Chemotherapy in soft tissue sarcoma

The Scandinavian Sarcoma Group experience

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ABSTRACT The Scandinavian Sarcoma Group (SSG) started its first chemotherapy study in soft tissue sarcoma (STS) in 1981 (SSG I). This study evaluated single agent doxorubicin given adjuvant in a prospective randomized trial in patients with high-grade STS. Neither overall survival nor disease-free survival was improved. Combination chemotherapy was hereafter studied in a phase II study (1991–1994) combining ifosfamide and continuous infusion etoposide with growth factor support (SSG X). The response rate in previously untreated patients was high (42%), but complete remissions were few. Analysis made on patients operated after chemotherapy indicated improved survival in this subgroup. Meta-analyses of adjuvant chemotherapy for localised resectable STS in adults, including the SSG I trial, has indicated improved disease-free survival and a trend towards improved overall survival. Presently, SSG is testing whether such a benefit can be found for adjuvant ifosfamide and doxorubicin treatment given after primary surgery in selected patients with high-grade STS and other well defined unfavourable prognostic factors (SSG XIII).

Knowledge in sarcoma biology has increased significantly during recent years, and it has resulted in one specific targeted therapy i.e. the tyrosine kinase inhibitor imatinib mesylate (Gleevec®). A high activity in metastatic and locally advanced gastrointestinal stromal cell tumors (GIST) has been proven and the drug is now in routine clinical use. The latest SSG trial in STS activated in the end of 2003 (SSG XVIII) studies imatinib mesylate adjuvant in a randomized phase II trial comparing one and three years of treatment after radical surgery in patients with a high risk of recurrence.

New insights in molecular medicine applied in multidisciplinary clinical trials is the only way forward discriminating the different STSs and finding complementary targeted therapies.

Chemotherapy in soft tissue sarcoma

Soft tissue sarcomas (STSs) are rare solid tumors of mesenchymal origin accounting for only 1% of adult malignancies. The rarity of STS has lead to difficulties in accrual of sufficient number of patients for randomized trials and most chemotherapy studies throughout the years have been small phase II studies. STS in adults comprise a heterogeneous group of malignancies (Enzinger and Weiss 1988) with different prognostic features and different sensitivities to cytotoxic drugs. Some of the known factors of importance for chemotherapeutic sensitivity are presented in Table 1. STSs as a whole are considered to be moderately responsive to chemotherapy. Doxorubicin was initially considered the most active single agent in these tumors and was always included in early chemotherapy studies in the 1970s and 1980s 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 has shown similar activity (Stuart-Harris et al. 1983, Antman et al.

Table 1. Factors of importance for drug sensitivity

Factor	Responsive	Resistant	References
Histology	Fibrosarcoma Liposarcoma	Leiomyosarcoma	Singer et al. 1995 Van Glabbeke et al.1999
Liver metastases	Not present	Present	Van Glabbeke et al.1994 Jaques et al. 1995 Saeter et al. 1995 Saeter et al. 1997 Van Glabbeke et al.1999
Malignancy grade 1991	High	Low	van-Haelst-Pisani et al. Van Glabbeke et al.1999
Age	Low	High	Van Glabbeke et al.1994 Van Glabbeke et al.1999
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
KIT mutation in GIST (response to imatinib)	Exon 11	Exon 9 or -	Heinrich et al. 2003.

