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A comprehensive review and analysis of the effect of ruxolitinib therapy on the survival of patients with myelofibrosis

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Myelofibrosis is a hematological malignancy with a median survival of approximately 5 to 7 years. Allogeneic stem cell transplantation is the only therapeutic modality that provides a cure for myelofibrosis patients. Recently, ruxolitinib has been shown in 2 phase 3 studies to be effective in reducing splenomegaly and improving symptoms in myelofibrosis patients. Although conventional markers of disease burden (marrow histopathological features, cytogenetic and molecular markers, and reversal of cytopenias) were not uniformly improved, a survival advantage in favor of ruxolitinib therapy was demonstrated. The use of historical control cohorts to compare survival was implemented in 2 different analyses of patients enrolled in the phase 1/2 studies and has further added fuel to the controversy surrounding the significance of this survival advantage. Ruxolitinib therapy results in a dramatic reduction in circulating proinflammatory cytokine levels, which has been associated with improvement in symptoms and performance status and may provide a link to improved survival. We analyze the various data published and place in perspective the significance of the prolongation of survival associated with ruxolitinib therapy. This critical review of these data may allow physicians to more rationally assess the benefits that can be anticipated with the appropriate use of this therapy. (*Blood*. 2013;121(24): 4832-4837)

Introduction

Advanced forms of myelofibrosis (MF), a chronic myeloproliferative neoplasm, are associated with limited patient survival and significant morbidity.[1] Primary myelofibrosis (PMF), polycythemia vera–related myelofibrosis, and essential thrombocythemia-related myelofibrosis are collectively referred to as MF, although the natural course of these 3 seemingly related diseases may differ.[2] MF is characterized by progressive splenomegaly, cytopenias, a leukoerythroblastic blood picture, debilitating constitutional symptoms, cachexia, and a worsening performance status.[3] These constitutional symptoms (fevers, night sweats, and weight loss), bone pains, muscles aches, pruritus, abdominal discomfort, early satiety, and profound fatigue are common features of MF that can dramatically compromise the quality of life of patients and contribute to disease-associated morbidity. The palliation of these symptoms is increasingly being recognized as a valid end point for clinical trials of novel therapeutic agents and is often the therapeutic goal of such drugs. Over the last 20 years, therapies that attempt to lessen the degree of anemia (recombinant erythropoietin, danazol, thalidomide, lenalidomide, and pomalidomide), myeloproliferation and splenomegaly (melphalan, hydroxyurea, interferon, cladribine), and marrow fibrosis (pirfenidone, monoclonal antibodies to transforming growth factor β) have each been evaluated in clinical trials with modest efficacy.[4-18] The use of none these agents has been associated with a clear survival benefit for MF patients. In fact, only recently have randomized phase 3 trials been completed in patients with MF that provide the foundation for evidence-based therapeutic decisions.

In November of 2011, ruxolitinib (Jakafi, Incyte) was approved in the United States for the treatment of patients with intermediate-risk or high-risk MF as assessed by the International Prognostic Scoring System (IPSS). The approval of this potent selective oral Janus kinase (JAK) 1/2 inhibitor was based on the results of 2 pivotal phase 3 studies.[19,20] Preclinical studies as well as phase 1/2 clinical trials have demonstrated the safety profile of this small-molecule tyrosine kinase inhibitor and established spleen volume reduction and symptom improvement as valid therapeutic end points.[21] Interestingly, *JAK2V617F* allele burdens have not been shown to be significantly modified by ruxolitinib treatment, yet clinical benefit was achieved irrespective of *JAK2V617F* status. The fact that ruxolitinib is effective in patients lacking *JAK2V617F* underscores the pathophysiological consequence of hyperactivity of the JAK signal transducer and activator of transcription pathway that is characteristic of MF. Moreover, cytokine profiling of MF patients has revealed a heightened proinflammatory cytokine signature that can be downregulated with ruxolitinib therapy and has been associated with symptom improvement. Thus, the concept that meaningful MF disease modification by ruxolitinib may also involve a reduction in symptomology rather than a reduction in bone marrow fibrosis or a reduction in the malignant cell burden is gaining acceptance.

