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Augmented Berlin-Frankfurt-Münster Therapy in Adolescents and Young Adults (AYA) with Acute Lymphoblastic Leukemia (ALL)

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Abstract

Background—Various trials report improved outcomes for adolescents and young adults (AYA) with acute lymphoblastic leukemia (ALL) treated with pediatric- based regimens. This prompted the investigation of the pediatric Augmented Berlin-Frankfurt-Münster (ABFM) regimen in AYA patients. Results were compared with the hyper–fractionated cyclophosphamide, vincristine, Adriamycin and dexamethasone (hyper-CVAD) regimen in a similar population.

Methods—Eighty-five patients age 12 to 40 years with Philadelphia chromosome- (Ph) negative ALL were treated with ABFM from 10/2006 through 4/2012. Their outcome was compared to 71 historical AYA patients treated with hyper-CVAD from our institution. Patient and disease characteristics, as well as status of minimal residual disease (MRD), were analyzed for their impact on outcomes.

Results—The complete remission (CR) rate with ABFM was 94%. The 3-year complete remission duration (CRD) and overall survival (OS) rates were 70% and 74%, respectively. The 3-year CRD and OS were 72% and 85%, respectively, with age 21 years, and 69% and 60%, respectively, with age 21-40 years. Initial white blood cell count was an independent predictive factor of OS and CRD. The MRD status on Day 29 and Day 84 of therapy were also predictive of long-term outcomes. Severe regimen toxicities included transient hepatotoxicity in 35-39%,

pancreatitis in 11%, osteonecrosis in 11%, and thrombosis in 22%. The 3-year OS rate was 74% with ABFM versus 71% with hyper-CVAD; the 3-year CRD rate was 70% with ABFM versus 66% with hyper-CVAD.

Conclusion—ABFM was tolerable in AYA patients with ALL but was not associated with significant improvements in CRD and OS compared with hyper-CVAD.

INTRODUCTION

In retrospective comparisons, the outcomes of adolescent and young adults (AYA) with acute lymphocytic leukemia (ALL) treated on pediatric protocols have been superior to outcomes of similar patients treated on adult protocols (1-4). An exception is Usvasalo, et al (5), which showed no difference in outcome between adult and pediatric-based treatment. Several studies have investigated pediatric-based regimens in adult ALL up to age 55 years (6-8). Older adults (age 40-45 years) had significantly worse toxicities with pediatric based regimens (7). Nachman and colleagues demonstrated that the ABFM regimen can be successfully administered to patients up to the age of 21 years, and was associated with a very favorable survival, particularly in patients with a rapid response to induction therapy (9). To improve the outcome of AYAs with ALL at our institution, ABFM therapy was investigated in newly-diagnosed patients 40 years with Ph-chromosome negative ALL. This regimen was chosen due to the success of ABFM therapy in patients 16-21 years old and its acceptable toxicity profile. Herein we report our results with ABFM and compare outcomes with hyper-CVAD in a similar historical AYA population.

METHODS

Study Group

Patients with Ph-negative ALL and age 12 to 30 years were initially enrolled. After evaluating toxicities in the first 10 patients, the upper age limit was expanded to 40 years. The diagnosis of ALL was confirmed by marrow morphology and flow cytometry. Other eligibility criteria included ECOG performance status of 3 and adequate renal and hepatic functions (unless the abnormalities were attributed to leukemia). Steroid treatment prior to enrollment was limited to 3 days initially, but this restriction was removed later. The protocol was approved by the M.D. Anderson Cancer Center Institutional Review Board, and informed consent for therapy was obtained according to the Declaration of Helsinki and our institutional guidelines.

Treatment

Treatment details are shown in Table 1 and have been previously published (10). Chemotherapy started within 72 hours of the first intrathecal chemotherapy. Bone marrow was re-assessed at Day 15. Patients with less than 5% marrow blasts by Day 15 were treated in the rapid responder group. They received one Consolidation 1 phase and one Consolidation 3A/3B phase of therapy. Slow responding patients received two Consolidations 1 phases and two Consolidations 3A/3B blocks of therapy. Patients with > 5% blasts in the marrow on Day 29 received two weeks of Extended Induction. At the end of the Extended Induction, patients with >5% marrow blasts were taken off study. Early

responders received 12 intrathecal therapies (IT), while slow responders received 16 ITs. Patients with overt leukemia in the spinal fluid were treated with intensified ITs (see Table 1). Radiation for overt CNS leukemia was recommended.

