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Incremental value of the bone marrow trephine biopsy in detecting residual leukemia following treatment for Acute Myeloid Leukemia

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ABSTRACT

Most guidelines suggest that only the bone marrow aspirate (BMA) is necessary to assess residual disease following intensive chemotherapy for Acute Myeloid Leukemia (AML) with the bone marrow trephine biopsy (BMTB) recommended in cases of a poor quality BMA. We performed a retrospective study evaluating this in a cohort of patients receiving intensive chemotherapy for AML. Residual disease was assessed by morphological examination of the BMA and BMTB ± immunohistochemistry. Of the 647 marrows 32.6% were interim marrows performed prior to peripheral count recovery, 41.7% were end of induction (EOI) marrows and the remaining were 'other marrows'. The BMA and BMTB findings were concordant in 92.8% of cases. The BMTB led to a change in diagnosis from 'no leukemia' to 'residual leukemia' in 5.2% of interim, 3.7% of EOI and 2.4% of 'other' marrows. The BMA alone had a sensitivity of 86.8% in detecting residual leukemia and of 82.3%, 82.5% and 94.2% for interim, EOI and 'other marrows', respectively. Despite the high concordance between the BMA and the BMTB the poor sensitivity of the BMA in detecting residual leukemia, particularly at EOI, may lead to an overestimation of the complete remission rates which may have therapeutic and clinical trial implications.

1. Introduction

Acute Myeloid Leukemia (AML) is an aggressive hematological malignancy the initial treatment of which consists of intensive chemotherapy designed to achieve a complete remission (CR) [1]. Response assessment following chemotherapy generally requires a bone marrow aspirate (BMA) and/or bone marrow trephine biopsy (BMTB). Recommendations from leading hematopathologists suggest that the BMTB is unnecessary for the investigation of suspected acute leukemia or for the assessment of residual disease after treatment [2]. Similarly, recommendations of the National Comprehensive Cancer Network (NCCN) [3], the European LeukemiaNet [4] and the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia (IWG-AML) [1] suggest that a BMTB is not routinely indicated but may be necessary if the aspirate is dilute, hypocellular, inaspirable or without spicules. The European LeukemiaNet guidelines further suggest that the BMTB is optional in both general practice and

Abbreviations: BMA, bone marrow aspirate; BMTB, bone marrow trephine biopsy; IWG-AML, International Working Group for Diagnosis; IDAC, idarubicin and cytarabine; FLAG, Fludarabine; EOI, end of induction; IHC, immunohistochemistry; MPFC, multiparametric flow cytometry; MRD, minimal residual disease.

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within clinical trials [4]. In contrast, guidelines of the International Council for Standardization in Hematology suggest that the BMA and BMTB provide complementary information and should be performed together [5].

Due to these conflicting recommendations and the paucity of evidence we sought to determine whether the BMTB provides additional sensitivity beyond the BMA alone for the detection of residual leukemia following chemotherapy for AML.

2. Methods

2.1. Patient population

The charts of all non-acute promyelocytic leukemia AML patients aged ≥17 years treated with intensive induction chemotherapy between 2004 and 2013 were reviewed. Patients receiving only supportive care or non-intensive chemotherapy, those lacking marrow assessments after chemotherapy, those with only a BMA or those with a non-assessable BMTB were excluded from analysis. Prior approval was obtained from the ethics review board of the University of Alberta.

The diagnosis of AML was determined according to the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues [6]. All patients underwent cytogenetic assessment and were classified as having favourable, intermediate or adverse karyotype based upon the Medical Research Council guidelines [7–9]. As molecular analysis for FLT3 and NPM1 mutations was only available for patients after 2009 it was not included in the analysis.

2.2. Chemotherapy regimens

Most patients received anthracycline based chemotherapy (typically idarubicin together with continuous infusion cytosine arabinoside [IDAC]). Patients not eligible for anthracycline based chemotherapy most commonly received FLAG (fludarabine, cytosine arabinoside and filgrastim). For patients receiving IDAC an 'interim' bone marrow was done at day 14–21. All patients had an end of induction (EOI) bone marrow to ascertain residual disease following recovery of peripheral blood counts. Patients with delayed marrow recovery generally had bone marrow studies performed between days 35–42 following chemotherapy initiation.

