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Therapy of refractory/relapsed acute myeloid leukemia and blast crisis of chronic myeloid leukemia with the combination of cytosine arabinoside, tetrahydrouridine, and carboplatin*

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Summary. Eight patients, of whom four had acute myeloid leukemia (AML) and four had chronic myeloid leukemia (CML) blast crisis, were treated with a combination of cytosine arabinoside (ARA-C: 1,600 mg/m^2 in three patients, 1,200 mg/m^2 in five patients), tetrahydrouridine (THU: 2,800 mg/m^2 in two patients, 2,646 mg/m^2 in one patient, 2,100 mg/m^2 in five patients), and carboplatin (900 mg/m^2 in four patients, 720 mg/m^2 in one patient, 450 mg/m^2 in three patients). As a result of this treatment, five of the eight patients became aplastic. Two of the four patients with CML blast crisis reverted to the chronic phase and two of the four patients with acute nonlymphocytic leukemia (ANLL) attained a remission (one partial remission and one complete remission). The major toxicities included myelosuppression, unacceptable hepatotoxicity, and diarrhea. Pharmacokinetics studies revealed that the addition of carboplatin did not significantly change the disposition of ARA-C. ARA-C levels were not significantly changed in comparison with those obtained in a prior study of ARA-C with THU (ARA-C plasma levels at 3 h, 2630 ± 1170 ng/ml).

Introduction

Since a significant proportion of patients with acute myeloid leukemia (AML) either fail initial induction therapy (30%–35%) or relapse within 2 years of achieving a complete remission (CR, 70%) [16, 18], the search for better salvage regimens remains vital. Tetrahydrouridine (THU) is a deaminase inhibitor that slows the degradation of cytosine arabinoside (ARA-C) to uridine arabinoside (ARA-U). This enzymatic inhibitor therefore prolongs the half-life of ARA-C in humans and has also been shown to increase ARA-C serum levels [8]. This change in the pharmacokinetic profile of ARA-C should allow for greater conversion of the prodrug ARA-C into the active cytotoxic agent ARA-cytidine triphosphate (ARA-CTP) [8, 13, 17]. In addition, inhibition of deamination leads to lower serum levels of ARA-U, which may be a neurotoxin [2, 10, 11, 14].

On the basis of an earlier study that revealed that CRs could be attained in refractory or recurrent acute leukemia or blastic crisis of chronic myelogenous leukemia (CML) with ARA-C and THU [9], because carboplatin has been shown to be an active agent in acute leukemia [12], and because ARA-C delays the recovery of DNA synthesis inhibited by cisplatin [3, 6], a phase I–II study was undertaken in the same population of patients using ARA-C with THU and with carboplatin. The objectives were to determine whether the combination of ARA-C/THU with carboplatin would increase the effectiveness of the single combination, to study the pharmacology of ARA-C when used in this combination, and to evaluate toxicity. We report on the response rate and unexpectedly severe toxicity seen in our first eight patients.

Patients and methods

Eligibility criteria for the study included histologically documented AML in first or second relapse or failure of initial induction therapy; preleukemic syndromes evolving into AML; blastic CML (myeloid); an age of >18 years; the completion of one to two prior chemotherapy regimens, with at least 1 week having elapsed since radiotherapy (RT), chemotherapy, or surgery; a Cancer and Leukemia Group B (CALGB) performance status (PS) of 0–2; a life expectancy of ≥6 weeks; no concomitant malignancy; no other serious medical or psychiatric illness; and informed written consent as per institutional guidelines. Between January and June 1990, eight patients were entered in this trial: four patients with CML in blast crisis, three patients with AML [based on French-American-British (FAB) criteria] that was either in relapse or refractory to treatment, and one patient with myelodysplasia transformed into AML. Required laboratory data included blood urea nitrogen (BUN), creatinine, and bilirubin levels of <1.5 × normal and hemoglobin

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Table 1. Patients' characteristics

