Aclacinomycin-A in the Induction Treatment of Childhood AML

F.M. Fink
E.R. Grümayer
G. Kardos
T. Revesz
H. Gadner
D. Schuler

St. Anna Children’s Hospital (Head: Prof. H. Gadner), Vienna, Austria
Department of Pediatrics II (Head: Prof. D. Schuler), Semmelweis Medical School, Budapest, Hungary

Key Words
AML
Aclacinomycin-A
Induction therapy

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: II (aclacinomycin-A (ACLA-A), VP-16 and ARA-C) and 12 (daunorubicin (DNR), VP-16, and ARA-C). 12 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 II, 4 after 12. 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 II received the whole AML-BFM-83 protocol. Comparison of the results of the 2 studies revealed a similar CR rate for II (our patients) and 12 (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. Cardiotoxicity of induction may be reduced by substitution of DNR by ACLA-A.

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 (I and II) have been used to achieve early complete remission (CR) (less than 5 % blast cells in bone marrow smears). The facultative course II, 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 II. 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 12-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 (I). 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 12-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 (II). Patients with initial very 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 6¼ years) have been treated. Following FAB criteria MI 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 II. 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

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 II 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 II). 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)

<table>
<thead>
<tr>
<th>Patients entered</th>
<th>27</th>
<th>95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths before treatment</td>
<td>0</td>
<td>7/95 ( 7.4%)</td>
</tr>
<tr>
<td>Early deaths</td>
<td>3/27 (11.1%)</td>
<td>6/95 (6.3%)</td>
</tr>
<tr>
<td>(due to hemorrhage)</td>
<td>2/3</td>
<td></td>
</tr>
<tr>
<td>Patients evaluable for treatment response</td>
<td>24/27 (88.9%)</td>
<td>82/95 (86.3%)</td>
</tr>
<tr>
<td>CR achieved</td>
<td>20/24 (83.3%)</td>
<td>73/82 (89.0%)</td>
</tr>
<tr>
<td>CR after first induction course</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 II (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.

Acknowledgment
For the good cooperation we would like to thank the colleagues in Austria and Hungary who entered patients in our study. We are grateful to the BFM study group for permission to publish preliminary data of the current AML study.

References
M. Fink, Univ.-Kinderkrankenhaus.