# Decision analysis for transplant candidates with primary myelofibrosis in the ruxolitinib era

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## Supplementary Methods

### *Transition probabilities (TPs)*

TPs after the decision of immediate hematopoietic cell transplantation (HCT) were determined based on a study on myelofibrosis that used the European Society for Blood and Marrow Transplantation (EBMT) database,(1) and are summarized in Table 1. The cumulative incidence of relapse at 1 and 5 years was 16% and 26%, and that of non-relapse mortality (NRM) at 1 and 5 years was 26% and 37%, respectively.(1) Considering the competing risks, TPs for relapse after immediate HCT were determined to be $1 – (1 – 0.16)^{1/4} = 0.043$ for 1–4 cycles and $1 – (1 – (0.26 – 0.16)/(1 – 0.16 – 0.26))^{1/16} = 0.012$ for 5–20 cycles. Similarly, TPs for NRM after immediate HCT were $1 – (1 – 0.26)^{1/4} = 0.073$ for 1–4 cycles and $1 – (1 – (0.37 – 0.26)/(1 – 0.26 – 0.16))^{1/16} = 0.013$ for 5–20 cycles. Since the hazard ratio (HR) for NRM in patients aged ≥ 60 was 1.56 and 35% of patients were aged ≥ 60,(1) TP = 0.061 for 1–4 cycles and 0.011 for 5–20 cycles in patients with age < 60, and TP = 0.095 for 1–4 cycles and 0.017 for 5–20 cycles in patients with age ≥ 60 met these conditions. Because death due to relapse after immediate HCT at 1 and 5 years was observed in about 60% and 85% of the patients who experienced relapse, respectively,(1) TPs for death due to relapse after immediate HCT were determined to be $1 – (1 – 0.6)^{1/4} = 0.2$ for 1–4 cycles and $1 – ((0.85 – 0.6)/(1 – 0.6))^{1/16} = 0.059$ for 5–20 cycles.

TPs after the decision of delayed HCT after ruxolitinib failure are also summarized in Table 1. The overall survival (OS) after ruxolitinib was 78% at 3 years and did not reach a plateau,(2) resulting in a TP for death without HCT of $1 – 0.78^{1/12} = 0.02$ for 1–20 cycles. According to several clinical trials of ruxolitinib, a rapid reduction of splenomegaly is observed within 3 months.(3-5) Indeed, 53.4% of patients experienced a clinical benefit within 3 months and no patients showed this benefit thereafter in the COMFORT-II study.(5) Although the

most common hematologic adverse events were anemia and thrombocytopenia, all patients could continue ruxolitinib with dose modifications and supportive care in this study. Thus, TPs for a ruxolitinib response were determined to be 0.53 for 1 cycle and 0 for 2–20 cycles. Because the probability of a continuous response at 3 and 5 years was 51% and 48% among patients with an initial ruxolitinib response,(5) TPs for relapse after a ruxolitinib response were determined to be $1 – 0.51^{1/12} = 0.055$ for 1–12 cycles and $1 – (0.48/0.51)^{1/8} = 0.0075$ for 13–20 cycles. The previous study showed 72% of the patients could consider HCT following to JAK inhibitor failure.(6) Thus, we assumed that 72% of patients proceeded to HCT within 2 cycles after ruxolitinib failure, resulting in a TP for HCT after ruxolitinib of $1 – (1 – 0.72)^{1/2} = 0.47$ for 1–2 cycles after entering this state.

Based on the EBMT study, the cumulative incidence of relapse at 2 and 5 years was reported to be 20% and 26%, and NRM at 2 and 5 years was about 30% and 37%, respectively.(1) Considering the competing risks, the relapse rate was 0.2 between 0 and 2 years and $(0.26 – 0.2)/(1 – 0.2 – 0.3) = 0.12$ between 2 and 5 years, and the NRM rate was 0.3 between 0 and 2 years and $(0.37 – 0.3)/(1 – 0.3 – 0.2) = 0.14$ between 2 and 5 years, respectively. However, this study included both patients with and without exposure to ruxolitinib. Because ruxolitinib could be used simply as a bridge to HCT,(7) the data might not reflect the actual conditions for patients without a ruxolitinib response. On the other hand, another study by Shanavas et al. included patients who had been treated with JAK1/2 inhibitors prior to HCT and evaluated the outcome after HCT according to the response to these JAK1/2 inhibitors.(8) In patients without a ruxolitinib response, the cumulative incidence of relapse and NRM at 2 years was 13% and 37%.(8) Because the cumulative incidence of relapse at 5 years was not shown due to an inadequate follow-up time, we estimated the relapse rate between 2 and 5 years to be $0.13 \times (1 – 0.13 – 0.37) \times 0.12 / 0.2 = 0.039$ by using the relapse rate from the EBMT study.(1) As a result, TPs for relapse post-HCT after

