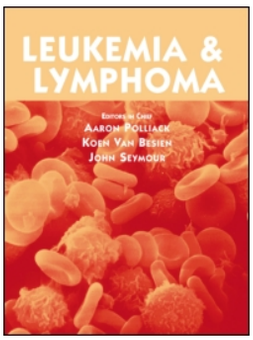

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Ruxolitinib – better prognostic impact in low-intermediate 1 risk score: evaluation of the 'rete ematologica pugliese' (REP) in primary and secondary myelofibrosis

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ABSTRACT

We evaluated ruxolitinib in 65 patients with myelofibrosis according to age, sex, time of diagnosis, grade of fibrosis, prognostic score risk, Janus kinase (JAK) status, primary or secondary myelofibrosis, previous treatment, and dosage. Outcome measures were response rate, time to response, duration of response, and event-free survival and survival. Kaplan and Meier curves show a significant difference in event-free survival according to the prognostic score, in favor of patients with low int1 ($p = 0.0009$). The Cox stepwise model confirmed the result, the int2 high-risk score being the most powerful negative independent parameter (0.001), followed by JAK (0.008); other parameters, such as diagnosis more than 5 years earlier, grade III–IV fibrosis, and ruxolitinib dose have a negligible impact. Time to response was shorter ($p = 0.001$) in primary myelofibrosis. In conclusion, ruxolitinib is effective, with a better outcome in patients with a low-int1 risk score. This may suggest considering an earlier administration in the disease course.

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Myelofibrosis; prognostic groups; response to ruxolitinib

Introduction

Myelofibrosis is a progressive hematological disease characterized by splenomegaly and debilitating symptoms, including fatigue, weakness, abdominal pain, cachexia, weight loss, night sweats, pruritus, and bone pain. Anemia, thrombocytosis or thrombocytopenia, leukocytosis or leucopenia may be present, and a blastic final transformation is one of the causes of death, among others due to impairment of the heart, liver, or renal function. Massive splenomegaly has a key role in decreasing survival and the therapy is designed to contain the progressive spleen volume increase and to improve the impaired hematological parameters. In fact, hydroxyurea is largely used as chemotherapeutic agent in patients with increasing splenomegaly with primary myelofibrosis, and in patients with essential thrombocythemia or polycythemia, even if its use is frequently limited by anemia and thrombocytopenia. Survival ranges from 2 to 10 years depending on prognostic factors and the disease score risk [1]. Ruxolitinib, a potent inhibitor of JAK pathways playing a key role in the proliferation of myelofibrosis and in the production of proinflammatory cytokines, which have a role in myelofibrosis via the JAK-1 and JAK-2 transducer signal, is now approved for the treatment of intermediate and high-risk patients, following the registration studies COMFORT I [2] and II [3]. Ruxolitinib is particularly indicated in patients with a large spleen because it induces a fast and durable volume reduction and reduces debilitating symptoms such as weakness, abdominal pain, weight loss, night sweats. Its efficacy was independent of the presence or absence of the V617F mutation [4] or of whether myelofibrosis was primary or secondary to thrombocythemia or polycythemia vera [2,3]. When considering the potentially better outcome of patients treated by ruxolitinib versus other therapies [3], it is important to understand which patient's subsets may benefit from ruxolitinib and with what timing. In fact, limited experience is available for the low-int1 risk score. To further this experience, we analyzed patients treated in the last 5 years in several institutions of the Apulia region in Italy; the aim of the study is to provide guidance for assigning ruxolitinib

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to patients with myelofibrosis in a synergic treatment plan, adaptable according to age and different prognostic categories.