Patient	Age (years)	Sex (M/F)	Diagnosis	PS	Prior treatment	Prior response
1	36	M	CML: first blast crisis	1	Hydroxyurea ± Alkeran	Remained in chronic phase
2	72	M	MDS/AML	1	ARA-C/DNR	CR
3	45	F	CML: blast crisis	2	Hydroxyurea, interferon mitoxantrone	PR PR PR
4	51	M	AML: first relapse	1	ARA-C/DNR	CR
5	39	M	AML: resistant	2	ARA-C/DNR	Refractory
6	66	F	AML: third relapse	1	ARA-C/DNR ARA-C/Mitoxantrone ARA-C infusion hydroxyurea	PR CR
7	50	F	CML: blast crisis	2	Busulfan	Remained in chronic phase
8	51	M	CML: blast crisis	2	Myeleran	Remained in chronic phase

MDS, Myelodysplasia; DNR, daunorubicin

Table 2. Doses given and patients' responses

Patient	Total doses given (mg)			Bone marrow aplasia	Results of treatment	Survival from treatment (days)
	ARA-C	THU	Carboplatin			
1	1,600	2,800	900	+	Chronic phase CML	217
2	1,600	2,646[a]	900	+	PR	86
3	1,600	2,800	900	+	PR	209
4	1,200	2,100	900	+	CR	287
5	1,200	2,100	720	–	Renal failure; death	6
6	1,200	2,100	450	–	Treatment failure	112
7	1,200	2,100	450	–	Chronic phase for 15 days; septic death	100+
8	1,200	2,100	450	+	Chronic phase for 14 days; CML	39

[a] By error in calculation, this patient received a slightly lower dose of THU. ARA-C and ARA-U plasma levels were comparable with those measured in patients 1 and 3

(Hb) values of >10 gm/dl. Table 1 lists the patients' characteristics, diagnosis, prior treatment, and response to prior treatment.

The chemotherapeutic agents were given as follows: carboplatin was given via pump 1 as a 72-h continuous infusion divided into nine consecutive 8-h infusions because of the instability of the drug in solution. Initial dosing was based on previous single-agent phase I data in leukemia [12] starting at 300 mg/m^2 daily (total dose, 900 mg/m^2) for four patients. Because of the observation of unexpectedly severe toxicity at this level, the total dose was subsequently modified to 720 mg/m^2 (one patient) and 450 mg/m^2 (three patients). Concurrent with carboplatin infusion, ARA-C and THU were given together as previously described [9, 17] via a second i. v. pump (pump 2) over 3 h every 12 h for eight doses. THU was given at 70 mg/m^2 (20% of the total dose) as a bolus i. v. injection prior to each 3-h infusion of 200 mg/m^2 ARA-C, with the remainder of the total THU dose (280 mg/m^2) being infused concurrently with ARA-C. The first three patients received eight doses, for a total of 2,800 or 2,646 mg/m^2 THU and 1,600 mg/m^2 ARA-C, but because of the development of unexpectedly severe toxicity, the subsequent five patients received six doses, for a total of 2,100 mg/m^2 THU and 1,200 mg/m^2 ARA-C.

The patients' responses were judged as follows: for CML, a response was defined as a return to the chronic phase; for AML, a CR consisted of an M0 or M1 bone marrow classification (0–5% blasts or 0–10% blasts and promyelocytes) as well as a peripheral blood count comprising a granulocyte count of >2,000/μl, a platelet count of >100,000/μl, and the absence of blasts. A partial response (PR) was any significant response short of that.

Blood and urine samples were obtained during therapy for studies of ARA-C and ARA-U pharmacokinetics. Response to treatment was evaluated by periodic bone marrow aspirations and biopsies. Toxicity was graded using the CALGB Expanded Common Toxicity Criteria (CALGB, unpublished data), which use a scale of 0–4, with 0 representing normal and 4 representing the most severe toxicity. Assays for ARA-C and ARA-U have been described elsewhere [8, 9]. Plasma samples were not analyzed for platinum.

