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Chemotherapy in Ewing's sarcoma

The Scandinavian Sarcoma Group experience

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The Ewing's family of tumors (EFT) consists of typical Ewing's sarcoma, peripheral malignant neuroectodermal tumor (PNET) and Askin's tumor. They are all malignant tumors that are histologically composed of undifferentiated uniform small round cells, most of them with a specific karyotype t(11:22) (q24;q12). Morphologically PNET differs from Ewing's sarcoma with more neural differentiation and has more often an extraskeletal localization.

The clinical behavior of these tumors are similar and the therapy follows the same basic principles; all subgroups are therefore currently included in the same treatment protocols. SSG has conducted two trials in Ewing's sarcoma, SSG IV and SSG IX. As part of the Scandinavian/Italian cooperation two treatment protocols for EFT, ISGSSG-3 and -4, were opened for localized disease and metastatic disease, respectively, in 1999 and are still ongoing.

SSG IV

The SSG IV protocol for Ewing's sarcoma of bone, which included patients with both localized and metastatic disease, was conducted from 1984 and 1990 with 52 patients recruited. Patients received 5 blocks of 12 weeks cycle of combination chemotherapy of vincristine, methotrexate, doxorubicin, cyclophosphamide, bleomycin and dactinomycin. After two induction cycles, local treatment was performed (week 24), radiotherapy as daily fractions of 2 Gy to a total dose of 40 or 60 Gy. 60 Gy was delivered to patients receiving radiotherapy alone or in combination with nonradical surgery

(Nilbert et al. 1998 and Alvegård et al. 1989). Local recurrence developed in 10 patients. Of the 47 patients with localized disease at presentation, 27 developed metastases. With 10-year median follow-up time, the metastasis-free and sarcoma-related survival at 5 years were 43% and 46%, respectively (Table 1).

SSG IX

The local recurrence rate in SSG IV was relatively high (19%) compared to other studies (Burgert et al. 1990 and Jürgens et al. 1988). Accordingly local treatment in the following SSG IX protocol was changed with earlier timing (week 9) and introduction of hyperfractionated and accelerated radiotherapy. Based on data from the CESS 86 study, cyclofosfamide was replaced by ifosfamide (Jürgens et al. 1988). At that time several reports had published promising results of cisplatin in both local and metastatic Ewing's sarcoma and the drug was therefore included in SSG IX (Castell et al. 1988 and Tursz et al. 1989). Thus, chemotherapy in SSG IX consisted of 4 cycles of a VAI (vincristine, adriamycin, ifosfamide)/PAI (cisplatin, adriamycin, ifosfamide) combination. The total treatment duration was scheduled to 35 weeks. SSG IX was open for all patients with Ewing's sarcoma, also extraosseous tumors. The aims of the study were to increase the sarcoma-related survival to 70% at 5 years and improve the local control rate to 90%.

In the period 1990–April 1999, 88 patients were recruited. The sarcoma-related and metastasis-free survival rates at 5 years for patients with localized disease were 70% and 58%, respectively. 9 patients

Table 1. Comparison of SSG protocols

| Study | Localized disease | | | Cytostatics | Radiotherapy | Local treatment ^a | | | 5-year survival ^b | | |
|------------|---------------------------|---------------------------|-----------|--|------------------------------------|------------------------------|------|----|---------------------------------------|---------------------------------------|---------------------------------------|
| | n | Period | Period | | | S | S&RT | RT | LRF | MF | SS |
| SSG IV | 52 | 47 | 1984–1990 | Doxorubicin Vincristine Cyclofosfamide Bleomycin Methotrexate Actinomycin | 2 Gy x 2 2 Gy x 30 | 19 | 15 | 13 | 81 | 45 | 49 |
| SSG IX | 88 | 73 | 1990–1999 | Doxorubicin Vincristine Ifosfamide Cisplatin | 1.5 Gy x 2 x 14 1.5 Gy x 2 x 20 | 43 | 17 | 28 | 90 | 58 | 70 |
| ISGSSG III | 159 (26 ^d) | 159 (26 ^d) | 1999– | Doxorubicin Vincristine Cyclofosfamide Ifosfamide Etoposide Actinomycin | 1.5 Gy x 2 x 14 1.5 Gy x 2 x 18 | 13 | 5 | 8 | 87 ^c (95 ^d) | 70 ^c (89 ^d) | 75 ^c (87 ^d) |

