Chemotherapy for osteosarcoma and Ewing's sarcoma

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Osteosarcoma

Osteosarcoma is usually a tumour of high grade malignancy, evolving from bone-forming cells near the growth zones of long bones. The aetiology is related to bone growth and the peak incidence is in the 14–16 year age group. Osteosarcoma has high tendency for the early development of lung metastases, and survival after surgical treatment alone is only 15–20% [1]. During the last two decades, the introduction of aggressive combination chemotherapy has dramatically improved long term outcome, with survival rates gradually rising to the 70% range. The most potent chemotherapeutic agents are doxorubicin, cisplatin, ifosfamide and high-dose methotrexate (HDMTX) [2–5].

Current protocol design and treatment results

In addition to post-operative, adjuvant chemotherapy, most treatment protocols include pre-operative (neoadjuvant) chemotherapy, an approach pioneered by Rosen *et al.* [6]. An example of such a protocol is outlined in Figure 1. The rationale for this approach is based on the early tumour dissemination in osteosarcoma, suggesting that chemotherapy should be instituted as early as possible, i.e. at the time of minimal metastatic tumour load. Secondly, as histologic response to chemotherapy is one of the most important prognosticators of long term outcome [7], the approach allows for the detection of poor histologic responders to neoadjuvant treatment, who can then be crossed over to other cytostatic agents post-operatively ("salvage chemotherapy"). Also, a good primary tumour response facilitates limb sparing surgery, possibly with a decreased risk of local recurrence. In disfavour of the neoadjuvant strategy is the possibility of increased tumour dissemination during chemotherapy in non-responding patients.

Initially pre-operative chemotherapy was based on high-dose methotrexate (HDMTX), but HDMTX as a single agent was only able to induce a good histologic

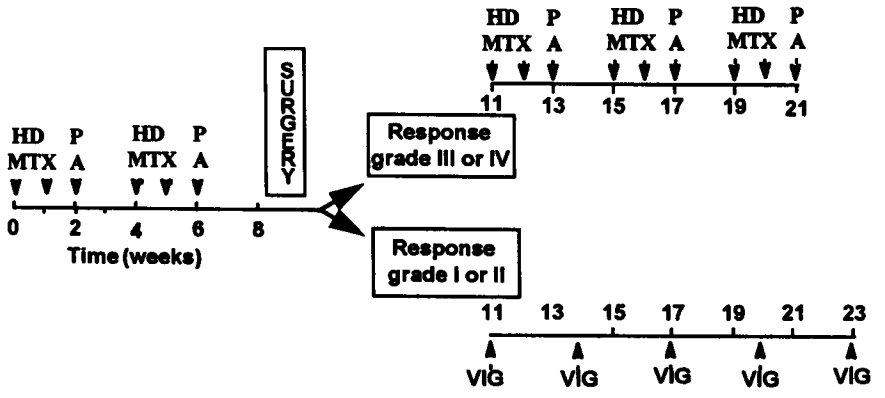

Figure 1. Outline of the Scandinavian Sarcoma Group protocol SSG VIII (from 1990 onwards) for patients <40 years with extremity-localized, non-metastatic, high-grade osteosarcoma.
HDMTX, high-dose methotrexate 12 g/m²; PA, cisplatin 90 mg/m² and doxorubicin 75 mg/m²; VIG, etoposide 600 mg/m² and ifosfamide 4500 mg/m².

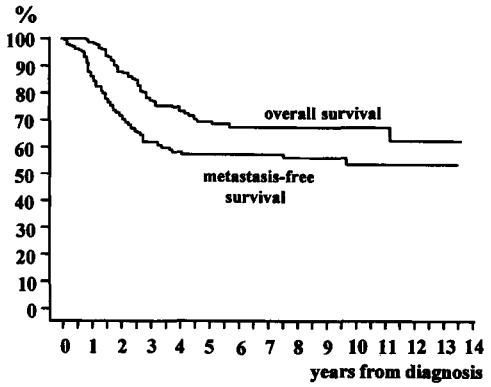

Figure 2. Combined results of protocols SSG II (T-10 protocol 1982–1989, 102 patients) and SSG VIII (1990 onwards, 97 patients), on metastasis-free and overall survival.

