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Revisiting the role of doxorubicin in the treatment of rhabdomyosarcoma: An up-front window study in newly diagnosed children with high-risk metastatic disease

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ABSTRACT

Purpose: Many cooperative groups have reported on the chemo-sensitivity of rhabdomyosarcoma (RMS). Doxorubicin has been tested but remains a controversial treatment option. We report here the results of the up-front evaluation of the efficacy of doxorubicin in children and adolescents with high-risk metastatic RMS.

Patients and methods: Patients younger than 18 years of age (>6 months) with newly diagnosed, histologically confirmed high-risk metastatic RMS were required to have measurable disease, to have undergone no prior chemotherapy or radiation therapy and to have normal liver, renal and cardiac function before treatment. Doxorubicin was administered intravenously over 48 h to a total dose of 60 mg/m^2. Two courses were given separated by a 21 day interval. Response to therapy was assessed by diagnostic imaging after the second course. The study was designed as a two-stage procedure according to the multistep plan described by Fleming.

Results: Twenty patients were eligible for analysis. Median age at diagnosis was 9.8 years (range from 2 to 16). Thirteen of the 20 patients treated in the first step responded to treatment, corresponding to an overall response to doxorubicin of 65% [95% confidence interval (CI), 44–85%]. The rates of CR and PR were 5% [95% CI, 0–14%] and 60% [95% CI, 39–81%], respectively. Four (20%) patients had progressive disease, corresponding to a progression rate of 20% [95% CI, 2–38%].

Conclusion: This window study provides the definitive demonstration of the efficacy of doxorubicin in untreated RMS. Given the inconclusive results obtained from previous

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studies using differing schedules chemotherapy incorporating doxorubicin, the next step should be a randomised study testing dose intensity in high-risk localised RMS. This issue is being addressed in a current European study (EpSSG RMS 2005).

1. Introduction

Rhabdomyosarcoma (RMS) is the most common type of soft-tissue sarcoma in the first two decades of life. The cure rate has improved steadily over the past 30 years with refinements in systemic therapy and advances in local therapy (surgery and radiotherapy). The chemo-sensitivity of RMS has been demonstrated by many cooperative groups from North America and Europe. Well-known drugs like vincristine, dactinomycin, cyclophosphamide and ifosfamide are widely used in treatment regimens for RMS. Doxorubicin has also been used but remains a controversial treatment option. The original phase II trials performed in RMS patients showed a response rate between 18% and 37%[1–3] and there is evidence that response rate correlates to the dose of doxorubicin.[2] Doxorubicin has also been used, either alone or in combination, to treat soft-tissue sarcomas in adults, with response rates between 18% and 34%.[4–7] Randomised phase III studies conducted by the North American Intergroup Rhabdomyosarcoma Study Group (IRSG) have assessed the combinations of doxorubicin in combination with other agents, but have failed to show any evidence of efficacy.[8–10] The European International Society of Paediatric Oncology Malignant Mesenchymal Tumours committee (SIOP MMT) designed a study for newly diagnosed, chemotherapy naïve patients with high-risk metastatic RMS (Arm 982 of the SIOP MMT 98 study[11]), consisting of an intensive schedule incorporating sequential combinations of high-dose therapy, local therapy (surgery and radiation) and maintenance chemotherapy. This 'core' protocol was preceded by two phase II window studies, one performed by the United Kingdom Children's Cancer Study Group (UKCCSG) exploring the efficacy of carboplatin and the other undertaken by the Société Française d'Oncologie Pédiatrique (SFOP) evaluating doxorubicin. This paper reports data relating only to the doxorubicin window study.

2. Patients and methods

2.1. Patients

Patients were eligible for study entry if they were aged $\geqslant$6 months to 18 years and had newly diagnosed, histologically confirmed high-risk metastatic RMS. The definition of high-risk disease was based on a previous retrospective analysis[12] and included all patients aged $\geqslant$10 years old, regardless of the site of their metastases, and all patients with bone or bone marrow involvement, regardless of their age. Other patients with metastatic disease were eligible for treatment in the overall protocol but were not eligible for the window studies. All patients were required to have radiologically measurable disease, to have received no prior chemotherapy or radiation therapy and to have normal liver, renal and cardiac function documented before treatment. The primary tumour was evaluated by computed tomograpy (CT) or magnetic resonance imaging (MRI), metastatic sites in the lungs by CT, bone marrow involvement by bilateral bone marrow aspirates and trephine biopsies and the presence of bone metastases by radionucleide bone scan supplemented as required by more detailed imaging (plain X-ray, CT or MRI) of involved sites. Protocol treatment must have been initiated within 8 weeks after any diagnostic surgical procedure. The study received ethical committee approval in all participating centres and all patients and/or their parents/guardians were required to give written informed consent prior to study entry, including specific consent for the window study.

2.2. Treatment plan

Doxorubicin was given as a continuous intravenous infusion over 48 h to a total dose of 60 mg/m^2. Two courses were given at a 21 day interval in the absence of progressive disease or excessive toxicity. Patients who showed progressive disease after the first course of doxorubicin were transferred immediately to the main (core) part of the overall MMT 98 study. GSF support was not used prophylactically.

2.3. Definition of response

Response to therapy was assessed by diagnostic imaging of measurable lesions after the second course of doxorubicin. Tumour size was calculated as the product of two perpendicular diameters on cross sectional imaging. A complete response (CR) was defined as the complete disappearance of all evidence of disease. A partial response (PR) was defined as a decrease of more than 50% of the area of all measurable lesions. A mixed response was a partial response of measurable lesions at one or more sites but no response at others. Objective response (OR) was defined as a decrease of less than 50%, but more than 25% of all measurable lesions. Stable disease (SD) was defined as a no decrease or an increase less than 25% of the area with no evidence of progression of any measurable lesion and the appearance of no new lesions. Progressive disease (PD) was defined as an increase of more than 25% in the area of any measurable lesion and/or the appearance of any new lesion. Central review was undertaken in all cases where the local investigator reported response (CR, PR and OR) or stable disease. Bone and bone marrow involvement were not considered adequately quantifiable variables for assessment of response over such a short period of evaluation and were not included in the assessment.