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Received: February 11, 2024.

Accepted: June 7, 2024.

Citation: Yosuke Okada, Hideki Nakasone, Shunto Kawamura, Kosuke Takano, Kazuki Yoshimura, Masaharu Tamaki, Akari Matsuoka, Takuto Ishikawa, Tomohiro Meno, Yuhei Nakamura, Masakatsu Kawamura, Junko Takeshita, Nozomu Yoshino, Yukiko Misaki, Machiko Kusuda, Aki Tanihara, Shun-ichi Kimura, Shinichi Kako, and Yoshinobu Kanda. Decision analysis for transplant candidates with primary myelofibrosis in the ruxolitinib era. *Haematologica*. 2024 June 20. doi: 10.3324/haematol.2024.285256 [Epub ahead of print]

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

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Running title: Decision analysis for PMF in the ruxolitinib era

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Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Funding statement

There was no funding relevant to the study.

Authors' Contributions

YO designed the study, collected, and analyzed data, and wrote the manuscript. HN designed the study, analyzed data, and wrote the manuscript. S Kawamura, TK, KY, MT, AM, TI, TM, YN, M Kawamura, JT, NY, YM, M Kusuda, AT, S Kimura, and S Kako wrote the manuscript. YK advised on the methods, wrote the manuscript, and were responsible for the projects.

Conflicts of Interest Disclosures for each author

There was no financial competing interest relevant to the study.

Abstract

The recent progress with ruxolitinib treatment might improve quality-of-life as well as overall survival in patients with primary myelofibrosis (PMF). Therefore, the optimal timing of allogeneic hematopoietic cell transplantation (HCT) remains to be elucidated in the ruxolitinib era. We constructed a Markov model to simulate the 5-year clinical course of transplant candidates with PMF, and compared outcomes between immediate HCT and delayed HCT after ruxolitinib failure. Since older age was associated with an increased risk of mortality, we analyzed patients aged < 60 and ≥ 60 separately in subgroup analyses. The expected life years was consistently longer in delayed HCT after ruxolitinib failure regardless of patient age. Regarding quality-adjusted life years (QALYs), a baseline analysis showed that immediate HCT was inferior to delayed HCT after ruxolitinib failure (2.19 versus 2.26). In patients aged < 60 , immediate HCT was equivalent to delayed HCT after ruxolitinib failure (2.31 versus 2.31). On the other hand, in patients aged ≥ 60 , immediate HCT was inferior to delayed HCT after ruxolitinib failure (1.98 versus 2.21). A one-way sensitivity analysis showed that the utility of being alive without chronic graft-versus-host disease after immediate HCT was the most influential parameter for QALYs, and that a value higher than 0.836 could reverse the superiority of delayed HCT after ruxolitinib failure. As a result, delayed HCT after ruxolitinib failure is expected to be superior to immediate HCT, especially in patients aged ≥ 60 , and is also a promising strategy even in those aged < 60 .

Introduction

Primary myelofibrosis (PMF) is characterized by stem cell-derived clonal myeloproliferation based on constitutive JAK-STAT signaling,(1) and patients with PMF often suffer from anemia, hepatosplenomegaly, and constitutional syndrome, which are associated with impaired quality-of-life (QoL).(2) The only curative treatment for PMF is allogeneic hematopoietic cell transplantation (HCT), but transplant-related mortality (TRM) after HCT remains a major problem.(3, 4) In addition, chronic graft-versus-host disease (GVHD) after HCT could considerably impair QoL.(5) Ruxolitinib is a selective inhibitor of JAK1/2 and has the potential to reduce disease-related symptoms and improve QoL.(6) Moreover, the decrease in the size of the spleen with ruxolitinib was reported to correlate with longer overall survival (OS).(7) Thus, progress in treatment with ruxolitinib might affect the decision regarding the timing of HCT for transplant candidates.(8) Immediate HCT at the time of diagnosis is currently recommended for International Prognostic Scoring System (IPSS) intermediate-2 and high-risk patients in the recommendations from European LeukemiaNet.(9-11) However, pretransplant ruxolitinib may be able to delay HCT until disease progression, while unfavorable outcomes after HCT have also been reported after disease progression with ruxolitinib.(12) Therefore, the optimal timing of allogeneic HCT for PMF remains to be elucidated in the ruxolitinib era.

Ideally, a randomized prospective trial is recommended to compare the outcomes of these clinical strategies. However, this seems impractical. A decision analysis is an alternative statistical technique that makes it possible to evaluate clinical decisions under uncertain conditions. QoL can also be considered in the analytic method as quality-adjusted life years (QALYs). Cipkar et al. previously performed a decision analysis to determine the optimal timing of HCT for PMF, in which the effect of ruxolitinib for survival was not considered.(13) Using a Markov model, we performed a decision analysis for transplant

candidates with PMF to determine the optimal strategy between immediate HCT after diagnosis and delayed HCT after ruxolitinib failure.(14)

Methods

Patients

Based on the recommendations from European LeukemiaNet, we considered adult patients with PMF who were categorized into the IPSS intermediate-2-risk and high-risk groups and had an HLA-matched donor as candidates for this analysis, since upfront HCT was recommended as an initial therapy in these patients.(10, 11, 15) We assumed that all patients in our model had splenomegaly at the time of diagnosis. A large cohort and long-term observation are required for the Markov model to define appropriate transition probabilities (TPs) and utilities that change with time. Thus, we referred to the report from Hernández-Boluda et al.(16) to estimate the clinical course of immediate HCT, which was a retrospective study including 2916 patients. Regarding the clinical course of delayed HCT after ruxolitinib failure, we mainly referred to the report from Harrison et al.,(17) which was long-term comparison in the Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment (COMFORT)-II trial including 219 patients.

