Chemotherapy in Ewing's sarcoma

The Scandinavian Sarcoma Group experience

Inkeri ELOMAA[1], Carl BLOMQVIST[1], Gunnar SAETER[2], Mef NILBERT[4], Odd R MONGE[3], Thomas WIEBE[4], Thor A ALVEGÅRD[4]

During the past 15 years the Scandinavian Sarcoma Group has treated 140 patients with Ewing's sarcoma. Two protocols have been used. SSG IV included 52 patients between 1984 and 1990 and SSG IX, 88 patients since 1990. After 5 years of treatment, local recurrences occurred in 19% of the patients (M0 + M1) in the SSG IV group and 10% in the SSG IX group. Distant metastases developed in 57% of the M0–patients in the SSG IV group and in 33% in the SSG IX group. Tumor–related survival (overall) of M0–patients was 49% in SSG IV and 70% in SSG IX, and the metastasis–free survival rate 45% and 58%, respectively.

Patients having a localized extremity tumor had a survival rate of 90% (SSG IX). In both treatment groups, good responders to chemotherapy had a better survival rate than poor ones (SSG IV, $p<0.02$, GI–II vs. G II–IV and SSG IX, $p<0.003$, GI–III vs. G IV). In conclusions local control and survival rates were better with SSG IX than SSG IV.

[1]University Hospital, Helsinki, Finland, [2]The Norwegian Radium Hospital, Oslo, Norway, [3]The Haukeland Hospital, Bergen, Norway, [4]University Hospital, Lund, Sweden

Correspondence: Professor Inkeri Elomaa, M.D., Dept. of Oncology, University of Helsinki, Box 180, FI–00029 Helsinki, Finland. Tel: 352 9 471 3202. Fax: 352 9 471 4201. e–mail: inkeri.elomaa@helsinki.fi

The Scandinavian Sarcoma Group has collected 140 patients with Ewing's sarcoma over a period of 15 years. Between 1984 and 1990, 52 patients were treated according to the SSG IV protocol and since 1990, 88 patients according to the SSG IX protocol. The second protocol was introduced because of a high 3–year local recurrence rate (26%) with the first one (Alvegård et al. 1989). The 3–year survival rate of 43% was comparable to the results of other cooperative groups i.e. 30–60% (Rosen et al.1981, Bacci et al. 1985 and 1989, Wilkins et al. 1986, Jurgens et al. 1988, Hayes et al. 1989, Nesbit et al. 1990, Burgert et al. 1990). Most patients with a local failure also developed distant metastases. The reasons for treatment failure were probably delays in a administration of local therapy, long intervals between chemotherapy cycles and long breaks between split–course radiotherapy. Thus the purpose of the second protocol was to improve the local control and, if possible, also increase the survival rates.

The new protocol was based on the experience of German Cooperative Ewing's sarcoma studies (CESS 81,86) (Jürgens et al. 1988, Dunst et al. 1988): local therapy was given earlier, patients were operated on whenever possible, radiotherapy was combined with surgery, when necessary, and both radiotherapy and chemotherapy were intensified. Radiotherapy was given in a hyperfractionated accelerated fashion. Chemotherapy given at the same time as radiotherapy, included ifosfamide and cisplatinum as new agents (Bone et al. 1987, Castello et al. 1988, Jurgens et al. 1988, Dunst et al. 1988, Tursz et al. 1989).

Treatment protocols

The SSG IV protocol (Figure 1) consisted of five 12–week cycles of combination chemotherapy, including vincristine, methotrexate, doxorubicin, cyclophosphamide, bleomycin and dactinomycin (Nilbert et al. 1998). After two initial cycles, local treatment was given. The dose of radiotherapy was 60 or 40 Gy, depending on the location of the tumor or the radicality of surgery. Postoperative radiotherapy was given to patients who had had a marginal or intralesional operation. Inoperable tumors received 60 Gy and vertebral tumors 40 Gy. The duration of treatment was 60 weeks.

The SSG IX protocol (Figure 2) featured four chemotherapy cycles, each consisting of two courses of VAI (vincristine, adriamycin, ifosfamide), alternating

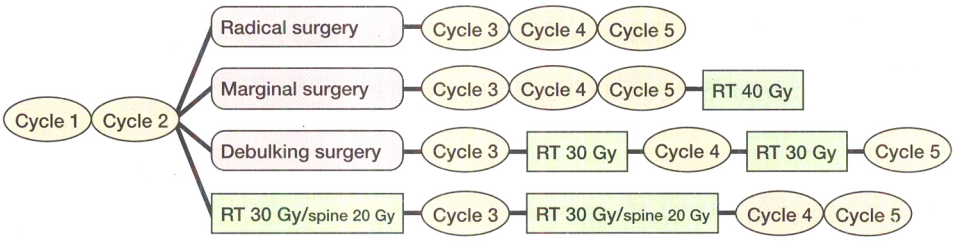

Figure 1. ***SSG IV protocol.***
Each 12–week cycle consisted of:
cyclophosphamide 1200 mg/m² on days 1 and 56, 600 mg/m² on days 28, 29;
doxorubicin 30 mg/m² on days 1, 2, 56, 57;
methotrexate 18 mg/m² on days 1, 2, 56, 57;
vincristine 1.5 mg/m² on days 1, 7, 14, 21, 28;
bleomycin 15 mg/m² on days 28, 29;
dactinomycin 0.6 mg/m² on days 28, 29.
RT = conventionally fractionated radiotherapy: 60 Gy for inoperable or intralesionally resected non–spinal tumors, and 40 Gy to spinal tumors or following marginal surgery.