The current focus of therapeutic development has been based on targeting the malignant hematopoietic stem cell from which hematopoiesis in MF originates. Investigational agents are currently under evaluation with the hope of offering not only improvements in symptoms, organomegaly, and cytopenias but also the elimination of peripheral blood leukoerythroblastosis, bone marrow fibrosis, abnormal bone marrow histopathological features, and the eradication of clonal hematopoietic cells carrying abnormal molecular and cytogenetic markers. It has been the belief that only with significant reduction in "malignant hematopoietic cell burden" can modification of the natural history of MF be achieved. The recent published results of 2 pivotal phase 3 studies of ruxolitinib in patients with MF have, however, led to a re-evaluation of this concept. The initial report of a survival benefit in the COMFORT-1 study, and now

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more recently in the COMFORT-2 trial, has challenged the assumption that improved survival can only be achieved with the reduction of conventional biomarkers that reflect disease burden as assessed by histopathological or molecular parameters. We present a comprehensive review and discussion of published and presented survival data on MF patients treated with ruxolitinib in order to place such reports in perspective so as to allow practicing clinicians to make informed decisions about the use of this costly therapeutic option.

Focus on survival analysis

Comparison cohorts

The analysis of long-term outcomes of 107 intermediate-2–risk and high-risk MF patients treated with ruxolitinib at the MD Anderson Cancer Center (MDACC) in the phase 1/2 study (INCB18424-251) was recently reported.[22] The overall survival (OS) of this trial population was compared with a matched (based on meeting the eligibility criteria for the 251 study) historical control cohort of 310 MF patients from 3 institutions (MDACC in the United States, University of Pavia in Italy, and the Hospital of Niguarda in Milan, Italy). The control group had a median year of first diagnosis of 2002 and median start date of observation of 2004. IPSS scores were assigned retrospectively to the patients in the historical control group at time of first observation, and the log-rank test and Cox proportional hazard model adjusted for IPSS risk score were used to compare OS in these 2 groups. After a median follow-up of 32 months, 58 patients were still receiving ruxolitinib and 33 deaths occurred for an OS of 69% in the ruxolitinib treatment arm. Fourteen deaths occurred while receiving ruxolitinib therapy or within 30 days of discontinuation and 19 deaths occurred off study. None of the deaths were attributed to ruxolitinib, and the causes included myocardial infarction/cardiac arrest (4), multiorgan failure (3), disease progression (2), sepsis (1), pneumonia (1), brain aneurysm (1), pancreatic mass with liver metastasis (1), and abdominal aortic aneurysm (1). There were a total of 187 deaths in the historical control group. The OS was significantly better in the ruxolitinib treatment group as compared with the historical cohort in an analysis adjusted for IPSS risk group (hazard ratio [HR] = 0.58; 95% CI, 0.39-0.85; $P = .005$). The 1-, 2-, and 3-year survival rates in high-risk ruxolitinib-treated patients were statistically superior at 95%, 83%, and 63% as compared with 81%, 58%, and 35% in the historical control group (HR = 0.50; 95% CI, 0.31-0.81; $P = .006$). Although not statistically significant, there was a trend toward superior survival rates in the intermediate-risk group patients treated with ruxolitinib. Survival rates within the ruxolitinib treatment group were similar between the high-risk and intermediate-2–risk patients at 1, 2, and 3 years of 95%, 83%, and 63% and 97%, 79%, and 70%, respectively (HR = 1.36; 95% CI, 0.64- 2.89; $P = .43$). Additional exploratory analyses revealed that spleen volume reduction alone was associated with a survival advantage in ruxolitinib-treated patients. Sixty-three percent of ruxolitinib-treated patients achieved >50% reduction in spleen volume with a median duration of approximately 2 years. Patients with >50% reduction in splenomegaly were found to have superior survival when compared with patients who achieved <25% spleen reduction ($P < .0001$). Patients who achieved a reduction in palpable spleen length between 25% and 50% had an OS that was intermediate between the 2 extremes in reduction of spleen length. Sex, white blood cell count, cytogenetic abnormalities, and anemia did not influence survival in these analyses. The leukemic transformation rate was similar in the ruxolitinib-treated patients as compared with the historical cohort (0.036 per patient-year compared with 0.038 per patient-year, respectively), but the duration of follow-up was likely too short to make valid conclusions.

