherapy, all protocols since 1980 have included a neoadjuvant phase. All neoadjuvant treatment protocols have included high-dose methotrexate with leukovorin rescue (MTX) in varying combinations with doxorubicin (DOX) ± cisplatin (DDP) ± ifosfamide (IFO) ± bleomycin, cyclophosphamide, and dactinomycin (BCD), followed by definitive surgery and postoperative continuation of chemotherapy, as outlined below:

Chemotherapy in the neoadjuvant COSS-studies

	DOX	MTX	DDP	BCD	IFO
COSS-80					
- DDP arm	4 x 90 mg/m ²	14 x 12 g/m ²	4 x 120 mg/m ²	none	none
- BCD arm	4 x 90 mg/m ²	14 x 12 g/m ²	none	4 courses	none
COSS-82					
- study arm	none	8 x 12 g/m ²	none	4 courses	none
- control arm	4 x 60 mg/m ²	8 x 12 g/m ²	4 x 120 mg/m ²	none	none
<i>in case of poor response to standard treatment, salvage chemotherapy with different drugs was used postoperatively</i>					
COSS-86					
- low risk	4 x 90 mg/m ²	12 x 8 g/m ²	4 x 120 mg/m ²	none	none
- highrisk	5 x 90 mg/m ²	14 x 8 g/m ²	5 x 120- 150 mg/m ²	none	5 x 6 g/m ²
COSS-86B	4 x 90 mg/m ² <i>continuous infusion</i>	12 x 8 g/m ²	4 x 120 mg/m ²	none	4 x 6 g/m ²
COSS-91	4 x 60 mg/m ²	8 x 12 g/m ²	4 x 120 mg/m ² (5h vs. 72h iv)	none	4 x 6 g/m ²
COSS-86C	4 x 90 mg/m ² <i>continuous infusion</i>	12 x 8 g/m ²	4 x 120 mg/m ² (5h vs. 72h iv)	none	4 x 6 g/m ²

Over the years, over 150 institutions have entered patients into COSS studies. These were eligible as study patients if they were ≤ 40 years of age and were registered within three weeks of biopsy of a primary, previously untreated high-grade central osteosarcoma of an extremity, were free of detectable metastases (including skip lesions) and had no unrelated ailment prohibiting chemotherapy.

From 1980, when neoadjuvant chemotherapy was introduced into the treatment concept until 1996, when the last completed study was closed, 925 such patients were enrolled, with a median follow-up of over 6 years for surviving patients. Evaluated on an intention-to-treat basis, the actuarial probabilities to survive and to survive without relapse at 15 years were 68% and 61%, respectively. For this group, tumor response to preoperative neoadjuvant

chemotherapy and tumor size at diagnosis were significant prognostic factors: Actuarial overall (event-free) survival rates were 80% (74%) if preoperative chemotherapy resulted in > 90% tumor necrosis (good response) and only 52% (44%) in case of poorer response. In addition to a lower rate of systemic metastases, a good response to preoperative chemotherapy was also associated with a lower risk of local failure (particularly in case of limb-salvage surgery). Local failure was almost completely incompatible with long term survival.

The association between tumor response and relapse-free survival, which had first been noted by Rosen et al. [1], could be verified in the first neoadjuvant study of our group, COSS-80 [2]. The treatment concept of the following study, COSS-82, was formulated under the impression of data from the Memorial Sloan Kettering Cancer Center, which suggested that poor responders might be salvaged by postoperative chemotherapy modifications [3]. The aim of study COSS-82 was to determine in a randomized setting whether less aggressive chemotherapy - high-dose methotrexate (MTX) and BCD - might be used upfront and if the drugs most likely to cause severe late effects - doxorubicin (DOX) and cisplatin (DDP) - might be reserved for those patients who responded poorly to less toxic preoperative treatment [4]. As expected, the response rate was lower in the „mild« study arm compared to the "aggressive" control arm, which included aggressive preoperative treatment with three drugs (MTX, DOX, DDP) to begin with. Unfortunately, however, no salvage effect for poor responders was observed, despite switching chemotherapy postoperatively, so that prognosis was significantly inferior for patients in the study arm [4].

