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ORIGINAL ARTICLE

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Treatment with all-trans retinoic acid in acute promyelocytic leukemia reduces early deaths in children

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Abstract All-trans retinoic acid (ATRA) is a known inducer of differentiation in acute promyelocytic leukemia. To improve the outcome of children with acute promyelocytic leukemia, ATRA has been applied since 1994 as an additional induction element inthe AML-BFM 93 study. In a retrospective study, we compared 22 children treated with ATRA (median age: 9.3 years; range: 1.8–16.3) with 22 patients receiving conventional therapy (median age: 12.3 years; range: 3.2–16.7). Twenty-one of the children achieved complete remission. Only one patient died early from bleeding complications after 3 days administration of ATRA. In the control group, seven early deaths occurred (Fisher exact test; $p<0.04$). Two children died from intracerebral hemorrhages. Two patients suffered from sepsis during aplasia after induction therapy, and one child did not respond to treatment. The 5-year overall survival (OS) and event-free survival (EFS) of the children who received ATRA followed by chemotherapy were significantly bettercompared with conventionally treated children [OS: 0.87±0.9 vs 0.45±0.11, p (log rank) <0.003; EFS: 0.76±0.11 vs 0.43±0.11 p (log rank) <0.02]; the median observation time was 2.8 years (19–76 months). However, nearly all children suffered from common side effects such as headache, fever, joint, muscle and bone pain, weight gain, or dermatitis. In three patients, a retinoic acid syndrome was observed. Interruption of ATRA treatment and application of dexamethasone, necessary in 12 children, controlled theadverse effects. ATRA treatment could be resumed in 18 patients. In conclusion, ATRA treatment during induction could avoid early deaths in children with acute promyelocytic leukemia with considerable but manageable toxic side effects.

Keywords Acute promyelocytic leukemia · All-trans retinoic acid · Childhood · Toxicity

Introduction

Acute promyelocytic leukemia (APL), characterized by the chromosomal translocation t(15;17) (q22;q21) encoding for the fusion gene PML/RARα [11, 16], has a favorable prognosis compared to other FAB subtypes of acute myeloid leukemia [10, 15], but overall survival is impaired by a high rate of early deaths caused by fatal bleeding events and severe sepsis [17]. Promyelocytic blasts cause the severe coagulation disorder intensified by the release of procoagulant and proteolytic factors after blast lysis [7].

The application of all-trans retinoic acid (ATRA) has improved the prognosis in APL over the last 10 years. The underlying molecularpathogenesis is explained by the reduced retinoic acid sensitivities of a nuclear receptor corepressor binding to PML-RARα. This fusion protein inhibits the dissociation of the histone deacetylase corepressor complex. As the ATRA sensitivity of the corepressor association with the PML-RARα is lower than with the wild-type RARα, pharmacological concentrations of ATRA enable the corepressor dissociation, the association of the coactivator (SRC-1) with histone ace-tylation activity, and thereby further transcription and/or differentiation [14]. This led to complete morphological remissions in 80–90% of the patients [11]. The down-regulation of the procoagulant activity of promyelocytic blasts and endothelial cells might reduce the bleeding risk and the deliberation of pro-

This study was performed on behalf of, and within the framework of, the German-Austrian-Swiss cooperative trial AML-BFM 93

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teolytic substances [7, 9]. Moreover, maturation of neutrophils increased their immunological function and reduced the risk of severe infections.

However, ATRA treatment alone is not able to sustain remission, and toxicity of ATRA, especially in children, has not been completely evaluated. Severe side effects such as retinoic acid syndrome (RAS), a complex of fever, capillary leakage, hyperleukocytosis, leukocyte organ infiltration, and pseudo-tumor cerebri were responsible for therapy-related mortality and morbidity in adults [6, 12] impairing overall prognosis. We retrospectively analyzed the effectivity of the ATRA treatment combined with chemotherapy in children with APL and the management of associated side effects.

