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Final results of a single institution experience with a pediatric-based regimen, the augmented Berlin–Frankfurt–Münster, in adolescents and young adults with acute lymphoblastic leukemia, and comparison to the hyper-CVAD regimen

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Abstract

Several studies reported improved outcomes of adolescents and young adults (AYA) with acute lymphoblastic leukemia (ALL) treated with pediatric-based ALL regimens. This prompted the prospective investigation of a pediatric Augmented Berlin–Frankfurt–Münster (ABFM) regimen, and its comparison with hyper-fractionated cyclophosphamide, vincristine, Adriamycin, and dexamethasone (hyper-CVAD) in AYA patients. One hundred and six AYA patients (median age 22 years) with Philadelphia chromosome- (Ph) negative ALL received ABFM from October 2006 through March 2014. Their outcome was compared to 102 AYA patients (median age 27 years), treated with hyper-CVAD at our institution. The complete remission (CR) rate was 93% with ABFM and 98% with hyper-CVAD. The 5-year complete remission duration (CRD) were 53 and 55%, respectively ($P = 0.98$). The 5-year overall survival (OS) rates were 60 and 60%, respectively. The MRD status on Day 29 and Day 84 of therapy was predictive of long-term outcomes on both ABFM and hyper-CVAD. Severe regimen toxicities with ABFM included hepatotoxicity in 41%, pancreatitis in 11%, osteonecrosis in 9%, and thrombosis in 19%. Myelosuppression-associated complications were most significant with hyper-CVAD. In summary, ABFM and hyper-CVAD resulted in similar efficacy outcomes, but were associated with different toxicity profiles, asparaginase-related with ABFM and myelosuppression-related with hyper-CVAD.

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Additional Supporting Information may be found in the online version of this article.

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Introduction

The outcomes of adolescent and young adults (AYA) with acute lymphocytic leukemia (ALL) treated on pediatric protocols were reported to be superior to those of similar patients treated with adult protocols in historical retrospective comparisons [1–4], with one exception [5]. Most of the adult ALL regimens in the analysis had abandoned many of the basic therapeutic principles used in pediatric ALL, opting for shorter maintenance durations, lower dose-schedules of the non-myelosuppressive ALL drugs (steroids, vincristine, asparaginase), and favoring AML-like strategies including autologous and allogeneic stem cell transplantation (SCT) early in complete remission (CR). These comparative analyses encouraged studies of pediatric-based regimens in adults with ALL up to age 55 years [6–8]. Older adults treated on pediatric regimens (age ≥40–45 years) had significantly worse toxicities, mostly related to asparaginase [7]. Recently, a United States intergroup study treated 318 AYA with a pediatric-inspired regimen (COG regimen). Among 296 evaluable patients, the estimated 5-year OS rate was 62%, and the 5-year event-free survival rate 50% [8].

The ABFM regimen is an established pediatric ALL regimen which resulted in very favorable outcomes in childhood ALL [9,10]. We investigated the ABFM regimen at our institution for the treatment of newly diagnosed patients 40 years or younger with Ph-chromosome negative ALL. This analysis updates the ABFM final results and compares them to those obtained with hyper-CVAD in a similar historical AYA population.

Methods

Study group

The ABFM was the frontline regimen in patients with Ph-chromosome negative ALL aged ≤40 years from October 2006 until March 2014. The eligibility criteria were previously detailed, and included ECOG performance status of ≤3 and adequate renal and hepatic functions (unless the abnormalities were attributed to leukemia) [11]. The details of hyper-CVAD were previously published [12,13]. The protocols were approved by the M.D. Anderson Cancer Center Institutional Review Board. Informed consent was obtained according to the Declaration of Helsinki and our institutional guidelines.

Treatment

Treatment details of the ABFM regimen have been previously published [10,11,14; Supporting Information Table I]. Bone marrow was reassessed at Day 15. Patients with <5% marrow blasts on Day 15 were treated in the rapid responder group, and received one Consolidation 1 phase and one Consolidation 3A/3B phase of therapy. Slow responding patients received two Consolidations 1 phases and two Consolidation 3A/3B blocks of therapy. Patients with > 5% blasts in the marrow on Day 29 received 2 weeks of extended induction. At the end of the extended induction, patients with >5% marrow blasts were taken off study. Early responders received 15 intrathecal therapies (IT); slow responders received 22 ITs. Patients with overt leukemia in the spinal fluid were treated with intensified ITs

(Supporting Information Table I). Radiation for overt central nervous system (CNS) leukemia was recommended.