Model structure

We constructed a decision tree and compared QALYs of two strategies: “immediate HCT” and “delayed HCT after ruxolitinib failure”. Based on previous published reports, a response to ruxolitinib was defined as at least a 35% reduction in spleen volume.(18, 19) Ruxolitinib failure was defined as the lack of a reduction in the spleen volume of > 35% from the baseline or an increase in spleen volume after a > 35% reduction was achieved. In the group that received “delayed HCT after ruxolitinib failure”, patients received ruxolitinib as an initial therapy, and proceeded to HCT after ruxolitinib failure.

In the decision tree (Figure 1), the square on the left is a decision node, and we can choose either “Immediate HCT” or “RUXO” strategies. Each decision is followed by a Markov node, which includes several Markov health states including an only-absorbing state of “Death”. Each branch proceeds to a chance node, and each node has 2 to 4 possible states with a specific TP (Table 1). In the subgroup analyses, we separately analyzed patients aged < 60 and ≥ 60 because age ≥ 60 was reported to be associated with an increased risk of non-relapse mortality (NRM).(16) The cycle length was 3 months, and the analysis was performed for 20 cycles, or 5 years. QALYs were calculated by multiplying QoL score for the health states (utilities) by the number of years for which a patient was expected to live in the health states. QALYs for each decision were calculated based on the probability weighting of QALYs obtained by the Markov processes with an annual discount rate of 3%, which is a standard method based on the concept that the future value of life years (LYs) is less than the current value (Table 2).(20, 21) For calculating utilities, we referred to the reports from Kurosawa et al., Shanavas et al., Harrison et al., and Mesa et al..(6, 12, 18, 22) Details of TPs and utilities are provided in the *Online Supplementary Methods*.(23)

This study was approved by the Institutional Review Board of Jichi Medical University Saitama Medical Center.

Results

Baseline analysis

The 5-year OS calculated in this model was 47.1% for immediate HCT and 60.1% for delayed HCT after ruxolitinib failure after the clinical decisions, which seemed compatible with the original OS (Figure 2).(16, 17) QALYs were 2.19 and 2.26 after the decisions for immediate HCT and delayed HCT after ruxolitinib failure, while the expected LYs without adjusting for QoL were 3.22 and 3.96 years, respectively.

Sensitivity analyses

In one-way sensitivity analyses, the utility of being alive without chronic GVHD after immediate HCT was the most influential parameter for QALYs, followed by the utility of a ruxolitinib response, a TP for NRM after immediate HCT, the utility of ruxolitinib failure, and the utility of being alive without chronic GVHD post-HCT after ruxolitinib failure (Figure 3A). The superiority of delayed HCT after ruxolitinib failure was reversed if the utility of being alive without chronic GVHD after immediate HCT was higher than 0.84 or the TP for NRM after immediate HCT was 0.9 times lower than the original value. When the utilities of a ruxolitinib response and failure were lower than 0.595 or 0.449, and the utility of being alive without chronic GVHD post-HCT after ruxolitinib failure was lower than 0.669, the superiority of delayed HCT after ruxolitinib failure was also reversed.

Next, we performed probabilistic sensitivity analyses using a Monte Carlo simulation. Out of 1000 simulations, delayed HCT after ruxolitinib failure was superior to immediate HCT in 95.8% (Supplementary Figure S1A).

Subgroup analyses according to age

In patients aged < 60, immediate HCT was equivalent to delayed HCT after ruxolitinib failure, with QALYs of 2.31 versus 2.31. On the other hand, in patients aged \geq 60, immediate HCT was inferior to delayed HCT after ruxolitinib failure, with QALYs of 1.98 versus 2.21. Expected LYs were shorter in the strategy of immediate HCT compared with delayed HCT after ruxolitinib failure in patients aged < 60 (3.39 versus 4.04 years) and in those aged \geq 60 (2.93 versus 3.88 years, respectively).

Similar to the results in the entire cohort, one-way sensitivity analyses showed that the impact of the utility of being alive without chronic GVHD after immediate HCT was most influential in both age groups. In the age < 60 group, the superiority of delayed HCT after

ruxolitinib failure was reversed when the utility of being alive with and without chronic GVHD after immediate HCT was higher than 0.662 and 0.803, that of a ruxolitinib response and failure was lower than 0.646 or 0.496, and that of being alive with and without chronic GVHD post-HCT after ruxolitinib failure was lower than 0.632 and 0.791, and that of relapse after immediate HCT and post-HCT after ruxolitinib failure was higher than 0.517 and 0.429, respectively (Figure 3B). Moreover, immediate HCT was superior to delayed HCT after ruxolitinib failure when the TP for NRM after immediate HCT and post-HCT after ruxolitinib failure was 0.991 times lower and 1.029 times higher, that of relapse after immediate HCT and post-HCT after ruxolitinib failure was 0.983 times lower and 1.121 times higher, that of death due to relapse after immediate HCT was 0.959 times lower, that of HCT after ruxolitinib failure was 0.937 times lower than the original values, and that of a ruxolitinib response and failure was lower than 0.485 or 1.085 times higher. Instead, in the age ≥ 60 group, the superiority of delayed HCT after ruxolitinib was reversed only when the utility of being alive without chronic GVHD after immediate HCT was higher than 0.926 (Figure 3C).

