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RESEARCH ARTICLE

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Characteristics and outcome in patients with central nervous system involvement treated in European pediatric acute myeloid leukemia study groups

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Abstract

Background: There is no consensus on the treatment for pediatric patients with acute myeloid leukemia and initial central nervous system (CNS) involvement.

Methods: To evaluate different CNS-directed treatment options (intrathecal [IT] therapy, CNS irradiation, hematopoietic stem cell transplantation [HSCT]), 261 patients (excluding acute promyelocytic leukemia) with initial CNS involvement treated in trials with similar intensive chemotherapy by four cooperative European study groups (1998–2013) were studied and compared with CNS-negative patients from the Berlin–Frankfurt–Münster group.

Results: Patient characteristics in the different study groups were comparable. Young age, high white blood cell count, extramedullary involvement other than the CNS, monoblastic morphology, and inv(16) were associated with CNS involvement (each $P < 0.0001$). There were no major differences in outcome between the study groups. The cumulative incidence of relapse (CIR) regarding the CNS was higher in initially CNS-positive versus initially CNS-negative patients (all: 8 ± 2% vs. 3 ± 1%, $P_{(Gray)} = 0.001$; isolated: 4 ± 1% vs. 1 ± 0%, $P_{(Gray)} = 0.03$). However, global outcome of

Abbreviations: AIEOP, Associazione Italiana Ematologia Oncologia Pediatrica; AML, acute myeloid leukemia; BFM, Berlin–Frankfurt–Münster; BSPHO, Belgian Society of Paediatric Haematology Oncology; CIR, cumulative incidence of relapse; CNS, central nervous system; CR, complete remission; DCOG, Dutch Childhood Oncology Group; EFS, event-free survival; FAB, French–American–British; HD-Arac, high-dose cytarabine; HR, high risk; HSCT, hematopoietic stem cell transplantation; IT, intrathecal; NOPHO, Nordic Society of Pediatric Haematology and Oncology; OS, overall survival; SR, standard risk; TRM, treatment-related mortality; WBC, white blood cell

the CNS-positive cohort (overall survival, 64 ± 3%; event-free survival 48 ± 3%; and CIR 33% ± 3%) did not differ significantly from CNS-negative patients. Risk groups defined by cytogenetics were of likewise prognostic significance in CNS-positive and -negative patients. CNS treatment with cranial irradiation was not superior compared to IT therapy and systemic chemotherapy (± HSCT).

Conclusion: Although CNS relapses occurred more frequently in initially CNS-positive patients, their global outcome was similar as in CNS-negative patients. Intensified IT therapy was heterogeneous; however, at least eight applications, preferably with triple IT chemotherapy, seem to be appropriate to accompany dose-intensive systemic chemotherapy.

KEYWORDS
acute myeloid leukemia, children, CNS involvement, treatment

1 | INTRODUCTION

Central nervous system (CNS) involvement at diagnosis in pediatric acute myeloid leukemia (AML) has an incidence of 6–29%.[1–3] The influence on outcome is unclear and, although an increased incidence of isolated CNS relapse was described in children with CNS disease at diagnosis, most evidence points toward a lack of prognostic impact on event-free survival (EFS).[3–5] Factors associated with CNS leukemia in AML include hyperleukocytosis, monocytic leukemia (French–American–British [FAB] M4 or M5, including M4eo with inv(16)), *KMT2*A gene rearrangement, and younger age.[1,6] A lack of correlation with race, sex, liver or spleen size, FAB subtype, coagulation abnormalities, hemoglobin or platelet, and white blood cell (WBC) count at diagnosis has been shown in other studies.[2,7]

A common aim of the international Berlin–Frankfurt–Münster (I-BFM) AML Study Group is to optimize the diagnostics and treatment in children with AML in order to improve outcome. In view of a future common European AML trial, homogeneity in standard treatment arms and the use of common definitions and patient subgroup identification are required.

One of these subgroups, currently treated differently in various protocols by several collaborative groups, comprises patients with initial CNS involvement. The current treatment includes intrathecal (IT) therapy with various chemotherapeutical agents and doses, with or without cranial irradiation (CRT). Moreover, indications for hematopoietic stem cell transplantation (HSCT) in first complete remission (CR) vary significantly.

