Original Article

Does Day 14 Bone Marrow Status Predict Response to Chemotherapy in Acute Myeloid Leukemia? Experience of a Hemato-Oncology Care Center from Eastern India

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Abstract

Background: Acute myeloid leukemia (AML), the most common type of acute leukemia in adults, yet continues to have the lowest survival rate of all leukemias. The present study aimed to study ability of Day 14 marrow status to predict the remission status in AML. **Materials and Methods:** This prospective, observational study conducted in 30 AML patients who received "induction remission" as per standard guidelines and undergone bone marrow (BM) aspiration and biopsy on day 14 and day 28. Complete remission (CR) defined as per standard criteria. SPSS 15.3 was used to perform statistical analysis. **Results:** Median BM blast count on day14 was 10.6% (range, 1–50). Patients achieving remission in day 28 + BM had mean day 14 BM blast count of 8.52% compared to 21.00% in those who did not achieve remission. Majority (90.9%) of the patients with ≤15% BM blast on D14 was in remission. Comparing D14 BM blast% with CR, blast >15% cut off (across all the cut offs, i.e., 5%, 10%, 15%, or 20%) was the best to find those who entered remission; but the negative predictive value (NPV) was poor across all groups. **Conclusions:** There is a trend toward early relapse in patients with higher blast on D14. However, D14 BM marrow blast >15% has a poor NPV for predicting relapse.

Keywords: *Acute myeloid leukemia, day 14 bone marrow, induction chemotherapy, remission status*

Introduction

Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults; continues to have a dismal prognosis and the lowest survival rate of all leukemias. While results of treatment have improved steadily in younger adults over the past 20 years, there have been limited changes in survival among individuals of age >60 years.[1,2]

Although the incidence of acute leukemias accounts for <3% of all cancers, these disease constitute the leading cause of death due to cancer in children and younger adults. AML accounts for approximately 25% of all leukemias in adults in the West and constitutes the most frequent form of leukemia.[2,3] Though the research has been robust in the past 2–3 decades but the clinical translation is still not marked as happened in chronic leukemias. Over the last three decades, "3 + 7" regimen with daunorubicin and cytarabin was and has remained the standard chemotherapy in AML. Although the remission rates have improved, the best consolidation regimens and transplantation are still in search; there is only a marginal improvement in the terms of survival over the last two decades. In the recent decades, newer prognostic markers are being explored which can predict the overall survival (OS) and progression-free survival. These prognostic markers have changed the basic paradigm of the management of AML following remission induction. Bone marrow (BM) evaluation by aspiration and biopsy after 7–10 days of induction remission is being explored as a prognostic marker; studies have shown conflicting results in different trials. In some centers in the West, it has become a standard practice to perform BM aspiration and trephine biopsy and to go for re-induction chemotherapy if there is presence of significant disease, as it predicts inferior rate of remission. In India, few centers have started to practice it, but not become widely accepted by many others. With this background, this study was planned to evaluate the status of day14

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BM after induction chemotherapy and compare it with day 28 + marrow. The present study done with the aims and objectives of (1) to evaluate the D14 BM status on both aspiration and biopsy with respect to cellularity and blast percentage, (2) to correlate with BM remission status on recovery of counts, i.e., on D28 or more, and (3) ability of D14 marrow status to predict the remission status and correlate with OS.

Materials and Methods

This was a prospective, noninterventional, observational study conducted in 30 patients with diagnosis AML over a period of 2 years from January 2010 to December 2011 admitted to the Department of Hematology, NRS Medical College, Kolkata. AML was diagnosed based on the WHO 2008 Criteria for diagnosis of AML.[4] The patients included in the present study were based on the following inclusion and exclusion criteria:

Inclusion criteria

1. All patients with definite diagnosis of AML
2. Age 12 years or more
3. Only patients who were alive to evaluate for the evaluation of remission status on D28 or more are included for analysis and statistical correlations.

Exclusion criteria

1. Patients who are <12 years
2. Patients with acute promyelocytic leukemia (APL) defined as the presence of PML-RARA by reverse transcriptase-polymerase chain reaction (RT-PCR) in a suspected AML-M3 (APL) morphology on BM evaluation
3. Patients with mixed phenotypic acute leukemia (MPAL).

Study tools

Written consent

All patients had undergone following evaluation with prior written consent in their mother tongue.