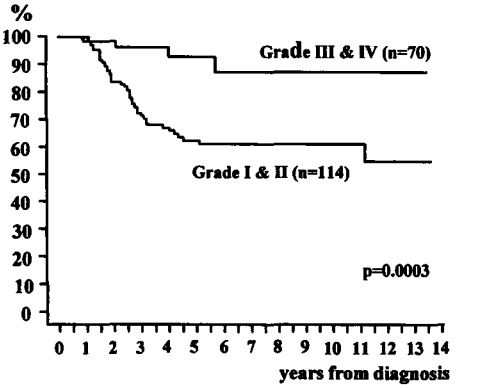

Figure 3. Combined results of Scandinavian Sarcoma Group osteosarcoma studies SSG II and SSG VIII; overall survival by histologic response to pre-operative chemotherapy. Patients were divided into good (grade III-IV) and poor (grade I-II) responders according to Huvos [54].

response in 15–20% of the patients [2, 3, 8]. In the SSG VIII protocol, the addition of cisplatin/doxorubicin and dose escalation of HDMTX from 8 g/m^2 to 12 g/m^2 led to an increase in the fraction of good responders from 18% to 58% [9]. Other centres have also obtained good response in 60–70% of patients using various combinations of HDMTX, cisplatin, doxorubicin and ifosfamide [5, 10–12]. Some prefer to deliver cisplatin intraarterially, and although their results suggest that this may give better tumour response than intavenous treatment [13–15], the matter remains controversial [16]. As regards the effect on micrometastatic disease, which remains the main chemotherapy target, both routes of administration appear to give equivalent systemic drug levels and comparable results as regards long term outcome [13, 16, 17].

Has the neoadjuvant strategy been successful? In terms of metastasis-free and overall survival for the whole patient material, the results are quite impressive (Figure 2). However, despite cross-over for poor responders to other agents, the prognosis for poor responders remains significantly inferior to that of good responders in most series [2, 9, 10, 18] (Figure 3). One exception was found in the second neoadjuvant study at the Rizzoli Institute, where poor responders were crossed over to an ifosfamide and etoposide-containing regimen, and where both good and poor responders had 5-year metastasis-free survival rates in excess of 60% [5]. In a recent randomized study conducted by the Pediatric Oncology Group (POG), preliminary data indicate no difference in disease-free survival between the patients given both pre- and post-operative chemotherapy as compared to post-operative chemotherapy alone [19]. However, in this study poor responders in the neoadjuvant arm were not crossed over to other agents, and thus the "salvage strategy" was not addressed.

In conclusion, the exact contribution of pre-operative and salvage chemotherapy remains unclear. Nevertheless it appears wise to maintain these approaches in order to facilitate limb-sparing surgery [13]. Furthermore, as poor response remains one of the most important prognostic factors for survival, the identification of these patients is mandatory for the development of more effective treatment approaches.

Dose-response relationships and dose intensity

Serum methotrexate (MTX) levels vary considerably between patients, and there are also considerable variations from course to course for the same patient. This may be caused by variables such as age and renal MTX excretion, but are also influenced by treatment-related factors such as MTX infusion time, hydration volume and diuresis [2, 20–22]. It is thus not surprising that an impact of MTX dose level on outcome may be difficult to identify. However, by systematically studying serum MTX levels, several groups have been able to demonstrate significantly positive relationships between serum MTX levels and both tumour response and survival [2, 9, 21–23]. Consequently, it has been recommended that the MTX dose for the individual patient should be adapted to his pharmacokinetic profile, and that the target for the serum MTX concentration should be at least 1000 μM at the end of a 4 hour infusion [23].

Retrospective studies have also demonstrated that *dose intensity* for other agents are of significant importance, and doxorubicin dose intensity is significantly correlated to both tumour response and relapse-free survival [24, 25].

