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VM26 Therapy in Children with Drug-refractory Lymphocytic Leukemia

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Introduction

Despite modern chemotherapy, about one-half of children treated for acute lymphoblastic leukemia (ALL) will relapse, either during or after the treatment course [2]. The reasons for this circumstance almost always can be traced to the failure of chemotherapy to eradicate or permanently suppress all leukemia cells. This is especially so for patients whose leukemia is biologically disposed to the rapid development of drug resistance. Different combinations and higher dosages of previously used antileukemic drugs will induce new remissions, but these are generally brief, giving way to progressively more resistant disease. At St. Jude Children's Research Hospital, Phase I and II trials of potentially valuable antileukemic agents are conducted in patients with drug refractory lymphocytic leukemias. We report here a series of such investigations with the podophyllum compound VM26 (see Table 1), a semisynthetic derivative of the May-apple plant (*Podophyllum peltatum*). First used in clinical trials in the early 1970's [4, 9], VM26 has major cytotoxic activity in mitosis [17] as well as the premitotic interval [8] of the cell cycle. The oncolytic effects of this compound and its congener, VP16-213, were assessed in a preliminary study in patients with advanced unresponsive leukemia who had experienced multiple bone marrow relapses.

Patients, Methods, and Results

Phase I/II Studies. As single agents, the epipodophyllotoxins induced objective responses in 9 of 29 children evaluated; most important, they were effective after established drugs had lost any demonstrable oncolytic activity. In responding patients, rapid reductions in leukocyte counts of 80% or more with clearing of circulating lymphoblasts and a decrease in the proportion of bone marrow lymphoblasts (> 50%), as well as disappearance of large tumor masses or malignant effusions, were observed. These results, defined as "oncolytic responses", provided evidence of a rapid antileukemic effect. However, with this single-drug therapy, no complete marrow remissions were induced. In addition to providing a clear indication that this new class of agents was active in children with refractory lymphocytic leukemia, the initial trials demonstrated that the epipodophyllotoxins could be administered without producing prohibitive toxicity. Myelosuppression was the most pronounced side effect produced by either VM26 or VP16-213 but, in general, was no more severe from that induced by most other antileukemic drugs [10]. Bleyer et al. [1] reported similar results in subsequent Phase II studies.

Table 1. Clinical trials of VM26 in childhood leukemia (1973–1980)

Treatment	No. of patients	Clinical status of leukemia	Responses	CR
VM26 (or VP16-213)	29	Advanced	9 (0.31)	0
VM26 + ara-C	33	Advanced	10 (0.30)	9 (0.27)
VM26 + ara-C	26	Second remission	Median 7 months	
VM26 + ara-C	14	Induction failures	9 (0.64)	9 (0.64)
VM26 + P + VCR	53	Advanced	26 (0.49)	17 (0.32)

CR: complete remission; P: prednisone; VCR: vincristine

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Results

Early Results of Combination Chemotherapy

As with most drugs, the epipodophyllotoxins have increased antitumor effects when used in combination. In animal studies with L1210 murine leukemia, performed at our institution, VM26 and cytosine arabinoside (ara-C) acted synergistically in curing or extending the life-spans of leukemic mice [11]. By analysis of variance, the basis of the enhanced effect appeared to be a potentiation of ara-C activity by VM26; this information, together with the performance of the podophyllotoxin in Phase I studies, formed a rationale for using combinations of the two agents in patients with ALL for whom all other therapeutic possibilities had been exhausted.

The regimen was given initially to 33 children with multiple hematologic relapses [14]. Because there was inadequate information on the use of VM26 in combination chemotherapy for human subjects, the treatment design incorporated five increasing dosages of VM26 (50, 75, 110, 165, or 200 mg/m^2/dose) combined with a constant dosage of ara-C (300 mg/m^2/dose). Each dosage combination was given twice a week for 4 weeks (total of 8 doses). The initial dosage of VM26 50 mg/m^2/dose, furnished a base of comparison for results of the previous single-drug study. The podophyllum compound was administered in 30- to 45-min i.v. infusions at a concentration of 1 mg/ml in a solution of 5% glucose and normal saline ($\frac{1}{3}$ dilution) to prevent crystallization. Cytosine arabinoside was diluted to a final concentration of 50 mg/ml and administered by rapid i.v. injection immediately after the VM26 infusion. No other antileukemic drugs were used for remission induction; antimicrobial agents, transfusions or blood products and general supportive care were provided as required.

Ten of the 33 patients attained remissions (nine complete and one partial). Of the 23 non-responders, nine could not complete the study owing to their debilitated physical condition. Drug-induced toxicity was noted over the full range of VM26 dosage; again myelosuppression was the most frequent and most severe side effect observed. It occurred at each level of dosage, but was most prolonged at 200 mg/m^2, with 3 rather than 2 weeks required for hematologic recovery.

An optimally effective dosage of VM26 for combination with ara-C was not clearly established by this study; instead, remissions were induced over the entire range of podophyllotoxin dosage (total dosages of 325–1,320 mg/m^2 vs 400–1,600 mg/m^2 for patients who failed to respond). Because the independent contribution by VM26 in combination therapy is likely to be dosage dependent, we suggest that the drug be used at maximally tolerated dosage. In view of the more protracted myelosuppression after treatment with 200 mg/m^2, that dosage appears to be equal to or greater than 165 mg/m^2 but less than 200 mg/m^2.

