Chemotherapy in osteosarcoma: The Scandinavian Sarcoma Group experience

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Chemotherapy in osteosarcoma

The Scandinavian Sarcoma Group experience

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Osteosarcoma is the most common bone tumor in children and adolescents. The most common sites are the distal femur and proximal tibia, and some 15–20% of patients have clinically detectable metastases at the time of diagnosis. Most studies in osteosarcoma include only patients with "classical osteosarcoma", a good prognostic group of patients without metastases at presentation, extremity localized tumors and age ≤ 40 years. However, nonclassical osteosarcoma represents more than 40% of the entire high-grade osteosarcoma population, emphasizing the need for focus also on this group of patients in clinical research (Huvos 1991, Saeter and Bruland 1998).

The modern multidisciplinary approach to the osteosarcoma patients has significantly improved outcome, especially for the patients with classical disease. Before the introduction of intensive polyagent chemotherapy, 2-year overall survival around 15–20% was reported (Harvei and Solheim 1981, Friedman and Carter 1972). With today's combination of chemotherapy and surgery long-term survival rates of more than 70% have been reported in several studies (Saeter et al. 1991, Bacci et al. 1993, Fuchs et al. 1998, Smeland et al. 2003).

Important treatment principles such as neoadjuvant chemotherapy were already established during the pioneering phase in the 70-ties (Rosen et al. 1979, Jaffe 1976). The rationale for preoperative chemotherapy was to achieve immediate effect on metastatic disease, facilitate limbsaving surgery by delineation of the primary tumor and third the possibility to tailor the postoperative chemotherapy by assessment of the histologic response on the resected tumor specimen. Rosen et al. (1982) with the T-10 protocol, reported improved outcome by selection of the postoperative chemotherapy based on the histologic response to preoperative chemotherapy, a strategy since then utilized in all Scandinavian osteosarcoma studies.

Classical osteosarcoma

SSG II

The breakthrough in osteosarcoma treatment in Scandinavia was the SSG (Scandinavian Sarcoma Group) II study (1982–1989), based on Rosen's T-10 protocol. All patients received 4 cources of high-dose methotrexate preoperatively. Good responders continued with a methotrexate, BCD (bleomycin, cyclophosphamide and dactinomyocin), doxorubicin combination whilst poor responders were salvaged with replacement of cisplatin for methotrexate (Saeter et al. 1991) The projected 5-year metastases-free and sarcoma-specific survival rates were 56% and 66%, respectively (Table 1, Figure 1). In contrast to the original report by Rosen et al. the salvage approach with exchange of cisplatin for methotrexate to poor responders did not improve outcome for this group of patients with a persistent difference in metastases-free survival of 25%. The importance of methotrexate administration/elimination was emphasized by the correlation between serum levels of methotrexate and histologic response.

Table 1. Comparison of SSG protocols

Study	No of (Scandinavian) patients	Period	Preoperative regimen	Percentage of good responders	5-year survival [a] ILRF	MF	SS
SSG II	97	1982–1989	MTX	17	95	54	64
SSG VIII	113	1990–1997	MTX, CDP, DOXO	58	93	63	74
ISGSSG I	57	1997–2000	MTX, CDP, DOXO, IFO	58	94	65	69

[a] 5-year survival: LRF local recurrence-free, MF metastasis-free, and SS sarcoma-specific

SSG VIII

The SSG VIII study (1990-97) was based on the experience from the SSG II study and modified accordingly. The percentage of good responders in SSG II was only 17%. In an attempt to increase the number of good histologic responders and by that outcome, cisplatin and doxorubicin were added to methotrexate in the preoperative phase. As salvage therapy to poor responders, ifosfamide in combination with etoposide, which appeared successful in the Rizzoli IOR-II study, replaced the three drugs given upfront (Bacci et al. 1993). 113 patients were included in the study. 58% of the patients achieved a good histologic response to chemotherapy. The 5-year sarcoma specific and metastases-free survival rates were 74% and 63% respectively (Table1, Figure 1). Thus, although with some improvement in survival rates, the substantial improvement in percentage of good responders compared to SSG II was not translated into a similar improvement in outcome. The etoposide/ifosfamide replacement combination did not improve outcome in poor histologic responders and a major conclusion from the SSG VIII study was that poor response does not justify discontinuation of the drugs used upfront (Smeland et al. 2003).

