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High-Dose Cytosine Arabinoside and Idarubicin Treatment of Chronic Myeloid Leukemia in Myeloid Blast Crisis

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Chronic myeloid leukemia in myeloid blast crisis (CML-MBC) is highly resistant to standard induction chemotherapy regimens. Anecdotal results from previous clinical trials support the concept of dose escalation in patients with CML-MBC. Eight patients with CML-MBC were treated with cytosine arabinoside (Ara-C) 1.5–3.0 g/m^2 intravenously over 1 hr every 12 hr for 12 doses and idarubicin 12 mg/m^2 intravenously daily for 3 days. Sixteen previous reports describing the use of Ara-C-based chemotherapy regimens in patients with CML-MBC were also reviewed. Our patients' median age was 62 years (range, 42–69 years). One patient achieved complete hematologic remission (95% confidence interval, 0.3%, 53%).

The median survival for our patients was 7.3 months. These results were not different from previous published reports using Ara-C-based chemotherapy regimens to treat CML-MBC. In summary, the combination of high-dose Ara-C and idarubicin did not improve the overall prognosis of patients with CML-MBC. Innovative approaches need to be explored for this patient population. Am. J. Hematol. 67:119–124, 2001.

Key words: chronic myeloid leukemia; myeloid blast crisis; treatment; cytosine arabinoside; idarubicin; outcome

INTRODUCTION

Chronic myeloid leukemia in myeloid blast crisis (CML-MBC) is a highly resistant disease. A variety of chemotherapy regimens have been studied in clinical trials [1–24]; some regimens have included cytosine arabinoside (Ara-C) in an assortment of doses. Most trials yielded low complete remission rates and short disease-free survival (DFS) in responders, as well as short overall survival. Of note, in one study responses occurred only in patients who received at least 12 g/m^2 (total dose) of Ara-C [14]. Interestingly, three of five responders to high dose Ara-C received 15–18 g/m^2 of Ara-C. Further, mitoxantrone dose, in combination with intermediate dose Ara-C, was escalated during induction therapy up to 80 mg/m^2, and responses were seen only in the cohort of patients who received the higher doses of mitoxantrone [12]. These data suggested that higher doses of chemotherapy may be beneficial for patients with CML-MBC.

At Roswell Park Cancer Institute (RPCI) we have recently completed a clinical trial for patients with newly diagnosed untreated acute myeloid leukemia (AML), using high-dose Ara-C with full-dose idarubicin, followed by growth factor support as a remission induction regimen. The overall remission rate was 74% for de novo AML patients and 38% for secondary AML patients [25]. Because of the beneficial effect of higher doses of Ara-C in AML patients [25–27], the presence of a steep dose–response curve for Ara-C in experimental tumor systems [28,29], and the fact that dose escalation appears to be important in CML-MBC [14], we have studied this regimen in patients with CML-MBC.

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MATERIALS AND METHODS

Patients

Eight patients with CML-MBC were treated at RPCI in a pilot study between June 1994 and August 1998. Patients were not excluded because of age, performance status, or prior treatment in chronic and accelerated phases. This regimen was the initial treatment for CML-MBC for all patients. Studies were approved by the RPCI Institutional Review Board. Informed consent was obtained from all patients.

Patients were extensively evaluated prior to treatment. To define the cellular characteristics of the blast cells, bone marrow smears were stained with Wright-Giemsa, myeloperoxidase, Sudan black B, chloroacetate esterase, and α-naphthyl butyrate [30]. The definition of CML-MBC was determined by the presence of >30% blasts in the bone marrow [31]. Pretreatment bone marrow cells were immunophenotyped by multiparameter flow cytometry using panels of three monoclonal antibodies, as previously described [32]. Cases were called antigen positive if the antigen was expressed on ≥10% of the gated cells and if expression on the surface of the cells in the abnormal population was confirmed by visual analysis. For cytogenetic analyses, bone marrow samples were processed using short-term unstimulated cultures (24–72 hr). Clonality criteria and descriptions of chromosome aberrations were according to the International System for Human Cytogenetic Nomenclature (1995) [33]. A minimum of 20 bone marrow metaphase cells were analyzed in patients designated as having a normal karyotype.