Obviously, selection bias and time bias will always complicate comparisons with historical controls, and the effects of these sometimes cannot be fully appreciated. The historical control group was composed of patents at the 3 institutions who met each of the eligibility criteria for inclusion in the phase 1/2 study. The 2 groups were comparable with regards to their baseline features but differed in that higher white blood cell count and greater spleen size predominated in the ruxolitinib treatment group while older age and lower hemoglobin levels were more frequent in the control group. The finding of a superimposable survival curve for high-risk and intermediate-2–risk MF patients treated with ruxolitinib is intriguing and suggests that ruxolitinib therapy may downgrade an individual's prognostic score category and improve predicted survival.

A sponsor-independent report of the long-term outcomes of 51 MF patients who participated in the same phase1/2 study was subsequently published by the Mayo Clinic group.[23] The patients treated at this institution had a median age of 61 years, 18% had unfavorable cytogenetic patterns, 84% were positive for *JAK2V617F*, and 14%, 22%, 48%, and 18% belonged to low-risk, intermediate-1–risk, intermediate-2–risk, and high-risk groups by dynamic IPSS (DIPSS), respectively. The median survival for patients belonging to these risk groups was 185, 78, 35, and 16 months for low, intermediate-1, intermediate-2, and high risk, respectively ($P < .001$ for all comparisons). The reported rate of discontinuation of ruxolitinib was 51%, 72%, and 89% at 1, 2, and 3 years, respectively. The reasons for discontinuation were progressive disease or loss/lack of response in 40% and toxicity with or without progressive disease or lack of response in 34%. Five patients (11%) developed serious withdrawal/rebound symptoms when acutely discontinuing therapy. The symptoms associated with withdrawal were characterized by rapid return of symptoms, painful splenomegaly, acute hemodynamic instability, and even a shock-like state. Eighteen patients (35%) died, and 5 patients (10%) underwent leukemic transformation. Using a similar comparative analysis to that employed by investigators at MDACC, this group also identified a cohort of 410 PMF patients who were seen at the Mayo Clinic and treated with "standard therapies" over the last 10-year period. Survival was reported to be similar when these 2 groups were compared using an unadjusted analysis ($P = .43$) and remained similar when adjusted for DIPSS ($P = .58$) assessments of disease status. The reasons for the discrepancies in the conclusions drawn from these reports from MDACC and Mayo Rochester are not readily apparent but highlight the deficiencies of relying on conclusions drawn from analyses generated from data at single institutions where clinical practices may dramatically differ.

Prospective studies

The COMFORT-1 trial was a randomized trial comparing ruxolitinib therapy to placebo in MF patients with advanced forms of the disease. OS was a secondary end point in the COMFORT-1 trial, and at the time of primary data cutoff, 10 deaths were observed in the ruxolitinib arm (6.5%) and 14 deaths in the placebo arm (9.1%) (HR = 0.67; 95% CI, 0.3 to 1.5; $P = .33$).[19] A planned additional data cutoff was also conducted after an additional 4-month follow-up period. At a median follow-up of 52 and 51 weeks, 13 (8.4%)

Table 1. Causes of death reported in COMFORT-1 in both the ruxolitinib and placebo treatment arms at the time of primary data cutoff

Ruxolitinib arm		Placebo arm	
Cause	Number of cases	Cause	Number of cases
Muscular weakness and general deterioration	1	Staphylococcal infection	1
Subdural hematoma	1	Gastrointestinal hemorrhage	1
Acute myeloid leukemia	1	Intestinal perforation	1
Pneumonia	2	Pneumonia	1
Renal failure	1	Multiorgan failure	1
Sepsis	2	Sepsis	2
Metastatic non–small cell carcinoma	1	Disease progression	4
Total	**9**	**Total**	**11**

