Prognostic and therapeutic implications of early treatment response assessment in acute myeloid leukemia

Vinod Pullarkat*, Ibrahim Aldoss

Department of Hematology and Hematopoietic Cell Transplantation, City of Hope Medical Center, 1500, Duarte, CA 91010, United States

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Contents

1. Introduction .................................................. 00
2. Search strategy and selection criteria ........................................ 00
3. Does early blast clearance correlate with clinical outcomes? ........ 00
4. Does earlier achievement of complete remission predict better outcome in AML? ..................................... 00
5. Is there a role for giving a second induction cycle based on interim marrow findings? And if so, what is the optimal regimen? .... 00
6. Conclusions .................................................. 00
Authors and contributors ........................................ 00
Conflict of interest statement ....................................... 00
Acknowledgments .................................................... 00
References .......................................................... 00
Biographies .......................................................... 00

Abstract

Early assessment of disease response to induction chemotherapy is important in acute myeloid leukemia (AML) in order to plan future therapy and identify chemorefractory disease. Such assessment is customarily performed by examining the bone marrow at around day 14 after initiation of chemotherapy. However, criteria for assessment of residual leukemia in day 14 bone marrow specimens as well as the significance of partial response on long term outcomes remain unclear. Clinical practices vary regarding the therapeutic intervention for residual disease and include readministration of the original induction therapy or use of a different reinduction regimen. In this article, we critically examine the prognostic significance of residual disease detected on interim bone marrow examination as well as data on reinduction therapy with the original induction regimen versus an alternate regimen. We emphasize the need for standardizing reporting of interim bone marrow assessment as well as evaluating new technologies and biomarkers for early assessment of disease response and chemosensitivity in AML.

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1. Introduction

Acute myeloid leukemia (AML) is a heterogeneous leukemia characterized by diverse genetic and clinical features as well as response to chemotherapy. The treatment of AML entails induction therapy with the goal of debulking disease and restoring hematopoiesis followed by post-remission therapy aimed to eliminate residual leukemia. The majority of AML protocols and guidelines utilize an interim bone marrow (BM) biopsy done at day 14–16 after initiation of chemotherapy as a tool to predict response early in the course of induction therapy in order to guide further treatment. However, given the absence of evidence from systematic studies, using interim BM biopsy results to guide further management...
is challenging. Data are lacking as to what is considered an optimal response, borderline residual leukemia, significant residual disease and refractory leukemia in the interim BM biopsy findings, and then, what should be the most appropriate approach for each individual response type. In this review, we will address the implication of early response assessment in AML, discuss the various definitions of response in the interim BM biopsy used among different studies and attempt to formulate an evidence-based approach to tailoring therapy based on interim assessment of disease response from available published data.

2. Search strategy and selection criteria

References for this review were identified through searches of PubMed with the search terms “interim bone marrow”, “Day 14 marrow”, “response assessment”, “acute myeloid leukemia” from 1985 until March, 2014. Articles were also identified through searches of the authors’ own files and bibliography of retrieved articles. Only papers published in English language were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

3. Does early blast clearance correlate with clinical outcomes?

This concept that early blasts clearance during induction therapy in AML serves as a surrogate for leukemia sensitivity and therefore improved clinical outcome serves as the rationale for early marrow evaluation during induction therapy to predict response and individualize additional treatment. Is this hypothesis accurate?

A couple of retrospective studies have examined the correlation between early peripheral blood (PB) blast clearance and clinical outcomes. Arellano et al. reviewed 162 newly diagnosed AML cases with circulating PB blasts identified by morphology. The median time for blast clearance was 5 days, and patients were stratified into 2 subcategories based on the time required for PB blast clearance; early blast clearance if blasts disappeared within 6 days and delayed blast clearance if blasts required more than 6 days to disappear from PB. The study reported superior day 14 (D14) marrow blast clearance (84% vs. 60%, \( P = 0.0018 \)), complete remission (CR) rate (90% vs. 55%, \( P = 0.012 \)), leukemia-free survival (LFS) (\( P < 0.0017 \)) and overall survival (OS) (\( P < 0.0001 \)) in the early blast clearance cohort compared to the delayed blast clearance cohort [1]. In another study, Elliott et al. analyzed 86 AML patients with circulating PB blasts. Three prognostic subgroups were defined based on the time required to clear PB blasts; Good- (\( \leq 3 \) d), intermediate-(4–5 d) and poor-risk (\( \geq 6 \) d). The relapse risk rate was independently related to the time needed for PB blast clearance [Good = 12.5%, intermediate = 27%, and poor = 78%; \( P < 0.001 \)] [2].

