Treatment of Osteosarcoma. The Scandinavian Sarcoma Group Experience

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Abstract Results from four consecutive trials, conducted from 1982 by members of the Scandinavian Sarcoma Group, are reviewed. A total of 330 classical osteosarcoma patients were enrolled. In all trials chemotherapy was based on the three active drugs, methotrexate, doxorubicin and cisplatinum and for the latter trials also ifosfamide. Post-operative chemotherapy was stratified by histological response to up-front treatment.

Introduction

Despite the fact that osteosarcoma (OS) is the most common primary solid bone tumor, it is a rare disorder that displays considerable heterogeneity and appears in clinical entities showing a considerable span in tumor biology and prognosis.[1–4] Most commonly, OS strikes children and young adults as classical OS; i.e., extremity-localized primary tumor, of high-grade histology, with no overt metastasis detectable at diagnosis and at age below 40 years of age – the cohort studied in most OS clinical trials.

Evidence from the prechemotherapy era has revealed that micrometastases were present in the majority of OS-patients[5] who usually died despite primary amputation.[6] This constitutes the rationale for the adjuvant chemotherapy currently given to all patients with high-grade histology.[7]

The Scandinavian Sarcoma group (SSG) was established in 1979 and comprises multidisciplinary teams with oncologists, both adult and pediatric; surgeons; radiologists; pathologists; nuclear medicine specialists; and tumor biologists from the Nordic countries. These countries have similar social structures, modern medical care paid by the government and an effective registration of all cancer patients. The aims of SSG are

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the timely referral of all sarcoma patients to centralized centers with complete facilities and experience for multidisciplinary care to improve the outcome of these patients.

Ongoing protocols have defined the standard treatment of OS in Scandinavia. This paper attempts to briefly review the SSG experience in treating OS-patients, with the focus on the results obtained in the various clinical trials in classical-OS run by this organization. Experiences from the still ongoing trial Euroboss, bone sarcoma in patients above 40 years of age, and the recently closed ISG/SSG-2; only published in abstract[8] for patients with pelvic OS or primary metastatic disease, will not be addressed.

Materials and Methods

Since 1982, members of the SSG have enrolled 330 classical OS patients into four consecutive trials (Tables 1 and 2). Results from three of these trials have been published.[9–12] In all the trials, chemotherapy was based on the three active drugs, methotrexate (MTX), doxorubicin, and cisplatinum (cis-Pt), and for the latter three trials, ifosfamide was also used. Postoperative chemotherapy was stratified by histological response to up-front treatment.

SSG II. This trial was based on Rosen's T-10 protocol[7] of four courses of high-dose MTX given preoperatively. "Good Responders" continued with MTX postoperatively with the addition of BCD (bleomycin, cyclophosphamide and dactinomycin). "Poor Responders" were salvaged by a combination of doxorubicin and cis-Pt.[9] Of the 114 pts. included in the period 1982–1989, 97 were eligible for analyses.

SSG VIII. This was the second OS-trial, running from 1990 to 1997; 113 patients were enrolled and eligible.[10] Here, both doxorubicin and cis-Pt were given in addition to high-dose MTX preoperatively. Good responders continued the three drug combination postoperatively, whereas the poor responders were shifted to courses of standard dose ifosfamide and etoposide.

ISG/SSG I. The low incidence of OS is a strong argument for international collaboration. From 1997 to 2000 a total of 177 eligible pts. were included in ISG/SSG I conducted in collaboration with the Italian Sarcoma group.[11] A total of 57 pts. were recruited from SSG centers. The trial was undertaken to explore the effect of adding high-dose ifosfamide (15 g/m^2) to MTX, cis-Pt and doxorubicin also in the preoperative phase. Patients were scheduled for surgery at week 13, and 58% achieved a good histological response according to the Huvos grading system.