ruxolitinib failure were $1 – (1 – 0.13)^{1/8} = 0.017$ for 1–8 cycles and $1 – (1 – 0.039/(1 – 0.13 – 0.37))^{1/12} = 0.0067$ for 9–20 cycles. In the same way, the NRM rate at 2 and 5 years was estimated to be 0.37 x (1 – 0.37 – 0.13) x 0.14 / 0.3 = 0.086.(1) Therefore, TPs for NRM post-HCT after ruxolitinib failure were $1 – (1 – 0.37)^{1/8} = 0.056$ for 1–8 cycles and $1 – (1 – 0.086/(1 – 0.37 – 0.13))^{1/12} = 0.016$ for 9–20 cycles. As in the calculation of TPs for NRM after immediate HCT, we separately set TPs for NRM post-HCT after ruxolitinib failure according to patient age. Since the HR of NRM in HCT for PMF patients aged ≥ 60 was 1.56 (1) and about 50% of patients were aged ≥ 60 in the study on HCT with prior exposure to JAK inhibitors,(8) TP = 0.044 for 1–8 cycles and 0.013 for 9–20 cycles in patients aged < 60, and TP = 0.069 for 1–8 cycles and 0.02 for 9–20 cycles in patients aged ≥ 60. Because the cumulative incidence of death due to relapse post-HCT was reported to be 75% at 2 years and 85% at 5 years in the EBMT study, the mortality rate after relapse was 0.75 between 0 and 2 years and (0.85 – 0.75)/(1 – 0.75) = 0.4 between 2 and 5 years.(1) In patients without a ruxolitinib response, the probability of OS at 2 years was reported to be 55%.(8) Because the cumulative incidences of relapse and NRM at 2 years were 13% and 37%, the cumulative incidence of death due to relapse in this study was (100 – 55) – 37 = 8%, and the mortality rate at 2 years after relapse was 0.08 / 0.13 = 0.62. Thus, we estimated the mortality rate after relapse between 2 and 5 years to be 0.62 x (1 – 0.62) x 0.4 / 0.75 = 0.13.(8) Therefore, TPs for death due to relapse post-HCT after ruxolitinib failure were determined to be $1 – (1 – 0.62)^{1/8} = 0.11$ for 1–8 cycles and $1 – (1 – 0.13/(1 – 0.62))^{1/12} = 0.034$ for 9–20 cycles, respectively. Leukemic transformation (LT) occurs in about 4% of patients with PMF,(9) resulting in a TP for LT of $1 – (1 – 0.04)^{1/20} = 0.002$ for 1–20 cycles. Since we targeted transplant candidates in the current study, 80% of the patients were determined to undergo HCT after LT within 2 cycles and the others were considered to die at 2 cycles after entering the corresponding state. Thus, the TP for HCT after LT was $1 – (1 – 0.8)^{1/2} = 0.55$ for 1–2

cycles. Takagi et al. showed that the 6-month and 2-year OS in HCT after LT were about 50% and 29%, respectively, and few patients survived after relapse post-HCT.(10) Therefore, we did not set a TP for relapse post-HCT after LT, and TPs for death post-HCT after LT were $1 - 0.5^{1/2} = 0.29$ for 1–2 cycles and $1 - (0.29/0.5)^{1/6} = 0.087$ for 3–8 cycles, respectively.

Basically, plausible ranges were set to be 0.8 – 1.2 times each baseline value.(11, 12) Real-world data showed that the most common reason for JAK inhibitor failure was loss of spleen response, and about a half rate of the patients could not continue JAK inhibitor because of intolerant cytopenia.(6) Since we set that 47% of the patients treated with ruxolitinib did not experience a spleen response in our model, we assumed that ruxolitinib failure by cytopenia could occur at most 23%. Moreover, in the COMFORT-II study, decrease in hemoglobin levels after ruxolitinib initiation occurred during the first 12 weeks,(5) which was equal to 1 cycle in our model. Thus, in sensitivity analyses, plausible range of ruxolitinib response was set to be 0.30 – 0.53.

