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Bone marrow necrosis in acute leukemia: clinical characteristic and outcome

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Abstract

Background—Bone marrow necrosis (BMN) is characterized by infarction of the medullary stroma, leading to marrow necrosis with preserved cortical bone. In reported small series, BMN in hematological malignancies is associated with poor prognosis. We sought to find the impact of BMN on clinical outcome in a relatively larger cohort of patients with acute leukemias.

Methods—Overall we evaluated 1691 patients; 1051 with acute myeloid leukemia (AML) and 640 with acute lymphocytic leukemia referred to our institution between 2002 and 2013. Patients with AML and ALL were evaluated separately to determine the incidence of BMN, associated clinical features and its prognostic significance.

Results—At initial diagnosis; BMN was observed in 25 (2.4%) patients with AML and 20 (3.2%) patients with ALL. In AML, BMN was significantly associated with FAB AML M5 morphology (32% vs 10%, p = 0.002). The complete remission (CR) rate in AML with and without BMN was 32% and 59% respectively (p = 0.008). Likewise, CR rate in ALL with BMN was also inferior; 70% vs 92% (p = 0.005). The median overall survival (OS) in AML with BMN was significantly poorer; 3.7 months compared to 14 months without BMN (p= 0.003). Similarly, the median OS in ALL with and without BMN was 61.7 and 72 months respectively (p = 0.33).

Conclusion—BMN is not a rare entity in AML and ALL, but is infrequent. BMN in AML and in ALL is suggestive of inferior response and poor prognosis.

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Keywords

Bone marrow necrosis; acute myeloid leukemia; acute lymphocytic leukemia

Introduction

Bone marrow necrosis (BMN) is a distinct clinicopathological entity characterized by infarction of the medullary stroma leaving an amorphous eosinophilic background, ill-defined necrotic cells and preserved cortical bone.[1] Definition excludes bone marrow necrosis without hematopoietic dysfunction or bone marrow necrosis extending to cortical bone.[2] Histopathological biopsy specimens show loss of normal architecture as well as loss of medullary fat spaces.[1,3] BMN has been a rare reported finding at presentation, rather more commonly reported at autopsy.[4]

In one series, BMN was classified into grade I (mild necrosis) defined as focal necrosis occupying less than 20% of marrow, grade II (moderate necrosis) involving 20–50%, and grade III (severe necrosis) occupying more than 50% of bone marrow biopsy.[5] Wide varieties of conditions are associated with BMN, ranging from infections and sepsis to sickle cell disease, metastatic carcinoma and hematological malignancies. However, more extensive bone marrow necrosis is more commonly associated with hematological malignancies.[2,3,6–18] BMN has been reported specifically in both acute myeloid (AML) and acute lymphoblastic leukemias (ALL).[11,13–16,18] In the published literature, the incidence of BMN ranges from 0.5% to 33%, however higher frequency usually been reported in patients after severe infections and typically involve focal areas of bone marrow (grade I).[5] On the other hand, in leukemia it is relatively less frequent (0.5%), and typically has large foci of marrow necrosis (grade III).

Few case reports and small series have suggested that the presence of BMN in acute leukemia is associated with lower remission rate and dismal prognosis. Moreover, in several instances it has been reported as after effects of intensive leukemia therapy.[19,20] The clinical characteristics and outcomes of patients with BMN in leukemia remain largely unknown. The purpose of this study was to determine the incidence, identify the associated features and ascertain the clinical impact of BMN at initial diagnosis in larger group of patients with ALL and AML.

Patients and methods

Clinical data for patients with newly diagnosed AML and ALL presenting to the Department of Leukemia at the University of Texas – MD Anderson Cancer Center (MDACC) between January 1st, 2002 and December 31st, 2013 were reviewed. Overall 1691 patients; 1051 acute myeloid leukemia (AML) and 640 patients with acute lymphocytic were evaluated for incidence of BMN, associated clinical feature and impact on clinical outcome. The majority of the patients were treated in clinical trials approved by the Institutional Review Board (IRB) and conducted in accordance with the Declaration of Helsinki. All patients signed an informed consent document approved by the IRB before enrolling on the trials. IRB

approval was also obtained for reviewing the records of patients treated outside clinical
trials.

Bone Marrow Evaluation and Cytogenetics and Molecular Markers

Bone marrow aspirate smears with core biopsies were performed on all patients at the time
of presentation. Bone marrow aspirate smears were assessed by Wright-Giemsa stain
followed by cytochemical analysis for myeloperoxidase and α-naphthyl butyrate esterase, as
previously described.[21] Bone marrow necrosis was defined as necrosis of the myeloid
tissues and stroma without involvement of the cortical bone, verified by hematopathologist
at MD Anderson Cancer Center. Bone marrow necrosis grade III[5]; occupying 50% of
marrow space were included in the analysis. Focal bone marrow necrosis (occupying one
high power field/or combined area of involvement occupying less than 20% of bone marrow
specimen), moderate bone marrow necrosis (occupying more than one high power but less
than $10 \times$ field/or combined area of involvement occupying between 20%-50% of bone
marrow specimen), necrosis extending to cortical part of bone, and bone marrow necrosis
after chemotherapy were excluded from the analysis. Patients who were initially treated
outside and later referred to MD Anderson Cancer Center (MDACC), their initial bone
marrow specimen were reviewed by hematopathologist at MDACC for presence or absence
of BMN.