1989, Antman 1992, Connelly and Budd 1996). The third main drug for the treatment of STS has been DTIC which as a single drug gives a response rate of about 20%. It has been considered to be of special interest in the treatment of leiomyosarcoma (Baker et al. 1987). Dose intensified chemotherapy is at best reported to give response rates of up to 50–60% in nonrandomized trials (Elias et al. 1989, Bramwell 1991, Blum et al. 1993, Steward et al. 1993, Frustaci et al. 1997, Reichardt et al. 1998, Patel et al. 1998). Larger randomized trials, have failed to show response rates in this magnitude (Nielsen et al. 1998, Le Cesne et al. 2000). Most remissions are partial, and complete remissions can be expected in < 10% only (Reichardt 1997, Nielsen et al. 1998, Le Cesne et al. 2000). Complete remission after first line chemotherapy, when seen, is a predictor of long-term survival, and 5 year survival has been demonstrated in 8 % of patients compiled from different EORTC protocols (Blay et al. 2003). No definite proof for improved survival in advanced STS has been documented in randomized studies, documentation is also lacking for the palliative value. It has also been questioned whether survival in adult patients with extremity soft tissue sarcoma has improved at all over the past decades (Weitz et al. 2003).

A special problem in the evaluation of treatment in locally advanced or metastatic sarcoma is the interpretation of response. Bulky tumor, considered nonresponsive by noninvasive investigations, can after surgery and pathologic examination be shown to contain only small foci of viable tumor. New targeted therapies are more likely to give growth arrests rather than objective tumor regression necessitating new response criteria (Verweij et al. 2002).These are just some of the factors besides the heterogeneity among the more than 30 types of sarcomas described contributing to difficulties in comparing different studies which often display different response rates with similar or identical chemotherapy regimens.

Adjuvant chemotherapy

The SSG I study (Figure 1)

Following adequate local treatment every third patient with STS will develop distant metastases. The treatment of micrometastases is therefore important and notable responses in advanced disease gave hope of curative treatment when the tumor load in the patients treated was smaller, i.e. in the adjuvant setting. It was decided to start such an adjuvant study by the SSG. This first study in STS (SSG I) was launched in January 1981 (Alvegård et al. 1989). In February 1986 at study termination 240 patients with high-grade (III + IV) STS

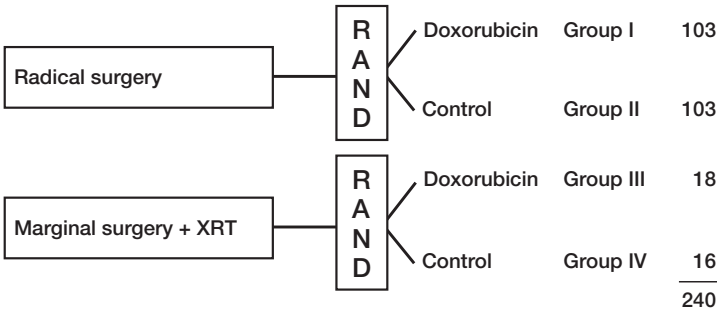

Figure 1. The SSG I protocol (Alvegård et al. 1989).

had been entered into this adjuvant chemotherapy trial. 18 centres in Sweden, Norway, Finland and Denmark together recruited the patients in 5 years. After radical surgery patients were randomized to 9 monthly courses of doxorubicin administered as an i.v. bolus (60 mg/m^2) or no additional treatment. In marginally operated patients (n = 34) postoperative radiotherapy was administered prior to 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 given according to the protocol was without 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 from the MRC statistical centre in Cambridge was published 1997 in the Lancet (Tierney et al. 1997). This study was based on individual patient data from 14 randomized trials including 1568 patients comparing adjuvant doxorubicin-based chemotherapy versus no treatment in localized STS. The SSG I study was the second largest of the included studies. Evidence was provided that adjuvant doxorubicin-based chemotherapy significantly improved the time to local recurrence and distant metastasis as well as overall recurrence-free survival. A trend towards improved overall survival was found. It was concluded that future randomized trials must be larger if likely to pick up the moderate treatment effects that can be awaited. Besides trial size important problems include patient heterogeneity and the fact that the largest effects of adjuvant treatment is found in extremity STSs. No detectable differences has been found in other subgroups such as histological type or malignancy grade. Of later adjuvant studies the one conducted by the Italia Sarcoma Group has raised much interest. The initial report (Frustaci et al. 2001) reported significantly improved survival in the chemotherapy arm in the study that was closed prematurely. With a longer follow up the difference is no longer significant (Frustaci et al. 2003) and more, adequately sized prospective studies are needed. One such large randomized clinical trial (EORTC Protocol Number 62931) is currently closed and included a non-chemotherapy control arm.