Baseline investigations

Detailed history taken and clinical evaluation done. Baseline investigations included: (a) complete hemogram including peripheral smear examination; (b) immunophenotyping from PB or BMA as per discretion; (c) BM aspiration (Biopsy if required) and cytogenetics; (d) Blood biochemistries: Glucose, renal functions, liver function tests, uric acid; (e) anti-HIV-I and II antibody, HBsAg, Anti-hepatitis C virus; (f) PT activated partial thromboplastin time, if required; and (g) electrocardiography, echocardiography, as per discretion.

Induction remission

All patients received "induction remission" as per standard current guidelines with injection daunorubicin 60 mg/m^2 on Days 1, 2, and 3 and injection cytarabine100 mg/m^2 as continuous intravenous infusion from day1 to 7.

BM aspiration/biopsy

All patients underwent BM aspiration/biopsy on day14 and day 28 of induction if peripheral blood is in complete remission (CR) or CRi. Those patients whose counts did not recover on day 28 and marrow was hypocellular, underwent repeat BM aspiration/biopsy on day 35. BM marrow materials processed as per standard guidelines and estimated the percentage of blasts. No therapeutic modifications were done based on marrow status on day 14.

Response evaluation

CR as per standard definition;[4] those who did not achieve CR, defined as treatment failure. No therapeutic modifications were done based on marrow status on day 14.

Statistical analysis

SPSS 15.3 (SPSS Inc., 233 South Wacker Drive, 11th Floor, Chicago, IL 60606-6412) was used to perform statistical analysis. Depending on the normalcy of distribution curve and skew deviation mean or median was compared using independent *t*-test or nonparametric *t*-test such as Mann–Whitney's were used, respectively. Chi-Square test used for comparing categorical variables. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

Results

In the present study, 70% (n = 21/30) were male; mean and median age was 38.56 years and 38.5 years respectively (range, 16–72). The salient clinical features and laboratory parameters at presentation are shown in Table 1. Fever (93.3%) and weakness (93.3%) were the dominant symptoms at presentation. Bleeding symptoms were present in 40% of patients. Majority (90%) of the patients had sternal tenderness. Liver and spleen enlargement found in 19 (63.35%) and 27 (90%) patients, respectively. Leukemia cutis observed in two (6.7%) patients. Mean hemoglobin concentration at presentation was 73 g/L (range, 45–128). Median total white blood cell count and peripheral blood blast percentage was 39,189 cells x 10^3/µl (range: 1500–181,000) and 63.86% (range, 23%–95%), respectively. Auer rods were seen in 16.7% of patients. All the patients were *de novo* AML except one had therapy related AML with a history of carcinoma breast and received cyclophosphamide based chemotherapy earlier. According to the WHO classification majority (80%; n = 24) belonged to the group of AML, not otherwise specified (AML-NOS). Moreover, according to the French-American-British (FAB) type, most of the cases belonged to M1 (36.7%), M2 (26.7%) and M4 (20%). As per the WHO 2008 classification,[4] majority (80%; n = 24) of the patients had AML-NOS and one patient had

Table 1: Salient clinical features and laboratory parameters at presentation of the patients included in the study (*n*=30)

Parameters studied	Result
Fever, *n* (%)	28 (93.3)
Bleeding, *n* (%)	12 (40)
Weakness, *n* (%)	28 (93.3)
Lymphadenopathy, *n* (%)	14 (46.7)
Sternal tenderness, *n* (%)	27 (90)
Hepatomegaly, *n* (%)	19 (63.3)
Splenomegaly, *n* (%)	27 (90)
Leukemia cutis, *n* (%)	2 (6.7)
Hemoglobin (g/L), mean (range)	73 (45-128)
Total White cell count (cells $\times 10^3/\mu l$), median (range)	39.189 (1.500-181.000)
Neutrophil (%), median (range)	23.79 (0-81)
Peripheral blood blast (%); median (range)	44.73 (5-99)
Lactate dehydrogenase (IU/L) at diagnosis; mean (range)	586 (250-1200)
Bone marrow blast (%) at diagnosis; median (range)	(23-95)
Presence of Auer rods, *n* (%)	5 (16.7)
FAB type AML, *n* (%)	
M0	2 (6.7)
M1	11 (36.7)
M2	8 (26.7)
M4	6 (20)
M5b	1 (3.3)
M6	2 (6.7)
WHO classification, *n* (%)	
AML with Recurrent Genetic abnormality (non-APL)	5 (16.7)
t-AML	1 (3.3)
AML-NOS	24 (80)
Risk stratification (based on karyotyping), *n* (%)	
Good	4 (13.3)
Intermediate	21 (70)
Poor	5 (16.7)