Cytogenetic analysis was assessed by G-banding with at least 20 metaphases counted, as
previously described.[22] Cytogenetics risk stratification was based on Medical Research
Council (MRC) adult and children leukemia parties; MRC AML 10 trial.[23] FLT3-ITD and
codon 835 point mutations in the activating loop of the tyrosine kinase domain of FLT3
were analyzed using genomic DNA extracted from bone marrow aspirate specimens by
polymerase chain reaction assays followed by capillary electrophoresis. Mutations in NRAS
and KRAS were assessed by polymerase chain reaction analysis followed by
pyrosequencing, as described previously.[24]

Response Criteria

Response to therapy was classified according to the International Working Group (IWG)
criteria 2003.[25] A complete remission (CR) was defined by the presence of < 5% blasts in
the bone marrow with recovery of peripheral counts with absolute neutrophil count >
1000/μL and platelet count > 100,000/μL. Relapse from CR was defined as the reappearance
of peripheral blasts; or greater than 5% blasts in the bone marrow; or the occurrence of
extramedullary disease. Early mortality was defined as death within 4 weeks of diagnosis.
An antecedent hematologic disorder (AHD) was defined as an abnormality in blood counts
for at least 1 month before presentation to our institution.

Statistical Analysis

Patient characteristics were tabulated by status of BMN. Differences between categorical
covariates were tested using Fisher's exact tests, and differences between continuous
covariates were compared by the Wilcoxon rank-sum test. Overall survival (OS) was
defined as the time interval between treatment start date and death date, and was censored at
last follow-up date for patients who were alive. Event-free survival (EFS) was defined as the

time interval between treatment initiation date and the date of resistance, relapse, or death, whichever came first, and was censored at last follow-up date for patients who were alive without relapse. Relapse-free survival (RFS) among CR patients was defined as the time interval between response dates and date of relapse or death, whichever came first, and was censored at last follow-up for patients who were alive without relapse. Survival curves were estimated using the Kaplan-Meier methods[26] and compared using two-sided log-rank tests. Univariate and multivariate Cox proportional hazards regression models were used to assess the association between patient characteristics and OS, EFS or RFS.[27] Univariate and multivariate logistic regressions were applied to evaluate the association between patient characteristics and CR or early induction death. A stepwise variable selection was applied with p-value of less than 0.05 for entry and more than 0.1 for removal. BMN were added to the reduced model if it was not selected in the stepwise variable selection. Predictive variables were transformed as appropriate. Statistical analyses were performed using SAS 9.3, and graphics were created using Stata 13.1.

RESULTS

Baseline characteristics

Bone marrow necrosis was found in 20 (3.2%) and 25 (2.4%) patients with ALL and AML respectively, at initial diagnosis. The clinical characteristics of patients with AML and ALL with BMN at diagnosis are presented in Tables I and II.

Among AML patients, median age at diagnosis was 68 and 62 years with and without BMN respectively (p = 0.19). Three (12%) patients with BMN and 178 (17%) patients without BMN had a history of antecedent hematological disorder (p = 0.60). Poor risk CG was observed in 11 (44%) and 321 (31%) of patients with and without BMN respectively (p = 0.19). The most common morphological classification according to French-American-British (FAB) in patients with BMN was AML M5 32% and AML M4 20% compared to 10% and 15% in patients without BMN (p = 0.002 and 0.40) respectively.

On the other hand, patients with ALL were relatively younger, with median age at diagnosis 51.5 and 42 years in patients with and without BMN respectively (p = 0.58). Interestingly, patients with BMN had a median bone marrow (BM) blast percentage of 38.5% compared to 80% without BMN (p = 0.004). Among the 15 patients with BMN, evaluable for immunophyenotyping, all had B-cell lineage ALL, compared to 84% in patients without BMN (p = 0.15).

Treatment and Outcome

AML patients with BMN—Patients received different induction chemotherapy regimens based on available clinical trials, age and performance status. For the purpose of analysis induction chemotherapy regimens were grouped as follows: high-dose Ara C-based (HDAC 1000mg/m^2/dose), low dose Ara C- based (LDAC; 20–500mg/m^2/dose), hypomethylating agent (HMA; azacytidine or decitabine) based, and investigational agents on clinical trial. (Only a few patients received highly investigational agents as frontline therapy because treating physician felt that due to age, co-morbidities and performance status patients were

not fit for intensive therapy). As shown in Table I, no significant differences were observed in the use of each strategy. Four (16%) patients with BMN did not receive induction therapy; 2 died before initiating therapy due to sepsis/multiorgan failure and 1 was lost to follow.