Treatment Plan

All patients received high-dose Ara-C. Two patients received 3.0 g/m^2 (<50 years of age), and six patients received 1.5 g/m^2 [≥50 years of age (because on an increased risk of cerebellar toxicity in this group of patients)] administered over 1 hr every 12 hr for 12 doses and idarubicin (12 mg/m^2) administered over 30 min daily on days 2, 3, and 4 of Ara-C (following doses 3, 5, and 7 of Ara-C). This regimen was followed by daily growth factor support with granulocyte (G) colony-stimulating factor (CSF) (4 patients), granulocyte-macrophage (GM) CSF (1 patient), or both (3 patients) starting 12 hr after the last Ara-C dose.

Response Criteria

Response criteria were as described previously [31]. Complete hematologic remission (CHR) was defined as <5% bone marrow blasts with normal peripheral counts and differential, a granulocyte count >10^9/l, a total white blood cell count <10×10^9/l, and a platelet count >100×10^9/l lasting for at least 4 weeks. Patients who achieved CHR were categorized further according to suppression of metaphases with t(9;22) as follows: no cytogenetic response, 100% metaphases with t(9;22); minimal cytogenetic response, 35–90% metaphases with t(9;22); partial cytogenetic response, 1–34% metaphases with t(9;22); and complete cytogenetic response, no metaphases containing the t(9;22). Hematologic improvement (HI) was based on the same criteria used for CHR but allowed persistence of thrombocytopenia (<100×10^9/l) and less than 5% blasts in the peripheral blood. A return to second chronic phase indicated the disappearance of blastic phase features and a return to a chronic phase CML picture, i.e., peripheral blasts <15%, peripheral blasts and promyelocytes <30%, peripheral basophils <20%, and platelets >100×10^9/l. All other responses were considered failures. Remission duration was defined from the date of attainment of remission to the date of relapse. Survival was defined from the date of diagnosis of blast crisis to the date of death. No patient underwent allogeneic stem cell transplantation.

Statistical Considerations

Using Bayesian methodology an estimate of the probability distribution for a parameter can be generated. For this study the parameter of interest is the response rate. Previously published data were used to estimate a set of weights, called the prior distribution. These weights update the observed response data to produce a probability distribution of the response rate, called the posterior distribution [34].

The previously published trial similar to the current study is the CML-MBC trial with intermediate-dose cytarabine plus idarubicin [10]. Their 25% response rate can be approximated in the Bayesian framework as a beta distribution (with parameters 1 and 3 to yield an expected response rate equal to that published by Schneller et al. [10]). Based on the binomial responses observed in the present study, the β posterior probability distribution for response rate can be directly computed.

RESULTS

Patient Population

Median patient age was 62 years (range 42–69). Five patients were female, and three were male. All had myeloid blast crisis. Cytogenetic analyses demonstrated t(9;22) in seven patients. The eighth patient had t(9;22) by fluorescence in situ hybridization and by reverse-transcriptase polymerase chain reaction but not by conventional cytogenetics. Five of the patients had additional chromosomal abnormalities (Table I). The median duration of chronic phase in all patients was 115 months (range 45–228 months). All patients had received hydroxyurea during the chronic phase. Some received additional modes of therapy (Table I).

