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CASE REPORT

Philadelphia Chromosome-Positive de Novo AML or Blast Phase CML? Case Report and Short Literature Review

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Abstract

The BCR::ABL1 translocation and the accompanying Philadelphia chromosome represents the first mutation which defined a disease, chronic myeloid leukemia. It also represents the first druggable target for which a specific compound was developed and accepted in current clinic practice, imatinib. Despite these, there are still areas in which the diagnosis and the best treatment sequence still needs investigation. One such context is the diagnosis and management of BCR::ABL1 positive myeloid neoplasms with ≥20% blasts, more specifically

the differentiation between myeloid blast phase chronic myeloid leukemia and BCR::ABL1 positive acute myeloid leukemia. In this paper we present our recent experience with a BCR::ABL1 positive myeloid neoplasms with ≥20% blasts.
***Keywords**: de novo BCR::ABL1 AML, myeloid, blast phase CML*

Introduction

The 2016 revision of the 4th World Health Organization (WHO) classification of myeloid neoplasms edition (Arber et al, 2016) saw the introduction of a provisionary entry: AML with BCR::ABL1 translocation. Although in May 2022, with the publication of the new 5th edition of the World Health Organization (WHO) classification (Khoury et al, 2022), AML with BCR::ABL1 was included as a definitive category of de novo AML, clear criteria to help differentiate de novo AML from blast phase (BP) chronic myeloid leukemia (CML) have yet to be formally accepted by the WHO.

While BCR::ABL1 AML is a rare entity, representing approximately 1% of AMLs (Grimwade et al, 2016; Döhner et al, 2017), it benefits from targeted therapy with tyrosine kinase inhibitors (TKI) (Döhner et al, 2017). However, to complicate the management of these patients, there is no clear consensus regarding treatment sequence of TKI, chemotherapy, and allogeneic hematopoietic stem cell transplant (alloHSCT). In Table 1 we summarized current recommendations for the treatment of AML with BCR::ABL1 and myeloid BP CML.

We present here a recent case of BCR::ABL1 positive myeloid neoplasm with ≥20% bone marrow (BM) blasts. This case serves as a starting point for a short review of literature published on AML with BCR::ABL1 translocation, and primary BP CML (mainly). Finally, we present our newly elaborated local protocols for managing patients with BCR::ABL1 positive myeloid neoplasm with ≥20% BM blasts.

Case report

A 57-year-old, male patient, presented to our department to further investigate complete blood count (CBC) abnormalities. The clinical exam and the history of the patient were unremarkable, except for mild hepatomegaly: 1-2 cm below costal margin measured by palpation. The local CBC and blood lab tests revealed leukocytosis (WBC= 98500/μL), with basophilia (BA= 3.7%, 3645/μL) moderate anemia (Hgb= 10.3 g/dL) and mild thrombocytopenia (PLT= 72000/μL) and an elevated LDH 1075 U/L. During the initial presentation, the patient presented a syncope episode for which he underwent a CT examination. The CT scan excluded a central nervous system or venous thromboembolism causes for the syncope, however revealed hepato-and splenomegaly: 15 cm, respectively,12cm.

Bone marrow aspirate was performed revealing a hypercellular marrow consisting of 80% myeloid cells: 40% myeloblasts, and 40% myeloid Precursors (8% promyelocytes, 5% myelocytes, 10% metamyelocytes, and 3% unsegmented granulocytes). Flow cytometry revealed 43% CD34+ myeloid precursors with aberrant CD9+ and CD123+ expression. Cytogenetic analysis revealed complex translocations involving chromosomes 6, 9 and 22 with 12 trisomy leading to the formation of the Philadelphia chromosome in 100% of analyzed metaphases (Figure 1). The final karyotype was: 47,XY,t(6,9,22)(6pter>6q21::q11.2>qter;9pter>9q34::6q21>6qter;22pter>q11.2::9q34>9

qter),+12[21].RT-PCR identified the p210 BCR::ABL1mRNA isotype, with negative NPM1 and FLT3-ITD mutations.

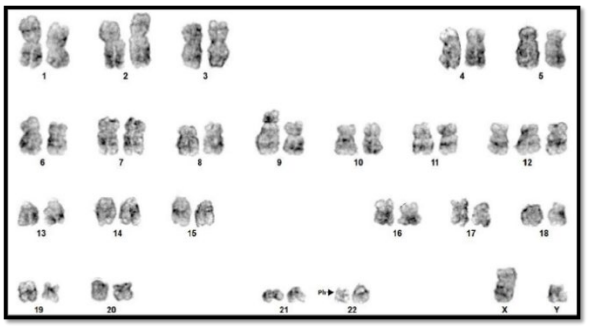

Figure1. Patient kariogramm revealing complex modifications: t(6;9;22), +12, Philadelphia chromosome identified in 100% of analyzed metaphases.

