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LETTER TO THE EDITOR

Quality of life independently predicts overall survival in myelofibrosis: Key insights from the COntrolled MyeloFibrosis Study with ORal Janus kinase inhibitor Treatment (COMFORT)-I study

Patient-reported outcomes (PROs) have considerable value for survival prediction, and generally include both quality of life (QOL) and symptom measures. A recent meta-analysis of 44 phase II or III randomised clinical trials found that overall survival (OS) was associated with at least one *baseline* PRO domain in 93% of studies, after controlling for pertinent clinical variables like performance status (PS), tumour staging and serum markers.[1] In a systematic review of 138 studies, 87% reported at least one PRO being significant for OS prognostication.[2] Myelofibrosis (MF) is associated with splenomegaly, cytopenias and a high symptom burden.[3] In two phase III clinical trials, ruxolitinib was associated with improvements in splenomegaly, symptom burden, QOL measures and OS.[4–6] In MF, symptoms have been shown to be highly prevalent and are incorporated into response criteria and clinical trials assessments. Key symptoms are also associated with decreased QOL in patients with myeloproliferative neoplasms (MPNs).[7] The objective of this analysis was to evaluate the prognostic relevance of baseline QOL on OS among patients with MF enrolled in the COntrolled MyeloFibrosis Study with ORal Janus kinase (JAK) inhibitor Treatment (COMFORT)-I trial.

Data from the COMFORT-I trial of ruxolitinib versus placebo for patients with intermediate-2 or high-risk MF (ClinicalTrials.gov Identifier: NCT00952289) was obtained from Incyte© for independent analysis.[4] PRO variables considered for prognostication of OS included total symptom score (TSS), functional subscales, global health status (GHS)/QOL, and fatigue. Clinical factors included age, sex, International Prognostic Scoring System (IPSS) risk score, PS and treatment arm (see Supplementary Appendix for details on measures). Analysis of OS included both the intention-to-treat method and censoring placebo patients at the time of crossover. A multivariable Cox proportional hazards model was used to examine the effect of symptoms and GHS/QOL baseline measures when controlling for clinical factors. Due to the substantial amount of crossover to ruxolitinib in the placebo arm, the rank-preserving structural failure time method (RPSFT) was also evaluated.

The COMFORT-I study enrolled 309 patients (155 ruxolitinib, 154 placebo); 111 (72%) placebo patients ultimately crossed over to ruxolitinib.[4] Baseline GHS/QOL was available in 296 patients and did not differ by treatment arm (Table S1). Symptom burden and fatigue were significantly higher in patients with lower GHS/QOL scores (Table S2). In addition, IPSS risk and European Organisation for the Research and Treatment of Cancer (EORTC) domains differed significantly by GHS/QOL median-split quantile groups. The mean (SD) GHS/QOL was 59.6 (22.0) in patients with a PS of 0, 51.7 (22.1) in patients with a PS of 1 and 43.8 (20.6) in patients with a PS of 2/3 ($F = 7.97$, $p < 0.001$). The mean (SD) GHS/QOL was 55.8 (22.3) for intermediate-2 versus 50.9 (22.5) for high-risk patients ($p = 0.07$) and TSS was 19.8 (11.1) for intermediate-2 versus 16.1 (11.4) for high-risk score ($p = 0.005$). TSS was inversely correlated with GHS/QOL ($r = -0.36$; $p < 0.001$); symptom item correlations ranged from $r = -0.14$ for night sweats to $r = -0.38$ for bone/muscle pain (Table S3).

Long-term analysis reported OS results favouring ruxolitinib (hazard ratio [HR] 0.69, 95% confidence interval [CI] 0.50–0.96; $p = 0.03$).[8] Higher GHS/QOL score at baseline (>median vs. ≤ median) was associated with increased OS on both intention-to-treat analysis (HR 0.69, 95% CI 0.49–0.96; $p = 0.03$) and when patients on placebo were censored at crossover (HR 0.57, 95% CI 0.37–0.88; $p = 0.001$) (Figure 1). On univariate analysis, OS was also significantly associated with age, sex, physical functioning, PS and IPSS risk score (Table S4). Multivariable results demonstrated a significant effect for baseline GHS/QOL (HR 0.92, 95% CI 0.85–0.99; $p = 0.03$ for a 10-point increase, Table 1). Results were consistent for both analysis methods. Optimism corrected measures of Harrell's C-index were 0.66 and 0.69 respectively. The RPSFT method also estimated a HR for GHS/QOL of 0.92 (95% CI 0.85–0.99). In a time-dependent model assessing GHS/QOL by the median grouping, HRs were decreased