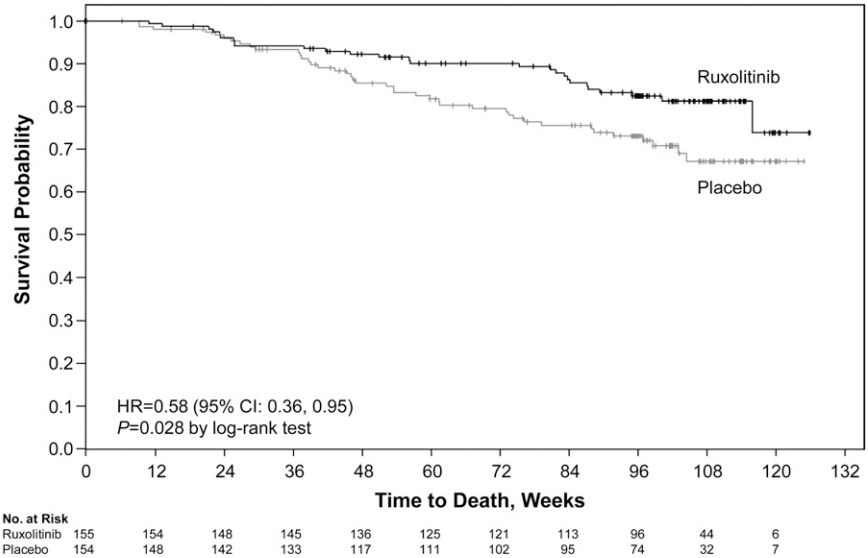
patients in the ruxolitinib arm and 24 (15.7%) in the placebo arm had died either during the study or during the follow-up period, respectively. Despite the crossover design and the intention-to-treat analysis model, the group of patients randomized up front to ruxolitinib versus placebo had a better median OS with a statistically significant HR of 0.499 (0.254, 0.98; $P = .0395$). The causes of death for patients in both arms at the time of primary data cutoff are shown in Table 1.

Further subgroup analyses, intended only to assess the uniformity of treatment effect found in the overall patient population, did not demonstrate a difference in OS when patients were stratified by *JAK2V617F* status (positive vs negative), IPSS risk category (high risk vs intermediate-2), baseline hemoglobin (≥10g/dL vs ≤10 g/dL), or spleen length (≤10 cm vs >10 cm) and age (≤65 vs >65 years).[24]

Long-term follow-up of COMFORT-1 patients recently presented by Verstovsek et al[25] continues to demonstrate an OS benefit in favor of ruxolitinib therapy after an additional year of observation (HR = 0.58; 95% CI: 0.36, 0.95; $P = .028$) (Figure 1). This difference remained statistically significant across all MF subgroups, starting drug doses, baseline risk status, and hemoglobin level. Spleen volume reduction, symptom improvement, and adverse event profile remained stable over this additional year of follow-up. Rates of transfusion requirement decreased in the patients randomized to ruxolitinib with time and were comparable to that which was observed in the placebo arm.

Survival was a prespecified secondary end point in a time-to-event analysis conducted at week 48 in the COMFORT-2 trial. In this trial, the outcomes of MF patients receiving ruxolitinib were compared with those of patients receiving best-available therapy (BAT). A total of 44 (30%) patients in the ruxolitinib treatment arm had evidence of disease progression versus 19 (26%) in the BAT arm (HR = 0.81; 95% CI, 0.47 to 1.39). Leukemia-free survival (HR = 0.65; 95% CI, 0.18 to 2.31) and overall survival (HR = 0.70; 95% CI, 0.2 to 2.49) were not found to be statistically significant at this prespecified time. After an additional 2-month follow-up (median, 61.1 weeks), 11 deaths occurred (7.5%) in the ruxolitinib arm and 4 (5.5%) in the BAT arm (HR = 1.01; 95% CI, 0.32, 3.24). The median survival time had not yet been reached. Due to the study design (2:1 randomization in favor of the ruxolitinib arm, crossover from BAT to ruxolitinib) and intention-to-treat analysis, it was not possible to detect a true difference in time to progression-free survival, leukemia-free survival, or OS since too few patients remained in the BAT arm (27% lost to follow-up, 25% crossed over to ruxolitinib, 12% had withdrawn consent). The causes of death in the COMFORT-2 study at a median of 61.1 weeks of follow-up are shown in Table 2.

The COMFORT-2 study was amended to allow for longer-term follow-up of patients in the extension phase of the study, and the results have been recently summarized by Cervantes et al.[26] Overall, 72.6% of patients in the ruxolitinib arm and 61.6% in the BAT arm in the extension phase received ruxolitinib. Fifty-six percent of patients randomized to ruxolitinib upfront remained on treatment at the time of this analysis; the primary reasons for discontinuation of therapy were progressive disease (8.2%), adverse events (2.1%), and other (4.1%). After a median follow-up of 112 weeks, an additional 9 and 12 deaths occurred in the ruxolitinib and BAT treatment arms, respectively, resulting in a total of 20 (14%) and 16 (22%) deaths overall. Therefore, at this unplanned



P-values and confidence intervals are unadjusted for repeat analyses.

