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Original Paper

Response of Previously Untreated Metastatic Rhabdomyosarcoma to Combination Chemotherapy with Carboplatin, Epirubicin and Vincristine

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This study aimed to assess the response to a novel combination chemotherapy containing carboplatin plus epirubicin in previously untreated children with metastatic rhabdomyosarcoma. 81 children (≤18 years) were treated between 1989 and 1994 with a combination of carboplatin, epirubicin and vincristine, given as initial therapy as part of a multicentre European trial (SIOP Intergroup Study of Stage IV Malignant Mesenchymal Tumours in Children). The chemotherapy regimen (CEV) was: carboplatin 500 mg/m² plus epirubicin 150 mg/m² administered on day 1, and vincristine 1.5 mg/m² administered on days 1 and 7. Response was evaluated at day 21. 2 patients achieved complete remission and 41 patients partial remission, with an overall response rate of 53% (95% confidence interval 45–76%). Three patients showed progressive disease (4%). Toxicity was mainly haematological, with 52% experiencing grade IV neutropenia and 34% grade IV thrombocytopenia. Mucositis and infections were not severe. There were no toxic deaths. The combination of carboplatin, epirubicin and vincristine is effective and well tolerated in patients with metastatic rhabdomyosarcoma.

Key words: rhabdomyosarcoma, carboplatin, epirubicin, vincristine
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INTRODUCTION

RHABDOMYOSARCOMA WHICH is metastatic at diagnosis has historically had a very poor prognosis [1, 2]. When treated with regimens containing standard doses of vincristine, actinomycin-D and cyclophosphamide, with or without doxorubicin, long-term survival rates range from 10 to 20% [3, 4]. Ifosfamide has been shown to be effective as a single agent in children with unresectable rhabdomyosarcoma [5]. Intensive regimens with high-dose ifosfamide replacing cyclophosphamide have improved the outlook for patients with non-metastatic disease [6]. However, there has not been a significant benefit to metastatic patients [7]. Novel therapeutic strategies or drug combinations are therefore required in this group of patients.

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In a previous SIOP study (MMT 84), patients resistant to standard chemotherapy with ifosfamide, vincristine and actinomycin-D, were retreated with a combination of cisplatinum and doxorubicin. This was shown to be a highly effective regimen, with 40% of patients achieving a complete or partial response [8]. Single-agent cisplatin has been shown to be effective in children with rhabdomyosarcoma refractory to conventional chemotherapy [9]. Other studies have shown response rates of 33 and 78%, respectively, to a cisplatin plus etoposide combination in relapsed [10] and untreated patients [11] with rhabdomyosarcoma. A rapid cisplatin and etoposide combination has also been shown to be effective in children with relapsed or refractory soft tissue sarcomas [12]. Doxorubicin and vincristine have been proven historically to be active against childhood rhabdomyosarcoma [13–15].

Carboplatin, an effective second-generation platinum analogue, although myelosuppressive, has been found to be less

nephrotoxic, ototoxic and neurotoxic than cisplatin [16]. Early data suggests that carboplatin at high doses may add to the activity of an ifosfamide-based regimen in paediatric solid tumours with use of haemopoietic growth factors [17]. There are no published studies of single-agent epirubicin in rhabdomyosarcoma and its use is based on comparable efficacy in some adult cancers, and the demonstration that epirubicin in combination with ifosfamide is effective in adults with locally advanced or metastatic sarcomas [18]. Use of high-dose epirubicin has not been associated with echocardiographic abnormalities in a series of pilot combination chemotherapy protocols in patients not pretreated with other anthracyclines or mediastinal radiation [19].

The SIOP European Intergroup Study of Stage IV Malignant Mesenchymal Tumours in Childhood was launched in 1989 with the objective of improving survival in stage IV patients [20]. With the evidence for the activity of anthracyclines and platinum drugs in rhabdomyosarcoma, it was decided to incorporate these into an effective ifosfamide-based multidrug regimen (Figure 1). Epirubicin and carboplatin were considered in view of their reduced toxicity profile. In order to assess the response rate in previously untreated patients, the combination of carboplatin, epirubicin and vincristine (CEV) was used as initial therapy.

We report here the extended results of the response to this combination chemotherapy, preliminary results of which have been published previously in abstract form [21].

PATIENTS AND METHODS

Patients were registered in the Intergroup Study of Stage IV Malignant Mesenchymal Tumours of Childhood of the International Society of Paediatric Oncology (SIOP). Patients were recruited from France, United Kingdom, Italy, Germany, Ireland, Spain and The Netherlands. The protocol was approved by the ethical committee of each participating institution.