ISG/SSG I

The low incidence of osteosarcoma is a strong argument for broad international collaboration. Based on common understanding of osteosarcoma treatment and future projects a collaboration was established with the Italian Sarcoma Group (ISG). With a joint study the anticipated accrual per year would increase from 15–20 to 80–100 patients. The first Italian and Scandinavian osteosarcoma protocol, ISG/SSG I, was undertaken to explore the effect of adding high-dose ifosfamide (15g/m^2) in first line treatment to cisplatin, doxorubicin and methotrexate. 183 patients were recruited from

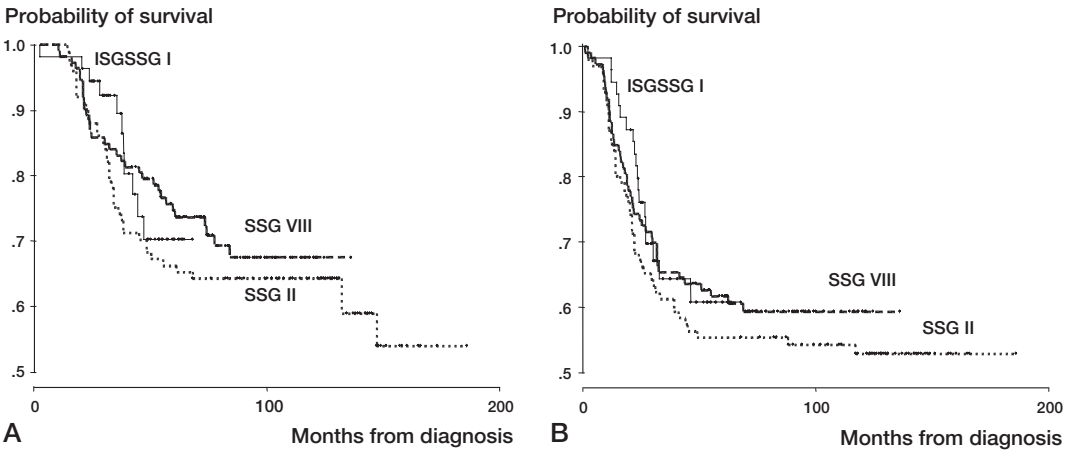

Figure 1. SSG Studies: A) sarcoma-specific survival and B) metastases-free survival.

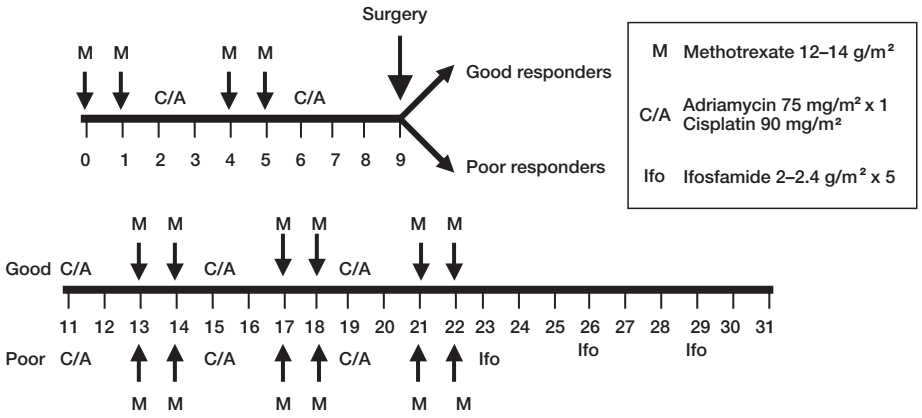

Figure 2. SSG XIV protocol.

