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Epipodophyllotoxins in the treatment of childhood cancer

Gaston K. Rivera[1, 2], **Ching-Hon Pui**[1, 2], **Victor M. Santana**[1, 2], **Charles B. Pratt**[1, 2], **William M. Crist**[1, 2]

[1] Department of Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA
[2] Department of Pediatrics, University of Memphis, College of Medicine, Memphis, Tennessee, USA

Abstract. We reported marked biologic activity with the epipodophyllotoxins in phase I/II studies of childhood cancer conducted in the 1970s. We have since extensively used the combination of teniposide and ara-C in the treatment of acute lymphoblastic leukemia (ALL). Initially we treated patients with refractory disease and found that the combination lacked clinical cross-resistance with standard antileukemic drugs. This formed a rationale to move teniposide and/or etoposide to front-line therapy of childhood ALL. The superior results projected for our last trial, an overall cure rate of about 75%, are attributable in part to early use of epipodophyllotoxins. This class of agents is also used extensively in the treatment of newly diagnosed childhood solid tumors, including neuroblastoma, medulloblastoma, rhabdomyosarcoma, and germ-cell tumors. Secondary leukemias following treatment with epipodophyllotoxins have been reported in a small subset of patients. Current data show that the most important risk factor is the schedule of drug delivery, which has led to appropriate protocol modifications.

Key words: Epipodophyllotoxins – Childhood cancer

Background

The phase I/II studies that introduced the epipodophyllotoxins into the treatment of childhood cancer were conducted at St. Jude Children's Research Hospital from 1973 to 1975. These clinical trials were based on our studies showing the remarkable in vivo cytotoxicity of these agents against murine L1210 leukemia [58]. We reported marked biologic activity for both teniposide (VM-26) and etoposide (VP-16) when used as single agents in a variety of relapsed or refractory malignancies [57]. The significance of these early studies was that within acceptable ranges of acute toxicity (primarily myelosuppression), a new class of agents could induce antitumor responses when established cytotoxic agents were no longer effective. These preliminary findings were confirmed and extended to include complete remissions obtained in studies by the Childrens Cancer Group [3, 7] and other investigators [40] using higher doses of VM-26/VP-16. The excellent antitumor activity of the epipodophyllotoxins in this setting may reflect their mechanisms of action, which differ from those of the drugs used in initial therapy. These agents inhibit the ligase activity of topoisomerase II [8, 71], resulting in protein-associated double-strand DNA breaks as well as sister chromatid exchange [31, 32].

Table 1 depicts the treatment responses observed in the early phase I/II St. Jude trials, which accrued 29 patients with refractory leukemias and 19 with disseminated solid tumors. Note that the doses used were 2- to 3-fold lower than those used currently. The first protocol, designed as a cross-over study, showed that some patients who did not respond to one compound would respond to the other. These findings provided the basis for disease-specific combination chemotherapy protocols in relapsed and, subsequently, newly diagnosed childhood cancers. As with virtually all cytotoxic agents, the epipodophyllotoxins were more effective when combined with other drugs, particularly cytosine arabinoside (ara-C) [58] or methotrexate [81].

In this paper we summarize and reassess the experience with epipodophyllotoxins in the treatment of childhood cancer, with emphasis on the acute leukemias. The role of these agents in inducing second cancers is examined and future directions are suggested.

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Correspondence to: Gaston K. Rivera, Department of Hematology-Oncology, St. Jude Children's Research Hospital, P.O. Box 318, Memphis, TN 38101, USA

Acute lymphoblastic leukemia

The initial trials of epipodophyllotoxins in patients with refractory acute lymphoblastic leukemia (ALL) combined VM-26 with ara-C in the treatment of patients who had had multiple hematologic relapses. The choice of VM-26 rather than VP-16 was largely arbitrary. Unfortunately, randomized studies comparing the efficacy of VM-26 versus VP-16 as single agents or in combination were never conducted. Of 33 patients treated, 10 achieved a complete remission despite prior resistance of their disease to all front-line drugs, including steroids, vincristine, anthracyclines and L-asparaginase [60]. These results were confirmed in adolescent and adult patients with refractory ALL by other investigators who used the same doses and schedules [28, 76].

