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Chemotherapy in osteosarcoma

The Scandinavian Sarcoma Group experience

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Osteosarcoma is usually a tumor of high–grade malignancy that leads to early pulmonary metastatic dissemination. Many children and adolescents are affected and, with surgical treatment alone, the long–term survival rate is only 15–20%. Since the late 1970s, the addition of combination chemotherapy has gradually improved these results. Early moderate efforts led to survival rates of 30–45%, followed by a major breakthrough with the introduction of high doses of methotrexate (HDMTX), as advocated by Jaffe and Rosen et al. Preliminary results of treatment with the HDMTX–based T–10 protocol at the Memorial Sloan Kettering Cancer Center indicated a good histological response to preoperative HDMTX in 39% of patients and a 93% event–free survival rate, after a median observation period of 20 months. Histological response to preoperative (neo–adjuvant) chemotherapy was early recognized as an important prognostic factor for subsequent survival. Two features thus rapidly became regular components of osteosarcoma protocols: the administration of preoperative chemotherapy to induce tumor necrosis and facilitate limb–sparing surgery and the incorporation of altered "salvage" chemotherapy for the postoperative treatment of poor histological responders. They formed the background for the first Scandinavian Sarcoma Group osteosarcoma study (SSG II).

SSG II study

SSG II was started in June 1982 and stopped in May 1990. Eligibility criteria included high–grade extremity osteosarcoma, non–metastatic disease and age <40 years. The study was designed as a phase II evaluation of the T–10 protocol, described by Rosen et al., and the main end–points were tumor response to a single agent HDMTX, MTX pharmacokinetics, metastasis–free survival rate and overall survival. The five–year results were published in 1991 and have been updated.

Preoperative chemotherapy consisted of 4 weekly courses of HDMTX, 8 g/m^2 (12 g/m^2 for children <8 years) and postoperative chemotherapy, was based on HDMTX and doxorubicin for good responders and on cisplatin/doxorubicin for poor responders (Figure 1). The study comprised 102 eligible patients from 8 institutions in Norway, Finland and Sweden. Median age was 16 years, the male/female ratio was 1.9 and there was a conventional tumor distribution (half localized in the distal femur, one quarter in the proximal tibia).

Results

After a median follow–up of 9 years, 5–year metastasis–free and overall survival rates were 56% and 66%, respectively (Figure 2). These results represented a vast improvement over historical controls. In contrast to the first report by Rosen et al., only 17% of patients were good histological responders to a single preoperative agent, HDMTX. This modest response rate has since been confirmed by reexamination of the Memorial Sloan Kettering data, with exclusion of patients who received agents other than MTX in the preoperative phase. In SSG II, salvage chemotherapy with cisplatin/ doxorubicin for poor responders was unsuccessful, showing a persistent difference in both