Figure 1. Kaplan-Meier analysis of OS by treatment group in COMFORT-1. An updated survival analysis of patients randomized to ruxolitinib therapy with a median follow-up period of 102 weeks from the COMFORT-1 study continued to demonstrate a survival advantage in favor of ruxolitinib despite an intention-to-treat analysis. This advantage remained consistent across all patient subgroups analyzed.

Table 2. Causes of death reported in COMFORT-2 in both the ruxolitinib and BAT treatment arms after a median total follow-up of 61.1 weeks

Ruxolitinib arm		Best available therapy	
Cause	Number of cases	Cause	Number of cases
Myelofibrosis	2	Pneumonia, septic shock, multisystem organ failure, and acute myeloid leukemia	1
Hepatic failure, cerebral hemorrhage, and portal vein thrombosis after surgery for metastatic squamous cell carcinoma of the head and neck	1	Postsplenectomy *Klebsiella pneumoniae* sepsis	1
Pulmonary edema and cardiac arrhythmia	1	Splenectomy, peritoneal hemorrhage, and respiratory failure	1
Retroperitoneal hemorrhage after an orthopedic procedure	1	Renal failure and acute myeloid leukemia	1
Intestinal perforation associated with terminal ileitis	1		
Respiratory infection	1		
Cardiac arrest and myelofibrosis	1		
Cardiac failure	1		
Pulmonary extramedullary hematopoiesis and pulmonary failure	1		
Posttransplantation lymphoproliferative disorder and multiorgan failure	1		
Total	**11**	**Total**	**4**

analysis, a modest survival advantage in favor of ruxolitinib treatment (HR = 0.52; 95% CI, 0.27-0.99; P = .041) was observed (Figure 2).

How do we interpret these data?

Although the contributory factors that led to the improved survival achieved in COMFORT-1 with ruxolitinib therapy were not clear, several explanations have been proposed: improvement in symptoms with a concomitant upgrade in performance status; reduced risk of leukemic transformation due to an alteration of the cytokine milieu that favors disease progression; reduced incidence of life-threatening thrombotic events; and suppression of more aggressive MF subclones that reside within the spleen, which has been reduced in size by ruxolitinib therapy. Beyond the clinical trial setting, ruxolitinib is primarily prescribed to MF patients with the expectations of ameliorating symptoms and reducing splenomegaly based on the convincing results of the COMFORT studies. Although the survival data in COMFORT-1 do show a modest but statistically significant improvement in OS compared with placebo and longer-term follow-up of COMFORT-2 demonstrates improved survival with ruxolitinib treatment, it would be premature to initiate treatment with ruxolitinib with the primary goal of prolonging survival in a given MF patient. The median survival of patients with MF is approximately 5 to 7 years, and the major causes of death are due to transformation to acute leukemia (~31%), progressive disease (~18%), thrombosis and cardiovascular complications (~13%), infections (~11%), bleeding (~5%), portal hypertension (~4%), and secondary malignancies (~4%).[27] In a retrospective analysis of 802 PMF patients from 4 European countries, improved survival was seen when comparing the period of diagnosis of 1980 to 1995 (n = 434 patients) and 1996 to 2007 (n = 368 patients).[28] An improved relative survival was appreciated in women, patients <65 years of age, and patients with low-risk or intermediate-1–risk disease by IPSS. Reduction in disease-specific mortality was not appreciated in patients with intermediate-2–risk or high-risk disease.

Presently, data are not available to determine whether ruxolitinib can reduce the risk of leukemic transformation, thrombotic risk, or the risk of developing secondary malignancies in MF patients. There would be no reason to believe that ruxolitinib would reduce infectious complications in MF patients, and in fact its use may increase this risk as a virtue of its myelosuppressive effect. It would seem plausible that the reduction in splenomegaly that occurs in MF patients treated with ruxolitinib may also result in reduction in associated portal hypertension, and this may afford patients protection from attendant complications (bleeding, thrombosis), imparting a survival advantage.

