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Original Research

Results of methotrexate-etoposide-ifosfamide based regimen (M-EI) in osteosarcoma patients included in the French OS2006/sarcome-09 study

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Abstract ***Background:*** In most countries, reference chemotherapy for osteosarcoma is MAP regimen (M = high-dose methotrexate, AP = doxorubicin-cisplatinum). In France, the standard preoperative chemotherapy for children/adolescents combines M and etoposide-ifosfamide (EI), based on the OS94-trial. We report the safety and efficacy results of patients ≤25 years treated with preoperative M-EI regimen enroled in the French OS2006-study, between 2007 and 2014.

Methods: Treatment comprised preoperative chemotherapy with the 7 M-courses and 2 EI-courses, then surgery and postoperative chemotherapy assigned by risk's groups: standard-risk (good histological response without metastases) received 12 M-courses, 3 EI-courses; high-risk (poor histologic response, initial metastases or unresectable primary) received 5 M-courses alternated with 5 AP-courses. 253 patients were randomised to receive (n = 128) or not (n = 125) zoledronate.

Results: 409/522 patients enroled in the OS2006 study who received preoperative M-EI were analysed. Median age was 14.3 years (4.7–24.5), with 55 patients aged 18–25 years. Primary tumour location was limb in 383 patients (94%) and 85 (21%) presented metastases. Median chemotherapy duration was 37.4 weeks. 381 (96%) patients underwent surgery, 258 patients (65%) had a good histologic response. 187/324 patients (58%) with localised disease did not receive doxorubicin nor cisplatinum. Toxicity was evaluated in the randomised study: most patients experienced ≥1 severe toxicity (grade IV haematological or grade III/IV extra-haematological). Median follow-up was 4.8 years, and 168 patients had events. Five-year event-free survival was 56% (95% CI, 51–62%) and overall survival 71% (66–76%).

Conclusion: M-EI regimen/strategy was feasible for patient aged ≤25 years with survival rates are comparable to those obtained with MAP regimen.

1. Introduction

Worldwide, most groups consider the MAP regimen (high-dose methotrexate-doxorubicin-cisplatinum) as the reference chemotherapy for treating osteosarcoma [1–5]. In France, a different strategy was adopted to limit long-term toxicity of doxorubicin and cisplatinum [6,7]. The randomised OS94-trial compared preoperative methotrexate-etoposide/ifosfamide (M-EI) to methotrexate-doxorubicin regimen, with postoperative chemotherapy adapted to risk factors of relapse. The M-EI arm gave a significantly higher good histologic response (GHR) rate (56% vs 39%, p = 0.009) and a slightly better event-free survival (EFS) (hazard ratio [HR] = 0.71, 95% CI: 0.5–1.06, p = 0.09) [8]. With this strategy, AP chemotherapy was restricted to patients with high-risk factors: initial metastases, poor histological response (PHR) or unresectable primary tumours. In France, preoperative M-EI regimen with postoperative AP in high-risk patients became the standard treatment for children/adolescents with osteosarcoma. Although efficacy of a risk-adapted postoperative chemotherapy strategy has not been demonstrated, it was adopted to allow high-risk patients with osteosarcomas to be exposed to all drugs considered effective in osteosarcoma [9].

Herein, we report the safety and efficacy results of patients in the OS2006-study treated with the M-EI regimen.

2. Methods

2.1. Study design and participants

OS2006-study was a national study for patients with a localised/metastatic high-grade osteosarcoma, including a phase-III randomised trial evaluating zoledronate (NCT00470223; http://www.unicancer.fr/protocole-sarcome-09) [10]. Study participants not enroled in the randomised part of the study were treated with the same chemotherapy (according to age) without zoledronate, and prospectively registered in the OS2006-database. The protocol was approved by an independent ethics committee and the institutional review boards.