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Case Report

Molecular Monitoring in Adult Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia with the Variant e13a3 *BCR-ABL1* Fusion

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Monitoring *BCR-ABL1* transcript levels in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) is a widely adopted method to assess response to therapy. However, a small minority of Ph+ ALL patients express variant *BCR-ABL1* transcript types, usually due to splicing of alternative *BCR* or *ABL1* exons. Whether patients expressing these rare, variant *BCR-ABL1* transcripts have a distinct phenotype or response to therapy is not known due to the limited number of reported cases. Here, we report the presenting features of Ph+ ALL in a young adult with a variant e13a3 *BCR-ABL1* fusion. Molecular monitoring reflected the disease response from diagnosis through allogeneic stem cell transplantation which resulted in undetectable e13a3 *BCR-ABL1* transcripts. This case highlights the value of molecular monitoring in Ph+ ALL patients with variant *BCR-ABL1* transcripts and the requirement for standardization of such assays.

1. Introduction

Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) in adults is an aggressive disease that responds poorly to conventional chemotherapy. Despite improvements in survival with the addition of tyrosine kinase inhibitors (TKI) to chemotherapy, hematopoietic allogeneic stem cell transplantation (ASCT) remains the only curative option in those eligible patients [1]. Molecular monitoring of *BCR-ABL1* transcripts is a valuable tool in assessing individual patient response to chemotherapy and ASCT [2–4]. The most common *BCR-ABL1* transcripts in Ph+ ALL are the e1a2, e13a2, and e14a2 fusions [5]; however, approximately 5% of adult patients express variant *BCR-ABL1* transcripts [6]. Of these variants, the e13a3 (b2a3) *BCR-ABL1* type is extremely rare with scant information regarding optimal therapeutic approach [7, 8]. Characterisation of these rare *BCR-ABL1* variants also affords the selection of appropriate primer/probe combinations for reverse-transcriptase quantitative PCR (RT-qPCR) assessment of residual disease. The presentation and clinical course of a patient with e13a3 *BCR-ABL1* Ph+ ALL is reported.

2. Case Report

A 23-year-old male presented with chest pain and dyspnoea, a hemoglobin count of 7.4 g/dL, platelet count of $<10 \times 10^9$/L, and white cell count of 11.6×10^9/L. Bone marrow (BM) biopsy and aspirate demonstrated a 95% infiltration of lymphoblasts (Figure 1). Immunophenotyping of the BM aspirate showed lymphoblasts were CD10-, CD19-, CD20-, CD34-, TdT-, and HLA-DR-positive. Cytogenetic analysis revealed a complex clone in 10 cells analysed by G-banding

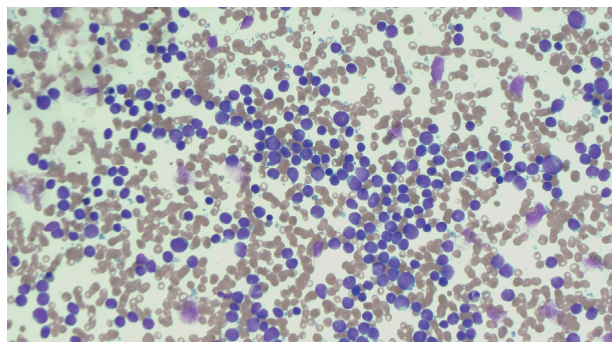

Figure 1: Bone marrow morphology at diagnosis showing infiltration by lymphoblasts.

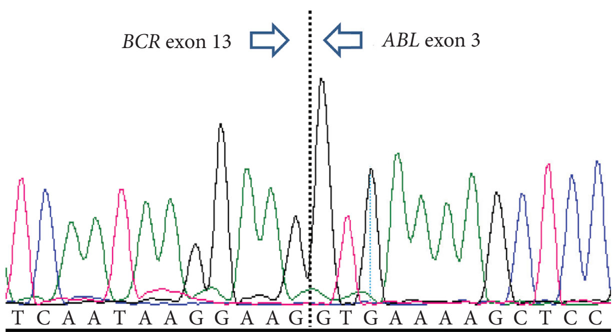

Figure 2: Sanger sequencing demonstrating presence of the e13a3 *BCR-ABL1* fusion gene.

containing various structural and numerical abnormalities including a derivative chromosome 22 from a translocation between the long arms of chromosomes 9 and 22. The composite karyotype was 44–48, *XY*, +*X*, *t*(1; 14)(p32; q32), −3, −6, add(6)(p21), add(7)(p21), add(8)(p21), −10, add(12)(p13), +16, add(19)(p13), der(22)*t*(9; 22)(q34; q11.2), +1~2mar, inc [cp10]. Interphase FISH analysis showed the presence of *BCR-ABL1* rearrangement in 64/100 cells analysed. Standardised RT-PCR and Sanger sequencing demonstrated e13a3 *BCR-ABL1* transcripts [9] (Figure 2). E13a3 *BCR-ABL1* transcripts lack *ABL1* exon a2, thus prohibiting the use of a standardised primer/probe combination for e13a2/e14a2 *BCR-ABL1* qPCR [10]. A modified *BCR-ABL1* qPCR assay was therefore adopted utilising *BCR* forward primer ENF501F2 [9] with *ABL1* reverse primer ENR1063 and *ABL1* probe ENP1043, the latter both complementary to *ABL1* exon a3 sequence [11]. The *BCR-ABL1* standard curve was constructed using serial dilutions of an e14a3 *BCR-ABL1* plasmid over a five log range (100% to 0.001% *BCR-ABL1* transcripts) with *ABL1* as the reference gene as previously described [12]. Best practice guidelines for *BCR-ABL1* qPCR and data interpretation were followed [13]. Presentation e13a3 *BCR-ABL1* transcripts were of a high level (*BCR-ABL1*/*ABL1* 75.7%) consistent with a diagnosis of pre-pre-B cell Ph+ ALL.