The hyper-CVAD regimen and results have been previously published [12,13]. For this comparison, we included only patients ≤40 years old. Among such patients, 46 (45%) had CD20-positive ≥20% expression on leukemia cells; 40 received rituximab 375 mg/m^2 for eight doses in the first four induction-consolidation courses, and six received ofatumumab. Of note, central nervous system (CNS) prophylaxis consisted of eight ITs over the first four courses, compared with 15–22 ITs on the ABFM regimen.

Other diagnostic and monitoring procedures were previously detailed [11]. Four-color multi-parameter flow cytometry (FCM) was performed to evaluate minimal residual disease (MRD) in the first part of the study (until February 2009); six-color FCM was used thereafter. Rapid Ph-chromosome testing was verified with conventional cytogenetics, fluorescent in situ hybridization (FISH), and PCR testing. Bone marrow morphology and minimal residual disease (MRD) were assessed on Day 28 and on approximately Day 84 of treatment on ABFM and on Day 21 then approximately every 3 months on hyper CVAD. B-cell markers included, CD10, CD13, CD15, CD19, CD20, CD22, CD34, CD38, and CD58 (sensitivity 10^{-4}). For MRD assessment in T-cell ALL, a panel of T-cell markers was used which included CD1a, CD1, CD2, CD3 (surface and cytoplasmic), CD4, CD5, CD7, CD8, CD 10, CD13, CD33, CD38, CD56, and TdT. Standard cytogenetic studies were evaluated at diagnosis, and on Days 28 and 84 of therapy on ABFM and on Day 21 then approximately every 2–3 month on hyper CVAD. Spinal fluid was assessed for malignant cells by cytopathology and Coulter counting, and CNS disease defined as per pediatric ALL guidelines [15]. During the course of the ABFM study, the PEG-asparaginase dose was capped at 3,750 U, the content of one vial. This was adopted due to the expense of individual vials, and to avoid excessive toxicities from PEG-asparaginase.

Response criteria and toxicity

A complete response (CR) was defined as <5% blasts in the bone marrow and normal peripheral blood counts, in the absence of extramedullary disease. Induction death included deaths prior to Day 29 of treatment (Day 42 if extended induction). Relapse was defined as recurrence of ALL at any site. Toxicities were defined by National Cancer Institute Common Terminology Criteria, version 3.0.

Statistical considerations

The endpoints of both ABFM and hyper-CVAD trials were CR, CR duration (CRD), and overall survival (OS). The CRD was measured from the date of CR until relapse. Differences in CR rates were analyzed by the chi squared or Fisher's exact tests. The CRD and OS times were assessed by the Kaplan–Meier method [16]. Characteristics associated with differences in CRD and OS were assessed by log-rank testing [17]. Cox proportional hazard regression was used to evaluate factors predicting CRD and OS [18]. Factors with a P value ≤0.10 by univariate analysis were entered into the multivariate analysis. A P value of <0.05 was considered statistically significant. Statistical analyses were performed with IBM PASW Statistics 19 for Windows (SPSS, Chicago, IL).

Results

Patient study group

A total of 106 patients aged 12–40 years with newly diagnosed Ph-negative ALL were treated with ABFM (Table I). Table I compares the characteristics of patients treated with ABFM and with hyper-CVAD. The median follow up is 66 months (range 17–107 months) on ABFM, and 88 months (range 1–152 months) on hyper-CVAD.

Treatment results

Overall, 99 of 106 patients (93%) achieved CR on ABFM, and 100 of 102 patients (98%) on hyper-CVAD. There was one induction death due to sepsis on ABFM, and one induction death due to sepsis on hyper-CVAD. Resistance was noted in six patients (6%) on ABFM and one patient on hyper-CVAD (1%).