The patient first received 3 days of hydroxyurea as debulking therapy, after which underwent standard induction intensive chemotherapy as per the 7+3 protocol without the addition of a TKI. This was because molecular testing was prioritized for FLT3-ITD and NPM1 screening, with the RT-PCR result for BCR::ABL1 coming during the first week of aplasia post-induction. Based on the criteria for differentiating myeloid BP- CML from BCR::ABL1+ AML previously published (Neuendorff et al, 2016), after corroborating all clinical and laboratory data, we considered that the patient presented primary BP-CML.
This is based on the following: organomegaly (clinical and imagistic), peripheral blood basophilia ≥2%; complex chromosomal modifications and the presence of Philadelphia chromosome in 100% of metaphases; and the identification of the p210 isoform of the BCR:ABL1mRNA.

After the first induction cycle, the patient developed grade 4 anemia, thrombocytopenia, and neutropenia requiring red blood cell and thrombocyte transfusion support, and broad-spectrumantibiotics and antifungal medication,with. At the 14th day after induction therapy finished, the patient presented 25% circulating blasts on peripheral blood film examination and grade 4 thrombocytopenia (PLT= 4000/µL). Currently, the patient was started on imatinib, as per the 2020 ELN CML guidelines (Hochhaus et al, 2020), after the platelet count was above 10000/µL threshold, roughly 4 weeks since first diagnosis. We have started the search for a donor for alloHSCT.

Review of literature

Although great progress has been made in understanding AML in the last 20-30 years, ultimately only in the last 4-5 we saw novel therapies being accepted for the treatment of specific molecular subtypes of AML (Döhner et al, 2022). Unfortunately, even though the BCR::ABL1 translocation was the first mutation that benefited for targeted therapy, advanced CML cases and AML harboring BCR::ABL1 fusion still have an unfavorable prognosis frequently requiring alloHSCT were eligible for a chance at remission (Table 1).

Table 1. Treatment recommendations for *BCR::ABL1* AML & myeloid BP-CML

Guidelines	*BCR::ABL1* clinical entity	Treatment recommendation
2017 AML ELN guidelines (Döhner *et al*, 2017)	AML with *BCR::ABL1* translocation	Targeted TKI treatment, no other information given Indirect alloHSCT indication if eligible, because of genetic risk classification
2017 CML ESMO guidelines (Hochhaus *et al*, 2017)	BP-CML	alloHSCT in selected patients. In some cases, TKI monotherapy +/- chemotherapy can be used for bridging or debulking before alloHSCT
2020 CML ELN (Hochhaus *et al*, 2020)	BP-CML	Primary BP: start imatinib, change to 2nd gen TKI according to mutations Progression to BP: dasatinib/ponatinib + FLAG-IDA, followed by alloHSCT
2021 CML NCCN guidelines (Deininger *et al*, 2020)	BP-CML	alloHSCT eligible: AML induction therapy with 1st or 2nd gen TKI alloHSCT ineligible: 1st or 2nd gen TKI
2021 AML NCCN guidelines (Pollyea *et al*, 2021)	No specific mentioning of AML with *BCR::ABL1* translocation	N/A Indirect alloHSCT indication if eligible, because of genetic risk classification

2022 AML ELN guidelines (Döhner *et al*, 2022)	AML with *BCR::ABL1* translocation	N/A Indirect alloHSCT indication if eligible, because of genetic risk classification

AML – acute myeloid leukemia; CML – chronic myeloid leukemia; BP-CML – blast phase chronic myeloid leukemia; ELN – European LeukemiaNet; TKI – tyrosine kinase inhibitor; alloHSCT – allogeneic hematopoietic stem cell transplant; FLAG-IDA – fludarabine cytarabine filgrastim idarubicine

AML cases with BCR::ABL1 transcript were first recognized in the 1990s and early 2000s. These studies proposed several differences based on genetic and molecular data such as: differentiating AML with BCR::ABL1 by myeloid BP CML by the BCR::ABL1 isoform: p190 vs p210, respectively (Berger, 1993; Cuneo et al, 1996; Melo, 1996); or that the presence of the Ph chromosome in 100% of metaphases and the association with additional cytogenetic abnormalities are more likely to be associated with BP-CML (Berger, 1993; Johansson et al, 2002; Soupir et al, 2007; Neuendorff et al, 2016). However, later studies published found that de novo AML with BCR::ABL1 was associated in around 50% of cases with the p190 isoform (Keung et al, 2004; Soupir et al, 2007; Nacheva et al, 2013; Konoplev et al, 2014; Neuendorff et al, 2016). Regarding the cytogenetic abnormalities other case series reported that complex cytogenetic changes are also encountered in BCR::ABL1 AML (Cuneo et al, 1996; Paietta et al, 1998; Keung et al, 2004; Nacheva et al, 2013).