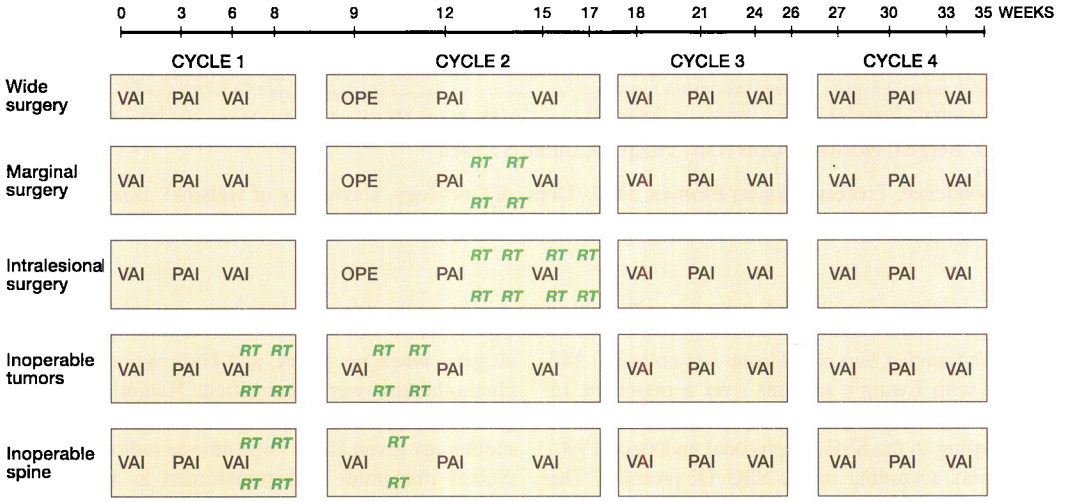

Figure 2. ***SSG IX protocol.***
V, vincristine 1.5 mg/m² for 1 day; A, doxorubicin 30 mg/m² for 1 (PAI) or 2 (VAI) days (A was deleted after 510 mg/m² in adults and after 450 mg/m² in children); I, ifosfamide 1 g/m²/day for 5 days; P, cisplatin 90 mg/m² for 1 day; OPE, surgery; RT, hyperfractionated radiotherapy (1.5 Gy twice daily) to total dose 60 Gy for inoperable or intralesionally resected non–spinal tumors, and 42 Gy to spinal tumors or following marginal surgery.

with one course of PAI (cisplatin, adriamycin, ifosfamide) at 3 week interval (Elomaa et al. 1996). The total treatment time was 35 weeks. Local therapy was given in week 9. Inoperable or non–radically–operated patients received hyperfractionated accelerated radiotherapy, 1.5 Gy twice daily, between chemotherapy courses in a total dose of 42 to 60 Gy, depending on surgical radicality and the location of the tumor.

Patients and tumors

Characteristics of the patients and tumors treated in the trials are given in Table 1.

Local therapy

The local therapy is described in Table 2. The response of the tumor to chemotherapy was evaluated using Huvos' grading system (Huvos 1991).

Results

After 5 years, local recurrences occurred in 19% of the patients (M0+M1) in the SSG IV group and 10% in the SSG IX group. Distant metastases developed in 57% of M0–patients in the SSG IV group and in 33% in the SSG IX group (Table 2). Tumor–related surviv-

Table 1. Characteristics of patients and tumors in SSG IV and SSG IX

	SSG V	SSG IX
Institutions	12	12
Patients no.	52	88
age (range)	17 (4–44)	20 (5–65)
M0	47	73
M1	5	15
Tumor site		
extremity	26	34
central	14	31
other	11	23
Tumor size, mean (range)	8 (2–38)	11 (2–23)

Table 2. Local therapy, tumor response and results of SSG IV and SSG IX

	SSG IV n 52	SSG IX n 88
Surgery	35	60
amputation	13	8
local excision		
wide	7	35
marginal	15	14
intralesional		3
Radiotherapy	32	45
primarily	17	28
postoperatively	15	17
Tumor response	29	57
GI	17 (0.6)	8 (0.1)
GII		15 (0.3)
GIII	12 (0.4)	10 (0.2)
GIV		24 (0.4)
Local recurrence (5–year)	10 (0.2)	9 (0.1)
Metastases (5–year)	27 (0.6)	24 (0.3)
5–year TRS (OS) (M0)	49%	70%
5–year MFS (M0)	45%	58%