Probabilistic sensitivity analyses showed that QALYs were better after the decision for delayed HCT after ruxolitinib failure in 54.9% of the patients in the age < 60 group and in 100.0% of those in the age ≥ 60 group (Supplementary Figure S1B and S1C).

Discussion

Using a Markov model, we performed the current decision analysis to compare the use of immediate HCT after diagnosis and delayed HCT after ruxolitinib failure for transplant candidates with PMF who had an HLA-matched donor. To the best of our knowledge, this is the first study to evaluate the optimal timing of HCT for PMF in the ruxolitinib era. We found that these strategies had similar QALYs in the age < 60 group, while delayed HCT after ruxolitinib failure led to superior QALYs in the age ≥ 60 group. Expected LYs were longer in delayed HCT after ruxolitinib failure compared with immediate HCT in both age groups. Thus,

immediate HCT might contribute to an improved QoL in return for a risk of TRM, while delayed HCT after ruxolitinib failure is expected to result in longer survival with relatively impaired QoL.

In one-way sensitivity analyses, the utility of being alive without chronic GVHD after immediate HCT strongly influenced the results. Chronic GVHD strongly contributes to the QoL after HCT,(24) and the incidence of chronic GVHD decreases over time. Thus, QoL might tend to gradually recover after HCT, and we determined the utilities of being alive with and without chronic GVHD after HCT based on the data of current GVHD-free, relapse-free survival (GRFS).(25) Although these studies were not aimed only at PMF, QoL and the incidence of chronic GVHD did not seem to be affected by the type of disease.(26) Nevertheless, QALYs after the decision of delayed HCT after ruxolitinib failure were superior to those compared with immediate HCT in the current study. The utility of a ruxolitinib response also strongly affected QALYs. Ruxolitinib reduces spleen volume and myelofibrosis-associated symptoms such as fatigue, insomnia, and appetite loss.(19) Therefore, patients who achieve marked reductions in these symptoms are likely to benefit from the strategy of delayed HCT after ruxolitinib failure.

As shown in the subgroup analyses, the utility of being alive without chronic GVHD after immediate HCT strongly influenced the results in both age groups. In the age ≥ 60 group, no other parameters could reverse the superiority of delayed HCT after ruxolitinib failure, and delayed HCT after ruxolitinib failure might be a promising strategy. On the other hand, in patients aged < 60 , immediate HCT seemed to give results equivalent to those with delayed HCT after ruxolitinib failure, and the superiority of delayed HCT after ruxolitinib failure could be reversed depending on several parameters. Therefore, both strategies seem to be worth considering in the age < 60 group.

Most previous studies that have compared HCT treatment and non-HCT treatment showed that HCT could achieve long-term survival instead of impaired QoL because of chronic GVHD.(21, 22) On the other hand, QoL in patients with PMF-associated symptoms was inferior to that in those with chronic GVHD in studies on PMF.(6, 18) Thus, HCT for PMF might be expected to improve QoL from the baseline along with the risk of TRM. As a result, for transplant candidates with PMF, we might need to select between immediate HCT to improve QoL and delayed HCT after ruxolitinib failure to prolong survival duration.

The prognosis of patients treated with ruxolitinib in the current study seemed to be better than those in reports based on real-world data.(27, 28) TPs in delayed HCT after ruxolitinib failure were determined based on data from several clinical trials,(7, 17) whereas those in immediate HCT were based on a database study.(16) Baseline conditions in cohorts registered in clinical trials tend to be better than those in the real world. Thus, the prognosis of delayed HCT after ruxolitinib failure might be overestimated in the current study, while we also considered real-world data about ruxolitinib failure in sensitivity analyses. Further studies based on real-world data are warranted to compare immediate HCT and delayed HCT after ruxolitinib failure. In addition, OS after immediate HCT might be slightly lower than the previous report.(16) It might be because exact rate of death due to relapse was not available, and we calculated TPs for death due to relapse based on the estimated rate. However, considering that we assumed patients with higher disease risk in our model, the setting seemed to be appropriate. Moreover, our results seemed to be inconsistent with the previous study from Kröger et al., in which the outcomes after HCT were equivalent between no or lost response to pre-HCT ruxolitinib and those without pre-HCT ruxolitinib treatment.(29) The discrepancy could be explained by the difference in analyzed-timepoints. The previous study compared their survival from the day of HCT, while we compared the survival time from the decision of strategies at diagnosis. When the time to HCT from

diagnosis was taken into consideration, our study demonstrated that delayed HCT after ruxolitinib failure would be superior to immediate HCT.

Our study had some limitations. First, TPs in immediate HCT were derived from a single retrospective study.(16) In that study, most of the graft source was peripheral blood (PB), and more than half of patients underwent HCT from unrelated donors. Different background data could change the results of the current study. Since the incidence of chronic GVHD especially affected QoL, the graft source and donor type should be considered in individual estimations. Indeed, a lower risk of GVHD was reported in bone marrow transplantation (BMT) from a haploidentical donor with posttransplant cyclophosphamide (PTCy) compared with peripheral blood stem cell transplantation (PBSCT) from an HLA-matched unrelated donor.(30) PTCy should be incorporated and evaluated in our model in the future. Moreover, we determined QoL after HCT based on chronic GVHD status, while GVHD alone is not the whole story of QoL after HCT. Second, in the current model, a response to ruxolitinib was assumed based on a decrease in spleen volume. Thus, it can be difficult to assess the response to ruxolitinib in patients who do not have splenomegaly. The clinical decision for HCT in the real world might be based on transfusion dependency, adverse cytogenetics, and high-risk mutations in addition to a ruxolitinib response.(9, 31, 32) Third, some TPs and utilities were not available from previous published data, and were estimated by combining several reports. When making decisions based on the current model, these limitations should be considered.

