Leukemia Research xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Ruxolitinib treatment for myelofibrosis: Efficacy and tolerability in routine practice

Martin H. Ellis[a,b,1], Noa Lavi[c,d,*,1], Elena Mishchenko[e], Najib Dally[f], David Lavie[g], Anna Courevitch[h], Odit Gutwein[i], Shlomo Bulvik[j], Andrei Braester[k], Evgeni Chubar[l], Sigal Tavor[m], Adrian Duek[n], Ilya Kirgner[b,o], Maya Koren-Michowitz[b,n]

[a] Department of Hematology, Meir Medical Center, Kfar Saba, Israel
[b] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[c] Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel
[d] Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, Haifa, Israel
[e] Hematology Unit, Bnai-Zion Medical Center, Haifa, Israel
[f] Department of Hematology, Ziv Medical Center Associated with the Bar Ilan University, Faculty of Medicine, Safed, Israel
[g] Department of Hematology and Bone Marrow Transplantation, Hebrew University-Hadassah Medical Organization, Jerusalem, Israel
[h] Department of Hematology and Bone Marrow Transplantation, Soroka Medical Center, Beer-Sheva, Israel
[i] Department of Hematology, Assaf Harofeh Medical Center, Ramla, Israel
[j] Department of Hematology, Laniado Hospital-Sanz Medical Center, Netanya, Israel
[k] Department of Hematology, Western Galilee Hospital, Nahariya, Israel
[l] Department of Hematology, The Emek Medical Center, Afula, Israel
[m] Maccabi Health Organization, Tel Aviv, Israel
[n] Division of Hematology and Bone Marrow Transplantation, Sheba Medical Center, Tel Hashomer, Israel
[o] Department of Hematology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

ARTICLE INFO

Article history:
Received 30 April 2015
Received in revised form 28 July 2015
Accepted 6 August 2015
Available online xxx

Keywords:
Ruxolitinib
Myelofibrosis
Population study

ABSTRACT

Ruxolitinib has been shown in two randomized clinical trials to be effective in alleviating systemic symptoms and reducing spleen size in patients with myelofibrosis (MF). We retrospectively evaluated efficacy and tolerability of ruxolitinib in a cohort of unselected MF patients treated in routine clinical practice. One hundred and two patients who began ruxolitinib therapy were identified in 13 participating centers. Ninety three of the patients receiving ruxolitinib for at least 3 months were evaluated for treatment efficacy and toxicity. Median age at ruxolitinib initiation was 67 years. Indications for treatment were constitutional symptoms (15%), symptomatic splenomegaly (6%) or both (76%). Two patients received ruxolitinib for other indications. The median initial ruxolitinib dose was 30 mg/day. Median duration of therapy was 11 months. Eighty two patients (88.2%) responded to therapy, 76 (84.4%) patients had improvement in constitutional symptoms and 60 patients (70.6%) had reduction in spleen length. While on ruxolitinib, 30% of patients had grade 3–4 anemia and 12.9% of patients had grade 3–4 thrombocytopenia. Thirteen patients (14%) discontinued therapy. This analysis of a cohort of MF patients treated with ruxolitinib in routine clinical practice demonstrates the efficacy and tolerability of this drug outside of a highly monitored clinical trial setting.

1. Introduction

Activation of the JAK-STAT pathway contributes to the pathogenesis of the Philadelphia negative myeloproliferative neoplasms (Ph-MPN). Development of JAK inhibitor therapies was thus a rational step following the discovery of the JAK2V617F activating mutation in the majority of the Ph-MPN patients [1–4]. The JAK1/JAK2 inhibitor ruxolitinib has shown clinical benefits in intermediate and high risk myelofibrosis (MF) patients and was the first JAK2 inhibitor approved by health authorities for these indications [5]. Two phase III clinical trials, COMFORT I and COMFORT II [6,7] demonstrated that treatment with ruxolitinib resulted in reduction of splenomegaly and improvement in systemic symptoms in a significant proportion of MF patients. However, some

* Corresponding author at: Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, 8, Ha'Aliya Street, Haifa 31096, Israel.
E-mail address: lavi.noa@gmail.com (N. Lavi).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.leukres.2015.08.003
0145-2126/

Table 1
Baseline characteristics of patients in pivotal randomized control trials and the current study.

	Current study $N=93$	COMFORT I $N=155$	COMFORT II $N=146$
Median age [range] years	67 [32–84]	66 [43–91]	67 [35–83]
Myelofibrosis subtype (%)			
Primary myelofibrosis	47.3	45.2	53
Post polycythemia vera myelofibrosis	31.2	32.3	33
Post essential thrombocythemia myelofibrosis	18.3	22.6	14
Myeloproliferative neoplasm-unclassified	3.2	Not included	Not included
Risk status (%)			
DIPSS for current study, IPSS for COMFORT I and II			
Low	1.1	Not included	Not included
Intermediate-I	11.8	Not included	Not included
Intermediate-II	62.4	41.3	40
High	24.7	58.1	60
Previous hydroxyurea use (%)	74	67.1	75
Median platelet count [range] $\times 10^{-9}$ L	230 [50–980]	262 [81–984]	244
Median Hemoglobin [range] (g^{-1} L)	105 [70–169]	105 [66–170]	Not available
Median palpable spleen length [range] (cm)	12 [0–34]	16 [0–33]	14 [5–30]
JAK2 V617F positive (%)	73.8	72.9	75

controversy exists regarding the ultimate usefulness of this drug in clinical practice because of issues related to the proportion of patients remaining on therapy, response duration and the effect on overall survival [8–11].

