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High-Dose Cytosine Arabinoside and Mitoxantrone: A Highly Effective Regimen in Refractory Acute Myeloid Leukemia

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In a clinical phase I/II study, high-dose cytosine arabinoside and mitoxantrone (HAM) were given in combination to 40 patients with refractory acute myeloid leukemia. All patients had received a 9-day combination of thioguanine, Ara-C, and daunorubicin (TAD-9) as standardized first-line treatment. Refractoriness was defined as (a) nonresponse against two TAD-9 induction cycles, (b) early relapse within the first 6 months on monthly maintenance or after TAD-9 consolidation, (c) relapse after 6 months with nonresponse against one additional TAD-9 cycle, and (d) second and subsequent relapses after successful TAD-9 therapy at the preceding relapse. Therapy consisted of HD-Ara-C 3 g/m^2 every 12 hours on days 1 through 4; mitoxantrone was started at 12 mg/m^2/day on days 3, 4, and 5 and was escalated to 4 and 5 doses of 10 mg/m^2/day on days 2 through 5 and 2 through 6. Of the 40 patients, 21 achieved a complete remission (53%), 1 patient had a partial remission, and 5 patients were nonresponders. Thirteen patients died in aplasia due to infections (n = 11), pericardiac effusion, or acute cardiomyopathy. Nonhematologic side effects consisted predominantly of nausea and vomiting, mucositis, and diarrhea. Central nervous system (CNS) symptoms were observed during six treatment courses. Recovery of blood counts occurred at a median of 27 days from the onset of treatment; the median time to complete remission was 36 days. Two of the 21 responders underwent successful bone marrow transplantations. The median remission duration for the remaining 19 patients is 4.5 months, and the median survival time is 9 months. These data emphasize that HAM has high antileukemic activity in refractory AML and strongly suggest starting the combination at earlier stages in AML therapy.

DESPITE INTENSIVE induction therapy and subsequent myelosuppressive treatment in remission, most patients with acute myeloid leukemia (AML) still relapse with their disease and ultimately die of drug-resistant leukemia. High secondary remission rates and even prolonged survival have recently been reported, however, with administration of high-dose cytosine arabinoside (HD-Ara-C) alone or in combination with anthracyclines, asparaginase, or *m*-AMSA.[1-6] Patients with leukemias refractory to conventional-dose Ara-C especially benefitted from the addition of anthracyclines.[5] These data are in accordance with previous cell kinetic studies revealing a conditioning effect of Ara-C for the subsequent administration of daunorubicin or doxorubicin.[7-10] They are further supported by recent experimental results indicating a time-dependent synergistic effect of high-dose cytosine arabinoside (HD-Ara-C) and mitoxantrone.[11]

These findings and the significant antileukemic activity of mitoxantrone as a single agent[12-16] as well as its low cardiac toxicity[17-20] prompted us to initiate a phase I/II study of HD-Ara-C and mitoxantrone (HAM) in patients with refractory AML. All patients were recruited from the multicenter German AML Cooperative Group trial[21,22] and had therefore received a standardized first-line treatment with a 9-day combination of thioguanine, Ara-C, and daunorubicin (TAD-9).

HD-Ara-C was given every 12 hours at a dose of 3 g/m^2 by a 3-hour infusion to compensate for its rapid metabolic clearance and because steady-state plasma levels are not achieved before ~45 minutes.[23] The 3-hour infusion is also thought to reduce cerebellar toxicity associated with short-term administration.[24,25] The number of HD-Ara-C infusions was restricted to 8 to avoid the sustained nonhematologic side effects reported for repetitive doses beyond 8 to 10.[2,4,25] To take advantage of the previously mentioned conditioning effect of Ara-C, mitoxantrone was started on day 3 at 12 mg/m^2/day and was repeated on days 4 and 5. In subsequent patients, the total dose was escalated to 10 mg/m^2/day for 5 days, which is in the range of the most effective single-agent regimens.[12-16]

Patients were eligible for the HAM regimen only if they were refractory to prior treatment.[26] Hence, they had either failed on two TAD-9 courses for induction treatment, had relapsed within the first 6 months on monthly maintenance including conventional dose Ara-C or after TAD-9 consolidation, were nonresponders to an additional TAD-9 course in later occurring first relapses, or had second or subsequent recurrences after successful TAD-9 therapy at the preceding relapse.