Materials and methods

Patients

Six institutions of the Apulia region in the south of Italy participated in this study through the cooperative scientific network of the 'Rete Ematologica Pugliese.' All consecutive patients (Table 1) with primary myelofibrosis or secondary to thrombocythemia and polycythemia vera, previously treated by standard treatments or never treated, who entered the treatment with ruxolitinib since 2012 were enrolled in this evaluation. The study data were acquired after obtaining informed consent from each patient. The diagnosis of myelofibrosis, dated since the first bone biopsy proving the presence of fibrosis in the marrow, was accrued and clinical and hematologic data were confirmed to be compatible. This procedure was adopted for both primary myelofibrosis and secondary to thrombocythemia or polycythemia. The accrual to treatment with ruxolitinib started in 2012 when the drug became available and was freely given by Novartis oncology for all patients. As from March 2014, the NIH (National Institute for Heath) approved the treatment of patients with a high-int.2 score. Table 1 illustrates the patients characteristics. In total, 65 patients were enrolled, aged between 31 and 85 years (mean 66.2 years); 34 (52%) were males and 31(48%) females. Forty-three patients had primary myelofibrosis (66%); 16 patients (25%), mean age 64.7 years, had myelofibrosis secondary to thrombocythemia and six patients (9%) had myelofibrosis secondary to polycythemia vera. All patients had a palpable spleen at least 5 cm below the costal margin without signs of deep thrombosis of the portal or splenic veins. The diagnosis of myelofibrosis was made on bone biopsy and the grading of fibrosis was reported according to World Health Organization (WHO) criteria [5] between 1 and 4. The International Prognostic Score System [1] was also applied, grading the disease as low, intermediate I, intermediate 2, or high-risk score. Patients included in the evaluation had a life expectancy of more than 6 months, a performance status on the Eastern Cooperative Oncology Group criteria [6] of three or less, the presence of less than 10% of circulating blasts, a platelets count of more than $50 \times 10^3/\mu L$, a spleen size of at least 5 cm below the left costal margin. The eligibility criteria for entry to treatment with ruxolitinib were a normal liver and renal function.

Table 1. Patients characteristics.

Total	65
Diagnosis of myelofibrosis	2002–2015
Mean age (range)	66.2 y (31–85)
Males/females	34/31
Primary myelofibrosis	43
Secondary myelofibrosis:	
Thrombocytemia/polycythemia	16/6
Spleen size (5–22 cm from costal margin)	65
Grade of fibrosis I/II/III/IV	10/18/26/12
Score llow/int1/int2/high	10/12/24/19
JAK+/JAK−	49/16
Hydroxyurea yes/no	39/26
Platelets >200/100–200/100–50/$10^3/\mu L$	41/19/5

Prognostic evaluation

The patients were grouped (Table 2) according to age over or up to 65 years, sex, time of diagnosis of myelofibrosis, subdividing patients between those diagnosed before 2011 or after (more or less than 5 years), primary or secondary, grade of fibrosis I–II versus III–IV, prognostic score low-intermediate 1 versus high-intermediate 2, the presence or not of the JAK-2 mutation, previous treatment or not with hydroxyurea, primary myelofibrosis versus secondary to polycythemia or thrombocythemia, and RUXOLITINIB dosage 40 mg per day versus less. Outcome measures were the response rate in terms of a reduction in spleen volume, freedom from negative events, and survival. In addition, we did a comparative evaluation of the speed of response according to the above prognostic groups. The reduction in spleen volume as the criterion for response was considered as an objective parameter evaluated by ultrasound, calculating volume by length, transverse

Table 2. Response, mean time to response.

Prognostic groups (No of Patients)	Response %	*p*	Time to response (weeks)	*p*
Equal or <65 versus >65 years (31 versus 34)	79% versus 66%	0.07	7.9 versus 7.8	0.9
Males versus females (34 versus 31)	68% versus 77%	0.08	7.8 versus 7.9	0.9
<5 years versus >5 years (33 versus 32)	80% versus 66%	0.06	6.9 versus 10.2	0.005
Fibrosis 1–2 versus 3–4 (28 versus 37)	77% versus 68%	0.08	7.8 versus 8.2	0.7
Score low int1 versus high int2 (22 versus 43)	87% versus 66%	0.005	8.1 versus 7.8	0.9
JAK + versus JAK − (49 versus 16)	78% versus 56%	0.06	8.2 versus 6.3	0.06
Primary versus secondary MF (44 versus 21)	74% versus 68%	0.3	6.0 versus 11.4	0.001
Hydroxyurea versus no (39 versus 26)	64% versus 90%	0.06	8.1 versus 7.8	0.8
Ruxolitinib 40 mg versus <40 mg (36 versus 29)	71% versus 74%	0.7	8.3 versus 7.6	0.5

diameter, and anteroposterior width. A reduction by at least 30% of spleen volume was considered an objective response; the time to reach this response was calculated from the beginning of ruxolitinib treatment. Freedom from negative events was taken as the interval time from the beginning of ruxolitinib to the progression of disease, death, or severe side effects ascribed to ruxolitinib and requiring interruption of therapy; negative events due to ruxolitinib during therapy were subjective symptoms or objective signs such as hematological alterations. Survival was calculated from the beginning of ruxolitinib treatment until death.