2.3. Bone marrow evaluations

Bone marrow studies were performed using a combination of Jamshidi® bone marrow biopsy/aspiration needle (BMTB) and the Jamshidi® Illinois sternal/iliac aspiration needle (BMA) or just the Jamshidi® bone marrow biopsy/aspiration needle for both the BMA and BMTB. BMA was collected in ethylenediaminetetraacetic acid. Particle and direct smear preparations were made at the bedside or in the laboratory within one hour of receipt of the BMA. BMA slides were stained with a May Grunwald Giemsa stain. BMTB were collected in B-Plus fixative with subsequent transfer to formalin for a minimum of 2 h, decalcification for one hour, sectioning and staining with Hematoxylin & Eosin prior to evaluation with light microscopy.

All marrow samples were evaluated by hematopathologists. As there are no standard definitions for BMA and BMTB characteristics such as 'hemodilute' or 'aparticulate, BMAs were subjectively evaluated for their cellularity, whether they were hemodilute, and for the presence or absence of spicules/particles. As per IWG-AML criteria, >200 cells were counted prior to determining the leukemic blast counts. Marrow cellularity was estimated using the BMTB. The BMTB was graded as inadequate, adequate or good/excellent based upon the quantity of assessable marrow. Immunohistochemistry (IHC) and immunophenotyping by multiparametric flow cytometry (MPFC) were not used routinely but were performed in selected cases when blast count was unclear and at the discretion of the hematopathologists with the choice of reagents based upon the diagnostic immunophenotype.

Table 1
Patient characteristics.

	Number (%)
Total Number of Patients	n = 246
Patient Characteristics	
Age, y, median (Range)	54.8 (17–77)
Age <60	169 (69%)
Male	138 (56%)
Cytogenetics	
Favourable	32 (13.0%)
Intermediate Risk	160 (65%)
Unfavourable Risk	47 (19.1%)
Not Available	7 (2.8%)

Response assessment after chemotherapy was as per IWG–AML recommendations and based upon review of the BMA, the BMTB ± IHC and, if performed, MPFC. Briefly, patients were considered to be in a morphological leukemia free state if there was an absence of blasts containing Auer rods and neither the BMA nor the BMTB demonstrated ≥5% blasts regardless of BMTB cellularity [1]. Patients were considered to have residual leukemia if either the BMA, the BMTB ± IHC or MPFC confirmed the presence of ≥5% blasts. Minimal residual disease (MRD) analysis was not performed. BMA and BMTB samples were considered concordant if blast cell count in both the BMA and the BMTB showed no evidence of residual leukemia, or both showed residual leukemia. They were considered discordant if one showed residual disease and the other did not.

2.4. Statistical analysis

The primary endpoint was the rate of concordance between BMA and BMTB. A secondary endpoint was to ascertain the sensitivity and specificity of the BMA relative to the "gold standard" combination of BMA, BMTB (±IHC) and immunophenotyping by MPFC. Chi-square or Fisher's exact test, as appropriate, were used when comparing categorical variables. Student's *t*-test was used to compare the mean of two groups and Wilcoxon rank sum test were used for non-normally distributed continuous data. Logistic regression was used for multivariate analysis. Results were considered significant if two-tailed P-value was <0.05. Sensitivity, specificity, positive predictive value and negative predictive value were calculated using MedCalc software version 15.11 (MedCalc Software bvba, Ostend, Belgium). SPSS version 15 (IBM Corporation, Armonk, NY, U.S.A) was used for all other statistical analysis.

3. Results

3.1. Patient selection, BMA and BMTB characteristics

The baseline patient characteristics are shown in Table 1. A total of 246 patients received intensive induction chemotherapy and had at least one bone marrow evaluation post induction. Six hundred and forty seven marrow samples from the 246 patients had both a BMA and a BMTB and were included in the analysis (Table 2). The median number of bone marrows per patient was 2 (range 1–9). Four hundred and forty-three (68.5%) marrow samples were from patients treated for initial disease and 38 (5.9%) following treatment for relapsed disease. Approximately one-third (32.6%) of the marrow samples were interim marrows procured at a median of 14 days (range 13–22 days), while 270 (41.7%) were EOI marrows