Scandinavian experience in classical osteosarcoma

Results of the SSG XIV protocol

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Background and purpose The Scandinavian Sarcoma Group (SSG) XIV protocol was based upon the organisations experience from 3 previous osteosarcoma trials and was considered best standard of care for patients with extremity localised, non-metastatic osteosarcoma. We report the outcome of this protocol.

Patients and methods From March 2001 to April 2005, 63 patients recruited from 10 centres in Finland, Sweden and Norway were included in this analysis. Patients received pre-operative chemotherapy consisting of 2 cycles of paired methotrexate (12 g/m^2), cisplatin (90 mg/m^2) and doxorubicin (75 mg/m^2). Good histological responders continued with 3 cycles postoperatively whilst poor responders were salvaged with the addition of 3 cycles of ifosfamide (10–12 g/m^2). Outcome data was compared to previous SSG osteosarcoma trials.

Results With a median follow-up of 64 months for survivors, the projected metastasis-free and sarcoma-related survivals at 5 years were 69% and 77%, respectively. 84% of the patients were treated with limb salvage surgery (49 patients) or rotationplasty (4 patients). 3 toxic deaths (5%) were recorded, all related to acute chemotherapy toxicity. The 5-year metastasis-free survival of patients receiving salvage therapy was 47% compared to 89% for good histological responders that only received the 3 drug combination postoperatively.

Interpretation Outcome in the SSG XIV protocol compares favourably to previous SSG osteosarcoma trials and other published trials. The addition of ifosfamide to poor responders as an add on treatment did not improve outcome for poor responders to a similar level as for good responders. In a multi-institutional setting limb salvage surgery can safely be used in more than 80% of the patients.

Current management of high-grade osteosarcoma comprises pre- and postoperative chemotherapy in combination with complete surgical removal of all tumour sites (Link et al. 1986, Fuchs et al. 1998, Bacci et al. 2000). With this strategy, long-term overall survival rates of 70% are reported for patients with non-metastatic, extremity localized (classical) osteosarcoma and more than 80% of the patients are managed by limb-salvage surgery (Bielack et al. 2002, Smeland et al. 2003, Ferrari et al. 2005). Preoperative chemotherapy offers an opportunity to modify postoperative chemotherapy according to histological response. Although never proven effective in a randomized trial, this principle has been used in several osteosarcoma trials (Rosen et al. 1979, Rosen et al. 1982, Winkler et al. 1988).

The active drugs in osteosarcoma are doxorubicin, methotrexate, cisplatin, and ifosfamide, but

there is no general agreement on their optimal combination (Fuchs et al. 1998, Ferrari et al. 2005, Meyers et al. 2005, Lewis et al. 2007). In the SSG VIII study all patients received a preoperative combination of methotrexate, doxorubicin, and cisplatin (Smeland et al. 2003). Poor responders were salvaged with an exchange to a combination of ifosfamide/etoposide postoperatively. The overall results were good with 5-year metastasis-free and sarcoma-related survival of 63% and 74%, respectively. However, the ifosfamide/etoposide replacement combination resulted in a poor outcome of poor responders. In the recent Italian/Scandinavian ISG/SSG 1 protocol dose intensification by addition of high-dose ifosfamide up-front to all patients failed to improve outcome (Ferrari et al. 2005). In a previous trial from the Rizzoli institute addition of ifosfamide (9 g/m^2) to poor responders resulted in a similar outcome for poor as for good responders and, this together with the COSS-86 study also using all 4 active drugs, represent the best survival data published (Bacci et al. 1993, Fuchs et al. 1998). Thus, based on SSG's own experience and that of other intergroups, the SSG XIV protocol was considered best standard therapy in classical osteosarcoma. All patients received a 3-drug combination of methotrexate, doxorubicin and cisplatin both pre- and postoperatively and poor histological responders were salvaged with the addition of high-dose ifosfamide.

Patients and methods

Patients

From March 2001 to April 2005, 71 patients with high-grade extremity localized osteosarcoma from 6 centres in Sweden, 3 centres in Norway and 2 centres in Finland, were treated according to the SSG XIV protocol. Eligibility criteria were age ≤ 40 years and no evident metastases by mandatory use of chest CT and whole body bone scan at presentation. The primary tumor was assessed by plain radiographs, technetium 99-MDP bone scan, CT scan and MRI of the entire bone involved. 8 patients were excluded due to metastatic disease (n=6), a revised diagnosis of clear cell sarcoma (n=1) or malignant fibrous histocytoma (n=1) rendering 63 patients eligible for this analysis. The diagnosis of osteosarcoma was confirmed by open biopsy in all cases. The SSG pathology panel reviewed all slides and agreed on diagnosis, subtype, and malignancy grade. The median age at diagnosis was 15 (8-39) years. 40 (64%) patients were male. Tumor localizations were femur (n=34), tibia (n=15), humerus (n=6), fibula (n=4), radius (n=2) and other (n=2).

Chemotherapy

Chemotherapy consisted of 2 cycles of paired methotrexate (MTX), 12 g/m^2, doxorubicin (ADM), 75 mg/m^2 and cisplatin (CDP), 90 mg/m^2 pre-operatively and 3 cycles post-operatively (Figure 1). Poor histological responders continued to receive 3 courses of ifosfamide (IFO), 10 g/m^2 as an add on treatment.

With good bone marrow tolerance the protocol allowed escalation of the IFO dose with 20% for the next course. MTX was administered in a 4-hour infusion with 11 doses of leucovorin (folinic acid) as rescue (8 mg/m^2) every 6th hour, beginning 24 hours after starting the MTX infusion (Ferrari et al. 2005). CDP was delivered as a 48-hour continuous infusion intravenously and was followed by ADM given as a 4-hour continuous infusion. IFO, in combination with an equal amount of mesna, was delivered as continuous infusion at a dose of 2 g/m^2/day for 5 consecutive days. Postoperative chemotherapy was scheduled to begin 7 days after surgery. All drugs were given as single agents per course.

Complete blood counts and renal and liver function were monitored before each chemotherapy administration. No dose reduction was allowed, and if the absolute granulocyte count was equal to or less than 1000/μL (500 for MTX cycles), and/or the platelet count was equal to or less than 100.000/μL (60.000 for MTX cycles), chemotherapy was delayed until recovery. After each cycle, the blood count was monitored twice weekly starting on day 7 from the beginning of the chemotherapy infusion. G-CSF support was given according to the ASCO guidelines (1994).

Surgery and histological response assessment

The type of surgery was chosen depending on the size and the location of the tumor, neurovascular involvement and skeletal maturity. For limb salvage surgery, it was mandatory that the preoperative staging showed the possibility of achieving