The aim of this study was to compare the efficacy of different CNS-directed therapy strategies in CNS-positive patients in trials conducted recently by four cooperative European AML study groups. This was done by retrospectively comparing patient and leukemia characteristics, outcome data (EFS, overall survival [OS], cumulative incidence of relapse [CIR], and CNS relapse), and toxicity between the study groups.

The ultimate goal of this project was to define the most appropriate CNS treatment for children with AML, which can be applied in future trials. From these data, we can deduce that cranial irradiation at least is not necessary in most CNS-positive patients.

2 | METHODS

2.1 | Patients

Patients with de novo AML and initial CNS involvement aged 0–17 years were studied and treated according to a protocol conducted by the following European study groups: Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP, Italy); BFM (Germany, Austria, Switzerland, Czech Republic); Belgian Society of Paediatric Haematology Oncology (BSPHO, Belgium); Dutch Childhood Oncology Group (DCOG, The Netherlands); and Nordic Society of Pediatric Haematology and Oncology (NOPHO, Denmark, Finland, Island, Norway, Sweden) between January 1998 and December 2013. Excluded were patients with secondary AML, acute promyelocytic leukemia, and Down syndrome. CNS-negative patients from the same era treated on AML-BFM regimens were selected as a reference cohort.

Written informed consent from patients, parents, or guardians was obtained in accordance with the Declaration of Helsinki.

2.2 | Treatment

The study groups applied different consecutive protocols, previously described and evaluated in a recommendation paper by an international expert panel.[1]

The treatment was given according to the treatment protocols AIEOP 2002/01,[3] BFM 98 and 2004,[8,9] MRC12 and MRC15,[10,11] DB (Dutch-Belgian) AML-01,[12] and NOPHO AML 93 and 2004.[13,14] DCOG patients were included in MRC 12 and MRC 15 protocols and from March 2010 in the DB AML-01 protocol, the latter being conducted together with BSPHO (for details, see Supplementary Table S1).

The intensity of induction/consolidation or intensification chemotherapy was comparable with four to five blocks of intensive chemotherapy (NOPHO: six blocks) and included high-dose cytarabine (HD-AraC) two or three times.[1] Overall treatment results in the study groups were comparable with a 5-year pOS and pEFS in the AIEOP group (n = 482) of 68 ± 2% and 55 ± 3%, in the BFM group (n = 1284) 68 ± 1% and 53 ± 1%, in DCOG/BSPHO patients (n = 309) 59 ± 3% and 45 ± 3%, and in NOPHO (n = 423) 70 ± 2% and 50 ± 3%, respectively.

Maintenance therapy was only given in the BFM group: daily thioguanine 40 mg/m^2 orally and cytarabine 40 mg/m^2 subcutaneously 4 days monthly for 1 year.

IT therapy was given in all CNS-positive patients at least four times (AIEOP), usually 8–10 times (NOPHO and DCOG/BSPHO) and mostly as triple therapy (methotrexate, prednisone, cytarabine in an age-dependent dose, twice weekly until blasts resolve plus two injections extra). In the BFM group, only IT cytarabine was applied 11–12 times.

CRT was performed in the BFM group in all CNS-positive patients with 18 Gy for children above 24 months and 15 Gy in patients of 15–24 months. CNS-negative patients were randomized to receive 12 versus (vs.) 18 Gy.[6] None of the other groups performed cranial irradiation—with the exception of the DCOG patients >2 years included in the MRC12 protocol.

Allogeneic or autologous HSCT in first remission (CR) was most frequently performed in the AIEOP group. All high-risk (HR) patients (patients without t(8;21) or inv(16), see below) with an HLA-identical family donor were eligible for allogeneic HSCT. All other HR patients were eligible for autologous HSCT.[3] All other groups limited allogeneic HSCT to a small group of HR patients with a matched sibling donor or did not recommend HSCT at all (DB AML-01 protocol).[15]

2.3 | Statistical analysis

For the primary objective, the different regimens for CNS-positive patients (for details, see Supplementary Table S1) were compared by analyzing EFS, OS, and CIR for both all CNS-positive patients and CNS relapse.