Second line chemotherapy for metastatic relapse

Following aggressive first line chemotherapy, the pattern of metastases in patients who relapse has changed in comparison to the pre-chemotherapy era, with significantly fewer lung metastases appearing after longer disease-free intervals [26–29]. This development has facilitated surgical resection of pulmonary metastases, and in selected centres up to 60% of patients who develop metastases may undergo "radical" metastasectomy. In these metastasectomized patients, long term survival has been reported in up to 50%, but this is often dependent on re-thoracotomies for further relapses [28, 30–32]. In multivariate analyses the most important prognostic factors for survival after metastatic relapse appear to be the accomplishment of radical metastasectomy, the time to metastases (>1.5–2 years favourable), the number of metastases (solitary or <4-6 favourable), and the administration of aggressive second line chemotherapy [28, 29, 31–33]. The impact of second line chemotherapy was seen also following previous treatment with modern chemotherapy protocols, and the second line treatment was dominated by ifosfamide, etoposide and further dose escalations of MTX [28, 32].

Future perspectives

To reach a the metastasis-free survival of 55–65% and an overall survival 65–75%, several drug combinations of varying complexity and toxicity may be used. It appears that the results in high grade osteosarcoma have reached a plateau phase due to inherent drug resistance, and that further improvement with conventional chemotherapy will be limited. Novel treatment strategies are thus needed, and candidate approaches include high dose treatment with stem cell rescue for poor prognostic groups, the use of bone-seeking isotopes [34], interferon [35], radioimmunotherapy [36] and immunotherapy with muramyl tripeptide phosphoethanolamine (MTP-PE) [37]. Novel approaches are also needed for patients falling outside the "classical osteosarcoma" group, i.e. patients with detectable metastases at presentation, non-extremity tumours that may be surgically inaccessible, or patients over the age of 40 where aggressive HDMTX-containing chemotherapy may be contraindicated. These patients are more numerous than what is often appreciated, and together constitute approximately 40% of all patients with high-grade osteosarcoma [38].

Finally, the toxicity of osteosarcoma protocols remains an important concern. It is therefore of major importance to identify reliable prognostic factors that can identify patients with little or no risk of metastatic disease, so that where toxic chemotherapy can be reduced or withheld. The best method for prognostication would be the direct demonstration of micrometastatic disease in the lungs or in peripheral blood. This may become possible with immunoscintigrapy or immunohistochemistry utilizing monoclonal antibodies [36, 39].

The Ewing family of tumours

These include Ewing's sarcoma, primitive neuroectodermal tumour (PNET) and undifferentiated small cell variants. These tumours generally have a similar prognosis and are treated according to similar multimodality protocols. Unlike osteosarcoma, the Ewing tumour family evolve from primitive cells of neural origin in the marrow space and occur more frequently in the axial skeleton. The tumour is fast growing and has considerable radiation sensitivity, making radiotherapy a valuable alternative or supplement for local tumour control [40].

Like osteosarcoma, Ewing's sarcoma is characterized by the early appearance of distant metastases, and in the absence of chemotherapy only 5–10% of patients become long term survivors [41]. Modern treatment is based on aggressive neoadjuvant chemotherapy combined with local surgery and/or radiotherapy. The most active chemotherapeutic agents are generally held to be cyclophosphamide, doxorubicin and ifosfamide. Other active agents include dactinomycin, melphalan, vincristine, BCNU and etoposide, and most of these agents yield response rates as single agents over 30% [40].

Protocol design and treatment results

Following several small phase II studies suggesting dramatic improvements in survival with chemotherapy, the first large scale randomized study (IESS-I) was started in 1973, showing that the addition of doxorubicin to "standard" chemotherapy with vincristine, dactinomycin and cyclophosphamide ("VAC") significantly improved 5-year relapse-free survival from the 25% to the 60% range [42]. In the subsequent IESS-II study, the four-drug combination from IESS-I given on a moderate-dose weekly basis was compared to a regimen with higher dose intensity, showing a further improvement in relapse-free survival from 56% to 73% with the more aggressive regimen [43]. Several other cooperative groups and large single institutions have since reported relapse-free survival rates of 50–70% using relatively aggressive "conventional" regimens [44–47].