Therapy with ruxolitinib

The basic dosage of ruxolitinib was 20 mg twice a day, 40 mg total, for patients with normal hematological parameters, reduced to 30 mg/day in patients with a platelet count of between $100 \times 10^3/\mu L$ and $200 \times 10^3/\mu L$, and 20 mg/day in patients with platelet levels between $100 \times 10^3/\mu L$ and $50 \times 10^3/\mu L$. The hemoglobin level was not considered a limit for ruxolitinib dosage. Adjustments of dose were done twice monthly following the hematological parameters and clinical tolerance. The therapy was maintained, with a reduction to half the previous dose of ruxolitinib in patients whose platelets reduced to less than $50 \times 103/\mu L$ and were shown to be responsive. In cases of resistance or progression the drug was withdrawn. The drug was discontinued also in cases of severe side effects or complications. A dose increase from baseline to a maximum of 40 mg was made in patients showing improved hematological parameters. The need for transfusion of packed red cells following ruxolitinib was not considered a major side effect requiring discontinuation or reduction of therapy. The need for transfusions of concentrated platelets units if platelets dropped under $20 \times 10^3/\mu L$ was recorded and considered a parameter for therapy interruption and perhaps complete discontinuation.

Follow-up, evaluation, time to response, and duration of response

Patients were followed fortnightly at each institution for the first 6 months and then monthly, by physical examination and blood screening, evaluating hematological parameters, renal and liver function. The heart was evaluated when necessary. Follow-up was calculated from the beginning of ruxolitinib to the last follow-up or to a negative event, such as disease progression or toxic effects, requiring interruption of the drug, or death. The response was evaluated every 15 days from the start of therapy and accrued when a reduction in spleen size by at least 30% was recorded. The time for this response was calculated for every responder patient and reported according to the prognostic risks group. The duration of response was the time from the recognition of response to its loss.

Toxicity and side effects

Toxicity was expected, as well as hematological alterations due to ruxolitinib such as anemia, thrombocytopenia, and leucopenia with an absolute reduction of neutrophils. However, hematological toxicity was considered a reason for reduction or interruption of therapy in cases of thrombocytopenia; anemia was not considered a criterion for modifying therapy and leucopenia was generally negligible (Table 4). Side effects were reported as modifications of clinical status under therapy with ruxolitinib or alterations of relevant parameters for renal, liver, pancreatic and cardiac function (Table 4)

Statistical analysis

Chi-square p value was calculated from contingency tables for response, mean time to response and duration of response (Table 2) and for the incidence of negative events due to disease such as progression or death (Table 3), using Fisher's exact test [7] which is particularly indicated for small samples [8]. Response was evaluated on the reduction of spleen volume by ultrasound, considered as a reduction by 30% or more of the original volume. Time to response was calculated from the start of therapy with ruxolitinib, and the reduction of spleen size was expressed as the median weeks necessary. The duration of response was calculated from the time of response to a re-growth of the spleen, death, or discontinuation of ruxolitinib. Differences were also calculated as survival and event-free survival (EFS) according to the prognostic risk group, estimated by the Kaplan–Meier method. Risk groups were those reported in Table 1. A further analysis was done by Cox regression model to assess the predictive power of each variable for survival and event-free survival; significance was set at $p < 0.05$.

Results

Prognostic groups, as reported in Table 2, showed a homogeneous distribution of the patients for age equal or <65 years or >65 years, sex, time of diagnosis <5 years or >5 years. Fibrosis grade III–IV was present

Table 3. Negative events due to disease, progression, or death.

Prognostic groups	Progression	*p*	Death	*p*
Equal or <65 versus >65 years	6 versus 7 (19% versus 21%)	0.9	0 versus 9 (0% versus 26%)	0.05
Males versus females	7 versus 6 (21% versus 19%)	0.9	6 versus 3 (18% versus 10%)	0.5
<5 years versus >5 years	6 versus 7 (21% versus 22%)	0.8	4 versus 5 (12% versus 16%)	0.9
Fibrosis 1–2 versus 3–4	5 versus 8 (18% versus 21%)	0.7	2 versus 7 (7% versus 18%)	0.09
Score low int1 versus high int2	1 versus 12 (5% versus 28%)	0.001	1 versus 8 (5% versus 19%)	0.05
JAK + versus JAK -	8 versus 5 (16% versus 31%)	0.3	3 versus 6 (6% versus 38%)	0.05
Primary versus secondary MF	9 versus 4 (20% versus 19%)	0.2	6 versus 3 (14% versus 29%)	0.06
Hydroxyurea versus no	9 versus 4 (23% versus 15%)	0.2	7 versus 2 (18% versus 8%)	0.06
RUXOLITINIB 40 versus <40 mg	9 versus 4 (25% versus 14%)	0.2	4 versus 5 (11% versus 19)	0.9

Table 4. Hematological needs and clinical status before, during, and after ruxolitinib.