AML: Acute myeloid leukemia, NOS: Not otherwise specified

therapy-related AML (t-AML). Based on karyotyping, 70% (n = 21) patients belonged to intermediate risk group. Recurrent genetic abnormality detected in five (16.7%) patients; three had t (8; 21), one with inv (16) and the other had KMT2A (11q23) rearrangement. Median BM blast count on day 14 was 10.6% (range, 1–50). On day 14 marrow assessment, 14 (46.7%) patients had <5% blasts, 11 (36.7%) had 5%–19% blasts and 5 (16.7%) had ≥20%. As shown in Table 2, patients achieving remission in day 28 + BM, had a mean day 14 BM blast count of 8.52% in contrast to 21.00%) in those who did not achieved remission. Poor risk group had high mean D14 blast count of 23% in contrast to nonpoor risk group (8.12%). On median follow up of 80 days (range, 40–540), "no relapse" group had shown lower (6.95%) mean D14 blast% than the "relapse" group (14.8%). In search to look for the correlation of D14 BM blasts with other baseline parameters (age, Hb%, TLC, LDH, and day 0 BM blast%), none had shown statistical significance; though the patients (n = 22) with ≤15% blasts on D14 marrow had lower day 0 mean blast load (60.27%) in comparison to 68.12% in those who had >15% blasts on D14 marrow. Majority (90.9%) of the patients with ≤15% BM blast on D14 was in remission after induction therapy and of the 5 patients with >15% BM blast on D14 showed remission in D28 + marrow, three had relapsed on a median follow-up of 80 days [Table 3]. On statistical calculation of ability of D14 marrow cut off 15% blasts to predict the remission, found the sensitivity, specificity, PPV, and NPV of 80%, 60%, 90.9%, and 37.5%, respectively. On further calculation of ability of D14 marrow cut off 15% blasts to predict the relapse, found the sensitivity, specificity, PPV, and NPV of 90%, 60%, 90%, and 60%, respectively.

Discussion

As published in the literature,[5] the most common FAB subtype is M2; in our study, it was M1, probably because of selection bias or chance phenomenon, as patients who were willing to undergo intensive chemotherapy and those who survived induction were only included in the study. Cytogenetic analysis with metaphase karyotyping is a key component of the initial evaluation of a patient with

Table 2: Correlations of bone marrow remission status with D14 marrow blast %, cytogenetic abnormality and aberrant antigen expression on flow cytometry (*n*=30)

Parameters	Sub groups	Number of patients, *n*	BM day14 blast (%) Mean (%)±SD	*P*
Day28+remission status	BM not in remission	5	21.00±17.64	*P*=0.034
	BM in remission	25	8.52±7.61	
Cytogenetics poor versus others	Not poor risk	25	8.12±7.46	*P*=0.01
	Poor risk	5	23.00±16.00	
Aberrant Antigen expression on flow cytometry (two patients diagnosed by cytochemistry)	Aberrant Ag expressed	13	8.53±8.20	*P*=0.49
	No expression of aberrant Ag	15	12.40±12.91	
Median follow up of 80 days (range, 40-540) (patients who didn't enter remission, excluded)	No relapse	20	6.95±7.04	*P*=0.02
	Relapse	5	14.80±7.12	

BM: Bone marrow, SD: Standard deviation

Table 3: Bone marrow blast 15% cut off and remission status after induction therapy (*n*=30)

Blast cut off on D14	BM final remission status, *n* (%)		Total
	BM not in remission	BM in remission	
≤15% BM blast on D14	2 (9.1)	20 (90.9)	22 (100)
>15% BM blast on D14	3 (37.5)	5 (62.5)	8 (100)
Blast cut off on D14	**Relapse status, *n* (%)**		**Total**
	Not relapsed	**Relapsed**	
≤15% BM blast on D14	18 (90)	2 (10)	20 (100)
>15% BM blast on D14	2 (40)	3 (60)	5 (100)