The conclusion from COSS-82 was that chemotherapy for osteosarcoma should be as aggressive as possible right from the beginning, in order to achieve good tumor response in as many patients as possible, which could then be expected to translate into an improved outcome. Therefore, the follow-up study COSS-86 included chemotherapy which was intensified compared to the previous protocols. Four-drug treatment with MTX, DOX, DDP and the additional agent IFO was given to all but a minority (< 25%) of patients without any of three defined risk factors who were considered to be at low risk for poor response and relapse. The latter received 3-drug therapy with MTX, DOX, and DDP. In order to evaluate whether loco-regional intensification might be feasible, part of the high-risk patients received their preoperative DDP i.a., while the others received DDP i.v.. Analyzed on an intention to treat basis for 171 eligible patients, aggressive combination chemotherapy according to COSS-86 led to actuarial overall and event-free survival expectancies of 72% and 66% at ten years. These results were the best which our group had ever achieved. No benefit of i.a. DDP application was observed. The results in this unselected group of patients again argued for the value of giving intensive systemic chemotherapy right from the start of treatment.

An attempt to improve treatment results even further by condensing chemotherapy, undertaken together with the Istituto Ortopedico Rizzoli (study COSS-91/IOR), was terminated prematurely because preliminary response data among COSS-patients indicated unsatisfactory results. Survival data, however, were later found to equal those of study COSS-86.

While being highly effective, aggressive chemotherapy as detailed above was also rather toxic, with a combined early and late therapy related mortality rate of up to approximately 3%. Late effects which were particularly worrisome were anthracycline cardiotoxicity and cisplatin related ototoxicity, with several cases of terminal heart failure and high frequency of hearing loss well into the speech range, and to a lesser extent nephrotoxicity.

In order to reduce cardiotoxicity, DOX application was altered from short to continuous 48-hour infusions in 1988. When the results achieved with the otherwise highly similar COSS-86 based follow-up protocols COSS-86B & C, which included continuous DOX infusions, are compared to those achieved with the original COSS-86 protocol, which incorporated short DOX infusions, there is no hint that changing to a less cardiotoxic DOX schedule might have reduced the therapeutic efficacy of polychemotherapy. Severe cardiotoxicity was observed less frequently since switching to continuous DOX infusions. In contrast to our earlier experience, no more cases of terminal heart failure occurred.

In order to reduce ototoxicity, a randomized trial DDP application was randomized in studies COSS-91/86C, again comparing shorter (5h) with prolonged (72h) infusions. Preliminary results indicate no loss of treatment efficacy, but markedly less hearing loss with the continuous DDP application schedule.

In addition to the "study" patients with primary localized extremity osteosarcoma, COSS has also followed patients with disseminated disease, patients with axial tumor sites, and those with osteosarcoma variants. For 101 patients with isolated pulmonary metastases, overall survival was 29% at > 10 years. The survival rate was 41% for those patients in whom complete surgery of both the primary tumor and the pulmonary metastases was performed. A low number of metastases, a good radiologic response of the metastases, and a good histologic response of the primary tumor were associated with a more favorable outcome. The prognosis was extremely poor for patients with primary metastases to distant bones, who often presented with far advanced disease and only rarely achieved complete surgical remissions. While approximately one half of patients with primary skip-metastases as the only sign of dissemination survived, prognosis was poor when skip metastases were found in combination with other metastases.

Our group's current protocol, COSS-96, is trying to use risk adapted therapy for localized extremity osteosarcoma. An aggressive COSS-86 based 4-drug regimen is used for all patients. Risk stratification is based on the observation that both tumor response and tumor size influence prognosis. Postoperative therapy is shortened for patients with small tumors responding very well to chemotherapy. Patients with large tumors that respond very poorly are switched to alternate drugs. Following our positive experience in relapsed osteosarcomas, carboplatin plus etoposide is being given postoperatively to these high-risk patients. The majority of patients make up an intermediate risk group, where a randomized question concerning the use of DOX and DDP or MTX in the late phase of treatment is being asked. Based on the results of our previous trials, DOX and DDP are given as continuous infusions. Patients with primary metastatic disease and those with osteosarcomas of the trunk are also treated with intensive, COSS-86 based 4-drug chemotherapy, with aggressive local (surgical) treatment of all foci whenever possible.

REFERENCES:

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