Results

Response

Eight patients, including five men and three women ranging in age from 36 to 72 years (mean, 51 years), were

Table 3. Toxicities encountered

Patient	Toxicities and complications[a]								Peak laboratory values			
	Liver	Diarrhea	Infection	Hemorrhage	Stomatitis	Hematologic	Renal	Pulmonary	Bilirubin[b]	Grade	LDH[c]	Alk.phos.[c]
1	4	4	3	3	2	4	0	0	11.9/0.3[d]	II	549/2,100[d]	374/418[d]
2	3	3	3	2	2	4	2	0	3.2/1.9	II	685/ 274	309/ 52
3	3	4	3	4	3	4	1	0	2.2/0.4	II	769/ 898	293/ 82
4	3	4	3	2	0	4	3	3	1.8/0.4	II	615/ 329	293/ 49
5	4	4	3	4	0	4	4	0	3.3/1.1	II	828/ 159	307/360
6	0	2	3	2	2	4	2	0	0.5/1.0	0	5,359/4,030	309/410
7	3	0	3	3	3	2	4	1	2.9/0.5	II	1,216/ 295	722/291
8	3	4	3	1	3	4	0	1	3.1/1.8	II	931/1,855	490/304

[a] CALGB grading 0–4
[b] Expressed in mg/dl
[c] Expressed in IU/l
[d] Values represent peak value/baseline value
LDH, Lactic dehydrogenase; ALK.phos., alkaline phosphatase

treated. Table 2 lists the drug doses each patient received and the responses obtained. In this group of heavily pretreated patients, two PRs and one CR were observed. Examination of the bone marrow revealed that five of the eight patients became aplastic by day 15 and that one additional patient experienced a prolonged nadir with hypocellular but not aplastic marrow (Table 2). All of the patients receiving the higher doses became aplastic; the three who did not become aplastic (patients 6–8) received lower doses of the agents. Included among the responders were two patients with CML blast crisis that reverted to the chronic phase, one PR in AML, and one CR in AML in a patient who subsequently underwent autologous bone marrow transplantation (patient 4). This patient died of cytomegalovirus infection at 6 months after the transplant while in remission.

Toxicities

Table 3 lists the toxicities encountered. Hepatic toxicity and diarrhea were the most prominent side effects, reaching grade 4, and were seen at the first dose level. Patient 1 experienced hyperbilirubinemia, showing a total bilirubin value of 11.9 mg/dl and an alkaline phosphatase level of 418 mg/dl, as well as grade 4 diarrhea. A sonogram revealed only sludge in the gallbladder with normal ducts. Patients 2 and 3 experienced similar toxicities but had lower total bilirubin values of 3.5 and 2.5 mg/dl, respectively. As ARA-C is known to be a hepatotoxin [5, 7], patient 4 was given six instead of eight doses of ARA-C and THU. Despite this 25% dose reduction, hyperbilirubinemia with grade 4 bloody diarrhea occurred, requiring treatment in an intensive-care unit (ICU). None of the four patients from whom sonograms were obtained had any finding other than sludge (of no clinical significance) in the gallbladder to explain the observed abnormalities. As a further reduction in the dose of ARA-C might have limited the benefit of this schedule-dependent agent, the carboplatin dose was instead decreased for subsequent patients. Patient 5 received 720 mg/m^2 (a 20% dose reduction) and patients 6–8 received 450 mg/m^2 (a 50% dose reduction). Patients experienced the toxicities commonly associated with bone marrow aplasia, but the most clinically significant nonhematologic toxicities seen at all dose levels were hyperbilirubinemia and diarrhea. Changes in serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT), although not included in the eligibility criteria, were of grade 3 toxicity in only two subjects (patients 1 and 2) but were insignificant in all other patients. No neurotoxicity was observed.