MATERIALS AND METHODS

Between January 1985 and March 1986, 40 patients entered the study from seven centers in Germany. Their ages ranged from 18 to 66 years (median 45 years). All patients had received one to two courses of the TAD-9 regimen for induction, consisting of thioguanine 200 mg/m^2/day on days 3 to 9, Ara-C 100 mg/m^2/day by continuous infusion on days 1 and 2 followed by short-term infusions of Ara-C 100 mg/m^2 every 12 hours on days 3 to 8, and daunorubicin 60 mg/m^2/day on days 3 to 5 (TAD-9). For postinduction treatment, patients received TAD-9 consolidation and/or monthly maintenance therapy with subcutaneous Ara-C alternately combined with daunorubicin, thioguanine, or cyclophosphamide.[21,22]

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Besides Ara-C at conventional dosage, all patients were therefore exposed to daunorubicin at cumulative doses between 180 and 990 mg/m^2 (median 450 mg/m^2). All patients were refractory to conventional therapy as defined earlier (Table 1).

In three cases, AML was preceded by myelodysplastic syndrome. Two additional patients had secondary leukemias after radiation and chemotherapy for breast cancer and malignant seminoma, respectively. Four patients with early relapses had central nervous system (CNS) involvement.

Prior to therapy all patients gave informed consent after having been advised about the purpose and investigational nature of the study as well as of potential risks.

Therapy consisted of HD-Ara-C 3 g/m^2 every 12 hours by a 3-hour infusion on days 1 through 4. Mitoxantrone was started at 12 mg/m^2/day as a 30-minute infusion on days 3, 4, and 5 and was escalated in subsequent cases to four and five doses of 10 mg/m^2/day on days 2 through 5 and 2 through 6, respectively (Fig 1). For the prophylaxis of HD-Ara-C–induced photophobia and conjunctivitis, all patients received glucocorticoid eye drops every 6 hours starting before the first dose and continuing for 24 hours after the last dose of HD-Ara-C.

Toxicity was quantitated according to the World Health Organization (WHO) grading system.[27] For the most frequently encountered side effects, toxicity grades 3 and 4 are thereby defined as follows: nausea and vomiting—vomiting requiring therapy (grade 3); intractable vomiting (grade 4); diarrhea—repetitive diarrhea for >2 days requiring therapy (grade 3); severe hemorrhagic diarrhea with dehydration (grade 4); mucositis—ulcers requiring liquid diet only (grade 3); alimentation impossible, parenteral nutrition required (grade 4); and hepatic—increase in liver enzymes or bilirubin to 5 to 10 times the normal values (grade 3) or to >10 times the normal values (grade 4). In addition, cardiac function was monitored in all patients by echocardiographic measurement of left ventricular shortening fraction prior to therapy and at 4- to 6-week intervals thereafter.

Evaluation of antileukemic efficacy was based on CALGB criteria.[28,29] Complete remission was defined by the disappearance of leukemic blasts from the bone marrow and blood as well as from possible extramedullary sites, including the cerebral fluid, and the normalization of peripheral blood counts to thrombocytes >100,000/μL and granulocytes >1,500/μL. The duration of critical cytopenia was evaluated by the time for granulocyte recovery to >500/μL and thrombocytes to >20,000/μL from the onset of treatment.

Table 1. Patient Characteristics and Entry Criteria

Characteristics	
n	40
Age	18–66 yr (median 45 yr)
Sex	
F	21
M	19
FAB subtypes	
M1	3
M2	14
M3	—
M4	13
M5	9
M6	1
Previous dose of daunorubicin	180–990 mg/m^2
Entry Criteria	n
Primary nonresponse against two	
TAD-9 induction cycles	10
Early relapse within first 6 months	13
TAD-9–resistant late relapse	8
Second and higher relapse	9

