High-Dose Cytosine Arabinoside and Mitoxantrone (HAM) for the Treatment of Refractory Acute Lymphoblastic Leukemia

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Summary
In a clinical phase-II study 11 patients with refractory ALL were treated with high-dose AraC and mitoxantrone in combination (HAM). Refractoriness was defined as: 1. primary resistance against the BMFT induction protocol; 2. first relapse with non-response to the B-ALL/NHL regimen as salvage treatment; 3. second and subsequent relapses. Therapy consisted of HD AraC 3 g/m² every 12 h by a 3-h infusion on days 1–4 and mitoxantrone 10 mg/m² on days 2–6. Seven of the 11 patients achieved a complete remission, 1 patient was refractory against 2 HAM cycles and 3 patients died during bone marrow aplasia. Toxicity was acceptable, consisting mainly of nausea and vomiting, mucositis and diarrhea. One patient who had completed the prophylactic CNS treatment with intrathecal MTX and cranial irradiation immediately before entering the HAM protocol developed severe signs of cerebral toxicity. These data indicate a significant activity of HAM in refractory ALL and suggest that the combination should be applied at earlier stages of ALL treatment.

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Zusammenfassung und Schlüsselwörter
Introduction
Substantial progress has been achieved in the treatment of adult acute lymphoblastic leukemia within the last 10 years and long-term remissions are nowadays achieved in 40–50 % of patients [1, 2]. These encouraging results are based on the application of multiple-drug regimens for induction and consolidation therapy and on the identification of risk factors resulting in risk-adapted treatment stratifications [1]. The prognosis of patients with poor risk factors, namely, age above 35 years, high white blood cell count and zero immunophenotype, still remains dismal, however, and the majority of these leukemias relapse within the first 2 years after successful induction treatment. Attempts to re-induce remissions by regimens used in AML therapy or B-ALL/NHL revealed limited responses only, and the application of new agents or drug combinations appears to be highly warranted in the search for more effective regimens in this group of patients. The promising response rates with HD-AraC and mitoxantrone (HAM) in refractory AML [3] prompted us to evaluate the antileukemic activity of HAM also in patients with ALL who were resistant to conventional treatment.

Patients, Treatment Protocol and Methods
Between May 1985 and June 1986 11 patients with primary refractory or relapsed ALL were started on the HAM regimen. Ages ranged from 17–68 years. Patients were considered refractory to prior therapy and eligible for the present phase-∏ study under the following conditions: 1. primary resistance against first-line therapy according to the BMFT protocol (n = 4); 2. first relapse with non-response to the B-ALL/NHL regimen as first salvage treatment (n = 4); 3. second and subsequent relapses (n = 3).

Therapy was adapted from the HAM regimen applied in refractory AML and consisted of HD-AraC 3 g/m² every 12 h by a 3-h infusion on days 1–4 and mitoxantrone 10 mg/m²/d by a 30-min infusion on days 2–6.

Toxicity was evaluated according to WHO criteria. The assessment of the antileukemic activity was based on CALGB criteria.

Results
Ten of the 11 patients were treated with 1 HAM cycle, 1 patient received a second course. Seven of the 11 patients achieved a complete remission. The median time to CR was 34 days (range 28–43 days). Two

12

patients died during bone marrow aplasia due to infections and one case succumbed to a possible cerebral toxicity from the applied protocol. One patient with a Philadelphia chromosome positive ALL was resistant against 2 HAM cycles. The assessment of response to HAM in relation to the above-outlined entry criteria showed no differences. Two of the 4 patients with ALL who were resistant to the BMFT induction protocol and who had also received the B-ALL/NHL regimen went into CR. Out of 4 patients in first relapse and non-response to the B-ALL/NHL protocol 3 achieved a CR after HAM and 2 out of 3 cases with second or third relapse were successfully reinduced by HAM.

Toxicity was acceptable and consisted mainly of nausea and vomiting, mucositis and diarrhea. One 42-year-old female patient who had completed her prophylactic CNS treatment with intrathecal MTX and cranial irradiation 2 weeks before entering the HAM protocol developed
signs of cerebral toxicity with convulsions and somnolence and died 2 weeks after the end of therapy. Cardiac side effects were not encountered, although all patients had been exposed to daunorubicin at a median dose of 200 mg/m² (range 140–670 mg/m²).

Discussion
In contrast to the promising results with high-dose AraC alone or in combination with anthracyclines, m-AMSA or asparaginase in refractory acute myeloid leukemia, only limited experience has been obtained until now concerning high-dose AraC treatment of resistant acute lymphoblastic leukemia. Recent reports indicate a significant antileukemic activity which, however, appears to be inferior to comparable data in AML [4, 5]. Based on the considerable single-agent efficacy of mitoxantrone in ALL [6, 7] and on a possible synergistic effect of HD-AraC and mitoxantrone [8], the 2-drug combination (HAM) was applied in the present phase-II trial to heavily pretreated patients with refractory ALL. The timing and doses of HAM were adapted from the preceding phase-I study in refractory AML which produced complete remissions in 53 % of patients [3].

Despite intensive prior therapy with the BMFT induction protocol in all patients and the B-ALL/NHL regimen as primary salvage regimen in 8 patients, 7 out of 11 patients achieved a complete remission with HAM. Toxicity was acceptable, except for 1 case with severe cerebral side effects consisting of convulsions and somnolence and subsequent lethal outcome. This patient had received prophylactic CNS therapy with intrathecal MTX and cranial irradiation 2 weeks before entering the HAM protocol.

Although all remissions were of short duration lasting no longer than 4 months, these data indicate a substantial antileukemic activity of HAM in refractory ALL and suggest that the 2-drug combination should be applied at earlier stages of ALL treatment.

References


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