The majority of early response assessment studies have used an interim BM biopsy to assess treatment response. However, it must be highlighted that the criteria for assessment of these biopsies are not standardized across studies. While there is no debate that clusters of leukemic blasts in a cellular marrow at day 14 constitutes unequivocal evidence of residual leukemia, the significance of scattered blasts cells in a hypocellular marrow at this time point is not clear and cannot be considered as definite evidence of residual disease. Many studies do not mention marrow cellularity and morphologic assessment of aspirate smears or immunohistochemistry of bone marrow biopsy specimens are variably used to calculate blast percentages.

Liso et al. have examined the association between D14 marrow findings and the probability of achieving complete remission (CR) in 198 subjects with AML. Among patients younger than 60 years, stratification based on a cutoff of 22% residual blasts was used for calculating test sensitivity and specificity, while for older patients (\( \geq 60 \) years), a blast count of 15% was chosen instead. In the younger cohort, the CR rate if D14 blasts were \( \leq 22% \) was 79% compared to 19% if D14 marrow contained \( > 22% \) blasts (\( P < 0.0001 \)), and the calculated sensitivity and specificity of the test was 94% and 71%, respectively. In the older cohort, the CR rate if D14 marrow blasts were \( \leq 15% \) or \( > 15% \) was 67% and 19%, respectively (\( P = 0.0001 \)), and the reported sensitivity and specificity was 67% and 81%, respectively [3]. Hussein et al. chose a cutoff of 5% blasts in D14 marrow for stratifying treatment response in 130 patients with newly diagnosed AML undergoing induction therapy. Ninety percent of patients with D14 blasts \( \leq 5% \) achieved CR compared to only 57% if \( > 5% \) blasts were present on D14 marrow, and all the patients who achieved CR in the latter cohort had D14 blasts between 5% and 15% [4].

The GOELAMS study group prospectively treated over 800 patients with AML on the LAM-2001 protocol applying a risk-adapted regimen. The study mandated re-induction cycle with intermediate-dose cytarabine given on D17 from the initial standard induction regimen (7 + 3) if D15 marrow showed \( \geq 5% \) blasts based on morphology. Sixty-nine percent of 795 evaluable patients achieved D15 blasts <5%, and both low initial WBC and unfavorable cytogenetics were predictors of residual D15 blasts. While 7% of favorable cytogenetics group had residual D15 blasts, 53% of the unfavorable cytogenetics group had residual leukemia on D15. Of the 250 patients with D15 blasts \( \geq 5\% \), 211 (84%) received a second course of induction. Patients with D15 blasts \( \geq 5\% \) had longer median time to neutrophil (23 vs. 33 days, \( P < 0.0001 \)) and platelet count recovery, longer hospitalization duration (39 vs. 28 days, \( P = 0.0001 \)) and higher risk of septicemia and death in aplasia (7% vs. 2%, \( P = 0.001 \)) compared to patients with D15 blasts <5%. In spite of the fact that the majority of patients with D15 blasts \( \geq 5\% \) had undergone a second induction with intermediate-dose ara-C, the overall CR rate (69% vs. 92%, \( P < 0.0001 \)), 5-year event-free survival (EFS) (25% vs. 48%, \( P < 0.0001 \)), relapse-free survival (RFS) (37% vs.
53%, \( P=0.0016 \) and OS (36% vs. 55%, \( P<0.0001 \) were inferior compared to patients with D15 blasts <5%. Subset analysis based on cytogenetics showed that D15 blasts significantly influenced CR, EFS and OS in patients with intermediate-risk but not in patients with adverse cytogenetics [5].

The German AML Cooperative Group (AMLCG) 1992 study combined double induction approach with TAD/HAM (TAD = 6-thioguanine, cytarabine and daunorubicin; HAM = high dose cytarabine and mitoxantrone) in 449 newly diagnosed AML patients. The second cycle of induction with HAM was given on D21 irrespective of D16 marrow results. Day 16 blast percentage (<10% vs. ≥10%) significantly correlated with CR rate (\( P<0.0001 \)), EFS (\( P<0.0001 \)), RFS (\( P<0.0049 \)) and OS (\( P<0.0001 \)) [6].