1997 to 2000. Patients were scheduled for operation at week 13 and 58% achieved a good histologic response according to Huvos (Table 1). With a median follow-up of 47 months the projected 5-year metastases-free and sarcoma-specific survival rate are 65% and 69%. Thus, the addition of high-dose ifosfamide to methotrexate, doxorubicin and cisplatin neither improves histologic response nor outcome in localized osteosarcoma compared to 4-drug regimens in which standard dose ifosfamide were used (as for SSG VIII) (Smeland et al. 2003b).

Current protocol-SSG XIV

The ISG/SSG I study was closed in Dec 2000 and replaced by the ongoing Scandinavian interim protocol, SSG XIV. The SSG XIV is based on the experience from SSG VIII and ISG/SSG I. With no effect of adding high-dose ifosfamide to the preoperative regimen, patients are given a 3-drug combination upfront. In contrast to the replacement principle utilized in SSG VIII poor responders are salvaged by addition of ifosfamide (10–14 g/m^2) (Figure 2). By Dec 2003 44 patients are recruited.

Toxicity/long-term side effects

Standard osteosarcoma chemotherapy is intensive and considerable acute toxicity and long-term side effects are to be expected. The most common lifethreatening event is the doxorubicin associated cardiotoxicity, reported in most previous osteosarcoma series. In recent studies the problem is reduced by the use of cardioprotection, either as long-time infusion of doxorubicin (as in SSG protocols) or by addition of specific cardioprotectors (Bielack et al. 1996). Acute bone marrow toxicity is substantial even with extensive use of growth factor support. In ISG/SSG I with a maximum intensity of conventional chemotherapy, 59% of all cources were followed by grade IV neutropenia and 33% by grade IV thrombocytopenia (Smeland et al. 2003b). The partial alleviation of bone marrow suppression by growth factor necessitate increased awareness to other potential serious acute toxicities. In ISG/SSG I 3 treatment related deaths were reported, all due to a combination of sepsis and electrolyte imbalance whilst in SSG XIV 2 patients have died in a mixed pattern of neutropenia, infection and severe colitis.

Given the intensive polyagent chemotherapy for most patients in young years, studies on long-term toxicities in osteosarcoma survivors are relevant. A SSG project is undertaken to explore long-term side effects, quality of life, functional level and social impact of previous treatment in bone sarcoma survivors and more insight into this field of oncology is expected to evolve within the next decade.

Future project – Euramos

During the SIOP meeting in Brisbane, fall 2001, an international alliance with the aim to improve survival in osteosarcoma was established, Euramos (European American Osteosarcoma Study Group). In addition to SSG, the European Osteosarcoma Intergroup (EOI), Cooperative Osteosarcoma Study Group (COSS) and the American, Children Oncology Group (COG) joined the alliance.

At that time all 4 groups had recently finished or were soon to finalize their ongoing protocol with no obvious design for a next study. The common experience was that a limit had been reached in improvements in survival with currently available chemotherapeutics. No new drugs were in pipeline and further improvements in survival may only come from biologically-driven therapeutic developments. The obvious power of such broad collaboration is the ability to conduct large randomized trials with rapid accrual that would allow quick and effective investigation of new agents or treatment principles.