^a Local treatment: S surgery and RT radiotherapy
^b 5-year survival: LRF local recurrence-free, MF metastasis-free, and SS sarcoma-specific
^c 3-year survival
^d Scandinavian patients

(10%) developed local recurrence. Thus, the aims of the study were achieved (Table 1, Figure 1) (Elomaa et al. 2000). The improved local control probably reflects a combined effect of more and better surgery, earlier timing of local treatment and the use of hyperfractionated/accelerated irradiation (Elomaa et al. 1999 and 2000). Multivariate analyses of prognostic factors for outcome revealed weight loss, (presence of) metastasis at time of diagnosis, inadequate surgical margins and poor histologic response to chemotherapy as independent adverse factors.

ISG/SSG III and IV protocols

As part of the collaboration between the Italian and Scandinavian Sarcoma groups two protocols for EFT were developed; ISG SSG III for localized disease and ISG SSG IV for patients with metastatic disease. Very high-risk patients with multiple bone or visceral metastases at presentation were not eligible to neither protocol. With the current understanding of the common tumor biology for all entities in the EFT, with the ISG/SSG III and IV protocols, all are treated according to the same protocol. The chemotherapy treatment in the ISG SSG III and IV protocols are mainly based on the

Table 2. Multivariate analysis of prognostic factors for outcome in SSG IX

| Factor | Grouping | p |
|----------------------------|----------------------------|-------|
| Weight loss | Yes | 0.02 |
| Metastases at presentation | Yes | 0.002 |
| Surgical margins | Intralesional and marginal | 0.004 |
| Response to chemotherapy | Huvos I + II | 0.003 |

experience from the Rizzoli Institute in Bologna with a 4-drug regimen containing vincristine, adriamycin, actinomycin-D and cyclofosfamide (VACA) considered as standard treatment (Bacci et al. 1991). More recent studies have revealed a benefit of addition of etoposide and ifosfamide to the VACA regimen in the induction phase (Bacci et al. 1998 and Rosito et al. 1996).

Response to induction chemotherapy is an important prognostic factor for outcome in EFT (Elomaa et al. 1999 and 2000 and Picci et al. 1993 and 1997) and postoperative chemotherapy in ISG SSG III is stratified accordingly. For patients not operated, a radiology based system for response evaluation has been developed. Retrospective

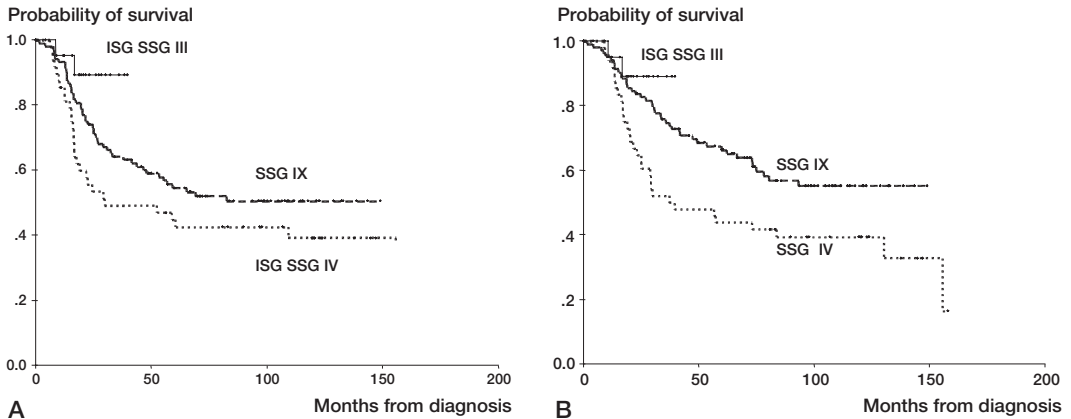


Figure 1. SSG Studies: A) metastasis-free survival (localized disease) and B) sarcoma related survival (localised disease).

analyses of Scandinavian and Italian data have revealed that total disappearance of the soft tissue mass is closely related to histologic response and metastasis-free survival. Accordingly in the ISG SSG III protocol patients with poor response (histologically or radiologically) are salvaged by high-dose chemotherapy with stem cell support as for patients with metastatic disease.