Investigators at M.D. Anderson Cancer Center have reviewed data from 586 AML patients who had had D14 and D21 bone marrow examinations during induction therapy. The probability of observed CR correlated inversely with D14 and/or D21 blast count, and the analysis demonstrated a dynamic relationship between D14, D21 and recovery marrow findings. Most patients with low blasts on D14 marrow (<20% or too few to count) had low blasts on D21 marrow as well, and the majority of those patients achieved CR especially if blasts remained low in D21 marrow. In contrast, patients who had ≥20% blasts on D14 marrow had only a 50% chance of dropping marrow blasts <20% on D21 and 62% chance of achieving CR if blasts decreased. However, CR rate was only 31% if blasts remained ≥20%. Patients who had ≥60% blasts on D14 did exceptionally poorly with only 16% likelihood of attaining CR [7].

Another study has examined if residual blasts in BM biopsy done on day 6 can aid in predicting response. Of 164 patients who received induction therapy in this study, 103 patients (63%) were classified as responders with <5% blasts on D6 marrow, and 61 patients (37%) were deemed non-responders with ≥5% blasts on D6 marrow. Early response was an independent predictor of a higher CR rate (86% vs. 36%, \( P<0.0001 \)) and 2-year OS (56% vs. 44%, \( P=0.002 \), although relapse rate was not significantly different [8]. Ofran et al. have used D5 BM residual blast percentage (≤10% vs. >10% blasts) to assess prognosis of 79 AML patients evaluated prospectively. Early response (blasts ≤10%) on D5 BM was seen in 33% of enrolled patients and it was a predictor for having no residual blasts on D14, achieving CR, higher OS and lower relapse rate. The 10% blast cutoff had a sensitivity of 80% and specificity of 74% for achieving CR, and the 2-year relapse rate was as low as 8% for rapid responders [9].

Given the problem of accurately assessing disease burden by morphology in BM biopsy specimens that are often paucicellular or BM aspirates that are hemodilute, other techniques to assess early disease response have been explored. Flow cytometric analysis is practical given the fact that AML blasts often have characteristic immunophenotypes identified at diagnosis. Gianfaldoni et al. prospectively used PB flow cytometric analysis for an aberrant leukemia immunophenotype daily during induction therapy and showed a clear difference in outcomes among responders and non-responders judged by blast reduction as early as 24 h after initiating induction therapy. In their analysis of 61 patients with AML, the CR rate was 76% for those who achieved >2 log reduction in PB blasts on D5 compared to 5% CR rate for those who did not, and PB blasts clearance correlated with D14 marrow findings as well [10]. In another study, Lacombe et al. prospectively investigated daily PB flow cytometric analysis in 130 AML patients during induction. The study reported that all patients (n = 81) with 90% PB blast reduction by D5 achieved CR compared to only 61% of those (n = 49) who required more than 5 days for blast clearance (\( P<0.0001 \)) [11].

Given the fact that the Wilms tumor antigen (WT1) is ubiquitously overexpressed in AML, assessment of WT1 transcripts in peripheral blood was evaluated in one study as a marker of chemotherapy sensitivity. Gianfaldoni et al. employed real-time PCR to quantify PB WT1 transcripts on days 1 and 5 of induction therapy in 57 patients with AML. These investigators showed a correlation between the ratio of WT1 transcript reduction (from D1 to D5) and CR rate (\( P=0.0006 \)), DFS (\( P=0.024 \)) and OS (\( P<0.001 \)) [12].

Increase in bone marrow microvascular density is seen in the bone marrows of AML patients with active disease. Hence, there has been interest in using dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI) to non-invasively image changes in bone marrow vasculature and correlate these parameters with treatment response and overall outcome. In 80 newly diagnosed AML patients, D0 and D7 dynamic MRI was performed at baseline (day 0) and 7 days after chemotherapy initiation (day 7) during induction phase and changes in angiogenesis parameters were evaluated prospectively. The study found a significant association between reduction in angiogenesis peak measured by MRI at D7 compared to day 0 with higher probability of achieving CR (\( P=0.022 \)), as well as superior LFS (\( P=0.007 \)) and OS (\( P=0.003 \)) [13]. Other studies from the same group have found a correlation between bone marrow angiogenesis measured by DCE-MRI at diagnosis with probability of remission and clinical outcomes [14,15].

4. Does earlier achievement of complete remission predict better outcome in AML?

Many protocols incorporate a second identical induction cycle for those patients with residual leukemia on D14 marrow, and identical post-remission treatment is given subsequently regardless of whether CR is achieved with 1 or 2 cycles of induction therapy. However, there is controversy regarding the significance of the amount of therapy needed to achieve CR. Among 576 patients enrolled in 2 randomized studies performed by the AMLCG who were induced with 1 or 2 cycles of TAD regimen, 65% achieved CR, and among
those, 68% attained it after 1 cycle while 32% required a second cycle. Reaching CR within 30 days was the only predictive factor for remission duration in this study (\(P=0.017\)) [16].