All patients were aged 18 years or less at diagnosis and had previously untreated rhabdomyosarcoma, with pathology being confirmed by central review. 81 patients were enrolled between 1989 and 1994 (Table 1). Staging was carried out clinically and radiologically (CT scan of primary site, chest X-ray or CT scan, isotope bone scan, abdominal CT scan and brain CT scan for primary tumours arising from the extremities). All patients had examination of bone marrow from outside any area of bone involvement, with two aspirates and two trephines. Stage IV tumours were defined as those with distant metastases at diagnosis, including distant lymph node involvement with or without local or regional lymph node involvement. The majority of tumours (73%) were large (>5 cm), and regional (60%) and distant lymph node (46%)

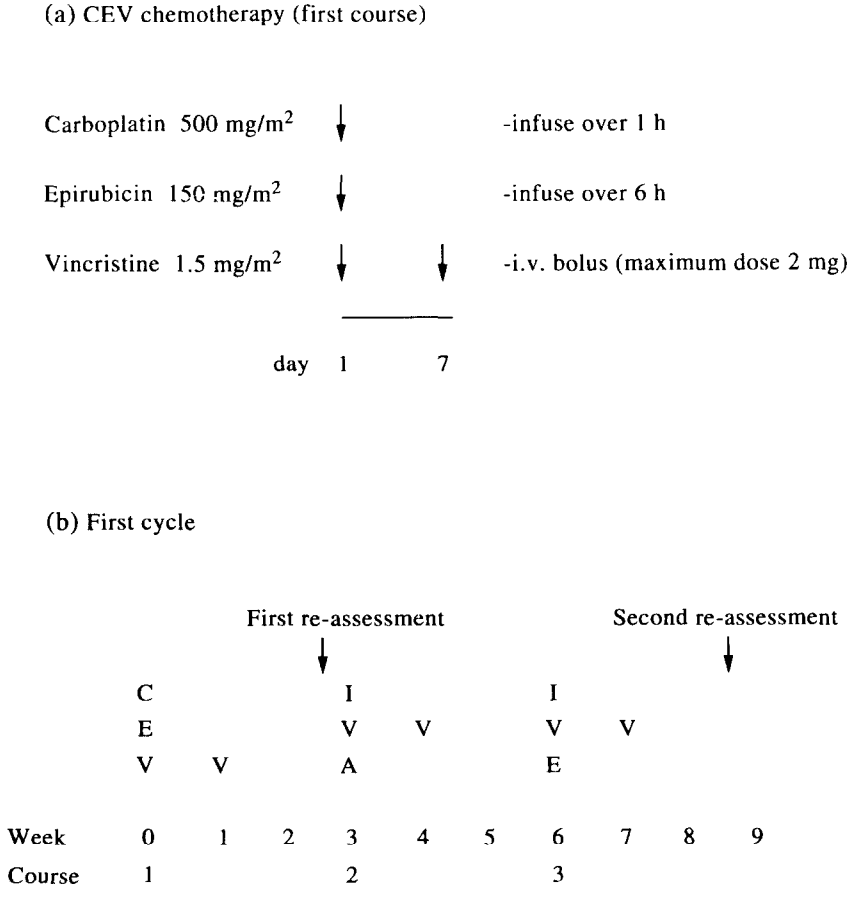

Figure 1. Overall chemotherapeutic strategy (SIOP intergroup study, stave IV-9 and MMT IV-91). Patients are re-assessed after the first course to exclude progressive disease and document response to CEV. Good responders after the first cycle received a total of four cycles of chemotherapy (12 courses) in the MMT-89 protocol and three cycles (nine courses) plus high-dose melphalan with autologous bone marrow rescue in the MMT IV-91 protocol. Varying combinations of surgical excision and radiotherapy were used in both protocols. I, ifosfamide 3 g/m²/day days 1–3; A, actinomycin-D 1.5 mg/m² bolus day 1; E, etoposide 200 mg/m² days 1–3.