On ABFM, 39 patients (37%) have relapsed and 28 of them (72%) have died; 8 patients died in CR, 4 of them after an allogeneic stem cell transplantation (SCT). On hyper-CVAD, 39 patients (38%) have relapsed and 30 of them (77%) have died; 7 patients died in CR, one of them after an allogeneic SCT. Overall, 17 patients underwent allogeneic SCT in first CR, including 11 of 106 patients (10%) on ABFM and 6 of 102 (6%) patients on hyper-CVAD. Reasons for transplantation included slow clearance of MRD or high risk cytogenetic or molecular findings such as MLL gene rearrangement. Ten patients (7 on ABFM and 3 on HCVAD) of the 17 patients (11 ABFM and 6 HCVAD) transplanted have died, 5 (3 ABFM and 2 HCVAD) remain in CR, and 2 (1ABFM and 1 HCVAD) are alive with relapsed disease. Rapid response by marrow morphology on Day 15 was 83% with ABFM and 72% with hyper-CVAD.

Isolated CNS relapse occurred in 16/208 (7.7%) patients, including 9/106 on ABFM (8.5%) and 7/102 on hyper-CVAD (6.9%). Ten patients have relapsed in the CNS and the bone marrow, 6 on ABFM and 4 on hyper-CVAD. Forty-six (22%) patients had marrow relapse alone. The median time to relapse was 20 months for ABFM and 17 months for HCVAD.

Remission duration and survival—On ABFM, 66 of 106 patients (62%) remain alive with a median follow-up of 66 months (range 17– 107 months). On hyper-CVAD, 64 of 102 patients (63%) remain alive with a median follow-up of 88 months (range 1–152 months). The 5-year OS was 60% with ABFM and 60% with hyper-CVAD (Fig. 1A). The 5-year CRD rates were 53 and 55%, respectively (Fig. 1B). For patients ≤21 years, the 5-year OS rates were 65 and 68%, respectively (Fig. 1C). For patients >21 years the 5-year OS rates were 57 and 58%, respectively (Fig. 1D). For patients with CD20-positive expression <20%, the 5-year OS rates were 69% with ABFM and 61% with hyper-CVAD; for patients with CD20-positive expression ≥20% the 5-year OS rates were 46 and 61%, respectively (the differences were not statistically significant).

Outcome by MRD status—The outcome of patients by MRD status is detailed in Supporting Information Table II. The 5-year OS rate was 75% with a Day 29 MRD-negative status versus 40% with MRD-positive status (Fig. 2A; $P = 0.004$). The 5-year CRD rate was 64% with a Day 29 MRD negative status versus 33% with MRD-positive status (Fig. 2B; P

= 0.017). There were no differences in CRD or survival rates by MRD status (positive or negative) with ABFM versus hyper-CVAD (data not shown).

The 5-year OS rate was 75% with a Day 84 MRD-negative status versus 22% with MRD-positive status ($P = 0.0004$). The corresponding CRD rates were 63% versus 26% ($P = 0.0018$; Supporting Information Table II).

Prognostic factors—On univariate analysis, the following factors were adverse for OS ($P \leq 0.10$): D21-28 and D84 MRD positive status, leukocytosis $>50 \times 10^9$/L, older age, karyotype other than normal, and slow responder status/Day14 high marrow blasts (Supporting Information Table III). On multivariate analysis, only leukocytosis ($P \leq 0.001$) and Day 21–28 MRD-positive status ($P \leq 0.001$) remained independently adversely associated with worse survival. In a second model, we included MRD status on Day 84: WBC at diagnosis ($P \leq 0.001$) and Day 84 MRD-positive status ($P \leq 0.001$) were independently associated with worse survival. As expected, D21-28 and D84 MRD-positive status were highly correlated. Adverse factors were similar with ABFM and hyper-CVAD.

Regimen toxicities

Adverse events associated with the ABFM regimen, particularly hepatic toxicity, were significant but expected (Table II). Grade 3–4 hyperbilirubinemia was observed in 38%, and grade 3–4 liver enzyme elevations in 41%. Liver toxicity resolved in most patients, but resulted in chemotherapy dose reductions and omissions per protocol guidelines. Hypofibrinogenemia was prominent (35%), but did not result in grade 3–4 bleeding. Thrombosis, mostly associated with central line catheters, occurred in 19%; stroke-like events developed in three patients. Toxicities that led to permanent changes in therapy consisted of osteonecrosis (9%), severe allergic reactions to PEG-asparaginase (19%), and pancreatitis (11%). The incidence of osteonecrosis is comparable to the incidence seen in adolescents treated on pediatric trials [10]. A higher incidence of severe asparaginase allergic reactions was noted on this study than in the pediatric literature [19]. Neuropathy was not prominent; only six patients had grade 3 neuropathy. Infections and febrile episodes during induction and later in therapy were common and did not significantly differ between the age groups. Fever or documented infections were noted in 22% of patients during induction, and in 63% during consolidations. Table II compares rates of treatment-associated adverse events with ABFM versus hyper-CVAD.