The AML patients with BMN had significantly lower rate of complete remission of 32% compared to 59% in patients without BMN (p = 0.008). Three (12%) and 37 (3.6%) patients had early death (< 4 weeks of diagnosis), with and without BMN respectively (p = 0.07) (Table III).

ALL patients with BMN—Almost all patient with ALL received hyper-CVAD[28] based induction chemotherapy regimens or the augmented Berlin-Frankfurt-Munster (BFM) regimen.[29] Majority of patients treated with hyper-CVAD also received either an anti-CD20 monoclonal antibody such as Rituximab or Ofatumumab based on leukemic cell CD20 expression or a tyrosine kinase inhibitor (imatinib or dasatinib) if philadelphia chromosome positive. As shown in Table II, no significant difference was observed based on induction regimens patients received in each group. Two patients with BMN did not received induction chemotherapy; one died before initiating treatment due to sepsis and the other preferred to be treated at an outside facility.

The complete remission rate in ALL group was also significantly inferior in those who had BMN (70%) compared to 92% who did not (p = 0.01). Seventeen (3%) patients without BMN and 1 (5%) patient with BMN had early death (in < 4 weeks) (p = 0.44). (Table III)

Survival

AML patients with BMN—The median relapse free survival (RFS) was 15 months in patients with BMN, whereas 11 months for patients without BMN (p = 0.58) (Table 3, Figure 1A).The overall survival (OS) was severely compromised in patients with BMN, with median of 3.7 months compared to 14 months without BMN (p = 0.003) (Figure 1B). Similarly, patients with BMN had a median event free survival (EFS) of 3.4 months compared to 9 months in AML patients without BMN (p = 0.04) (Figure 1C).

ALL patients with BMN—Among patients with ALL, the median RFS was 59.5 months in patients with BMN compared to 55 months without BMN (p = 0.71) (Table III, Figure 2A). The median EFS was not significantly inferior in patients with BMN, 49.2 months compared to 48.2 months without BMN (p = 0.47) (Figure 2B). The median OS was inferior in patients with BMN; 61.7 months compared to 72 months without BMN, but not significant (p = 0.33) (Figure 2C).

Univariate and multivariate analysis

Age, log (WBC), cytogenetics and BMN were included in the univariate and multivariate models for both AML and ALL patients. Pre-chemo or radiotherapy was also included for AML patients. The tables IV–VII list the results of univariate and multivariate analysis. Logistic regression analyses for CR rates and early induction deaths, and Cox regression analyses for RFS, OS and EFS were used for evaluation. Multivariate analysis in AML with

BMN showed a significant effect on OS (HR=2.31; 95% CI; 1.40–3.81, p = 0.001) and EFS (HR=1.97; 95% CI; 1.22–3.20, p=0.01). Although, AML with BMN showed significant effects on CR and early induction death in the univariate model but did not show a significant effect in multivariate model. In ALL, BMN did show a significant effect on CR in univariate model (HR; 0.21, 95% CI; 0.08–0.56, p =0.002) but not in the multivariate model. For early induction death, RFS, OS and EFS, BMN failed to show significance in ALL.

DISCUSSION

In our series of 640 patients with ALL and 1051 patients with AML, the incidence of BMN was 3.2% and 2.4%, respectively. BMN in AML was associated with poorer outcome with significantly inferior OS and EFS. However in ALL, BMN had lower CR rate but it did not had an impact on survival outcome.

BMN is a rare finding, to the best of our knowledge, there are no previous published reports regarding the incidence, clinical characteristics and outcomes in a larger group of patients with acute leukemia. Overall incidence of BMN in hematological malignancies have been reported in a range of 0.15%–0.32%, in unselected ante mortem bone marrow biopsies.[4] Our results, therefore, suggest that BMN at initial diagnosis is an underreported entity.

In our series, among the AML patients with BMN, higher proportion of patients had the FAB-M5 histology, compared to AML without BMN, signifying that it is more prevalent among patients with M5 histology.[30] None of the patients in our series had the FAB-M7 histology suggesting that, despite its association with marrow fibrosis, the M7 histology is not associated with BMN. Furthermore, possible associations with specific cytogenetic abnormalities were evident. Among 23 evaluable AML patients with BMN, 70% had intermediate or adverse cytogenetics, while none had favorable cytogenetics. More importantly, 44% of the patients with BMN at diagnosis had a complex karyotype, significantly higher than the reported historical cohorts.[31] None of 9 AML patients with BMN, evaluated for the presence of *FLT3*-ITD and *RAS* mutations had the aberration, while only 2 of 7 evaluable patients had a *NPM1* mutation; this may indicate that BMN is solely a result of a proliferative disease associated with a proliferative genotype. In the present series, the presence of BMN was associated with a worse outcome among the patients with AML with a median OS of only 3.7 months.[32] Primary resistant disease, appeared to be the main reason for these poor outcomes, as BMN at initial diagnosis was significantly associated with lower CR rate compared to patients without BMN.