The SSG XIII study (Figure 2)

After discussions within the SSG and contact with other co-operative sarcoma groups it was decided not to start another phase III study on adjuvant chemotherapy. Instead a phase II study in a well defined group of patients selected as having a high risk of developing metastases was constructed, based on simple defined prognostic factors. This SSG trial is a prospective phase II study for high-risk soft tissue sarcoma of the extremity and trunk wall. The prognostic system proposed by Gustafson (1994, 2003) is used for patient selection. Patients with high risk of metastatic disease are defined as patients operated for STS grade III and IV and in addition displaying at least two of the following factors: tumor size >8 cm, macroscopic and/or microscopic tumor necrosis and vascular invasion. Patients above 70 years of age are not included. The main objective is to determine whether adjuvant chemotherapy in addition to local treatment will improve survival in this subgroup of patients.

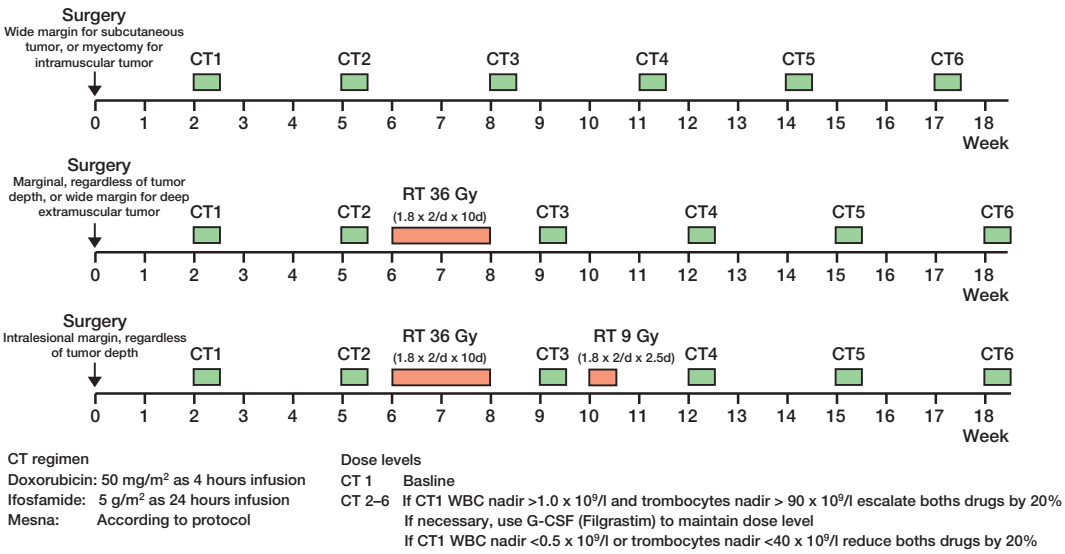

Figure 2. The ongoing SSG XIII protocol.

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 is projected to rise from about 50% to 70%. Toxicity will be monitored closely. Chemotherapy consists of doxorubicin, 50 mg/m^2 as a 4 hour infusion, combined with ifosfamide, 5g/m^2 as a 24 hour infusion. Dose escalation is recommended if tolerable. Treatment is repeated every 21 days for a total of 6 courses. Radiotherapy between chemotherapy courses is given to marginally and intralesionally operated patients as well as to patients operated with wide margins but with a deep seated tumor.

The protocol has recruited 75 patients at the end of 2003. Toxicity has been moderate and the adjuvant treatment well tolerated in general.