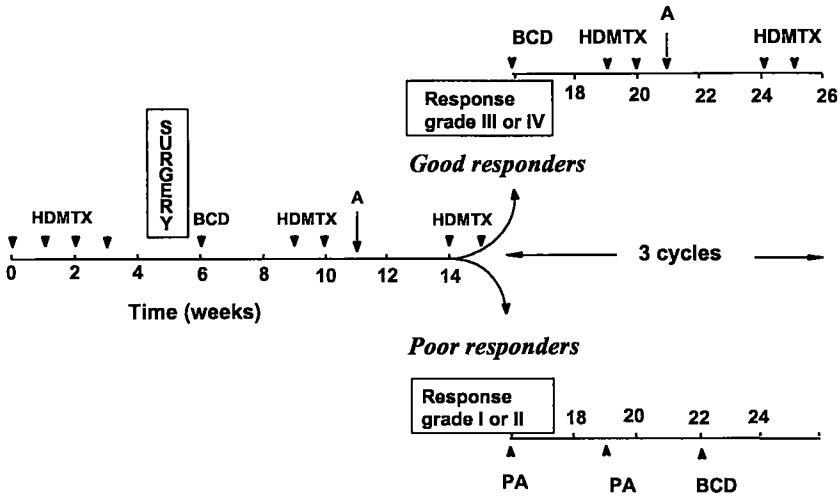

Figure 1. The T–10 protocol as used in the SSG–II study. HDMTX: high–dose methotrexate 8 g/m² for patients ≥8 years and 12 g/m² for younger patients, BCD: bleomycin 30 mg/m², cyclophosphamide 1200 g/m² and dactinomycin 1.2 mg/m², PA: cisplatin 120 mg/m² and doxorubicin 60 mg/m², A: doxorubicin 90 mg/m². Response grade I: no identifiable chemotherapy–induced necrosis, grade II: identifiable effect but large areas of viable tumor remaining, grade III: only small scattered foci of viable tumor, grade IV: no viable tumor.

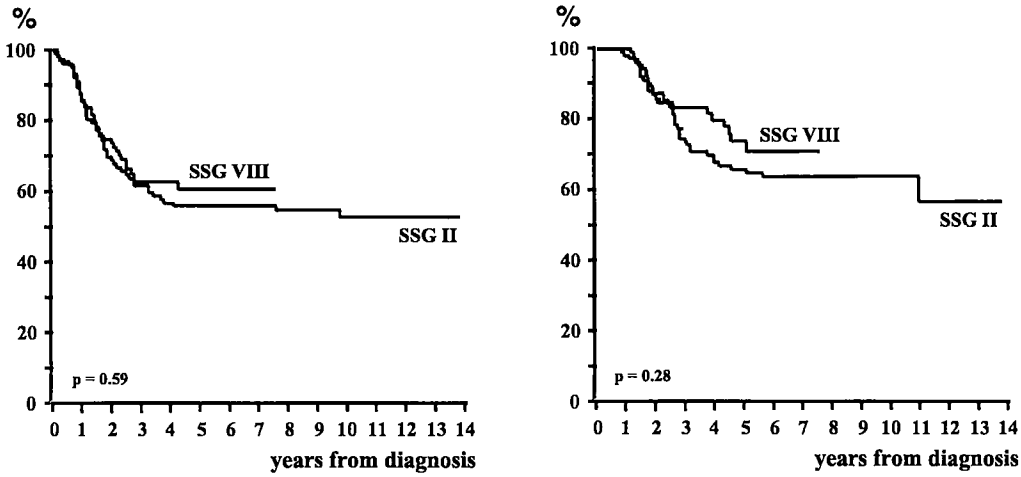

Figure 2. Metastasis–free (left) and overall survival (right) for studies SSG II and SSG VIII. Median follow–up for SSG II was 106 (59–163) months and for SSG VIII 43 (1–91) months .

the metastasis–free survival (50% vs. 75%) and overall survival rates (55% vs. 88%), as compared to good responders.

SSG II was the first study to show significant correlations between histologic response and serum levels of MTX. Poor responders had significantly lower serum MTX values after the same dose, and this correlation persisted in a multivariate analysis. The results also indicated an improved metastasis–free survival rate with increasing serum MTX levels irrespective of histological response, but these differences did not reach significance. A significant correlation between serum MTX and metastasis–free survival has since been reported by several other groups, and all these data have contributed to consolidate the position of HDMTX in most osteosarcoma protocols.

In SSG II, 73% of the patients had undergone amputations. Among the 23% who underwent limb salvage, allograft reconstruction was the commest method. Local tumor control was excellent, with <5% risk of local recurrence at 5 years.