Among the evaluable ALL patients with BMN, all had B-cell lineage disease, and none had T-cell lineage. Only 2 patients had Philadelphia chromosome, despite the relative advanced median age of the patients in this series. Similar to AML patients, ALL patients with BMN, had significantly inferior CR rate compared to patients without BMN . Though, the inferior response rate did not translated into significantly inferior RFS,EFS, or OS.

Several issues need to be addressed in future studies. Apart from one series, to date there is no standardized grading system to evaluate the extent of necrosis, and the clinical impact of

the extent of BMN remains unknown. Furthermore, the underlying pathophysiology of BMN remains poorly understood. Although hypoxemia resulting from the failure of the microcirculation may be a critical event, the role of various toxins, cytokines and vasoactive substances released from the malignant cells as well as the supporting cells in the microenvironment, in the pathogenesis of BMN is not known.[23] To date, no studies have assessed the potential role cytokines in the underlying pathogenesis of BMN. Further studies are therefore needed to better elucidate these potential mechanisms. In summary, BMN is an infrequent, but not a rare finding in both AML and ALL. It occurs more commonly with the FAB-AML M5 histology. Furthermore, BMN is suggestive of lower CR rate and overall survival, in patients with AML and ALL.

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Figure 1.
Kaplan Meier curves using log rank test for (A) relapse free survival (B) overall survival and (C) event free survival in acute myeloid leukemia (AML) patients with and without bone marrow necrosis (BMN).
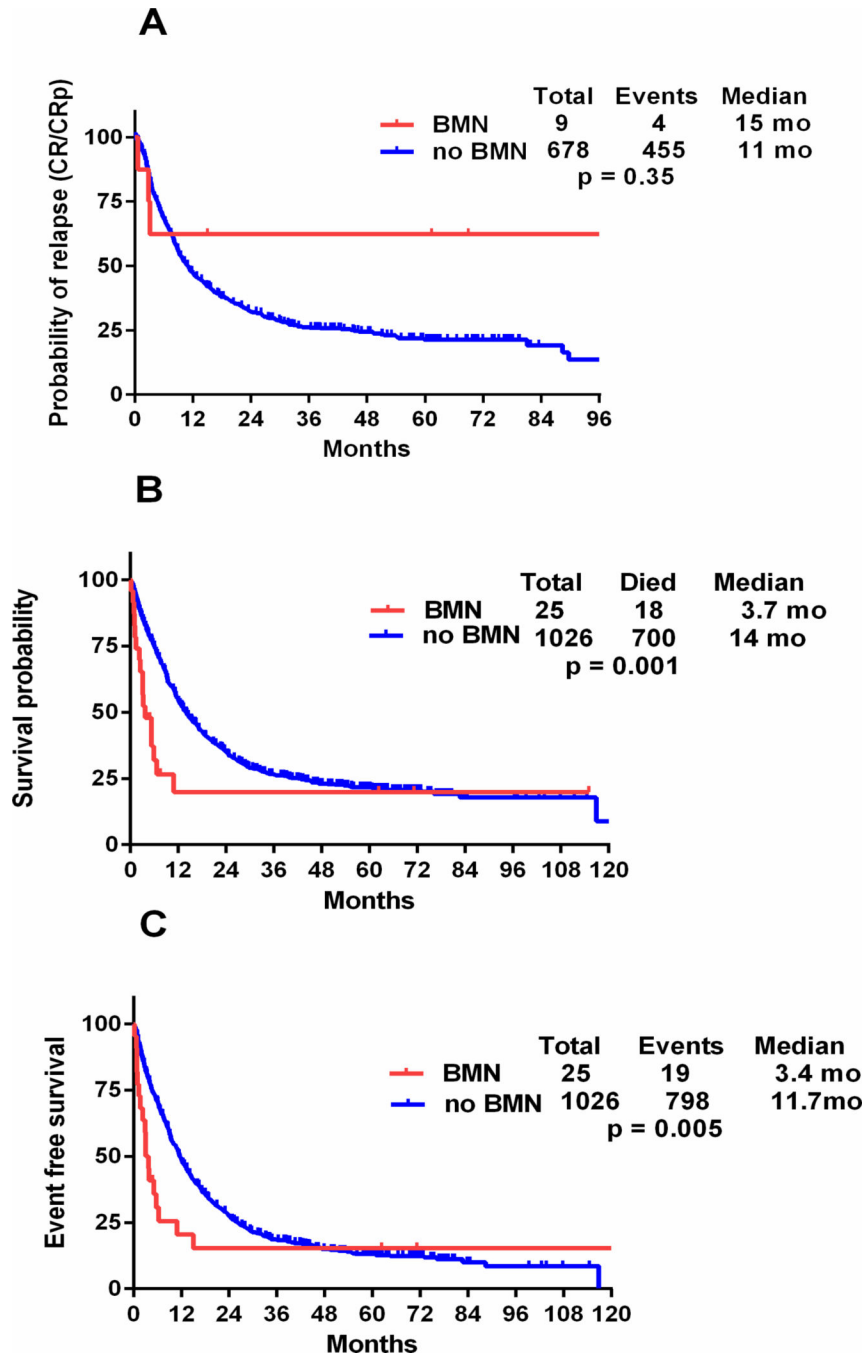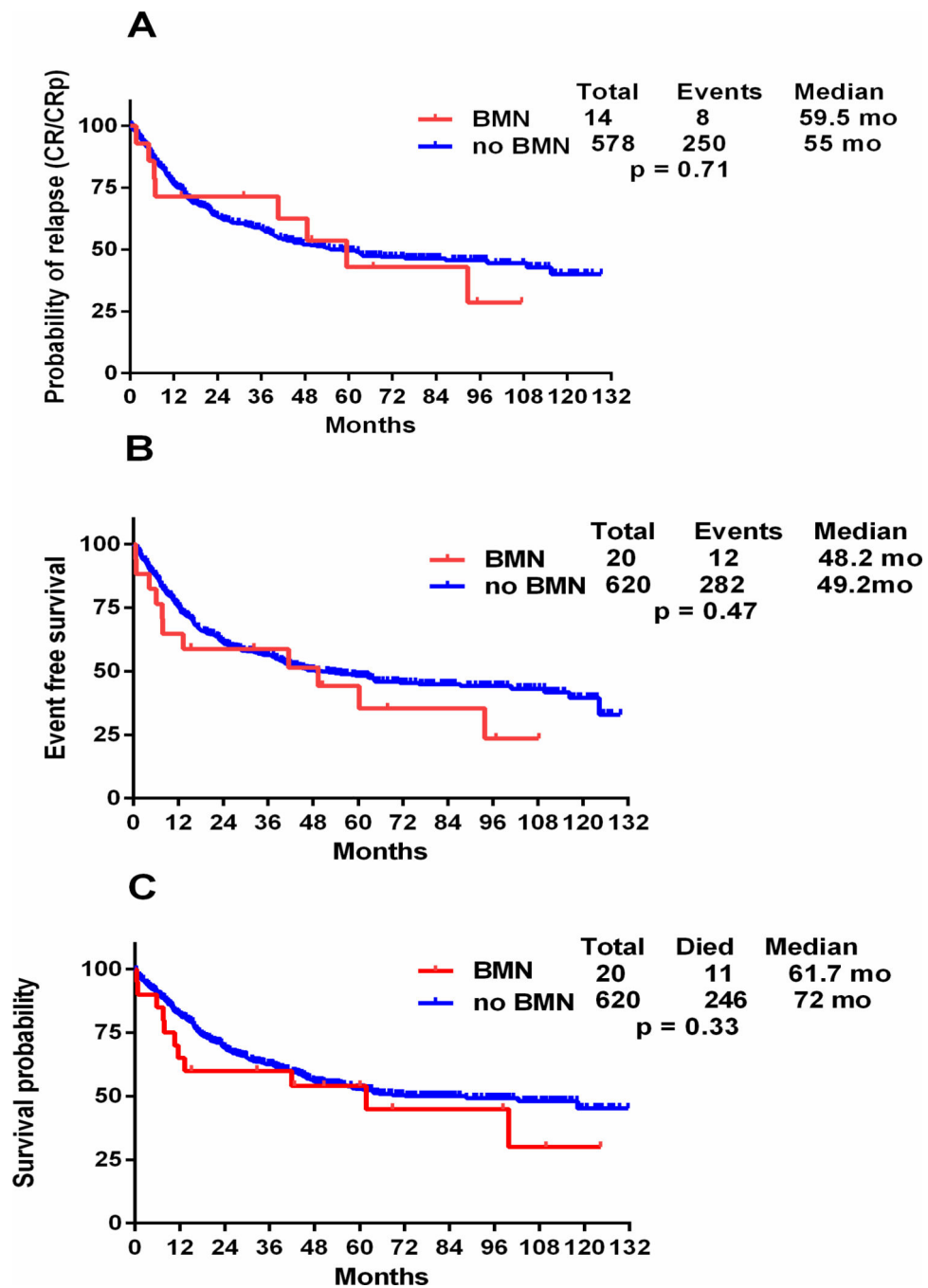
Figure 2.
Kaplan Meier curves using log rank test for (A) relapse free survival (B) event free survival and (C) overall survival in patients with acute lymphocytic leukemia (ALL) with and without bone marrow necrosis (BMN).