Advanced disease

The SSG X study (Figure 3)

The SSG X was a prospective phase II study designed to evaluate response and toxicity to ifosfamide in combination with continuous etoposide infusions (Saeter et al. 1997). This combination had shown promising results in a Norwegian study (Saeter et al. 1995). Etoposide being a topoisomerase II inhibitor with cell cycle phase specificity was introduced as a 72 hour infusion since 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^2, as a 72 hour infusion, and ifosfamide, 1500 mg/m^2 for 3 days, followed by G-CSF support (VIG-regimen). 107 patients were entered between July 1991 and January 1994. Toxicity was comparatively mild and mainly hematological with grade 4 leucopenia and neutropenic fever being registered in 8% and 5% of courses, respectively. The eligible 92 patients displayed 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 VIG-treatment was further studied in three SSG institutions. 41 patients were treated with the VIGA regimen and a clinical tumor response was seen in %. It was apparent that the addition of doxorubicin to VIG increased toxicity and gave comparable response rates. All in all, responses in 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)) are in the same range. To optimise the treatment for metastatic STSs SSG will in 2004 provide treatment recommendations for these patients.

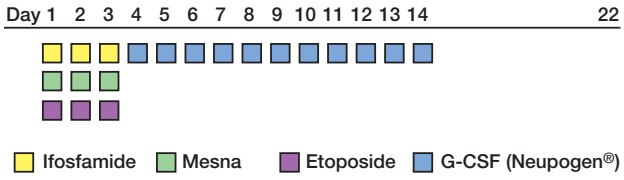

Figure 3. The SSG X protocol (Saeter et al. 1997).

Surgery after chemotherapy

Surgery plays a major role in resectable STS but its role in locally advanced and metastatic STS is not firmly established. Resection of lung metastases may however 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 investigated and this also gives an opportunity to investigate residual tumor histologically. A pathologic complete response indicates a better prognosis. In a retrospective analysis of SSG patients treated with the VIG-regimen (Saeter et al. 1995, Saeter et al. 1997) and with VIG + doxorubicin (VIGA), IVADIC (Wiklund et al. 1992), or various regimens all including doxorubicin, this has been further clarified. Wiklund et al. reported an SSG series in 1997. 38 patients with complete remission were characterized. Additional surgery was an important factor for control of metastatic disease. Histological response to chemotherapy was shown to be a strong predictor for survival in these patients with advanced STSs operated after chemotherapy. By histological evaluation it was possible to separate the patients with clinical PR into good (one third) and poor (two thirds) histological response with subsequent impact on prognosis (Wiklund et al. 1997). Neoadjuvant chemotherapy in advanced STS has not been evaluated in a randomized setting. The major metastatic site in STS is the lung, and SSG joined EORTC in a study of lung metastases from STS where the role of preoperative chemotherapy with doxorubicin and ifosfamide with G-CSF support versus metastasectomy alone was evaluated but the study was closed 2000 due to poor recruitment (EORTC Protocol No. 62933/SSG XII).

Gastrointestinal stromal tumors (GIST)

Sarcomas arising in the retroperitoneum or abdominal cavity constitutes about 20-25% of all soft tissue sarcomas. Treatment recommendations for these tumors are summarized in: SSG XVII. Recommendations for the Diagnosis and Treatment of Abdominal, Pelvic and Retroperitoneal Sarcomas. 2002.The most common mesenchymal tumor in the gastrointestinal tract is the gastrointestinal stromal cell tumor (GIST). In a large Swedish cohort the incidence was found to be 16 new cases per million inhabitants yearly (Kindblom et al. 2002). GIST is supposed to arise from the cells of Cajal which are the pacemaker cells of the gastrointestinal tract (Kindblom et al. 1998). Most of the GISTs are located in the stomach (50–60%) but the tumor can be found from the oesophagus to the rectum. Diagnostic uncertainties has previously lead to the belief that GIST has been neurogenic (neurofibroma, schwannoma) as well as myogenic (leiomyoma, leiomyoblastoma, leiomyosarcoma) by origin. GIST is presently defined as a spindle cell, epithelioid or sometimes pleomorphic mesenchymal tumor that expresses KIT protein usually detected by CD 117 as part of an immunohistochemical pattern. There is still no generally accepted malignancy grading in primary GIST and it is difficult from the histological picture to separate malignant from benign. The most commonly used criteria rely on tumor size and mitotic index registered with light microscopy (Table 2) (Flecher et al. 2002).