Toxicity from chemotherapy was dominated by bone marrow depression following the BCD combination (Figure 1) and cisplatin/doxorubicin. Hearing loss in the high–frequency area and/or tinnitus due to cisplatin 120 mg/m² in a 4–hour infusion were seen in

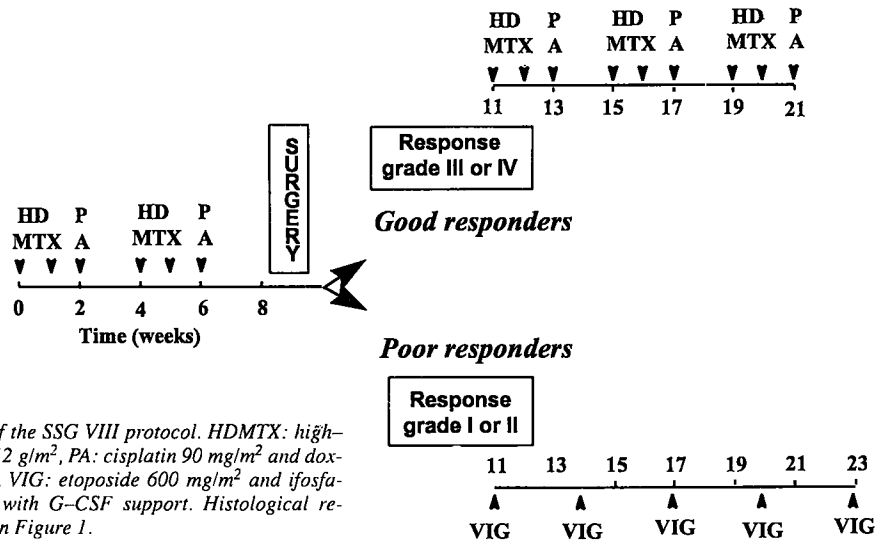

Figure 3. Outline of the SSG VIII protocol. HDMTX: high–dose methotrexate 12 g/m², PA: cisplatin 90 mg/m² and doxorubicin 75 mg/m², VIG: etoposide 600 mg/m² and ifosfamide 4500 mg/m² with G–CSF support. Histological response grading as in Figure 1.

approximately one third of patients. MTX toxicity was mild. 15% of HDMTX courses were complicated by delayed MTX excretion, but these episodes generally had no clinical importance. There was no evidence of faster MTX excretion in young children. Interestingly, institutions adhering strictly to the protocol (total hydration 7000 mL/m^2 over 72h) had lower mean serum MTX values (0.16 vs. 0.60 (mol/L at 48h), lower incidence of delayed MTX excretion (2% vs. 24%) and a higher incidence of grade I histological response (31% vs.15%) than institutions which regularly reported a ≥20% reduction in hydration volume. Since this reduction did not lead to an increase in renal toxicity, it was later concluded that the hydration volume in our T–10 regimen may have been excessive.

SSG VIII study

This subsequent study began in June 1990 and ended in February 1997. The design (Figure 3) and main features were based on the results of the SSG II:

1. Cisplatin and doxorubicin were added to HDMTX in the preoperative treatment to increase the percentage of good histological responders to a target of 60%.
2. The BCD combination was omitted because of its contribution to toxicity while its anti–osteosarcoma effect was questioned.
3. Since poor histological responders had a significantly lower survival rate than good responders, the "salvage chemotherapy" strategy was continued, but the postoperative chemotherapy was changed to an ifosfamide/etoposide combination (VIG) for poor responders. The choice of these agents was supported by preliminary data from the 2nd Rizzoli neoadjuvant study. Etoposide was administered in a 72–hour continuous infusion due to the phase specificity of this agent, and its use was supported by early data from SSG studies in soft tissue sarcoma.
4. Overall treatment time was shortened from 43 to 26 weeks to increase the dose intensity and limit cumulative toxicity.
5. As more data became available about the SSG II results two modifications of the protocol were introduced from February 1993. First, the correlation between serum MTX, histological response and survival led to an increase in the MTX dose to 12 g/m^2 for all patients. Secondly, the lack of separation of the survival curves in grade I and grade II responders led to a cross–over to VIG salvage treatment also in the latter group that is grade II responders also received the salvage treatment for poor responders.