The most adverse prognostic factor in EFT at time of diagnosis is presence of metastases. In this group, patients with lung metastases or single bone metastasis are identified as a relatively good prognostic subgroup (Cotterill et al. 2000). This group of patients is eligible to the ISG SSG IV protocol. The chemotherapy includes maximum dose-intensity of the known active drugs utilized in ISG SSG III including high-dose therapy by a melphalan-myeleran combination for all patients. Data from the European Bone Marrow Transplantation Register suggest a benefit of this combination compared to other regimens although never proven in a randomized trial (Ladenstein et al. 1995).

Local treatment in both protocols follows the principles from the SSG IX protocol with an aggressive surgical approach combined with accelerated hyperfractionated radiotherapy. Preliminary data suggest similar practice and results regarding decision of local treatment modality and local control (Table 1).

Conclusion and prospect

Conventional poly-agent chemotherapy in combination with surgery and/or radiotherapy is highly

successful in low-risk patients with long-term survival rates more than 70% in several reports (Elomaa 1999 and 2000, Cotterill et al. 2000 and Bacci et al. 2004). High-risk patients characterized with metastases at presentation, non-extremity localization or poor response to induction chemotherapy require additional treatment. The preliminary results from ISG SSG III with salvage treatment to poor responders by megatherapy seems promising, but caution should be taken with the short follow-up since there is a tendency to late relapses in EFT (Figure 1) (Nilbert et al. 1998 and Bacci et al. 2004). For subgroups of patients including high-high risk (extensive metastatic disease at presentation) and relapsed patients the outcome is still dismal and even high-dose chemotherapy with stem cells support has failed to improve prognosis (Meyers et al. 2001). The role of high-dose chemotherapy in an intermediate prognostic group (poor responders with localized disease and restricted metastatic disease) as in ISG SSG III and IV seem justified. Regarding chemotherapy details, the inclusion of alkylating agents in the treatment of EFT is well established, but the benefit of the more toxic ifosfamide compared to cyclofosfamide is still debated (addressed in the ongoing Euro-Ewing protocol).

In SSG there has been a development to more surgery as local treatment (Table 1). Several lines of evidence support this strategy. Radical surgery is associated with better local control and outcome and less risk of secondary malignancies (Elomaa et al. 2000, Bacci et al. 2004 and 2004). With the

chemo-irradiation approach utilized in EFT protocols the risk of developing secondary malignancies is considerable and especially acute myelogenous leukemia and radiation-induced osteosarcoma (2 patients in SSG IX and 1 in SSG IV).

We have some insight into the biology of EFT by the identification of the unique chromosomal translocation and the transforming activity of this chimeric gene product (EWS/FLI) (Turc-Carel et al. 1988 and May et al. 1993). However, this knowledge has as yet not been translated into effective novel therapeutic approaches. Attempts have been taken to induce a specific immune response by vaccination with EWS/FLI derived peptides, but have so far failed to give any clinical important responses (Dagher et al. 2002).

In conclusion, today's multi-modal standard therapy has improved the prognosis significantly for patients with no metastases at presentation and extremity-localized tumor. The effect of megatherapy is still debated but seems promising for patients in an intermediate risk group. For patients with extensive metastatic disease at presentation or recurrent disease the prognosis is still dismal. The tendency for late relapses, the risk of secondary malignancies and long-term toxicity strongly arguments for long-term follow-up of EFT patients and the importance of tailoring the optimal treatment for each group of patients according to risk of relapse.

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