GIST expresses the oncogene KIT which encodes for a tyrosine kinase receptor (Hirota et al. 1998). Mutations in KIT, usually in exon 11, are seen in 85% of all GIST-patients resulting in a constant activation that gives rise to in an increased proliferation and reduced apoptosis. This is considered as the primary cause of GIST development. A new drug imatinib mesylate (Gleevec®), that inhibits the KIT-receptor has meant that for the first time effective medical treatment is now available as part of the treatment of GIST (Joensuu et al. 2001, Demetri et al. 2002) Treatment with imatinib in metastatic or unresectable GIST gives sustained

Table 2. GIST malignancy grading (Fletcher 2002)

Risk	Tumor size	Mitotic index
Very low risk	< 2 cm	< 5 / 50 HPF
Low risk	2 – 5 cm	< 5 per/50 HPF
Intermediate risk	< 5 cm 5 – 10 cm	6 – 10 /50 HPF < 5 per 50 HPF
High risk	> 5 cm > 10 cm any	> 5 per 50 HPF any > 10 per 50 HPF
Very high risk [a]	Tumor metastatic at presentation	

HPF = high power field
[a] Category not included by Fletcher but eligible for the

objective responses in the range of 50% (Demetri et al. 2002). As follow up data is accumulating imatinib resistance is unfortunately becoming the major clinical problem (Weisberg et al. 2003).

The SSG XVIII study (Figure 4)

The effectiveness of imatinib mesylate in locally advanced and metastatic GIST has lead to an interest also in neoadjuvant and adjuvant treatment. In the adjuvant setting after radical surgery it is reasonable to investigate if imatinib may prevent recurrence and effect overall survival. Ongoing or planned studies in the US and Europe (EORTC) will randomize patients after surgery to one or two years of imatinib treatment versus untreated controls. Neoadjuvant studies are also on their way. An adjuvant randomised phase II Scandinavian study within the SSG (SSG XVIII) will start in the beginning of 2004. This study will include patients with a high or very high risk of recurrence i.e. patients with large tumors, high mitotic tumor index or metastases at surgery (Table 2). This patient population has a > 50% risk of recurrence and this justifies treatment. Randomization is made between one and three years of imatinib 400 mg daily. 80 patients will be entered into the study. Patients above 18 years of age with histologically documented resectable GIST will be eligible for the study. Recurrence-free survival will be the primary endpoint.

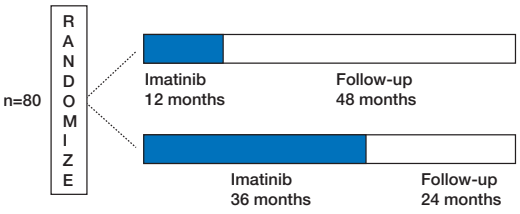

Figure 4. The SSG XVIII protocol (activated December 2003).

