Idarubicin in Refractory Acute Leukemia

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Key Words

Idarubicin
4-demethoxydaunorubicin
Acute leukemia

Summary

10 patients with resistant or relapsed acute leukemia (9 AML, 1 ALL) were treated with idarubicin (4-demethoxydaunorubicin) in combination with cytosine arabinoside +/- etoposide. All patients had been heavily pretreated. 9 AML-patients had previously received 2-4 cycles of TAD-9 regimen. 2 complete and 1 partial remission were achieved. 1 patient died from septicemia in bone marrow aplasia without leukemic cells. 6 patients did not respond to idarubicin-based salvage treatment. The median survival from start of therapy was 4 months. Idarubicin-based combination chemotherapy is effective in relapsed acute leukemia, even in patients intensively pretreated with anthra-cyclines.

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Zusammenfassung und Schlüsselwörter

10 Patienten mit resistenter oder rezidivierter akuter Leukämie (9 AML, 1 ALL) wurden mit Idarubicin (4-Demethoxydaunorubicin) in Kombination mit Cytosinarabinosid +/- Etoposid behandelt. Alle Patienten waren intensiv vorbehandelt. Die 9 AML-Patienten hatten zuvor 2 bis 4 Zyklen des TAD-9 Regime erhalten. Es wurden zwei komplette und eine partielle Remission erzielt. Ein Patient starb an den Folgen einer Sepsis bei Knochenmarkaplasie ohne Nachweis von Leukämiezellen. 6 Patienten sprachen nicht auf die idarubicinhaltige Kombinationstherapie an. Die mediane Überlebenszeit nach Therapiebeginn betrug 4 Monate. Eine idarubicinhaltige Kombinations-Chemotherapie ist wirksam bei rezidivierter akuter Leukämie, selbst bei Patienten, die intensiv mit Anthrazyklinen vorbehandelt sind.

Idarubicin – 4-Demethoxydaunorubicin – Akute Leukämie

Introduction

Idarubicin is the 4-demethoxy derivative of daunorubicin [1]. In preclinical studies 4-demethoxydaunorubicin proved five times more potent than daunorubicin against the L1210 and P388 leukemia [7]. The cardiotoxicity of idarubicin compared to adriamycin and daunorubicin was lower resulting in a higher therapeutic index than the parent drugs have [6]. Idarubicin may be administered both intravenously and orally [9]. The intestinal absorption rate is about 30% [12]. Thus, the dosage has to be increased 3 to 4 times when given orally. Intravenously administered, the terminal half-life of idarubicin is 18.4 h. Only 6.5% of the drug will be eliminated in the urine within 24 h [12]. Idarubicin has a major and at least one minor metabolite. The plasma half-life of the major metabolite, 13-hydroxy-idarubicin, is 50 to 55 h [12]. Cytosine arabinoside does not significantly alter the pharmacokinetics of idarubicin.

Patients and Methods

We have treated 10 acute leukemia patients with idarubicin. All patients had been intensively pretreated. 1 patient had acute lymphatic leukemia in first relapse, which was refractory to treatment with the German ALL/AUL protocol [10]. 9 patients suffered from acute myeloid leukemia. They had been previously treated with 2 to 4 courses of the TAD-9 regimen [3]. One of these patients was primarily resistant to TAD-9 therapy, 3 patients had early relapse after 2½, 4 and 6 months of complete remission, respectively. 5 patients had a second or further relapse of AML.

The 7 male and 3 female patients had a median age of 42 years. The youngest patient was 30, the oldest 70 years of age. All patients received idarubicin in combination with other cytostatic drugs. The first 5 patients received idarubicin in sequential combination with cytosine arabinoside according to a proposal of Polli et al. [13].

Idarubicin was given intravenously 10mg/m² daily for the first 3 days of treatment. Cytosine arabinoside was administered on the following

5 days as intravenous bolus injection 2 times 120mg/m² daily.

The other patients were treated with a protocol of Carella et al. [5]. 8mg/m² idarubicin was given intravenously daily for 3 days. Patients received additionally etoposide 150mg/m² daily on the same days and cytosine arabinoside 150 mg/m² as 24 h intravenous infusion from day 1 to 5 of therapy.

6 patients received one, 4 patients two cycles of an idarubicin-based combination chemotherapy.

Response to treatment was judged according to the CALGB criteria.

Results

The only patient with ALL did not respond to treatment with idarubicin and cytosine arabinoside. She died 3½ weeks after start of that therapy.

The AML-patient, who was primarily resistant to 2 cycles TAD-9, had no remission after treatment with two courses of the Carella protocol and was switched to another therapy.

of 3 patients with early relapse within 6 months after achieving complete remission came into partial remission. It was obtained after one cycle of the 3-drug combination, but complete remission could not be achieved by a further cycle. The other 2 patients with early relapse did not respond to one or two courses, respectively.

out of 5 patients with second relapse came into complete remission. Both were achieved after one idarubicin course. 1 patient received the 2-drug and the other the 3-drug combination. The patient responding to the 2-drug combination had been heavily pretreated with anthracyclines. He had previously received 1,080 mg daunorubicin and 1,050 mg aclacinomycin A. 2 AML-patients with a second or fourth relapse, respectively, showed a marked decrease of initially high peripheral white blood cell counts, but had no significant blast

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cell reduction in the bone marrow. Therefore they had to be classified as treatment failures. The last patient with second relapse died from septicemia 4 weeks after beginning idarubicin and cytosine arabinoside therapy. He had bone marrow aplasia without blast cells. This patient had been pretreated with 4 courses of TAD-9 with a cumulative daunorubicin dose of 1,420 mg. A follow-up therapy with a total dose of 840 mg aclacinomycin A in combination with cytosine arabinoside had not had altered the leukemic infiltration in the bone marrow. Meanwhile 8 of 9 AML-patients have died. Their median survival from start of idarubicin combination salvage

therapy was 4 months ranging from 1 to 10 months. The duration of the 2 complete remissions was 2 and 4 months, respectively. The treatment was relatively well tolerated. However, all patients needed platelet transfusions and antibiotic therapy. Some patients suffered from diarrhea. 2 patients had a short and reversible liver function abnormality. No patient showed clinical signs of congestive heart failure or cardiac arrhythmias.

Discussion

In the literature, 14 complete remissions in 79 previously treated acute leukemia patients were achieved by single agent treatment with idarubicin [4, 8, 11, 13]. These patients had AML as well as ALL. The pretreatment of the patients was different and in most instances not so aggressive as the TAD-9 regimen. The kind of relapse was not exactly stated. The same holds true for the published results with idarubicin and cytosine arabinoside combination therapy. Thereby, 5 complete remissions were obtained in 28 pretreated patients [2, 13]. Our results with idarubicin-based combination treatment confirm a complete remission rate of about 20% in heavily pretreated patients.

In conclusion, idarubicin in combination with cytosine arabinoside +/- etoposide is effective in relapsed acute leukemia, even in intensively pretreated patients. The combination of idarubicin and cytosine arabinoside +/- etoposide does not show a complete cross-resistance to other anthracycline containing regimens, e.g. the TAD-9 protocol. The duration of remission and survival in heavily pretreated patients is short. In our opinion idarubicin is a promising drug and deserves further evaluation in the treatment of acute leukemia.

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