Long-Lasting Complete Remission After Prolonged Administration of Etoposide in a Child With a Second Recurrence of Alveolar Rhabdomyosarcoma

Amalia Schiavetti,[1] Manuel A. Castello,[1]* Frederic Gauthier,[1] and Odile Oberlin[1]

The authors report a case of alveolar rhabdomyosarcoma (RMS) of the thigh complicated by two successive distant relapses shortly after radio- and chemotherapy, treated with etoposide, and resulting in complete long-lasting remission. The schedule of etoposide was 100 mg/m^2/d intravenously for three days weekly for 3 weeks, with an interval of 1 week between courses. This was administered for 11 months. The child is alive without disease and off therapy 20 months after completion of etoposide treatment. Preclinical studies and experience in adults have suggested that the cytotoxic effects of etoposide show a marked dependence on schedule. A divided dose regimen of single-agent etoposide has previously been shown to have activity in relapsed rhabdomyosarcoma, but the outcome or the duration of complete response has not yet been fully evaluated. In our poor-prognosis case, the prolonged administration of etoposide achieved a long-lasting complete response. **Med. Pediatr. Oncol. 28: 144–146.**

Key words: rhabdomyosarcoma; children; etoposide

INTRODUCTION

The prognosis for alveolar rhabdomyosarcoma (RMS) of the extremities is worse than that for other sites or for embryonal RMS, even though the clinical group (or extent of disease at diagnosis) is still the most important prognostic variable [1]. The presence of recurrences and their number further worsens the prognosis. We report a case of alveolar RMS of the thigh, with two successive distant lymph node relapses shortly after radio- and chemotherapy, treated with prolonged administration of etoposide, and resulting in complete long-lasting remission.

Factors predictive of poor prognosis in this case were the tumor site (limb location), the alveolar histology, and the two successive distant relapses. Only etoposide therapy induced complete and long-lasting remission after the second distant relapse: at present, the child is alive without disease, and off therapy for 20 months.

CASE REPORT

A 30-month-old baby girl presented with a 5-cm mass on the lateral portion of the right thigh. Complete surgical resection was carried out and histologic examination revealed alveolar RMS. The neoplasia was at stage II according to the Intergroup Rhabdomyosarcoma Study (IRS) system [2] because the resection was macroscopically, but not microscopically, complete.

The child received local radiotherapy (40 Grays), and nine courses of chemotherapy according to the Italian Trial for Rhabdomyosarcoma. Each course consisted of ifosfamide (3 g/m^2 for two days), actinomycin D (1.5 mg/m^2 on the first day), and vincristine (1.5 mg/m^2 also on the first day). This was repeated every 3–4 weeks.

The patient then developed a 3.2-cm nodular mass in the right iliac region 2 months after the last course of chemotherapy. Needle biopsy was performed and histologic examination showed a recurrence of RMS. Two courses of chemotherapy with carboplatin (1,000 mg/m^2) associated with etoposide (300 mg/m^2) were administered in one day, and a partial reduction of the neoplastic mass was obtained. Complete surgical removal was then carried out and several lymph node biopsies were obtained. Histologic examination confirmed alveolar RMS. Radiotherapy (40 Grays) was administered to the aortic lymph nodes and to the right inguinal, iliac and femoral lymph nodes; this was associated with two courses of carboplatin (600 mg/m^2) and etoposide (200 mg/m^2). Afterwards, chemotherapy with carboplatin (1,000 mg/m^2) and epirubicin (70 mg/m^2) in one day was given every 4 weeks for a total of four courses. Shortly after the fourth course, the child had a second distant lymph node recurrence in the right iliac region, with compression of the right ureter with hydronephrosis, and of the sigma.

[1]Department of Pediatrics, University of Rome "La Sapienza," Rome, Italy; Department of Pediatric Surgery, Hopital Bicetre, Le Kremlin-Bicetre, and Department of Pediatrics, Institute Gustave Roussy, Villejuif, France.

*Correspondence to: Manuel A. Castello, M.D., Department of Pediatrics, University of Rome "La Sapienza," Viale Regina Elena, 324-00161 Rome, Italy.

Received 10 January 1996; accepted 22 February 1996.

For palliation, prolonged administration of etoposide was started. Etoposide (100 mg/m^2/d in a 1-hour infusion for 3 days weekly) was administered for 3 weeks. There was a 1-week interval between courses. The child achieved complete remission after 5 months as shown by abdominal MRI. Etoposide was administered for another 4 months. Open needle biopsy was carried out and histologic examination was negative for neoplastic cells. Etoposide (50 mg/m^2/die/orally) was then administered over a 2-month period on 3 consecutive days weekly for 3 consecutive weeks, with a 1-week interval afterwards. From diagnosis up to the present, the child received a total etoposide dose of 4.7 g.

Etoposide toxicity was very mild, the only reaction being a slight myelosuppression. The child received 3 red blood cell transfusions and 1 platelet transfusion. Chemotherapy was delayed three times for periods ranging from 4 to 7 days. Myelosuppression occurred during the first 2 months of etoposide infusion and seemed to be related to previous chemotherapy. At present, the child is alive without disease 20 months after termination of etoposide therapy. Long-term follow-up is necessary in order to evaluate the possible late toxic or leukemoid effects.

