Chemotherapy in soft tissue sarcoma

The Scandinavian Sarcoma Group experience

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The first chemotherapy study of soft tissue sarcoma (STS) by the Scandinavian Sarcoma Group was started in 1981 (SSG I). It evaluated the single agent adjuvant doxorubicin in a randomized setting in patients with high–grade STS. No improvement was noted in the overall survival or disease–free survival rate. More intense chemotherapy was thereafter (1991–1994) evaluated in a phase 2 study, introducing ifosfamide and a continuous infusion of etoposide with growth factor (SSG X). The response rate of previously untreated patients was high (42%), but complete remissions were few. Analysis of patients undergoing surgery after preoperative chemotherapy suggested an increased survival. A recent meta–analysis of adjuvant chemotherapy for localized resectable STS in adults, including the SSG I trial, indicated a better disease–free survival and possibly improved overall survival (Thierny et al. 1997). At present, we are studying whether such a benefit can be shown in patients with high–risk prognostic criteria by giving adjuvant ifosfamide and doxorubicin treatment after primary surgery (SSG XIII). In the latter SSG study, started on July 1, 1998, the adjuvant therapy is evaluated in a phase 2 study in selected patients with high–grade STS and other unfavorable prognostic factors.

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Knowledge of sarcoma biology has increased significantly during recent years and it has already affected diagnostic precision and reliability of prognoses. Findings in this area should lead to development of additional therapeutic procedures for use in the treatment of advanced sarcoma.

Chemotherapy of soft tissue sarcoma

The rarity of STS has led to difficulties in accrual of a sufficient number of patients for randomized trials and too many chemotherapy studies throughout the years have been small phase II studies. STS in adults comprises a heterogeneous group of malignancies (Enzinger and Weiss 1988), with different prognostic features and various sensitivities to cytotoxic drugs (Table 1).

STS cases in general are considered to be moderately responsive to chemotherapy. For a long time doxorubicin was regarded as the most active single agent in such tumors and was always included in early chemotherapy studies showing response rates of 15–35% (O'Bryan et al. 1973, Blum and Carter 1974, Benjamin et al. 1975, Gottlieb et al. 1975, Blum 1975, Creagan et al. 1977, O'Bryan et al. 1977, Schoenfeld et al. 1982, Borden et al. 1987, Antman 1992). Later, ifosfamide was shown to be equally effective (Stuart–Harris et al. 1983, Antman 1992, Antman et al. 1989, Connelly and Budd 1996). The third main drug for treatment of STS has been DTIC which, as a single drug, gives a response rate of about 20%. This drug has been thought to be of special interest in the treatment of leiomyosarcoma (Baker et al. 1987). Recently combination chemotherapy has been reported to give response rates up to 45% (Elias et al. 1989, Bramwell 1991, Blum et al. 1993, Steward et al. 1993). Most remissions are partial, and complete remissions can be expected in less than 10% (Reichardt 1997). No definite proof of improved survival in advanced STS has been documented; indeed, documen-

Table 1. Factors of importance for chemotherapeutic sensitivity for soft tissue sarcomas

Factor	Responsive	Resistant	Ref.
Histology	Fibrosarcoma	Leiomyosarcoma	Singer et al. 1995
Liver metastases	Not present	Present	Van Glabbeke et al. 1994 Jaques et al. 1995 Saeter et al. 1995 Saeter et al. 1997
Malignancy grade	High	Low	van–Haelst–Pisani et al. 1991
Age	Low	High	Van Glabbeke et al. 1994
Performance status	Good	Bad	Pinedo et al. 1984 Van Glabbeke et al. 1994
S–phase fraction	High	Low	Schmidt et al. 1993
P–glycoprotein	–	+	Levine et al. 1997

tation is also lacking about its palliative value. A special problem in the evaluation of treatment in locally advanced or metastatic sarcoma is the interpretation of the response. Bulky tumor, found to be unresponsive in non–invasive investigations, may after surgery and pathologic examination, be shown to contain only small foci of viable tumor. This is only one of the factors, besides heterogeneity, among the more than 30 types of soft tissue sarcomas, said to contribute to difficulties in comparing studies which show varying response rates using similar or even identical chemotherapy regimens.