Routine morphology and blast percentage in the marrow were assessed with Wright-Giemsa staining. Myeloperoxidase immunohistochemistry and four color flow cytometry (FCM) were performed. Rapid fluorescent in-situ hybridization (FISH) established preliminary Ph chromosome status using BCR-ABL probes. Rapid Ph chromosome testing was corroborated with conventional cytogenetics and PCR testing. Bone marrow morphology and minimal residual disease (MRD) were assessed on Day 29 and on approximately Day 84 of treatment. B-cell markers included CD9, CD10, CD13, CD15, CD19, CD20, CD22, CD34, and CD58 (sensitivity 10^{-4}). MRD in the T-cell patients was followed using a panel of T-cell markers that included CD1, CD2, CD3 (surface and cytoplasmic), CD4, CD5, CD7, CD8 and CD 10. Standard cytogenetic studies were evaluated at diagnosis, and on Days 29 and 84 of therapy. PCR for t(12;21), BCR-ABL and MLL-rearrangements were performed at diagnosis (Asuragen LTX assay). Spinal fluid was assessed for malignant cells by cytopathology and Coulter counting. CNS disease status was defined as per pediatric ALL guidelines (11). During the course of the study, the PEG-asparaginase dose was capped at 3,750 units, which is the content of one vial. This was adopted due 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. Induction death included all deaths prior to Day 29 of treatment (Day 42 if extended induction). Patients who had more than 5% blasts at Day 42 were removed from the study. Relapse was defined as recurrence of ALL at any site. Toxicities were defined by National Cancer Institute Common Toxicity Criteria, version 3.0.

Statistical Considerations

The endpoints of this single institution trial of ABFM therapy were CR, complete remission 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. Unadjusted CRD and OS analyses were evaluated with Kaplan-Meier plots (12), and characteristics associated with differences in CRD and OS were assessed by log-rank testing (13). Cox proportional hazard regression (14) was used to evaluate factors predicting CRD and OS. Factors with a p-value .10 by univariate analysis were entered into the multivariate analysis. We found that MRD at Days 29 and 84 or greater were collinear and could not be included in the same model. Therefore, we constructed separate models to assess the effect of MRD at Days 29 and 84, separately. A p-value of <.05 was considered statistically significant. All statistical analyses were performed with IBM PASW Statistics 19 for Windows (SPSS Inc., Chicago, Illinois).

RESULTS

Patient Study Group

A total of 85 patients between the ages of 12 and 40 years with newly diagnosed Ph-negative ALL were treated with ABFM (Table 2). The median follow up is 40 months (range, 4 to 70 months). The ALL morphology was pre-B in 69 and T-cell in 16. The ECOG performance status was 2 in 9%; no patients had a performance status of 3. Forty percent of patients had a diploid karyotype. The karyotype was hyperdiploid in 20% of patients 21 years and in 18% of patients 21 years. Seven patients had CNS blasts at diagnosis on cytopathology review; only one patient had CNS 3. Three patients had Down Syndrome.

Treatment Results

Overall, 80 of 85 patients (94%) achieved CR (Table 3). There was one induction death due to sepsis. One patient with trisomy 21 died of sepsis while in CR after completing induction, and one patient with Down Syndrome died of multi-organ failure, also secondary to sepsis, after completing consolidation 1.

Twenty-five patients have relapsed, and 14 of them have died. Eighteen of the relapsed patients were rapid early responders. Eight patients died in CR, four of them post-allogeneic SCT.

Seven patients underwent allogeneic stem cell transplantation in first morphologic CR, 2 of whom were 21 years or younger. Reasons for transplantation included slow clearance of minimal residual disease or high risk cytogenetic findings such as MLL gene rearrangement. Four of the 7 transplanted patients have died, two remain in CR, and one patient is alive with relapsed disease.

Rapid response by marrow morphology on Day 15 was 76%, 80% in patients 21 years and 73% in patients > 21 years (p=not significant). Isolated CNS relapse occurred in 6 (7%) patients; 3 patients(4%) have relapsed in the spinal fluid and the bone marrow. Sixteen (19%) patients had marrow relapse alone. The median time to relapse was 21.9 months in patients 21 years and 11.5 months in patients > 21 years.