Over the years, the trend has been for shortening of total treatment time from up to 18 months to 6–12 months, with a higher chemotherapy dose intensity. Due to the variation in tumour localisation and inter-

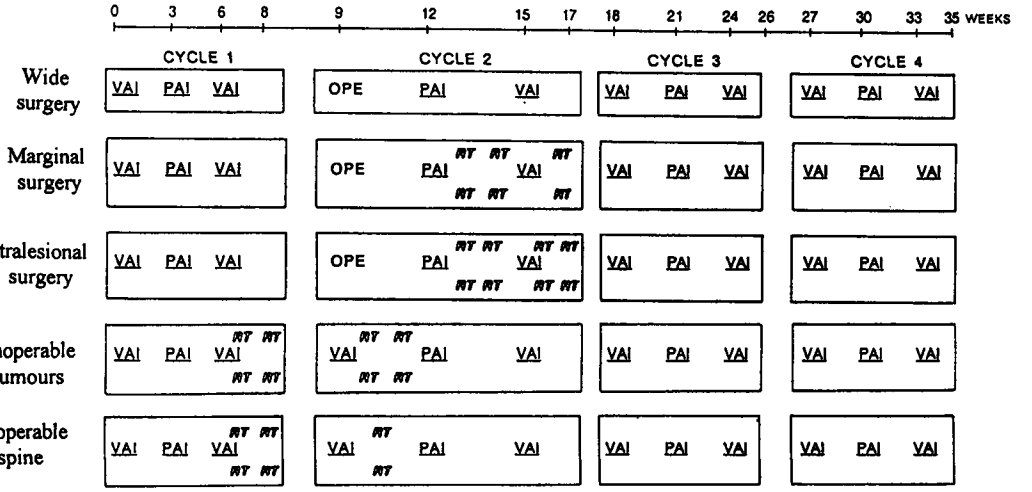

Figure 4. Outline of the ongoing Scandinavian Sarcoma Group SSG IX protocol in Ewing's sarcoma. V, vincristine 1.5 mg/m^2; A, doxorubicin 30 mg/m^2/day for 1 (PAI) or 2 (VAI) days; I, ifosfamide 1 g/m^2/day for 5 days; P, cisplatin 90 mg/m^2. OPE, surgery. RT, hyperfractionated radiotherapy (1.5 Gy twice daily) to total dose 60 Gy for inoperable or intralesionally resected non-spinal tumours, and 42 Gy to spinal tumours or following marginal surgery.

play between surgery and radiation therapy in the primary tumour management, Ewing's sarcoma protocols are generally quite complex in design (Figure 4). However, after the initial dramatic improvement in survival, the prognosis in Ewing's sarcoma has shown only modest improvement. Recent results suggest that the addition of ifosfamide and etoposide may be of additional benefit, possibly lifting the 3-year overall survival to the 80% range [48]. Most modern Ewing's sarcoma protocols include both pre- and post-operative chemotherapy, and although histologic response to pre-operative chemotherapy is a strong prognostic factor for outcome, salvage chemotherapy for poor responders has not been explored to the same degree as in osteosarcoma.

Future perspectives

The major challenge is to improve results in patients where results remain poor (survival 20–40%), i.e. patients with metastatic disease, large primaries, unfavourable sites (particularly pelvic tumours), and following poor histologic response to pre-operative chemotherapy. The introduction of high-dose treatment with bone marrow or peripheral stem cell rescue show promise in such patients [49, 50]. However, while a considerable number of phase II studies studies have been published, their results are difficult to interpret due to small size, diversity in patient selection, diversity in high-dose regimens, and short follow-up [51]. It appears logical that the high-dose concept in poor prognosis Ewing's sarcoma should be tested in a prospective randomized trial. However, due to the rarity of this disease, this would require a considerable international cooperative effort.

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