Table 1 SSG osteosarcoma clinical trials

SSG II (classical) 1982–1989
SSG VIII (classical) 1990–1997
ISG/SSG I (classical) 1997–2000
ISG/SSG II (high-risk) – closed/unpublished
SSG XIV (classical) 2001–2005
Euroboss (>40 years) – ongoing

Table 2 Summary of osteosarcoma trials conducted by the Scandinavian Sarcoma Group

Trial	No. of pts.	5 years MFS %	5 years EFS %	5 years OS %	No. LR
SSG II	97	55	54	64	5
SSG VIII	113	63	61	74	8
ISG/SSG 1	57	60	59	72	3
SSG XIV	63	69	65	77	2

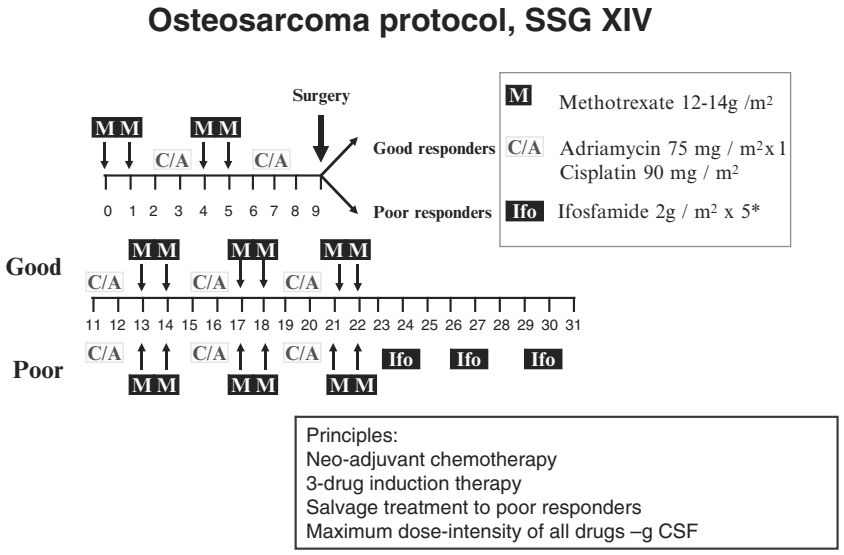

Fig. 1 Osteosarcoma protocol, SSG XIV

SSG XIV. Our last OS-trial was activated in February 2001, as an interim protocol before the start of Euramos 1. Chemotherapy was then considered standard therapy based on SSG's own experience as well as from international experience (Fig. 1). The design was based on a 3-drug combination given up-front – Mtx, Doxo, CDP (as in SSG VIII)– and not a 4-drug regimen with ifosfamide (as in ISG/SSG 1). Salvage therapy for poor responders consisted of the addition of high-dose ifosfamide and not a replacement (as in SSG VIII).

The rationale was to keep a maximum dose-intensity of all three proven active drugs. The use of g-CSF was according to ASCO guidelines, and was given to patients after a previous episode of neutropenic fever or delayed recovery. Based on hematological nadir values, a 20% dose increase of ifosfamide was recommended. However, this was feasible only in four patients.

Out of 63 eligible patients, 34 (55%) were from Sweden (6 centers), 25 (40%) from Norway (3 centers; my own Institution recruited 17 pts), three from Finland, and one from Iceland. The mean age was 16 years (8–39), with three patients above 30 years of age. The male/female ratio was 1.8. The anatomical site of the OS was the femur in 34 cases, the tibia in 15, the humerus in 6, the fibula in 4, and other sites in 3 cases; one case was with missing information.

