Chemotherapy for Osteosarcoma without High-Dose Methotrexate: Another Piece in the Puzzle

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Osteosarcoma is a rare tumor which remains a major model in multidisciplinary oncology, bringing together pediatrician and adult oncologists, orthopedic surgeons, and pathologists, all requested for the optimal care of the patients [1].

Treatment with neoadjuvant [2] and/or adjuvant [3] chemotherapy is an undisputed standard for the management of these tumors, on the basis of randomized trials showing an improvement in relapse-free survival in patients treated with adjuvant or neoadjuvant chemotherapy vs. abstention [3, 4]. Neoadjuvant and adjuvant chemotherapy have yielded similar results in a small randomized trial comparing the 2 approaches [5]. Several cytotoxic agents have a demonstrated antitumor activity in osteosarcoma, namely high-dose methotrexate (HDMTX), doxorubicin, CDDP, and ifosfamide [1–7]; cyclophosphamide and vincristine were also frequently used but their antitumor activity is probably more limited, and these drugs are not included in modern chemotherapy regimens [1]. The above mentioned active cytotoxic agents have different toxicity profiles and constraints for administration and management. The administration of HDMTX requests a careful follow-up of patients for the monitoring of drug elimination, resulting in repeated 3–4 days hospitalizations of the patients, but its toxicity profile is otherwise favorable with limited alopecia and hematological toxicities. Conversely, doxorubicin, CDDP (cis-diaminedichloroplatinum; cisplatin), and ifosfamide treatments are associated with hematological toxicity, cardiac or renal side effects, and ototoxicity [1].

Determining the optimal combination of these agents for the management of patients with non-metastatic osteosarcoma has been the major question addressed by the clinical trials on osteosarcomas in the last 20 years [7–10]. Still, definitive answers are pending:

1) Should postoperative chemotherapy be adapted according to the quality of histological response to neoadjuvant chemotherapy on the primary tumor?

2) Should HDMTX be included in multi-agent protocols for osteosarcoma, or should more simple chemotherapy regimens be preferred?

The first question is currently being addressed by the EURAMOS trial, which randomizes different postoperative treatments according to the quality of the histological response achieved with a preoperative treatment combining HDMTX with CDDP and doxorubicin; in the postoperative phase ifosfamide is introduced for patients with poor histological response. The EURAMOS trial brings together cooperative groups from Europe and USA [11].

The second question has been explored by several randomized clinical trials, and uncontrolled clinical trials and is still a matter of discussion [9, 10]. The first trial of the European Osteosarcoma Intergroup randomized HDMTX and doxorubicin with CDDP vs. the combination of doxorubicin and CDDP only [9]. The latter combination was found associated with improved disease-free survival, but concerns regarding the suboptimal dose intensity in the HDMTX arm led investigators to perform a second randomized trial, which compared the multidrug treatment derived from the T10 regimen [12] vs. a two-drug regimen with doxorubicin and CDDP (AP) in a larger (n = 407) cohort of patients [10]. In this latter trial, the AP combination yielded similar results in terms of survival, with a simplified treatment procedure for the patients and less protocol violations. Thus, combination chemotherapy regimens without HDMTX are considered by many investigators as efficient but simpler than HDMTX-based regimens while others still consider HDMTX as a necessary component of first-line treatment of osteosarcomas. To further investigate this question, additional series of patients with a long-term follow-up would be useful.

The report by P.R. Tunn and P. Reichardt in the current issue of ONKOLOGIE [13] adds novel information to this debate. These authors report here on a retrospective analysis of a non-

HDMTX-based regimen administered in 53 patients with osteosarcomas between 1983 and 1992. As expected a long follow-up is available for this series which include an exhaustive series of patients included in one institution. This is therefore a 'real life' situation, with a reasonable number of patients, in an admittedly retrospectively selected series from a single hospital. The authors have used a regimen which includes, in addition to CDDP at a 120 mg/m² and doxorubicin at a 60 mg/m² dose, cyclophosphamide and vincristine. Although the contribution of the 2 latter drugs is unclear, the combination of doxorubicin and CDDP, is given at a bit lower dose intensity than in the recent European Osteosarcoma Intergroup trials. In addition, no ifosfamide was given in these patients although this drug is a component of most recent chemotherapy regimens.

The outcome of these patients was found to be favorable: 45% of patients achieved a good histological response (<10% residual cells), with 10-year event-free (EFS) and overall survival (OS) being 58 and 67% respectively. Although this series included no patients aged above 40 years, a subgroup with a worse prognosis [14], and only tumors of the extremities, these results are comparable to those achieved within clinical trials

performed by the major cooperative groups in the field of osteosarcoma. For example a recent analysis of prognostic factors in 1,702 patients included in the studies of the COSS reported 58 and 61% EFS and OS, respectively, at 10 years [15]. The number of patients remains limited in this study though, precluding any well powered analysis of prognostic factors.

These survival results are consistent with recent publications of treatment series with non-HDMTX-based regimens, based on AP with [7, 8] or without [9, 10] ifosfamide. Interestingly, several of these non-HDMTX-based chemotherapy regimens were developed in adult patients while pediatricians tend to conserve the use of HDMTX in their current protocols [16–18].

This retrospective study confirms, in a series with a long-term follow-up, that treatment with chemotherapy regimens not including HDMTX can provide long-term survival at similar rates than the more complex regimens based on HDMTX. This study adds one piece to the puzzle which figures what is the optimal cytotoxic treatment for localized osteosarcoma. It is likely that this corpus of information will be used for defining the future protocols of adult patients. For children, however, most protocols still include HDMTX in 2007.

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