COMMENTARY

blood advances

TO THE EDITOR:

Does ruxolitinib really prolong survival in individuals with myelofibrosis? The never-ending story

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We read with interest the recent article by Guglielmelli et al[1] in which they report new evidence showing ruxolitinib prolongs survival in individuals with myelofibrosis. The authors analyzed data from a registry of so-called real-world data from European centers. From 2013 to 2014, 1292 individuals with myelofibrosis were registered, 1010 (78%) of whom were analyzed; 645 (50%) were alive at the study start and were followed for 4 years, including 487 receiving hydroxyurea and 108 receiving ruxolitinib. The authors selected 100 participants (8%) from this cohort for propensity score matching, 50 from each therapy group. They report that those receiving ruxolitinib lived a median of 3 years longer than those receiving hydroxyurea.

The never-ending saga of trying to decipher whether ruxolitinib increases survival began in 2012, when the 2 COMFORT randomized controlled trials were published.[2,3] One-year follow-up data from the COMFORT-I study suggested better survival in participants at intermediate-2 risk or greater compared with controls, a finding confirmed in long-term follow-up.[3] No survival benefit was reported in the initial report of the COMFORT-II study, where participants were assigned to receive ruxolitinib versus best available therapy.[4] In contrast, follow-up at 3 years indicated improved survival with ruxolitinib.[5]

Results of these trials were greeted enthusiastically by the scientific community. The claim that ruxolitinib prolongs survival appeared in many commentaries and reviews, despite 3 subsequent publications questioning the validity of this conclusion.[6-8] Using the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach, we downgraded evidence from the COMFORT studies because of performance and attrition biases.[7,9] We argued survival data from these studies failed to meet optimal information size criteria, advising confidence in estimates of a survival advantage should be downgraded for imprecision (too few events). Another analysis using GRADE and a Cochrane systematic review reached similar conclusions.[6,8]

Getting the survival question right is vital because it affects the decision of whether to recommend ruxolitinib therapy when the goal is prolonging survival rather than reducing splenomegaly or improving constitutional symptoms. Six additional studies[1,10-14] addressed the question of whether ruxolitinib or the cognate JAK2 inhibitor momelotinib improves survival, the latest of which is that by Guglielmelli et al.[1] Although designs of these studies differ, they are fundamentally case-control analyses (Table 1). We have discussed limitations of case-control studies elsewhere.[15] Although Guglielmelli et al used propensity score matching, this does not overcome the limitations of such studies, including selection bias for nonconsecutive enrollment and unjustified exclusion of 22% of patients. Another issue is the use of DIPSS to match cases with controls.[16] DIPSS score was an inclusion criterion of the COMFORT trials, and in some countries, it is a criterion for the use of ruxolitinib; however, it is not usually a criterion for decision making regarding ruxolitinib use in individuals who need therapy but are not enrolled in clinical trials. For example, in those with an intermediate- or high-risk DIPSS score with leukocytosis, increased blasts (or elevated $CD34^+$ blood cells), anemia, or thrombocytopenia without symptomatic splenomegaly, we and many others prefer hydroxyurea to ruxolitinib. Matching only for DIPSS score ignores prognostic impacts of hemoglobin, white blood cell concentration, and percentage of blood blasts. This bias has been highlighted by others.[10]

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Table 1. Synopsis of results of case-control studies comparing effect of ruxolitinib versus conventional therapy on survival in myelofibrosis