Apart from cytogenetic and RT- PCR data, clinical data and initial laboratory findings have been investigated to help orient the diagnosis. Of the readily available clinical and labora tory data–organomegaly, particularly splenomegaly, is a finding which helps orient the diagnosis towards BP-CML (Soupi et al, 2007). A consistently reported finding wthat peripheral basophilia ≥2% is associated with BP-CML (Cuneo et al, 1996; Soupir et al, 2007; Konoplev et al, 2014; Pastoret & Houot, 2017). A set of criteria, which took into account almost all cited articles, to help differentiate between myeloid BP-CML and de novo AML with BCR::ABL1 translocation were published in 2016 (Neuendorff et al,2016).

Treatment options for these two entities (Table 1) differ mainly in that primary myeloid BP-CML can be treated at first solely with TKI according to the 2020 ELN CML guideline (Hochhaus et al, 2020). Whereas both myeloid BP-CML and de novo AML with BCR::ABL1 translocation require high dose chemotherapy induction coupled with TKI, continued with alloHSCT (Hochhaus et al, 2020; Deininger et al, 2020). The role of alloHSCT in de novo AML with BCR::ABL1 translocation was evaluated in an European Society for Blood and Marrow Transplantation retrospective study (Lazarevic et al, 2018), showed that after alloHSCT these patients have a relatively favorable outcome with a 5 year non-relapse moratlity of 18.1% (95% CI: 9.2 – 29.4), leukemia-free survival of 44.2% (95% CI:31.1–57.3), and a 5 year overall survival of 53.8%(95%CI:40.4–67.3).

In this case, due to limited diagnostic resources, the RT-PCR result for the BCR::ABL1 transcript came too late to add targeted TKI therapy to the induction scheme. After this event, and our review of the specialty literature, we adopted the following protocol (Figure 2) to help us prioritize BCR::ABL1 testing, and to differentiate between myeloid BP- CML and AML with BCR::ABL1 translocation to provide for each patient, the best tailored treatment local available.

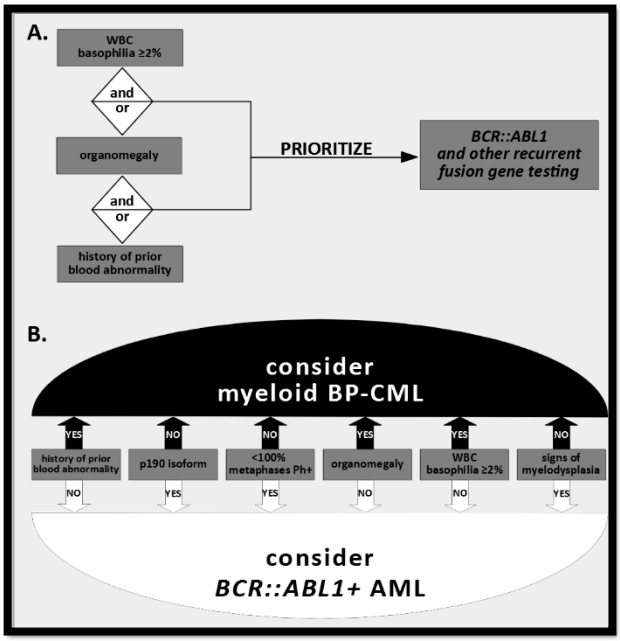

Figure 2. Local protocol for: **A.** Prioritizing BCR::ABL1 and other recurrent fusion gene testing for cases with ≥20% myeloblasts on PB or BM. **B.** Differential diagnosis of BCR::ABL1 positive myeloid neoplasms with ≥20% myeloblasts.

PB – peripheral blood;

BM – bone marrow; **AML**– acute myeloid leukemia; **BP-CML** – blast phase chronic myeloid leukemia;

Ph+ - Philadelphia chromosome positive

Conclusions

Differentiating myeloid BP- CML and AML with BCR::ABL1 translocation is an important step in evaluating each patient with ≥20% myeloid bone marrow blasts with BCR::ABL1 translocation. This process is facilitated by local protocols which guide diagnostic testing prioritization in a limited resource situation, while also differentiating between myeloid BP-CML and BCR::ABL1+ AML, therefore providing the therapeutic options for each patient.

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