Impact of ruxolitinib on survival of patients with myelofibrosis in the real world: update of ERNEST Study

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Abstract:

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To the Editor

Survival in patients with myelofibrosis (MF) is shorter compared with the general population, with median overall survival (OS) of 6-7 years\(^1\); MF is also associated with profound negative effects on quality of life. Conventional treatment options for MF have limited efficacy in improving symptomatic manifestation and lack disease modifying potential; the only curative approach is stem cell transplantation, reserved to a minority of patients. The JAK1/2 inhibitor ruxolitinib (RUXO) has shown activity by reducing splenomegaly and improving constitutional symptoms, favorably impacting on quality of life. Although post-hoc analysis of pooled data from the randomized COMFORT-I and COMFORT-II trials reported improvement of survival\(^2,3\), this remains debated since the studies were not powered to show effects on OS. In 2013 the ERNEST project -whose acronym defines its purpose: European Registry for myeloproliferative Neoplasms: towards a better understanding of Epidemiology, Survival and Treatment\(^3\)- was founded to prospectively enroll MF patients with the epidemiological goal of assuring reliability, representativeness and comparability of real-world data across international centers with expertise in the management of MF. The project, promoted by the European LeukemiaNet (ELN), was coordinated by FROM - Foundation for Research at Papa Giovanni XXIII hospital in Bergamo (Italy) and supported by Novartis through a research collaboration. From February 2013 to May 2014, the ERNEST registry enrolled 1292 MF patients from 13 centers in 5 European countries. Current study describes updates (cut-off at December 31, 2018) of those patients who were alive and/or in active surveillance on November 2014\(^4\) in ERNEST centers from Italy, Spain and Sweden, which have agreed to update their respective data. Consequently, 282 out of 1292 patients were excluded from the present analysis. Institutional Review Board and Ethical Committee of each participating Centre approved the study, which was conducted in accordance with the Declaration of Helsinki.

This manuscript reports analysis of 1010 patients with the aim to analyze the impact of RUXO on OS by using prospectively collected real-world data.

Statistical analysis was carried out at the bio-statistical laboratory of FROM. Continuous variables were summarized with median along with interquartile range (IQR), and categorical ones were presented as frequencies and percentages. Characteristics of the study population were stratified for survival, and differences between groups were tested with the \(\chi^2\) test (or Fisher’s exact test where appropriate) or rank-sum test for categorical or continuous variables,
respectively. OS was estimated by Kaplan–Meier method and analyzed according to MF diagnosis, prognostic risk category (IPSS\textsuperscript{5}, DIPSS\textsuperscript{6}, MYSEC-PM\textsuperscript{7}) and treatment exposure, with the log rank test. Using a multivariable Cox proportional hazard model, association with OS was evaluated for the following variables: age, gender, MF diagnosis, year of diagnosis, prognostic risk category and cytoreductive therapy. A propensity score (PS) matching analysis\textsuperscript{8} was performed to balance patients who had been treated or not with RUXO, by forming matched sets of 1 treated and 1 randomly-sampled, non-treated, patient (1:1 matching) who shared similar PS. The PS was estimated by logistic regression of exposure to RUXO on baseline covariates at the time of treatment start. Matching was done using the nearest neighbor method without replacement and with caliper of width equal to 0.2 of the pooled standard deviation of the PS logit. For all tested hypotheses, two-tailed p values < 0.05 were considered significant. Statistical analysis was performed using STATA Software, release 16 (StataCorp LP, College Station TX, USA).