***Utilities***

First, we calculated the utilities in the decision for immediate HCT. The utility of each health state was incorporated into the model to reflect quality-of-life (QoL) between 0 (dead) and 1 (optimal health state). In a previous study, the utility of being alive without relapse post-HCT was reported to be 0.65 and 0.80 with and without chronic graft-versus-host disease (GVHD).(13) Solomon et al. reported that disease-free survival (DFS) and active chronic GVHD were 68% and 23% at 1 year, 60% and 14% at 2 years, 54% and 7% at 3 years, and 52% and 4% at 4 years after HCT, respectively.(14) Thus, the utility of being alive without relapse after immediate HCT was determined to be $0.8 \times (0.68 - 0.23)/0.68 + 0.65 \times 0.23/0.68 = 0.75$ at 1 year, $0.8 \times (0.60 - 0.14)/0.60 + 0.65 \times 0.14/0.60 = 0.77$ at 2 years, $0.8 \times (0.54 - 0.07)/0.54 + 0.65 \times 0.07/0.54 = 0.78$ at 3 years, and $0.8 \times (0.52 - 0.04)/0.52 + 0.65 \times 0.04/0.52$

= 0.80 at 4 years. The utility of relapse after immediate HCT was set at 0.50, which was shown to be the baseline QoL among patients with primary myelofibrosis (PMF) (Table 2).(15, 16)

Next, we determined the utilities in the decision for delayed HCT after ruxolitinib failure. As mentioned above, the baseline utility of patients with PMF was set at 0.50.(15, 16) The utility was reported to improve to 0.65 with a ruxolitinib response,(15, 16) and those for ruxolitinib failure and LT were determined to be 0.50 and 0.40, respectively. Because the cumulative incidence of extensive chronic GVHD at 2 years was 17% and 29% in patients with and without a ruxolitinib response prior to HCT,(8) we estimated that the incidence of active chronic GVHD post-HCT after ruxolitinib failure was 29/17 = 1.71 times higher than that after immediate HCT. Thus, the utilities of being alive without relapse post-HCT after ruxolitinib failure were determined to be 0.8 x (0.68 – 0.23 x 1.71)/0.68 + 0.65 x 0.23 x 1.71/0.68 = 0.71 at 1 year, 0.8 x (0.60 – 0.14 x 1.71)/0.60 + 0.65 x 0.14 x 1.71/0.60 = 0.74 at 2 years, 0.8 x (0.54 – 0.07 x 1.71)/0.54 + 0.65 x 0.07 x 1.71/0.54 = 0.77 at 3 years, and 0.8 x (0.52 – 0.04 x 1.71)/0.52 + 0.65 x 0.04 x 1.71/0.52 = 0.78 at 4 years, respectively (Table 2).

Finally, in both strategies, the utility of 1 cycle at 3 months post-HCT was determined to be 0.50 considering the toxicity of the early phase post-HCT. In addition, we treated the utility of being alive without relapse post-HCT at 5 years to be the same as that at 4 years. As with TPs, plausible ranges were set at 0.8 – 1.2 times each baseline value.

***Statistical analyses***

Statistical calculations were performed using TreeAge Pro 2022 software (Williamstown, MA, USA) and EZR version 1.61 (Jichi Medical University Saitama Medical Center), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 4.2.2, Vienna, Austria).(17)

### *Sensitivity analyses*

To evaluate the robustness of the decision model, we performed one-way sensitivity analyses for TPs and utilities. In these analyses, the decision tree was recalculated using various TPs and utilities in the probable range, and we determined which decision contributed the most to better QALYs. Sensitivity analyses for the utilities of being alive without relapse after HCT were performed based on plausible ranges of those with and without chronic GVHD. Based on a one-way sensitivity analysis, we drew Tornado diagrams. We also performed probabilistic sensitivity analyses using a Monte Carlo simulation with various TPs and utilities in the plausible range (n = 1000).

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## Supplementary Figure Legends

**Supplementary Figure 1 Results of a probabilistic sensitivity analysis with 1000 simulations.**

Histograms show incremental quality-adjusted life years (QALYs) of “Delayed hematopoietic cell transplantation (HCT) after ruxolitinib failure” – “Immediate HCT” for patients in the (A) entire cohort, and the (B) age < 60 and (C) age ≥ 60 groups.

# Supplementary Figure 1