Table 1. Clinical features of patients with stage IV rhabdomyosarcoma

Number of patients	81
Sex	
Male	40
Female	41
Median age	8 years
Age range	2 months–18 years
Site	
Parameningeal (PM)	7
Head and neck, non PM	3
Bladder–prostate (B–P)	8
Genitourinary, non B–P	5
Limb	32
Others	23
Unknown	3
Histology	
Embryonal	41
Alveolar	31
Other	9

Table 2. Tumour extent and pattern of spread

	No. of cases
Tumour size*	
T1	1
T1a	4
T1b	12
T2a	12
T2b	47
T*x*	5
Lymph node involvement	
N0	20
N1	49
N*x*	12
Metastases	
Bone marrow	33
Bone	27
Distant nodes	37
Lung	39
Subcutaneous	14
Liver	3
Intra-abdominal	5
Other	2

* Tumour size determined by clinical and radiological assessment; T1, tumour confined to organ of origin, a = ≤5 cm, b = >5 cm; T2, tumour involving contiguous organ or tissue or with adjacent malignant effusion or multiple tumours within one organ, a and b as for T1.

involvement was common. 10 patients were classified as stage IV because of distant lymph node involvement only. All also had regional lymph node involvement. The lymph nodes were called 'involved' because of obvious enlargement on imaging (CT scan). Histological confirmation of involvement with rhabdomyosarcoma was performed in 6 cases of regional and 1 case of distant lymph node involvement. 33 cases (41%) had bone marrow involvement, 27 (33%) had bone involvement, 39 (48%) had lung involvement and 14 (17%) had subcutaneous involvement (Table 2). The median age of this group of patients was considerably older than for rhabdomyosarcoma patients as a whole (8 versus 5 years). This emphasises that older patients are more likely to have aggressive disease with poor prognosis biological features, such as alveolar histology (38 versus 15%).

The chemotherapy regimen was: carboplatin 500 mg/m^2 i.v. over 1 h, epirubicin 150 mg/m^2 i.v. over 6 h, and vincristine 1.5 mg/m^2 (maximum dose 2 mg) as an i.v. bolus (Figure 1a). Courses 2 and 3 were ifosfamide based (Figure 1b).

Response at both primary and metastatic sites was evaluated on day 20 after the first course of combination chemotherapy. Assessment was carried out clinically and radiologically (including X-ray, CT scan and ultrasonography if necessary). Primary tumour and metastases were measured in terms of surface area, wherever possible. For bone marrow involvement at presentation, a minimum of two bone marrow aspirates at different sites were performed at reassessment. Standard response criteria were used (see Table 3 legend).

RESULTS

Response data

43 out of 81 patients studied showed a response (response rate of 53%; 95% confidence interval = 45–76%). 2 patients achieved a complete remission after the first course, and 41 patients achieved a partial response at all sites evaluated. A further 12 patients (15%) showed an objective response with a 25–50% reduction in tumour size. 11 patients had a heterogeneous response, achieving PR at one or more sites, but a less than partial response at others. Only 3 patients had progressive disease after their first course of chemotherapy. Of these, 1 died of progressive disease, 8 days after commencing chemotherapy (Table 3). One of the 2 patients achieving complete remission after one course of chemotherapy had alveolar histology, but both had only one metastasis at diagnosis.

Toxicity data

Toxicity data are available on 71 of 81 patients (Table 4). The major toxicity was haematological. Sixty-nine per cent of patients developed grade III or IV neutropenia and 49% developed grade III or IV thrombocytopenia. Anaemia was less severe, with only 4% developing grade IV anaemia. Infections were of moderate severity in 32% of patients and severe in 8%. Severe mucositis was uncommon, with only 6% of patients experiencing grade III or IV toxicity. The only patient with significant renal toxicity was in acute renal failure at diagnosis, prior to commencing chemotherapy. No significant increases in liver enzymes were observed. The median time to commencement of the second course of chemotherapy was 22 days (range 17–46 days), which was only 1 day longer than the planned interval between chemotherapy courses. There were no toxic deaths after the first course of chemotherapy.

DISCUSSION

Although there has been steady improvement in the management of children with non-metastatic rhabdomyosarcoma over the years, metastatic rhabdomyosarcoma has been associated with a uniformly poor outlook.

The combination of carboplatin, epirubicin and vincristine (CEV) has been shown by the data presented to be effective in inducing responses in these patients (overall response rate

Table 3. Response rate to first course of carboplatin–epirubicin–vincristine (CEV)

Histological diagnosis	Response at day 21 (No. of cases) CR	PR	HR	OR	NR	PD	Total no.	Overall response (CR + PR) (%)
RMS-embryonal	—	20	7	6	7	1	41	49
RMS-alveolar	1	17	4	4	3	2*	31	58
RMS-NOS	1	4	—	2	2	—	9	56
Total	2	41	11	12	12	3	81	53%

CR, complete clinical and radiological remission; PR, ⩾50% reduction in the sum of the products of the maximal perpendicular diameters of the tumour; HR (heterogeneous response), PR at one or more sites but less than PR at other sites but no PD; OR (objective response), >25% but <50% reduction in tumour size; NR (no response), <25% reduction in tumour size; PD, progressive disease; RMS, rhabdomyosarcoma; NOS, not otherwise specified.