Remission Duration and Survival—Sixty (71%) patients remain alive with a median follow-up of 40 months (range 4-75 months). The 3-year OS and CRD rates were 74% and 70%, respectively the 3-year OS and CRD rates were 85% and 72%, respectively, for patients 21 years, and 60% and 69%, respectively, for patients > 21 years (Figure 1 A and B). The difference in the 3-year OS rates for the two age groups was borderline significant (p=0.055).

Outcome by MRD Status—The outcome of patients by MRD status is detailed in Table 3. The 3-year OS rate was 82% with a D29 MRD negative status versus 65% with MRD-positive status (Figure 1C; p=0.02). The 3-year CRD rate was 75% with a Day 29 MRD negative status versus 59% with MRD-positive status (Figure 1D; p=.2).

The 3-year OS rate was 83% with a Day 84 MRD-negative status versus 66% with MRD-positive status (p=0.02). The corresponding CRD rates were 82% versus 20% (p=0.01; Table 3). The results within age groups are shown in Table 3.

Prognostic Factors—On univariate analysis, the following factors were adverse for OS (p 0.10): D29 and D28 MRD positive status, leukocytosis > 50 x 10^9/L, older age (continuous variable; Figure 1A), and slow responder status. There were interactions between age and MRD status. On multivariate analysis, only leukocytosis (p .001) and Day 28 MRD-positive status (p=0.05) remained independently adversely associated with survival. In a second model, we included MRD status on Day 84, age, WBC at diagnosis, response type (rapid vs. slow), and cytogenetics (diploid vs. not diploid). Only WBC at diagnosis was independently associated with OS (p=.003).

On univariate analysis, the following factors were adverse for CRD (p 0.10): D84 MRD positive status and leukocytosis > 50 x 10^9/L (Figure 2B). On multivariate analysis, only leukocytosis remained independently adverse (p=0.04).

Comparison of ABFM and hyper-CVAD

The hyper-CVAD regimen details and results have been previously published (15). In this comparison, we included only patients 40 years old. Among such 71 patients, 37 (52%) had CD20-positive expression on leukemia cells 20% (median 77%; range 25-99%), and received rituximab 375mg/m^2 for 8 doses in the first 4 induction-consolidation cycles.

Comparing ABFM with hyper-CVAD, there were no statistical differences in CR rates (CR rate 94% with ABFM versus CR in 70/71 patients on hyper-CVAD = 99%), or in CRD or OS rates between the two treatment regimens (Figures 2 C and D). The 3-year OS rate was 74% with ABFM versus 71% with hyper-CVAD; the 3-year CRD rate was 70% with ABFM versus 66% with hyper-CVAD. When OS and CRD were further analyzed in multivariate analyses including age, presenting WBC, and MRD status at the end of induction therapy, no statistically significant differences in outcome were detected by treatment regimen (data not shown).

Regimen toxicities

Toxicities associated with the ABFM regimen, particularly hepatic toxicity, were significant but expected (Table 4). Grade 3-4 hyperbilirubinemia was observed in 39%, and grade 3-4 liver enzyme elevations in 35%. Liver toxicity resolved in most patients, but resulted in chemotherapy dose decrements and omissions per protocol guidelines. Hypofibrinogenemia was prominent (36%), but did not result in excessive bleeding. Thrombosis, mostly in the upper extremities where central lines were located, occurred in 22%; stroke-like events developed in 3 patients. Toxicities that led to permanent changes in therapy consisted of osteonecrosis (11%), severe allergy to PEG-asparaginase (21%) 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 allergy was noted on study than in the pediatric literature (16)Neuropathy was not prominent; only 4 patients had vincristine held due to 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.

DISCUSSION

In this experience in newly diagnosed AYA patients with ALL, the ABFM regimen resulted in a CR rate of 94%, a 3-year OS rate of 74%, and a CRD rate of 70%. Severe toxicities of the regimen were significant but expected, and mostly related to PEG-asparaginase based therapy: hepatotoxicity in 35-39%, pancreatitis in 11%, osteonecrosis in 11%, and thrombotic events in 22%.