BM: Bone marrow

AML; specific cytogenetic abnormalities in AML have considerable prognostic significance and affect treatment planning. Good cytogenetic risk was present in 13.3% of patients, intermediate in 70% of patients and 16.7% of patients had poor cytogenetic risk. In a study by Kern *et al*.,[6] the distribution of cytogenetic based risk categories was 10%, 48.3%, and 13.1% for favorable, intermediate, and unfavorable risk category; cytogenetic not available in 28.5% cases. In one of the largest MRC-10 study among 5876 younger adult AML patients, the distribution of patients across cytogenetic risk groups was 23%, 68%, and 9% in good, intermediate and poor risk.[7] In our study, in three (10%) patients there was no yield on karyotyping; repeat cytogenetics were performed during the remission status evaluation or a RT-PCR for AML translocations were done and patients were re-classified. In two patients, t (8;21) was present and in one none of the tested cytogenetic molecular markers were present and cytogenetics study during remission status evaluation yielded normal cytogenetics.

In the present study, all patients received daunorubicin on D1-3 and cytarabine 700 mg/m^2 as continuous intravenous infusion over 7 days. All patients underwent a marrow aspiration and biopsy on D14 of chemotherapy. No therapeutic modifications were done based on marrow status on day 14. Twenty five (83.3%) patients achieved CR following "3 + 7" chemotherapy and 5 (16.7%) patients did not achieve CR [Table 2]. Patients with poor cytogenetic risk had higher mean blast% on D14 when compared to intermediate and good risk (23.0 vs. 8.12, $P = 0.01$). There was no statistical correlation between any other baseline factors and D14 marrow blast percentage, including age, baseline hemoglobin, total white cell count, peripheral blast percentage, LDH, BM blast percentage, and expression of aberrant antigens in flow cytometry.

On recovery of counts on D28 or later (but, irrespective of the counts BM examination was done latest on D36), the mean BM blast was 21.00 ± 17.64% vs. 8.52 ± 7.61% ($P = 0.034$) in those who did not achieve remission and those who achieved remission. Similar reports were shown previously in the study by Liso *et al*.[8] They had showed a 4% median blast among those who entered remission when compared to 42% among those who did not achieve remission ($P < 0.0001$). After comparing the remission status and D14 BM, across all the cut offs i.e., 5%, 10%, 15%, or 20%, blast >15% cut off was the best to find those who enter remission; but the NPV was poor across all the groups. Still there are many patients who enter remission even if they have higher blast percentage on D14 marrow. Twenty (90.9%) patients with ≤15% blasts on D14 marrow entered remission, but only 37.5% of patients in >15% blasts on D14 marrow did not enter remission. The sensitivity, specificity, PPV, and NPV were 80%, 60%, 90.9%, and 37.5%, respectively. Five patients relapsed during follow-up (which is short to comment firmly on relapse rates). The median follow-up was 80 days ranging from 40 to 540 days. The mean D14 blasts among those who relapsed were significantly higher when compared to those who maintained remission (14.80% ± 7.12% vs. 6.95% ± 7.04%; $P = 0.02$). When a cut off of 15% was

taken, 90% (n = 18/20) patients with ≤15% blasts on D14 marrow did not relapse and 60% (n = 3/5) patients with >15% blasts on D14 marrow relapsed. The sensitivity, specificity, PPV, and NPV were 90%, 60%, 90%, and 60%, respectively. Since follow-up duration is short, a definite comment on NPV cannot be made.

Yanada *et al*.[9] from M. D. Anderson Cancer Center, USA evaluated kinetics of blasts during AML induction with high dose Ara-C along with anthracycline. In their study, patients with <20% blasts on D14 had a probability of 61%–71% attaining CR; the sensitivity, specificity, PPV and NPV were 89.6%, 39.8%, 72.57%, and 68.28%, respectively. In the present study, the sensitivity with 15% cut off was in concordance with these findings; however, it showed a higher specificity, PPV, and a lower NPV. The probable reason for this finding may be due to small number of patients and different induction regimens used. Even in their study, they showed approximately half of the patients with 20%–59% blasts in D14 BM still enter remission without any intervention. The risk of re-induction in AML patients based on D14 marrow could not be clearly made out and the mortality due to additional myelosuppressive therapy may be determinal in some patients.