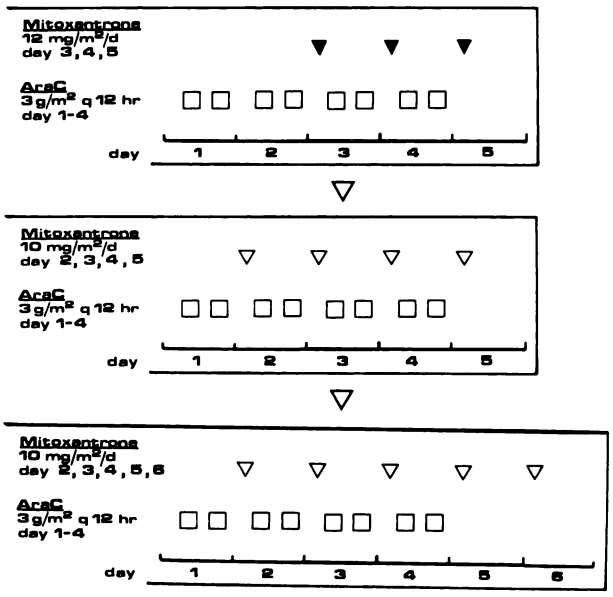

Fig 1. Schema of the high-dose cytosine arabinoside (HD-Ara-C)/mitoxantrone (HAM) protocol indicating the uniform dosage of HD-Ara-C 3 g/m^2 every 12 hours on days 1 through 4 and a dose escalation for mitoxantrone from 12 mg/m^2/day on days 3 through 5 to four and five doses of 10 mg/m^2/day on days 2 through 5 and 2 through 6.

RESULTS

Thirty-seven of the 40 patients were treated with one course of HAM, and three patients received a second cycle of the same regimen, accounting for 43 treatment courses. Eight cycles were carried out at the starting dose of mitoxantrone of 12 mg/m^2/day × 3. In 16 and 19 courses, respectively, mitoxantrone was escalated to 4 and 5 doses of 10 mg/m^2/day.

Nonhematologic toxicity. A summary of the nonhematologic side effects is given in Table 2. Nausea, vomiting, diarrhea, and mucositis were the most frequent side effects, occurring in 39 (91%), 35 (81%), and 30 (69%) of the 43 treatment courses. Severe side effects with toxicity grades of 3 and 4 according to WHO criteria were seen only in 9 (21%), 9 (21%), and 7 (16%) patients. Apart from more pronounced mucositis at the highest dose of mitoxantrone,

Table 2. Nonhematologic Toxicity

Toxicity	n (%)	WHO Grade I/II (%)	WHO Grade III/IV (%)
Nausea/vomiting	39 (91)	30 (70)	9 (21)
Diarrhea	35 (81)	26 (60)	9 (21)
Mucositis	30 (70)	23 (53)	7 (16)
Hepatic	11 (26)	9 (21)	2 (5)
Cardiac	8 (19)	5 (12)	3 (7)
CNS	6 (14)	2 (5)	4 (9)
Skin	5 (12)	5 (12)	—
Eye	4 (9)	4 (9)	—
Renal	3 (7)	3 (7)	—

Numbers and corresponding percentages in parentheses refer to all 43 treatment courses (100%).

Table 3. Entry Criteria and Treatment Response to HAM

Response	CR	PR	ED	NR	
Primary nonresponse	1	—	6*	3	10
Early relapse (<6 months CR)	9	1	2	1	13
TAD-9–resistant late relapse	3	—	5†	—	8
Second and higher relapses	8	—	—	1	9
	21	1	13	5	40

HAM, HD-Ara-C and mitoxantrone; CR, complete remission; PR, partial remission; ED, early death; NR, non-response.

*Includes one death due to pericardiac effusion.

†Includes one death due to acute cardiomyopathy.

toxicity was not different among the three applied dose escalations.

Two fatal cardiac events occurred at the lowest dose of mitoxantrone. One 31-year-old woman patient who had received 360 mg/m^2 of daunorubicin during prior therapy died of sudden cardiac failure 12 hours after the first dose of mitoxantrone. Autopsy revealed an acute cardiomyopathy. The other patient succumbed to a massive pericardiac effusion because of leukemic infiltration. Atrial flutter was observed in a third patient with preexisting cardiac arrhythmias during the initial HD-Ara-C infusion but was easily controlled by antiarrhythmic medication and did not cause cessation of treatment. Minor arrhythmias not requiring therapy occurred in two patients; in three additional patients, a reduction of left ventricular shortening fraction was revealed 3 to 8 weeks after HAM without any clinical signs of cardiac insufficiency.

In addition to two patients with transient dysdiadochokinesia, four patients aged 54, 59, 60, and 64 years had more severe CNS symptoms consisting of dysarthria, ataxia, balance disturbances, and somnolence. The clinical symptoms were completely reversible within 2 to 3 weeks in two patients; the other two died of septicemia during bone marrow aplasia.

Hematologic effects and antileukemic efficacy. Twenty-one of the 40 patients (53%) achieved complete remission (CR), 19 of them after one HAM course and 2 of them after two HAM courses. One additional patient obtained a partial remission (PR) with a normalization of peripheral blood counts but a residual leukemic cell population in the bone marrow of 15% blasts.

In five patients (13%), the leukemic blasts persisted or recovered after bone marrow aplasia; they were therefore considered nonresponders.

