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Short communication

High-dose VP16 cisplatinum in soft tissue sarcoma of children

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Abstract. Nine children with soft tissue sarcomas, five of them rhabdomyosarcomas with initial metastatic disease, (one patient, partial response, one patient), refractory primary, (two patients, relapse, five patients) were treated with a combination of high-dose VP16 (100 mg/m^2 daily for 5 days) and cisplatin (40 mg/m^2 daily for 5 days). The response rate was five out of nine or 55% ($\pm$32%) (two complete and three partial, responses). Three of the five responders had rhabdomyosarcomas. The duration of response was 4–58 months (median 11 months). The toxicity was mainly hematological. Thus, the high-dose VP16–cisplatin association warrants further evaluation in soft tissue sarcoma in children.

Introduction

The treatment of soft tissue sarcoma (STS) in childhood is specific for several reasons. Such tumors are usually highly chemosensitive. Moreover, local treatments (surgery and/or radiotherapy) induce major late sequelae that are now recognized as unacceptable for the 50% long-term survivors [4, 5, 7, 15]. Major improvement has been achieved with the use of neoadjuvant chemotherapy using vincristine, dactinomycin, doxorubicin, cyclophosphamide (VAC-VAd, VACA) and, more recently, ifosfamide (IVA-IVAd) [10]. With such associations, more than 50% of children with localized STS become long-term survivors without the need for additional aggressive local treatment. For those patients with a poor prognosis (localized parameningeal, or initially metastatic disease or relapse after conventional treatments) alternative treatments are required. They may include a multidisciplinary approach associating chemo-radiotherapy and surgery, with or without high-dose chemotherapy followed by autologous bone marrow rescue for responders. Several second line therapies have been described, including VINCAEPI and daily oral low dose VP16 [13, 19]. The goal of this report is to describe an alternative second-line chemotherapy that could be used in STS of childhood.

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Material and Methods

Between April 1987 and February 1992 nine children under 16 years of age with metastatic, recurrent or unresponsive histologically proven STS were treated with etoposide (VP16) and high-dose cisplatin at the Centre Léon Bérard, Lyon, France. Eligibility requirements for this study included: presence of measurable disease, normal renal function assessed by serum creatinine level, a 3-week interval since any prior chemotherapy, and a life expectancy of at least 6 weeks. Pretreatment investigations included: complete physical examination, measurement of lesions by Ultrasonography or CT scan, chest X-ray, complete blood count, renal and hepatic function tests.

Patients. Patients' characteristics are summarized in Table 1. Briefly, there were seven boys and two girls aged 23–186 months at diagnosis (median = 75 months) and 31–235 months at the start of the trial (median = 79 months). Five patients had a rhabdomyosarcoma, two a synovial cell sarcoma, one, hemangiopericytoma and one desmoplastic small round cell tumor. Initial stages were as follows: stage I, one patient: stage II, four patients; stage III, two patients; stage IV, two patients. The status at the start of the trial was as follows: one patient with metastatic disease received the VP16/CDDP combination as first-line therapy. One patient was in the first PR, two had primarily refractory disease, and five patients had relapsed (two untreated, one sensitive, two resistant). Prior therapy included IVA (ifosfamide, vincristine, dactinomycin, 2–6 courses) in all eight pretreated patients. Three patients had received 1–2 courses of a carboplatinum-containing regimen (VINCAEPI, vincristine, carboplatin, teniposide) and two a doxorubicin-containing regimen.