Representatives from each group have worked out a study design for the Euramos 1 study (Figure 3). The standard arm will be the control arm in the COG, INT 0133 study, selected as the randomized trial with best result reported (Meyers et al. 2001). All patients with resectable high-grade osteosarcoma and age ≤ 40 y are eligible. Patients will receive a standard 3-drug induction regimen (methotrexate-doxorubicin-cisplatin=MAP). Postoperative therapy is determined by the histological response of the tumor. Good responders (< 10% viable tumor) will be randomized to continue with MAP, or receive interferon-α as maintenance therapy after MAP (MAPifn). Poor responders will be randomized to continue with MAP or to receive the same regimen with the addition of ifosfamide and etoposide (MAPIE). Event-free survival is the primary endpoint. In addition, to report on survival and toxicity parameters, assessment of quality-of-life and ancillary biological studies are included. For SSG, the chemotherapy in Euramos 1 is similar to the current standard Scandinavian therapy (SSG XIV protocol) with a 3-drug MAP induction regimen and addition of an ifosfamide based salvage therapy to poor responders. With the Euramos collaboration, for the first time, the efficacy of salvage therapy for poor responders is tested in a randomized trial. Good responders are randomized to receive standard 3-drug regimen or addition of interferon-α as maintenance therapy. The use of interferon therapy in osteosarcoma has been pioneered by Strander and collegues (1995) at the Karolinska Hospital in Sweden and their findings has had decisive impact for including interferon in the Euramos 1 protocol. In the period 1971–1990, all patients submitted to the hospital (n=89) with

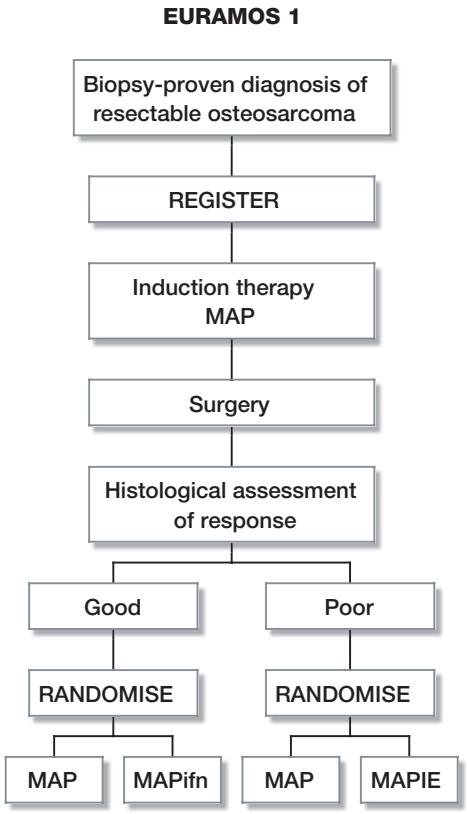

Figure 3. Euroamos 1 flow chart. MAP = methotrexate-adriamycin-cisplatin, IE = ifosfamide/etoposide, and IFN = interferon-alpha.

localized osteosarcoma were given interferon-α as single adjuvant to surgery. For patients with classical osteosarcoma (n=64) the projected sarcoma related survival rate was 40% for the period 1971–1984 and 69% for the patients treated with a higher interferon dose in the period 1985–1990 (Figure 4). The data clearly demonstrates an activity of interferon in osteosarcoma. The question addressed in Euramos 1 is whether interferon in combination with today standard management improves survival.

With some hurdles still to pass, the expectation is to open the Euramos 1 protocol for patient recruitment summer 2004.

Prognostic factors in classical osteosarcoma

The most important prognostic factors in osteosarcoma at time of diagnosis are presence or not of metastatic disease and tumor site (extremity vs. axial) (Bielack et al 2002). In addition, treatment

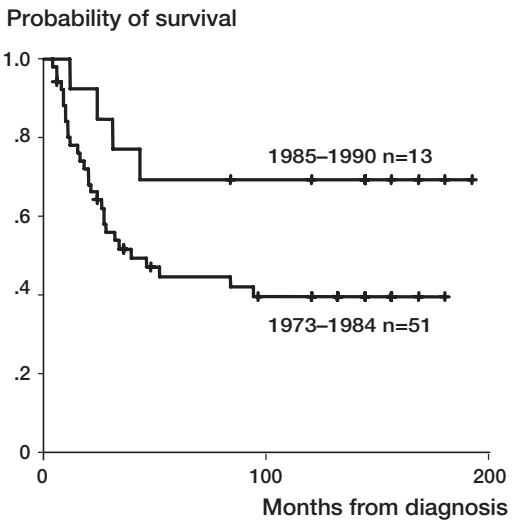

Figure 4. Interferon-alpha as single adjuvant to surgery in localized osteosarcoma (Karolinska Hospital experience). Sarcoma-related survival.