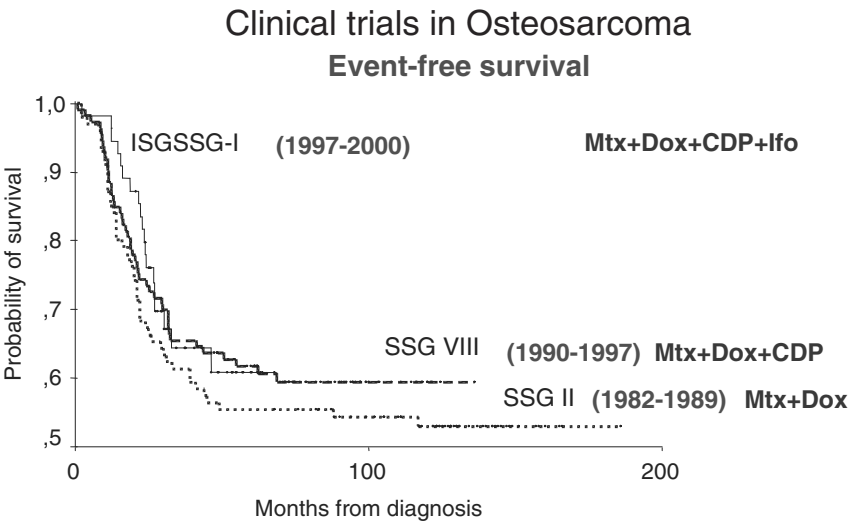

Fig. 2 Clinical trials in osteosarcoma

Results

The results from the three previously published OS-trials are illustrated in Fig. 2. A steady increase in the rate of limb salvage surgery has been documented within SSG, as in other collaborative groups, and with an acceptably low number of local recurrences (Fig. 3).

SSG II. Results from this first OS-trial of SSG showed an event-free survival, EFS, of 54%, at 5 years, a metastasis free survival, MFS of 55% and an overall survival, OS, of 64%. Only 17% of the pts. were classified as good responders, and a 25% difference in MFS between good and poor responders was demonstrated.[9] Hence, in contrast to the original report by Rosen et al., the salvage approach did not improve the outcome for the poor responders. Furthermore, the importance of MTX administration/elimination was emphasized by the correlation between serum levels of MTX and histological response.[9]

SSG VIII. In this second trial an MFS of 63%, at 5 years, an EFS of 61%, and an OS of 74% were obtained.[10] With the three active drugs given up front, 58% of the patients were classified as good responders histologically. Although some improvement in outcome was observed when compared to SSG II, the substantial increase in the percentage of good responders did not translate into a similar improvement in the outcome. Unfortunately, the poor responders were not adequately salvaged, and their inferior survival of 53% may indicate that discontinuation of the three active drugs postoperatively is not justified.

ISG/SSG I. Results from the complete trial have already been published.[11] Results for the 57 SSG-pts showed an MFS of 60%, an EFS of 59% and an OS of