Table 2 summarizes the results of the early combination chemotherapy trials. The activity shown by VM-26 and ara-C against refractory leukemia suggested that the combination lacked cross-resistance, at least clinically, with the standard antileukemic drugs. This information was used to design a series of secondary protocols for patients with relapsed ALL who had been treated initially on Pediatric Oncology Group (POG) protocols. Approximately half of the 350 children treated with these retrieval regimens were cured [6, 66, 73, 83, 84]. To expand our studies and to determine if VM-26 was synergistic with other commonly used agents, we combined the epipodophyllotoxin with prednisone and vincristine. A complete remission rate of 32% was obtained among 56 children with multiple relapses of ALL [63]. Next, we tested VM-26 in combination with methotrexate as a "therapeutic window" prior to reinduction therapy for relapsed ALL. The rationale for this approach was that intracellular levels of antifolate were augmented by VM-26 in Erlich ascites tumor cells [85], leading to clinical synergism [39]. Investigators from the Southwest Oncology Group later reported significant activity for the combination of VM-26 and ifosfamide in refractory adult ALL [72]. We also found that VP-16 in combination with prednisone and vincristine induced complete remission in patients with relapsed ALL, despite repeated earlier use of steriods and vinca alkaloids [1].

In a pivotal study, we found that patients who did not attain an initial complete remission with multiagent regimens including prednisone, vincristine, daunomycin, and L-asparaginase, with or without ara-C, responded to the ara-C/VM-26 combination. Of the 14 patients treated, 9 obtained a complete remission, providing clinical evidence that effective chemotherapeutic agents with different mechanisms of action could overcome drug resistance [61]. These results were confirmed in POG studies [5, 38].

The first protocol to include epipodophyllotoxins in the treatment of newly diagnosed leukemia was the high-risk arm of St. Jude study X, which accrued patients with ALL from 1979 to 1983. Half of the children enrolled on this study had hyperleukocytosis (WBC, $\geq 100 \times 10^9$/l), a feature historically associated with cure rates of only 20%–25%. The VM-26 plus ara-C combination was used as the sole intensification chemotherapy in an otherwise standard regimen. The cytotoxic effects of eight up-front doses of VM-26 plus ara-C given over 4 weeks prior to induction treatment were so pronounced that the combination had excessive toxicity as "priming therapy." The two drugs alone induced complete remissions in three of the first ten patients treated, but one child died of hyperkalemia secondary to massive tumor lysis and two children died of fungal infections associated with prolonged myelosuppression [56, 64]. The up-front window therapy was reduced to four doses of VM-26 plus ara-C given over 2 weeks, with four additional doses being given as consolidation of early remission after hematopoiesis had been restored with prednisone, vincristine, and L-asparaginase induction therapy. With this modification, the cure rate for these very high-risk patients was approximately doubled [12, 50]. While refining early therapy for high-risk patients with ALL in this and other studies, we encountered serious toxicities, which were addressed by prompt protocol amendments [65].

Our next major research question was based on the Goldie-Coldman hypothesis [19], which suggested that intensive early treatment followed by rapidly rotated drug combinations given as postremission therapy might improve leukemic cell kill. The goal was to prevent development of drug resistance by exposing leukemic blasts to multiagent drug combinations rather than traditional two-drug continuation therapy with 6-mercaptopurine (MP) and methotrexate (MTX). Three or four different combinations were needed to test this hypothesis. The combination studies described above had identified the epipodophyllo-

Table 1. Early phase I/II studies of epipdophyllotoxins in childhood cancer

Patient groups:			
Refractory leukemia [57]	$n = 29$	Advanced solid tumors [57, 59]	$n = 19$
Acute lymphoblastic leukemia	$n = 17$	Neuroblastoma	$n = 13$
Acute myeloblastic leukemia	$n = 12$	Others	$n = 6$

Doses and schedules (twice weekly for 4–6 weeks):
VM-26 50 mg/m² →100 mg/m²
VP-16 75 mg/m² →150 mg/m²

Responses: 9/29 patients with refractory leukemia had profound oncolytic responses, 5 to VP-16 (total dose, 600–1500 mg/m²) and 4 to VM-26 (total dose, 225–800 mg/m²). Of 13 children with disseminated neuroblastoma, 3 attained partial remission in response to VM-26 (total dose, 175–800 mg/m²)

Table 2. Early epipdophyllotoxin combination chemotherapy trials for remission induction in relapsed or refractory childhood ALL

	Patients (n)	Complete remission
Relapsed ALL:		
VM-26 + ara-C [60]	33	27%
VM-26 + Pred + VCR [63]	56	32%
VP-16 + Pred + VCR [1]	46	34%
Refractory ALL:		
VM-26 + ara-C [61]	14	64%
VM-26 + ara-C [38]	26	48%

