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Concomitant ruxolitinib with cytarabine-based induction chemotherapy in secondary acute myeloid leukemia evolving from myeloproliferative neoplasm

TO THE EDITOR: Myeloproliferative neoplasms (MPNs) can transform into acute myeloid leukemia (post-MPN AML), which is resistant to conventional chemotherapy and has a median survival of only 3–5 months [1]. Although allogeneic stem cell transplantation seems to improve the prognosis of these patients, most patients with post-MPN AML are ineligible for transplantation because of advanced age and/or comorbidities [2]. Therefore, there is an unmet need for the treatment of post-MPN AML.

Cytogenetic or molecular abnormalities associated with poor prognosis, such as complex karyotypes and *TP53* mutations, are common in post-MPN AML [3]. As these molecular abnormalities are related to aggressive cancer cell behavior, they may serve as markers of response to targeted therapy. For example, some AMLs harbor the *BCR-ABL1* fusion gene, and clinical outcomes have dramatically improved with the introduction of *BCR-ABL1* tyrosine kinase inhibitors such as imatinib and nilotinib [4]. A gain-of-function mutation in *Janus kinase 2* (*JAK2*), *V617F*, is a hallmark of *BCR-BL1*-negative MPN (including polycythemia vera and essential thrombocythemia) and plays an important role in myeloid cell proliferation [5]. Additionally, *JAK2-V617F* is present even after progression to AML in approximately 35–50% of cases [3]. Therefore, ruxolitinib (a selective *JAK* inhibitor) has been explored as a single agent for the treatment of post-MPN AML. In a previous investigational study of ruxolitinib for refractory leukemia, including post-MPN AML (irrespective of *JAK2* mutational status), 3 of 18 patients with post-MPN AML achieved complete remission (CR) [6]. However, results from *BCR-ABL1*-positive AML suggest that tyrosine kinase inhibitors alone are insufficient to control acute-phase leukemia. Considering these points, we designed a trial to examine ruxolitinib in combination with intensive cytotoxic chemotherapy for patients with post-MPN AML in good physical condition. We included patients regardless of *JAK2* mutational status, considering the importance of *JAK2* signaling in post-MPN AML [7, 8]. This study was terminated early after the enrollment of only two patients owing to slow recruitment. In this report, we present two cases of post-MPN AML treated with ruxolitinib in combination with AML-style induction chemotherapy (Table 1).

STUDY DESIGN

This was an investigator-initiated phase II open-label single-arm study. Adult (age ≥18 yr) patients with cytologically confirmed AML following MPN were eligible if they had adequate physical condition and organ function and could tolerate cytotoxic induction chemotherapy. The major

Table 1. Summary of two patients treated with the ruxolitinib combination regimen.

	Case 1	Case 2
Age	62	74
Gender	F	M
MPN type	Essential thrombocythemia	Polycythemia vera
AML diagnosis	Feb 2019	Mar 2019
JAK2 status	Negative	Positive
Other molecular status	Complex karyotype, *TP53, ROS1, FGFR4* mutations	Not assessed
Treatment	5+2 induction chemotherapy with ruxolitinib	5+2 induction chemotherapy with ruxolitinib
Response to induction	Complete remission	Partial remission
Response to consolidation	Not assessed (EOT)	Not assessed (EOT)
EOT reason	Septic pneumonia	Deteriorated condition
Duration of response	3 months +	24 months +
OS	3 months	24 months +
Outcome	Deceased	Medically stable after EOT

Abbreviations: AML, acute myeloid leukemia; EOT, end of trial; MPN, myeloproliferative neoplasm; OS, overall survival.

exclusion criteria were: 1) a diagnosis of any serious secondary malignancy within the last two years and 2) prior treatment with ruxolitinib.

A combination of cytarabine (200 mg/m^2) and idarubicin (12 mg/m^2) was administered for induction chemotherapy. Both 7+3 and 5+2 regimens were allowed, and the regimen was determined based on the patient's age and fitness. In both the induction and consolidation phases, ruxolitinib (15 mg) was administered twice daily for 14 days after the completion of cytotoxic chemotherapy to avoid severe marrow suppression. The ruxolitinib dose was adjusted based on the occurrence of adverse events. Bone marrow examination was performed on day 35 or when there was evidence of hemogram recovery – whichever occurred first. The responses were evaluated according to the criteria reported by Cheson *et al*. [9].

The primary endpoint of this study was the overall response rate (sum of CR and CR with incomplete platelet recovery), considering the potential of ruxolitinib to delay platelet recovery. Considering the outcome of the blast crisis in CML [10], we hypothesized that this combination strategy would be meaningful if more than 35% of the patients achieved CR. As the CR rate of conventional induction in post-MPN AML is approximately 5% [3, 11, 12], we planned to enroll 17 patients (significance level, 5%; power, 90%) (ClinicalTrials.gov identifier, NCT03558607).