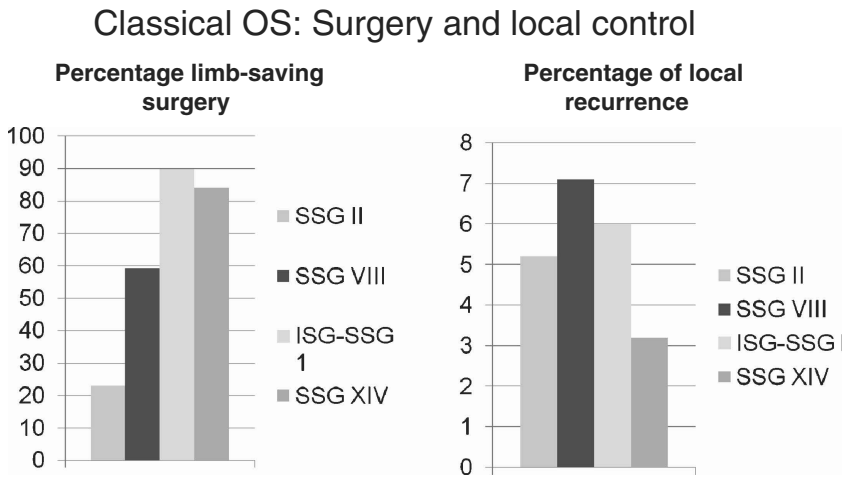

Fig. 3 Surgical development

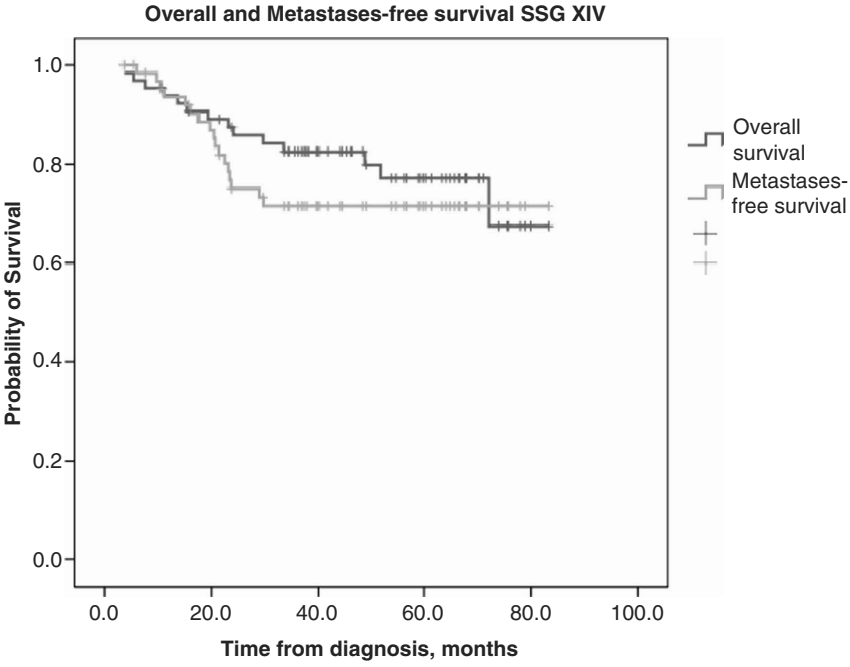

Fig. 4 Overall and metastases-free survival, SSG XIV

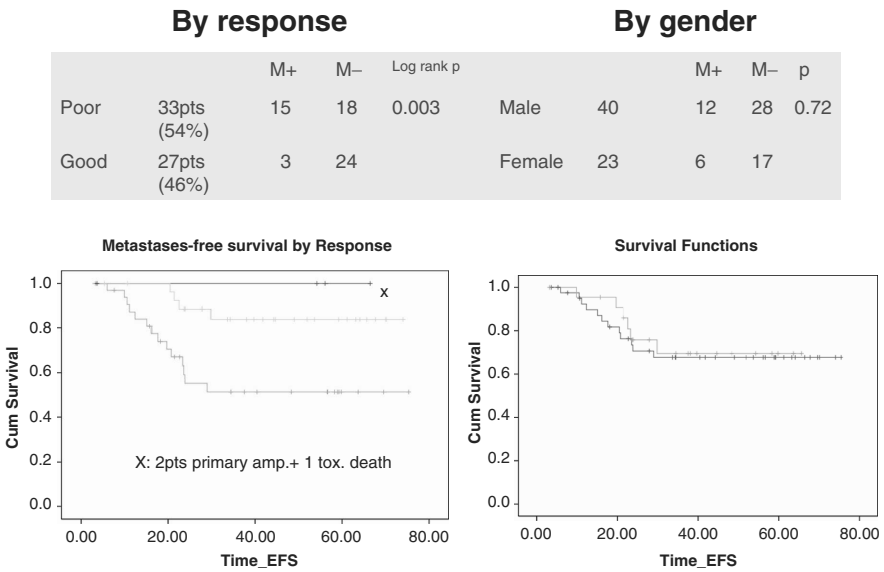

Fig. 5 Metastases-free survival by response to chemotherapy and gender, SSG XIV

72% (Table 2 and Fig. 2). Thus, the addition of high-dose ifosfamide up front seemingly improved neither histological response nor outcome.

SSG XIV. The latest clinical trial conducted by SSG over the period 2001–2005; SSG XIV enrolled 71 pts., 6 of whom had overt metastases at diagnosis and two had a non-osteosarcoma histology upon histopathological revision, leaving 63 eligible pts. As many as 30% of the patients had a longer time-course of completing chemotherapy than what was prespecified in the protocol.