The patient commenced induction treatment with rituximab, dexamethasone, vincristine, and daunorubicin, with imatinib 400 mg oral daily started on day 15. After phase-one induction, the bone marrow aspirate demonstrated a complete morphological response with residual disease detected by immunophenotyping and RT-qPCR (*BCR-ABL1*/*ABL1* 8.11%). After phase-two induction, the bone marrow *BCR-ABL1*/*ABL1* level had fallen to 0.053%. Following high-dose methotrexate, the pre-ASCT *BCR-ABL1* level was 0.034%. The patient proceeded to ASCT from an unrelated donor after cyclophosphamide and total body irradiation conditioning and recommenced continued imatinib maintenance. *BCR-ABL1* transcripts were not detected in the peripheral blood at one, two, and three and a half months post-ASCT (Figure 3). Continued close molecular monitoring is planned.

3. Discussion

E13a3 *BCR-ABL1* transcripts lack *ABL1* exon a2 that encodes part of SH3 domain thought to contribute to leukemogenesis by inhibition of the kinase domain and by STAT5 activation [6]. In chronic myeloid leukemia patients, this transcript results in an indolent and TKI-responsive form of disease [14–16]; however, its prognostic significance in adult Ph+ ALL patients remains unknown due to the limited number of annotated cases. While the possibility exists of lymphoid blast crisis in chronic myeloid leukemia (CML), this transformation in e13a3 *BCR-ABL1* CML is rare [17]. In the absence of basophilia, thrombocytosis, and splenomegaly, this case likely represents *de novo* Ph+ ALL. Additional chromosomal abnormalities and complex karyotypes are frequently observed in Ph+ ALL, as witnessed in this case. There is some suggestion that in Ph+ ALL, additional cytogenetic abnormalities are associated with a shorter overall survival and might therefore be used for

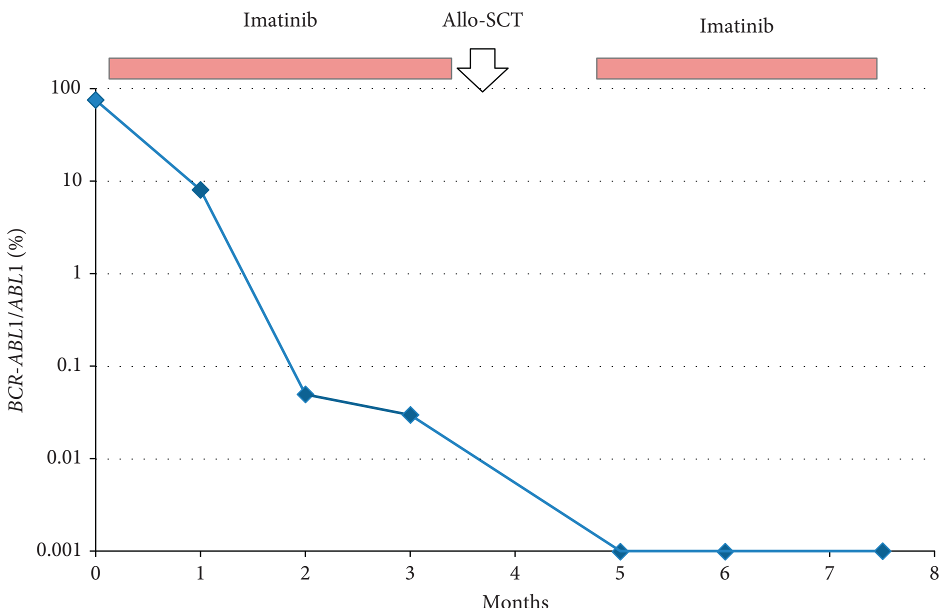

Figure 3: Molecular monitoring of e13a3 *BCR-ABL1* transcripts throughout clinical course. AlloSCT: allogeneic stem cell transplantation.

stratification purposes [18]. In the post-ASCT setting, monitoring *BCR-ABL1* transcript levels is an essential component of Ph+ ALL patient management [19] with effective standardisation of RT-qPCR assays for this and other variant *BCR-ABL1* fusion transcripts required [20].

Reporting of further cases would enable identification of any phenotypic characteristics of e13a3 *BCR-ABL1* Ph+ ALL and help establishing optimal treatment strategies for patients with this rare genotype.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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