EFS was measured from the date of diagnosis to the date of the first event (relapse, secondary malignancy or death), or to the date of last follow-up. Patients who failed to achieve CR were classified as nonresponders and considered as failures at day 0. OS was measured from the date of diagnosis to the date of death from any cause or last follow-up. Probabilities of survival were estimated by the method of Kaplan and Meier, and compared with the log-rank test. Functions of CIR and death in CR were constructed according to Kalbfleisch and Prentice. Cox regression was used in order to take known risk factors into account.

The effects of treatment with or without CRT and with or without maintenance were analyzed by comparing the data from the BFM-group (with CRT and maintenance) with those from the other groups according to the intention to treat principle irrespective of the fact that some patients did not receive CRT and/or maintenance (e.g., because of early events).

The different induction regimens were compared by analyzing the rates of CR and treatment-related mortality (TRM). Logistic regression was used in order to take known risk factors into account. All tests are descriptive; *P*-values below 5% will be considered to be indicative for true effects.

2.4 | Definition

CNS involvement was defined as >5 leukocytes/μl in the cerebrospinal fluid with leukemic blasts on cytomorphological examination or intracranial infiltrates on imaging or neurological symptoms consistent with AML (cranial nerve involvement). A cell count ≤5/μl with blasts in cytospin in a bloodless puncture was not considered as an initial CNS involvement. CNS2, defined as ≤5 leukocytes/μl in the cerebrospinal fluid and proven blasts in cytospin, was not separately reported, but included in the CNS-negative group, because outcome data were similar to other CNS-negative patients without blasts in cytospin. CNS2 patients had no increased CNS relapse rate (data from BFM, not shown).

Blood-contaminated CSF samples were considered as CNS-positive in case of a WBC count >5/μl, predominantly leukemia cells after cytospin and a ratio of erythrocyte/leukocyte count in the centrifuge preparation <100:1 or a higher percentage of leukemia cells in the CSF than in blood.

A CNS relapse was considered either isolated in the CNS or combined in case of association with bone marrow or other extramedullary involvement.

Simplified risk groups were defined only according to cytogenetics: standard risk (SR) = favorable cytogenetics [t(8;21)/*RUNX1/RUNX1T1* or inv(16) or t(16;16) and/or *CBFB/MYH11*)], HR definition: all others.

3 | RESULTS

3.1 | Patient characteristics

Two thousand four hundred ninety-eight de novo AML patients aged 0–17 years from four European study groups were evaluated. After exclusion of patients with absent or doubtful data on initial CNS involvement, 261 out of 2,365 patients (11.0%) were considered as CNS positive. The distribution in the study groups was as follows: AIEOP 38/459 (8.3%), BFM 155/1284 (12.1%), DCOG/BSPHO 33/252 (13.1%), and NOPHO 35/418 (8.4%) (Supplementary Table S2).

Initial patient and leukemia characteristics in CNS-positive patients were generally comparable between the patient cohorts of the study groups (for details, see Supplementary Table S2).

The CNS-positive patients had a median of 11.3 leukocytes/μl in the spinal fluid and blasts were seen microscopically (cytospin) in 86.2% of patients. In 12.0% and 9.7% of patients, cranial nerve involvement and intracranial infiltrates, respectively, were reported. A traumatic lumbar puncture was found in 30.1% patients, which was not associated with a higher CNS-relapse rate (with vs. without a traumatic lumbar puncture: 7 ± 3% vs. 8 ± 2%, $P = 0.88$). When comparing characteristics of CNS-positive patients with CNS-negative patients (Supplementary Table S2), there were significant differences in age (median age 3.8 years vs. 9.2 years, $P < 0.0001$), which was due to a high proportion of infants <2 years (41.4% vs. 21.3%, $P < 0.0001$). The male/female ratio was slightly higher in CNS-positive patients ($P = 0.09$).