The projected MFS at 5 years was 69%, EFS was 65% and OS, 77% (Fig. 4). This is, seemingly, the best outcome observed in the trials run by SSG (Table 2) with 49 patients alive; of these, 41 are in CR 1. Differences in the outcome based on response to chemotherapy and gender are presented in Fig. 5.

Out of the 63 eligible patients, 41 were alive and with NED at a mean follow up of 64 months. Eleven died of OS, three succumbed to a treatment related event (see below), one died in an accident with NED, and one patient was lost to follow up. Twenty-two events were registered: 17 metastases, 2 local recurrences (one coinciding with metastases) and 3 toxic deaths. In all three cases, it was a neutropenic fever with sepsis, in two of which a severe colitis was the suspected cause. Unfortunately, two of the patients did not receive adequate antibiotic treatment/management: one due to patient delay, and the other due to a doctor's delay. A 15 year old female patient experienced a grade IV cardiotoxicity, but has since recovered.

In SSG XIV, a limb salvage procedure was performed in 90% of the pts, compared to 27%, 58% and 88% in the three former studies. The local recurrence rate was 3% in SSG XIV compared to 5%, 7%, and 5% in the other trials, respectively (Fig. 3).

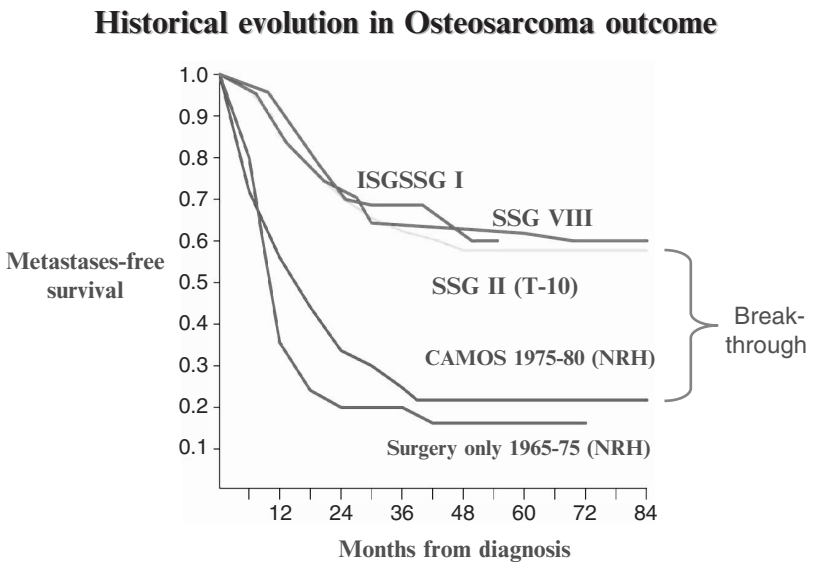

Fig. 6 Historical evolution in osteosarcoma outcome. The Scandinavian Sarcoma Group (SSG) and The Norwegian Radium Hospital (NRH) experience

Discussion

Major achievements have been obtained in the treatment of OS over the past three decades.[1,2] This was made possible through well designed clinical trials and by establishing multidisciplinary teams, by centralization and international collaboration. For SSG, the breakthrough in chemotherapy came in the early 1980s with the introduction of SSG II; but since then, improvement has been modest. Further improved management of OS has been possible through advances in imaging and orthopedic surgery. Compared to historical controls from my own Institution, the gain in survival is unquestionable (Fig. 6), in agreement with international experience.[1,2] This refinement has been made despite the lack of recent randomized controlled clinical trials. The results from the SSG OS-trials compare well with the best published data.[12] Nevertheless, additional endpoints to survival such as long term toxicity and quality of life are lacking in most published reports.