related factors important for outcome are tumor necrosis and surgical margins. Of these, in classical osteosarcoma only tumor necrosis will be relevant. Several attempts have been undertaken to identify prognostic factors within the group of classical osteosarcoma with the purpose to develop a risk-adapted therapy; i.e. to reserve the most toxic treatment for patients with highest risk of relapse. In several reports including from SSG, tumor volume has turned out as a consistent independent factor for outcome (Smeland et al. 2003, Smeland et al. 2003, Saeter et al. 1999) (Table 2). However, attempts to stratify therapy based on well accepted risk factors have so far failed. Associated to the ISG/SSG I protocol were two research projects evaluating the prognostic impact of micrometastases or P-glycoprotein expression. The results remain to be analyzed. P-glycoprotein over-expression is reported to have adverse impact in classical osteosarcoma for patients treated with a methotrexate, doxorubicin, cisplatin combination (Serra et al. 2003). Identifying tumurs with increased levels of P-glycoprotein may have predictive impact; i.e. at clinical onset select chemotherapeutics known to be unaffected by P-glycoprotein expression to these patients. In Scandinavian studies sex is an independent prognostic factors (Table 2), not observed in historical controls treated with surgery only or patients given

Table 2. Prognostic factors for outcome in SSG VIII

		HR	95% CI	p
Gender	*male*	*4.1*	*1.8–9.7*	*0.001*
Tumor volume	*> 190 mL*	*2.8*	*1.3–6.1*	*0.01*
ALP	*elevated*	*3.2*	*1.5–6.6*	*0.003*
Mean Mtx at 24h	*> 4500*	*0.3*	*0.1–0.7*	*0.003*

suboptimal chemotherapy (Harvei and Solheim 1981, Saeter et al. 1995). This may reflect some unknown sex dependent genetic factor important for treatment efficacy and this issue is subjected to an ongoing SSG project.

Metastatic relapse

An important feature of osteosarcoma is the possibility to achieve long-term remission and even cure after relapse (Figure 5). Analysis of SSG data has shown the importance of radical surgery, relapse-free interval and adequate second line chemotherapy for outcome (Saeter et al. 1995). The importance of surgical remission and relapse-free interval has later been confirmed by other groups (Ferrari et al. 2003). The benefit of second line chemotherapy is still questionable. The current guidelines in SSG are to offer chemotherapy to the patients with early relapse (< 18 months from diagnosis) and/or multiple metastases. As part of the Euramos and Euroboss protocols, reports will be send to a study secretariat in Munster upon relapse to prospectively record relapse and relapse treatment (Euroles study).

Nonclassical osteosarcoma

More than 40% of all osteosarcoma are nonclassical (Saeter and Bruland 1998). Generally all high-grade osteosarcoma exhibits the same aggressiveness emphasizing the importance of giving the patients adequate chemotherapy. To obtain surgical remission in axial tumors is often a challenge and local treatment has to be supplemented with radiotherapy, either as external beam radiation or boneseeking radioisotopes. Age itself has never been demonstrated to represent a poor prognostic factor, but chemotherapy has to be adjusted to age which may affect outcome.

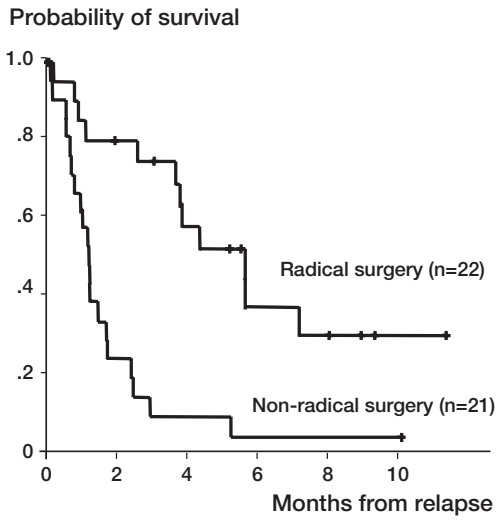

Figure 5. Post-relapse outcome, SSG VIII.