Table I

Baseline characteristics of AML patients with bone marrow necrosis (n = 1051)

Variables	Median [range], number (%)		
	Without BMN (n= 1026)	With BMN (n=25)	P value
Age, years	62 [14–88]	68 [25–83]	0.19
WBC × 10^9/L	3.8 [0.2–433]	12.4 [0.7–269.4]	0.07
BM Blast %	42 [0–99][a]	59 [1–95][a]	0.08
Antecedent hematological disorder	178 (17)	3 (12)	0.60
Cytogenetics			
Poor risk	321 (31)	11 (44)	0.19
Diploid	452 (44)	7 (28)	0.15
Intermediate risk	206 (20)	5 (20)	> 0.99
Unknown	47 (5)	2(8)	0.33
Molecular mutation			
FLT3 ITD **(n= 957; without BMN [948], with BMN [9])**[*]	148 (16)	0 (0)	0.37
NPM1 **(n= 598; without BMN [591], with BMN [7])**[*]	135 (23)	2 (29)	0.66
RAS **(n= 878; without BMN [869], with BMN [9])**[*]	92 (11)	0 (0)	0.61
FAB			
M0	56 (5)	2 (8)	0.64
M1	127 (12)	2 (8)	0.76
M2	185 (18)	2 (8)	0.29
M3	0 (0)	0 (0)	
M4	151 (15)	5 (20)	0.40
M5	101 (10)	8 (32)	0.002
M6	54 (5)	0 (0)	0.63
M7	9 (1)	0 (0)	> 0.99
RAEB- type 1	140 (14)	1 (4)	0.24
Unknown	203 (20)	5 (20)	> 0.99
Induction chemotherapy			
HDAC-based	542 (53)	9 (36)	0.11
HMA-based	162 (16)	6 (24)	0.27
LDAC based	218 (21)	3 (12)	0.33
Investigational agents	104 (10)	3 (12)	0.73
Not treated	0 (0)	4(16)	<0.0001

No; number of patients, WBC; white blood cell count, BMN; bone marrow necrosis, AHD; antecedent hematologic disorder, Chemo; chemotherapy, XRT; radiation therapy, HDAC; high dose cytarabine, LDAC; low dose cytarabine, HMA; hypomethylating agent, FAB; French American British classification, RAEB; refractory anemia with excess blast.

[a] Some patients receive treatment outside and achieve response, which represent lower BM blast at the time of referral

[*] Number of patients evaluated for mutations.

Table II

Baseline characteristics of ALL patients with bone marrow necrosis

Variables	Median [range], No. (%)		
	Without BMN (n= 620)	With BMN (n= 20)	P value
Age, years	42 (13–84)	51.5 (17–69)	0.58
WBC × 10^9/L	5.45 (0–602.4)	5.05 (0.0–11.5)	0.38
BM Blast %	80 (0–100)[a]	38.5 (0–91)[a]	0.004
ALL Lineage[®]			
B-Cell	509 (84)	15 (100)	0.15
T-Cell	99 (16)	0 (0)	
Cytogenetics			
Diploid	194 (31)	4 (20)	0.34
MLL	7 (1)	0 (0)	> 0.99
Ph+	160 (26)	2 (10)	0.12
Else	259 (42)	14 (70)	0.02
Treatment			
Hyper-CVAD[28] +/– monoclonal Abs or TKI[*]	509 (82)	15 (75)	0.38
Augmented BFM[29]	111 (18)	3 (15)	> 0.99
Not treated [¥]	0 (0)	2 (10)	0.001

No; number of patients, WBC; white blood cell count, BMN; bone marrow necrosis, BM; bone marrow, MLL; mixed lineage leukemia, Ph+; philadelphia chromosome positive

[a]Some patients receive treatment outside and achieve response, which represent lower BM blast at the time of referral.

[*]Patients received HyperCVAD with monoclonal antibodies (ofatumumab or rituximab) based on CD20 expression or TKI (tyrosine kinase inhibitor) if Ph+.

[®]Overall; 17 (2.6%) patients were non-evaluable for immunophenotyping.

1 died without receiving treatment and 1 received treatment outside MD Anderson Cancer Center.

Table III

Clinical outcome

	Median [range], No. (%)						
	AML			ALL			
	With BMN	Without BMN	P value	With BMN	Without BMN	P value	
Number	25 (2.4)	1026 (97.6)		20 (3.1)	620 (96.9)		
CR	8 (32)	607 (59)	0.01	14 (70)	570 (92)	0.01	
CR/CRp	9 (36)	678 (66)	0.003	14 (70)	579 (93)	0.002	
Early death[*]	3 (12)	37 (3.6)	0.07	1 (5)	17 (3)	0.44	
RFS (months)	NA [2.9, NA]	11 [9.7–12.6]	0.42	59.5 [40.6, N/A]	55 [47.8, 109]	0.71	
OS (months)	3.7 [2.4–10.9]	13.9 [12.7–15.5]	0.001	60.8 [11.5, N/A]	87.2 [55, NA]	0.34	
EFS (months)	3.7 [2.3–5.8]	9.4 [8.9–10.5]	0.005	49.2 [7.7, N/A]	48.2 [39.9, 76.2]	0.47	

AML; acute myeloid leukemia, ALL; acute lymphoblastic leukemia, BMN; bone marrow necrosis, CR; complete remission, RFS; relapse free survival, OS; overall survival, EFS; event free survival, N/A missing value.

[*] Early death; less than 4 weeks of induction chemotherapy.