Patients and methods

Study population

All patients (n=28) with APL registered in the German-Austrian-Swiss cooperative trial for the treatment of acute myeloid leukemia (AML-BFM 93; total study population, n=471) were evaluat-

Table 1 Patient data

Patient	Study	Gender	Age (years)	WBC (10^9/l)	Hb (g/dl)	Platelet count (10^9/l)	Bone marrow blasts (%)	Re-mission	Time to relapse (months)	Alive/dead	Follow-up (months)
1	AML-93	M	1.8	60.4	4.1	90	72	CR		Alive	52.3
2	AML-93	F	2.3	7.7	7.6	5	30	CR		Alive	22.2
3	AML-93	M	2.4	20.3	6.6	120	92	CR	14.1	Alive	21.0
4	AML-93	M	3.1	2.6	7.9	12	82	CR		Alive	23.4
5	AML-93	F	3.2	6.5	11.3	310	2	CR		Alive	72.6
6	AML-93	M	3.6	64.1	8.7	32	91	CR		Alive	23.6
7	AML-93	F	4.2	2.7	8.1	25	78	CR		Alive	19.1
8	AML-93	M	4.4	2.4	10.3	296	75	CR		Alive	19.2
9	AML-93	M	4.5	6.2	12.3	64	70	CR		Alive	56.9
10	AML-93	F	6.5	2.6	6.5	15	88	CR		Alive	47.6
11	AML-93	M	7.2	6.9	n.a.	21	84	CR	30.1	Alive	69.6
12	AML-93	F	8.4	18.3	5.5	20	90	CR		Alive	19.4
13	AML-93	F	10.2	1.4	11.4	24	80	CR		Alive	75.8
14	AML-93	F	10.3	4.4	9.3	15	90	CR		Alive	21.2
15	AML-93	F	10.9	1.7	6.6	22	91	CR		Alive	19.0
16	AML-93	M	12.2.	9.8	9.1	17	98	CR		Alive	35.4
17	AML-93	M	13.0	58.7	13.5	36	95	CR		Alive	66.3
18	AML-93	M	13.3	6.8	8.2	16	71	CR	26.5	Dead	26.5
19	AML-93	F	13.8	0.9	8.7	27	75	CR		Alive	49.7
20	AML-93	F	14.4	0.4	8.3	15	90	CR		Alive	58.5
21	AML-93	M	15.5	2.8	7.6	17	73	ED		ED	0.1
22	AML-93	F	16.3	1.5	5.9	7	86	CR		Alive	31.8
Median		1:1	9.3	5.3	8.2	21.5	83	CR n=21; ED n=1		Alive n=20	33.6
23	AML-87	F	3.2	2.9	8.3	10	87	CR		Alive	96.3
24	AML-87	F	3.7	4.2	11.6	27	90	PR	4.1	Dead	8.5
25	AML-93	F	3.8	48.7	8.2	22	94	CR		Dead	2.7
26	AML-87	F	5.9	6.1	5.4	11	95	CR		Alive	74.4
27	AML-87	M	6.0	33.8	5.1	45	92	ED		ED	0.2
28	AML-87	F	10.6	1.8	9.4	48	100	CR	21.1	Alive	86.7
29	AML-87	M	11.1	1.7	9.2	58	70	CR		Alive	9.5
30	AML-93	F	11.6	41.1	10.9	21	93	ED		ED	0.1
31	AML-93	M	11.6	2.9	9.2	15	62	CR		Alive	6.5
32	AML-87	F	11.7	2.2	8.3	24	69	CR		Alive	75.5
33	AML-87	M	12.1	13.5	8.1	42	90	ED		ED	0.3
34	AML-93	M	12.4	2.8	6.3	39	93	ED		ED	0.5
35	AML-87	M	12.5	2.9	8.3	34	79	CR		Alive	98.9
36	AML-87	M	12.8	89.0	8.5	15	97	CR		Alive	103.4
37	AML-87	F	13.2	24.2	10.2	38	81	ED		ED	1.4
38	AML-87	F	13.7	2.5	9.8	28	90	CR		Alive	64.3
39	AML-87	F	13.7	2.8	10.3	158	92	CR		Alive	112.6
40	AML-87	M	13.8	6.2	10.6	11	100	CR	12.1	Dead	19.4
41	AML-93	M	15.4	60.7	11.7	11	93	CR	4.2	Dead	47.1
42	AML-87	M	15.6	1.9	5.4	23	72	ED		ED	0.2
43	AML-93	F	16.2	23.1	8.9	25	80	ED		ED	0.2
44	AML-87	M	16.7	2.9	9.4	24	88	CR		Alive	98.4
Median		1:1	12.3	3.6	9.1	24.5	90	CR n=14; ED n=7; PR n=1		Alive n=11	11.2, alive: 81.1