Reference	Case identification	Method of matching	Cohort, n		Time point for survival measurement	Survival		Difference in survival	Conclusion reported
			Control	Ruxolitinib		Control cohort	Ruxolitinib cohort		
10	Ruxolitinib and controls: patients at Mayo Clinic in most recent 10-y period	DIPSS-plus score	410	51	Ruxolitinib: therapy initiation Controls: initial referral to center	NR	DIPPS-plus low, 185 mo Intermediate-1, 78 mo Intermediate-2, 35 mo High risk, 16 mo	$P = .58$ (with adjustment for DIPSS-plus)	No significant difference in survival rate for ruxolitinib-treated patients compared with those treated with standard therapy
11	Ruxolitinib: patients at MDACC who participated in INCB 18424-251 trial Controls: historical control group*	Trial enrollment criteria	310	107	Ruxolitinib and controls: first observation at center	NR	OS rate, 69%	HR, 0.58 (95% CI, 0.39-0.85); $P = .005$ (with adjustment for IPSS risk status)	Seems to be survival advantage for patients treated with ruxolitinib (finding should be interpreted with caution)
12	Ruxolitinib: patients who received ruxolitinib in randomized treatment arm or after crossover from best available therapy in COMFORT-II trial Controls: patients entered in database and not receiving any experimental drug	IPSS intermediate-2 or high risk Blasts <10%	350	100	Ruxolitinib: therapy initiation Controls: first documentation of intermediate-2– or high-risk status	Median OS, 3.5 y (95% CI, 3.0-3.9)	Median OS, 5 y (95% CI, 2,9-7.8)	HR, 0.61 (95% CI, 0.4-0.9); $P = .005$	Risk of death might be reduced by 40% to 50% by introducing ruxolitinib in treatment of patients with primary myelofibrosis
13	Momelotinib: patients who received momelotinib in a phase 1/2 clinical trial (NCT00935987) Controls: retrospective cohort of JAK inhibitor treatment–naive patients from authors' institutional database	DIPSS-plus risk status	442	100	Momelotinib: from tdate of study entry Controls: NR	Median OS, 3.2 y	Median OS, 3 y	$P = .44$	Comparison of momelotinib-treated patients with risk-matched myelofibrosis cohort not receiving treatment with momelotinib did not reveal significant difference in survival data
14	Ruxolitinib and controls: SEER (ICD-O-3)	By y of diagnosis	975	1045	Diagnosis	4-y RSR, 54%	4-y RSR, 57%	$P = .776$	No difference in survival between pre- and postruxolitinib cohorts
1	Ruxolitinib and controls: ad hoc registry (ERNEST study)	Propensity score matching analysis on baseline covariates including DIPSS	50	50	Start of hydroxyurea or ruxolitinib therapy	Median OS, 3.4 y	Median OS, 7.7 y	$P = .002$	Compared with treatment with hydroxyurea, ruxolitinib treatment was associated with significant OS benefit

CI, confidence interval; DIPSS, Dynamic International Prognostic Scoring System; HR, hazard ratio; ICD-O-3, International Classification of Diseases for Oncology, third edition; IPSS, International Prognostic Scoring System; MDACC, MD Anderson Cancer Center; NR, not reported; OS, overall survival; RSR, relative survival rate; SEER, Surveillance, Epidemiology, and End Results.

*Databases of 3 international institutions.

The report by Guglielmelli et al[1] also lacks other data that would make it more credible, such as whether the effect of ruxolitinib on survival correlated with ruxolitinib dose intensity. Moreover, the authors did not report causes of death, thereby preventing us from knowing whether the survival benefit they observed resulted from slowing disease progression, reducing risk of transformation to acute myeloid leukemia, and/or other mechanisms.

Consistency of results is a criterion for quality of evidence in the GRADE platform.[9] Of the studies we have discussed, 3 reported survival differences[1,10,12] and 3 reported neutral results.[11,13,14] One study reported more new cancers in ruxolitinib receipients.[14]

Many investigators have stressed the need for a randomized controlled trial specifically designed and powered to evaluate whether ruxolitinib improves survival in myelofibrosis.[10] We agree, and we continue to believe this is an unmet urgent clinical need despite substantial barriers to its execution. Ethical reasons have been put forth against a randomized trial comparing conventional drugs (eg, hydroxyurea) with ruxolitinib in individuals with myelofibrosis requiring therapy for disease progression, because it would contradict the notion of equipoise. We disagree for the reasons we have discussed here. We acknowledge that a randomized controlled trial comparing ruxolitinib with hydroxyurea would face recruitment challenges because most physicians and patients would prefer ruxolitinib, despite uncertainty about a survival benefit. We suggest the solution lies in innovative trial designs, such as partially randomized individual preference trials, which assign potential participants with a preference to that therapy while randomly assigning those without a preference.[17] We also acknowledge a funding problem. Over the last 20 years, there has been a huge shift in the funding of cancer clinical trials from public to pharmaceutical sources.[18] Almost all phase 3 trials are now funded by the pharmaceutical industry. Impartiality is best guaranteed by funding from nonprofit entities.

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