Three of the four patients with initial CNS involvement had no evidence of residual leukemic blasts in the cerebral fluid 1 week after completion of HAM without any intrathecal therapy and went into CR; the fourth patient died in aplasia due to an overwhelming infection.

Thirty-three of the 40 patients developed fever during bone marrow aplasia, and 11 (28%) died of infections between days 7 and 36 (median day 14) from the onset of therapy. Posttreatment bone marrow smears were available in nine cases and revealed residual leukemic blasts in only one patient. The two additional deaths caused by acute cardiomyopathy and pericardiac effusion occurred on days 2 and 7, respectively.

Analysis of response in relation to the previously defined entry criteria (Table 3) revealed similarly high CR rates in patients with early relapses (9 of 13) in TAD-9–resistant late relapses (3 of 8) and in patients with second and subsequent leukemic recurrences (8 of 9). Of the ten primary nonresponders only one patient achieved a CR. This group includes, however, two cases with antecedent myelodysplastic syndromes, two with additional ineffective salvage treatment by COAP or Aclacinomycin A and VP 16 and the patient who died of a pericardiac effusion (Table 4).

In patients achieving a CR (n = 21) or PR (n = 1), the median recovery time of granulocyte counts to >500/μL and thrombocyte counts to >20,000/μL was 27 days (range 21 to 150 days) from the start of treatment. The median time to complete remission was 36 days (range 24 to 190 days). No cases of prolonged aplasia occurred except for one patient at third relapse who had been exposed to previous multiple intensive regimens and who fulfilled CR criteria after 190 days.

Of the 21 CR patients, two underwent allogeneic bone marrow transplantations after 1$^+$ and 2$^+$ months of CR and both are presently in continuous CR at 16$^+$ and 20$^+$ months. Four patients are in ongoing remission at 1$^+$ to 7$^+$ months, whereas 15 relapsed after 1 to 8 months. The median remission duration is 4.5 months. Of the 15 relapsed patients, 8 were successfully reinduced with a modified HAM regimen, and 7 were refractory or died. The overall survival

Table 4. Characteristics of Primary Nonresponders Against Two TAD-9 Courses

Age (yr)	Antecedent Hematological Disorder	Additional Pretreatment	HD-AraC/Mitoxantrone Dose	Response	Cause of Death
46	—	—	I	ED day 36	Infection
47	—	5 × COAP	I	NR	—
59	—	—	II	ED day 5	Pericardiac effusion
51	—	—	2 × II	ED day 7 Second course	Infection
66	—	Acla/VP 16	II	NR	—
55	—	—	III	NR	—
50	—	—	III	ED day 14	Infection
59	Sideroachrestic anemia	—	III	ED day 35	Infection
60	Sideroachrestic anemia	—	III	ED day 19	Infection
67	—	—	III	CR	—

times are 3 months for all patients and 9 months for the 21 CR cases.

DISCUSSION

In refractory and relapsed acute leukemias, clinical phase I/II studies are performed not only as salvage therapy for patients with advanced disease but also as a search for new agents or drug combinations with antileukemic activity that will broaden the spectrum of leukemia treatment and may subsequently be incorporated into first-line therapy. The clinical evaluation of these trials and the interstudy comparison of treatment results are substantially hampered, however, by the great heterogeneity of patients entered on phase I/II protocols. In addition to various forms of first-line therapy, differences in the duration of the preceding remission and in the definition of patient eligibility may cause divergent results and must be considered.[30,31]

The present phase I/II study combining HD-Ara-C and mitoxantrone (HAM) was based on the first-line multicenter trial of the German AML Cooperative Group[22] and was thus applied under standardized conditions for the initial treatment by TAD-9, producing a 62% CR rate in 844 adults of all ages. Furthermore, rigid criteria for the definition of refractoriness against first-line therapy were applied according to the analysis of relapse pattern and response to reinduction attempts with the TAD-9 regimen initially used. This evaluation indicated a substantially inferior remission rate in patients relapsing within the first 6 months (19% CR) as compared with later relapses (45% CR). TAD-9 was also ineffective in cases with second and subsequent leukemic recurrences producing 21% CR. Hence, patients were eligible for HAM only if they had either failed on induction therapy, relapsed within 6 months during intensive monthly maintenance treatment or after a full-dose induction-type consolidation, were nonresponders to a reinduction attempt with TAD-9 at later recurrences, or were at second or subsequent relapses. Under these prerequisites, the response rate of 53% CR demonstrates a substantial antileukemic activity of HAM in refractory AML.

