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The road not taken: Exploring non-transplant options in De Novo philadelphia positive acute myeloid leukemia

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ABSTRACT

Acute myeloid leukemia (AML) is a heterogeneous disease with diverse molecular cytogenetic characteristics. Philadelphia-positive acute myeloid leukemia, a rare subtype of AML, is traditionally considered a high-risk, with the standard recommendation being an allogeneic hematopoietic cell transplant (HCT) in first remission. More recently, with better characterization and understanding of AML biology, novel therapies have been introduced. Drawing parallels from the advances seen in Philadelphia-positive acute lymphoblastic leukemia (ALL), the question arises whether potent tyrosine kinase inhibitors (TKI), such as ponatinib, in combination with AML-directed therapies, could be used in Philadelphia-positive AML, potentially eliminating the need for HCT in the first remission.

In this report, we review the literature on Philadelphia-positive AML, study a case where HCT was omitted, and explore potential signals that could support successful HCT omission.

1. Introduction

Philadelphia-positive acute myeloid leukemia (pH-positive AML) is characterized by the translocation and fusion of the *ABL* gene (9q34) and *BCR* (22q11), resulting in *BCR::ABL1* rearrangement, a hallmark of this rare AML subtype. This subtype of leukemia is extremely rare, accounting for less than 0.5 % of all AML cases[1–3]. In the recent WHO classification, de novo AML with *BCR::ABL1* fusion is defined by the presence of *BCR::ABL1* without evidence of underlying chronic myeloid leukemia (CML) and does not meet the criteria for other leukemia entities, such as mixed-phenotypic acute leukemia or other AML subtypes [4]. De novo AML with *BCR::ABL1* fusion rarely has extramedullary involvement[5]. The usual presentation includes leukocytosis, anemia, and thrombocytopenia. Compared to patients with blastic phase CML, patients with de novo *BCR::ABL1* fusion AML tend to have a higher blast percentage, a lower percentage of basophils, and a lower frequency of splenomegaly[1,2]. It has a male predominance, and the majority of cases (70–80 %) involve transcripts that encode for the p210 protein [1–3,6]. Additional chromosomal abnormalities are detected in 50–60 % of cases[1–3,6]. Genetic mutations are frequently observed, with *the RUNX1* mutation being the most common (40 %), followed by *ASXL1, BCOR, IDH1/IDH2*, and *SRSF2*, each notable in 10–15 % of cases[3,7]. The 2022 ELN classification designates *BCR::ABL1* rearrangement as an adverse-risk AML, recommending HCT in the first remission[8].

In this report, we present a compelling case of a successful HCT omission in *BCR::ABL1* rearranged AML. By examining this exception, we aimed to identify the possible key elements that contributed to the successful outcome.

2. Case report

A 30-year-old male was referred to our center with a history of bruises and epistaxis. Initial laboratory workup revealed leukocytosis (WBC 25.5 $\times$ 10^9/L) with 25 % blast and thrombocytopenia. Cytogenetic analysis identified a t(9; 22)(q34; q11) translocation without additional abnormalities. The myeloid FISH panel showed *BCR::ABL1* rearrangement in 90 % of the sorted nuclei, while next-generation sequencing (NGS) of a 40-gene myeloid malignancy panel revealed no additional mutations. RNA sequencing using quantitative polymerase chain reaction (qPCR) identified the transcript corresponding to the P210 protein. Clinically, no splenomegaly or lymphadenopathy were present. The patient was diagnosed with de novo Philadelphia-positive

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Table 1
Features required for potential SCT omission in Philadelphia-positive AML.

No additional cytogenetic abnormalities
Complete molecular response (MR4 by three months or second conslidation)[+]
No history or features suggestive of antecedent CML
The use of TKI with activity against T315I
No myeloid mutation detected on NGS

Abbreviations: AML, acute myeloid leukemia, MR, molecular response, CML, chronic myelogenous leukemia, TKI, tyrosine kinase inhibitors, and NGS, next-generation sequencing.
[+] Optimal timepoint needs to be further evaluated for Philadelphia-positive AML.

