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Letter to the Editor

High-dose Ara-C plus VM-26 in Adult Acute Lymphoblastic Leukemia

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DESPITE high initial response rates, the cure of adult patients with acute lymphoblastic leukemia (ALL) remains elusive, as does effective treatment for those ALL patients with refractory or relapsed disease. Cytosine arabinoside (Ara-C) has been shown to be a useful agent in adult ALL, both at conventional doses (100-200 mg/m^2/day) and at very high doses (3 g/m^2 every 12 hr) [1-4]. Ara-C is capable of promoting leukemia cells out of a resting phase and into active cell cycling, thereby increasing their susceptibility to other cell cycle phase-specific chemotherapy agents [5]. A new such agent is teniposide (VM-26), a semisynthetic epipodophyllotoxin which has major cytotoxic activity in the G_2 and M phases of the cell cycle [6]. It has been shown to have activity against childhood ALL both alone and in combination with Ara-C in conventional doses [7, 8].

We have combined a 6-day high-dose Ara-C regimen with two weekly doses of VM-26 to treat five adults with refractory or relapsed ALL. Four had previously had a complete response to initial treatment using vincristine, prednisone and daunorubicin, but the duration of these remissions ranged from only 3 to 12 weeks. One had twice previously received Ara-C at 200 mg/m^2/day for 5 days with 6-thioguanine and daunorubicin and attained a complete remission; a second remission was later achieved with vincristine and prednisone. The fifth patient had not had a response to 5 weeks of vincristine-prednisone-daunorubicin induction therapy prior to entering this study. None of these patients had received intrathecal methotrexate or cranial irradiation. All patients had a performance status $\geq$70 (Karnofsky) at the time of treatment.

High-dose preservative-free Ara-C (3 g/m^2 every 12 hr) was given for 12 doses as a 60- to 75-min intravenous infusion. VM-26 (100 mg/m^2) was given as a 1-hr intravenous infusion immediately following bone marrow examinations on days 7 and 14. Two patients received a second course of high-dose Ara-C and VM-26, so that seven courses of therapy were evaluable.

During treatment the patients' bone marrows were examined weekly with an aspirate and core biopsy. The marrow cellularity and fraction of leukemic blast cells are shown in Table 1. During five of the seven treatment courses the marrow was already significantly hypocellular on day 7 prior to the first dose of VM-26; three cases were <5% cellular and two were 10-15% cellular. In four of these five cases residual lymphoblasts were present in the hypocellular marrow prior to the first dose of VM-26 on day 7, but in two cases these lymphoblasts were no longer observed prior to the second dose of VM-26 on day 14. In a third case small clusters of immature cells, which were interpreted as residual leukemia, were also seen on day 14 prior to the second dose of VM-26. In four of the five patients with hypocellular marrows on day 7, normal marrow regeneration followed, and a complete marrow remission was achieved. In the fifth case (No. 3015), although 65% of the nucleated marrow cells present on day 14 were lymphoblasts, no residual leukemia was identified in subsequent marrow exams on days 28 and 60, despite no further therapy after the second dose of VM-26 on day 14. This patient eventually died of infection on day 64, with a hypoplastic but regenerating marrow.

Complete hematologic remissions were

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Table 1. *Response to treatment with high-dose Ara-C plus VM-26*

Patient No.	Age/sex	Course No.	Bone marrow cellularity and percentage of leukemic blasts: Pretreatment	Day 7	Day 14	Day 28	Day 42	Response	Duration
3007	22 M	I	85 (66)*	<5(50)	<5(5)	70(0)		CR	3 weeks
		II	80 (5) liver (+)	<5(10)	<5(0)	10(0)	50(0)	CR (marrow) liver (+)	33 weeks†
3010	52 F	I	20 (-)‡ CSF (+)	<5(-)‡	<5(0)	20(0)		CR CSF (-)	17 weeks
3013	28 M	I	50 (52)	15(2)	<5(0)	35(0)		CR	7 weeks
		II	90 (89)	50(93)				died day 12 (sepsis)	
3015	22 F	I	40 (15)	10(67)	20(65)	5(0)	5(0)§	died day 64 (pneumonia)	
3016	49 F	I	50 (80)	30(47)	30(62)	ND		NR	

ND = not done; CR = complete remission; NR = no remission; CSF = cerebrospinal fluid.
*Lymphoblasts as a percentage of nucleated marrow cells.
†Patient received maintenance chemotherapy; a third liver biopsy had no leukemic infiltrate.
‡Not evaluable due to extensive marrow necrosis.
§Bone marrow exam on day 60.

achieved within 28, 29 and 33 days, but these remissions were of short duration (3–33 weeks). Two of these patients later received a second course of high-dose Ara-C and VM-26. One (No. 3013) died of septic shock on day 12; no significant anti-leukemic effect was observed in his day 7 marrow. A second patient (No. 3007) was re-treated after a leukemic infiltrate was identified in a percutaneous liver biopsy as well as in the marrow. After treatment there was persistent ALL in a second liver biopsy, although the marrow had returned to normal. With further chemotherapy this patient remained in remission for 33 weeks, and his liver was subsequently noted to be free from leukemia on a later biopsy. The single patient (No. 3010) who had had lymphoblasts present in the cerebrospinal fluid (CSF) prior to high-dose Ara-C and VM-26 was found to have normal CSF after treatment.

No cerebellar toxicity or ocular toxicity was observed. There was no significant pulmonary, skin or hepatic toxicity due to Ara-C, nor was hypotension during VM-26 infusion noted. Diarrhea was common but not severe. Prolonged myelosuppression was noted in one case and may have contributed to this patient's death from pulmonary infection. Immunosuppression was marked. There were three episodes of bacteremia during periods of severe granulocytopenia in these heavily pretreated patients.

In summary, we have safely escalated the dose of Ara-C and combined it with two doses of VM-26 to treat patients with adult ALL, with good clinical results. An obvious anti-leukemic effect could be observed immediately after the conclusion of the Ara-C therapy, and this treatment alone may have been sufficient to induce remission. However, at least two patients appeared to benefit specifically from the VM-26 therapy, as residual lymphoblasts observed in the marrow on the day of the second VM-26 dose were no longer present 2 weeks later. If such therapy proves useful in patients with refractory or relapsed ALL, it could be incorporated into intensive consolidation schedules for adults with ALL in first remission with the intent of increasing the duration of remissions and the fraction of patients who may be cured.

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