The initial WBC count was higher in CNS-positive patients (median 54.6×10^9/l vs. 15.2×10^9/l, $P < 0.0001$).

Extramedullary tumor involvement outside the CNS (excluding spleen and liver enlargement) was described in 39.9% of CNS-positive patients, which is significantly higher compared to patients without CNS involvement (21.6%, $P < 0.0001$).

FAB distribution was significantly different compared to patients without CNS involvement ($P < 0.0001$). This was due to a lower percentage of FAB M1/2 subtypes and more monoblastic subtypes (FAB M4/5).

There was a higher incidence of CNS involvement in patients with inv(16) ($P < 0.0001$) and a trend for lower incidence for t(8;21), ($P = 0.08$). No difference was observed for *KMT2A* rearrangements, *NPM1*, or *FLT3-ITD* mutations (Supplementary Table S2). The risk group distribution was similar in CNS-positive and CNS-negative patients.

According to logistic regression analysis, the variables age (<2 years), WBC (>100,000/μl), and the presence of inv(16) were risk factors for CNS involvement (all $P_{(chi)} < 0.0001$).

3.2 | Treatment results

Treatment results in CNS-positive patients were comparable among the four study groups (Figs. 1A–1C). Five-year OS and EFS estimates were in the same range ($P_{(log.rank)} = 0.90$ and 0.79, respectively) (Figs. 1A and 1B). There was no significant difference in CIR ($P_{(Gray)} = 0.14$), but it has to be mentioned that the nonresponse and TRM rates were slightly higher and relapse rates lower in patients from AIEOP compared to other groups (Fig. 1C, Table 1).

OS, EFS, and CIR for all CNS-positive patients (n = 261) were 64 ± 3%, 48 ± 3%, and 33 ± 3%, respectively. Results were comparable to those in CNS-negative patients (67 ± 1%, $P_{logrank} = 0.23$; 52 ± 2%, $P_{logrank} = 0.11$; and 32 ± 1%, $P_{(Gray)} = 0.57$, respectively).

The cumulative incidence of CNS relapse was 8 ± 2%, which was comparable among the different study groups. Comparing patients with or without initial CNS involvement, the CIR for non-CNS relapses and other events was similar ($P_{(Gray)} = 0.33$ and 0.88, respectively). However, the CIR for CNS relapse was higher in patients with initial CNS involvement compared to CNS-negative patients (8 ± 2% vs. 3 ± 1%, $P_{(Gray)} = 0.001$). Regarding only isolated CNS relapses, CIR rates were 4 ± 1% vs. 1 ± 0%, $P_{(Gray)} = 0.03$, (Figs. 2A and 2B). In the CNS-positive patient cohort, the CIR for CNS relapse was significantly higher in infants (<2 years) compared to older patients (16 ± 4% vs. 3 ± 2%, $P_{(Gray)} = 0.004$).

Risk groups: In the total group of CNS-positive patients, there were significant differences in OS and EFS rates in risk groups as defined (Figs. 3A and 3B). However, results were similar concerning CIR in CNS-positive patients (Fig. 3C). When comparing risk groups in CNS-positive vs. CNS-negative patients, EFS in SR CNS-positive patients was significantly inferior compared to SR CNS-negative patients ($P_{logrank} = 0.0024$, Fig. 3B).

Comparing CNS-positive SR patients in the different study groups, there were no differences in OS ($P_{logrank} = 0.43$); however, EFS in the BFM group was inferior ($P_{logrank} = 0.04$). CIR rates were comparable ($P_{(Gray)} = 0.30$). Results for HR patients in the different study groups were similar: OS ($P_{logrank} = 0.93$), EFS ($P_{logrank} = 0.75$), and CIR ($P_{(Gray)} = 0.19$).

By Cox regression analysis of CNS-negative and CNS-positive patients, only the cytogenetically defined HR risk group was an independent risk factor for EFS (hazard risk ratio = 2.74, 95% confidence interval 2.11–3.56, $P_{(chi)} < 0.0001$).