CASE 1

A 62-year-old Asian woman with no comorbidities was diagnosed with post-MPN AML and was enrolled in February 2019. She was initially diagnosed with *JAK2*-negative essential thrombocythemia in 1993 and treated with hydroxyurea and aspirin. Cytogenetic tests, including next-generation sequencing performed at the time of AML diagnosis, confirmed a complex karyotype with *TP53, ROS1,* and *FGFR4* mutations and no *JAK2* mutations. The patient was treated with 5+2 induction chemotherapy and ruxolitinib. On day 30, a bone marrow examination confirmed CR. Ruxolitinib-related toxicities were not observed during the induction phase. The neutrophil recovery time ($\geq 0.5\times10^9$/L) was 36 days, and the platelet recovery time ($\geq 20\times10^9$/L) was 32 days. After CR was achieved, the patient underwent consolidation chemotherapy with an intermediate dose of cytarabine in April 2019. Unfortunately, she developed neutropenic fever with septic pneumonia during the initial consolidation chemotherapy. As a result, the end of the trial procedure was performed, and the patient died of pneumonia in May 2019. Survival time after induction chemotherapy was 3 months.

CASE 2

A 74-year-old Asian man with chronic kidney disease (grade 3b) and hypertension was enrolled in April 2019. The underlying MPN was diagnosed as polycythemia vera in 1996. While being treated conservatively without ruxolitinib, the patient progressed to AML in March 2019, and the *JAK2 V617F* mutation was confirmed. The patient initially received decitabine monotherapy in March 2019; however, there was no response. He was enrolled in this clinical trial and started 5+2 induction chemotherapy with ruxolitinib. Bone marrow examination on day 28 indicated partial remission (blast count decreased from 21% to 7%). The neutrophil recovery time ($\geq 0.5\times10^9$/L) was 25 days, and the platelet recovery time ($\geq 20\times10^9$/L) was 31 days. However, his performance status deteriorated, his kidney function decreased to a glomerular filtration rate (GFR) of less than 15, and he started hemodialysis, resulting in intolerance to further cytotoxic chemotherapy. Therefore, the trial procedure ended in June 2019, and the patient received conservative treatment. Nevertheless, the leukemia did not progress further over the next two years, and the patient was medically stable for 24 months.

DISCUSSION

The treatment options for post-MPN AML are not well-defined. Additionally, the long clinical course of MPN is associated with advanced age at diagnosis in many patients with post-MPN. To address these issues, a recent phase II study evaluated the combination of ruxolitinib and decitabine in patients who are older and unfit [13]. However, we postulate that a combination of cytotoxic chemotherapy and ruxolitinib would be helpful for the older population. To the best of our knowledge, data on ruxolitinib combined with cytotoxic chemotherapy are scarce. Accordingly, we believe that our results provide meaningful evidence for improving the outcomes of patients with post-MPN AML, especially with an increasing number of older and fit patients.

In a phase II study of 25 older and unfit patients with post-MPN AML examining the combination of decitabine and ruxolitinib [13], the overall response rate was 44%, and the median response duration was 3.4 months. In our study, both patients responded, and no relapse was observed during follow-up. Notably, the second patient was in stable condition for more than 2 years after study enrollment. These results indicate the potential of combining ruxolitinib with standard chemotherapeutic agents. From a biological perspective, given that post-MPN AML is resistant to chemotherapy owing to frequent *TP53* loss [14], this combination strategy seems to overcome chemoresistance via synergism.

However, the toxicity of this regimen in older populations must be investigated. In these two patients, the neutrophil recovery times were 36 and 25 days, respectively, and the platelet recovery times were 32 and 31 days, respectively. This suggests that combination therapy did not jeopardize hemogram recovery after induction chemotherapy. However, non-hematologic toxicity remains a concern, as our patient developed septic pneumonia and chronic kidney disease. In two separate phase 2 trials combining ruxolitinib with decitabine, the starting doses of ruxolitinib were 25 mg bid and 50 mg bid, respectively [13, 15]. In our study, we employed a protocol that started with a 15 mg bid, with

the potential to escalate to a maximum of 25 mg bid. However, in contrast to decitabine, greater caution is necessary when combined with intensive cytotoxic chemotherapy. Thus, further research is needed to determine the appropriate dosing.

In summary, our case highlights that the combination of ruxolitinib and AML-style cytotoxic chemotherapy is an attractive option for older patients with post-MPN AML. Given the heterogeneity of this population and the lack of treatment options, further exploration of the role of ruxolitinib in combination with cytotoxic chemotherapy is required.

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Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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A challenging diagnosis of hepatosplenic T cell lymphoma in a 10-year-old child

TO THE EDITOR: Hepatosplenic T cell lymphoma (HSTCL) is a rare subtype of T cell lymphoma that accounts for less than 3% of all peripheral T-cell lymphomas. It is prevalent in adolescents and young adults (median age ~35 yr) and is derived from cytotoxic T cells, usually of γδ T cell receptor (TCR) type [1, 2].

HSTCL is characterized by a triad of cytopenia, B symptoms, and hepatosplenomegaly, usually without lymphadenopathy or peripheral lymphocytosis [3]. Furthermore, the disease progresses with a poor response to currently available therapies [4].