Willemze and colleagues[1] treated 14 similarly selected patients by a six-day course of HD-Ara-C alone and obtained 6 CR and 1 additional hematologic CR with persistent extramedullary leukemia; however, they reported considerable pulmonary toxicity in three patients. This side effect was not observed by Herzig and co-workers at the same dose level,[2] with which 12 of 19 evaluable patients with AML achieved a CR. Five patients dying during the first 3 weeks were considered inevaluable, and the responses were not classified according to prior therapy or relapse status. The overall study comprised 36 patients who had received different types of primary treatment and of whom only 14 were considered refractory against conventional-dose Ara-C. In a recent report by the same group,[5] 3 of 15 patients with AML resistant to conventional-dose Ara-C responded to 12 doses of HD-Ara-C whereas addition of an anthracycline produced 15 CR in 27 similarly selected AML patients. Remission rates for combinations of HD-Ara-C with *m*-AMSA range from 33% to 70%.[4,6,32,33] These trials are hardly comparable, however, because of different drug schedules and doses. In addition, information about the prior therapy and eligibility criteria including the resistance to conventional-dose Ara-C are not available. The latter data are given for two recent trials with sequential HD-Ara-C and asparaginase in children and adults[3,34] achieving CR in 42% to 68% of cases. The earlier study[3] also included patients without prior Ara-C treatment; in both trials, patients with late relapses were eligible if they were still receiving maintenance therapy.

These data emphasize the limits of interstudy comparison but strongly suggest that HAM is at least equivalent or possibly even superior to other HD-Ara-C regimens as well as to the combination of mitoxantrone and VP-16[35] in truly refractory AML. Preliminary results of a recent study using HD-Ara-C and mitoxantrone at a different dosage and timing confirm the high overall remission rate, although 4 of 10 patients needed more than one treatment cycle to obtain a CR.[36]

Analysis of treatment response according to the previously defined entry criteria revealed high remission rates in patients with early relapses and TAD-9–resistant late relapses as well as in second and subsequent recurrences, but only one CR in ten patients with primary resistance against two TAD-9 induction cycles. Although additional factors such as antecedent myelodysplastic syndromes and further salvage therapy must be taken into account in four patients, these results seem to imply that primary refractoriness against two TAD-9 cycles might not be overcome by HAM. Due to the relatively small number of truly evaluable primarily resistant patients, this conclusion must be considered preliminary and deserves confirmation by additional cases.

Despite intensive prior therapy and exposure to a median cumulative dose of 450 mg/m^2 of daunorubicin (range 180 to 990 mg/m^2), the toxicity of HAM was acceptable at all dose levels. The only cardiac death that was obviously related to therapy consisted of an acute cardiomyopathy in a 31-year-old patient without a prior history of cardiac disorder who had previously received 360 mg/m^2 of daunorubicin. Two cases of minor arrhythmias and one incidence of atrial flutter were observed during the first infusion of HD-Ara-C, as has been described by others,[1] and were easily controlled by antiarrhythmic medication. A second cardiac death was due to a massive pericardiac effusion because of leukemic infiltration and was not related to treatment toxicity. Three other patients developed a reduction of left ventricular shortening fraction 3 to 8 weeks after HAM without any clinical signs of cardiac insufficiency. The incidence and severity of CNS toxicity are comparable with that of other HD-Ara-C regimens,[4,5,34] as are the hematologic effects of HAM. Blood counts recovered to granulocytes >500/μL and thrombocytes >20,000/μL at a median of 27 days after the onset of therapy, and the median time to complete remission was 36 days. Corresponding recovery times are reported for combinations of HD-Ara-C with anthracyclines, *m*-AMSA, and asparaginase.[3,5,6,34]

The overall early death rate of 33%, which certainly exceeds the results of some other HD-Ara-C trials, must be judged in consideration of the rigid eligibility criteria for the present study. Patients with primarily refractory AML or nonresponse to TAD-9 at late occurring relapses are in continuous hypoplasia or aplasia for 4 to 8 weeks before

entering the HAM protocol. Therefore, they carry a high risk of acquiring severe infections, the major cause of death in 11 of the 13 cases. Ten of the 13 early deaths were observed in patients of the two mentioned subgroups. In this context, the low rate of 12% HAM-resistant leukemias must be emphasized as well; the rate compares favorably with those of other HD-Ara-C or mitoxantrone combinations.[6,34,35] Hence, despite selection of heavily pretreated patients with advanced disease and poor prognosis, HAM produced an encouraging high overall response rate, which strongly suggests incorporating the two-drug combination at earlier stages of AML treatment.

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