Pharmacokinetics

We have previously reported changes in the pharmacokinetics of ARA-C induced by THU when solid-tumor patients were treated with the combination [8]. Under the influence of THU, plasma ARA-C disposition was changed from a biphasic to a monophasic decay curve. The administration of carboplatin in this regimen was a compounding variable. Therefore, pharmacokinetics studies were done to determine whether ARA-C disposition had been perturbed. A comparison of the ARA-C and ARA-U plasma levels measured in this study together with a previous evaluation of ARA-C and THU treatment in patients with leukemia [9] revealed values of Cp3h (plasma levels at 3 h, the end of the ARA-C infusion) to be comparable for ARA-C but not for ARA-U [day 1: ARA-C – $2{,}630 \pm 1{,}170$ ng/ml (present study) vs $3{,}366 \pm 2{,}030$ ng/ml (prior study), $P < 0.05$ (no statistically significant difference); ARA-U – $1{,}520 \pm 1{,}120$ ng/ml (present study) vs $3{,}160 \pm 1{,}810$ ng/ml (prior study), $P < 0.01$ (statistically significant difference)].

Discussion

ARA-C can cause reversible intrahepatic cholestasis with elevated transaminases and bilirubin at both conventional [5] and high doses (HIDAC) [7]. In all, 75% of patients receiving HIDAC in Herzig et al.'s study [7] experienced mild to moderate hepatotoxicity (liver-function tests up to 5 times normal). Bilirubin levels as high as 23 mg/dl have

been reported [4]. Similar but less severe toxicities have been observed with conventional doses. In a phase I trial of ARA-C and THU in patients with previously treated acute leukemia, hepatotoxicity was reported as one of the observed toxicities but was not felt to be a major problem or to be dose-limiting [9]. In that study performed at a dose and schedule of ARA-C + THU identical to the one used in the present study, 61% of patients experienced hyperbilirubinemia but no grade IV hepatotoxicity was observed, and no dose reduction was necessary. In the present study, 86% of patients experienced hepatotoxicity, with one patient experiencing grade IV toxicity, and dose adjustment for toxicity was necessary in five of eight patients.

Phase I and II studies using carboplatin at conventional doses have failed to reveal significant hepatotoxicity; hematologic toxicity was dose-limiting [1]. Higher doses given either for acute leukemia or in association with bone marrow transplantation resulted in significant nonhematologic toxicity. Ototoxicity, nephrotoxicity, and diarrhea were noted at doses of >1,000 mg/m^2, and hepatotoxicity occurred at even higher doses [1]. In a study conducted at Dana Farber Institute using 2,000–2,400 mg/m^2, hepatotoxicity was considered to be dose-limiting [15].

From the present trial, it appears that when ARA-C, THU, and carboplatin are used in combination, hepatotoxicity and diarrhea may be additive and are dose-limiting. Therefore, the decision to modify doses was precipitated by the severe hepatotoxicity encountered. In a comparison of toxicities, substantial differences in severity and frequency were noted in this study versus previous studies, mainly in hepatic and renal toxicity, diarrhea, stomatitis, and hemorrhage, whereas emesis and infections showed only minor differences (Table 3).

The ratio of Cp3h ARA-U: ARA-C on day 1 was 0.70 ± 0.59 as compared with 0.95 for the previously studied group of leukemic patients treated with ARA-C and THU [9], with peak plasma ARA-U levels at 5–6 h following initiation of the treatment being continuously higher than plateau ARA-C levels at 11 h. Urinary excretion of ARA-C and ARA-U over the first 24 h was 61.8%, somewhat higher than that observed in our previous study (49.9%) [9]. Overall, ARA-U plasma levels were higher than ARA-C levels at 11 h, as previously observed [9]. The pharmacokinetics of ARA-C were not significantly different from those noted in our prior study of ARA-C and THU [9]. The smaller number of patients involved in the present study does not allow the conclusion that the observed increased levels of ARA-U might have contributed to or caused the severe liver toxicity encountered. Thus, the increased toxicity observed in this study cannot be explained by the effect of carboplatin on ARA-C pharmacokinetics.

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