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Treatment of the Lymphoid Blast Crisis of Chronic Myeloid Leukemia

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Abstract—*Ten patients with lymphoid-type blast crisis of chronic myeloid leukemia were treated with combination chemotherapy comprising doxorubicin, vincristine, L-asparaginase, and prednisone. Once remission was achieved in* 9 (90%), *consolidation with doxorubicin, vincristine and cyclophosphamide was given, and then maintenance chemotherapy with* 6*-mercaptopurine and methotrexate. Median remission duration was* 12 *months* (*range* 2–18) *and survival* 17 (*range* 3–29). *Drug-related toxicity was manageable, leading to a major schedule alteration in* 3 *cases. These data suggest that combination chemotherapy including doxorubicin improves the prognosis of lymphoid blast crisis in chronic myeloid leukemia.*

INTRODUCTION

CHRONIC myeloid leukemia (CML) usually terminates in an acute blastic phase of either myeloid (70%) or lymphoid (LB-CML, 30%) type. The results of therapy for this phase of CML are universally very poor, with survival being measured in weeks [1]. An advantage in terms of induction of remission, albeit of short duration, in favor of patients with lymphoid type has been observed using vincristine and prednisone [2–5]. Recent experience with a relatively intensive regimen comprising doxorubicin, L-asparaginase (ASP), cyclophosphamide (CY), vincristine (VCR) and prednisolone (PDN) in adult acute lymphoblastic leukemia (ALL) has been encouraging [6]. It was therefore decided to treat patients with LB-CML with the same regimen.

PATIENTS AND METHODS

Patient details

Ten patients who developed LB-CML after a chronic phase (Table 1) form the basis of the study. In each case the Philadelphia chromosome had been detected prior to the acute transformation, but no further cytogenetic study was carried out. Blast cells represented at least 30 and 70% of the total white cells in the peripheral blood and bone marrow smears, respectively. The cells had morphological and cytochemical features of undifferentiated L_2 blasts according to the F.A.B. classification for acute leukemia [7]. Surface marker analysis with monoclonal antisera and immunofluorescence staining for the nuclear terminal transferase (TdT) were performed in cases 2–9, and showed intense positivity for the 'common'—ALL antigen, HLA–DR and TdT determinants in the vast majority of blast cells.

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Treatment regimen

Details of the protocol are published elsewhere [6]. This was derived from the HEAV'D regimen [8] and consisted of an induction phase (Course 1: doxorubicin 30 mg/m^2 i.v. and VCR 2 mg i.v. day 1; ASP 10,000 IU/m^2 i.v. days 1–14; PDN 40 mg/m^2 i.v. days 1–21, then tapered.

Course 2: doxorubicin 25 mg/m^2 and VCR 2 mg i.v. day 21 or 28) followed by 4 consolidation courses (Courses 3 and 4: doxorubicin 25 mg/m^2 i.v. days 1–3; VCR 2 mg and CY 500 mg/m^2 i.v. day 2. Courses 5 and 6: doxorubicin 40 mg/m^2 i.v. day 1 and 30 mg/m^2 days days 2, 3; VCR 2 mg and CY 750 mg/m^2 i.v. day 2), and maintenance chemotherapy with oral 6-mercaptopurine (75 mg daily) and i.m. methotrexate (30 mg weekly). Central nervous system (CNS) prophylaxis with intrathecal 12.5 mg methotrexate and cranio-spinal irradiation (2400 rads) started as the peripheral blood was cleared of blasts. Supportive care was delivered as detailed [6].

Table 1. Clinical details of patients at presentation and outcome of treatment

Patient No.	Age/sex	Duration chronic phase (months)	Physical findings	Remission(s) duration (months)	Survival (months)	Notes
1	29 M	3	Splenomegaly	11,10,3.5	29	Remissions with HEAV'D-derived regimen.
2	21 M	32	None	18	19+	—
3	29 M	4	Hepatosplenomegaly	14	15+	—
4	50 F	35	Hepatosplenomegaly	9	11	ASP withdrawn day 6. No CY given. One further doxorubicin infusion after course 2.
5	43 F	35	Hepatosplenomegaly	16	17	Doxorubicin reduced to one day courses 3–6.
6	26 M	3	Splenomegaly	12*,5,4	22	ASP withdrawn day 3. Doxorubicin reduced courses 3–4, then COAP (×3).
7	35 F	60	Hepatosplenomegaly	—	—	Fatal cytomegalovirus pneumonia after course 2.
8	30 F	40	None	10+	11+	—
9	48 F	108	Hepatosplenomegaly	12	17	No CY given, reduced doxorubicin courses 3–6.
10	53 F	36	None	2+	3+	Severe liver dysfunction following ASP.