* Includes patient who died at day 8 with progressive disease.

Table 4. Toxicity after first course of carboplatin–epirubicin–vincristine (CEV)

Toxicity grade (WHO)	Neutropenia	Thrombocytopenia	Anaemia	Mucositis	Infection	Renal	Haematuria	Liver	Vomiting
1	7	10	11	15	14	3	0	13	1.5
2	10	7	41	8	32	1.5	1.5	3	4
3	17	15	18	3	7	0	1.5	0	1.5
4	52	34	4*	3	1.5	1.5†	0	0	1.5

Values given as % for the 71 patients evaluable for toxicity data.

* 1 patient with G6PD deficiency had acute haemolysis. † This patient had acute renal failure at presentation.

of 53%). It is well tolerated, with major toxicity being haematological with 52% patients developing grade IV neutropenia and 34% patients grade IV thrombocytopenia. A small minority of patients had severe infections (8%) but there were no toxic or infectious deaths. Use of high-dose epirubicin in this combination did not significantly increase toxicity. In view of its controllable emetogenicity and short infusion time, CEV can be administered on an outpatient basis.

Testing new agents in previously untreated patients allows assessment of the activity of drugs before the development of clinical drug resistance, thus potentially providing a more accurate estimate of the efficacy of novel compounds. Response rate in this study was determined at 3 weeks after commencing treatment, and after only a single course of chemotherapy. 2 patients (2.5%) achieved a complete response at all sites after the first course. The overall response compares well with a study which assessed response to two courses of ifosfamide in previously untreated patients with unresectable and/or metastatic rhabdomyosarcoma (53%; 95% confidence interval = 45–76% versus 86%; 95% confidence interval 65–97%) [5]. Of interest, 18 out of 31 patients with alveolar histology in this study achieved at least a partial response (response rate 58%) after a single course, emphasising that this aggressive subtype can be very chemosensitive in its initial stages.

It is very difficult to compare the response rate following one course of CEV with that using other published combination regimens. Comparisons cannot be made with the IRS study data because of the early use of local radiotherapy and the later time of assessment [22, 23]. Early assessment around 7–9 weeks following combination chemotherapy with VACA or VAIA showed overall response rates of 55 and 71%, respectively, but this study was limited to stage III patients [24]. If the small number of stage IV patients were selected out from a further study, an overall response rate of 60% was achieved using conventional VAC chemotherapy, where response was assessed prior to course 3 [25]. The combination of DTIC and doxorubicin achieved an overall response rate of 65% after three courses of treatment [26], and a rapid schedule comprising weekly vincristine, doxorubicin and cyclophosphamide has been reported to achieve a 78% overall response rate where disease was reassessed at weeks 10–12 [27]. In adult metastatic soft tissue sarcoma, a 45% response rate was achieved after two cycles of ifosfamide and doxorubicin [28]. In summary, it is clear that a variety of combination chemotherapy schedules will achieve an overall response rate in the region of 50–70% after two or three cycles. It is, however, impossible to conclude whether the comparable response rate after only one course of CEV would have been achieved with these standard regimens if patients had been reassessed at week 3.

The response to a platinum-based combination chemotherapy is in keeping with previous preliminary data showing responses to a cisplatinum–doxorubicin combination in patients with resistant rhabdomyosarcoma [8]. The use of epirubicin in a high dose in this combination may add to its efficacy. Patients treated with a regimen containing a similar high dose of epirubicin have not shown any early echocardiographic changes [19]. Thus, it is hoped that the choice of newer anthracycline and platinum analogues will help to reduce

toxicity. Further evaluation of CEV combination chemotherapy as part of the Intergroup Study of Stage IV Malignant Mesenchymal Tumours in Childhood is necessary to delineate its role in inducing long-term remission in this group of patients.

In conclusion, the efficacy and tolerability of a single course of CEV combination chemotherapy in previously untreated children with metastatic rhabdomyosarcoma is demonstrated by the data presented and, moreover, it can be administered on an outpatient basis.

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