Adjuvant chemotherapy

SSG I study (Figure 1)

Despite adequate local treatment, every third patient with STS develops distant metastases. The treatment of micrometastases is therefore important and notable responses in advanced disease raise hopes of curative treatment if the tumor load in treated patients can be reduced, i.e. by giving adjuvants. Therefore the SSG decided to start such study of STS in January 1981 (Alvegård et al. 1989). When it ended in February 1986, 240 patients with high grade (III + IV) STS had been included in this first trial of adjuvant chemotherapy. It recruited patients from 18 institutions in Sweden, Norway, Finland and Denmark. After radical surgery, patients were randomized to 9 monthly courses of doxorubicin administered as an i.v. bolus (60 mg/m), or no additional treatment. In marginally–operated patients (n 34), postoperative radiotherapy was given before chemotherapy. When the study was reported with a median follow–up of 40 months, there was no significant difference between the four treatment groups regarding overall survival, disease–free survival or local tumor control. It was concluded that adjuvant doxorubicin, as administered, gave no benefit. A standard treatment program for soft tissue sarcoma in the Scandinavian countries was introduced by the SSG and adjuvant chemotherapy was abandoned.

Meta–analysis

An important quantitative meta–analysis of updated data from available randomized adjuvant chemotherapy trials at the MRC statistical center in Cambridge was reported in 1997 in The Lancet (Tierney et al. 1997). It was based on individual data from 14 randomized trials, including 1568 patients and compared adjuvant doxorubicin–based chemotherapy versus no treatment in localized STS. The SSG I study was the second largest of the studies included. Evidence was provided that adjuvant doxorubicin–based chemotherapy significantly prolonged the time to local recurrence and distant metastasis, as well as the overall

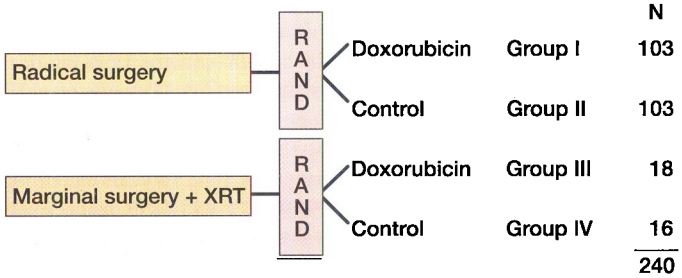

Figure 1. The SSG I protocol (Alvegård et al. 1989).

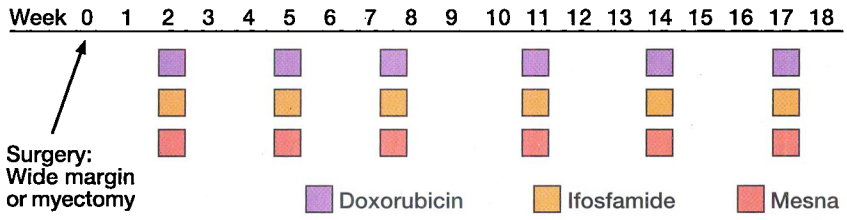

Figure 2. The present SSG XIII protocol.

recurrence–free survival rate. A trend towards an improved overall survival was also found. It was concluded that future randomized trials must be larger if they were to detect the moderate effects of treatment that might occur. Besides trial size, important problems include patient heterogeneity and the fact that therapy with adjuvants is beneficial primarily in extremity STS. No differences in response have been noted in other subgroups, such as histological type or malignancy grade.

SSG XII study

During 1995, the EORTC (Soft Tissue and Bone Sarcoma Group) and Scandinavian Sarcoma Group agreed on an intergroup, prospective, randomized, phase III study of metastasectomy and chemotherapy in patients with lung metastases from soft tissue sarcoma. Those with lung metastases (≤ 5) who are to undergo radical resection of metastases will be randomized to receive premetastasectomy chemotherapy (treatment arm 1) or no chemotherapy (treatment arm 2). Patients following treatment arm 1 will receive 3 preoperative chemotherapy cycles and will continue chemotherapy (2 cycles) after metastasectomy, if there is a complete or partial clinical response on CT scan or a grade III or IV histological response, regardless of clinical response. If no necrosis at all is detected, the patients will not be given post–operative chemotherapy.

In SSG institutions, chemotherapy will consist of:

1. Doxorubicin, 75 mg/m^2 bolus i.v., day 1.
2. Ifosfamide, 5 gr/m^2 24 hours, day 1.
3. G–CSF (Neupogen Roche), 1.0 ml (0.3 mg) s.c./ daily days 3–13.
4. Cycles to be repeated every 21 days.

Inclusion criteria. The following histiotypes are included: malignant fibrous histiocytoma, liposarcoma, synovial sarcoma, malignant paraganglioma, fibrosarcoma, leiomyosarcoma, angiosarcoma (including hemangiopericytoma), neurogenic sarcoma, unclassified sarcoma, and miscellaneous sarcoma (including mixed mesodermal tumors of the uterus).