Table IV

Univariate Logistic Regression and Cox proportional Hazards Models for AML patients

A) Complete remission (Logistic Regression)			
Variable	**Odds Ratio**	**95% CI**	**P Value**
Age	0.96	0.95, 0.97	<0.001
Log (WBC)	0.90	0.82, 0.99	0.03
Prior Chemo or XRT	0.49	0.35, 0.68	<0.001
Diploid/Int vs Poor risk CG	2.26	1.73, 2.96	<0.001
BMN vs. No BMN	0.33	0.14, 0.76	0.01

B) Early induction mortality (Logistic Regression)			
Age	1.04	1.02, 1.07	0.002
Log (WBC)	1.23	0.98, 1.54	0.07
Prior Chemo or XRT	1.20	0.55, 2.66	0.65
Diploid/Int vs Poor risk CG	0.54	0.28, 1.03	0.06
BMN vs. No BMN	3.65	1.04, 12.72	0.04

C) Relapse free survival (Cox model)			
Variable	**Hazard Ratio**	**95% CI**	**P Value**
Age	1.02	1.01, 1.03	<0.001
Log (WBC)	1.10	1.03, 1.18	0.01
Prior Chemo or XRT	1.50	1.17, 1.93	0.002
Diploid/Int vs Poor risk CG	0.55	0.45, 0.67	<0.001
BMN vs. No BMN	0.67	0.25, 1.80	0.43

D) Overall survival (Cox model)			
Age	1.03	1.02, 1.04	<0.001
Log (WBC)	1.09	1.03, 1.15	0.002
Prior Chemo or XRT	1.73	1.44, 2.08	<0.001
Diploid/Int vs Poor risk CG	0.45	0.39, 0.53	<0.001
BMN vs. No BMN	2.14	1.34, 3,42	0.001

E) Event free survival (Cox model)			
Age	1.02	1.02, 1.03	<0.001
Log (WBC)	1.11	1.05, 1.17	<0.001
Prior Chemo or XRT	1.52	1.27, 1.82	<0.001
Diploid/Int vs poor risk CG	0.52	0.45, 0.60	<0.001
BMN vs. No BMN	1.90	1.21, 3.01	0.01

CI; confidence interval, WBC; white blood cell, BMN; bone marrow necrosis, CG; cytogenetics, Int; intermediate risk CG, Chemo; chemotherapy, XRT; radiotherapy.

Table V

Multivariate Logistic Regression and Cox Proportional Hazards Models for AML patients

A) Complete remission (Logistic Regression)			
Variable	**Odds Ratio**	**95% CI**	**P Value**
Age	0.95	0.94, 0.97	<0.001
Log (WBC)	0.80	0.72, 0.88	<0.001
Prior Chemo or XRT	0.66	0.46, 0.94	0.02
Diploid/Int vs Poor risk CG	2.28	1.70, 3.05	<0.001
BMN vs. No BMN	0.45	0.18, 1.13	0.09

B) Early induction mortality (Logistic Regression)			
Age	1.05	1.02, 1.09	0.001
Log (WBC)	1.37	1.08, 1.74	0.01
Diploid/Int vs Poor risk CG	0.50	0.25, 0.97	0.04
BMN vs. No BMN	3.14	0.86, 11.45	0.08

C) Relapse free survival (Cox model)			
Variable	**Hazard Ratio**	**95% CI**	**P Value**
Age	1.02	1.01, 1.03	<0.001
Log (WBC)	1.18	1.10, 1.27	<0.001
Prior Chemo or XRT	1.31	1.01, 1.71	0.05
Diploid/Int vs Poor risk CG	0.55	0.44, 0.68	<0.001
BMN vs. No BMN	0.84	0.31, 2.25	0.72

D) Overall survival (Cox model)			
Age	1.03	1.03, 1.04	<0.001
Log (WBC)	1.19	1.12, 1.26	<0.001
Prior Chemo or XRT	1.34	1.14, 1.67	0.001
Diploid/Int vs Poor risk CG	0.46	0.39, 0.54	<0.001
BMN vs. No BMN	2.31	1.40, 3.81	0.001

E) Event free survival (Cox model)			
Age	1.03	1.02, 1.03	<0.001
Log (WBC)	1.19	1.13, 1.26	<0.001
Prior Chemo or XRT	1.26	1.05, 1.53	0.02
Diploid/Int vs poor risk CG	0.52	0.45, 0.61	<0.001
BMN vs. No BMN	1.97	1.22, 3.20	0.01

CI; confidence interval, WBC; white blood cell, BMN; bone marrow necrosis, CG; cytogenetics, Int; intermediate risk CG, Chemo; chemotherapy, XRT; radiotherapy.

