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Presence of chemotherapy-induced toxicity predicts improved survival in patients with localised extremity osteosarcoma treated with doxorubicin and cisplatin: A report from the European Osteosarcoma Intergroup

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ABSTRACT

Aim: Chemotherapy-induced toxicity is an independent prognostic indicator in several cancers. We aimed to determine whether toxicity was related to survival and histological response in high-grade localised extremity osteosarcoma. We undertook a retrospective analysis of patients treated within three consecutive randomised controlled trials (RCTs) of the European Osteosarcoma Intergroup.

Methods: Between 1982 and 2002, 533 patients were randomised to six cycles of doxorubicin 75 mg/m^2 and cisplatin 100 mg/m^2. Toxicity data were collected prospectively and graded according to the World Health Organisation (WHO) criteria. Standard univariate and multivariate models were constructed to examine the relationship between reported toxicity, survival, and histological response.

Results: Five- and 10-year overall survival was 57% (95% confidence interval (CI) 52–61%) and 53% (49–58%), respectively. Grades 3–4 oral mucositis (hazard ratio (HR) 0.51, 95% CI 0.29–0.91), grades 1–2 nausea/vomiting (HR 0.37, 95% CI 0.16–0.85), grades 1–2 thrombocytopenia (HR 0.49, 95% CI 0.27–0.87), good histological response (HR 0.42, 95% CI 0.27–0.65), and distal tumour site (HR 0.45, 95% CI 0.28–0.71) were associated with improved survival in multivariate analysis. The only factors that were independently associated with histological response were older age (odds ratio (OR) 0.18, 95% CI 0.04–0.72) and chondroblastic tumour (OR 0.28, 95% CI 0.10–0.77), both being associated with a significantly lower chance of achieving a good response.

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Conclusion: Chemotherapy-induced toxicity predicts survival in patients with localised extremity osteosarcoma. Investigation of the pharmacogenomic mechanisms of constitutional chemosensitivity underlying these observations will present opportunities for personalising treatment and could lead to improved outcomes.

1. Introduction

Osteosarcoma is the commonest primary bone sarcoma affecting young people. The prognosis of patients with high-grade localised extremity osteosarcoma improved dramatically with the introduction of multi-disciplinary treatment (surgical resection in conjunction with perioperative multi-agent chemotherapy) but over the past two decades there have been no further improvements in survival.

Histological response to pre-operative chemotherapy is strongly related to the outcome, with patients who achieve a good histological response having a better prognosis than those who do not.[1–4] However, identifying other factors that are reliably prognostic for survival or predictive of response to treatment has been problematic and, although evidence for the influence of several other factors, including histological subtype,[5] has been reported, none routinely influence practice.

In other cancers, chemotherapy-induced toxicity has been shown to be an independent prognostic indicator, with those patients who report greater toxicity also having improved survival. The strongest association has been with myelosuppression. Prognostic effects of chemotherapy-induced neutropenia have been demonstrated in breast,[7] gastric,[6] lung[7,8] and ovarian cancer[9] in adults; and in children and adolescents receiving maintenance treatment for acute lymphoblastic leukaemia.[10,11] Chemotherapy-induced lymphopenia has been shown to be prognostic in advanced breast cancer, soft-tissue sarcoma, and diffuse large B-cell lymphoma.[12] If a similar association between toxicity and either histological response or survival was found in patients with osteosarcoma, an understanding of the underlying genetic and other mechanisms which may explain this constitutional chemosensitivity could lead to the testing and development of therapeutic strategies to exploit or circumvent these phenomena, with the prospect of greater individualisation of treatment and improved outcomes.

The European Osteosarcoma Intergroup (EOI) has completed three randomised controlled trials (RCTs), involving over 1000 patients with localised extremity osteosarcoma. The same 'standard' treatment arm was used in all three, creating a uniquely large cohort treated in a standard manner and followed prospectively.

To explore whether chemotherapy-induced toxicity was associated with outcome in patients with high-grade osteosarcoma, we undertook a retrospective analysis exploring factors relating to survival and histological response in this cohort.

2. Patients and methods

2.1. Patients

Between 1982 and 2002, three consecutive EOI chemotherapy RCTs (MRC BO02/EORTC80831, BO03/80861, BO06/80931) randomised 1067 patients. In each, one arm of the randomisation was a 'standard' treatment: six 3-weekly cycles of doxorubicin 25 mg/m^2/d for 3 d, plus cisplatin 100 mg/m^2 as a continuous 24-h infusion on day 1. Hydration schedules were protocol-specified but other supportive care, including antiemetic regimens, was in accordance with the local practice at trial sites. Surgery was scheduled after either three (BO02 and BO03) or two (BO06) cycles. Full details of each trial are reported elsewhere.[4,13,14] Ninety-nine patients were randomised to standard treatment in BO02 (1983–1986),[13] 199 in BO03 (1986–1991),[4] and 245 in BO06 (1993–2002).[14] Ten patients electively treated with post-operative chemotherapy alone in BO02 were excluded from this study, in line with previous reports from this series.[5,13,15] In total, 533 patients were included in the current combined analysis (Fig. 1).

Patients aged $\leqslant$40 years with histologically proven, high-grade, localised extremity osteosarcoma, and adequate renal and cardiac function were eligible. Patients who had received prior chemotherapy or had a previous malignancy were ineligible. Ethics approval was granted at all institutions, and written informed consent obtained from the patient or parent, in accordance with the local regulatory guidelines. Patients were randomised within 35 d after diagnostic biopsy. The resected specimen was examined histologically to assess response to pre-operative chemotherapy. Good histological response was defined as $\geqslant$90% necrosis in the tumour resected. Both the diagnostic pathology and response assessment were reviewed by the EOI pathology sub-committee.

2.2. Data

In each RCT, toxicity data were collected prospectively at each cycle of chemotherapy using standardised case-report forms and graded at site according to the World Health Organisation (WHO) criteria[16] for haematological toxicity, infection, mucositis, nausea/vomiting, neurological toxicity and cardiac toxicity. Renal toxicity was not specifically recorded in BO06 so this factor was not included in this combined analysis. The worst grade of toxicity for each patient in any pre-operative cycle was used in analyses of histological response, and the worst grade of toxicity per-patient for all cycles was used in the analyses of overall and progression-free survival. Data