CR complete remission, *PR* partial remission, *ED* early death, *n.a.* not available

ed; the incidence of AML FAB M3 was 5%. Historical controls were recruited from the trial AML-BFM 87 (n=16) (Table 1).

Diagnosis

The diagnosis was established by typical morphological features. Bone marrow slides of all patients were reviewed centrally. As previously demonstrated, morphological diagnosis was sufficient to confirm APL [3]. The detection of fusion protein PML/RARα and/or karyotype t(15;17) was successful in 21 of the 28 patients recruited from the AML-BFM 93 study. In the historical control group, cytogenetic analysis was available only in a minority of patients (n=2).

ATRA treatment

Twenty-two children in the study AML-BFM 93 had received ATRA since 1994 as an additional element of the induction therapy. ATRA treatment was recommended to start 3 days before the induction therapy. In children with increased white blood counts (n=3), ATRA and cytosine arabinoside (ara-C) 100 mg/m^2 per day were simultaneously administered. The initial recommendation of 45 mg/m^2 of ATRA (as for adults; n=7) was reduced to 25 mg/m^2 per day after severe symptoms (headache, fever without infection, bone, joint, and muscle pain, and weight gain) were observed in our first patients and reported by others [12, 21].

Chemotherapy

All patients received chemotherapy according to the study protocol of AML-BFM 93 (Fig. 1). The treatment schedule consisted of an induction therapy with ara-C 100 mg/m^2 per day (d1), and two continuous infusions, 2×100 mg/m^2 per day (d3–8), and randomized either daunorubicin 2×30 mg/m^2 per day (d3–5) or idarubicin 12 mg/m^2 per day (d3–5), and etoposide 150 mg/m^2 per day (d6–8), followed by a consolidation phase with 6-thioguanine (6-TG) 60 mg/m^2 per day (d1–43) orally, prednisolone 40 mg/m^2 per day orally (d1–43), vincristine 1.5 mg/m^2 per day (d1, 8, 15, 22), adriamycin 30 mg/m^2 per day (d1, 8, 15, 22), ara-C 75 mg/m^2 per day (d3–6, d10–13, d17–20, d24–27, d31–34, d38–41), cyclophosphamide 500 mg/m^2 per day (d29, 43), and intensification therapy with high-dose ara-C 2×3 g/m^2 per day (d1–3), VP16 125 mg/m^2 per day (d2–5). CNS prophylaxis consisted of ara-C administered nine times intrathecally in an age-dependent standard dosage and cranial irradiation with 18 Gy. Maintenance therapy with 6-TG 40 mg/m^2 per day orally and ara-C 40 mg/m^2 per day s.c. on 4 consecutive days monthly for a total duration of 1 year completed the treatment.

Three patients were pretreated with ara-C after having started ATRA treatment before induction chemotherapy according to the protocol; the courses of two of these patients have been published [18].

Control group

Twenty-two patients with APL not receiving ATRA were recruited from the former trial AML-BFM 87 (n=16) and from study AML-BFM 93 (n=6) (Table 1). Four of the latter patients had not received ATRA for the following reasons: lack of precise recommendations until 1994 regarding the administration and dosage of ATRA and the presumed higher risk of toxicity in children (two patients), hyperleukocytosis (one patient survived life-threatening bleeding during induction therapy, relapsed after 3 years, and was then treated with ATRA as part of the reinduction therapy), and misdiagnosis in a patient with M3v and fatal intracerebral bleeding leading to death within 3 days. In two patients there was no evident reason why ATRA had not been given.