TABLE I. Patient Characteristics*

No.	Age/sex	Cytogenetics	PB blast count (%)	BM blast count (%)	Previous therapy	Duration of chronic phase (months)
1	66/M	47,XY,t(9;22)(q34;q11), +der(22)t(9;22)(q34;q11) [16] 46,XY,t(9;22)(q34;q11) [2]; 46,XY [2]	18	69	HU	166
2	64/F	46,XX,t(9;22)(q34;q11)	65	37	HU/LD Ara-C	45
3	60/F	46,XX,t(9;22)(q34;q11) [2] 46,XX,t(9;22)(q34;q11),add(15)(q25) [18]	18	32	HU	60
4	69/M	46,XY FISH & RT-PCR positive	2	37	BU/HU	132
5	42/F	46,XX,t(9;22)(q34;q11) [4] 47,XX,+8,t(9;22)(q34;q11),del(11)(q14) [2] 49–53,XX, +8, +8,t(9;22)(q34;q11),del(11)(q14),del(12)(p12) [9], +13 [9], +19, +20 [12], +der(22)t(9;22)(q34;q11) [4], +mar1 [1], +mar [1]	38	33	HU/BU/IFN	120
6	64/F	46,XX,t(9;22)(q34;q11) [19], 46,XX [1]	73	69	HU/IFN	72
7	48/F	46,XX,t(9;22)(q34;q11)	6	25	BU/HU/ICE/VCT/IL-2/IFN	110
8	56/M	46,XY,t(9;22)(q34;q11),t(14;17)(q31;q12),del(20)(q12q13)	12	21	BU/HU	228

*Abbreviations: Bu, busulfan; FISH, fluorescence in situ hybridization; HU, hydroxyurea; ICE, idarubicin; Ara-C, and etoposide prior to autologous transplantation; IFN, interferon-alpha; IL-2, interleukin-2; LD-Ara-C; low-dose Ara-C; RT-PCR, reverse-transcriptase polymerase chain reaction; VCT, etoposide, cyclophosphamide, and total body irradiation as pre-conditioning for autologous transplantation.

Response and Survival

One patient (12.5%) achieved CHR and minimal cytogenetic response [17 of 20 metaphases with t(9;22) and disappearance of clonal evolution, three metaphases with normal karyotype]. This lasted 2 months before disease relapse. No patient achieved complete cytogenetic remission. One patient achieved hematologic improvement that lasted 3 months. Return to chronic phase was documented in two patients for 2 and 3 months. Three patients had refractory disease. One patient died with aplasia 1.6 month following the start of therapy. Two patients (one with relapse after CHR, one with refractory disease) went on to receive additional therapies: etoposide (3.6 g/m^2 by continuous infusion) and cyclophosphamide (50 mg/kg for 4 days) with growth factor support in one patient, and Dacarbabazine, as part of a Phase I study, in the other. All other patients were treated with hydroxyurea and supportive care following determination of refractory disease. The median survival of all eight patients was 7.3 months (range 1.3–11.5 months; eight deaths). The survival of the patient who achieved CHR was 7 months.

Using the Bayesian framework the estimated probability of a response rate exceeding 25%, given the observations of this study, is only 0.2. An alternative statement of the result from the Bayesian perspective is that the prediction of the probability of a response on this regimen is 17%. This is insufficient promise to justify additional patients entering this pilot study.

Toxicity

All patients received the intended therapy (two received 3.0 g/m^2 and six received 1.5 g/m^2 of Ara-C). The toxicities of the regimen in CML-MBC patients were not different from those in previously untreated AML patients [25]. The most common toxicities were mild to moderate mucositis, diarrhea, and skin erythema. All patients developed neutropenic fever. One patient died with pancytopenia. Cerebellar toxicity was not seen in any of the patients.

DISCUSSION

CML-MBC continues to represent the most resistant form of leukemia. In the current study, the combination of high-dose Ara-C and idarubicin resulted in a CHR rate of 12.5% (95% confidence interval for CHR, 0.3%, 53%) with a median survival of 7.3 months.

We evaluated the studies published in the English literature through MEDLINE according to the Ara-C dose administered. Sixteen studies (summarized in Table II) and one additional case report, utilizing varying doses of Ara-C, were analyzed [1–16]. As shown in Table II, the median CHR rate of the different studies was 25% (range 0–65%) independent of Ara-C dose. The survival of patients in the different studies was 1.3–15 months (10 studies included data) and the survival of responding patients was 6–13 months (8 studies included data) regardless of Ara-C dose. Of interest is the study by Spriggs et al. [11] that described two patients who were treated with Ara-C at a total dose of 15 g/m^2 and survived >12 months. However, the small number of patients in that study precludes any conclusions. On the basis of our data and the literature, we conclude that Ara-C dose does not have an effect on achievement or maintenance of CHR in this patient population.