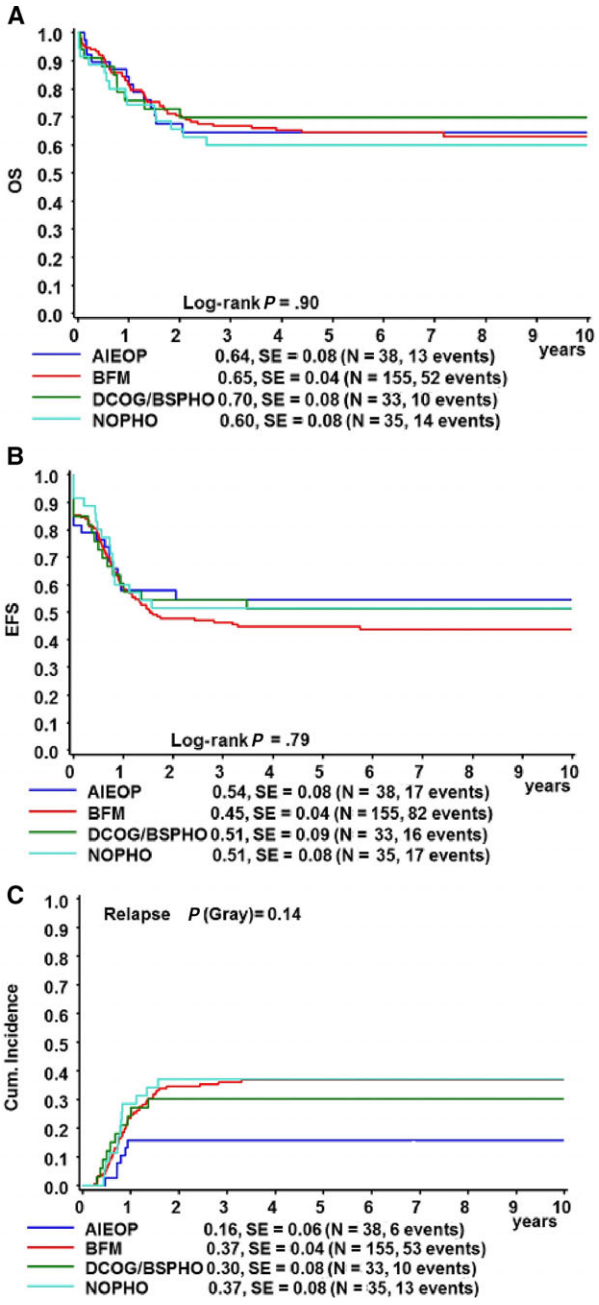

FIGURE 1 Five years overall survival (A), event-free survival (B), and cumulative incidence of relapse (C) in CNS-positive patients of the four study groups

3.3 | Treatment

CRT was only performed in case the patient achieved CR and no HSCT was given. Mainly patients from the BFM group (n = 74) and five patients of the Dutch group were irradiated.

Comparing BFM results (with CRT in 74/155 patients) with those of the other groups (in which only five patients received CRT and no maintenance was given), there was no difference in outcome by intend to treat analysis, which indicates no benefit of CRT and maintenance (Figs. 4A–4C).

HSCT in CR1 was frequently performed in AIEOP patients (68%) and rarely in others (11.5%). Results for EFS were better by trend

TABLE 1 Results in CNS-positive patients from the study groups and comparison with CNS-negative patients

	Group								Total			
	AIEOP		BFM		DCOG/BSPHO		NOPHO		CNS positive		CNS negative[a]	
	N	%	N	%	N	%	N	%	N	%	N	%
Total	38	100.0	155	100.0	33	100.0	35	100.0	261	100.0	1,129	100.0
Early death	–	–	7	4.5	2	6.1	3	8.6	12	4.6	27	2.4
Nonresponse	7	18.4	16	10.3	3	9.1	–	–	26	10.0	100	8.9
CR	31	81.6	132	85.2	28	84.8	32	91.4	223	85.4	1,002	88.8
Relapse (CI)	6	16	53	37	10	30	13	37	82	33	353	32
TRM in CCR (CI)	4	11	4	3	–	–	1	3	9	4	37	3
Secondary malignancy	–	–	2	1.3	–	–	–	–	2	0.8	20	1.8
LFU in CCR	9	23.7	5	3.2	–	–	–	–	14	5.4	56	5.0
CCR	12	31.6	68	43.9	17	51.5	18	51.4	115	44.1	536	47.5

CR, complete remission; CI, cumulative incidence; TRM, treatment-related mortality.
[a]CNS-negative patients from the same era treated on AML-BFM regimens.

