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# 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



**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.


*Keywords:* Acute myeloid leukemia; Chemosensitivity; Early response; Day 14 bone marrow; Reinduction

## 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

* Corresponding author. Tel.: +1 626 218 3279; fax: +1 626 930 5446.
*E-mail address:* vpullarkat@coh.org (V. Pullarkat).

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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.