The results of this trial were retrospectively compared to the historical data with Hyper-CVAD regimen in a similar population at our institution, in relation to CR, OS, and CRD. The two populations, those treated with ABFM and those treated with Hyper CVAD were well matched (Table 2). The patients treated with Hyper CVAD, while all being between age 16 and 40, were older, with a median age of 26 years (p<0.001). Presenting WBC, performance status, and blast phenotype were not statistically different between the two groups. 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, but the toxicity profiles were different: asparaginase-related with ABFM, myelosuppression with HCVAD. It is thus reasonable to extrapolate that other "adult ALL" regimens were inferior to "pediatric" regimens because they may have mimicked more adult AML-like regimens: reliance on allogeneic and autologous stem cell transplantation in first CR, less consolidations and shorter maintenance durations, and less intrathecal chemotherapy. The hyper-CVAD regimen maintained the core principles of the pediatric ALL regimens but reduced reliance of asparaginase (17). Therefore, the current shift to pediatric-based therapy for AYA patients with ALL, especially those   21 years, may need further assessment.

A high WBC at presentation remained an independent predictor of OS in multivariate analysis. Historically, T-cell ALL patients may present with high WBC and yet may have acceptable OS (18). 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 stem cell transplantation) or novel strategies (e.g. new monoclonal antibodies).

Molecular or flow cytometry studies measuring MRD have strongly predicted for relapse in pediatric ALL studies (19-25). In AYAs with ALL, MRD status at the end of induction therapy has also been associated with survival differences (26,27). In our study, a negative MRD status by multicolor flow cytometry on Day 29 and Day 84 was associated with improved survival (Table 3). A similar effect of MRD on prognosis was noted with the hyper- CVAD regimen (15). Thus, patients with MRD positivity in CR may be considered for allogeneic stem cell transplant or for novel therapies while in first morphologic CR (28). Concerns over toxicities of pediatric-based therapies are legitimate, and mostly asparaginase-related: hepatotoxicity (35-39%), pancreatitis (11%), osteonecrosis (11%), thrombosis (22%). Infectious complications during prolonged steroid administration may be

problematic. Infectious death during induction occurred in one patient, a death rate comparable to other studies in children and in adults during ALL therapy (29,30). There were 8 deaths in CR, two of the deaths were patients with Down Syndrome, and four were after allogeneic stem cell transplantation. All patients were given anti-bacterial and anti-fungal prophylaxis during periods of severe neutropenia. Avascular necrosis appears to be less prominent in AYA up to age 40 than in teen-age patients (31,32). Hypofibrinogenemia, while frequent, did not cause bleeding. Thrombosis was higher than reported in pediatric patients (33), and most thrombi were related to central lines.

The rate of CNS relapse was similar to published pediatric and adult studies, yet the number of intrathecal treatments was less than in prior pediatric trials of ABFM (9). Intrathecal therapy has side-effects such as impaired cognitive function, seizures and white matter damage. Decreased intrathecal treatments might be feasible and beneficial to AYA patients in future treatment regimens.

Adherence to therapy may limit the effectiveness of the chemotherapy (34,35). Non-compliance may be related to the age group or to the complexity and length of the treatments. Several AYAs (n=10; 12%) withdrew from treatment. Older adults on even simpler regimens for leukemia still have issues with compliance (36), and AYA patients may be even less compliant (37). Breaks in therapy due to toxicities also occurred. Such deviations in therapy undermine cure rates in children with ALL (38). One in five patients had severe allergic reactions to PEG-asparaginase. Decreases in planned doses of asparaginase result in decreased event-free survival (39). In this study, patients switched to Erwinia asparaginase after severe allergic reactions to PEG-asparaginase, a strategy that has resulted in effective asparagine depletion in patients with allergic reactions to E.coli asparaginase (40). Approximately 10% of patients on this study developed pancreatitis, an incidence similar to that in children (41). These patients did not receive further asparaginase.

In summary, AYA patients with ALL treated with ABFM had high OS and CRD rates, and tolerated this pediatric regimen with acceptable toxicity. OS and CRD rates were comparable to those obtained with hyper-CVAD, an adult leukemia regimen.