Exclusion criteria. Patients less than 15 years or more than 70 years of age, performance status of (2 (WHO criteria), other severe medical illness, other distant metastases and/or local recurrence, previous chemotherapy for metastases, second primary cancer and patients in whom regular follow–ups are impractical or not feasible.

The SSG institutions started to randomize patients from July 1996.

The principal endpoint is overall survival. Secondary endpoints are disease–free survival and side–effects. To detect an improvement of 15% in the 3–year overall survival, 340 patients must be included in the study. The final analysis will be done after 190 deaths have occurred.

SSG XIII study (Figure 2)

After discussions in the SSG and contact with other cooperative sarcoma groups, it was decided not to start another phase III study of adjuvant chemotherapy. Instead a phase II study in a well–defined group of patients selected as being at high–risk of developing metastases was started, based on simply defined prognostic factors. This new SSG trial is a prospective phase II study for high–risk soft tissue sarcoma of the extremity and trunk wall. The main objective is to determine whether adjuvant chemotherapy, in addition to local treatment, will improve survival in a subgroup of patients at high–risk of developing metastases. In such patients, adjuvant therapy would be entirely justified and we plan to use the prognostic system described by Gustafson (1994). Patients at high–risk of metastases are defined as patients operated on for STS grades III and IV and, in addition, having at least 2 of the following factors: tumor size >8 cm, macroscopic and/or microscopic tumor necrosis as well as vascular invasion. Patients over 70 years of age will not be included. The study is based on the assumption that the calculated improvement in metastases–free survival at 5 and 10 years can be raised from 40% and 32% to 70% and 60%, respectively. The overall survival should rise from about 50% to 70%. Toxicity will be monitored closely. Chemotherapy consists of doxorubicin, 50 mg/m in a 4–hour infusion, com-

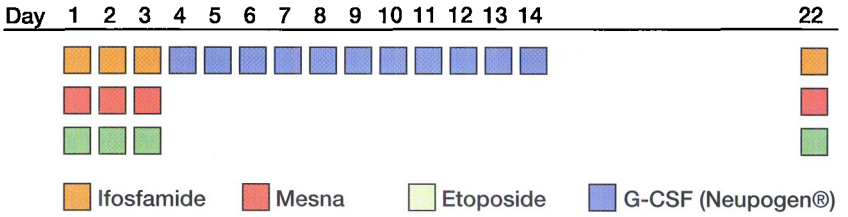

Figure 3. The SSG X protocol (Saeter et al. 1997).

bined with ifosfamide, 5 g/m in a 24–hour infusion. 6 courses of treatment will be given every 21 days. Marginally– and intralesionally–operated patients as well as patients operated on with wide margins but, with a deep–seated tumor will receive radiotherapy between the courses of chemotherapy.

Advanced disease

SSG X study (Figure 3)

SSG X was a prospective phase II study designed to evaluate response and toxicity to ifosfamide in combination with continuous infusions of etoposide (Sæter et al. 1997). This combination had shown promising results in a Norwegian study (Saeter et al. 1995). Etoposide, a topoisomerase II inhibitor with cell–cycle phase specificity was introduced given in a 72–hour infusion, as a bolus injection had been shown to be inactive in STS. The study population consisted of patients with metastatic or locally–advanced STS. The chemotherapy consisted of a combination of etoposide, 600 mg/m, in a 72–hour infusion, and ifosfamide, 1500 mg/m for 3 days, followed by G–CSF (VIG–regimen) (Figure 2). 107 patients were included in this study between July 1991 and January 1994. Toxicity was comparatively mild and mainly hematological, with grade 4 leucopenia and neutropenic fever recorded in 8% and 5% of the courses, respectively. The 92 eligible patients had an overall response rate of 42% (11% CR, 31% PR). Of the 20 patients with liver metastases, none responded. The addition of doxorubicin (A) to the VIG treatment was further studied in three SSG institutions. A total of 41 patients were treated with the VIGA regimen and a clinical response of the tumor occurred in 46%. The addition of doxorubicin to VIG increased the toxicity but gave comparable response rates. The responses to the regimens used by SSG (VIG, VIGA, VI—without G–CSF), EORTC (doxorubicin/ ifosfamide) or others (IVADIC—ifosfamide, vincristine, doxorubicin, and dacarbazine (Wiklund et al. 1992)) were similar.