Hematological need	Before	During	After (>8 weeks follow-up)
Transfusion PRC	15 (23%)	24 (37%)	10 (15%)
Erythropoietin	12 (18%)	16 (25%)	8 (12%)
Transfusion PLT	None	1 (2%)	None
Neutropenia	none	1 (2%)	None
Clinical status:			
Weight loss	13 (20%)	8 (12%)	3 (5%)
Asthenia	32 (49%)	30 (46%)	12 (18%)
Low-grade fever	9 (14%)	7 (11%)	1 (2%)

PRC: packed red cells; PLT: platelets.

in 58% of patients and grade I–II in 42%; there was a major difference between patients with a high-int.2 (43–66%) versus low-int.1 score (22–34%). Patients were prevalently JAK + (49–75%), and 68% (43) had primary myelofibrosis versus 32% (22) secondary to polycythemia and thrombocythemia. More than half of the patients (39–60%) had already been treated with hydroxyurea and 55% (36) of patients were given 40 mg RUXOLITINIB versus 45% (29) 30 mg or less. The response and time to response according to age, sex, primary or secondary myelofibrosis and dose of ruxolitinib showed negligible differences. Some positive impacts, but no significant differences, were recorded in the groups with a diagnosis made less than 5 years before, grade of fibrosis 1–2, JAK + and no previous treatment with hydroxyurea. The only parameter, which resulted significantly positive for response, was a low-int1 score, with an 87% response rate versus 66% for a high-int2 score ($p < 0.005$). The mean time to response (Table 2) in terms of a minimum reduction by 30% of spleen volume was generally nearly 8 weeks, but we found a difference, according to the time of diagnosis, with a significant reduction of the time to response in patients diagnosed in the last 5 years, being 6.9 weeks versus 10.2 weeks for those diagnosed more than 5 years before ($p < 0.005$). The same was found for patients with primary myelofibrosis, who had a shorter time for response, 6 weeks, versus 11.4 weeks for those with secondary myelofibrosis ($p < 001$). The duration of response is still under evaluation because most responder patients are still in response and only eight lost the response; seven of them had a int2-high-risk score. In any case, the low-int1 score has a chance of a greater duration of response than the high-int2 score, 21.9 months versus 17.7 months ($p < 0.05$), primary myelofibrosis has less chance of duration of response than secondary myelofibrosis, 18.7 months versus 21.9 months ($p < 0.05$), as also patients receiving less than 40 mg/day ruxolitinib, 17 months versus 21.4 months ($p < 0.02$). Negative events due to disease (Table 3) were considered as progression and death. Two patients included in the low-int1 prognostic score group who responded to therapy with ruxolitinib underwent bone marrow transplantation, which was successful in terms of take and GVHD. After 13 and 15 months follow-up following transplantation, they show no evidence of disease recurrence. Age over 65 years was significantly associated with death ($p < 0.05$) but not progression. The only parameter associated to the risk of disease progression was the high-int2 score, with 12 events versus 1 in the low-int1 ($p < 0.001$). Death was also associated with a high-int2 score, eight events (19%) versus 1 (5%) in low-int1 patients ($p < 0.05$) and was associated with JAK, showing a substantial difference, 38% in JAK – versus 6% in JAK + patients ($p < 0.05$). Event-free survival and survival were calculated for the prognostic groups, including sex, grade of fibrosis, score risk, JAK mutation and ruxolitinib dose. Kaplan and Meier curves (Figures 1 and 2) show a significant difference for event-free survival only for the prognostic score, in favor of patients with low-int1 ($p = 0.0009$) although survival was not significantly different, but a negative trend was recorded for the high-int2 group. The Cox stepwise model confirmed the result, the int2-high-risk score being the most powerful negative and independent parameter (0.001) for prognosis, followed by JAK (0.008). These parameters had a greater weight than other parameters such as diagnosis made more than 5 years earlier (0.171) grade III–IV fibrosis (0.167) and dose of ruxolitinib less than 40 mg (0.628). Hematological support before, during and after 8 weeks of therapy with ruxolitinib and modifications of clinical symptoms are summarized in Table 4. Packed red cell transfusions were needed before therapy in 23% of patients, which increased at the beginning of therapy with ruxolitinib to 37% and dropped to 15% following a