Wheatley et al. have constructed a prognostic index for risk-adapted therapy using data from 1171 adult and pediatric patients enrolled in the MRC AML-10 study. This study employed preassigned identical double induction therapy irrespective of D14 marrow results. The overall CR, partial remission (PR) and refractory disease rate in the study were 67%, 17% and 16%, respectively. PR in this study was defined as D14 blasts between 5% and 15%, and for those who achieved PR after the first cycle of induction, 89% attained CR after the second cycle, and if CR was attained, the relapse rate was similar to patients who achieved CR after one cycle. However, although 65% of patients with refractory disease achieved CR after the second cycle, almost half of those relapsed in the first year and they had an adverse prognosis [17].

The Eastern Cooperative Oncology Group (ECOG) protocols routinely mandate a D10 to D14 marrow during induction therapy, and reinduction therapy with the same regimen is given if unequivocal residual leukemia is present in a non-hypocellular marrow. Afterwards, uniform consolidation therapy is given irrespective of whether 1 or 2 cycles of induction were required to achieve CR. An analysis of 6 consecutive ECOG studies including almost 2000 patients with AML asked the question whether the clinical outcomes are similar for patients who achieved CR after 1 or 2 cycles of induction. Sixty-four percent of all patients achieved CR, and the absolute percentage of CR was 47% after one cycle and 17% for the second cycle. Cytogenetics and clinical factors failed to predict the number of cycles needed to achieve CR. The 5-year and 10-year LFS and OS were similar in patients who required 1 or 2 cycles to achieve CR [18].

5. Is there a role for giving a second induction cycle based on interim marrow findings? And if so, what is the optimal regimen?

The main controversy is whether to administer the same induction regimen or a different chemotherapy regimen in patients who have responded but are considered to have residual disease in interim bone marrow examination. Attempts have been made to answer this question in a few trials aimed at tailoring induction therapy to disease risk or early response.

The German AMLCG randomized 725 patients with AML to double induction with TAD/TAD or more intensive second induction with TAD/HAM. The second cycle was started on D21 before complete remission criteria were met and regardless of D16 marrow findings. Although CR rate and hypoplastic death were not different between the two groups, subset analysis recognized a group of patients with poor prognosis who benefited from TAD/HAM induction over TAD/TAD induction. The poor prognostic group included those with D16 residual blasts ≥ 40%, unfavorable cytogenetics and high lactate dehydrogenase level at presentation. [(CR = 65% vs. 49%; \(P=0.004\), (EFS = 17% vs. 12%; \(P=0.012\), (5-year OS 24% vs. 18%; \(P=0.009\)] [19].

Heil et al. treated 305 AML patients prospectively with response-directed double induction therapy. The high-risk group included patients with D15 BM blasts ≥5% or unfavorable cytogenetics. All patients received the first induction cycle with idarubicin, cytarabine and etoposide, following which the standard risk (SR) group received a second similar cycle on D21 while the high risk (HR) group received a more intensive second induction with high-dose cytarabine and amsacrine. High-risk group included patients with D15 BM blasts ≥5% or unfavorable cytogenetics. Despite the intensification of cytarabine dose in the HR cohort, CR rate (31% vs. 48%) and OS (34% vs. 46%) were superior in the SR group [20].

The LAM-2001 study showed inferior outcomes despite the administration of a second induction cycle with anthracycline and intermediate-dose cytarabine giving on D17 for patients with D15 blasts ≥5%, even after excluding patients with ≥5% D15 blasts who did not receive the second cycle of induction [5].

Wakita et al. randomized 245 elderly (65–80 years of age) patients with AML to either fixed or individualized induction therapy. All subjects were induced with daunorubicin and cytarabine following which additional therapy with daunorubicin and cytarabine was given based on D8 and D10 marrow findings in the individualized cohort. Although a higher cumulative dose of daunorubicin and cytarabine was delivered in the individualized cohort, clinical outcomes (CR, LFS, OS and early death) were similar for both groups [21]. Of 748 patients enrolled in the E3489 study and induced with the standard 7 + 3 regimen (idarubicin 12 mg/m² X3 days and cytarabine 100 mg/m² daily X7 days), only an additional 10% of patients achieved CR with the second cycle of 7 + 3 [18].