Acknowledgments

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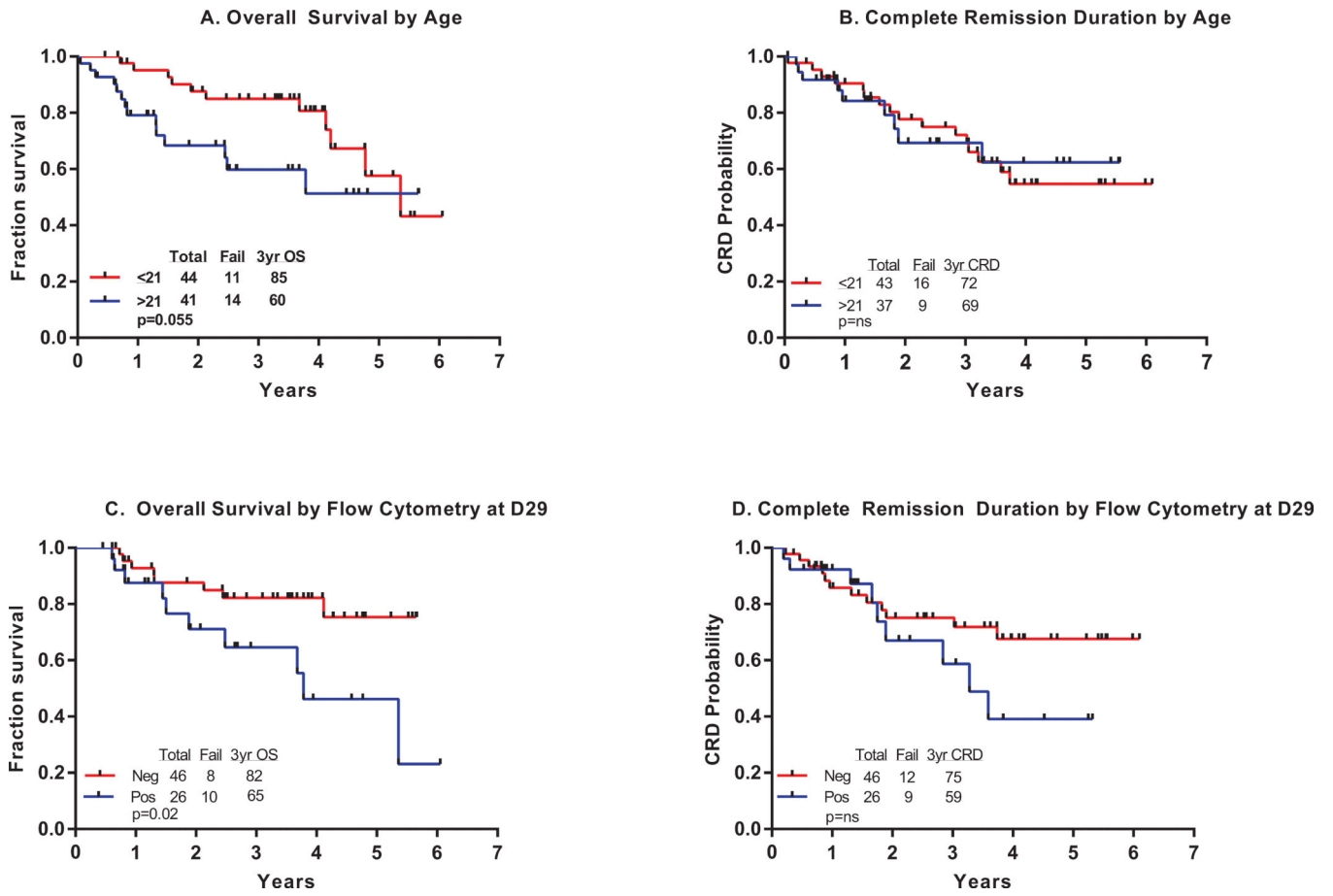
Figure 1A-1D.