In conclusion, for transplant candidates with PMF and an HLA-matched donor, immediate HCT and delayed HCT after ruxolitinib failure showed comparable QALYs in the age < 60 group. On the other hand, in the age \geq 60 group, delayed HCT after ruxolitinib failure is expected to be superior to immediate HCT. Consideration of the risk of chronic GVHD might help when making individual decisions.

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Table 1 Summary of transition probabilities

Immediate HCT				
Parameter	Cycle	Baseline Value (Plausible Range)		
		Entire cohort	Age < 60	Age ≥ 60
Relapse after immediate HCT	1–4	0.043 (0.034 – 0.052)		
	5–20	0.012 (0.0096 – 0.014)		
Death from relapse after immediate HCT	1–4	0.2 (0.16 – 0.24)		
	5–20	0.059 (0.047 – 0.071)		
NRM after immediate HCT	1–4	0.073 (0.058 – 0.088)	0.061 (0.049 – 0.073)	0.095 (0.076 – 0.114)
	5–20	0.013 (0.010 – 0.016)	0.011 (0.0088 – 0.013)	0.017 (0.014 – 0.020)
Delayed HCT after ruxolitinib failure				
Parameter	Cycle	Baseline Value (Plausible Range)		
		Entire cohort	Age < 60	Age ≥ 60
Death after ruxolitinib prior to HCT	1–20	0.02 (0.016 – 0.024)		
Ruxolitinib response	1	0.53 (0.30 – 0.53)		
	2–20	0		
Relapse after ruxolitinib response	1–12	0.055 (0.044 – 0.066)		
	13–20	0.0075 (0.006 – 0.009)		
HCT after ruxolitinib failure	1–2*	0.47 (0.38 – 0.56)		
	3–20*	0		
Relapse post-HCT after ruxolitinib failure	1–8*	0.017 (0.014 – 0.020)		
	9–20*	0.012 (0.0096 – 0.014)		
Death from relapse post-HCT after ruxolitinib failure	1–8*	0.11 (0.088 – 0.130)		
	9–20*	0.033 (0.026 – 0.04)		
NRM post-HCT after ruxolitinib failure	1–8*	0.056 (0.045 – 0.067)	0.044 (0.035 – 0.053)	0.069 (0.055 – 0.083)
	9–20*	0.016 (0.013 – 0.019)	0.013 (0.010 – 0.016)	0.020 (0.016 – 0.024)
Leukemic transformation	1–20	0.002 (0.0016 – 0.0024)		
HCT after leukemic transformation	1–2*	0.55		
	3–20*	0		
Death post-HCT after leukemic transformation	1–2*	0.29 (0.23 – 0.35)		
	3–8*	0.087 (0.070 – 0.104)		
	9–20*	0		

* Cycle number after entering the corresponding state

HCT, hematopoietic cell transplantation; NRM, non-relapse mortality.

Table 2 Summary of utilities

Immediate HCT		
State	Cycle	Baseline Value (Plausible Range)
First cycle after immediate HCT	1	0.50 (0.40 – 0.60)
Alive without relapse after immediate HCT*	2–4	0.75
	5–8	0.77
	9–12	0.78
	13–20	0.80
Alive with chronic GVHD after immediate HCT	2–20	0.65 (0.52 – 0.78)
Alive without chronic GVHD after immediate HCT	2–20	0.80 (0.64 – 0.96)
Relapse after immediate HCT		0.50 (0.40 – 0.60)
Delayed HCT after ruxolitinib failure		
State	Cycle	Baseline Value (Plausible Range)
Ruxolitinib response		0.65 (0.52 – 0.78)
No response / Relapse after ruxolitinib response		0.50 (0.40 – 0.60)
Leukemic transformation		0.40 (0.32 – 0.48)
First cycle post-HCT after ruxolitinib failure	1	0.50 (0.40 – 0.60)
Alive without relapse post-HCT after ruxolitinib failure*	2–4	0.71
	5–8	0.74
	9–12	0.77
	13–20	0.78
Alive with chronic GVHD after ruxolitinib failure	2–20	0.65 (0.52 – 0.78)
Alive without chronic GVHD after ruxolitinib failure	2–20	0.80 (0.64 – 0.96)
Relapse post-HCT after ruxolitinib failure		0.50 (0.40 – 0.60)

* Baseline values of the utility of being alive without relapse after HCT in both strategies were calculated according to the rate of active chronic GVHD among disease-free survival (DFS) for each year after HCT and the utilities of being alive with and without chronic GVHD. Sensitivity analyses for the utilities of being alive without relapse after HCT were performed based on the plausible range of the utilities of being alive with and without chronic GVHD.

HCT, hematopoietic cell transplantation; GVHD, graft-versus-host disease.

Figure Legends

Figure 1 The decision tree.

The leftmost line shows the targeted patients. The square on the left is a decision node. The second line shows the two strategies that were compared: “Immediate hematopoietic cell transplantation (HCT)” and “Delayed HCT after ruxolitinib failure”. At the decision node, we could decide to proceed to either of these. A Markov node (circled M) leads to a chance node, which has 2 to 4 possible states.

Figure 2 Estimated overall survival after the decisions.

