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LETTER TO THE EDITOR

The role of ruxolitinib treatment in JAK-mutated Ph-like acute lymphoblastic leukemia

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Dear Editor,

I am writing to bring your attention to Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL), which is a recently identified subtype of high-risk (HR) B-lineage ALL. Ph-like ALL shares a gene expression profile like Philadelphia chromosome-positive (Ph-positive) ALL, but it lacks the BCR-ABL translocation. Instead, it is characterized by ABL class translocations, CRLF2 rearrangements, and other JAK pathway alterations [1]. Ph-like ALL demonstrates unfavorable clinical features, poor prognosis, and a diverse range of genetic alterations that activate cytokine receptor genes and kinase signaling pathways [2]. Consequently, it can potentially respond to treatment with tyrosine kinase inhibitor (TKI) therapy [3]. Ongoing trials investigating the use of ruxolitinib in the treatment of Ph-like ALL will shed light on the potential efficacy of combining ruxolitinib and chemotherapy in larger cohorts of patients with JAK pathway-mutant Ph-like ALL [4].

In August 2022, a 23-year-old man presented with a 10-day history of fatigue. Peripheral lymphadenopathy was observed during the physical examination. Bone marrow analysis revealed high cellularity with 88% blast cells displaying lymphoid characteristics. The patient was diagnosed with CD20 positive, CD22 positive, JAK2 positive, BCR-ABL1 negative, and CRLF2 negative Ph-like pre-B acute lymphoblastic leukemia (ALL). These mutations were screened by multiple FISH probes.

The patient received R-Hyper-CVAD as the initial treatment. After completing four courses, a bone marrow aspiration showed 90% blast cells. In second-line treatment FLAG (fludarabine 30mg/m^2 D1-5, cytarabine 2000mg/m^2 D1-5, filgrastim 0.5 µg/kg/day from D1 until neutrophil recovery), chemotherapy was started. After one cycle of FLAG, 60% blast cells were detected. One cycle of inotuzumab ozogamicin monotherapy in a dose of 0.8 mg/m2 on day 1, 0.5 mg/m2 on day 8, and 15 was then administered. On day 28, the patient experienced painful lymph nodes and 40% blastic cells in the bone marrow.

Subsequently, a combination therapy of ruxolitinib (25 mg twice daily from day 1 to 14), rituximab 375 mg/m^2 on days 1 and 11 Augmented Hyper-CVAD (vincristine 2-mg intravenous bolus weekly on days 1, 8, and 15; dexamethasone 80 intravenous or orally (p.o.) on days 1–4 and 15–18, and pegaspargase 2500 units/m^2 intravenous on day 1) was given. On day 28, the patient achieved a complete response with no minimal residual disease, which was assessed by flow cytometric analysis. Allogeneic stem cell transplantation was performed from a 9/10 HLA-compatible, unrelated donor as the next step in the treatment. On post-transplant day 66, the patient developed grade 4 acute gastrointestinal graft-versus-host disease (GVHD). Methylprednisolone was initiated at a dose of 2 mg/kg/day to manage the condition. The patient's clinical condition was closely monitored for 3 days, and due to worsening symptoms, a switch was made from cyclosporine A to tacrolimus, and mycophenolate mofetil was added to the treatment regimen. Despite these efforts, the condition could not be effectively controlled, leading to the addition of ruxolitinib and photopheresis to the treatment plan. Unfortunately, the patient had severe pancytopenia accompanied by bone marrow aplasia. On day 100, a bone marrow biopsy showed a complete remission. However, on day 166, Acinetobacter baumannii sepsis unfortunately led to death.

Previously six resistant ALL cases with JAK2 fusions or ALL harboring recurrent pathogenic mutations within the pseudokinase or kinase domain of JAK2 were reported. According to this report, rapid initial molecular diagnosis

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and immediate introduction of JAK inhibitor after identifying Ph-like signature could be an option to achieve better response or even remission in those patients [5]. In addition, the proliferation signal in Ph-like ALL is derived from several kinases, and parallel blockage of JAK 1&2, RAS, and mTOR is probably needed for leukemia cell elimination [6–9]. Thus, high ruxolitinib doses of at least 50 mg twice daily [10, 11] could be required to achieve clinical benefit. Phase II studies exploring the role of incorporating ruxolitinib in induction regimens for Ph-like ALL are ongoing. While the recommended dosage is twice daily at 50 mg each, our observation demonstrated that a daily dose of 2 × 25 mg of ruxolitinib may be sufficient to achieve a complete response in a resistant patient with Ph-like ALL [10, 11].

Based on our experience, we believe that ruxolitinib is an effective treatment option for JAK2 mutated Ph-like ALL. However, each patient's response and outcome may vary, and it is important to carefully assess and monitor the individual's condition throughout the treatment process.

Author contribution All authors contributed to writing, drafting, and editing of the manuscript. Additionally, all authors participated in the final revisions of the manuscript and deserve authorship.

Data availability The datasets that were utilized or examined during the current research can be obtained from the corresponding author upon a reasonable request.

Declarations

Ethical approval This letter does not contain any studies with human participants or animals performed by any of the authors.

Informed consent The authors declare that they have acquired consent forms from both the patient and their immediate family members. Within these forms, the patient has provided consent for the publication of their medical examinations and other clinical information in the journal. The patient acknowledges that their name and initials will not be disclosed, and measures will be taken to safeguard their identity. However, it should be noted that complete anonymity cannot be guaranteed.

Competing interests The authors declare no competing interests.

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