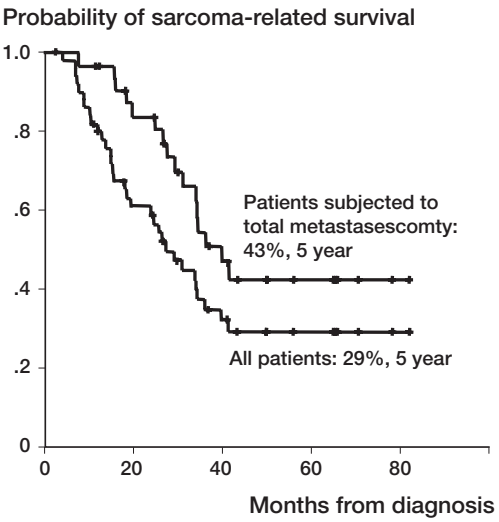

Figure 6. Outcome for high-risk osteosarcoma, ISG-SSG II.

ISG/SSG II

The ISG/SSG II protocol for high-risk patients with metastases at presentation and/or pelvic tumors was opened in 1998. Induction therapy was similar to ISG/SSG I whilst postoperative chemotherapy was terminated with 2 courses of high-dose chemotherapy with stem cell support with a carboplatin/etoposide combination. The aims of the study were:

- To increase the 5-year overall survival rate from 20% to 40% in patients with metastases on initial presentation.
- To increase 5-year overall survival rate from 40% to 60% in patients subjected to complete metastasectomy.

53 patients are included by Dec 2003. This probably represents the largest prospective treatment series with high-dose chemotherapy in osteosarcoma. Preliminary data shows a 5-year sarcoma-specific survival rate of 29% for all study patients and 41% for the patient subjected to complete metastasectomy (Figure 6). The conclusion from the ISG/SSG II study is that the study aims are not obtained and the study is therefore closed. Future patients with metastatic and/or pelvic tumors (and resectable) will be treated according to the Euramos protocol.

Euroboss

The Euroboss protocol is a joint European study by the SSG, ISG and COSS for patients aged 41–65 years. Compared to treatment protocols for children/adolescent, chemotherapy is adjusted with reduction in both doses per cource and cumulative doses. Methotrexate is restricted only to patients with no detectable histologic response after preoperative chemotherapy. The primary aims of the protocol are to evaluate clinical outcome and chemotherapy-related toxicity in patients with high-grade bone sarcoma. Eligible for the Euroboss study are all patients with pleomorphic/spindle cell high-grade primary bone tumors excluding chemotherapy resistant tumors such as chondrosarcoma. The study was opened in Scandinavia and Italy late in 2002 and is expected to run to 2005 with an accrual of 40 patients per year.

Prospects

The development in the field of osteosarcoma is to more international collaboration. For the next years for SSG this includes both the Euramos and Euroboss projects. The decision to join these projects is of major strategic impact. International collaboration requires adjustments and compromises for all participating groups, but for SSG with the ongoing and planned projects the main treatment principles remain unchanged while key questions, never possible to solve within the frame of SSG alone, can be addressed. With a population of 25 million it is impossible to run controlled trials in

the field of osteosarcoma. The challenge for SSG is to stay with its integrity and the true multidisciplinary environment within the organisation.

In addition to effectively run randomized trials, broad international collaboration opens for standardization in all aspects of diagnosis and treatment of osteosarcoma, also important for the quality of care and treatment success.

Major improvement in prognosis for osteosarcoma patients is probably dependent on development of biologically driven treatment strategies. For this, more insight into the fundamental biology of the disease is required. The planned ancillary biological studies to the treatment protocols offer a unique possibility to achieve this.

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