With the above design, the SSG VIII study aimed for a 15% increase in both metastasis–free and overall survival rates as compared to SSG II.

Results

From May 1990 to December 1997, 119 eligible patients were included from 14 Scandinavian centers. The median age, M/F ratio and tumor distribution were comparable to those in SSG II. Preliminary data indicate that the intensification of the preoperative regimen had led to an increase in the good histological response rate to 57%. As in SSG II, histological response was significantly related to the serum MTX level at 48 hours after starting the infusion, but not at 24 hours or at the end of the infusion, indicating that the rate of MTX elimination is important for tumor

Table 1. Potential prognostic factors. Age and serum MTX were first analyzed individually to find the cut–off level for maximum difference

Potential favorable factor	Univariate P–value	Multivariate P–value
Protocol SSG VIII	0.5	Not entered
48h serum MTX >0.6 μM	0.1	NS
Site other than femur or humerus	0.07	NS
Age 9–16	0.009	NS
Histological response grade III or IV	0.003	0.006
Female sex	0.0002	<0.001

NS not significant.

response. With a median follow–up of 43 months, the projected 5–year metastasis–free and overall survival rates were 61% and 74%, respectively, which is a 5–10% improvement over SSG II (Figure 2). Histological response remained significantly correlated to both the metastasis–free and overall survival rates and, despite evidence of considerable activity of ifosfamide/etoposide in metastatic osteosarcoma (see below), the complete change in postoperative chemotherapy to VIG was unable to improve the outcome in poor responders.

The frequency of limb–salvage surgery increased significantly, as compared to SSG II (58% vs. 27%), without an increase in the risk of local recurrence (6% at 5 years). As yet, no assessment has been done regarding the functional status and quality of life in amputated and resected patients. Chemotherapy toxicity has not been analyzed but, notably, 2 patients have died of treatment–related complications, 1 of acute cardiac dysfunction and 1 of secondary acute myelogenous leukemia.

Prognostic factors in localized extremity osteosarcoma

In an analysis which combined data from SSG II and SSG VIII (199 patients), the following potential prognostic factors for metastasis–free survival were tested in univariate analyses: age, sex, tumor site, treatment protocol, histological response and serum MTX level. Factors which gave univariate differences with a p-value <0.15 were entered in a multivariate analysis (Table 1). The only factors which showed independent prognostic value for improved outcome were female sex and good histological response to preoperative chemotherapy (Figure 4). The importance of response is well known from the literature. The importance of sex was reported by Bauer (1988) in a series of Swedish patients but has not been definitely confirmed. Such convincing findings in the Scandinavian population were similar in both studies and warrant further investigation. Since MTX pharmacokinetics has been shown to have prognostic importance, a sex–related difference in drug handling may be of importance and, although no differences were found in serum MTX in this study, they might exist for other cytostatic agents. It should, however, be noted that some potentially important prognostic factors were not analyzed e.g. tumor volume, serum alkaline phosphatase and histological subtype. The SSG study committee concluded that from the data available in the SSG studies and the literature, more studies were needed to detect prognostic factors that are clear and reproducible enough for use in a reliable system for