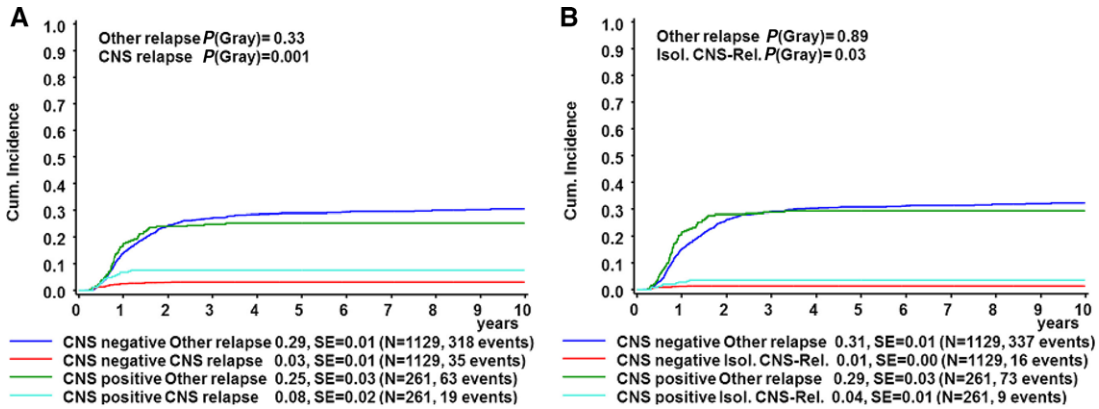

FIGURE 2 Five years cumulative incidence of (A) CNS-relapse and other relapses and (B) isolated CNS-relapse and other relapses in CNS-negative versus CNS-positive patients

in patients with HSCT compared to those with chemotherapy only ($P_{\text{Mantel–Byar}} = 0.09$), but OS was similar (Supplementary Figs. S1 and S2).

3.4 | Toxicity and secondary malignancies

Acute toxicity during induction and intensification courses was similar to those in CNS-negative patients. Especially peripheral and central neurotoxicities were rarely seen, also with CRT and maintenance (data not shown, from the BFM studies only).

There were two secondary malignancies (both acute lymphoblastic leukemia) in the CNS-positive cohort. There were also two patients with benign tumors (one cystadenoma and one hemangioma). The percentage of secondary malignancies was in the same range as in CNS-negative patients.

4 | DISCUSSION

The optimal treatment in AML patients with CNS involvement is still unknown. There is consensus that CNS treatment is necessary; however, the importance of the different treatment modalities is unclear.

IT and systemic chemotherapy including HD-AraC was given in all groups. For IT treatment, cytarabine is supposed to be the most important drug.[16] It was given as single drug in BFM (12 times) and together with methotrexate and prednisone as triple IT therapy at least six to eight times in the other groups (with the exception of the AIEOP study, which scheduled HSCT for most patients). Recently, IT triple was also adopted in the AML-BFM group. As there was no difference in outcome between the four groups and since there are also differences with regard to maintenance and CRT, we cannot state any influence of the frequency of IT therapy applications. However, according to the experience of several St. Jude studies in AML, triple IT therapy should be preferred.[16]

The role of cranial irradiation in AML (prophylactic or therapeutic) is controversial since many years. It seems to be effective in preventing CNS leukemia; however, due to the risk of late toxicities and secondary malignancies, most study groups have abandoned this option.[1] The AML-BFM 87 study was the only prospective study testing the benefit of cranial irradiation as CNS prophylaxis.[17] Results, including the nonrandomized patients, showed an increased risk of CNS and/or bone marrow relapses in nonirradiated patients. However, other studies with comparable overall outcomes did not support a benefit from CNS irradiation. This was also the case in our study, in which CNS

