Original Study

The Treatment Landscape of Myelofibrosis Before and After Ruxolitinib Approval

Andrew T. Kuykendall,[1] Chetasi Talati,[1] Najla Al Ali,[2] Kendra Sweet,[2] Eric Padron,[2] David A. Sallman,[2] Jeffrey E. Lancet,[2] Alan F. List,[2] Kenneth S. Zuckerman,[2] Rami S. Komrokji[2]

Abstract

The US Food and Drug Administration approval of ruxolitinib for intermediate- and high-risk myelofibrosis (MF) in 2011 changed the therapeutic landscape of the disease. We investigated the first-line treatment choices for MF patients in the pre- and post-ruxolitinib eras and found that the increased use of ruxolitinib has come at the expense of several agents, but has not significantly affected the utilization of hydroxyurea in the first-line setting.

Introduction/Background: Myelofibrosis (MF) is a chronic myeloproliferative neoplasm that presents with a heterogeneous clinical phenotype and prognosis. Before the US Food and Drug Administration approval of ruxolitinib, treatment options were varied and had limited effect. The increased use of ruxolitinib has drastically altered the MF treatment landscape. In this study, we aimed to clarify the clinical situations in which ruxolitinib is being used and analyze its effect on this landscape. **Patients and Methods:** We retrospectively assessed treatment choices for MF patients treated at our institution (n = 309). This population was divided into 2 cohorts on the basis of a diagnosis before (cohort BR: n = 174) or after (cohort AR: n = 135) ruxolitinib approval. Cohorts were further stratified for comparison according to presenting clinical factors. **Results:** Expectedly, the first-line use of ruxolitinib markedly increased after its approval. AR patients were less likely to receive erythropoiesis-stimulating agents (ESAs; $P = .0003$) and thalidomide ($P = .003$) than BR patients. In patients with MF-related symptoms and/or splenomegaly, increased use of ruxolitinib was associated with decreased use of first-line ESA ($P = .03$) or thalidomide ($P = .03$). In anemic patients, increased use of first-line ruxolitinib was associated with a decreased use of thalidomide ($P = .007$). In patients with severe leukocytosis, ruxolitinib use did not significantly increase and hydroxyurea was the preferred first-line agent. **Conclusion:** Overall, the increased use of ruxolitinib appears to have come predominantly at the expense of thalidomide and ESAs, while not having a large effect on the first-line use of hydroxyurea.

Clinical Lymphoma, Myeloma & Leukemia, Vol. ■, No. ■, ■-■
Keywords: Hydroxyurea, JAK2 inhibitor, Myeloproliferative neoplasm, Thalidomide, Treatment

Introduction

Myelofibrosis (MF) is a breakpoint cluster region-Abelson fusion gene (*BCR-ABL1*)-negative myeloproliferative neoplasm clinically characterized by splenomegaly (Sp), constitutional symptoms (CS), cytopenias, and a risk of transformation to acute myeloid leukemia. MF has a heterogeneous clinical phenotype and prognosis. Historically, treatment approaches have been diverse; selected in an effort to address the most concerning presenting symptom, with suboptimal response rates and the caveat that the treatment could worsen some aspects of the disease while alleviating others. Despite a litany of potential therapeutic agents, allogeneic stem cell transplantation remains the only therapy with curative potential.

On November 16, 2011, ruxolitinib gained US Food and Drug Administration (FDA) approval for the treatment of intermediate- and high-risk MF, the first drug to gain approval for this indication. The approval was on the basis of the results of the Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment I (COMFORT-I) and COMFORT-II studies, which compared ruxolitinib with placebo and best available therapy, respectively.[1,2] Both trials

[1]Department of Internal Medicine, Hematology & Medical Oncology Fellowship Program at Moffitt Cancer Center, University of South Florida, Tampa, FL
[2]Department of Malignant Hematology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Submitted: Jun 29, 2017; Accepted: Aug 1, 2017

Address for correspondence: Andrew T. Kuykendall, MD, University of South Florida, Morsani College of Medicine at Moffitt Cancer Center, 12902 Magnolia Dr, MCC-GME, Tampa, FL 33612
E-mail contact: Andrew.Kuykendall@moffitt.org

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2017.08.002

met their primary end point of reducing Sp, with the COMFORT-I trial meeting a key secondary end point of reduction of MF-related symptoms. Both studies showed an increase in Grade 3 anemia and thrombocytopenia, raising concern that preexisting cytopenias might potentially prohibit some MF patients from receiving the drug.

In practice, ruxolitinib is often used in MF patients whose disease is exemplified by CS and Sp. Before FDA approval, a number of agents were used in this symptomatic subgroup and, although we know that the use of ruxolitinib has increased, it is unclear at which previous agents' expense this has occurred and what is the current landscape of treatment. In this study, we aimed to investigate treatment trends before and after ruxolitinib approval, in an effort to better define the patients who are receiving ruxolitinib.