A combined analysis of 1505 AML patients induced with the 7 + 3 regimen from the Southwest Oncology Group (SWOG) and Cleveland Clinic identified 336 subjects who were not in CR on day 28 and received a second re-induction cycle of 7 + 3. Among those patients, 40% achieved CR, 14% died during the first 4 weeks of re-induction and 45% were alive not in CR. Probability of achieving CR with reinduction was associated with age (median 47 years for CR vs. 56 for no CR, \(P<0.001\)), the day of re-induction (median day 24 for CR vs. 20 for no CR, \(P=0.005\)), cytogenetics (CR = 75% for favorable, 35% for intermediate, and 18% for unfavorable, \(P=0.04\)) and AML type (CR = 42% for de novo vs. 16% for secondary). D14 marrow blasts, D14 cellularity, change in blast percentage or marrow cellularity and the day when the re-induction cycle began were not associated with re-induction CR rate [22].
6. Conclusions

There is a lack of data from systematic clinical trials to guide the interpretation of interim assessment of response to induction therapy in AML. This issue is further complicated by the variability in response definitions as well as lack of standardization of criteria for response in bone marrow biopsies. Despite these caveats, some general conclusions can be made.

Based on limited data it appears that early blast clearance data can be used in conjunction with cytogenetics to determine need for day 14 bone marrow evaluation (Fig. 1). Early disappearance of circulating blasts determined by morphology or flow cytometry in a patient with leukocytosis indicates chemo-sensitivity and bone marrow evaluation for response can be generally be postponed until blood count recovery, especially in patients with good risk cytogenetics, as up to 90% of those patients achieve CR. For patients who failed to clear PB blasts early (within 6 days), only 60% of those patients have an empty marrow on D14 and only half achieve CR. Interim bone marrow evaluation in such patients with delayed blast clearance can help in identifying refractory leukemia and assist in planning future therapy.

In general, studies have shown an association between D14 marrow findings and CR rate, and possibly long-term outcomes in the absence of double induction therapy. Based on available evidence it would be reasonable to assume that a blast count of under 20% on day 14 bone marrow is a predictor of favorable outcome in patients with favorable or intermediate risk cytogenetics even if additional induction therapy is not administered based on the day 14 bone marrow biopsy findings. There is a conflicting data regarding the significance of early CR (after 1 cycle of induction). The AMLCC study identified CR attained within 30 days as an independent prognostic factor, while analysis of 6 ECOG studies failed to demonstrate a difference in long-term survival when similar post-remission therapy was applied. However, an MRC analysis highlighted the observation that only persistent disease (defined as >15% residual blasts), but not a lesser blast percentage (5–15%), on D14 was associated with detrimental outcomes in patients who attained CR after the second cycle. Therefore, it appears that the degree of response as well as prognostic factors rather than number of induction cycles per se are determinants of overall prognosis.

There is no clear evidence about the best treatment for patients with residual blasts on interim marrow. There is no data to justify the use of a less intensive regimen than the initial induction therapy if the decision made to give more therapy. Most studies have utilized the same induction regimen for residual disease on D14. However, when a second 7 + 3 induction cycle was given for unequivocal residual disease on D14, only additional 10–15% of patients achieved

Fig. 1. Illustrative examples of induction therapy response in day 14 bone marrow specimens. (Panel A) Bone marrow evaluation on day 14 in a patient with inversion 16 AML. The marrow is markedly hypocellular with stromal chemotheraphy effect; however, CD34 stain (inset) shows about 10% residual blasts (A, H&E 40×; inset CD34 100×). (Panel B–C) No additional therapy was administered and patient achieved remission on day 28, with normocellular marrow and trilineage hematopoiesis (B, H&E 40×; C, H&E 100×). (Panel D) Unequivocal evidence of residual leukemia on day 14 in a patient with high risk AML associated with inversion 3 (D, H&E 40×; inset CD34 100×). No additional therapy was administered and patient had persistent blasts on subsequent biopsy (not shown).
CR. When the higher intensity (HAM) regimen was used in the German AMLCG study, only patients with high residual disease burden (≥40% blasts) on D16, in addition to those with unfavorable cytogenetics and high LDH, gained benefit from more intensive therapy compared to identical second cycle of induction (TAD X 2). It must be emphasized that the second cycle was actually administered on day 21 and hence the results may not be comparable to studies examining reinduction given around day 14. Hence it would appear appropriate to use a high dose cytarabine based regimen or another reinduction regimen in patients with high disease burden (over 40% blasts). In patients with lesser blast percentage, if a decision is made to administer another induction cycle, use of the prior induction regimen seems appropriate (Fig. 2).