Figure 3 Tornado diagram of a one-way sensitivity analysis for transition probabilities (TPs) and utilities in the (A) entire cohort, (B) age < 60 and (C) age ≥ 60 groups.

Plausible ranges are shown with respect to the original values. The x-axis shows the incremental quality-adjusted life years (QALYs) of “Delayed hematopoietic cell transplantation (HCT) after ruxolitinib failure” against “Immediate HCT”. The red and blue bars indicate increases and decreases in TPs and utilities from the baseline values. The width of each bar reflects the impact of the parameter.

cGVHD, chronic graft-versus-host disease; RUXO, ruxolitinib; NRM, non-relapse mortality; LT, leukemic transformation; SD, stable disease.

Figure 1

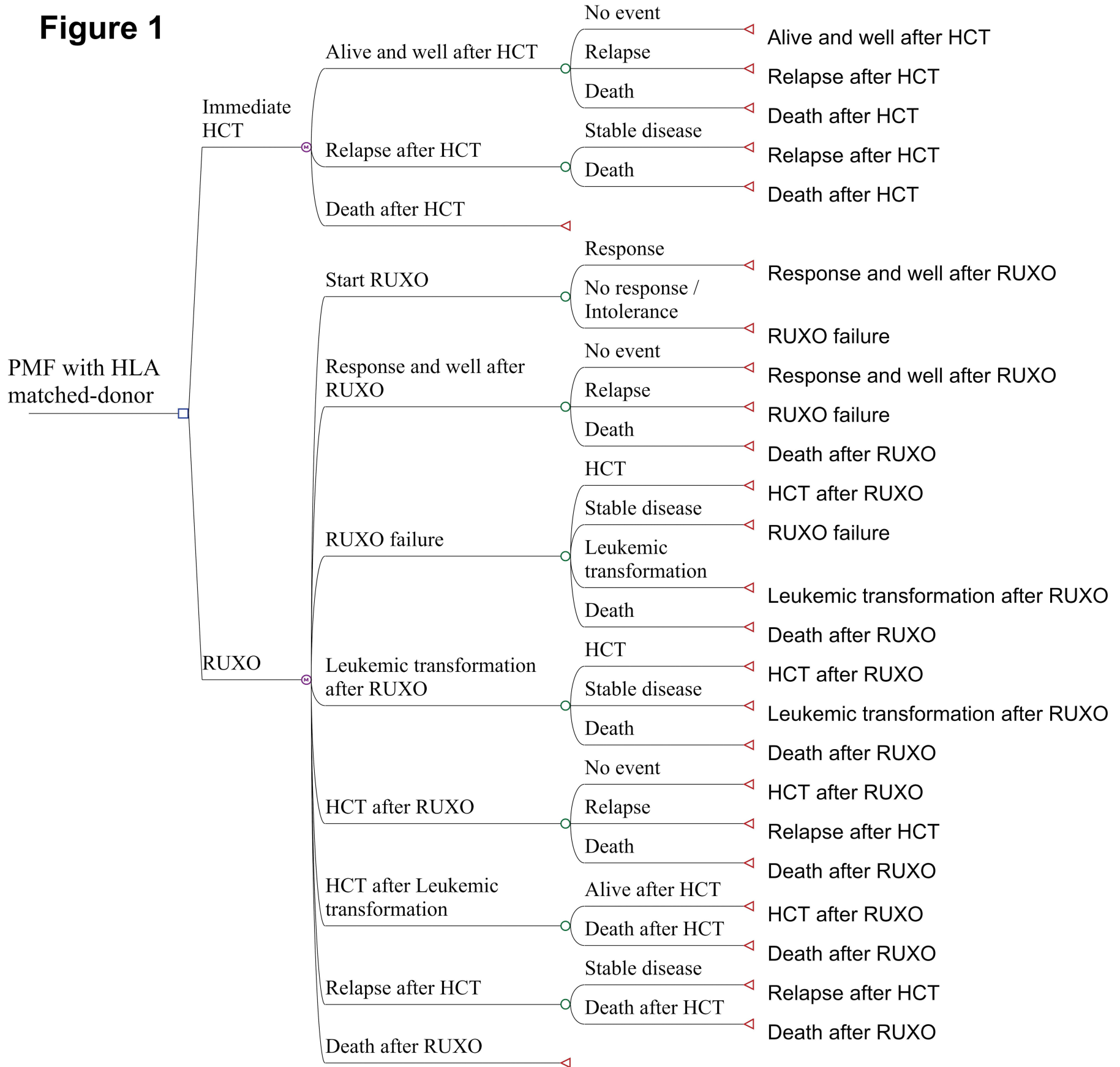


Figure 2

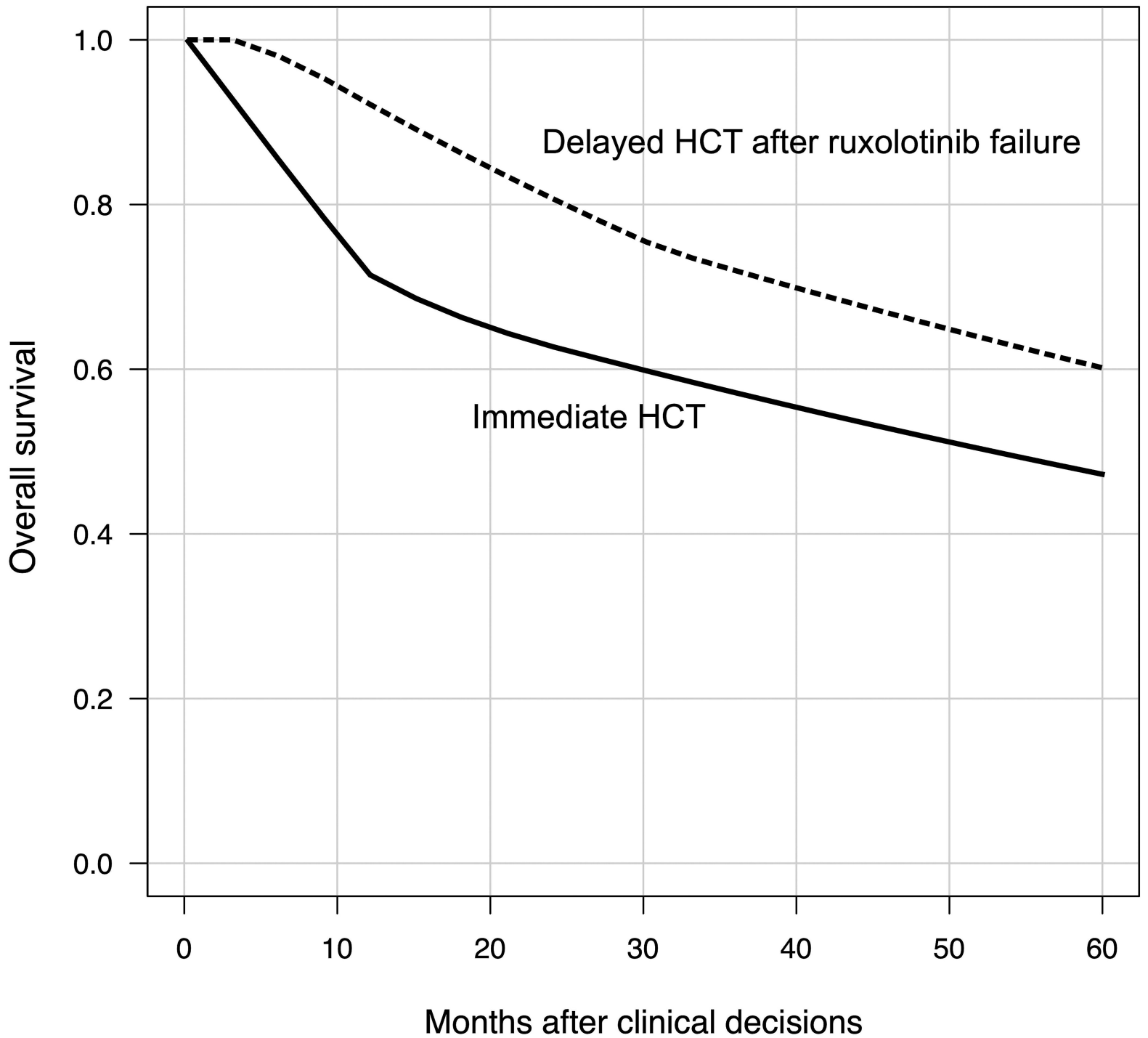
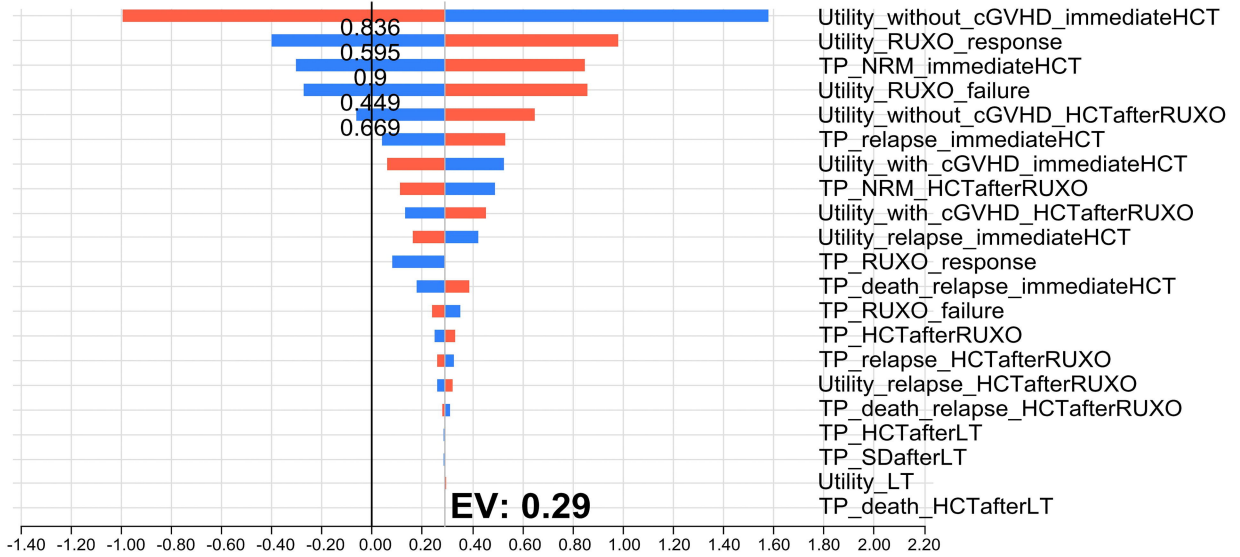