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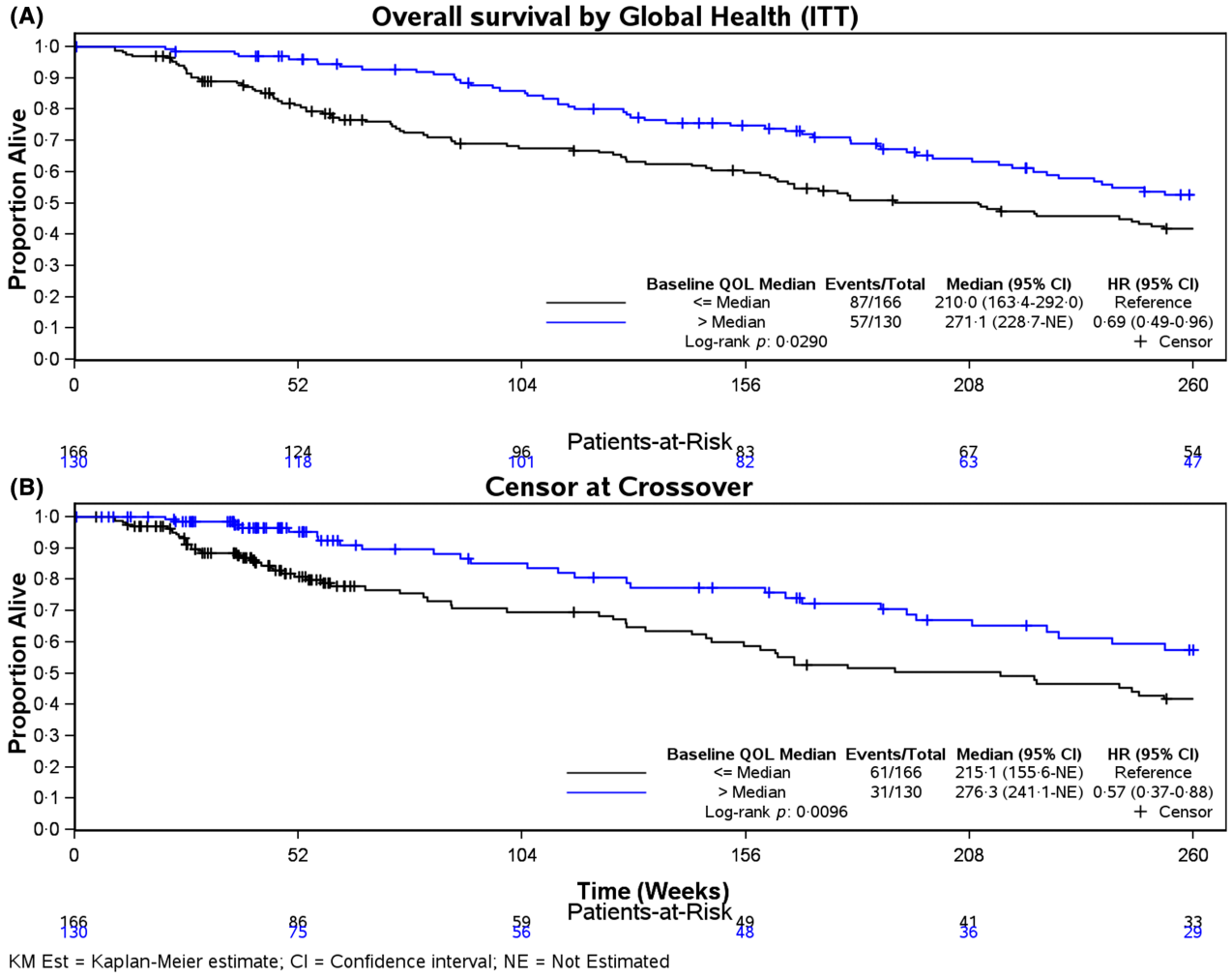

FIGURE 1 Overall survival stratified by baseline GHS/QOL median (<= median served as the reference group and is the group with lower QOL). Analysis was conducted by (A) intention-to-treat and (B) censored at time of crossover. CI, confidence interval; GHS, global health status; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; QOL, quality of life. [Colour figure can be viewed at wileyonlinelibrary.com]

for years 1 and 2, although sample size limited comparisons made (Figures S1 and S2).