Liso *et al*.[8] from Italy studied the effects of D14 marrow status on prognosis of AML. Patients received different induction regimens as per prevailing practice of the time; they analyzed a series of 198 patients (99 males and 99 females, aged 15–80 years, median 54 years) with *de novo* AML. The median D14 marrow blast was 4% (range, 0%–50%) in CR patients and 42% (range 2%–96%) in NR patients (P < 0.0001). Of the 97 patients who had a D14 marrow blast ≤22%, 77 (79%) achieved CR; conversely, of the 27 patients who had a D14 marrow blast >22%, 22 (81%) were NR (P < 0.0001). The sensitivity, specificity, PPV, and NPV were 93.9%, 71.4%, 79.38%, and 81.48%, respectively. They concluded the study by suggesting that the use of D14 marrow status in addition to other parameters such as cytogenetics may be a predictive test for CR, helping to identify those who will not attain CR. In another study by Hussein *et al*.[10] from Minneapolis, Minnesota, 130 patients with *de novo* AML were studied. Only 72 patients could be evaluated for D14 blast%; majority (81%) had major cytoreduction of ≤5%. However, failure to attain major cytoreduction had only 43% specificity of not attaining CR. In other words, though the cut off of 5% had a very good PPV for attaining CR, but >5% blasts on D14 had a poor ability to predict the patient for not attaining remission. NPV was just 29% which is in concordance with our study.

As of now, the concept of treatment of AML is to make the patient to get into remission by any possible means, including double induction with "3 + 7," high-dose cytarabine as induction or adding etoposide during induction. Most of these claims are based on a meta-analysis published by Rowe *et al*.[11] that focused on 1272 patients who achieved CR in 74% after one cycle and in 26% after two cycles. The outcome of patients who did not achieve CR or who had persistent disease on D10 to D14 was not addressed. Remission status following induction was just 48.71%. Of those who (n = 1035) did not achieve CR, only 557 received 2nd induction and of them 58.7% (n = 327/557) achieved CR. There was minimum information on:- mortality after 2nd induction, whether the 2nd induction was harmful to any subsets of patients or what happened to patients who did not achieve remission. Norkin *et al*.,[12] in their series of 297 AML patients who primarily received "3 + 7" induction, reported sensitivity of 88% on D14 BM when threshold blast count was <5%. In a study by Ofran *et al*.[13] compared D5 BM with D14, blast counts of <5% on D14 BM only predicted for remission in 80% cases. They had shown that, day 5 results are a stronger predictor of OS by multivariate analysis and better segregate long-term survivors than the day 14 BM blast (66% vs. 30%, P = 0.0001 and 48% vs. 37%, respectively, P = 0.04).

Very recently Covut *et al*.[14] studied comparison of peripheral blast clearance and day 14 BM biopsy in predicting remission status and survival in 183 newly diagnosed AML patients after 7 + 3 induction in AML and concluded that despite their prognostic value, neither of these methods were reliably specific tools for the decision of early re-induction. They also observed that morphological cellularity in day 14 BM was an independent prognostic factor for OS and relapse free survival. Terry *et al*.[15] in a critical review on Day14 BM in AML, concluded that, although blast counts on day 14 BM is highly sensitive in predicting remission on day28, but lack specificity. Thus, a significant proportion of patients with residual disease on day 14 BM would still attain CR without second cycle of induction therapy and it is not very clear whether second induction therapy based on day14 BM alters the outcome. They suggested routine use of day 14 BM in AML be re-evaluated, especially outside the context of clinical trials; not to be used for decision-making on whether to give second cycle of induction therapy.

With these available information and the results of our study it is possible to state that, lower the number of BM blasts% on D14, better the remission rates; but it is still not clear whether higher the number of blasts on D14 correlate very well with not attaining remission (NPV of the test was poor). It requires more studies on patients with residual leukemia on Day14 (stratified by blast %), randomized to second induction, further observation or higher intensity/investigational strategy, with the endpoint of survival and disease-free survival. As the duration of study was short, logical conclusion regarding relapse or outcome was not possible. Numbers of patients were small; based on cut off blast%, a logical clear cut prediction about those who are not going to remission would have been still

better if sample size was good enough. To note further, future studies will need to determine whether findings in our study are also applicable to patients with various adverse molecular subtypes (e.g., FLT3-positive/NPM1-negative patients).

Conclusions

Day14 BM blast percentage ≤15% has a good sensitivity, PPV for predicting remission. However, D14 BM blasts of >15% has a poor NPV for predicting resistant disease (not entering CR). There is a trend towards early relapse in patients with higher blast on D14. However, D14 BM blast >15% has a poor NPV for predicting relapse.

Ethics approval

The study was approved by the institutional ethical committee.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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