Figure 3

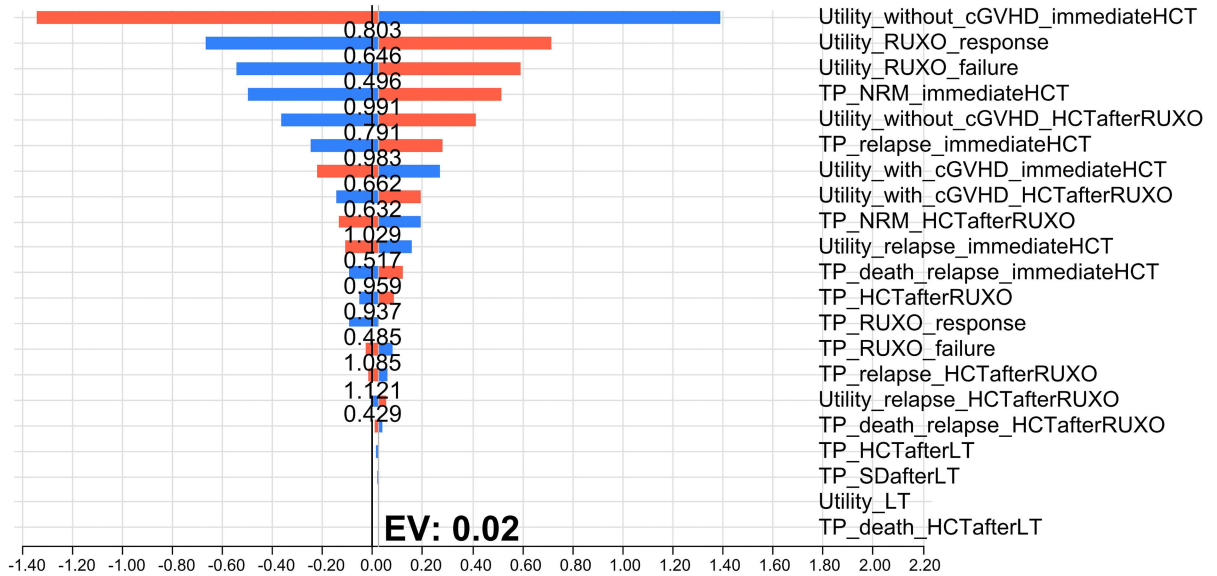
Tornado Diagram: Incremental Effectiveness