Incidence of CNS leukemia

Of interest, despite the higher number of ITs delivered on ABFM, the incidence of CNS leukemia (isolated or with marrow relapse) was higher on ABFM (15/106 = 14.2%) than on hyper-CVAD (11/102 = 10.8%).

Discussion

In this experience in newly diagnosed AYA patients with ALL, the ABFM regimen resulted in a CR rate of 93%, a 5-year OS rate of 60%, and a CRD rate of 53%. Severe toxicities of the regimen were significant but expected, and mostly related to PEG-asparaginase-based

therapy: hepatotoxicity in 41%, pancreatitis in 11%, osteonecrosis in 9%, and thrombotic events in 19%.

The results of ABFM were compared to the results with hyper-CVAD in a similar population at our institution. The two populations treated with ABFM and with hyper-CVAD were well-matched (Table I). However, patients treated with hyper-CVAD were older, (median age of 27 years versus 22 years for patients treated with ABFM; ($P < 0.001$). Despite the higher age in the hyper-CVAD group, a known adverse prognostic factor in ALL, the efficacy results were similar with ABFM and hyper-CVAD. The CR rates were 93% with ABFM and 98% with hyper-CVAD. The 5-year OS rates were 60 and 60%, respectively ($P = 0.99$). The 5-year CRD rates were 53 and 55%, respectively ($P = 0.98$). Outcomes with ABFM and hyper-CVAD were similar in the two age groups ≤21 years and >21 years. The toxicity profiles were different with ABFM and hyper-CVAD: asparaginase-related with ABFM, myelosuppression with H-CVAD.

The hyper-CVAD regimen maintained the principles of the pediatric ALL regimens but reduced reliance on asparaginase [12,13]. It is possible that other “adult” ALL regimens were inferior to “pediatric” regimens because they mimicked more adult AML-like regimens, relying on allogeneic and autologous SCT in first CR, using less consolidations and shorter duration of maintenance therapy, and administering less intrathecal chemotherapy. Therefore, the current shift to pediatric-based therapy for AYA patients with ALL, especially those ≥21 years, may need further assessment. In particular, with cumulative expertise with ABFM and hyper-CVAD, investigators may become more familiar and knowledgeable about treatment delivery and toxicity management of one or the other regimen, and utilize it more consistently and effectively.

Adverse prognostic factors for OS were leukocytosis and delayed response to therapy with persistent MRD positivity. T-cell ALL patients may present with high WBC and yet may have acceptable OS [20]. The T-cell ALL group in our study was too small to analyze the relative importance of morphology and WBC count. However, AYA patients with pre-B ALL and leukocytosis should be considered for additional intensifications (e.g., allogeneic SCT) or novel strategies (e.g., new monoclonal antibodies).

Molecular or flow cytometry studies measuring MRD have strongly predicted for relapse in pediatric ALL studies [21–25]. The MRD status at the end of induction therapy has also been associated with survival differences in adult ALL [13,26–29]. In our analysis, a negative MRD status by multicolor flow cytometry on Day 29 and Day 84 was associated with improved survival. Thus, patients with MRD positivity in CR may be considered for allogeneic stem cell transplant or for novel therapies, in particular monoclonal antibodies targeting CD19 or CD22, while in first morphologic CR [26,29].

The toxicities of pediatric-based therapies are mostly asparaginase-related: hepatotoxicity (41%), pancreatitis (11%), osteonecrosis (9%), thrombosis (19%). Infectious complications during prolonged steroid administration may be problematic. On ABFM there were eight deaths (8%) in CR, two of the deaths were patients with Down syndrome, and four were after allogeneic SCT. On hyper-CVAD, there were 7 (7%) deaths in CR, one after allogeneic

SCT. All patients were given anti-bacterial and anti-fungal prophylaxis during periods of severe neutropenia. Avascular necrosis on ABFM appears to be less prominent in AYA up to age 40 than in younger patients [30,31]. Thrombosis on ABFM was higher than reported in pediatric patients [32], and most thrombi were related to central lines.