There is a growing appreciation that MF is a hematologic malignancy that is accompanied by a remarkable elevation of proinflammatory cytokines that can exceed that which is seen in classic inflammatory diseases such as rheumatoid arthritis. The full significance of this inflammatory state is not yet known, but it is believed to be linked to overactive JAK signaling and may mediate many MF symptoms. Moreover, the modulation of these circulating inflammatory cytokines with anti-JAK therapy may provide a vital link between symptom improvement and potential survival benefit. Merely by improving a patient's overall sense of well-being, allowing the patient to improve his or her performance status, may be sufficient to reduce the risk of mortality. Performance status can be directly correlated with the OS of cancer patients, and those with debilitating disease are predicted to have more difficulty tolerating therapy and have reduced survival.[29-32] Additionally, the IPSS/DIPSS prognostic scoring systems recognize the presence of constitutional symptoms in patients with MF as a negative predictor of survival, and reversing this would be predicted to potentially downgrade an individual patient's risk score. Post hoc analysis of COMFORT-1 has demonstrated a correlation between weight gain and improvement in baseline hypocholesterolemia in ruxolitinib-treated patients compared with placebo-treated patients in terms of survival advantage.[22] The degree of cachexia at baseline was similar in the 2 treatment arms, and ruxolitinib-treated patients experienced weight gain (96%) and improvement in cholesterol levels (97%) whereas patients in the placebo arm experienced progressive weight loss and hypocholesterolemia. Kaplan-Meier analyses of OS were conducted in patients randomized to ruxolitinib and stratified into 2 groups based on the median values for maximum weight gain and for maximum increase in total cholesterol during the period of randomized treatment. Weight gain above the median was associated with prolonged survival relative to lesser degrees of weight gain (HR = 0.40; 95% CI: 0.18, 0.90; P = .022) as well as with cholesterol improvement above the median relative to lesser degrees of improvement (HR = 0.46; 95% CI: 0.21, 1.01; P = .048) in ruxolitinib-treated patients. Thus, the reduction of an inflammatory state with improvement of associated performance status and cachexia may in itself represent a form of disease modification contributing to improved survival.

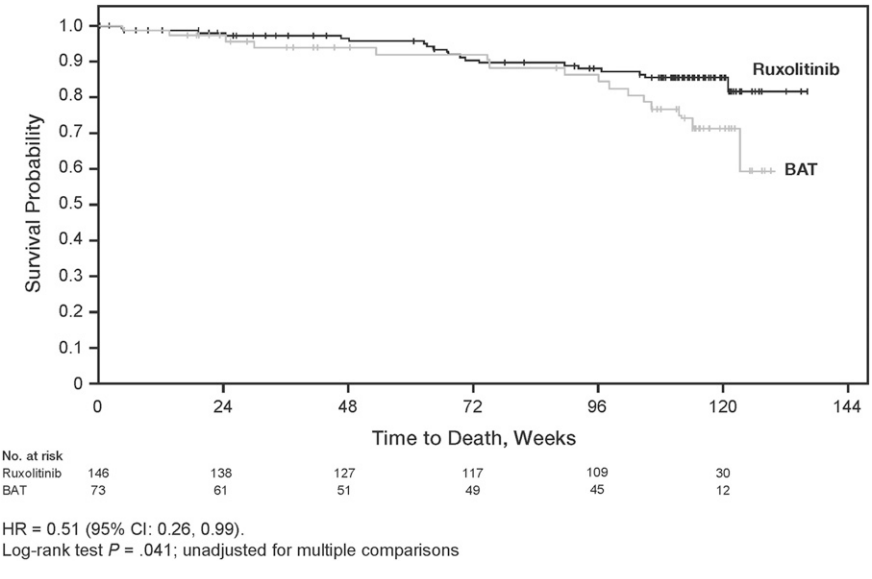


Figure 2. Kaplan-Meier analysis of OS by treatment group in COMFORT-2. Updated analysis of survival data from COMFORT-2 now shows a survival benefit in favor of ruxolitinib treatment compared with those patients randomized to BAT. At an unplanned analysis at a median follow-up of 112 weeks (ruxolitinib 113; BAT 108) and median duration of exposure of 111.4 weeks, patients who were randomized to the ruxolitinib arm showed longer survival than those randomized up front to BAT. This survival advantage remains statistically significant despite the fact that those BAT patients that were discontinued from the core study were immortalized and thus considered alive at the time of this analysis. Generously provided by Dr Francisco Cervantes.

Although splenomegaly is not a recognized risk factor for decreased survival and is not incorporated in the IPSS/DIPSS, it is associated with portal hypertension and portal vein thrombosis, which can influence outcomes in MF patients. The correlation between degree of spleen size reduction and survival in MF is of particular interest and may have important clinical implications, although this more dose-intensive approach remains investigational.