This trial demonstrated that combinations of VM26 and ara-C will induce complete remissions in a relatively high proportion of children with drug-refractory leukemia. Significantly, since seven of ten responders had received ara-C before in other drug combinations, its prior use did not appear to diminish the effectiveness of the combination. Explanations for the therapeutic efficacy of this combination are still being sought, but from available evidence our working hypothesis is that oncolytic contributions are made by each of the drugs with ara-C activity being potentiated by VM26.

Clinical studies to evaluate potentially useful antileukemic drugs have undergone major changes over the past 15 years. For example, when vincristine and daunomycin were first studied, the median duration of complete remissions was only about 1 year and prior chemotherapy was limited to only a few effective agents [7, 18]. In some instances, moreover, children who received these drugs were previously untreated [6]. The patients admitted to this trial, by contrast, had shown clinical resistance to all first-line chemotherapy, including prednisone, vincristine, daunomycin and asparaginase. Therefore, the induction of complete responses in about one-third of these children was encouraging, especially when one considers that ten patients did not complete a full course of therapy and may have become responders had they been treated under more favorable circumstances.

In earlier evaluations of VM26 and VP16-213, neither compound proved therapeutically superior to the other, their toxic effects were comparable, and both appeared to potentiate responses to ara-C in mice. Hence, the selection of VM26 for combined drug treatment of ALL was arbitrary and should not be construed as indicating any superiority of this agent over its congener.

VM26 and ara-C as Consolidation Therapy

A particularly difficult group of patients to treat are children who after an initial bone marrow relapse during therapy attain second remission. Generally, these remissions are short-lived and many therapeutic efforts to prolong their duration have been unsuccessful [3, 5, 12]. A comparative study was therefore

designed to determine if a brief intensive treatment with VM26 plus ara-C, after the reinduction of remission, would extend the duration of second hematologic remission in childhood ALL [16]. To test this hypothesis, at the date of second remission we randomized patients to receive or not to receive four doses of VM26 (165 mg/m^2) and ara-C (300 mg/m^2) over 2 weeks. Both treatment groups were comparable with respect to (i) prognostic features at diagnosis, (ii) development of a first marrow relapse during a similar initial treatment, and (iii) length of first marrow remission. In addition, all patients received identical reinduction therapy (prednisone, vincristine, daunomycin) and continuation therapy (weekly i.v. injections of vincristine and cyclophosphamide for 30 months plus intrathecal chemotherapy every 6 weeks). Thirty patients were randomized not to receive VM26 plus ara-C, and their median duration of second remission was 3 months (1−16 months). Only seven of 30 had prolonged second remissions (> 6 months) and none were taken off chemotherapy. By comparison, 26 children were randomized to receive VM26 + ara-C consolidation treatment, and their median duration of second remission was 7 months (2−47+ months), a significantly longer interval ($P = 0.04$) by logrank analysis. In this group, 14 of 26 children had prolonged second remissions and two are now off therapy, for 20+ and 22+ months, respectively, after successfully completing 30 months of continuation treatment. Reversible myelosuppression but no other untoward effects was observed in 25 of 26 patients treated with VM26 and ara-C. Analysis of selected patient variables in this study indicated a clear correlation of early VM26 + ara-C therapy with length of second remission. We concluded, then, that VM26 + ara-C significantly extended the duration of second remissions. Furthermore, in two of these patients, treatments were electively stopped, an unusual event following a marrow relapse on therapy.

VM26 and ara-C for Induction Failures

Lastly, a study was conducted in patients with ALL who failed to respond to initial induction therapy (induction failures) [15]. There were 14 newly diagnosed patients who did not attain remission following 6−12 weeks of treatment with prednisone, vincristine, daunomycin and asparaginase with or without ara-C. Nine of these patients had high-risk features at diagnosis, six had leukocyte counts exceeding 100,000 cells/mm^3, six had early CNS leukemia and five had E-rosette positive lymphoblasts. However, despite the presenting clinical and laboratory findings, each of the 14 patients had not attained an initial remission and consequently had a dire prognosis. The treatment plan for this group consisted of 4 weeks of combination chemotherapy with VM26 at 165 mg/m^2/dose and ara-C 300 mg/m^2/dose twice weekly. Three children did not respond and died, two responded but did not attain remission and likewise died, and nine attained complete remission. Of these nine patients, five had clinical high-risk features at diagnosis, three had T-cell leukemia and six had received previous ara-C therapy. Three of the nine responders are still in remission, two off therapy for 26+ months and surviving 5 years after diagnosis. In this study, the complete remission rate was 64%, providing firm evidence that the effectiveness of the drug combination could be extended to newly diagnosed unresponsive patients.

VM26, Prednisone and Vincristine Combination

To further exploit its therapeutic potential, we combined VM26 with prednisone and vincristine [13]. Only patients in relapse who repeatedly had received prednisone and vincristine were studied; the objective was to determine if drug synergism could be elicited with agents other than ara-C. Fifty-three patients with equally refractory lymphocytic leukemia were studied; 26 children responded to therapy with 17 attaining complete marrow remission. These results indicated that responses to VM26 therapy did not depend on the drug's combination with ara-C and, indirectly, provided evidence to suggest that clinical resistance to a compound or combination of compounds may be overcome by adding an effective new drug such as VM26 that has pronounced oncolytic activity and a different mechanism of antitumor activity.

Conclusion

The information from these trials should aid in the design of future treatment strategies for leukemia patients at high risk of early relapse. Since VM26 in combination chemotherapy effectively destroyed populations of leukemia cells not susceptible to the cytotoxic activity of conventional agents, its most important future role may be in alternate remission induction treatments or perhaps as an added component of primary treatments.

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