Kaplan Meier curves of Overall Survival and Complete Remission Duration by age and day 29 minimal residual disease.
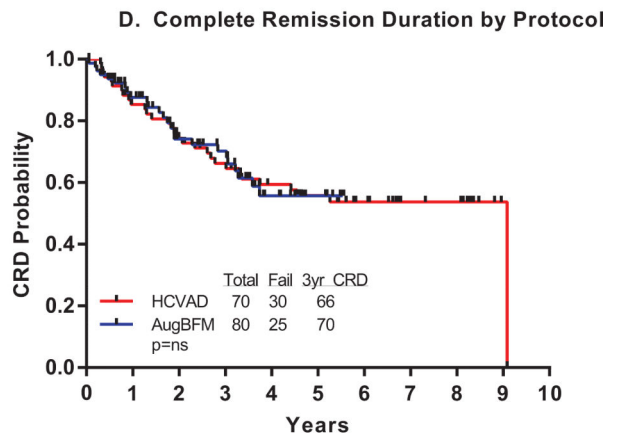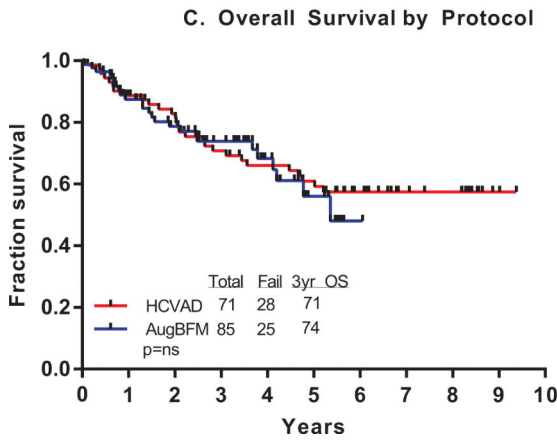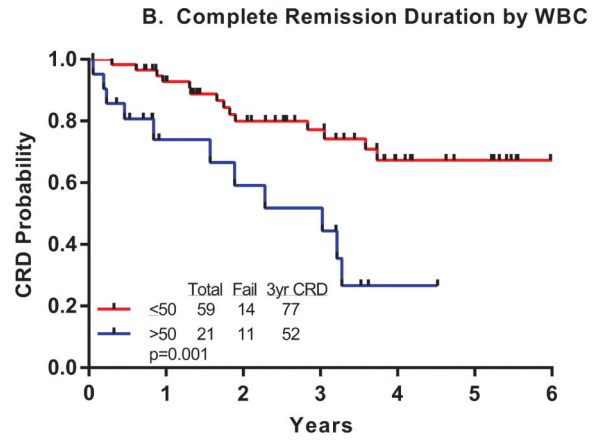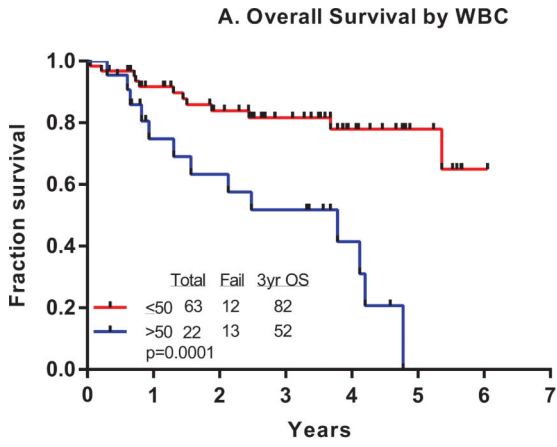
Figure 2A-2D.

Kaplan Meier curves of Overall Survival and Complete Remission Duration by presenting WBC and by protocol.

Table 1

Treatment

Induction (4 weeks)
Daunorubicin 25 mg/m2 weekly × 4 doses
Vincristine 2 mg weekly × 4 doses
Prednisone 60 mg/m2/day by mouth for 28 days
PEG-asparaginase 2500 IU on day 4 of induction
Intrathecal cytarabine day 1
Intrathecal methotrexate 12 mg on day 8 and day 29
Consolidation 1 (8 weeks)
Cyclophosphamide 1 gram/m2 week 1 and week 5
Cytarabine 75 mg/m2 SQ days 1-4 and 8-11
Mercaptopurine 60 mg/m2/day by mouth days 1-14
Vincristine 2 mg week 3 and week 4
PEG-asparaginase 2500 IU week 3 and week 4
Intrathecal methotrexate 12 mg weekly, weeks 1-4
Consolidation 2
Vincristine 2 mg every 10 days for 5 doses
Methotrexate IV every 10 days starting at 100 mg/m2 and increasing by 50 mg/m2 as tolerated
PEG-asparaginase 2500 IU weeks 1 and 4
Intrathecal methotrexate 12 mg week 1
Consolidation 3A
Doxorubicin 25 mg/m2 weekly × 3 doses
Dexamethasone 10 mg/m2 by mouth on days 1-7 and days 15-21
Vincristine 2 mg IV weekly × 3 doses
PEG-asparaginase 2500 IU in week 1
Intrathecal methotrexate 12 mg in week 1
Consolidation 3B
Cyclophosphamide 1 gram/m2 week 1
Cytarabine 75 mg/m2 SQ days 1-4 and days 8-11
Thioguanine 60 mg/m2/day for 14 days
Intrathecal methotrexate 12 mg week 1 and 2
Vincristine 2 mg weeks 3 and 4
PEG-asparaginase 2500 IU week 3
Maintenance (24 months)
Mercaptopurine 75 mg/m2 PO nightly
Methotrexate 20 mg/m2 PO weekly, hold on days of intrathecal methotrexate
Dexamethasone 6 mg/m2/day by mouth days 1-5 every 28 days
Vincristine 2 mg every 28 days
Intrathecal methotrexate 12 mg every 3 months for 4 doses