The rate of CNS relapse with ABFM was similar to published pediatric and adult studies. Interestingly, despite a higher number of ITs on ABFM (n = 15–22) than on hyper-CVAD (n = 8), the incidence of CNS leukemia was 14.2 and 10.8%, respectively. This may be due to the incorporation of high doses of methotrexate and cytarabine in the four even consolidation courses of hyper-CVAD, or the possibility that more ITs interspersed later in the course of maintenance therapy on ABFM do not reduce the incidence of CNS relapse.

In summary, ABFM and hyper-CVAD produced similar efficacy results in AYA patients with ALL, but were associated with different toxicity profiles. Future strategies incorporating novel monoclonal antibodies (blinatumomab, inotuzumab ozogamicin) [33–38] and chimeric antigen receptor (CAR)-T cells [39–41] in first remission, particularly in higher-risk patients (MRD-positive), may further improve outcomes and reduce the need for intensive and prolonged toxic chemotherapies.

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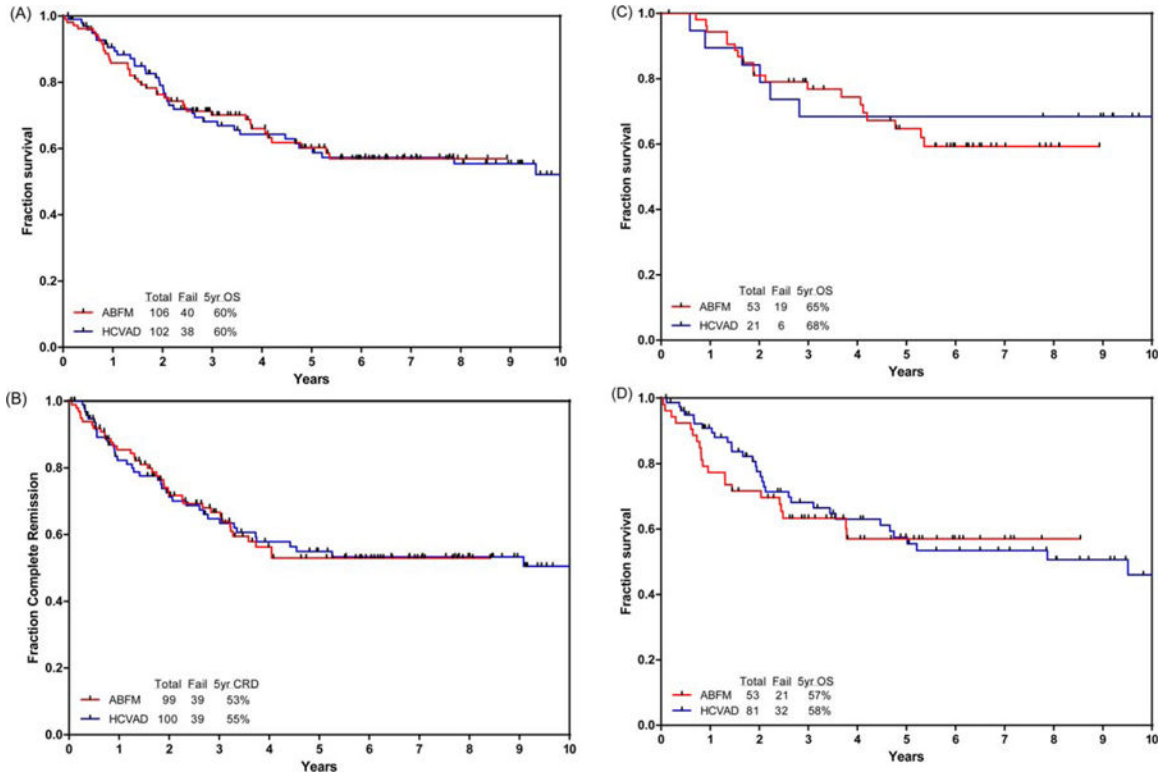

Figure 1.

Survival (A) and complete remission duration (B) with ABFM and hyper-CVAD. Survival with the two regimens among patients ≤21 years (C), and those ≥21 years (D).