DISCUSSION

Etoposide is a broad-spectrum cytotoxic drug employed in the treatment of many tumors. Optimal dosages and schedules of administration are varied. Etoposide has been shown to be a schedule-dependent drug following preclinical studies on leukemia in L1210 mice [3]. The first clinical study designed to investigate the effect of schedule on response rate showed an increase in response rate in cases of small-cell lung cancer when this drug was administered orally for 3 consecutive days per week, as compared to 1-day intravenous administration [4]. An inconsistency in this study was that the schedule of prolonged administration was oral, whereas the single-dose administration was intravenous.

Slevin et al. [5] documented the superiority of a 5-day schedule of intravenous etoposide (100 mg/m^2 for 5 days) when compared to the same total dose (500 mg/m^2) administered in a 24-hour infusion in patients with small-cell lung cancer. The response rate in patients treated with the single-day schedule was 10%, whereas the group treated with the 5-day schedule obtained a response rate of 89%. A subsequent study with intravenous etoposide showed a similar response rate for an 8-day regimen when compared to a 5-day regimen using the same total etoposide dose; however, myelosuppression was less severe with the 8-day regimen [6]. In an attempt to explain the improved efficacy of the protracted schedule, the pharmacokinetics of etoposide were investigated and it was postulated that the prolonged exposure to relatively low plasmatic concentrations (1 μg/mL) is more important for efficacy than the peak levels (10 g/mL) associated with conventional intravenous administration [7]. Myelosuppression, however, may be dependent on peak etoposide serum levels. In vitro studies using lymphoma and bronchogenic carcinoma cell lines appear to support this hypothesis [8].

A more protracted schedule of administration was also employed in other studies which demonstrated the feasibility of giving oral etoposide for 21 consecutive days at a daily dose of 50 mg/m^2; high response rates were achieved, particularly in small-cell lung cancer. Myelosuppression was the major toxicity and this was dose-limiting [9–11]. Further studies also evaluated the activity and toxicity of a more prolonged schedule of daily low-dose etoposide infusion in adult patients, first in etoposide-sensitive neoplasms (small-cell lung cancer, lymphoma, germ cell tumors), and afterwards in advanced malignancies [12,13]. In one of these studies [13], etoposide (18 to 25 mg/m^2 per day) was administered by continuous intravenous infusion for a period ranging from 15 to 561 days. Antitumor activity was demonstrated with this dose, but only 7 of 40 patients (18%) obtained objective responses. All 7 patients had neoplasms considered to be etoposide-sensitive (lymphoma and small-cell lung cancer).

Three studies on adult patients investigated the efficacy of etoposide in the treatment of advanced soft-tissue sarcomas [14–16]. In the first, etoposide was given at a dose of 130 mg/m^2 orally once a day for 5 days, and repeated every 3 weeks. The authors concluded that etoposide had no significant antitumor activity in pretreated adult patients with soft tissue sarcoma.

In other studies [15,16], etoposide was given orally (150 mg/m^2 for 15 days and 50 mg/m for 21 days every 3 and 4 weeks), and the conclusion was that in a pretreated population of patients with a variety of soft tissue sarcomas, daily oral etoposide, like intermittent bolus etoposide, had little antitumor effect.

In childhood cases, 21-day schedule oral etoposide was administered to 22 patients with relapsed or refractory disease [17]. Three of four soft tissue sarcomas evaluated for response showed stable disease; the remaining one had progressive disease. Palliative effects were documented in 11 of 15 patients who had pain prior to the beginning of therapy. The same etoposide schedule applied in our case was also administered by Phillip et al. [18] in 23 patients with relapsed or refractory soft tissue sarcomas. They reported an overall response rate of 42% in RMS. It could be hypothesized that the lack of efficacy of etoposide in adult soft tissue sarcomas might be due to schedule differences, i.e., every 3 weeks in adults versus every week in children.

Recently, in other phase II studies on oral etoposide conducted in recurrent childhood tumors, protracted ad-

ministration of etoposide was found to be effective in Primitive Neuroectodermal Tumor (PNE)/medulloblastoma, ependymoma and neuroblastoma [19–21]. The outcome or the duration of major response has not yet been reported either in relapsed RMS or in other recurrent childhood cancers.

Our childhood case affected with recurrent RMS of the thigh showed a dramatic complete response with an overall survival of 31 months. This child had previously received one standard intravenous dose of etoposide, but only prolonged divided dose regimen of etoposide was effective in achieving a complete long-lasting remission. At present the child is alive and well without disease, and off therapy for 20 months.

CONCLUSION

Preclinical experience and studies on adults suggest that prolonged divided dose regimen etoposide administration (oral or intravenous) is more effective than the same total amount administered in a single dose. The antitumor effect of this drug seems to be related to the duration of exposure to a low serum level of etoposide. In adult cancers, antitumor activity has been demonstrated against neoplasms considered etoposide-sensitive such as small-cell lung cancer, lymphomas and germ cell tumors, whereas the results of etoposide treatment have been disappointing in pretreated adult patients with relapsed soft tissue sarcomas.