RUXO vs. Immediate HCT

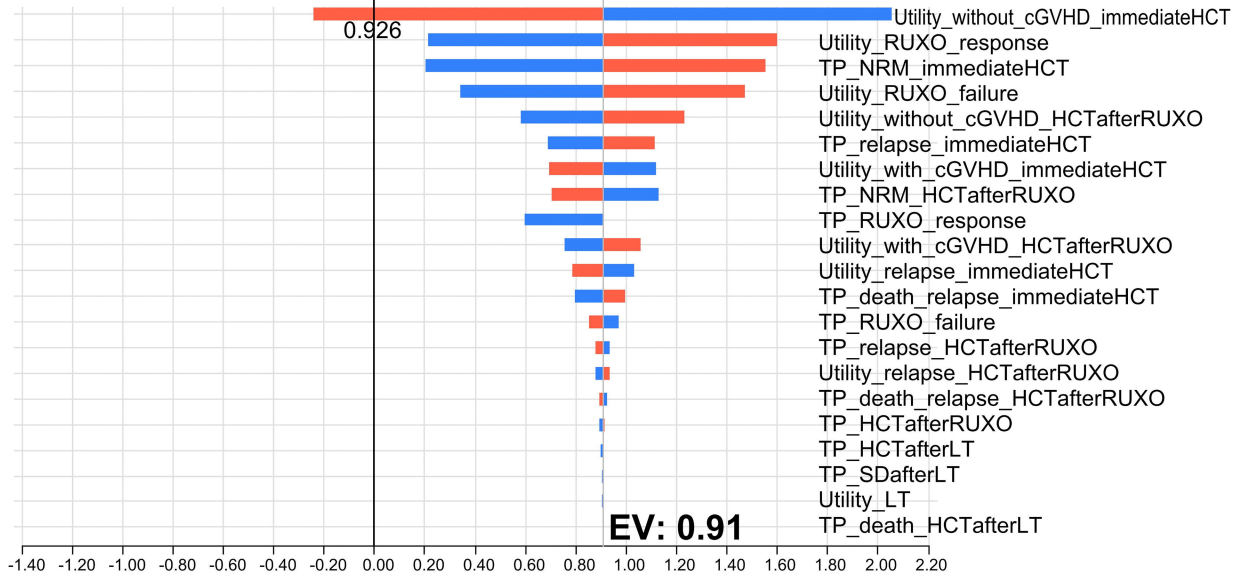
A



B



C



Favors immediate HCT

Favors delayed HCT after RUXO failure

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 $0.37 \times (1 - 0.37 - 0.13) \times 0.14 / 0.3 = 0.086$.(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 $0.62 \times (1 - 0.62) \times 0.4 / 0.75 = 0.13$.(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 $0.8 \times (0.68 - 0.23 \times 1.71)/0.68 + 0.65 \times 0.23 \times 1.71/0.68 = 0.71$ at 1 year, $0.8 \times (0.60 - 0.14 \times 1.71)/0.60 + 0.65 \times 0.14 \times 1.71/0.60 = 0.74$ at 2 years, $0.8 \times (0.54 - 0.07 \times 1.71)/0.54 + 0.65 \times 0.07 \times 1.71/0.54 = 0.77$ at 3 years, and $0.8 \times (0.52 - 0.04 \times 1.71)/0.52 + 0.65 \times 0.04 \times 1.71/0.52 = 0.78$ 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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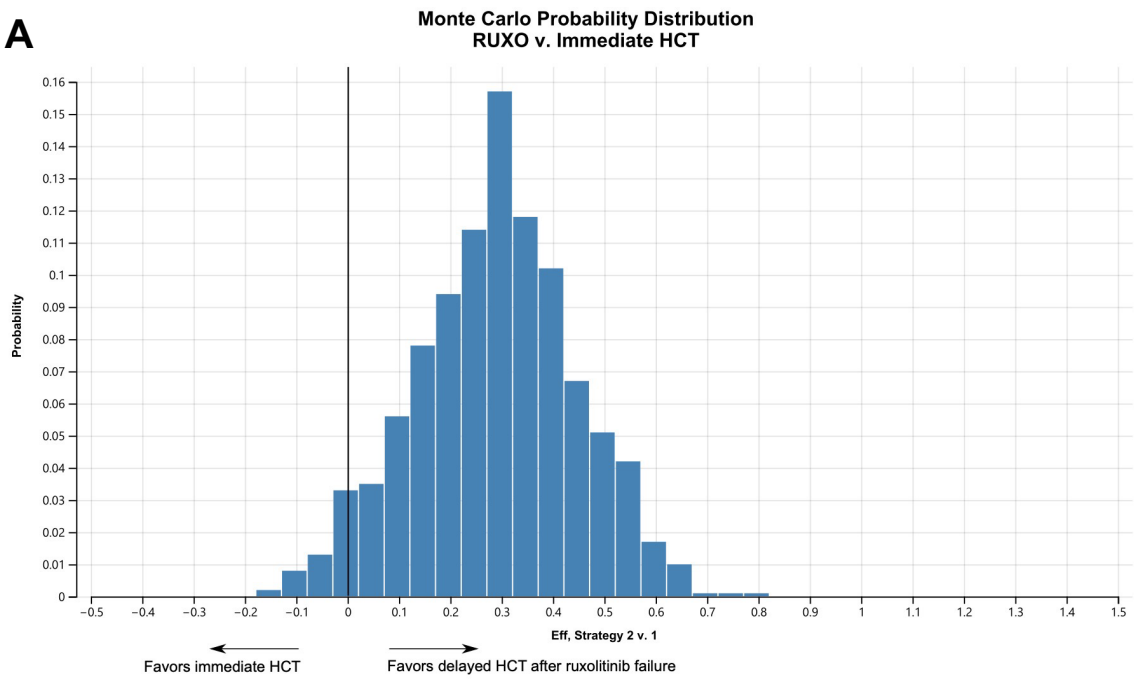
Supplementary Figure Legends

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

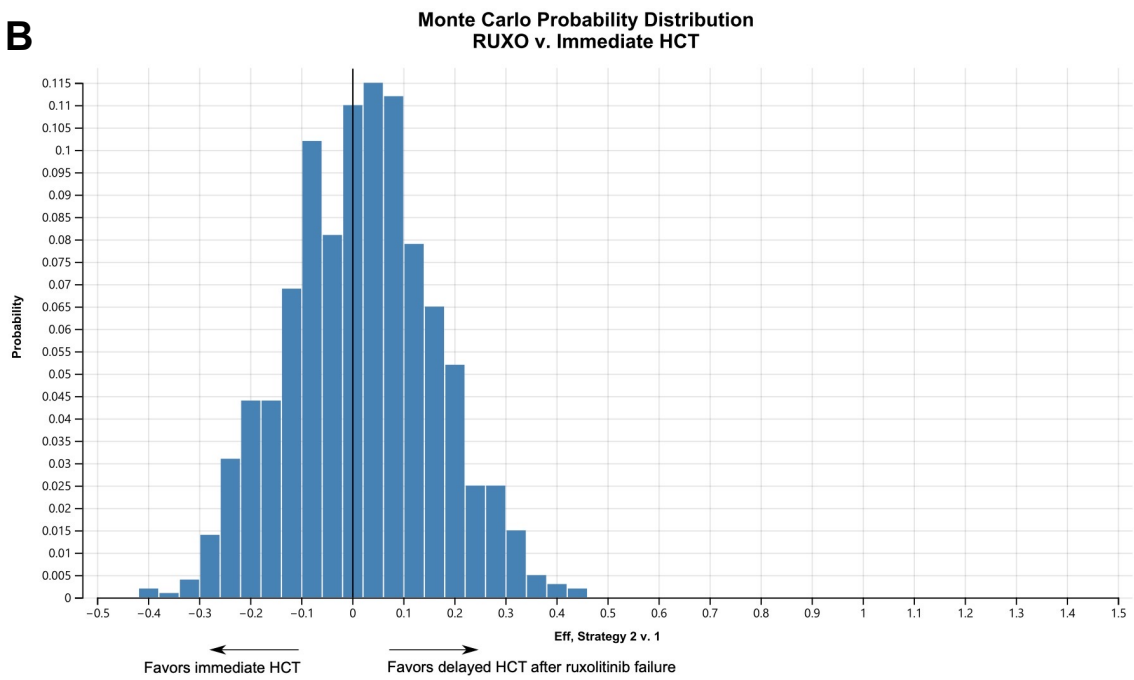
Histograms show incremental quality-adjusted life years (QALYs) of “Delayed hematopoietic cell transplantation (HCT) after ruxolitinib failure” – “Immediate HCT” for patients in the (A) entire cohort, and the (B) age < 60 and (C) age \geq 60 groups.

Supplementary Figure 1

A



B



C