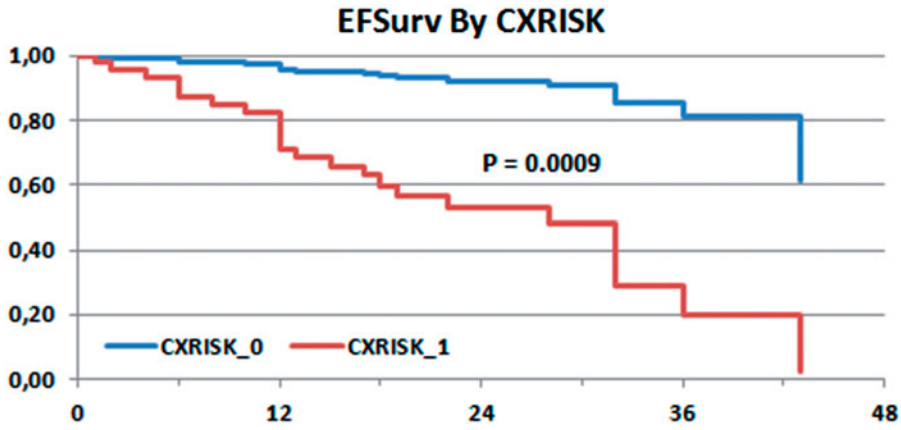

Figure 1. Event-free survival according to score risk. CXRISK_0 = low-int1, CXRISK_1 = high-int2.

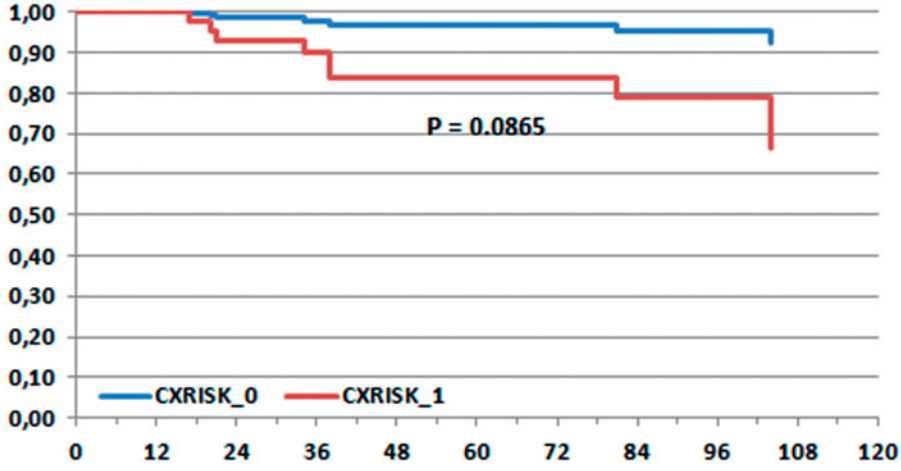

Figure 2. Survival according to score risk. CXRISK_0 = low-int1, CXRISK_1 = high-int2.

spleen volume decrease. Only one patient needed platelets transfusions, and only one had neutropenia. Clinically relevant symptoms at the beginning of therapy were weight loss, asthenia and mild fever; all three symptoms reduced significantly and progressively during the therapy in most patients. Table 5 shows side effects complained of by patients during therapy with ruxolitinib; arthralgia, myalgia, headache were more common but limited to 5% of patients. In general, ruxolitinib is well tolerated without relevant side effects.

Table 5. Symptoms and side effects during treatment with ruxolitinib.

Myalgia	3 (5%)
Arthralgia	2 (3%)
Headache	3 (5%)
Asthenia	1 (2%)
Herpes Zoster	1 (2%)
Gastric intolerance	1 (2%)
Platelets reduction	3 (5%)
Mild anemia	3 (5%)