Pred, prednisone; VCR, vincristine; ara-C, cytarabine

toxins as effective drug pairs, allowing us to design the subsequent St. Jude study for newly diagnosed patients, protocol XI [67]. In study XI, VM-26 plus ara-C and VP-16 plus cyclophosphamide were added to the traditional combination of prednisone plus vincristine and 6-MP plus MTX after remission induction. The rationale to treat each child intensively was that in both poor- and good-risk patients, bone marrow relapse was the principal obstacle to cure. At a median follow-up of 6 years, the 5-year event-free survival (EFS) is 72% (± 4%) – the best results yet achieved in the St. Jude program for newly diagnosed ALL. An overall cure rate of approximately 75% is projected for this study because about half of the children who ended their initial remission with an isolated central nervous system relapse have been salvaged with secondary therapy [68]. We attribute this superior outcome to four factors: (1) early intensification of therapy with VM-26, ara-C, and high-dose MTX (HDMTX), (2) the benefits of intensified postremission chemotherapy with rotations of the four drug pairs selected, (3) delivery of >90% of the planned chemotherapy, and (4) improved supportive care measures.

Non-Hodgkin's lymphoma

Since 1979, we have used regimens similar to those developed for high-risk ALL to treat advanced non-Hodgkin's lymphoma (NHL). The treatment plan of study X produced cures in 20 of 26 patients with stage III/IV lymphoblastic NHL without the use of radiation therapy for bulky disease or the use of anthracyclines [11]. On the basis of these findings, POG investigators incorporated VM-26 plus ara-C into multiagent chemotherapy protocols for advanced lymphoblastic lymphoma and T-cell ALL and also achieved an improved treatment outcome (M. Amylon, personal communication). Interestingly, French investigators have reported that the combination of VP-16 and high-dose ara-C is effective in treating relapsed NHL [18]. We currently treat patients with advanced lymphoblastic lymphoma on the same protocol used for high-risk ALL. Epipodophyllotoxin therapy is also used by European groups in multiagent treatment protocols for patients with advanced B-cell NHL/ALL, and these regimens have markedly improved survival [42, 54].

Acute myeloid leukemia

Unfortunately, modern intensive chemotherapy has not benefitted children with acute mycloid leukemia (AML) to a similar degree as obtained in children with ALL. The activity of VP-16 in phase I/II trials prompted a study in which VP-16 was combined with 5-azacytidine (5-AZ) to treat relapsed AML [62]. The achievement of complete hematologic remission in one-third of these patients [33] provided a rationale for moving this combination into St. Jude study AML-83 for newly diagnosed patients. However, the end results of that study were disappointing [27]. Our subsequent clinical trial, AML-87, tested the pharmacokinetic concept of targeted systemic exposure to VP-16 combined with either ara-C or 5-AZ. This treatment produced a modest cure rate of approximately 30%, similar to the results obtained with conventional chemotherapy dosing [26]. The ongoing AML-91 protocol uses standard dosing strategies to deliver VP-16, ara-C, and daunomycin prior to autologous or allogeneic bone marrow transplantation. Although little is known of the activity of VM-26 against AML, in a study of 37 relapsed patients, VM-26 combined with amsacrine (also a topoisomerase II inhibitor) produced a second remission rate of 43% [35].

Neuroblastoma and other solid tumors

The epipodophyllotoxins are now used in combination therapy for children with newly-diagnosed neuroblastoma, germ-cell tumors, medulloblastoma, rhabdomyosarcoma, and Hodgkin's disease. Our first studies of VM-26 used as a single agent in disseminated, treatment-refractory neuroblastoma showed partial responses in 3 of 13 patients and subjective responses in 9 [59]. The median dose of VM-26 was 600 mg/m^2 (range, 175–800 mg/m^2). These results, reported in 1977, were important because of the limited number of single agents with demonstrated effectiveness in the treatment of disseminated neuroblastoma. Furthermore, they provided the basis for combining epipodophyllotoxins with cisplatin. In vitro studies of bone marrow tumor cells from patients with disseminated neuroblastoma showed synergistic responses to VM-26 and cisplatin, even in samples from patients resistant to treatment with cisplatin alone [22]. Hence, researchers here and at other centers introduced VM-26 into combination chemotherapy protocols [2, 46, 77]. The impact of these changes in the treatment of neuroblastoma was recently reviewed [4]. We believe that the addition of VM-26 or VP-16 was at least partially responsible for improving the treatment outcome.

