Time without transfusion reliance: a novel patient-centric metric for new therapies in myelodysplastic syndromes

Myelodysplastic syndromes (MDS) are clonal myeloid malignancies associated with ineffective hematopoiesis, consequent cytopenias, and for many progression to acute myeloid leukemia (AML), which is associated with shortened survival and worse health-related quality of life (HRQoL).[1,2] Most patients with MDS are affected by anemia and its attendant symptoms, which can lead to blood transfusion dependency. Blood transfusions can be burdensome, costly, and are major contributors to poor HRQoL in patients with MDS.[2,3]

The efficacy of new therapies in MDS should be evaluated using both standardized measures of response rates and overall survival (OS), along with outcomes reflecting patient experience, including disease symptoms and HRQoL.[4] However, the demonstration of treatment benefit through patient-reported outcomes (PRO) has been challenging in the evaluation of novel therapies in hematologic malignancies. Some of the limitations of PRO in hematologic malignancy trials to date include lack of good quality HRQoL data, suboptimal timing of assessment of HRQoL methods, use of weak HRQoL instruments, low compliance over time of patients enrolled on prospective clinical trials, and inadequate statistical analyses.[1,2] Further, HRQoL measures do not distinguish between different causes of anemia in MDS, so similar HRQoL may be observed due to improvement of anemia from treatment *versus* continued red blood cell (RBC) transfusions. To date, analyses pertaining to RBC transfusions largely include descriptions of the number of transfused units received or aggregated assessments estimating the duration of transfusion-independence for each patient. Such approaches do not account for possible differential follow-up resulting from unbalanced efficacy between trial treatment arms, such as disease progression or OS, thus confounding treatment arm comparisons.

We propose a new aggregated measure combining clinical outcomes (OS, transformation to AML) and transfusion-dependency: the time without transfusion reliance (TWiTR) approach, inspired by the time without symptoms and toxicity (TWiST) analysis.[5,6] In TWiST analyses,[6-8] periods of treatment toxicity and disease progression assumed to reduce HRQoL are subtracted from the OS time for each patient. Similar to the TWiST approach, the TWiTR analysis subtracts periods of time from the OS of each patient when HRQoL is assumed to have deteriorated: i) the time period when patients experience disease progression and ii) the time period when patients are transfusion-dependent. Hence, three health states are defined in the TWiTR analysis: a transfusion dependence (TD) state that is defined as the sum of all TD periods experienced by the patient (replacing the toxicity state in the TWiST approach); a relapse (REL) state that is defined as the time between disease progression and death; and the TWiTR state that is defined as the time without TD or REL. Health state durations (OS or event-free survival [EFS] minus TD and REL) are then calculated using Kaplan-Meier estimates. The mean duration in each state can be estimated by the area under each survival curve obtained with Kaplan-Meier estimates[9] and can be weighted using a utility value, which can be derived from any utility-based instrument, attached to each state to obtain a quality-adjusted TWiTR (Q-TWiTR) that reflects both the duration of each state, and the corresponding HRQoL experienced by patients in this state.[5,7,9] A bootstrap approach[10] can be applied to estimate the 95% confidence interval (CI) for the mean Q-TWiTR for each arm and mean Q-TWiTR difference between arms.

The TWiTR approach was implemented in the context of a randomized phase II study of pevonedistat plus azacitidine (PEVO+AZA) *versus* azacitidine (AZA) alone in higher-risk MDS (HR-MDS), chronic myelomonocytic leukemia (CMML), and low-blast AML naïve to hypomethylating agents (P-2001; *clinicaltrials.gov Identifier: NCT02610777*[11]). The primary endpoint of the study was EFS, defined as transformation to AML or death for HR MDS/CMML, or death for low-blast AML, which was used to define the health states in the TWiTR analysis. The P-2001 study included two HRQoL measures: the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 items (QLQ-C30), an instrument designed for use in a wide range of cancer patient populations;[12] and the EQ-5D-5L, a self-administered instrument developed for use as a generic, preference-based measure of health outcomes, from which utilities can be derived.[13]

The P-2001 study enrolled 120 patients in a 1:1 randomization (PEVO+AZA: n=58, AZA: n=62). Of the total enrolled patients, 63 patients with HR-MDS had an HRQoL assessment at baseline, and at least one post-baseline HRQoL assessment. HRQoL measures were associated with different clinical outcomes independently of treatment arms (e.g., improved HRQoL in patients experiencing a complete remission compared to baseline; worse HRQoL in patients whose MDS transformed to AML); however, the HRQoL measures were similar between both treatment arms (PEVO+AZA *vs*. AZA) (*Online Supplementary Figure S2*).[1, 11]