Non-Ara-C-based induction regimens have also been described in the literature. These have included 5-azacytidine and etoposide [17], diaziquone and etoposide

TABLE II. Clinical Trials of Ara-C-Based Chemotherapy for CML-MBC*

	Regimen	Ara-C dose (g/m^2)	Number of patients	CHR rate (%)	Median survival (mos)	Median survival of CHR (mos)	1-Year survival (%)	Ref.
Low dose	Ara-C Dauno VP-16[a]	0.375	9	0	5.5	NA	33	1
	Ara-C VCR/PRED	0.500	20	33	2.9[c]	6.7[c]	NR	2
	Ara-C Dauno	0.700	4	25	NR	NR	NR	3
	Ara-C Dauno 5′-Aza/6-TG	0.750	30	0[b]	1.3	NA	0	4
	Ara-C VCR 6-TG/HU	0.500–1.0	30	17	3.0	NR	17	5
Intermediate dose	Ara-C THU/Carbo	1.2–1.6	4	25	5.2	7.2	0	6
	Ara-C VDS-P	0.9–1.8	16	62.5	8.0	11.5	25	7
	Ara-C Dauno	1.8	14[c]	50	NR	NR	29[d]	8
	Ara-C VP-16 Carbo	3.0	17[c]	65	NR	6.0[d]	24[d]	9
	Ara-C/Ida	6	16	25	4.0	7.8	19	10
High dose	Ara-C	9–18	6	33	15	>12	33	11
	Ara-C/Mito	15	6	50	NR	NR	NR	12
	Ara-C/Mito	18	12	17	NR	NR	NR	13
	Ara-C	6–24	13	31[b]	NR	NR	NR	14
	Ara-C	27–36	15	20	NR	NR	0	15
	Ara-C/Ida	18–36	8	12.5	7.3	7.0	0	This work

*Abbreviations: 5′-Aza, 5′-azacytidine; 6-TG, thioguanine; Ara-C, cytosine arabinoside; Carbo, carboplatin; CML-MBC, chronic myeloid leukemia in myeloid blast crisis; CHR, complete hematologic remission; Dauno, daunorubicin; HU, hydroxyurea; Mito, mitoxantrone; mos, months; NA, not applicable; NR, not reported; PRED, prednisone; THU, tetrahydrouridine; VCR, vincristine; VDS-P, vindesine, prednisolone; VP-16, etoposide.
[a]One patient received 6-TG instead of VP-16.
[b]CHR defined as <10% blasts.
[c]No distinction was made by the authors cited in these references between lymphoid and myeloid blast crisis.
[d]Patients proceeded to either allogeneic or autologous stem cell transplantation.

[18], mitoxantrone and 5-azacytidine [19], and single agents including carboplatin [20], 6-thioguanine [21], cladribine [22], mitoxantrone [23], and decitabine [24]. None of these studies have resulted in improved outcome for patients with CML-MBC.

The initial step toward improved prognosis and prolonged survival is attainment of CHR. Improvement of CHR rate will be achieved only through the development of new approaches. Of interest is the use of STI571, a synthetic protein kinase inhibitor that has shown selectivity for the Abl-related protein tyrosine kinase at the in vitro, cellular, and in vivo levels [36]. Specific inhibitors of the fusion BCR/ABL mRNA such a ribozymes, antisense oligonucleotides, and the catalytic RNA subunit of RNase P have also shown promise in early preclinical studies [37–39].

Following attainment of CHR, patients with CML-MBC have a very short DFS and overall survival unless they can undergo allogeneic stem cell transplantation in second chronic phase. The results of allogeneic stem cell transplantation in patients with overt blast crisis are extremely poor, with relapse occurring in most patients [40–42]. Patients in second chronic phase are more likely to benefit from allogeneic transplantation [40,43].

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