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Short communication

High-dose VP-16 with intermediate-dose cytosine arabinoside in the treatment of relapsed acute nonlymphocytic leukemia

Hon Y. Chan, Frederick J. Meyers, and Jerry P. Lewis

Department of Internal Medicine, Division of Hematology and Oncology, University of California, Davis Medical Center, 4301 X Street, Sacramento, CA 95817, USA

Summary. In a study of 11 adult patients with acute nonlymphocytic leukemia (ANLL), infusion therapy with high-dose VP-16 and intermediate-dose cytosine arabinoside was administered. Response was assessed with reference to bone marrow aspirations performed on days 1; 12, 13, or 14; and 21 of treatment. All 7 of the patients with ANLL in relapse achieved marrow hypoplasia, and 3 of them achieved complete response. LFTs were elevated in most patients but no evidence of hepatocellular necrosis was observed. It is concluded that the value of VP-16 in ANLL may have been underestimated in the past because of inadequate dosing.

Introduction

Most patients with adult acute nonlymphocytic leukemia (ANLL) who obtain a complete remission (CR) will relapse within 5 years [2]. Retreatment of relapsed ANLL with conventional regimens yields a CR rate of 25%–40%. Second remissions tend to be short, with median survivals of generally less than 6 months. Using regimens with cytosine arabinoside (Ara-C) in high doses of 3 g/m^2 every 12 h alone or in combination with daunorubicin, a CR rate of 65% has been reported at the price of severe toxicity [1]. A study by van Prooijen et al. [5], showed that similar therapeutic results with less severe toxicity can be achieved with intermediate dose Ara-C at 500 mg/m^2 every 12 h. VP-16 as a single agent has also demonstrated activity in treating ANLL.

Recent phase I-II trials of VP-16 have shown that the dose of VP-16 as a single agent can be escalated to 1200 mg/m^2 [3]. Therefore, we initiated a regimen combining intermediate-dose Ara-C and an escalated dose of VP-16 in patients with relapsed ANLL.

Materials and methods

Between April 1985 and April 1986, 11 patients were entered into the study (Table 1). Therapy consisted of VP-16 200 mg/m^2 i.v. as a 1-h infusion daily for 4 days and Ara-C 500 mg/m^2 i.v. as a 1-h infusion every 12 h for 12 doses. Patients were evaluated for both response and toxicity. Failures were classified as recommended by Preisler [4]. Bone marrow aspirations were done on day 1, between day 12 and day 14, and on day 21 to assess response.

Results

Table 1 summarizes treatment responses. Three of the seven patients with ANLL in relapse achieved CR, with the longest response lasting 13 months. There were no type 1 failures among these patients, that is all seven achieved marrow hypoplasia.

The regimen was well tolerated, with minimal nausea and vomiting during treatment. Elevated liver function tests (LFTs) were seen in nine of the 11 patients and were noted between 1 and 4 weeks after the initiation of chemotherapy (Table 1). The most common abnormality seen was an elevated total bilirubin which occurred in seven patients. The values ranged from 3 to 26 mg/dl. Autopsy results were obtained in three patients who had significantly elevated LFTs. One had disseminated fungal disease, one had passive liver congestion from congestive heart failure, and one had no demonstrable hepatocellular abnormality.

Discussion

High-dose VP-16 and intermediate-dose Ara-C can be effective in treating ANLL in relapse. Elevated LFTs are commonly seen, particularly an isolated elevation of serum bilirubin, but no evidence of hepatocellular necrosis was observed. The high dose of VP-16 used in this study is safe. The true value of VP-16 in ANLL may be underestimated because of inadequate dosing. Future trials should incorporate similar dose schemes.

Offprint requests to: Frederick J. Meyers

Abbreviations: ANLL, acute nonlymphocytic leukemia; CGL, chronic granulocytic leukemia; DNR, daunorubicin; VNC, vincristine; ID Ara-C, intermediate-dose Ara-C (500 mg/m^2 for 12 doses); HD Ara-C, high-dose Ara-C (3 g/m^2 for 12 doses); SGGT, serum glutamic transaminase; LDH, lactic dehydrogenase; SGOT, serum glutamic oxaloacetic transaminase

Table 1. Patients, treatment and responses

Pt.	Sex/age (years)	Diagnosis	Previous treatment	Response To current regimen	Duration (months)	Abnormal liver function tests
1	F/67	ANLL FAB M4	DAT and two consolidations ID Ara-C + DNR + VNC	CR	13	
2	M/44	ANLL FAB M2	DAT + three consolidations	Type 2 failure		
3	F/31	ANLL FAB M2	DAT + one consolidation ID Ara-C + DNR + VNC	CR	1[a]	Total bilirubin
4	M/74	ANLL FAB M2	DAT + three consolidations	Type 2 failure		Total bilirubin
5	M/30	ANLL FAB M2	DAT + three consolidations	CR	2	SGGT, LDH
6	F/56	ANLL FAB M4	DAT + two consolidations	Type 4 failure		Alkaline phosphatase, SGOT, total bilirubin, SGGT, LDH
7	M/63	ANLL FAB M1	DAT + six consolidations HD Ara-C × 1 ID Ara-C × 3	Type 2 failure		
8	M/67	ANLL FAB M4 secondary to thio-TEPA	None	Type 4 failure		Total bilirubin, SGGT
9	M/35	CGL in blast crisis	Busulfan Prednisone	Type 1 failure		Alkaline phosphatase, total bilirubin
10	F/38	CGL in blast crisis	Hydroxyurea Mithramycin	Type 4 failure		Alkaline phosphatase, SGOT, total bilirubin, SGGT, LDH
11	M/55	ANLL evolved from P. vera with myelofibrosis	None	Type 2 failure		Total bilirubin, SGGT

ANLL, acute nonlymphocytic leukemia; CGL, chronic granulocytic leukemia; Ara-C, cytosine arabinoside; DAT, diacetylthiamine; DNR, daunoribicin; VNC, vincristine; HD, high-dose; ID, intermediate-dose; LDH, lactic dehydrogenase; SGGT, serum transaminase; SGOT, serum glutamic oxaloacetic transaminase

[a] Patient died of sepsis during 1st consolidation

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