The applied chemotherapy was identical to the therapy in children receiving ATRA. Concerning the patients recruited from the AML-BFM 87 study, the intensity of induction chemotherapy was identical. The only difference in study AML-BFM 93 was a randomization between daunorubicin 180 mg/m^2 vs idarubicin 36 mg/m^2 total dose, whereas daunorubicin had been given to all patients in the AML-BFM 87 study.

Results

Patients

Patients receiving ATRA

In 19 of the 22 patients, the diagnosis was supported by karyotyping showing the chromosomal translocation t(15;17)(q22;21) or by detecting the PML/RARα rearrangement. Twenty-two patients were treated with ATRA: 11 girls and 11 boys with a median age of 9.3 years (range: 1.8–16.3) diagnosed as AML FAB M3 (n=19) or M3v (n=3). The median hematological pretreatment val-

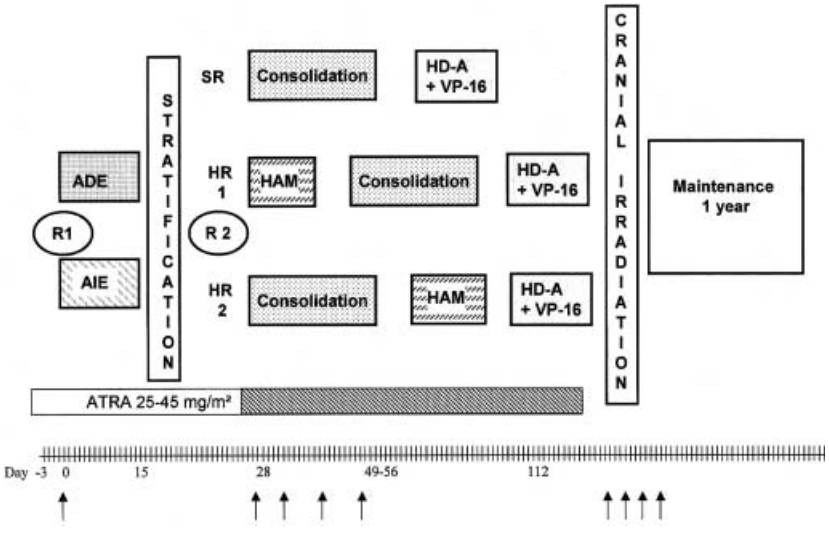

Fig. 1 *ADE* ara-C, daunorubicin, etoposide, *AIE* ara-C, idarubicin, etoposide, *HAM* high-dose ara-C, mitoxantrone, *HD-A-VP16* high-dose ara-C, etoposide, *SR* standard risk, HR high risk, *R* randomization, ↑ ara-C intrathecally

Table 2 Toxicity

ATRA-related toxicity Organ system	12/22 (55%) *n*	RAS (fever, pulmonary infiltrate/pleural effusion, weight gain, cerebral symptoms) Symptoms	3/22 (14%) *n*
Pulmonal system	3 (14%)	ARDS Pleural effusion Pulmonary infiltrate	2 (9%) 1 (5%) 1 (5%)
CNS	6 (27%)	Headache Intracranial pressure	6 (27%) 1 (5%)
Cardiovascular system	5 (23%)	Pericardial effusion Weight gain Arterial hypotension	1 (5%) 5 (23%) 2 (9%)
Liver/metabolic	12 (55%)	Raised transaminases Raised bilirubin Raised triglycerides	6 (27%) 1 (%) 2 (9%)
Hematological	4 (18%)	Hyperleukocytosis	4 (18%)
Skin/muscle/joint/bone	4 (18%)	Dry skin Itching Joint/bone/muscle pain Osteonecrosis	1 (5%) 1 (5%) 3 (14%) 1 (5%)

RAS retinoic acid syndrome, *CR* complete remission, *ARDS* adult respiratory distress syndrome, *CNS* central nervous system

ues showed leukocytes: 5.3 G/l (0.4–64.1 G/l), bone marrow blasts: 83% (2–98%), platelets: 21.5 G/l (5–310 G/l), Hb: 8.2 g/dl (4.1–12.3 g/dl).

