Case Report

Relapse after Prolonged Remission in Philadelphia-Like Acute Lymphoblastic Leukemia

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We describe a case of late relapse of Philadelphia-like acute lymphoblastic leukemia. The patient relapsed several years from diagnosis and responded to second salvage treatment. The case highlights the open questions regarding management of Philadelphia-like acute lymphoblastic leukemia.

1. Introduction

Recent advances identified a subgroup of Philadelphia (Ph) negative acute lymphoblastic leukemia (ALL) patients with dismal outcomes [1]. This group of patients has an expression profile similar to that of Ph positive ALL patients but lacks the characteristic **BCR-ABL1** gene fusion due to the translocation 9;22. This group encompasses a variety of kinase-activating lesions and is referred to as Ph-like ALL [2].

2. Case Description

We report the case of a 25-year-old young adult patient with relapsed Ph-like ALL at over 15 years from his initial ALL diagnosis at age 9. Patient’s initial treatment included a multiagent chemotherapy regimen for standard risk (SR) pre-B ALL in accordance with the Pediatric Oncology Group (POG) 9905 regimen D [3]. Cytogenetics at initial diagnosis showed a balanced translocation t(3;12)(q21;q24), and **BCR-ABL1** gene fusion was negative. Flow cytometry revealed immature B-lineage phenotype. This initial diagnosis was during an era prior to the recognition of Ph-like ALL. The patient achieved first complete remission (CR) at end of induction therapy, and he completed the full regimen of chemotherapy for SR pre-B ALL. He remained in remission until 13 years off therapy (over 15 years from initial diagnosis) when he presented with a one-month history of night sweats, generalized weakness, petechiae, weight loss, lymphadenopathy, and splenomegaly.

Initial laboratory evaluation showed white blood count (WBC) of 44 × 10³/mm³ with a differential of 54% blast, hemoglobin of 8.3 g/dL, and platelet count of 24.6 × 10³/mm³. CT scans revealed scattered lymphadenopathy throughout chest, abdomen, and pelvis. The patient underwent a BM biopsy with an aspirate revealing 85% blasts. The bone marrow (BM) core biopsy had cellularity of 95% mostly composed by lymphoblasts. Flow cytometry on BM revealed atypical precursor B-cells with the following phenotype: CD19+, CD10hi, CD34 heterogenous, CD20+, CD9+, CD5−, and CD33− (see Table 1 for details). This phenotype was similar to his original diagnosis over 15 years prior. BM karyotype was 46,XY,t(3;12)(q21;q24) [20]. The same karyotype was present in previous samples, and later remission testing revealed that this translocation was constitutional. FISH analysis revealed that 86% of the cells had a rearrangement involving the **CRLF2** gene at Xp22.33/ Yp11.32. BM metaphase FISH analysis demonstrated the
presence of the t(X; 14)(p22.33;q32.3), which results in IGH/ CRLF2 fusion. BM FISH analysis was negative for the BCR/ ABL1 gene fusion, MLL gene rearrangement, and the ETV6/ RUNX1 gene fusion. Initial analysis revealed one copy of pathogenic variant in the kinase region of the JAK2 gene (Nationwide Children’s Hospital). Notably, subsequent molecular analysis (Neogenomics) at a later point on his treatment was positive for a fusion (PAX5/ZCCHC7) transcript involving PAX5 and ZCCHC7 genes resulting from t(9;9)(p13.2;p13.2) translocation. In addition, significantly high levels of CRLF2 expression were detected. Moreover, mutations in JAK2, CHD2, FIP1L1, and KDM6A were detected. Of note, JAK2 mutations are common among CRLF2 rearranged cases [4]. The findings of CRLF2 rearrangement with JAK2 mutation are diagnostic of Ph-like ALL. Importantly, CSF assessment did not reveal presence of lymphoblasts.