Patients and Methods

This was a single-institution retrospective study of patients diagnosed with MF between February 2001 and June 2016. Primary MF (PMF) was defined according to World Health Organization 2016 criteria whereas post-polycythemia vera MF and post-essential thrombocythemia MF were defined according to the International Working Group for Myeloproliferative Neoplasms, Research and Treatment, respectively.[3,4] Using these criteria, we identified 312 eligible patients. Three patients were excluded because they received their first-line treatment on a clinical trial basis. Ultimately, 309 patients were divided into 2 cohorts. The cohort (BR) included patients diagnosed with MF before FDA approval of ruxolitinib (n = 174) whereas cohort AR was comprised of patients diagnosed on or after the FDA approval date (n = 135). We collected demographic and clinical data including date of diagnosis, presence of CS or Sp, laboratory values, Janus-associated kinase-2 (*JAK2*) *V617F* mutational status, and treatment history.

The primary aim of this study was to describe the first-line treatment choices for MF and investigate changes in first-line treatment patterns after approval of ruxolitinib by the FDA. Date of diagnosis was defined as the date of diagnostic bone marrow biopsy or, if not available, date the diagnosis was first assigned by a physician on review of clinical notes. Laboratory values and symptom presence was defined upon initial presentation to our institution and on the basis of review of the electronic medical record. First treatment was defined as the first medication prescribed to the patient for the intention of treating MF-related signs or symptoms. Single-agent corticosteroids were not considered an MF-directed therapy. Patients who received first-line therapy on a clinical trial basis were excluded from evaluation.

Statistical analysis was conducted for the group as a whole as well as for the 2 separate cohorts (BR and AR). Additionally, we analyzed predefined subgroups on the basis of presenting signs and symptoms as a whole and on the basis of the date of diagnosis in relation to ruxolitinib approval by the FDA. Differences between groups were assessed using the Student *t* test for continuous variables. Contingency tables were analyzed using Fisher exact test. All data were analyzing using Graphpad Prism version 6.07 (GraphPad Software, La Jolla, CA). A *P* value $< .05$ was considered statistically significant.

Results

Patient Characteristics

Table 1 shows the baseline characteristics of the 309 evaluable patients. The 2 cohorts had similar median ages at diagnosis and presentation and similar demographic makeup. An unknown *JAK2* mutation status was more common in the BR cohort. A higher proportion of the AR cohort presented with marked leukocytosis (> 25,000 white blood cells [WBC]/μL) and absolute monocytosis (> 1000 monocytes/μL). Using the dynamic international prognostic scoring system (DIPSS), the 2 cohorts were comprised of similar proportions of low-, intermediate-, and high-risk disease.

Table 1 Demographic and Clinical Characteristics in the Pre-Ruxolitinib and Post-Ruxolitinib Cohorts

Baseline Characteristics	Pre-Ruxolitinib Approval (n = 174)	Post-Ruxolitinib Approval (n = 135)
Median Age at Diagnosis, y	66	70
Median Age at Presentation, y	69	70
Male Sex	101 (58)	81 (60)
Primary Myelofibrosis	137 (79)	98 (73)
Post-PV Myelofibrosis	15 (8)	15 (11)
Post-ET Myelofibrosis	22 (13)	22 (16)
***JAK-2 V617F* Mutated**	87 (50)	82 (61)
***JAK-2* Mutation Status Unknown**	34 (19)	3 (2)
Splenomegaly	134 (77)	97 (73)
Constitutional Symptoms	61 (35)	53 (39)
Anemia (Hemoglobin <10 g/dL) or Transfusion-Dependent	95 (55)	74 (55)
Leukocytosis (WBC >25,000/μL)	22 (13)	30 (22)
Circulating Blasts ≥1%	49 (28)	38 (28)
Thrombocytopenia (<100,000/μL)	53 (30)	37 (28)
Monocytosis (>1000/μL)	26 (15)	34 (26)
Median Adjusted LDH (LDH/ULN)	1.85	1.88
DIPSS Score[a]		
0 (Low)	12 (7)	7 (5)
1 (Intermediate-1)	76 (44)	53 (39)
2 (Intermediate-2)	74 (43)	56 (41)
3 (High)	11 (6)	18 (13)

Data are presented as n (%) except where otherwise noted.
Abbreviations: DIPPS = dynamic international prognostic scoring system; ET = essential thrombocythemia; LDH = lactate dehydrogenase; PV = polycythemia vera; ULN = upper limit of normal; WBC = white blood cells.
[a]The DIPSS score was unevaluable in 1 patient in each cohort.

Treatment Trends

Figure 1 shows the spectrum and frequency of first-line treatment options in MF and the variation between first-line treatment choices in the pre- and post-ruxolitinib eras. In the BR cohort, 42 patients (24%) received ruxolitinib at some point during therapy, with 13 (31%) of those patients (7.5% overall) receiving a ruxolitinib as first-line therapy. In the AR cohort, 59 patients (44%) received ruxolitinib, with 41 (69%) of those (30.4% overall) receiving it as first-line therapy. AR patients were more likely to receive ruxolitinib overall (odds ratio [OR], 2.44; $P = .0004$) and as first-line therapy (OR, 5.40; $P < .0001$). The median time from diagnosis to receipt of ruxolitinib was 42.5 months in the