*Isolated CNS relapse.

Response to treatment

Achievement of remission required the patient to have no clinical evidence of disease, with a hemoglobin concentration of greater than 12 g/dl, platelets greater than 150×10^9/l and no blast cells in the peripheral blood; and the bone marrow to be normocellular or hypercellular consistent with chronic phase CML, and have less than 5% blast cells [2].

RESULTS

Nine out of 10 patients entered remission (duration 2–18 months, median 12). Seven patients have relapsed after 9, 11, 12, 12, 14, 16 and 18 months (5 bone marrow and 1 CNS), and 2 remain in remission at 2 and 10 months. A second remission was achieved in 2 of the patients who relapsed and, notably, 1 patient experienced 3 remissions with the same regimen (cumulative duration 24 months, Table 1). The survival from the onset of blastic transformation ranged from 3 to 29 months (median 17). In 2 cases ASP was withdrawn after a few days because of hyperglycemia and liver dysfunction. A moderate to severe degree of drug-related cytopenia developed in all cases, but there was only 1 early death. Two patients (cases 4 and 9) who had a particularly prolonged cytopenic phase were subsequently treated with a modified regimen without CY and reduced doxorubicin prior to commencing the maintenance phase. Five of the remaining patients received the full treatment program, and the other 2 received reduced doxorubicin for courses 3–6 (cases 5 and 6).

DISCUSSION

Once CML has progressed to blastic transformation, the outcome is inevitably fatal. Given that curative treatment is not available at present, a realistic goal would be to achieve temporary remission with as little toxicity as possible. The combination of VCR and PDN for the treatment of LB-CML certainly meets these criteria, although the results are inferior to those achieved in ALL [1–5]. The addition of other drugs to VCR and PDN has seldom been exploited in LB-CML, and then only marginally better results have been obtained [9–11] (see also Table 2).

Our preliminary data, in agreement with those recently reported by de Witte *et al.* [12], suggest that, by intensifying the treatment regimen, it is possible to achieve improved results in LB-CML with acceptable toxicity. In view of the clearly superior remission rates in adult ALL when an anthracyclin drug is added to the induction regimen [13], the results in this study are not unexpected. However, it should be mentioned that severe toxicity due to L-asparaginase was observed in 3 out of 10 patients. Thus, we cannot recommend its inclusion into an aggressive protocol for LB-CML, considering also the uncertain therapeutic advantage prod-

Table 2. Comparative results of treatment for LB-CML

Author (year)	No. of cases	Treatment	Remission No.(%)	Duration in months Median	(Range)	Survival in months Median	(Range)
Marks (1978)	13	VCR+PDN	8 (62)	5	(1.5–18)	NR	
Janossy (1979)	11	VCR+PDN± ASP	9 (82)	5	(2–15+)	8	(4–15+)
Griffin (1983)	11	VCR+PDN	6 (55)	NR		7	(1–15+)
Jain (1983)	15	L10/L10M Chemotherapy	10 (66)	7.5	(2–20)	15.7	(2–26)
Haines (1984)	8	+ autografting	NR*			6.5	(0.5–38)
de Witte (1986)	7	HOVON 1982 HEAV'D-derived	7 (100)	15	(5–37+)	15	NR
Present study	10		9 (90)	12	(6–18)	17	(3–29)

NR = not reported.
NR* = criteria for remission not reported (all 8 cases evaluated).

uced by the drug. In conclusion, a relatively intensive approach to the treatment of LB-CML has brought about a high remission rate of worthwhile duration in the limited number of patients so far entered into the study.

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