Four published reports based on 3 clinical trials address survival in the treatment of MF with ruxolitinib. The initial phase 1/2 (INCB018424-251) study of ruxolitinib in MF patients clearly defined the toxicity profile and tolerability of this agent and demonstrated a strong signal for clinical activity with intriguing correlative biological markers. The use of historical controls to compare survival in patients treated within the phase 1/2 study at different institutions can only serve to highlight reasons why the clinical practice and approach of different investigators can potentially lead to disparate results even with outstanding investigators. The COMFORT-1 study has demonstrated a statistically significant reduction in risk of death in patients that were treated with ruxolitinib, and this held true even with an intention-to-treat analysis and remains significant with long-term follow-up. The COMFORT-2 study was not able to adequately show a survival difference due to the study design and inadequacies of follow-up at time of primary analysis, but with long-term follow-up a survival benefit has now been reported.

These conclusions should, however, be considered preliminary since the improved OS was only observed when the COMFORT-2 study was amended to allow for patients to be observed during an extension phase. The survival analysis was not initially planned at the time of the conception of these studies, and almost half of the patients were no longer receiving treatment with ruxolitinib at the time of the analysis. It is also important to emphasize that both randomized studies were not constructed with sufficient patient numbers to determine the effect of the study drug on patient survival. These methodological issues surely have the potential to impact, to some degree, the conclusions derived from these studies. Studies that are appropriately powered to assess the effect of this therapeutic modality on long-term survival are still needed and would be preferable.

Many questions remain unanswered, including whether treating patients earlier in their disease course would offer a more profound improvement in survival. Whether other JAK2 inhibitors that are in different phases of clinical development will prove more effective than ruxolitinib is the subject of several ongoing investigations. Although individual investigators have claimed that some of these agents offer therapeutic advantages, such conclusions are likely premature since they are based on phase 1/2 trials results. The determination of the relative effectiveness of these promising agents will require the completion of carefully performed phase 3 trials. Whether combining ruxolitinib with other MF-directed therapies such as danazol, immunomodulatory agents, or erythropoiesis-stimulating agents would lessen treatment emergent anemia and allow for higher dosing of ruxolitinib, potentially improving survival benefit further, remains to be seen. Studies investigating the combination of ruxolitinib with drugs that inhibit the hedgehog signaling pathway (LDE225), collagen synthesis (GS-6624), or chromatin-modifying agents (azacitidine, panobinostat) are planned or ongoing. Trials combining ruxolitinib and panobinostat are now ongoing in Europe and at the Mount Sinai School of Medicine and are based on compelling preclinical studies and nonoverlapping mechanisms of action of these 2 agents. Since ruxolitinib therapy improves the quality of life of patients with advanced forms of MF, the enthusiasm of such patients to proceed with curative but admittedly risky allogeneic stem cell transplantation can be substantially reduced. Such delays in proceeding with transplant may be frequently ill advised since the progression to acute leukemia does not appear to be substantially affected by ruxolitinib therapy. Whether ruxolitinib treatment prior to hematopoietic stem cell transplant can improve patient performance status and the degree of splenomegaly and lead to more favorable outcomes is an important area of investigation that is being pursued by the Myeloproliferative Disorder Research Consortium.

Presently, ruxolitinib is the only Food and Drug Administration–approved therapy for the treatment of MF and is also the only therapy to date that has been reported to be associated with a survival benefit. Ruxolitinib has undoubtedly changed the MF treatment landscape and is an appropriate therapeutic option for many patients treated in the community. However, MF patients with platelet counts $<50 \times 10^9$/L and those with significant transfusion-dependent

anemia are often not ideal candidates for treatment with ruxolitinib, and this remains an unmet need. The evaluation of novel agents based on scientific rationale in well-designed clinical trials is the focus of current research efforts in myeloproliferative neoplasms. Future trial concepts will require end points that not only incorporate spleen reduction and symptom improvement but also evaluate bone marrow histopathology, elimination of cytogenetic markers, and depth of molecular responses. Whether newer agents seeking Food and Drug Administration approval will be required to be compared in randomized studies to ruxolitinib is not yet established, and whether OS will one day become a primary end point for such studies remains both speculative and optimistic.

Authorship

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