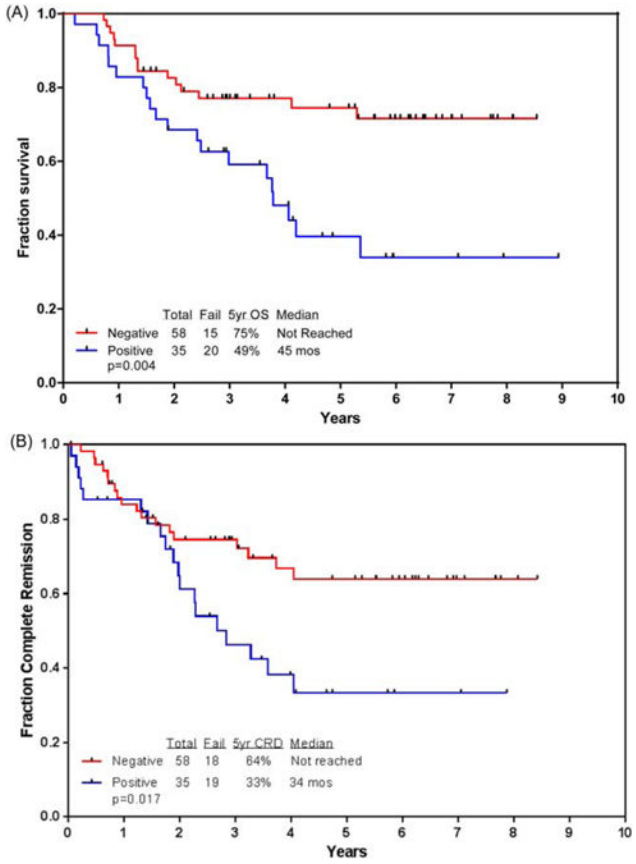

Figure 2.

Survival (A), and complete remission duration (B) by status of minimal residual disease on Day 29 marrow.

TABLE I

Characteristics of Patients Treated on Augmented BFM and on Hyper-CVAD

	Augmented BFM	HCVAD	*P* value
No. of patients	106	102	
No female (%)	41 [39]	37 [36]	0.72
Median age in years (range)	22 [13–39]	27 [15–40]	<0.001
No. with performance status 2 (%)	10 [9]	6 [6]	0.34
Median WBC at diagnosis (range)	15 (0.4–494.2)	7.1 (0.6–334.2)	0.32
No. with pre-B phenotype (%)	85 (80)	82 (80)	0.89
Blasts in blood (%), median (range)	25 (0–93)	22 (0–96)	0.98
No. with karyotype			0.49
Diploid	44	43	
Hyperdiploid	8	6	
Hypodiploid	5	0	
Pseudodiploid	14	13	
Complex (> 3 abnormalities)	21	21	
MLL, *t*(4;11)	3	6	
Not done/insufficient metaphases	1/10	1/12	
No. with positive CNS disease at diagnosis (%)	13 [12]	8 [8]	0.29
No. transplanted in first remission (%)	11 [10]	6 [6]	0.24
Time period	10/2006–3/2014	11/2002–7/2015	

WBC, white blood cell count; MLL, mixed lineage leukemia gene rearrangement; CNS, central nervous system.

TABLE II

Toxicities

Toxicity	No. with toxicity (percent)		
	ABFM (*n* = 106)	Hyper-CVAD (*n* = 102)	*P* value
Allergic reaction, asparaginase	20 [19]	6/53 patients who received asparaginase in maintenance intensifications [11]	0.23
Grade 3–4 hypofibrinogenemia	37 [35]	14 [14]	<0.001
Pancreatitis	12 (11	3 [3]	0.02
Grade 3–4 liver enzymes	43 [41]	45 (44)	0.60
Grade 3–4 bilirubin	40 [38]	18 [18]	0.001
Osteonecrosis	10 [9]	8 [8]	0.68
Thrombosis	20 [19]	12 [12]	0.16
Stroke-like event	3 [3]	0	0.09
neuropathy Grade 3–4	6 [6]	4 [4]	0.56
Induction infections grade 3–4	23 [22]	46 (45)	<0.001
Induction bleeding grade 3–4	1 [1]	5 [5]	0.09
Infections in CR first 60 days	32 [30]	61 (60)	<0.001
Bleeding in CR first 60 days	1 [1]	5 [5]	0.09
Deaths in CR	8 [8]	7 [7]	0.85
-myelosuppression	4 [4]	6 [6]	0.48
-post SCT	4 [4]	1 [1]	0.19