The prognosis for OS-patients with primary metastatic disease and also in cases of primary tumors located in the axial skeleton is still poor.[5,13] The scope beyond the classical OS is not often reported. Seeing adult patients as well, my Institution quite frequently experiences the many faces of this disease. The gruesome outcome of patients with axial OS, often dying from lack of local control without metastases, and the chemo resistant subclinical disease in patients presenting with overt metastases, remain two unsolved clinical challenges. The poor tolerance to toxic chemotherapy in the elderly also remains an obstacle.

The Scope Beyond the Classical OS-Patient

Table 1. Patient categories

Classical osteosarcoma		69 patients (45%)
Non-classical osteosarcoma		84 patients (55%)
Age >40 only	14	
Non-extremity only	18	
Metastatic only	20	
Several factors	32	

Fig. 7 Reprinted from the "Osteosarcoma Odyssey" (153 OS-pts, single Institution 1980-1997) From ref. 14

"Inadequate Treatment - 1"

Table 2. Patients who received inadequate treatment

	Incidence	*Reason for inadequacy*		
		Surgery	*Chemotherapy*	*Both*
Classical osteosarcoma	6/69 (9%)	0	6 (100%)	0
Non-classical osteosarcoma	61/84 (73%)	18 (30%)	9 (15%)	34 (56%)
Age >40 only	11/14 (79%)	0	7 (64%)	4 (36%)
Non-extremity only	12/18 (66%)	8 (67%)	1 (8%)	3 (25%)
Metastatic only	10/20 (45%)	8 (80%)	0	2 (20%)
Several factors	28/32 (88%)	2 (7%)	1 (4%)	25 (89%)

Fig. 8 Inadequate treatment defined as complete surgery with non-contaminated margins + at least 6 cycles of chemotherapy containing at least 2 of 4 active drugs

We have earlier published our single institution experience in such patients in the modern chemotherapy era,[13,14] from the Norwegian Radium Hospital. In this unselected material, it is seen that, in fact, more than 50% of the patients are not presenting with classical-OS (Fig. 7), and that inadequate treatment is very common (Fig. 8). Nonclassical OS-patients, as a group, have a dismal prognosis (Fig. 9a). However, among those few patients that did receive adequate treatment, the overall survival was approximately 50% (Fig. 9b).

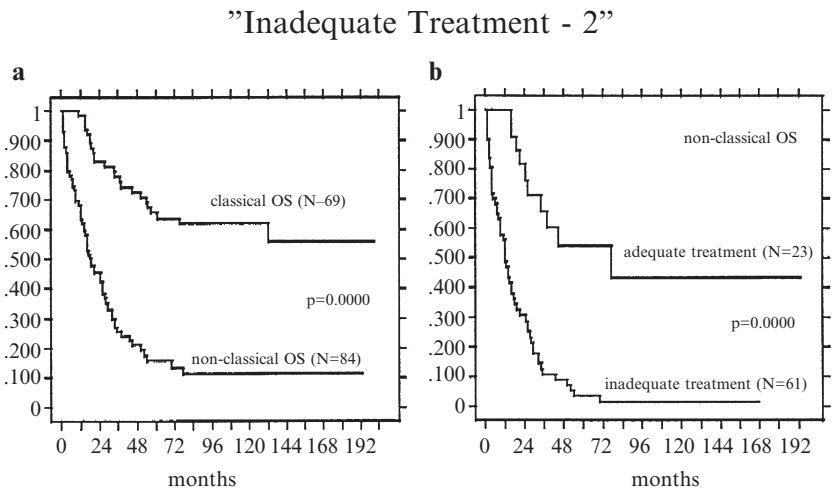

Fig. 9 Outcome in classical and non-classical osteosarcoma patients **(a)**. Impact of adequate treatment or not **(b)**. From Ref. 14

Conspectus

Further improvements in the outcome are unlikely with the currently available drugs. Novel treatment approaches based on knowledge of the tumor-biology of OS are required; they must be ideally individualized and more effectively tailored to combat chemo-resistant micrometastatic disease.[5,15] The continued efforts require a broad international collaboration.

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