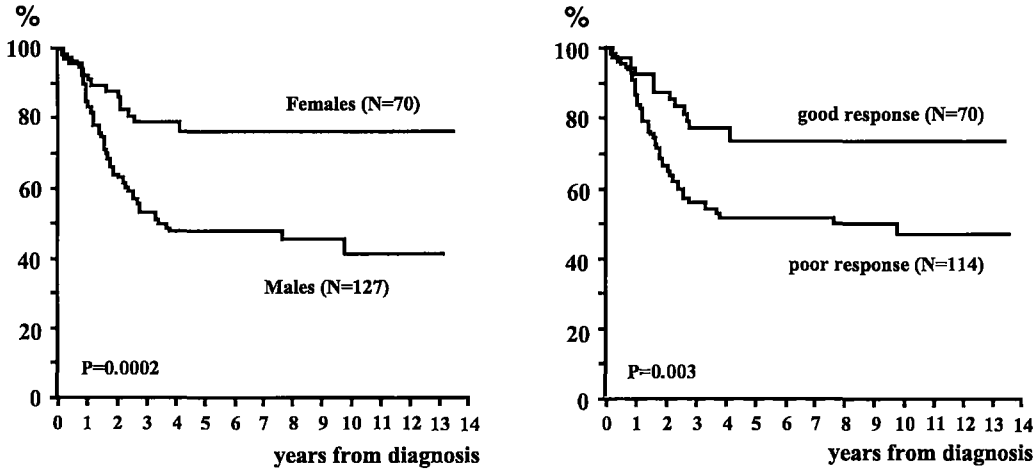

Figure 4. The SSG II and SSG VIII are analyzed together. Metastasis–free survival by sex (left) and histological response (right). These were the only significant prognostic factors in multivariate analysis.

Table 2. Potential prognostic factors for *improved survival* from the first metastatic event. "Adequate chemotherapy" was defined as at least 3 courses containing at least one agent of proven activity against osteosarcoma to which the patient had not previously been exposed, or retreatment with HDMTX at a dose increase of at least 50%

Potential favorable factor	Univariate P–value	Multivariate P–value
Female sex	0.6	Not entered
Primary tumor site other than femur or humerus	0.4	Not entered
Primary protocol SSG VIII	0.5	Not entered
Primary tumor response grade III or IV	0.07	NS
Age at metastases ≥20	0.008	NS
Only lung metastases	0.03	NS
Number of metastases <6	0.0000	NS
Relapse–free interval ≥2 years	0.0003	0.0000
Complete metastasectomy	0.0000	0.0000
Adequate second line chemotherapy	0.002	0.001

NS not significant.

predicting the risks of metastases and permitting individualization of treatment intensity in accord with the findings.

Treatment of metastatic relapse

In an analysis of 75 patients who developed metastases following primary treatment according to the SSG II or SSG VIII protocol, 90% had lung lesions and 22% had skeletal lesions at the first metastatic event. The median relapse–free interval was 18 (1–117) months and the median number of lesions was 3 (1–>10). The 5–year overall survival rate from the time of metastases was 30% for all patients. In the univariate analyses, the number of metastases, age at metastases, relapse–free interval and the presence of extrapulmonary lesions significantly influenced survival. Other significant findings were whether complete metastasectomy was performed and whether the patient had been given adequate second–line chemotherapy (as defined in Table 2). When all factors were subjected to multivariate analysis, only complete metastasectomy, a relapse–free interval of >2 years and the administration of adequate second–line chemotherapy had an independent positive effect on long–term outcome (Table 2). These findings largely concurred with the conclusions from a previous single institution study at The Norwegian Radium Hospital, particularly regarding the impact of complete metastasectomy and second–line chemotherapy. Both studies also stressed the value of repeated metastasectomies on new metastatic episodes with a limited number of lesions.

The effect of new types of chemotherapy on survival in relapsed patients who had previously completed aggressive primary chemotherapy was somewhat surprising. Although this second–line chemotherapy included a number of regimens such as with high–dose ifosfamide and dose escalations of MTX, it was dominated by the VIG regimen, where ifosfamide, in a dose of 1.5 g/m^2/day for 3 days (2–hour infusion), was combined with etoposide 600 mg/m^2 in a 72–hour infusion. The long–term infusion of etoposide was chosen because of its high degree of cell–cycle phase specificity, and its administration by continuous infusion which had given promising results in adult soft tissue sarcoma. Of 16 evaluable patients who received VIG for relapsed osteosarcoma, 6 obtained a partial clinical remission, 4 had stable disease and 6 had disease progression. However, in 10 patients who underwent subsequent metastasectomy, none showed a good histological response (Huvos grade III or IV) in the residual tumor.