Discussion

The issue of what is the best use of ruxolitinib in the context of myelofibrosis, either primary or secondary to polycythemia or thrombocythemia, is the focus of debate; early, in low-int1 disease or later, in high-int2 disease? The efficacy of ruxolitinib in improving symptoms, reducing spleen volume and perhaps increasing survival has been demonstrated in two landmark studies, COMFORT I and COMFORT II [2,3], in which ruxolitinib was superior to placebo [2], and best available therapy [3]. However, the awareness that ruxolitinib is not curative in myelofibrosis leads us to consider it as a new weapon to be allocated in the best way according to age, previous therapy, timing, disease score, clinical symptoms, type of disease. A further consideration is the dosage of therapy and possible modulations according to the number of platelets, as suggested in a recent work [9], and the association with other therapies such as erythropoietins or hydroxyurea. Finally, the question of the role of ruxolitinib as priming for bone marrow transplantation. In this study, in support of previous experiences [10], we investigated what happens in real life in several general hematology centers, where patients are treated as best they can on

the basis that the therapy for each patient is the rational product of reasoned debate and experience. In our study, patients were analyzed according to potentially prognostic groups, which were chosen rationally in order to template a possible homogeneous approach, based on differences between the groups. We found that results in patients under 65 years or over 65 years are quite similar, as also the response rate to ruxolitinib. Obviously, the policy in younger patients may be different in terms of management, and bone marrow transplantation may follow the priming therapy with ruxolitinib [11,12]. It was confirmed that a low or int1 prognostic score has a better response rate to ruxolitinib and a better duration of response; moreover, the better EFS is a strong argument for modifying the approach to the treatment of myelofibrosis. The recognition of a positive impact in these subsets of patients may be due to earlier start of therapy in the course of the disease or to less severe disease. If this second hypothesis is the case, it opens a good perspective for future trends. Prospective trials, finalized to see whether an earlier start of therapy in the course of myelofibrosis could lengthen the duration of response and survival, are warranted. The use of ruxolitinib before bone marrow transplantation as priming therapy in order to reduce the spleen and disease volume could be another matter of discussion and prospective trials in young patients. Another finding was the longer time required for response in patients with secondary myelofibrosis; we explain this by recalling that fibrosis in this subset of patients has a long-lasting history of formation and deposit, and generally, many years pass before a secondary myelofibrosis is suspected. This fibrosis is more stable and a longer time and therapy are needed to achieve a spleen reduction. When planning a therapeutic approach this must also be borne in mind, especially in the context of priming therapy for bone marrow transplantation. The spleen volume is correlated with symptoms, such as weight loss, due to a reduced food intake because of the stomach compression, especially in older patients. But it is not yet known whether in older patients and it is better to start therapy before symptoms appear; certainly our demonstration of a better outcome in patients with a low-int1 score suggests that therapy with ruxolitinib may be more efficacious earlier in the disease course. This consideration is supported by a recent report on the treatment of low-int1 risk patients, in which the authors concluded that ruxolitinib is beneficial in this subset of patients [13]. Our data show that the response rate to ruxolitinib is lower in patients already treated with hydroxyurea, although the results are not significant. This is understandable because already treated patients are generally those diagnosed more than five years before that generally have more advanced disease. A further consideration is that the reported hematological toxicity generally affects patients with more advanced disease [9,14]. Our patients series with anemia requiring transfusions before the start of ruxolitinib mostly included patients with a high-int2 risk and their need increased during the first weeks of therapy. A lower need for transfusions was recorded in patients responding to ruxolitinib, together with a reduction of symptoms. An association of ruxolitinib to erythropoietin may be useful in this phase, as suggested in another report [15]; our experience shows that some patients become sensitive to erythropoietin following ruxolitinib. As regards the hematologic status, we modulated the dose of therapy according to the presence of anemia and platelets number; patients who received less than 40 mg/day of ruxolitinib had a significantly shorter duration of response even if the response rate was similar in both patients groups. The patients receiving less than 40 mg/day are those with some hematological impairments and likely also with a worse risk score. Finally, as regards patients with JAK + or −, in our experience JAK – patients had an apparently worse outcome and higher death rate. It is not known whether, in patients with more advanced disease, there may be a down-regulation of the V617F mutation and an emerging clone that is responsible for progression and death. Finally, the idea of using ruxolitinib in priming for bone marrow transplantation in younger patients could not be explored but further observations in larger patients series are warranted.

In conclusion, our study demonstrates that ruxolitinib is an effective drug in myelofibrosis, either primary or secondary to polycythemia or thrombocythemia, in a variable proportion of patients. Outcome measures depended on the prognostic group, showing a better outcome for the low-int1 score risk group, worse for JAK patients. The major issue still to be addressed is when the best timing for ruxolitinib may be. Our data support the idea that prospective studies on patients in earlier phases of disease are warranted.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at http://dx.doi.org/10.1080/10428194.2016.1189547.

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