ATRA treatment

The ATRA dose varied between 15 and 45 mg/m^2 per day (mean 26 mg/m^2 per day). The time interval between starting ATRA treatment and chemotherapy was 2 days in two patients, 3 days in five patients, and 4, 5, 6, and 10 days in one patient each. Three patients received ATRA treatment after starting chemotherapy on days 5, 7, and 28. Different reasons were responsible for deviations from the treatment schedule. In four patients, the definitive diagnosis was delayed; therefore, ATRA treatment started after central evaluation. In six children, initial complications such as infection or bleeding caused a modified ATRA application; three children had a high blast count at diagnosis.

Course and outcome

Of the 22 patients treated with ATRA, 21 achieved complete remission (95%). One boy died early after severe bleeding and the development of ARDS after shock. Three patients relapsed after 14–30 months; one of them died from progressive disease. The estimated 5-year event-free survival was 0.76±0.11. Overall, 20 patients treated with ATRA and chemotherapy survived; the median follow-up was 34 months (range: 19–76).

Coagulation parameters

An abnormal coagulation profile including prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen was reported in ten patients receiving ATRA; seven were substituted with fresh-frozen plasma. In threepatients, a rapid improvement of the abnormal coagulation profile was achieved without plasma substitution. Normalization was documented in 12 patients after 14 days of ATRA treatment.

Adverse effects

ATRA toxicity was considerable, leading to a generalized severe capillary leakage syndrome together with leukocyte activation manifested as weight gain, pulmonary infiltrates or pleural effusions with acute respiratory distress, and fever without infection (retinoic acid syndrome) in three patients. Overall, 12 of 22 patients showed symptoms associated with ATRA (Table 2). All symptoms attributed to ATRA, except osteonecrosis, disappeared completely with adequate management consisting of reduction or interruption of ATRA treatment, application of steroids, and start of chemotherapy.

In detail, after occurrence of side effects, nine children received steroids 1 mg/kg. The ATRA dose was reduced in median from 38 mg/m^2 (15–45 mg/m^2) to 24 mg/m^2 (4–28 mg/m^2) in ten patients and had to be reduced even further in three patients, whereas in another three children the dose could be increased again. The median duration of ATRA administration was 38 days (6–138 days).

Control group

Twenty-two children, 11 females and 11 males, received no ATRA. Their median age at diagnosis was 12.3 years (range: 3.2–16.7). There was no major difference in he-

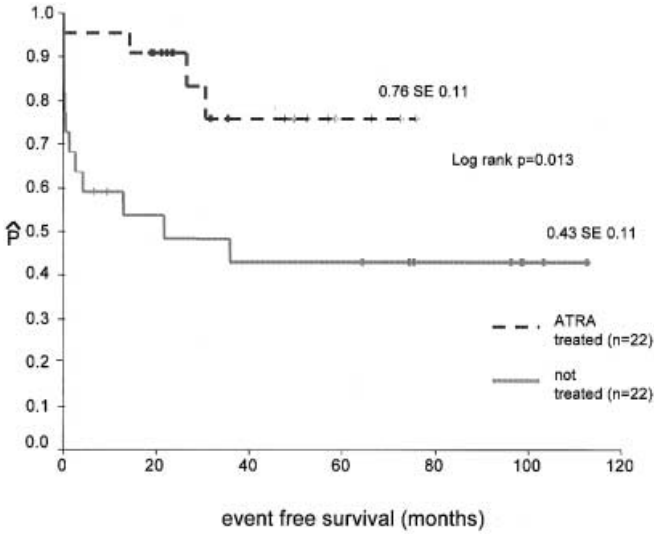

Fig. 2 Children with APL treated with chemotherapy alone (*solid line*) or with ATRA plus chemotherapy (*broken line*)

matological characteristics to the group receiving ATRA: WBC 3.6 G/l (1.7–89), bone marrow blasts: 90% (62–100%), platelets: 24.5 G/l (10–158), Hb: 9.1 g/dl (5.1–11.7). (Table 1).

