Aclacinomycin-A in the Induction Treatment of Childhood AML

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Key Words

AML

Aclacinomycin-A

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Summary

In the cooperative study AML-IGCI-84 27 children with AML (FAB M1 7 ×, M2 4 ×, M3 1 ×, M4 6 × and M5 8 ×; 1 megakaryocytic leukemia) have been treated. The median initial white blood cell count was 18.0 G/l (range 1.8-1,350.0 G/l). 1 or 2 courses of induction therapy were used: I (aclacinomycin-A (ACLA-A), VP-16 and ARA-C) and II (daunorubicin (DNR), VP-16, and ARA-C). II was used only if bone marrow contained > 5 % blast cells on day 21. II and consolidation treatment were identical with the current AML-BFM-83 protocol. 3 deaths before day 21 occurred (2 cerebral hemorrhages, 1. septicemia). 24 patients were evaluable for response, 20 (83.3%) achieved CR, 16 (66.7%) by I, 4 after II. 4 patients never reached CR, 3 of them had a PR after II. M5 patients did badly (2 early deaths, 2. PR, 4 CR). All patients without CR after I received the whole AML-BFM-83 protocol. Comparison of the results of the 2 studies revealed a similar CR rate for I (our patients) and II (BFM data): 80.0% vs. 82.2% (calculated for patients who ever reached CR). CR was reached before consolidation in all our CR patients compared to 82.2% of BFM patients. Early CR may be of long term prognostic significance. Cardiototoxicity of induction may be reduced by substitution of DNR by ACLA-A.

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Zusammenfassung und Schlüsselwörter

In der kooperativen Therapiestudie AML-IGCI-84 wurden 27 Kinder mit AML (FAB M1 7×, M2 4×, M3 1 ×, M4 6× und M5 8×; 1 megakaryozytäre Leukämie) behandelt. Die mediane initiale Leukozytenzahl betrug 18,0 G/l (1,8-1350,0 G/l). 1 oder 2 Induktions-therapieblöcke wurden verwendet: I (Aclacinomycin-A (ACLA-A), VP-16 und ARA-C) und II (Daunorubicin (DNR), VP-16 und ARA-C). II wurde lediglich eingesetzt, wenn das Knochenmark am Tag 21 > 5% Blasten enthielt. II und die Konsolidierungstherapie waren identisch mit dem gegenwärtigen AML-BFM-83 Protokoll. 3 Todesfälle ereigneten sich vor Tag 21 (2 Hirnblutungen, 1 Sepsis). 24 Patienten waren bezüglich des Ansprechens auf die Therapie evaluierbar, 20 (83,3 %) erreichten eine CR, 16 (66,7%) durch I, 4 nach II. 4 Patienten kamen nie in eine CR, 3 davon hatten eine PR nach II. Patienten mit M5 verliefen ungünstig (2 Fröhntodesfälle, 2 PR, 4 CR). Alle Patienten, die nach I nicht in CR waren, erhielten die vollständige Therapie entsprechend dem AML-BFM-83-Protokoll. Ein Vergleich der Ergebnisse der beiden Studien ergab eine ähnliche CR-Rate für I (unsere Patienten) und II (BFM-Daten): 80,0% vs. 82,2% (berechnet

für Patienten, die jemals eine CR erreichten). Bei alien unseren Patienten war die CR vor der Konsolidierungstherapie erreicht im Gegensatz zu 82,2% der BFM-Patienten. Eine frühe CR könnte günstig für die Langzeitprognose sein. Die Kardiotoxizität der Induktionstherapie kann möglicherweise durch den Ersatz von DNR durch ACLA-A reduziert werden.

AML – Aclacinomycin-A – Induktionstherapie

Since January 1984 27 children from Austria and Hungary with newly diagnosed acute myeloblastic leukemia (AML) have been treated in the cooperative study AML-IGCI-84. 1 or 2 courses of induction chemotherapy (II and I2) have been used to achieve early complete remission (CR) (less than 5 % blast cells in bone marrow smears). The facultative course I2, the consolidation as well as the maintenance treatment were identical with the complete study protocol currently used by the BFM group (AML-BFM-83), which was derived from the AML-BFM-78 protocol just by adding the course of induction chemotherapy I2 [1]. The induction chemotherapy consisted of ARA-C 100mg/m2 i. v. as a continuous infusion (i.v. CI) on days 1 and 2, followed by 100mg/m2 I2-hourly i.v. as a short infusion (i.v. SI) on days 3-7, aclacinomycin-A (ACLA-A) 25mg/m2 i.v. and VP-16 100mg/m2 i.v. SI on days 3-7 (II). If necessary (more than 5 % blast cells in bone marrow smears on day 21), a second course of induction chemotherapy was started consisting of ARA-C 100mg/m2 i.v. CI on days 1 and 2, followed by 100mg/m2 i.v. SI I2-hourly on days 3-8, daunorubicin (DNR) 60mg/m2 i.v.1 on days 3-5 and VP-16 150mg/m2 i.v. SI on days 6-8 (I2). Patients with initial very

In Summer 1984 the DNR regimen was changed from i.v.-injection to i.v. short infusion high peripheral WBC received a cytoreductive pretreatment with 6-thioguanine and ARA-C. The aims of our study were

to study the effectiveness of ACLA-A in AML induction chemotherapy and

to evaluate the prognostic influence of an early CR before the consolidation treatment.