The updated ERNEST registry cohort comprised 1,010 MF patients: 584 (57.8%) with primary MF (PMF), 207 (20.5%) with post-essential thrombocytopenia (PET)-MF and 219 (21.7%) with post-polycythemia vera (PPV)-MF. Overall, 365 patients had died by the end of 2014; clinical data and outcome of the remaining 645 cases were updated to the end of 2018. Patients’ characteristics are shown in supplementary Table S1. The median age was 63.7 years, 59.9% were male. According to the diagnostic period, 237 (23.5%) patients were diagnosed from 2001 to 2004, 371 (36.7%) 2005 to 2008 and 402 (39.8%) 2009 to 2012. In the overall cohort, 598 patients (59.2%) at enrollment had received cytoreduction therapy; 487 patients (48.2%) had received Hydroxyurea (HU) only, while 108 patients received RUXO. Of the latter, 69 (64%) were previously treated with HU and 2 (1.9%) with interferon. Among patients treated with cytoreduction during follow-up, at first administration, patients treated with RUXO were significantly younger (64.5 vs 67.0 years, p=0.02), had more commonly massive splenomegaly (≥20 cm from left costal margin (LCM)) 36.6% vs 6.0%, p<0.001) and suffered from constitutional symptoms (80% vs 49.1%; p=0.03) compared to those treated with HU only. Time to first treatment with HU (median time 0.0 year, range 0.0-1.2 years) was significantly shorter than RUXO (median 4.5 years, range 2.2-6.7; p<0.001). After a median follow-up of 5.2 years (range 2.3–8.2), 625 deaths occurred with a mortality rate (per 100 person-years) of 10.9 (95%CI 10.1-11.8). Median OS was 6.2 years (95%CI 2.8-12.6), with no significant difference according to diagnostic categories (P=0.49). Median OS of the entire study population, according to IPSS category considered at diagnosis, was not reached for low-risk, 7.7 years (95% CI: 3.8-12.9) for intermediate-1, 5.0 years (95% CI: 2.2-9.1) for
intermediate-2, and 2.8 years (95% CI: 1.5-5.0) for high-risk category (p<0.0001). According to MYSEC-PM score, the median OS of sMF was not reached for low-risk, 6.0 years (95% CI: 2.9-10.5) for intermediate-1, 3.2 years (95% CI: 1.8-6.0) for intermediate-2, and 1.8 years (95% CI: 0.7-7.1) for high-risk category (p<0.001). Median OS was significantly longer in patients treated with RUXO compared to HU (6.7 vs 5.1 years; P=0.001). Notably, in the entire study population the prognostic relevance of RUXO exposure was mostly restricted to patients that, at the time of treatment start, were in DIPSS higher risk categories (Intermediate-2 plus high-risk; HR 0.53; 95% CI, 0.35-0.82; P=0.004). In a multivariable Cox regression model adjusted for covariates measured at treatment start, age (linear covariate, HR: 1.03, 95% CI: 1.02-1.04, p<0.001), male gender (HR: 1.58, 95% CI: 1.24-2.03, p<0.001) and high DIPSS category (HR: 2.96, 95% CI: 1.63-5.38, p<0.001) were identified as factors negatively affecting OS. Conversely, protective variables were a more recent diagnosis (2009-2012 vs 2001-2004; HR: 0.47, 95% CI: 0.35-0.65, p<0.01) and exposure to RUXO (HR: 0.62, 95% CI: 0.40-0.95, p=0.029).

To assure comparability between patients treated with HU and RUXO, we conducted a PS matching analysis. Characteristics of patients treated with HU only and RUXO (received either as first line and second line after HU) before and after PS matching are reported in Supplementary Table S2 (n=50 in each group, regardless the diagnosis). Median OS was 7.7 years in patients treated with RUXO compared to 3.4 years in patients treated with HU-only (p=0.002; Fig.1). Furthermore, there was no difference in median OS depending on RUXO used as first line (n=23/50, 46%) or after HU (n=27/50, 54%): 6.4 vs 7.8 years, respectively (p=1.00).

In summary, in this long-term patient follow-up registry data, we show that HU remains the most frequently used treatment for MF patients in European countries, although a steady increase in ruxolitinib usage was observed in last years. Compared to HU, RUXO treatment was associated with significant benefit in terms of OS in multivariate analysis; benefit was also seen in PS analysis within the limits of small numbers. Our study offers a unique opportunity to provide real-life evidence on the impact of ruxolitinib on survival in patients with primary or secondary MF.
Data sharing statement

For data sharing, contact the corresponding author: tbarbui@fondazionefrom.it.

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Authorship Contributions

PG interpreted the data, and wrote the letter. TB conceived and designed the study, supervised the analysis and critically revised the letter. AG and AC contributed to dataset preparation, planned and performed statistical analyses. AM directed the project. AMV interpreted the data and critically revised the letter. PG, CM, BM, ER, AT, MCF, HP, CP, FM, DV, AR, FP, AAL and BA collected patient’s data of the study. All authors discussed the results and implications and commented on the manuscript. The authors had full editorial control of the paper and provided their final approval of all content.

Disclosure of Conflicts of Interest

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Figure 1. 10-year Overall Survival after start of hydroxyurea and ruxolitinib in the propensity score-matched groups.

Kaplan-Meier survival curves according to time to first administration of ruxolitinib (red solid line) or hydroxyurea (blue dotted line) after diagnosis. Numbers at risk are plot every year. P-values are calculated by log-rank test.
Figure 1

Overall Survival - PS matching

Survival probability

Years after start of hydroxyurea/ruxolitinib

N at risk

|           | HU | Ruxo |
|-----------|----|------|
| at risk   | 50 | 50   |
| 0-2 years | 30 | 42   |
| 2-4 years | 16 | 33   |
| 4-6 years | 6  | 25   |
| 6-8 years | 1  | 1    |

p = 0.002