Discussion and future prospects

After 35 years of chemotherapeutic experience in the treatment of STS the routine use in metastatic and locally advanced disease is still controversial (Rouessé 1998, Benjamin 1998). More effective treatments to reduce morbidity and mortality are needed. A vast number of new drugs have been tested for activity in STS but only modest activity has been shown for new compounds like the taxanes (van Hoesel et al. 1994, Balcerzak et al. 1995) and topoisomerase I inhibitors (Bramwell et al. 1995). Gemcitabine alone has not shown significant activity in soft tissue sarcoma (Okuno et al. 2003) but a combination of gemcitabine and docetaxel has shown interesting activity in a small series of leiomyosarcomas (Hensley et al. 2002). The success of targeted therapy in the form of imatinib mesylate (Gleevec®) has brought hopes for further breakthroughs in translational research although imatinib certainly is no panacea in sarcoma treatment in general (Verweij et al. 2003). As new efficient drugs fore the most common sarcoma types are yet to be found the optimization of the standard drugs (doxorubicin and ifosfamide) has been investigated extensively. Unfortunately the level of myelosuppression is comparable for both compounds, which makes combinations with optimal doses difficult. Dose-response has been shown for both doxorubicin (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 the use of combinations has not convincingly shown superiority to what has been shown with doxorubicin as a single drug as regards survival (Edmonson et al. 1993, Santoro et al. 1995). EORTC has found it still worth studying if addition of ifosfamide to doxorubicin alone is beneficial, and has recently started a randomized study of single agent doxorubicin versus doxorubicin plus ifosfamide as first

line treatment of advanced and metastatic soft tissue sarcoma (EORTC protocol 62012). Growth factors may allow for dose intensification (Steward et al. 1993) but routine growth factor use has so far not yielded better overall response rates (Nielsen et al. 1998, Le Cesne et al. 2000). Very high doses used in conjunction with stem cell support has only been marginally explored (Dumontet et al. 1992, Bokemeyer et al. 1997). Chemotherapy regimens found to be active in the treatment of advanced STS are logical to use in adjuvant treatment, especially in patients with a high risk of relapse and in the age group that can tolerate this type of therapy. The tendency for high-grade STS to early spread hematogenously has lead to several adjuvant treatment protocols. The role of adjuvant treatment in adult STSs is however still questionable. The meta-analysis of doxorubicin based adjuvant chemotherapy (Tierney et al. 1997) formed a basis for further studies. Although the meta-analysis was adequately performed it consisted of many poorly designed studies. The results need to be confirmed in adequately sized prospective studies. The Scandinavian Sarcoma Group has decided that adjuvant chemotherapy should be most likely to be of benefit in selected patients with a high risk of metastases although no subgroup with proven benefit has been identified so far. Several prognostic factors have been used to select patients with a high risk of metastatic disease in order to find out what patients should be treated and who should not. The SIN system used by SSG has recently been validated in a large series of sarcoma patients where it gave more clinically useful prognostic information than the AJCC system (Gustafson et al. 2003). The system provides two distinct prognostic groups, and has a high reproducibility. The SSG I study using single-agent doxorubicin would today be considered to be insufficient with respect to dose intensity, and from the available phase II data it appears reasonable to use a combination regimen. It should be emphasized, however, that the superiority of such a combination compared to single-agent doxorubicin has not been proven. It should also be noted that ifosfamide was not used in any of the studies included in the meta-analysis. Growth factor support enabling higher dose intensity was not routinely used in the earlier studies and could be a positive factor. A recently closed adjuvant study performed by the EORTC has randomized patients between untreated controls and chemotherapy including doxorubicin 75 mg/m^2, ifosfamide 5g/m2 and G-CSF (EORTC Protocol Number 62931). The”second generation” adjuvant trials are characterised by higher dose intensity, stricter inclusion criteria, usually combination chemotherapy with doxorubicin and ifosfamide and also adding growth factors. The only reported study so far is the one from the Italian Sarcoma Group.

The knowledge of the genetic abnormalities and molecular biology of sarcomas has expanded dramatically over the last years (Helman & Meltzer 2003, Borden et al. 2003). Only very few cytostatics of the traditional type will be introduced into clinical use in the nearest future, instead we will se more of signal transduction inhibitors, differentiation inducers, matrix metalloproteinase inhibitors, angiogenesis inhibitors and immunotherapy. New insights into the molecular mechanisms behind development and progression of STS will give a background for new treatment strategies that are highly warranted whether used alone or as a complement to existing therapies for more long-term disease control.

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