Treatment plan. Patients were hospitalized for treatment. Cisplatin was administered at a dose of 40 mg/m^2 daily for 5 days and VP16 at a dose of 100 mg/m^2 daily for 5 days, for two cycles, with an interval of 3–4 weeks between each cycle. As previously described [12], cisplatin was infused over a 1-h period in 100–250 ml of 5% dextrose solution with 3% sodium chloride added. Hydration, with normal saline and added potassium chloride (1.5 g/l) was begun 24 h before cisplatin and continued for 7 days (3 l/m^2 every 24 h). In addition, 10% calcium chloride 10 mg/m^2 per day and 50% magnesium sulfate 5 mg/m^2 per

Table 1. Patients' characteristics

Patient no.	Sex	Age at diag./ age at trial (months)	Primary (site)	Histological findings	Previous treatment	Status before trial	response (months)	Further treatment
1	M	46/ 46	Parameningeal	RMS	No treatment	Initial metastasis	PR(58)	IVA(3)+VP16/CDDP (1) + VIC ABMT
2	M	75/110	Limb	SYN SARC	IVA (5), ADRIA+CDDP (3)	Untreated local relapse	NR -	VP16/CDDP (2) + VIC ABMT
3	M	44/ 72	Abdomen	RMS	IVA (6), VINCAEPI (1)	Resistant local relapse	PD	Surgery+RT
4	M	76/ 79	Abdomen	DSRCT	IVA (2), VINCAEPI (1)	Primary refractory	PR(11)	Surgery+VP16/CDDP (2) + VCR MEL ABMT
5	M	170/184	Retroperitoneum	RMS	IVA (6)	Untreated local relapse	CR (7)	VP16/CDDP (1) + CBDCA MEl ABMT
6	M	159/161	Neck	SYN SARC	IVA (3)	Primary refractory	PR (14)	VP16/CDDP (1)+Surgery +VP16/CDDP (2)
7	F	23/ 31	Paraspinal	RMS	IVA (3), VINCAEPI (2)	Sensitive local relapse	CR (4)	VP16/CDDP (2) +Surgery+RT
8	M	28/ 31	Bladder	RMS	IVA (4)	Partial response	NR	VP16/CDDP (2) +Surgery+ VP16/CDDP (2)
9	F	186/235	Paraspinal	HEMANG	IVA (6), ADRIA+DTIC+ IFO (2)	Resistant distant rel	PD	VP16-p.o.

ABMT, Autologous bone marrow transplantation; CBDCA/MEL, carboplatin/melphalan; CR, complete remission; DSRCT, desmoplastic small round cell tumor; HEMANG, hemangiopericytoma; IVA, ifosfamide, vincristine, dactinomycin; NR, no response; PD, progressive disease; PR, partial response; RMS, rhabdomyosarcoma; SYN SARC, synovial cell sarcoma; VIC, VP 16, ifosfamide, cisplatin; VP16/CDDP, VP 16/cisplatin

Table 2. VO-16/CDDP

Chemotherapy administered over 5 days (days 1–5)

Hyperhydration administered days 0–6:
3 l/m^2 per day of Isotonic saline (0.9% NaCl) with 2 g KCl (20 mEq.) 10 ml/m^2 per day of $CoCl_2$ 5 ml/m^2 per day of $MgSO_4$ (50%) On days 4, 5, and 6, double amounts of Ca^{2+} and Mg^{2+}

Chemotherapy (days 1–5) VP-16 100 mg/m^2 per day in 100–250 ml 0.9% NaCl over 1 h at 10 a.m.

Cisplatin 40 mg/m^2 per day in 100–250 ml of 5% glucose made up to 3% NaCl, over 1 h at 6 p.m.

Monitor diuresis closely. If urine output <350 ml/m^2 in 3 h, give furosemide (Lasix) 1 mg/kg i.v.

Days/6, 7: fluid input reduced to 2 l/m^2 and 1.5 l/m^2 p.o. if tolerated

Days 10, 14: full blood count including platelets, electrolytes, liver function test

day were added on day 0, and systematically doubled from day 3 to day 6 VP16 was administered in 100–200 ml of normal saline over a 1-h period (Table 2).