Recently, prolonged etoposide administration in childhood patients has been found to be active in relapsed or refractory RMS as well as in PNET/medulloblastoma, ependymoma and neuroblastoma.

In our case, complete remission was achieved in the two RMS relapses using divided dose regimen of etoposide administered over a period of approximately 11 months. At present, the child is alive and disease-free 20 months after completion of chemotherapy. Therefore, a prolonged divided dose regimen of etoposide may represent an alternative therapy for high-risk cancer patients.

REFERENCES

1. Raney RB Jr, Tefft M, Hays DM, Triche TJ: Rhabdomyosarcoma and the undifferentiated sarcomas. In Pizzo PA, Poplack DG (eds): "Principle and Practice of Pediatric Oncology." Second Edition. Philadelphia: JB Lippincott Company, 1993, pp. 769–794.
2. Maurer HM: The Intergroup Rhabdomyosarcoma Study (N.I.H.): Objectives and clinical staging classification. J Pediatr Surg 10:977–978, 1975.
3. Dombernowsky P, Nissen NI: Schedule dependency of the antileukemic activity of the podophyllotoxin-derivative VP-16213 (NSC-141540) in L1210 leukemia. Acta Pathol Microbiol Scand (A) 81:715–724, 1973.
4. Cavalli F, Sonntag RW, Jungi F et al: VP16-213 monotherapy for remission induction of small-cell lung cancer: A randomized trial using three dosage schedules. Cancer Treat Rep 62:473–475, 1978.
5. Slevin ML, Clark PI, Joel SP et al: A randomized trial to evaluate the effect of schedule on the activity of etoposide in small-cell lung cancer. J Clin Oncol 7:1333–1340, 1989.
6. Slevin ML, Clark PI, Joel SP et al: A randomized trial to examine the effect of a more extended scheduling of etoposide administration in small lung cancer. Proc Am Soc Clin Oncol 8:236, 1989 (abstr).
7. Clark PI, Joel SP, Slevin ML: A pharmacokinetic hypothesis for the clinical efficacy of etoposide in small cell lung cancer. Proc Am Soc Clin Oncol 8:257, 1989 (abstr).
8. Wolff SN, Grosh WW, Prater K, et al: In vitro pharmacodynamic evaluation of VP 16- 213 and implications for chemotherapy. Cancer Chemother Pharmacol 19:246–249, 1987.
9. Hainsworth JD, Johnson DH, Frazier SR et al: Chronic daily administration of oral etoposide—a phase I trial. J Clin Oncol 7:396–401, 1989.
10. Johnson DH, Greco FA, Strupp J et al: Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer: A phase II trial. J Clin Oncol 8:1613–1617, 1990.
11. Clark PI, Cottier B, Joel SP, et al: Prolonged administration of single-agent oral etoposide in patients with untreated small cell lung cancer. Proc Am Soc Clin Oncol 9:226, 1990 (abstr).
12. Thompson DS, Hainsworth JD, Hande KR, et al: Prolonged administration of low-dose, infusional etoposide in patients with etoposide-sensitive neoplasms: A phase I/II study. J Clin Oncol 11:1322–1328, 1993.
13. Thompson DS, Hainsworth JD, Hande KR, et al: Prolonged administration of low-dose infusional etoposide in patients with advanced malignancies. Cancer 73:2824–2831, 1994.
14. Dombernowsky P, Buesa J, Pinedo HM, et al: VP-16 in advanced soft tissue sarcoma: A phase II Study of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer Clin Oncol 23,5:579–580, 1987.
15. Kampe CE, Lowenbaum S, Foster J, et al: Oral etoposide in the treatment of advanced refractory sarcomas. J Natl Cancer Inst 84:1836–1837, 1992.
16. Licht JD, Mazanet R, Loehrer PJ, et al: Phase IV trial of daily etoposide in the treatment of advanced soft-tissue sarcoma. Cancer Chemother Pharmacol 34:79–80, 1994.
17. Davidson A, Lewis I, Pearson ADJ, et al: 21-day schedule oral etoposide in children: A feasibility study. Eur J Cancer 29A, 16:2223–2225, 1993.
18. Phillips MB, Flamant F, Sommelet-Olive D, et al: Phase II study of rapid-scheduled etoposide in paediatric soft tissue sarcomas. Eur J Cancer 31:782–784, 1995.
19. Needle MN, Molley PT, Geyer JR, et al: A phase II evaluation of daily oral etoposide in the treatment of recurrent brain tumours and solid tumors of childhood. Med Pediatr Oncol 25:258, 1995 (Abstr).
20. Grodman H, Kretschmar C, Wolfe L: Activity of daily oral etoposide (E) in children with neural tumors: A preliminary pilot study. Med Pediatr Oncol 25:304, 1995 (Abstr).
21. Cappelli C, Hartmann O, Pein F, et al: Efficacy of palliative oral etoposide (E) in metastatic neuroblastoma (NB) relapsing after high-dose chemotherapy (HDCT). Med Pediatr Oncol 25:319, 1995 (Abstr).