Since 1988, multiagent chemotherapy with doxorubicin, cyclophosphamide, cisplatin, and VP-16 has been used at St. Jude Children's Research Hospital to treat new patients with advanced neuroblastoma. VP-16 was substituted for VM-26 because early trials showed antitumor effects for both compounds, and VM-26 remained an investigational agent in the United States until very recently. The simultaneous use of hematopoietic growth factors in ongoing combination chemotherapy studies has allowed further escalation of VP-16 to a cumulative dose of 3840 mg/m^2 over a 5-month treatment period. With this approach, we expect to improve the prognosis for these children.

VP-16 has also been actively used in combination chemotherapy for the treatment of a variety of recurrent childhood solid tumors. Most effective appear to be combinations with either cisplatin [45] or ifosfamide [36]. On the basis of these findings, we recently devised a three-drug regimen featuring ifosfamide and targeted doses of carboplatin and VP-16 – the so-called ICE regimen. We are encouraged by the promising responses seen in relapsed pediatric solid tumors such as rhabdomyosarcoma, Ewing's sarcoma, and Wilms' tumor [34]. Another recent use of VP-16 involved the treatment of relapsed tumors with high-dose chemotherapy followed by autologous marrow transplantation. In a pilot study conducted at this center, 26 children were treated with escalating doses of carboplatin

(maximal dose, 2100 mg/m^2) and VP-16 (maximal dose, 1500 mg/m^2); 11 patients achieved a clinical response (1 complete, 10 partial) despite prior treatment with standard-dose cisplatin and/or VP-16 [75]. The responses were mainly seen in children with neuroblastoma (6 of 16) or Hodgkin's disease (2 of 3).

Interestingly, the nonhematopoietic toxicities of the epipodophyllotoxins appear to differ for patients with solid tumors as compared with those with ALL. The grade I–II hypersensitivity reactions to VM-26, seen in patients with ALL, or to VP-16, observed in patients with Hodgkin's disease, are usually reversed rapidly by antihistamines and steroids [24, 29], whereas symptoms may be more severe in children with solid tumors and have included bronchospasm, cyanosis, and hypotension [23].

Secondary leukemias following treatment with epipodophyllotoxins

In 1989, we reported the St. Jude experience with secondary AML in children previously treated for ALL [47, 48], and shortly thereafter we described the potential role of the epipodophyllotoxins in the pathogenesis of secondary AML [49]. Reports implicating VP-16 in the development of therapy-related leukemia in adult patients treated for solid tumors soon followed [43, 52, 53]. The development of secondary AML in adult leukemia patients who had not received epipodophyllotoxins [17] and the occurrence of second malignant neoplasms after treatment for childhood cancer with other agents that target topoisomerase II were also reported in 1989 [13, 37]. Recently we identified four cases of secondary AML with 11q23 and 21q22 chromosomal rearrangements in the absence of prior treatment with epipodophyllotoxins [74] and suggested that other intercalating topoisomerase II inhibitors, when combined with alkylating agents and irradiation, may cause this complication. This association was established recently in a larger study of adults treated for various malignancies [44].

Secondary AML was first identified in patients whose leukemic blasts had new morphologic and biologic features at the time of bone marrow relapse following treatment for ALL. After a latency period of approximately 3 years, these children developed myeloid leukemia, usually classified as FAB M4/M5 in the French-American-British system and characterized by frequent 11q23 abnormalities. Sequential cytogenetics studies of the leukemic blast cells showed a different leukemic stemline. Of 734 consecutive patients with ALL whose treatment at our center included epipodophyllotoxins, 17 developed secondary AML as their first adverse event [47]. The overall cumulative risk for AML at 6 years was 3.8% (95% confidence interval, 2.3%–6.1%). Subsequently, by multivariate analysis we could establish a clear relationship between the schedule of administration of VM-26 or VP-16 and the risk for secondary AML [49], a finding later confirmed by other investigators [78, 82].

Current data show that the most important risk factor for epipodophyllotoxin-related AML in children treated for lymphoid malignancies is not the total dose but the schedule of drug delivery [49, 78]. The cumulative risk for secondary AML according to the schedule of epipodophyllotoxin administration in pediatric patients treated for NHL or ALL is summarized in Table 3. Overall, patients treated twice weekly or weekly with VM-26 or VP-16 have a disturbingly high incidence of secondary AML, whereas those receiving these agents every 15 days have a risk similar to that carried by patients not treated with epipodophyllotoxins. It is also possible that the timing of antimetabolite administration in relation to epipodophyllotoxin therapy is a risk factor, perhaps linked to DNA repair mechanisms [16]. Risk factors related to drug disposition have not been identified despite extensive pharmacodynamics studies [15]. We have been unable to compare the relative carcinogenic effects of VM-26 and VP-16 because our patients treated with VP-16 in the past have also received VM-26.