Results

27 patients were entered in the study. No patient died before treatment but 3 early deaths occurred before the first bone marrow control scheduled for day 21: 2 due to cerebral hemorrhage, 1 to septicemia. Thus 24 patients could be evaluated for treatment response, 15 boys and 12 girls aged 2 months to 14 years 10 months (median 6 1/4 years) have been treated. Following FAB criteria M1 morphology was diagnosed 7 times, M2 4 times, M3 once, M4 6 times, M5 8 times, and one megakaryocytic leukemia. Initial peripheral WBC was 2.0-1,350.0 G/l (median 18.0 G/l). CR was achieved in 20/24 patients (83.3%); in 16/24 (66.7%) by II, 4 times only after I2. All the 20 patients with CR had already achieved CR before consolidation therapy. 4 patients

Fink et al.: Aclacinomycin-A in the Induction Therapy of Childhood AML

155

never reached CR, 3 of them had a partial remission (PR) after II, 1 patient was non-responder (NR) to II. 3 patients died of disease without initial CR, 1 patient was alive without initial CR on the day of evaluation. 3 patients relapsed 2, 5, and 6 months after diagnosis, respectively. 2 patients died in first continuous CR (CCR) after 1 and 2 months, respectively, due to cerebral aspergillosis and septicemia (*Pseudomonas aeruginosa*). Currently 15 patients are in CCR with a follow-up time of 2-18 months, median 9 months, mean 9.3 months. Thus 75 % of all CR patients (15/20) are in CCR or 55.6 % of all patients entered in the study (15/27), respectively,

including the early deaths. Patients with M5 morphology did badly (2 early deaths, 2 PR, only 4 CR). 1 patient was treated by syngeneic bone marrow transplantation from his identical twin.

Discussion

In part the two questions of the study can already be answered:

(1) In our hands the induction chemotherapy with ACLA-A, VP-16 and ARA-C (II) was effective. In the 20 CR patients we already had 75 % CR (15/20) and 3 PR after II. Calculated for all patients evaluable for treatment response, 66.7% (16/24) achieved CR after II. Since the new induction therapy course II and, if necessary, the use of a second induction therapy course 12 which is identical with the BFM induction course, are the only differences between our study and the study protocol AML-BFM-83 a comparison of the results is useful (table I). In the BFM-83 study 7/95 patients died before treatment (in our study 0/27), 6/95 early deaths occurred (3/27), 5/6 due to hemorrhage (2/3). 82/95 patients were evaluable for treatment response (24/27). 73/82 patients (89%) achieved CR (20/24 – 83.3 %), 60/73 of those (82.2 %) after the induction therapy course (identical with 12). In our study (16/20 (80%) of all CR have already been reached after II. In the BFM-83 study 7/82 patients (8.5%) never achieved CR, in our study 4/24 (16.7%). 16/73 BFM patients (21.9%) relapsed and 1/73 patient (1.4%) died in

Table I. Comparison of the data from our study AML-IGCI-84 with the data from the study AML-BFM-83

AML-IGCI-84 (by August '85)

AML-BFM-83 (by January '85)

Patients entered

27

95

Deaths before treatment

0

7/95 (7.4%)

Early deaths

3/27 (11.1%)

6/95 (6.3%)

(due to hemorrhage)

2/3

5/6

Patients evaluable for

treatment response

24/27 (88.9%)

82/95(86.3%)

CR achieved

20/24 (83.3%)

73/82(89.0%)

CR after first

induction course

16/20 (80.0%)
 60/73(82.2%)
 CR before consolidation
 20/20(100%)
 60/73(82.2%)
 PR and NR
 4/24 (16.7%)
 7/82 (8.5%)
 Relapses
 3/20 (15.0%)
 16/73(21.9%)
 Deaths in CR
 2/20 (10.0%)
 1/73 (1.4%)
 In CCR
 15/20 (75.0%)
 55/73(75.3%)

15/27 (55.6%)
 55/95(57.9%)

CR, whereas 3/20 of our patients (15 %) relapsed and 2/20 (10%) died in CR. By the date of evaluation in the BFM-83 study 55/73 CR patients (75.3 %) were in CCR (January 1985, maximal follow-up time 24 months, median follow-up time not available), in our study 15/20 CR patients (75%) (maximal follow-up time 18 months, median 9 months). 55/95 of all BFM-83 patients (57.9%) are in CCR, 15/27 (55.6%) in our study.

All patients who were not in CR after II immediately received the complete BFM-83 induction and consolidation treatment. Therefore the difference in the rate of NR (8.5% vs. 16.7%) is difficult to explain. Anyway, the rate of CR after 1 induction therapy course is similar for II and I2 (83.3% vs. 82.2%) if calculated for all patients who ever achieved CR. Therefore the effectiveness of the two different induction therapy courses seems to be comparable.

At the present time cardiotoxicity of the induction therapy cannot be evaluated yet. In animal studies, however, ACLA-A showed to be less cardiotoxic than DNR [2, 3]. The use of ACLA-A instead of DNR for induction therapy may reduce the risk of therapy related deaths in some patients. (2) With the use of up to 2 induction therapy courses, all the CR have already been achieved before consolidation therapy as compared to 60/73 (82.2%) in the BFM study. Whether the early CR has a positive effect on the long-term remission rate is still speculative. In any case CR seems to be a good starting point for consolidation treatment. Long-term follow-up results are not yet available.

Amendment

One of the patients who were described as never having reached CR later achieved CR by the consolidation treatment, thus only 3 of the evaluable patients never reached CR.

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