The patient was treated with blinatumomab without significant complications. The BM biopsy after cycle 1 of blinatumomab revealed a reduction to the aspirate blasts to 41% while cellularity was decreased to 50–60% composed mostly by lymphoblasts. The peripheral WBC reduced to 7.51 × 10^3/mm^3 with 3% blasts. The hemoglobin improved to 11.4 g/dl and platelets to 158 × 10^3/mm^3. The patient then proceeded to the second cycle of blinatumomab, but within a few days, the WBC had increased from 5.84 to 108.6 × 10^3/mm^3 with 79% blasts. Blinatumomab was discontinued, and after cytoreduction, the patient received inotuzumab ozogamicin (InO) at the recommended dose and schedule. Repeat BM biopsy after cycle 1 of InO showed no morphologic evidence of leukemia. Flow cytometry as well as FISH analysis for CRLF2 rearrangement were negative (see table); karyotype was 46,XY,t(3;12)(q21;q24) [20]. The repeat CT scan showed improvement in diffuse lymphadenopathy and splenomegaly. The patient completed 2nd cycle without any complication, and another BM biopsy was performed again without morphological or flow cytometry evidence of ALL. Karyotype was again 46,XY,t(3;12)(q21;q24) [20], and therefore, it was considered to be most consistent with constitutional translocation.

Following further imaging studies, allogeneic bone marrow transplant (AlloHSCT) was pursued. Conditioning regimen was based on total body irradiation and cyclophosphamide while the donor was matched unrelated. The patient developed infectious complications, electrolyte abnormalities, and arrhythmias during his AlloHSCT course and expired. There was no evidence of veno-occlusive disease at the time of death.

### 3. Discussion

Children, adolescents, and adults with Ph-like ALL have a dismal prognosis [2, 5]. The use of dasatinib or ruxolitinib with chemotherapy in this subgroup of patients is underway (ClinicalTrials.gov Identifier: NCT02420717) in an attempt to improve outcomes [6].

Patients in CR remain at risk of relapse; the median EFS was 17.2 months for adult patients treated on the study of

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**Table 1: Summary of hematological and flow cytometry findings, molecular aberrations, and cytogenetics at various stages of clinical course.**

|                          | Relapse | Postcycle 1 blinatumomab | Blinatumomab treatment failure | Postcycle 1 inotuzumab ozogamicin | Prior to AlloHSCT |
|--------------------------|---------|--------------------------|-------------------------------|-----------------------------------|------------------|
| **WBC in 10^3/mm^3**     |         |                          |                               |                                   |                  |
| (blast percentage)       | 44 (54%)| 7.51 (5%)                | 108 (79%)                     | 7.45 (0%)                         | 6.45 (0%)        |
| **Platelet count (10^4/mm^3)** | 24.6    | 158                      |                               |                                   |                  |
| **Flow cytometry**       | Precursor B-ALL (76% blast) | Precursor B-ALL (32% blast) | Precursor B-ALL (79% blast) | No evidence of ALL |                  |
| **Bone marrow diagnosis**| Aspirate: 85% blasts | Aspirate: 41% blasts | Not performed | No evidence of ALL |                  |
| **Pertinent CD markers on bone marrow (peripheral blood at blinatumomab treatment failure)** | CD19+, CD10 high, CD45 low, CD34+, CD20+, CD99+, CD38+, CD58+, sIg−, CD5−, CD22+, CD13−/low, and CD33− | CD19+, CD10 high, CD45 low, CD34+, CD20+, CD22+, CD38+, CD58+, sIg−, CD13−, and CD33− | CD19+, CD20+, CD10hi, CD45lo, CD34 heterogeneous, CD117−, CD22+, CD38+, CD58lo, CD9+, surface Ig−, CD15−, and CD33− | Negative | Negative |
| **CRLF2 rearrangement at Xp22.33/Yp11.32** | 86% of cells positive | 40% of cell positive | 76% of cell positive | 46,XY,t(3;12)(q21;q24) [20] | 46,XY,t(3;12)(q21;q24.1)c [20] |
| **Karyotype**            | 46,XY,t(3;12)(q21;q24) [20] | 46,XY,t(3;12)(q21;q24.1) [20] | Fusion of PAX5-ZCCHC7. Mutation in JAK2, CHD2, FIP1L1, and KDM6A | 46,XY,t(3;12)(q21;q24.1)c [20] | 46,XY,t(3;12)(q21;q24.1)c [20] |
Patient consent was not obtained as deidentified information was used.

Conflicts of Interest

The authors do not have conflicts of interest to declare.

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