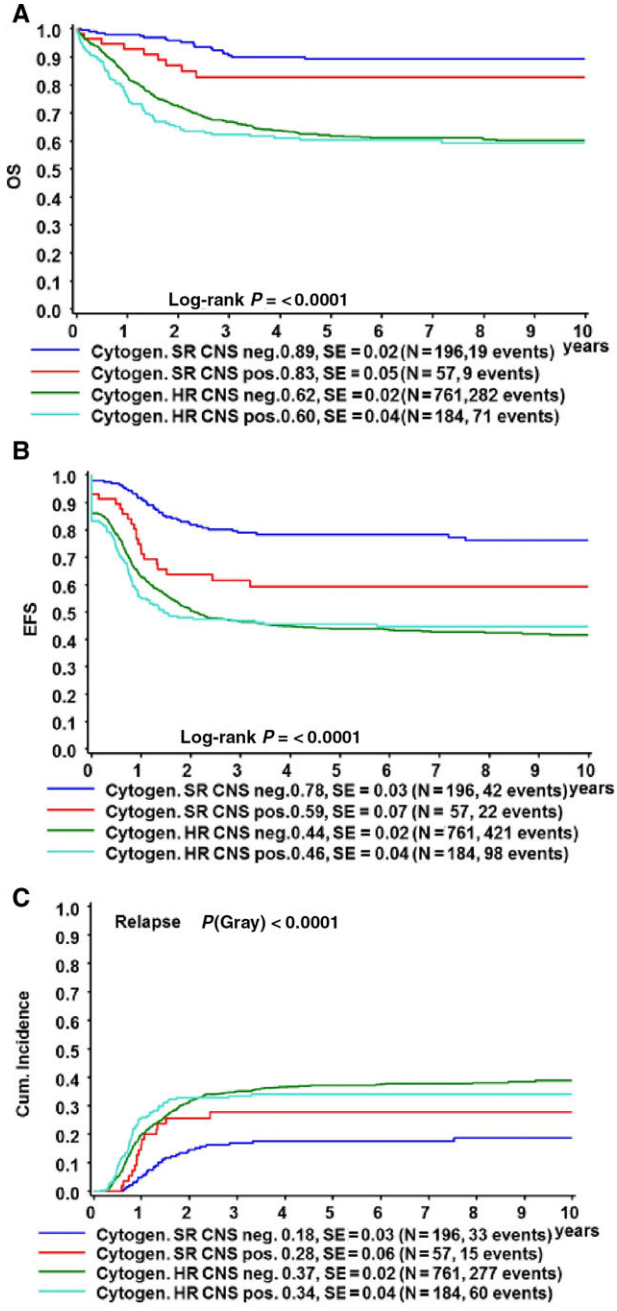

FIGURE 3 Five years overall survival (A), event-free survival (B), and cumulative incidence of relapse (C) in CNS-positive and CNS-negative patients with standard risk and high risk defined by cytogenetics