Table VI

Univariate Logistic Regression and Cox Proportional Hazards Models for ALL patients

A) Complete remission (Logistic Regression)			
Variable	**Odds Ratio**	**95% CI**	**P Value**
Age	0.98	0.96, 0.99	0.004
Log (WBC)	0.87	0.73, 1.03	0.09
Cytogenetics			
MLL vs Diploid	0.71	0.08, 6.20	0.55
Ph+ vs Diploid	2.28	0.98, 5.30	0.08
Else vs Doploid	1.13	0.62, 2.07	0.92
BMN vs. No BMN	0.21	0.08, 0.56	0.002

B) Early induction mortality (Logistic Regression)			
Age	1.04	1.01, 1.07	0.01
Log (WBC)	1.04	0.86, 1.27	0.66
Cytogenetics			
MLL vs Diploid	8.08	0.78, 83.67	0.10
Ph+ vs Diploid	1.55	0.41, 5.85	0.53
Else vs Doploid	1.46	0.44, 4.93	0.41
BMN vs. No BMN	1.87	0.24, 14.76	0.55

C) Relapse free survival (Cox model)			
Variable	**Hazard Ratio**	**95% CI**	**P Value**
Age	1.02	1.01, 1.03	<0.001
Log (WBC)	1.13	1.05, 1.21	0.001
Cytogenetics			
MLL vs Diploid	4.04	1.75, 9.34	0.001
Ph+ vs Diploid	1.62	1.16, 2.25	0.005
Else vs Doploid	1.47	1.09, 1.99	0.01
BMN vs. No BMN	1.14	0.57, 2.31	0.71

D) Overall survival (Cox model)			
Age	1.03	1.02, 1.03	<0.001
Log (WBC)	1.11	1.03, 1.18	0.004
Cytogenetics			
MLL vs Diploid	3.88	1.69, 8.96	0.001
Ph+ vs Diploid	1.60	1.15, 2.22	0.01
Else vs Doploid	1.36	1.01, 1.84	0.04
BMN vs. No BMN	1.34	0.73, 2.46	0.34

E) Event free survival(Cox model)			
Age	1.02	1.01, 1.03	<0.001

A) Complete remission (Logistic Regression)			
Variable	**Odds Ratio**	**95% CI**	**P Value**
Log (WBC)	1.13	1.06, 1.21	<0.001
Cytogenetics			
MLL vs Diploid	4.10	1.89, 8.90	<0.001
Ph+ vs Diploid	1.56	1.14, 2.13	0.01
Else vs Doploid	1.46	1.10, 1.93	0.01
BMN vs. No BMN	1.24	0.70, 2.21	0.47

CI; confidence interval, WBC; white blood cell, BMN; bone marrow necrosis, CG; cytogenetics, Int; intermediate risk CG, Chemo; chemotherapy, XRT; radiotherapy.

Table VII

Multivariate Logistic Regression and Cox Proportional Hazards Models for ALL patients

A) Complete remission (Logistic Regression)			
Variable	**Odds Ratio**	**95% CI**	**P Value**
Age	0.97	0.96, 0.98	< 0.001
Log (WBC)	0.83	0.68, 1.00	0.05
Cytogenetics			
MLL vs Diploid	0.82	0.09, 7.44	0.47
Ph+ vs Diploid	3.86	1.58, 9.40	0.02
Else vs Doploid	1.60	0.83, 3.06	0.85
BMN vs. No BMN	0.58	0.12, 2.76	0.49

B) Early induction mortality (Logistic Regression)			
Age	1.04	1.01, 1.07	0.01
BMN vs. No BMN	2.28	0.28, 18.58	0.44

C) Relapse free survival (Logistic Regression)			
Variable	**Hazard Ratio**	**95% CI**	**P Value**
Age	1.02	1.01, 1.02	<0.001
Log (WBC)	1.13	1.05, 1.21	0.001
Cytogenetics			
MLL vs Diploid	3.91	1.69, 9.04	0.001
Ph+ vs Diploid	1.21	0.85, 1.71	0.29
Else vs Doploid	1.45	1.07, 1.97	0.02
BMN vs. No BMN	1.21	0.59, 2.45	0.61

D) Overall survival (Cox model)			
Age	1.03	1.02, 1.04	<0.001
Log (WBC)	1.11	1.04, 1.19	0.003
Cytogenetics			
MLL vs Diploid	3.92	1.70, 9.06	0.001
Ph+ vs Diploid	1.09	0.77, 1.53	0.64
Else vs Doploid	1.26	0.93, 1.70	0.14
BMN vs. No BMN	1.01	0.50, 2.06	0.98

E) Event free survival (Cox model)			
Age	1.02	1.01, 1.03	<0.001
Log (WBC)	1.13	1.06, 1.21	< 0.001
Cytogenetics			
MLL vs Diploid	3.95	1.82, 8.59	0.001
Ph+ vs Diploid	1.16	0.83, 1.61	0.39
Else vs Doploid	1.38	1.04, 1.83	0.03

A) Complete remission (Logistic Regression)			
Variable	Odds Ratio	95% CI	P Value
BMN vs. No BMN	1.01	0.52, 1.97	0.98

CI; confidence interval, WBC; white blood cell, BMN; bone marrow necrosis, CG; cytogenetics.