Figures within parentheses are rate
TRS = tumor related survival; OS = overall survival;
MFS = metastasis free survival

al (overall) of M0–patients was 49% in SSG IV and 70% in SSG IX, and the metastasis–free survival rate 45% and 58%, respectively (Figure 3). Patients having a localized extremity tumor had a survival rate of 90% (SSG IX). In both treatment groups, patients who had a good response to chemotherapy, had a better survival rate than those with a poor response (in SSG IV, $p < 0.02$, GI–II vs. G II–IV and in SSG IX, $p < 0.003$, GI–III vs. G IV). Metastases at the time of diagnosis, localized extremity tumors and surgical margins influenced the outcome, whereas age, sex and tumor size had no significant effect on it. Early therapy–related side–effects were acceptable and no death occurred.

Discussion

The aims of improving local control (10%) and increasing the survival rate (70%) have been fulfilled with the SSG IX protocol. The results are superior to those of SSG IV and comparable to those of CESS86 (Jurgens et al. 1995) and the Italian Cooperative Study Group (Rosito et al. 1996) which have similar protocols.

The causes of improved local control are probably better surgery and hyperfractionated irradiation. Doxorubicin and cisplatnum, superimposed on radiotherapy, probably functioned as radiosensitizers. Intensification of chemotherapy with ifosfamide may have increased the survival rate. The overall survival rate of 70% is very satisfactory, since one third of the patients had centrally, located tumors which have been

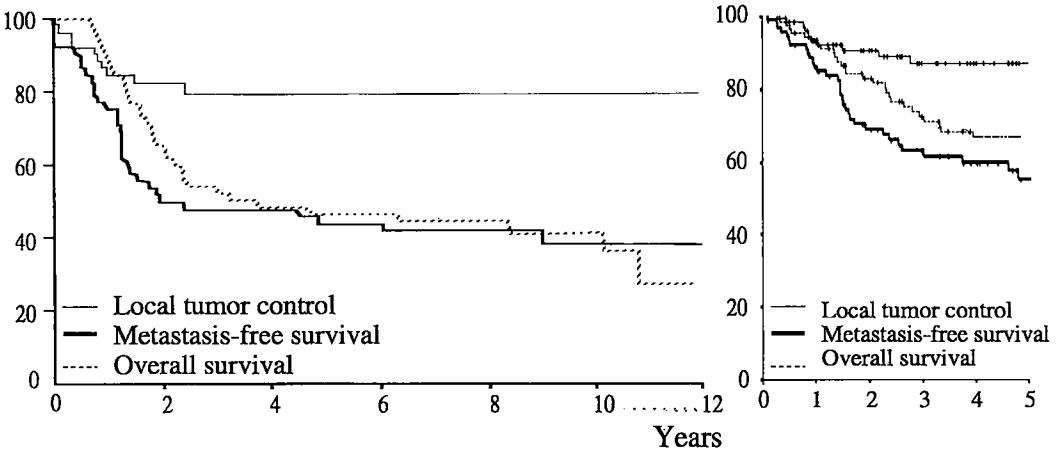

Figure 3. Cumulative proportion of local tumor control, metastasis–free survival and tumor–related survival (overall survival) according to SSG IV (left) and SSG IX protocols (right).

reported to have a poor outcome (Bacci et al. 1989, Fizazi et al. 1995, Hoffman et al. 1995, Burgers et al. 1997).

Metastatic disease, location other than in an extremity, surgical margins and treatment–induced tumor necrosis were prognostic factors in the SSG trials, as found in other series (Bacci et al. 1989, Cangir et al. 1990, Jurgens et al. 1995, Hoffmann et al. 1995, Burgers et al. 1997, Picci et al. 1993 and 1997, Wunder et al. 1995, Saeter et al. 1997). However, the best prognostic factor, tumor response, is not available at the beginning of therapy, when the stratification of patients to standard or high–dose therapys made.

Conventional multi–modality regimens seem to be adequate in low–risk patients e.g., localized extremity tumors. Many of these can be operated on and irradiated with wide margins which might affect outcome. High–risk patients, characterized as those with metastatic disease, pelvic tumors and large tumors, have poor results with standard treatments. Therefore some groups have used intensive chemotherapy for such patients and have reported promising short–term results (Horowitz et al. 1993, Burdach et al. 1993, Nooy et al. 1995, Pape et al. 1995, Valteau–Couanet et al. 1995, Ladenstein et al. 1996). However, the role of high–dose chemotherapy remains to be proved. Further intensification of therapy for all patients seems desirable, because most patients will develop unnecessary toxicy effects. We need early prognostic factors for stratification of patients into standard or intensified treatment protocols.

In conclusion, the SSG IX protocol was better than the SSG IV protocol in giving improved local control and survival rates. It was particularly effective in patients with localized tumors on the extremities. Early prognostic factors should be developed to distinguish low– and high–risk patients. It would than be easier to stratify patients for standard or intensified treatment protocols.

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