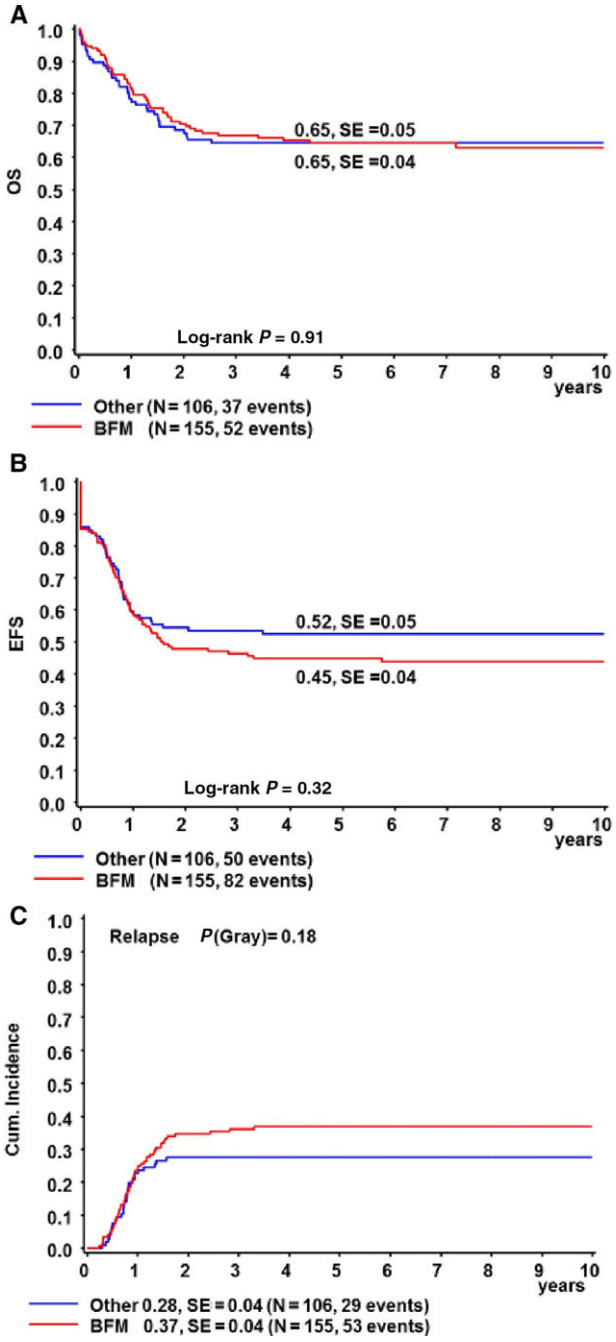

FIGURE 4 Five years overall survival (A), event-free survival (B), and cumulative incidence of relapse (C) in CNS-positive patients from the BFM group compared to other groups

irradiation did not affect OS, EFS, and CIR. On the other hand, independently from treatment, CNS relapse rates were higher in CNS-positive patients compared to CNS-negative patients ($P = 0.001$). Due to the low rates of CNS relapses and low patient numbers in these groups, it may be possible that a beneficial effect of CRT on CNS relapses cannot be shown and OS rates were not influenced, because relapse treatment was successful.

The indication for HSCT in CR1 was different in the study groups and mainly patients from the AIEOP study were transplanted. The conditioning regimens were based on busulfan, melphalan and cyclophosphamide, of which the first two are active drugs in the CNS. Results from our study showed a tendency of a lower CIR and better EFS in patients with HSCT, which did not translate into better survival rates.

Concerning other treatment elements, maintenance therapy, which was given only in the BFM group, did not influence outcome. The higher relapse rate in SR patients of the BFM group may be caused by reduction of chemotherapy (without HD-AraC/mitoxantrone = HAM) in AML-BFM 2004 study.[18] Together with similar results in HR patients in all groups (with similar intensity of chemotherapy), this indicates that the intensity of chemotherapy has the most important influence on prognosis.

Initial patient characteristics in CNS-positive patients mostly confirm published reports[5]: young age, high WBC, monoblastic morphology (FAB M4/5), and the cytogenetic abnormality inv(16) were associated with initial CNS involvement. *KMT2A* rearrangements were frequently found (25%), but not significantly more in CNS-positive patients ($P = 0.19$). This was in accordance with the finding of chromosome 11 abnormalities by Johnston et al.[5] However, others found an association with CNS disease between *KMT2A* abnormalities in infants[19] and in adult patients for extramedullary leukemia.[20]

In summary, we can conclude that AML patients with initial CNS involvement have a similar OS, EFS, and CIR as CNS-negative patients. However, CNS relapses were more frequent, which indicates that additional treatment (either CNS directed or systemic) is necessary and is still not optimal. CNS treatment with CRT seems to have no influence on general outcome. Intensity of systemic chemotherapy with or without HSCT seems to be more important. Intensified IT therapy was heterogeneous; however, at least eight applications, preferably with triple IT chemotherapy, seem to be appropriate to accompany dose-intensive systemic chemotherapy.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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