For patients with empty D14 marrow, most experts recommend postponing additional chemotherapy until marrow recovery. In patients with borderline residual blasts on D14, there is no enough data to guide further management, and there is even less data regarding how to utilize marrow cellularity data in treatment planning. Similarly, no data are available using FISH studies on interim bone marrow specimens in patients with cytogenetic abnormalities to guide further therapy. Most of the dilemma occurs in patients with low blast count (5–15% blasts on D14) in a hypocellular marrow. In such cases, several viable options can be pursued such as waiting until blood counts recovery and repeating bone marrow biopsy, repeating marrow biopsy on D21 for further evaluation or re-induction with similar or non-cross resistant regimen. Our preference is to wait until blood count recovery in patients with 5–20% blasts in interim bone marrow biopsies if they have favorable or intermediate risk on cytogenetic and molecular testing.

Although it seems reasonable to give additional chemotherapy early for residual blasts while the disease burden is lower, the downside of double induction therapy prior to peripheral blood count recovery is prolongation of neutropenic period, and consequently, increasing the risk of infectious complications, particularly invasive fungal infections. Even transient neutrophil recovery before the second induction cycle can allow some protection against infections and probably reduce treatment related mortality. The majority of patients with partial response on interim bone marrow examination recover their neutrophil counts at the end of induction despite some not meeting the criteria for CR based on residual blasts. Usually patients who will not have neutrophil recovery are those with preceding myelodysplastic syndrome or those who have considerable residual disease, and such patients can usually be identified from D14 marrow and selected for additional therapy early. Therefore, in our opinion the decision to proceed with double induction therapy based on day 14 bone marrow findings should be a balance between patient performance status, ability to tolerate neutropenic complications and degree of leukemia refractoriness. Currently there is no data supporting early administration of reinduction therapy in patients without adverse clinical and molecular prognostic factors. It must be mentioned that in patients with newly diagnosed AML, initiating intensive induction early did not impact clinical outcome compared to delaying therapy for a week or more [23].

In summary, it appears that interim bone marrow examination at day 14 has prognostic implications for all AML patients provided it is interpreted appropriately with consideration of marrow cellularity and patients’ cytogenetic and molecular risk factors. Unequivocal evidence of persistent disease on interim bone marrow in particular can help prognosticate patients and help plan future therapies like allogeneic hematopoietic stem cell transplantation or participation in clinical trials. In patients with good risk cytogenetic and/or molecular features, interim bone marrow examination appears unnecessary if patients have achieved early blast


Fig. 2. Proposed algorithm for early disease response assessment based on day 14 bone marrow biopsy. Early peripheral blood blast clearance denotes clearance of blasts from peripheral blood in <5 days, PB = peripheral blood, BM = bone marrow. Risk groups based on cytogenetic and molecular risk assessment.
clearance from peripheral blood as performing a day 14 bone marrow carries the risk of exposing them early to additional therapy which would likely have more toxicity due to prolongation of neutrophil and platelet recovery. Blast evaluation in paucicellular marrows is not standardized and is observer dependent which adds to the complexity of using interim bone marrow results for treatment planning in patients with partial response. Studies using fluorescence in situ hybridization (FISH) analysis and molecular studies for residual disease in interim bone marrow specimens as well as more standardized definition of early bone marrow response may in future allow us to prognosticate patients better.

Authors and contributors

V.P and I.A wrote the manuscript.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Reviewers

Professor Arnold Ganser, Hämatologie, Hämostaseologie, Onkologie und Stammzelltransplantation, Medizinische Hochschule Hannover, Carl-Neuberg-Str. 1, D-30625 Hannover, Germany.

Dr Jacob Rowe, Shaare Zedek Medical Center, Dept. of Hematology, 12 Shmuel Bayit, Jerusalem, 31096, Israel.

References

Biographies

Vinod Pullarkat is Associate Professor in the Department of Hematology and Hematopoietic Cell Transplantation at City of Hope Medical Center in Duarte, California, USA. His research interests include acute leukemia, myelodysplasia and hematopoietic stem cell transplantation.

Ibrahim Aldoss is Assistant Professor in Department of Hematology and Hematopoietic Cell Transplantation at City of Hope Medical Center in Duarte, California, USA. He specializes in acute leukemia and hematopoietic stem cell transplantation.