Evaluation of response. The response was defined after the second cycle of VP16/cisplatin with the exception of progressive disease (PD), which was recorded after one course. A complete response (CR) was defined as the disappearance of signs of tumor based upon clinical and imaging evidence. A partial response (PR) was defined as ≥50% reduction in the sum of the products of two perpendicular diameters of each measurable lesion for at least 4 weeks. All tumor regressions by <50% were considered to reflect no response (NR). PD was used to denote a ≥25% increase in the size of measurable lesions at any site involved and/or the appearance of new lesions.

Results

Responses (2 CR and 3 PR) were seen in five of the nine evaluable patients (55% ± 32%). Among the five patients with rhabdomyosarcoma, two CR and one PR were obtained. One of two patients with synovial cell sarcoma and one patient with desmoplastic small round cell tumor achieved PR. Two patients had PDs after one (RMS) or two courses (hemangiopericytoma). Of eight patients who had previously received IVA, four responded (2 CR, 2 PR). Of three patients who had received VINCAEPI, one achieved CR and one PR. No response was obtained in the two patients who had received a doxorubicin-containing regimen. The patient with initial metastatic RMS had a PR, as did two patients with primary refractory disease. One patient with untreated relapse and one patient with sensitive relapse attained CR. Duration of response ranged from 4 to over 58 months (median 14), but most of the patients received additive treatment.

Toxicity

Severe nausea and vomiting was observed in all patients and required specific management. Transient increase in the serum creatinine level was also frequently observed, but

the level returned spontaneously to its baseline before next following cycle in all patients. Hematological toxicity was not a major problem. In 17 evaluable courses, we saw: WHO grade 3 neutropenia in three patients and grade 4 in five patients; WHO grade 3 leukopenia in four patients and grade 4 in one patient; WHO grade 3 thrombopenia in two patients. Five patients had grade 3 toxicity for hemoglobin. Four patients received red blood cell transfusions and two patients required platelet transfusions. Weight loss $\geq 5\%$ was observed in two patients. No patient experienced neurological toxicity. Audiometric toxicity was not assessed. No infectious complications were observed. No patient died of any toxicity-related cause.

Discussion

In 1992, the role of cisplatin in the treatment of STS remains unclear. Several studies have reported a minimal activity of cisplatin (100–200 mg/m^2) in adult patients, with response rates ranging from 4% to 23% [1, 2, 8, 18]. However, these studies deal mainly with adult types of STS (e.g., leiomyosarcoma, synovial cell sarcoma, hemangiopericytoma, fibrosarcoma and liposarcoma), which are rare in children. The association of cisplatin CDDP (100 mg/m^2) and doxorubicin (60 mg/m^2) in 28 children with PR or NR to the IVA regimen gave a 40% response rate [16]. Etoposide has shown its efficacy as a low-dose oral continuous treatment in childhood rhabdomyosarcoma. Moreover, etoposide has a synergistic effect with cisplatin [9, 17]. Two pediatric studies using the combination of VP16 and cisplatin gave conflicting results: Raney [14] reported a 12.5% response rate in 16 evaluable children with STS (1 response among 7 patients with RMS, and 1 of 9 children with non-RMS disease). Carli [3] reported a 33.3% response rate among 27 relapsed children with STS (7 responses/21 RMS, 0/17 non-RMS). Both studies used conventional doses of cisplatin (ranging from 75 to 100 mg/m^2 and a 3-day schedule of VP16. The dose-effect relationship of cisplatin has been demonstrated by Ozols [11] in adults with germinal tumor and by Philip in children with neuroblastomas [12]. Our study, using a similarly high dose of cisplatin (200 mg/m^2) tends to demonstrate that there is a similar dose-effect relationship in STS. Moreover, two of three patients who had previously received VINCAEPI showed a response, suggesting a lack of cross-resistance between cisplatin and carboplatin, as suggested in other pediatric malignancies [6]. The response could be due to either agent, i.e., high-dose cisplatin or etoposide, and it is possible that there is no additional benefit of giving the combination as opposed to single-agent treatment. Though the numbers are small, the 5/9 response rate is very encouraging and requires further evaluation of this and similar treatment schedules.

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