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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.

2.4. Toxicity

Toxicity data were collected following each course of Doxorubicin and were graded according to the National Cancer institute Common Toxicity Criteria (CTC) version 2.0.

2.5. Statistical considerations

The SFOP window study was designed as an open, multicentre, up-front study utilising a two-stage procedure for determining patient recruitment according to Fleming's multistep plan.[13] The study was powered to confirm evidence for the efficacy of the drug if the response rate (CR + PR) was over 50 % and to conclude inefficacy if the response rate was lower than 30%. Utilising an α risk of 5% and a power of 80%, it was calculated that accrual would be stopped and doxorubicin considered effective if 11 or more favourable responses (CR + PR) were observed in the first 20 patients recruited to the study (rejecting the null hypothesis: $p \leqslant 30\%$). If, however, $\leqslant$6 favourable responses were observed, doxorubicin would not be considered for further testing (rejecting the H1: $p \geqslant 50\%$). If the response rate lay between these two values, an additional 15 patients would need to be recruited for a second step in the assessment. If 16 or more favourable responses were observed among these 35 patients, doxorubicin could be considered as an effective drug for further phase 3 studies in patients with RMS (rejecting the null hypothesis: $p \leqslant 30\%$), but if $\leqslant$15 favourable responses were observed, doxorubicin would not be considered for further testing.

Table 1 – Characteristics of the 20 evaluable patients receiving doxorubicin up-front window therapy

Characteristics	Number of patients	%
Age		
<10 years	9	45
$\geqslant$10 years	11	55
Sex		
Male	14	70
Female	6	30
Primary sites		
Extremities	5	
Parameningeal	5	
Retroperitoneum	3	
Bladder/prostate	3	
Orbit	1	
Liver	1	
Perineum	1	
Unknown	1	
Histology		
Embryonal RMS	9	45
Alveolar RMS	11	55
Metastatic sites[a]		
Lungs	8	
Bones	10	
Nodes	7	
Bone marrow	9	

a Eleven patients had more than one site of metastatic site.

3. Results

3.1. Patient characteristics

From January 1999 to August 2002, 27 patients from 15 SFOP centres were registered for the study. Seven patients were ineligible – two because no evaluation was performed after the second course of doxorubicin and five because imaging was not available for central review. Twenty patients were therefore eligible for the analysis at the end of the first step of the study. The characteristics of these patients are shown in Table 1. Median age at diagnosis was 9.8 years (range 2–16 years) and all patients fulfilled the criteria for high-risk disease as defined in the MMT 98 protocol.

3.2. Response rate

Thirteen of the 20 patients treated in the first step showed a favourable response after two courses of treatment, corresponding to an overall response to doxorubicin of 65% [95% confidence interval (CI), 44–85%]. The rates for CR and PR were 5% [95% CI, 0–14%] and 60% [95% CI, 39–81%], respectively. Amongst those achieving PR, the estimated level of response was more than 75% for 7 patients. One patient had an objective response, two patients showed no response and four had progressive disease corresponding to a progression rate of 20% [95%CI, 2–38%] (Table 2). Amongst these, two had early progression after the first course, documented at days 5 and 15, obliging the investigator to switch treatments before a second course at days 6 and 18, respectively. In accordance with the Fleming plan, the null hypothesis was rejected with an actual α of 4% and an actual β of 30%.

Seventy-two percent [95%CI, 46–98%] of the patients with alveolar RMS (aRMS) responded to doxorubicin versus 55% [95%CI, 23–87%] of the patients with embryonal RMS (eRMS) (p: ns).

3.3. Toxicity from doxorubicin window therapy

Eleven of the 20 patients had grade 3 or 4 haematological toxicity after course 1 and 8/18 after course 2, for a mean duration of 4 days. Two patients had grade 4 infection (septicaemia). No acute cardiac toxicity was reported and there were no unexpected serious adverse event. After completion of the window phase, all patients continued treatment according to the core elements of the SIOP MMT 98 study.

4. Discussion

This trial has clearly identified doxorubicin as an active agent in paediatric RMS. More than 50% of all patients with previously untreated metastatic disease responded (PR or CR) and toxicity was tolerable and manageable, consisting primarily of myelosuppression. The dose used in this study (60 mg/m^2/course) was chosen to allow the subsequent combination of doxorubicin with other drugs in future studies. No difference in response rates was observed between patients with aRMS and those with eRMS unlike results of a similar window study using topotecan.[14] Activity was sufficient

Table 2 – Summarising response by pathology and response category

	CR	PR	OR	SD	PD	Total
All patients	1	12	1	2	4	20
aRMS	1	7	0	0	3	11
eRMS	0	5	1	2	1	9

against both major histiotypes of RMS to justify its inclusion in future phase III studies.

Previous evaluation of the role of doxorubicin in rhabdomyosarcoma has been inconclusive. The IRS group tested the efficacy of doxorubicin in RMS in three randomised phase III trials. The IRS I study[9] was a randomised study testing VAC (vincristine, actinomycin D and cyclophosphamide) alone or in combination with doxorubicin in patients with locally advanced or metastatic disease (IRS clinical groups III and IV). The percentage of patients with or without doxorubicin achieving CR and remaining in remission over time was 39% versus 43% at 5 years ($p = 0.91$). In the IRS II study,[10] the dose of doxorubicin was intensified for patients with IRS clinical group III disease but the results showed that the regimen with doxorubicin was no more effective than the one without, and the overall conclusion of this study was that the role of doxorubicin in newly diagnosed patients remained to be determined. In the IRS III study,[8] the dose of doxorubicin was intensified for the first six months of therapy and evaluated in patients with microscopic residual disease (IRS clinical group II). Although the survival difference seen between regimens with and without doxorubicin was significant in IRS III ($p = 0.03$), when the results of the IRS II and IRS III studies were pooled to increase the power of the evaluation, the difference was no longer significant. The authors concluded that the benefit of doxorubicin for patients with RMS would require further study.[8] It is, however, important to note that the administration of doxorubicin was delivered over 12 months in IRS I and II, and over 6 months in IRS III. Given the requirement to limit cumulative dose exposure to doxorubicin, it is possible that the relatively low-dose intensity resulting from prolonged use could account for the disappointing results obtained in the previous studies.

The up-front window approach offers a strategy for evaluation of a drug in patients whose tumours have not been rendered drug-resistant by previous exposure to chemotherapy and provides an opportunity to estimate the optimal effective dose to be used in future phase III studies. For ethical reasons, such a strategy is appropriate only in patients with very high-risk disease and was justified in this context as the results of a previous meta analysis suggested that the high-risk patients recruited to this study would have less than 15% expected survival.[15] Previous studies of this nature in children with RMS have shown better results than when the same drug was utilised in a standard phase II setting in patients with relapsed or progressive disease.[14] A previous phase II window study conducted in children with newly diagnosed metastatic RMS demonstrated a response rate of 63% to the combination of ifosfamide and doxorubicin.[16]

In previous SIOP MMT studies, the association of ifosfamide, vincristine and actinomycin D (IVA) has been used as the standard chemotherapy for RMS. Recently published results of a pilot study to evaluate the toxicity of the addition of doxorubicin to this combination (IVADo) reported an acceptable toxicity profile and an 84% response rate for RMS after three courses of treatment.[17] The European Paediatric Soft-Tissue Sarcoma Study Group (EpSSG) has recently initiated a phase III randomised study comparing the toxicity and efficacy of IVA versus IVADo. It is hoped that the results of this ongoing study will definitively resolve the place for doxorubicin within combination chemotherapy regimens for advanced RMS.

Conflict of interest statement

None declared.

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