Slow responders repeat Consolidation 2 and Consolidation 3A/3B prior to maintenance
Testicular disease at diagnosis: if resolution by end of induction, then therapy continued. If abnormality persisted, then a biopsy was required and radiation administered if positive.
CNS disease at diagnosis: Intrathecal therapy given twice weekly until cleared, then weekly $\times$ 6 doses, then resume intrathecal treatments as per protocol. Radiation was recommended for overt CNS disease but was per investigator choice.

Table 2

Patient characteristics

Patient characteristics at the time of enrollment and comparison to the historical patients treated with hyper-CVAD

	Augmented BFM	HCVAD	p-value
No. of patients	85	71	
Male/Female	49/36	42/29	0.85
Median age in years (range)	21 (13-39)	26 (16-40)	<0.001
No. with performance status 2 (%)	8 (9)	4 (6)	0.38
Median WBC at diagnosis (range)	14 (0.4-494.2)	6.7 (0.6-334.2)	0.33
No. with Pre-B Phenotype (%)	69 (81)	62 (87)	0.30
Blasts in blood (%), median (range)	30 (0-93)	28 (0-96)	0.74
No. karyotype with (%)			
Diploid	34 (40)	30 (42)	
Hyperdiploid	16 (19)	15 (21)	
Hypodiploid	9 (11)	2 (3)	0.44
Pseudodiploid	17 (20)	12 (17)	
MLL	3 (4)	4 (6)	
ND/IM	1/5 (1/6)	0/8 (0/11)	
No. with CNS disease positive at diagnosis (%)	7 (8)	7 (10)	0.73
No. Transplanted in first CR (%)	7 (8)	6 (8)	0.96
Time period treated	10/2006 - 4/2012	11/2002 - 9/2011	

WBC, white blood cell count; MLL, mixed lineage leukemia gene rearrangement; ND, not done; IM, 1M=insufficient metaphases; CNS, central nervous system

Table 3

Treatment Response

Response of patients to ABFM therapy.

	Overall	21	>21	p-value (between 2 age groups)
Number treated	85	44	41	
No. CR Overall (%)	80 (94)	43(98)	37(90)	0.14
No. CR Day 29; (%)	77(91)	41(93)	36(88)	0.40
No. D29 MRD-negative/positive	46/26	25/12	21/14	0.50
No. Day 84 MRD-negative/positive	55/13	32/7	23/6	0.78
No. Relapses	25	16	9	0.14
No. Deaths	25	11	14	0.36
No. Deaths in CR	8	2	6	0.12
No. Transplant in CR	7	2	5	
Alive after transplant	3	1	2	
% CRD at 3yrs	70	72	69	0.95
MRD D29 negative/positive	75/59 p=0.2	74/67 p=0.83	76/43 p=0.09	0.60/0.16
MRD D84 negative/positive	82/20 p=0.01	78/30 p=0.28	89/0 p=0.005	0.21/0.03
% OS at 3yrs	74	85	60	0.055
MRD D29 negative/positive	82/65 p=0.02	91/82 p=0.15	72/49 p=0.12	0.22/0.07
MRD D84 negative/positive	83/66 p=0.02	90/83 p=0.02	73/42 p=0.47	0.26/0.24

N-number; CR=complete response; D29 MRD=Day 29 minimal residual disease

Table 4

Toxicities overall and by age.

Toxicity	Overall (n=85)	No. (Percent) Age 21 years (n=44)	Age > 21 years (n=41)
Allergic reaction, asparaginase	18(21)	9(20)	9(22)
Grade 3-4 hypofibrinogenemia	31 (36)	10(23)	21(51)
Pancreatitis	9(11)	4(9)	5(12)
Grade 3-4 elevated liver enzymes	30(35)	12(27)	18(44)
Grade 3-4 elevated bilirubin	33(39)	17(39)	16(39)
Osteonecrosis	9(11)	6(14)	3(7)
Thrombosis	19(22)	8(18)	11(27)
Stroke-like event	3(4)	1(2)	2(5)
neuropathy Grade 3-4	4(5)	2 (4)	2 (5)

• P-values not significant by age group, except for hypofibringogenemia (p=.006)