As the control group was mainly historical, we compared the early death rate in study AML-BFM 87 to that of study AML-BFM 93 for patients without APL to evaluate whether an overall improvement in the clinical management of toxicity could explain the decline of fatalities. We found no statistically significant difference, the early death rate in study AML-BFM 87 being 9% (24 of 268 patients) compared to 7% (17 of 242patients) in study AML-BFM 93 (2-tailed Fisher exact test: 0.52). Of 22 patients treated with chemotherapy and without ATRA, 7 died within the first 6 weeks. There were two fatal hemorrhages; the other deaths were caused by infections (n=2), multiorgan failure, respiratory insufficiency, and renal insufficiency due to tumor lysis syndrome. A complete remission was observed in 14 patients; one child attained only a partial remission. Relapse occurred in four patients within 4–21 months; three of them died from progressive disease. Up to now, 11 patients have survived with a median follow-up of 81 months.

Comparison of ATRA-treated children and the control group

The early death rate was significantly higher in patients without ATRA treatment compared to those receiving ATRA combined with chemotherapy (Fisher exact test: p<0.04). This led to a significantly improved estimation of 5-year event-free survival (ATRA group: P 0.76±0.11 vs control group: P 0.43±0.11; log rank p<0.02; Fig. 2) and a significantly increased probability of overall survival in the patients receiving ATRA and chemotherapy (P 0.87±0.9 vs P 0.45±0.11; log rank p<0.003).

Discussion

We retrospectively evaluated the risks and benefits of ATRA treatment as part of the remission induction in children with APL. According to Bapna et al. [2] and Fenaux et al. [10], the early death rate was significantly reduced by the treatment with ATRA.

In clinical studies using ATRA alone, morphological remissions could be obtained, but relapses were usually observed [13]. Therefore, the combination of ATRA and an intensive chemotherapy seemed to be more effective [1]. According to theresults of our previous studies BFM 78–87, relapse rate was low after an intensive multidrug treatment regimen. Therefore, ATRA was combined with this therapy protocol.

As in adults, our study started with the recommendation of ATRA 45 mg/m^2 [8, 19]. Based on reports of severe side effects [12, 21] and the evidence that reduced doses had similar effects and comparable pharmacokinetics in children, the dose was reduced to 25 mg/m^2 [4, 5].

As demonstrated above, the induction treatment between our control group of the AML-BFM 87 study and the patients receiving ATRA was similar. Therefore, the significant reduction of early fatalities in children with APL receiving ATRA as an element for remission induction was attributed to retinoic acid treatment.

The relapse rate of the children who had achieved complete remission did not differ significantly; however, the low number of patients and the known good prognosis in APL after having survived induction must be considered. Due to the application of ATRA, the extent of coagulation abnormalities in children with APL was reduced or corrected within 1 week. In addition, no life-threatening infections occurred in our study group. Anyhow, several authors could not find a reduction in early death rate in patients treated with ATRA because of side effects [21]. A remarkable rate of mortality has been associated with the retinoic acid syndrome and especially with pseudo-tumor cerebri. In children, this effect might even be more pronounced, but so far only few data are available about the risks and benefits of ATRA in pediatric patients [2, 19].

Side effects of ATRA treatment in our study group were observed in 12 children, culminating in a retinoic acid syndrome in 3 patients. They were successfully managed by dose reduction or interruption of ATRA treatment and the application of steroids. Nevertheless, it has to be confirmed by higher patient numbers whether the recommended lower dose of ATRA might reduce severe side effects.

According to our experiences, we recommend a dosage of 25 mg/m^2 per day, an early reduction or interruption of ATRA treatment, and probably most important the use of dexamethasone when symptoms of ATRA toxicity occur [1, 10]. The decrease in the early death rate and the prevention of severe ATRA toxicity enabled a further improvement of overall survival of children with APL.

Another advantage of ATRA is the chance to induce a second remission in case of relapse [20]. In our study, two children treated with ATRA after relapse achieved a second remission.

In conclusion, ATRA combined with intensive chemotherapy cannot only induce a stable continuous remission but also avoid early deaths in children with acute promyelocytic leukemia with considerable but manageable toxic side effects.

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