Surgery after chemotherapy

Surgery plays a major role in resectable STS, but not in locally–advanced and metastatic. However, resection of lung metastases may lead to long–term remissions (Putnam et al. 1984, Gadd et al. 1993, van Geel et al. 1996). Surgery after preoperative chemotherapy has also been studied and it also permits evaluation of residual tumor histologically. A complete response, as defined by the pathologist, indicates a better prognosis. In a retrospective analysis of SSG patients treated with the VIG regimen (Saeter et al. 1995, 1997), with VIG + doxorubicin (VIGA), IVADIC (Wiklund et al. 1992) or various regimens all including doxorubicin, has been done. In 1997, Wiklund et al. described results in SSG series of 38 patients in complete remission. Additional surgery was an important factor for control of metastases. Histological response to chemotherapy was shown to be a strong predictor of survival in patients with advanced STS who underwent surgery after chemotherapy. With histological evaluation, the patients having clinical PR could be divided into those with a good (one third) and poor (two thirds) histological response with subsequent effect on prognosis (Wiklund et al. 1997). No randomized studies on the value of neo–adjuvant chemotherapy in advanced STS have been carried out. The major metastatic site of STS is the lung, and SSG has joined EORTC in the previously described study of lung metastases from STS, where the role of preoperative chemotherapy with doxorubicin and ifosfamide with G–CSF versus metastasectomy alone, will be evaluated (EORTC Protocol No. 62933/SSG XII).

Discussion and future prospects

After 30 years of experience with chemotherapy in the treatment of STS, its routine use in advanced disease remains controversial (Rouesse 1998, Benjamin 1998). Clearly, more effective treatments are needed. Many new drugs have been evaluated for treatment of STS, new compounds like the taxanes (van Hoesel et al. 1994, Balcerzak et al. 1995) and topoisomerase I inhibitors are of only limited value (Bramwell et al.

1995). Since new effective drugs have yet to be developed, more satisfactory use of aveilable drugs (doxorubicin and ifosfamide) is essential. Unfortunately, both compounds cause similar degrees of myelosuppression, which makes it difficult to combine them. Dose–response has been shown for both adriamycin (O'Bryan et al. 1977, Borden et al. 1987) and ifosfamide (Le Cesne et al. 1995, Patel et al. 1997), when used as single drugs, but their combination has not been superior to doxorubicin as a single drug regarding survival (Edmonson et al. 1993, Santoro et al. 1995). Growth factors make it possible to raise the dose (Steward et al. 1993) but routine use of growth factor has not yet yielded better overall response rates. An increase in the dose by the use of growth factors has been tested in an ongoing randomized EORTC trial, where doxorubicin 50 mg/m is given together with ifosfamide and compared to doxorubicin 75 mg/m, ifosfamide and G–CSF. Hardly any studies have evaluated the use of very high doses of these drugs in conjunction with administration of stem cells (Dumontet et al. 1992, Bokemeyer et al. 1994). Future studies must focus on higher response rates and, especially, a higher rate of complete responses. Chemotherapy regimens of value in the treatment of advanced STS should be used in adjuvant treatment, especially in patients having a high risk of relapse who can tolerate this type of therapy. The tendency for high–grade STS to spread hematogenously at an early stage has led to several protocols for adjuvant treatment. The role of such treatment remains to be established, but a recently published meta–analysis (Tierney et al. 1997) can serve as a basis for additional studies. The Scandinavian Sarcoma Group has decided that adjuvant chemotherapy would probably benefit selected patients with a high risk of metastases, although no subgroup showing such a response has yet been identified. Several prognostic factors have been used to select patients with a high risk of recurrence to find out which patients should be treated and which should not. The SSG I study, using doxorubicin alone would today be considered insufficient as regards dose and, from the available phase II data, it seems desirable to use a combination regimen. It should be emphasized, however, such a combination has not proved better than doxorubicin alone nor was ifosfamide used in any of the studies in the meta–analysis. Growth factor support permitting higher dose intensity, was not given routinely in the earlier studies and might positively affect treatment outcome. In an ongoing adjuvant study of the EORTC patients are randomized to a control group and a chemotherapy group receiving doxorubicin, 75 mg/m, ifosfamide, 5g/m and G–CSF.

Knowledge of the molecular biology of sarcomas has expanded dramatically in recent years (Skapek et al. 1998, Mandahl et al. page 30 this issue). A more elaborate characterization of STS is emerging taking into account cell proliferation, apoptosis, necrosis, hypoxia and angiogenesis. Many antiangiogenic substances are currently being tested in clinical studies, and clinical gene therapy is being evaluated in several solid tumors. Deeper understanding of the molecular mechanisms underlying development and progression of STS will provide a background for new treatment strategies which are really needed, whether used alone or in combination with already well–known types of therapy.

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