In this study, the TD state was defined according to the 2006 International Working Group response criteria in MDS,[14] which defines TD as any transfusion (blood or platelets) within an 8-week period. In order to calculate the duration of the TD state while incorporating multiple episodes of TD during the follow-up period, the number of days of all TD periods after the start of treatment and before death or disease progression were summed. Thus, a TD period started at the first transfusion of a series of transfusions and ended after a period of 8 weeks without any transfusion. An ongoing TD period at the time of death or disease progression ended at the date of the event (*Online Supplementary Figure S1*).

The TWiTR analysis was conducted in the subpopulation of HR-MDS patients. The TD state was defined as the total of TD periods from the start of treatment period and before transformation to AML or death (EFS). The REL state was defined as the time between EFS and death (OS). The TWiTR state was defined as the time without TD or REL (i.e., EFS minus TD). For each arms, Kaplan-Meier curves were calculated for each health state to partition the OS time. The mean time spent by patients in each state was estimated using the area under the Kaplan-Meier curve. The observed utility values for each health state (TD, REL, and TWiTR) were calculated in HR-MDS patients. The TWiTR analysis revealed that HR-MDS

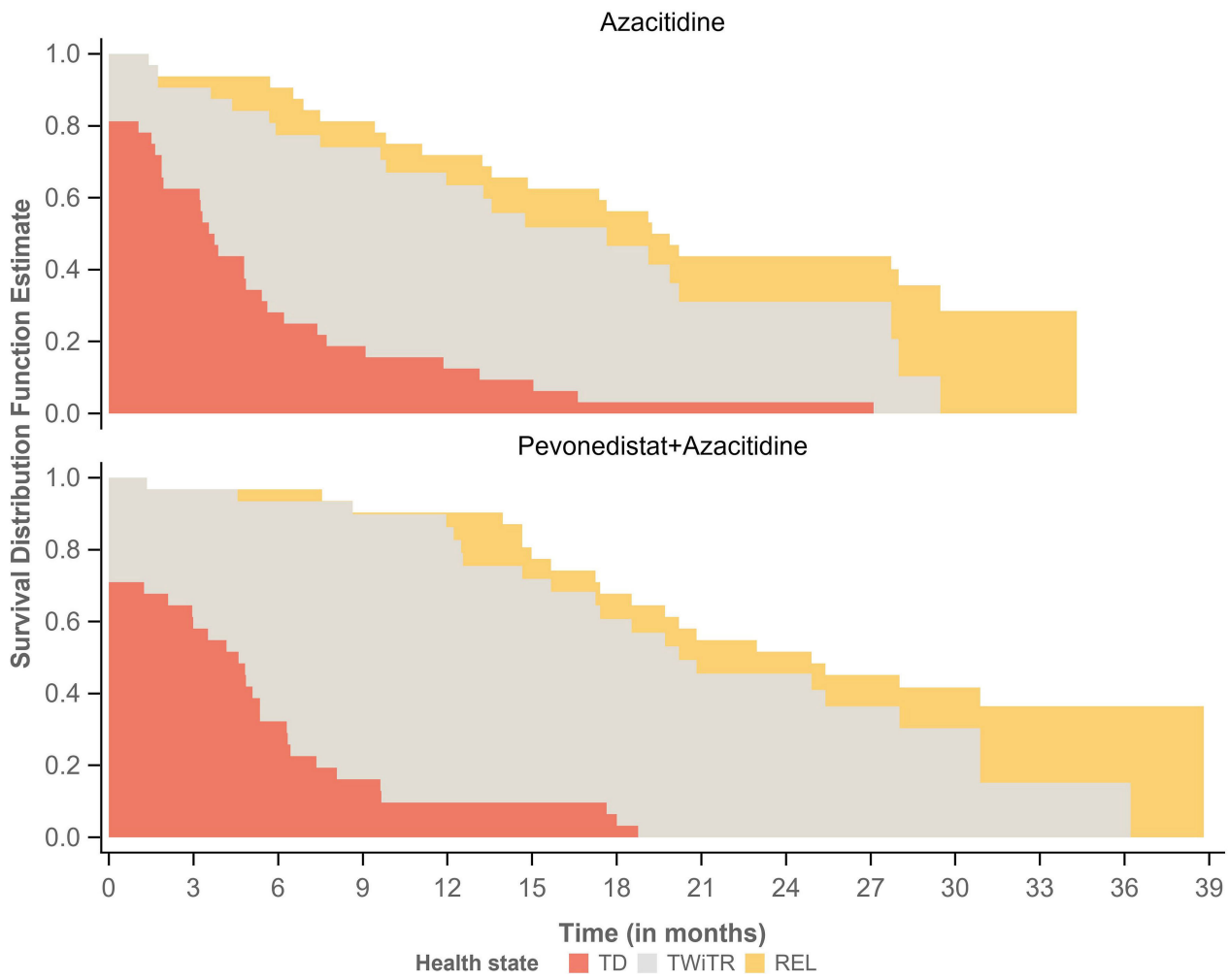

Figure 1. Partitioned survival plot of the transfusion dependence, time without transfusion reliance and relapse states in high-risk myelodysplatic syndromes subpopulation from the P-2001 study who had a patient-reported outcome assessment at baseline and at least one post-baseline assessment (N=63). TD: transfusion dependence; TWiTR: time without transfusion reliance; REL: relapse.

Table 1. Mean duration (in months) of transfusion dependence, time without transfusion reliance and relapse health states of the time without transfusion reliance analysis in the high-risk myelodysplastic syndromes subpopulation from the P-2001 study (n=63).

Health state	PEVO+AZA (N=31)	AZA (N=32)	Difference PEVO+AZA *vs.* AZA
Duration in each state in months, mean (95% CI*)			
TD	5.0 (3.1-7.0)	5.3 (3.2-7.5)	-0.3 (-3.2 to 2.5)
TWiTR	16.0 (13.2-18.8)	11.2 (8.2-14.3)	4.8 (0.7-8.9)
REL	1.8 (-1.5 to 5.1)	2.9 (-0.8 to 6.6)	-1.1 (-6.0 to 3.8)

*95% CI: 95% confidence interval estimated using a bootstrap approach; AZA: azacitidine arm; PEVO+AZA: pevonedistat+azacitidine arm; TD: transfusion dependence; TWiTR: time without transfusion reliance; REL: relapse. Difference PEVO+AZA *vs.* AZA: difference in mean duration in months between pevonedistat+azacitidine arm and azacitidine alone arm for each health state of the TWiTR analysis.