Background of current SSG osteosarcoma project

In previous SSG osteosarcoma studies, the three participating countries had only been able to include approximately 20 patients per year. Consequently, 6–8 years of recruitment had been necessary for a phase II study, and such a study duration was regarded as unduly long. In an evaluation of possible cooperation with institutions outside Scandinavia we preferred to work with one large experienced center than a group consisting of many individual institutions. The conclusions drawn from 5 studies conducted by the Istituto Ortopedico Rizzoli (IOR) in Bologna were similar to those of the SSG and formed a natural platform for a common strategy and future joint studies. Furthermore, as IOR is the largest single center in the world treating osteosarcoma, a cooperative study would recruit 80–100 patients each year. Thus, following initial discussions, a protocol planning committee was formed in 1995, with members from SSG, IOR and a few selected centers closely associated with IOR in the Italian Sarcoma Group (ISG).

Most studies of osteosarcoma reported in the international literature have included only the primary treatment of patients with non–metastatic extremity tumors. One of the basic strategies in the ISG/SSG cooperation was to develop a *comprehensive treatment program* with protocols that include most patient categories such as metastatic disease and certain locations other than on the extremities. The large number of patients recruited by the ISG/SSG group also made possible the inclusion of selected laboratory research projects in the ISG/SSG osteosarcoma protocols. These projects include detection of mi-

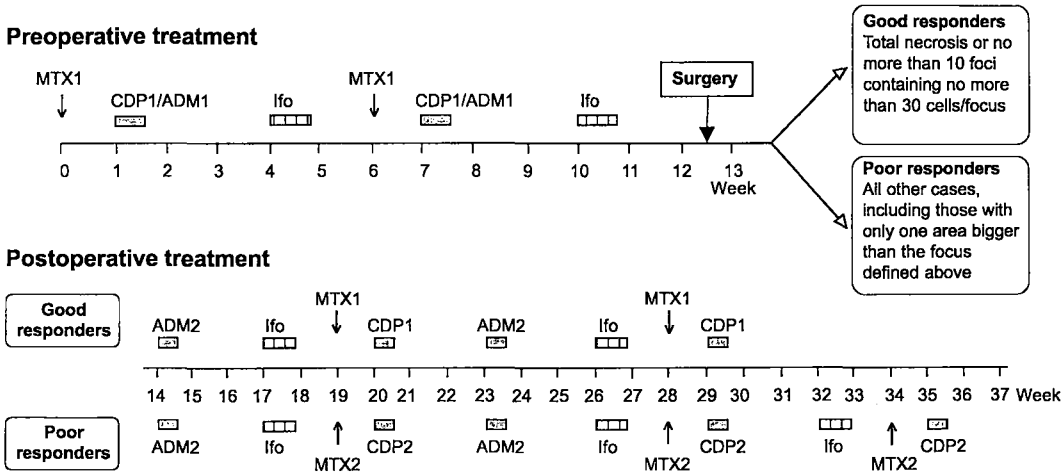

Figure 5. Outline of the ISG/SSG I protocol. MTX1: high–dose methotrexate 12 g/m² in 4h infusion as baseline dose with 2 g/m² dose escalation if 4h serum level in the previous course was <1000 (M, MTX2: high–dose methotrexate 3 g/m² above MTX1 level, CDP: cisplatin 120 mg/m² (CDP1) or 150 mg/m² (CDP2) in 48h infusion, ADM: doxorubicin 75 mg/m² (ADM1) or 90 mg/m² (ADM2) in 24h infusion, Ifo: ifosfamide 15000 mg/m² as 5 day continuous infusion.

crometastases in bone marrow and blood by monoclonal antibodies and immunomagnetic beads, a prospective evaluation of P–glycoprotein expression in the primary tumor and metastatic nodules, a pharmacokinetic study of all chemoterapeutic agents included and a detailed evaluation of renal toxicity.