In patients enrolled on the COMFORT-I trial, baseline QOL was independently associated with OS. This relationship remained even when adjusting for patient characteristics, disease risk score, PS, treatment arm and baseline symptoms. This is the first study that has identified this association among individuals with MF. Bankar et al.[9] found that higher frailty scores were associated with worse survival and increased JAK inhibitor therapy failure in 439 chronic phase MF patients. Other contemporary investigations have examined multiparameter flow cytometry as a substitute for blast count and response to ruxolitinib treatment after 6 months as potential predictors of survival.[10,11]

Improved survival seen with ruxolitinib use has been further validated on other real-world datasets, with the mechanism of improvement likely multifactorial including less debilitation, slower rates of leukaemic transformation, and fewer disease-associated complications.[12] Higher baseline QOL might also be associated with less disease-related debilitation, decreased hospitalisations, and fewer life-threatening complications. In this study, neither individual symptoms nor TSS at baseline appeared to be prognostic for OS, emphasising the importance of QOL *in addition* to symptom assessment. Baseline symptoms were significantly associated with QOL; however, when controlling for symptom burden, baseline GHS/QOL was the most prognostic variable. Similarly, Emanuel et al.[13] observed strong correlations (r >0.50) between the TSS (10-item version), functional subscales and GHS/QOL in >1400 patients with MPNs.

Quality of life may be important to show overall patient health status, but symptoms are important for more subtle disease monitoring. In a recent consensus of PROs for myelodysplastic disorders, both patients and haematologists selected general QOL as a core PRO for health assessment in clinical research and daily practice.[14] Due to the significant effects of ruxolitinib on PROs, we only analysed baseline QOL. QOL changes over time may be an important consideration when evaluating survival. In other settings, recent changes in QOL did not improve predictive ability as compared to patients' current QOL.[15] In conclusion, baseline QOL was found to independently predict survival in patients

TABLE 1 Multivariable Cox proportional hazards model for overall survival

	Intention to treat		Censor at crossover	
Model variables	**HR (95% CI)**	***p****	**HR (95% CI)**	***p****
TSS, *5-unit increase*	1.00 (0.92, 1.08)	0.99	0.99 (0.88, 1.10)	0.82
Age	1.05 (1.03, 1.08)	<0.001	1.05 (1.02, 1.09)	0.002
IPSS risk score				
2	Reference		Reference	
3	1.46 (0.96, 2.20)	0.08	1.28 (0.77, 2.12)	0.35
Sex				
Male	Reference		Reference	
Female	0.65 (0.45, 0.93)	0.02	0.49 (0.31, 0.77)	0.002
Treatment				
Placebo	Reference		Reference	
Ruxolitinib	0.85 (0.60, 1.21)	0.37	0.40 (0.22, 0.74)	0.004
GHS/QOL, *10-unit increase*	0.92 (0.85, 0.99)	0.03	0.84 (0.75, 0.94)	0.002
ECOG PS				
0	Reference		Reference	
1	0.81 (0.53–1.23)	0.32	0.86 (0.51, 1.45)	0.57
2–3	0.86 (0.48–1.53)	0.62	1.10 (0.53, 2.28)	0.80

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GHS, global health status; HR, hazard ratio; IPSS, International Prognostic Scoring System; QOL, quality of life; TSS, total symptom score.

*Wald chi-square test statistic.

with intermediate-2 or high-risk MF and provided prognostication above and beyond PS, standard disease risk scores, and patient-reported symptoms.

AUTHOR CONTRIBUTIONS

Heidi E. Kosiorek, Robyn M. Scherber, Ruben A. Mesa, Amylou C. Dueck: study conception and design, development of study protocol methods and analyses, review of statistical analyses, writing the first draft of the manuscript, critical revisions and submission of the manuscript, approval of the final manuscript version. Holly L. Geyer, Srdan Verstovsek, Blake T. Langlais, Gina L. Mazza, Jason Gotlib, Vikas Gupta, Leslie J. Padrnos, Jeanne M. Palmer, Angela Fleischman: review of study protocol, review of statistical analyses, critical revisions and submission of the manuscript, approval of the final manuscript version.

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KEYWORDS

myelofibrosis, prognostic factors, quality of life, survival

CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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