Table 3. Schedule dependency of epipodophyllotoxin-related secondary leukemia in children initially treated for ALL/NHL[a]

		Cumulative risk at 4–6 years (95% confidence interval)
Induction therapy only:		
Only 3 doses	St. Jude XI, low-risk [49]	0
Postremission therapy:		
Twice weekly q10w	St. Jude X, high-risk [49]	12.3 (5.7–25.4)
Twice weekly q10w	T-8801 [78]	18.4
Twice weekly q5w	Dallas-Fort Worth [82]	5.9 (2.7–9.1)
Weekly × 6 q12w	St. Jude XI, high-risk [49]	12.4 (6.1–24.4)
Every other week × 120 weeks	St. Jude XI, low-risk [49]	0
Every other week × 120 weeks	St. Jude XI, high-risk [49]	1.6 (0.4–6.1)
3–4 days, intermittent	B-8801 [78]	0

[a] Modified from Pui et al. [49]

It is important to note that secondary AMLs in our patients developed instead of rather than in addition to lymphoid hematologic relapses. Furthermore, treatment-related leukemias have not had a negative impact on overall survival. In study XI, the 5-year EFS of patients treated with the higher-risk weekly drug schedule did not differ from that of patients who received the other treatment regimens [69]. To date, 73 of the 85 patients (86%) treated with the weekly schedule have survived past the median time of occurrence of secondary AML.

DNA rearrangements of band 11q23 in the leukemic blasts, usually associated with a dire prognosis, are among the most common chromosomal aberrations in patients with leukemia and have been identified among patients with ALL, AML, and leukemias of ambiguous lineage. Importantly, the 11q23 abnormalities identified in secondary leukemias are molecularly indistinguishable from those of primary disease [25]. Recently, the *MLL* gene (for "mixed-lineage leukemia" or "myeloid-lymphoid leukemia"),

which is apparently critical in the pathogenesis of human leukemias and lymphomas with 11q23 chromosomal abnormalities has been cloned [9]. Researchers have developed DNA probes for the *MLL* gene that can detect rearrangements in DNA in leukemic blasts from any patient with leukemia who has the common 11q23 translocation [80]. It is conceivable that in the future, molecular markers detecting *MLL* abnormalities may permit monitoring of asymptomatic patients at higher risk of developing secondary AML and allow for a more timely therapeutic intervention [10].

Conclusions and future directions

The epipodophyllotoxins have contributed to improved overall cure rates among children with two of the most common pediatric cancers, ALL and neuroblastoma, especially among patients with higher-risk disease [4, 14, 51, 55, 70]. The spectrum of activity of the epipodophyllotoxins is remarkably broad [21, 41], and three recent observations illustrate new possible roles for VP-16. High-dose etoposide given prior to allogeneic bone marrow transplantation has proved particularly effective in adult patients with leukemia in first remission [79], and the provocative responses to prolonged oral VP-16 therapy obtained in patients with advanced malignancies who have often failed treatment with bolus i.v. therapy are encouraging [20]. Finally, ongoing studies demonstrate good central nervous system penetration of VP-16 in children with leukemia, a potentially important feature for successful therapy (M. Relling, personal communication).

The most disturbing complication of epipodophyllotoxin therapy remains the development of secondary leukemias in a small subset of patients. Although the pathogenesis of therapy-related leukemias is not yet well understood, the finding of a striking relationship between risk and frequency of VP-16/VM-26 administration [49] has led to protocol modifications that should decrease the incidence of secondary AML. Paradoxically, one can both treat and induce monoblastic leukemias using the podophyllum compounds. Until less toxic and equally or more effective agents become available, the epipodophyllotoxins will remain mainstays of treatment for high-risk childhood cancer. Another class of topoisomerase II inhibitors, the anthracyclines, are also highly effective anticancer agents and are currently widely used despite their serious long-term major organ toxicity [30]. The experienced therapist must weigh the risks and benefits of a specific chemotherapy regimen for the individual patient and decide whether the associated toxicity is acceptable in relation to the patient's prognosis.

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