Before starting of the ISG/SSG osteosarcoma studies, approximately 100 pilot patients had been treated in accordance with variants of the protocols, including the high–dose chemotherapy regimen with stem–cell rescue.

ISG/SSG I study

This study began on March 1, 1997. Eligibility criteria include high malignancy grade, age <40 years, non–metastatic disease and extremity localization. The protocol tries to maximize osteosarcoma chemotherapy as regards the choice and dose levels of, so that patients relapsing after such primary treatment are really refractory to " conventional" therapy (Figure 5). It includes high doses methotrexate (MTX) using a baseline dose of 12 g/m², which is increased in patients who do not attain an end–of–infusion serum MTX target concentration of 1000 μM in the previous course. Cisplatin, doxorubicin and high–dose ifosfamide are also given from the start. Postoperative therapy is based on successive courses of single agents to prevent undue delays in chemotherapy. Poor histological responders are given an extra chemotherapy cycle and the doses of MTX and cisplatin are increased. To synchronize evaluation of the histological response in ISG and SSG institutions, a new classification was introduced, based on the number of viable microscopic foci and of viable cells in each focus.

The protocol also includes treatment in the event of metastatic relapse: if a solitary nodule develops >30 months after diagnosis, metastasectomy alone is performed. In other cases, high doses of chemotherapy with carboplatin and etoposide precede metastasectomy and histological response to the high–dose salvage treatment is one of the endpoints.

The following aims of the study were defined using this aggressive approach:

1. To increase the rate of good histological response from 56% to 70% (assessed by Huvos' classification).
2. To increase the overall 5–year survival rate from 65% to 80%.
3. To improve the survival rate of poor histologic responders to that of good responders.
4. To increase the 5–year survival rate from 25% to 50% from the time of metastatic relapse.
5. To reduce long– and short–term toxicity by given prolonged infusions of most chemotherapeutic agents, extensive growth factor support and closely monitoring renal function, an integrate part of the protocol.

The results of the pilot series indicate that these aims are realistic. Patients will be admitted to the study over a 3–year period with an accrual of approximately 250 patients. As of Sept. 30. 1998, 95 patients have been included (71 from ISG and 24 from SSG), which accords with our target. The study monitoring committee meets twice yearly to review protocol compliance and toxicity.

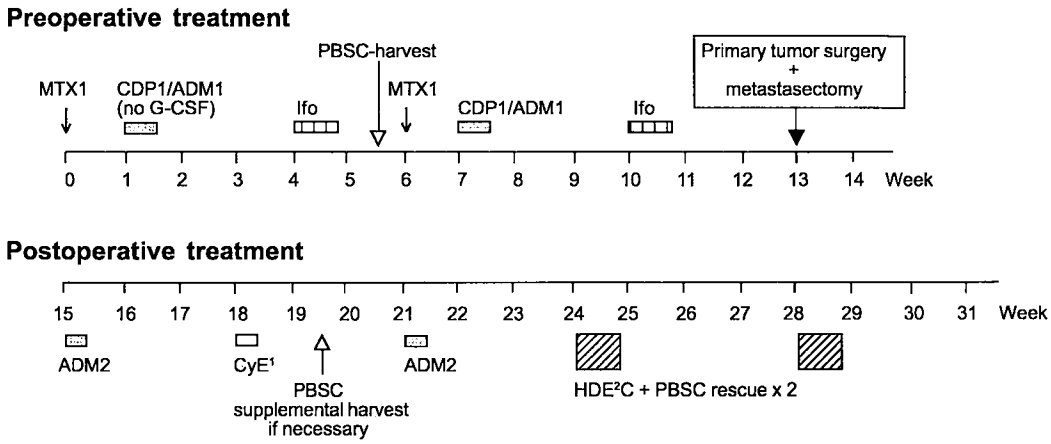

Figure 6. Outline of the ISG/SSG II protocol. Cy: cyclophosphamide 4000 mg/m² in 3h infusion, E¹: etoposide 600 mg/m² in 72h infusion, HDEC: etoposide 1800 mg/m² in 96h infusion and carboplatin. Other abbreviations as in Figure 5.