patients in the PEVO+AZA arm had a significantly longer duration of TWiTR compared with the AZA arm (Table 1: mean TWiTR duration 16.0 months *vs*. 11.2 months, respectively). As the mean TD duration was similar in both arms, for this study the TWiTR benefit was largely driven by a longer EFS in the PEVO+AZA arm (Table 1). Additionally, the mean EQ-5D-5L utility value was higher for the TWiTR state than for the TD and REL states (mean EQ-5D-5L utility value of 0.82 in TWiTR state *vs*. 0.77 in TD and REL states), suggesting that transfusion dependence may have negatively impacted HRQoL in MDS regardless of treatment. The partitioned survival plot from the TWiTR approach provides an overall picture of the duration in months in each health state in the HR-MDS subpopulation (Figure 1).

In conclusion, we have demonstrated a "proof of concept" application of the novel TWiTR analysis, a promising, innovative, patient-centered metric for the evaluation of new therapies for MDS in which transfusion dependence is clinically burdensome. TWiTR analysis involves a rigorous methodology that can be used as an assessment for the evaluation and comparison of novel treatment strategies in MDS and may serve as an effective complement to well-designed HRQoL analyses. Transfusion independence is a critical endpoint for improving the HRQoL of patients with MDS, even though hematologic improvement/transfusion independence may not always be included as an endpoint in HR-MDS clinical trials. Further application and investigation of TWiTR is warranted to determine its utility in MDS. Additionally, the TWiTR analysis can be potentially applied to prospective studies in lower-risk MDS in which transfusion independence and HRQoL may be the ultimate goal.[15]

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Contributions

All authors had substantial contribution in the drafting of the manuscript content and its critical revision; JFZ, JN, AR, LA and MAS conceived the analysis; AR designed the analysis, contributed to the conduct of the analysis, and interpreted the analysis; FM, JN, FK, HR and MD contributed to the design and the interpretation of the analysis; FM conducted the analysis.

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Data-sharing statement

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants data supporting the results reported in this article, will be made available within 3 months from initial request, to researchers who provide a

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methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization. Data requests should follow the process described in the data-sharing section on https://clinicaltrials.takeda.com/ and https://vivli.org/ourmember/takeda/.

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