While narrow eligibility criteria improve the validity of randomized clinical trials (RCT), these could limit the generalizability of study findings to the general population. We therefore retrospectively collected data on patients with MF receiving ruxolitinib in Israel after its approval by the Ministry of Health with the aim of determining the efficacy and tolerability of ruxolitinib in routine clinical practice.

2. Patients and methods

Patients with World Health Organization-defined primary myelofibrosis (PMF) or International Working Group for Myelofibrosis Research and Treatment (IWG-MRT)-defined post polycythemia vera myelofibrosis (PPV-MF) or post essential thrombocytosis myelofibrosis (PET-MF) treated with ruxolitinib for at least 3 months were included in the study.

Thirteen Israeli medical centers participated in the population study, which was approved by the corresponding Institutional Review Boards. Baseline clinical data were collected by retrospective individual chart review.

Response to treatment was reported by the treating physicians and analyzed as categorical variables (yes or no for constitutional symptom improvement and spleen size reduction), and as a continuous variable (decrease in spleen size in cm below the costal margin by palpation). Response to treatment was defined as symptomatic improvement, spleen size reduction or both.

2.1. Statistical analysis

Mann–Whitney *U*-test or *T*-test was used to determine significant differences between groups of patients. Differences between categorical parameters were tested by the Fisher exact test.

Logistic regression analysis was used to predict response to ruxolitinib by several independent parameters.

3. Results

3.1. Baseline characteristics

We identified one hundred and two patients beginning ruxolitinib treatment for MF between January 2012 and April 2014. The initial dose of ruxolitinib was the only parameter evaluated in all the 102 patients who started the medication during the study period. Ninety three patients who were treated for more than 3 months were included in the analysis of the treatment efficacy and toxicity. The remaining nine patients were not included into the efficacy analysis because of the short duration of their therapy. Six of these patients had started ruxolitinib 1–2 months prior to data collection. The other 3 of these 9 patients discontinued ruxolitinib after 1–2 months of treatment. Two of them stopped therapy due to its toxicity (anemia) and one patient died from pneumonia. Baseline characteristics of the study cohort are shown in Table 1. Median age at ruxolitinib initiation was 67 years (range 32–84), and therapy was commenced at a median of 6.5 years (range 0–24 years) after MF diagnosis. MF was most commonly primary, followed by PPV-MF and PET-MF in 47.3%, 31.2% and 18.3% of patients, respectively. Three patients (3.2%) were diagnosed with myeloproliferative neoplasm unclassified. The majority of included patients carried the JAK2 V617F mutation (73.8%). The baseline hemoglobin level was less than 100 g/L in 37 (39%) and less than 80 g/L in 10 patients (10%), while the platelet count was less than $100 \times 10^{-9}\,L^{-1}$ in 12 (13%). The Dynamic International Prognostic Scoring System (DIPSS) risk score before treatment initiation was intermediate-2 in 62.4% and high in 24.7% of patients. Six patients did not have splenomegaly at ruxolitinib initiation.

3.2. Indications for ruxolitinib treatment

Indications for treatment were constitutional symptoms in 14 patients (15%), symptomatic splenomegaly in 6 patients (6%) and both in 71 patients (76%). Two patients received ruxolitinib for other indications (non-constitutional symptoms and refractory thrombocytosis).

3.3. Ruxolitinib initial doses and dose modifications

Data on the initial dose of ruxolitinib were collected in all the 102 patients who started this therapy during the study period. The median initial dose of ruxolitinib was 30 mg per day (range 10–40 mg). The starting dose in most patients (61%) was in accordance with the company recommended dose depending on the platelet count, while 29% of the patients started ruxolitinib at a dose lower than and 10% started at a dose higher than the recommended one (Table 2).

Ninety three patients treated for more than 3 months were evaluated for ruxolitinib dose adjustment. Dose reductions were necessary in approximately 40% of patients. The starting dose was continued in 30% of patients, while 15% had an increase in the initial medication dose (Figs. 1 and 2).

3.4. Treatment efficacy

After a median treatment duration of 11 months of (range 3–31 months), 88.2% of patients had responded to therapy. Improvement in constitutional symptoms was seen in 76/90 patients (84.4%), and

Please cite this article in press as: M.H. Ellis, et al., Ruxolitinib treatment for myelofibrosis: Efficacy and tolerability in routine practice, Leuk Res (2015), http://dx.doi.org/10.1016/j.leukres.2015.08.003