ISG/SSG II study

This study began on March 1, 1998, and concerns patients who have a poor prognosis with aggressive conventional treatment. Eligibility criteria include high malignancy grade, age <40 years and metastatic disease on initial presentation or pelvic primaries, regardless of stage. The primary treatment is intensified by giving high doses of chemotherapy with peripheral stem–cell rescue. This strategy is based on the importance of a dose–response and dose–intensity relationship in osteosarcoma. The preoperative chemotherapy is identical with that of the ISG/SSG I protocol, but with peripheral stem–cell harvest after the first high doses of ifosfamide. Following surgery of the primary tumor and metastatic lesions (if possible), a short period of conventional chemotherapy precedes 2 courses of high doses of chemotherapy with carboplatin, etoposide (HDEC) and peripheral stem–cell reinfusion (Figure 6).

The following are the aims of the ISG/SSG II study:

1. To increase the 5–year overall survival rate from 20% to 40% in all eligible patients with metastases on initial presentation.
2. To increase the 5–year overall survival rate from 40% to 60% in patients subjected to complete metastasectomy.
3. To increase the 5–year survival rate from <40% to 60% and the local control rate from <50% to 80% in operable pelvic tumors.
4. To evaluate the histological response of the primary tumor and metastases as a prognostic factor for outcome.

Since resistance to clinical chemotherapy and micrometastatic spread are important features of a poor prognosis in patients with osteosarcoma, the research projects on micrometastasis and P–glycoprotein also form part of the ISG/SSG II study. The study should take about 4 years to accrue 60–80 patients with metastatic disease and 30–40 patients with pelvic tumors. A pilot series of approximately 20 patients has been treated with HDEC chemotherapy with acceptable toxicity. As with ISG/SSG I, the committee monitoring the study will review accrual and toxicity twice yearly.

Prospects

SSG investigators are, of course, aware that a 50–60% survival rate can be achieved with less intensive treatment than in the ISG/SSG I protocol, which consequently involving some degree of overtreatment for a substantial number of patients. However, the ISG and SSG agree that cure rates may be improved by further optimizing chemotherapy, since no well documented method is available that reliably predicts the risk of distant metastases in a given patient. In the current ISG/SSG I project, one of the major goals is to identify new prognostic factors (e.g. the detection of micrometastases) and to analyze all candidate factors in a multivariate setting with the aim of proposing risk–adapted treatment in our next osteosarcoma project.

The term "nonclassical osteosarcoma" may be used for patients with tumors localized outside the extremities, tumors secondary to irradiation or other bone disease and tumors arising in elderly patients. The results of treatment in all subgroups of nonclassical cases remain poor with a 15–25% survival rate. A recent study from The Norwegian Radium Hospital

indicates that as many as 45% of all patients with high–grade osteosarcoma may belong to this group. The need for an improvement in the results is obvious. One aspect may be the absence of design prospective studies for these patients. Such studies have been shown to improve the results in other malignant diseases and data in "classical" osteosarcoma patients accord with this view. The ISG/SSG II protocol is one step in this direction. However, many of these patients cannot be given aggressive multimodality treatment because of compromised organ function or surgically inaccessible tumors. Furthermore, among patients with localized "classical" osteosarcoma, the cure rate probably can not be raised above 80% with conventional chemotherapy, due to inherent resistance of the tumor cell.

New methods of treatment are consequently needed. The characterization of drug resistance may make it possible to modify resistance. Targeted radiotherapy is possible via isotopes directed with immunological or bone–seeking carriers. Other promising agents include immune response modifiers such as interferon and muramyl tripeptide phosphoethanolamine (MTP–PE). SSG and ISG institutions are at the forefront of research in several of these fields.

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