AML. The patient underwent induction therapy with 3 + 7, and dasatinib was added following the identification of *BCR::ABL1* fusion. His induction course was complicated by septic shock and pulmonary effusion, requiring ICU admission, thoracocentesis, and pleural decortication. Dasatinib was discontinued, and Imatinib was started but later held due to acute kidney injury. End-of-induction bone marrow evaluation showed morphological remission, and FISH for *BCR::ABL1* rearrangement was negative on 200 sorted nuclei. Quantitative PCR for *BCR::ABL1* was positive at 0.024 %. A pre-transplant evaluation revealed a reduced ejection fraction (40–45 %) and low forced expiratory volume in 1 second (FEV1) at 45 % with an FEV1/FVC ratio of 89 %, likely secondary to the induction complications. Given the borderline fitness for allogeneic HCT, the patient elected to delay the transplant after understanding the risks and benefits. The patient subsequently received consolidation therapy with azacitidine, venetoclax (14 days), and ponatinib (30 mg continuously). After the first cycle, bone marrow evaluation was consistent with the complete molecular response (MR4.5) with undetectable *BCR::ABL1* levels. He completed 12 cycles of azacitidine, venetoclax (10 days), and ponatinib, with disease assessment every three cycles, consistently showing MRD negativity by qPCR, with no emerging mutations on the NGS myeloid panel. The patient also received two intrathecal chemotherapy for CNS prophylaxis. After 18 months, the ponatinib dose was reduced to 15 mg. The patient has maintained an ongoing MRD-negative remission without HCT for 30 months after diagnosis.

3. Discussion

Inspired by the advances in the management of Philadelphia-positive ALL, where HCT omission has been successful using high-intensity chemotherapy or, in certain circumstances, immunotherapy (i.e. blinatumomab) combined with a third-generation TKI ponatinib [9,10]. Since our patient was deemed less fit for transplant, a non-transplant-based approach was used, and fortunately, it was effective. Factors that may contribute to the success of a non-transplant-based approach in Philadelphia-positive AML, summarized in Table 1, include the absence of additional cytogenetic abnormalities, as these indicate more genomic instability and could be driving the disease beyond the *BCR::ABL1* fusion itself and are associated with inferior outcomes in CML and Philadelphia-positive ALL. Another important factor is achieving a complete molecular response, which indicates a sensitive disease and *BCR::ABL1* fusion dependency. A complete molecular response might be defined as MR4 or better by the second consolidation (or at three months), drawing from the literature on Philadelphia-positive acute lymphocytic leukemia, chronic myeloid leukemia, and acute myeloid leukemia; however, this will need further evaluation to establish the optimal timepoint for Philadelphia-positive AML [11–17]. Third, no history or clinical features suggestive of chronic myeloid leukemia diagnosis and no prior TKI exposure. Blastic phase CML, particularly progression while on TKI, is indicative of refractory disease, and historical outcomes have been dismal [18]. The use of TKI with activity against T315I mutation transcript, such as ponatinib, has been associated with deeper responses in Philadelphia-positive ALL with decreased need for HCT in these cases [9,10,19]. As the most common escape mechanism noted in Philadelphia-positive acute lymphocytic leukemia is the T315I mutation, using TKI that prevents such escape mechanism, like ponatinib or olverembatinib, in Philadelphia-positive AML, is likely to be the best strategy [20–22]. Finally, the absence of common myeloid mutations that can independently drive the disease on a comprehensive myeloid gene panel. Notably, mutations such as ASXL1 and *IKZF1*[+] are associated with inferior outcomes in chronic phase CML and Philadelphia-positive ALL, respectively [23–25].

Reflecting on this case, where all five elements were present, it remains uncertain if the addition of venetoclax should be recommended. In preclinical models, simultaneous targeting of BCL-2 and BCR::ABL1 eradicated CML stem cells [26]. However, a clinical trial combining venetoclax with dasatinib in chronic phase CML showed no added benefit compared to historical data of single agent dasatinib [27]. In relapse/refractory Philadelphia-positive ALL, the combination of venetoclax and ponatinib increases the molecular response rates without new safety concerns, suggesting a strong synergy between TKIs and venetoclax in *BCR::ABL*-driven leukemia [28,29]. A phase II trial of venetoclax, ponatinib, and decitabine in patients with blastic-phase CML or Philadelphia-positive AML reported high response rates, with some patients not candidates for HCT maintaining ongoing responses [30].

In conclusion, while the omission of HCT in Philadelphia-positive AML is desirable; the risk of relapse remains significant. This report highlights clinical features that may predict successful HCT omission, but further prospective and retrospective studies are needed.

Informed consent

Obtained.

CRediT authorship contribution statement

Mohamed I Sharif: Conceptualization, Data curation, Validation, Writing – original draft, Writing – review & editing. **Ahmad S. Alotaibi:** Validation, Visualization, Writing – review & editing. **Ruah Alyamany:** Writing – review & editing. **Ali Alahmari:** Writing – review & editing. **Hanan Alkhaldi:** Writing – review & editing. **Ayman Saad:** Supervision, Writing – review & editing. **Mansour Alfayez:** Supervision, Validation, Writing – review & editing.

Declaration of competing interest

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Data availability

The authors declare that data supporting the findings of this report are available within the article.

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