How I treat transplant-eligible patients with myelofibrosis

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Introduction

- Despite the approval of Janus kinase inhibitors and novel agents for patients with myelofibrosis (MF), disease-modifying responses remain limited, and hematopoietic stem cell transplantation (HSCT) remains the only potentially curative treatment option.
- The number of HSCTs for MF continues to increase worldwide, but its inherent therapy-related morbidity and mortality limit its use for many patients.

Introduction

- Patients with MF often present at an older age, with cytopenia, splenomegaly, and severe bone marrow fibrosis, posing challenges in managing them throughout the HSCT procedure.
- Although implementation of molecular analyses enabled improved understanding of disease mechanisms and subsequently sparked development of novel drugs with promising activity.
- Prospective trials in the HSCT setting are often lacking, making an evidence-based decision process particularly difficult.

Topic question in Allogenic MPN patients

- 1-HSCT in High-Risk Myeloproliferative (payandeh-kermanshah)
- 2-Graft-versus-leukemia effect in MPD patients (Nasiri far-Sanandaj)
- 3-Controversies in treat choices,timing and indications (Farahat-Yazd)
- 4-Pre-and post-transplant to improve outcomes (razavi-uromie)
- 5- Conditioning regimens in MPD patients (rastegar-Ahvaz)
- 6-DLI in myelofibrosis (Asghari-uromie)
- 7- MPN Registry in north of Iran (Montazeri-sari)

Case 1

- A 69-year-old man with post-PV MF was referred for HSCT, having received the PV diagnosis 10 years ago and subsequent MF diagnosis 3 years ago.
- He was initially treated with phlebotomy and acetylsalicylic acid but showed disease progression: bone marrow fibrosis grade 3, beginning fatigue, spleen size 15 cm by ultrasound, and night sweats.
- his Karnofsky index was 100% without any other comorbidity.
- hemoglobin at 9.1 g/dL, leukocytes at 22×10^9/L, platelets at 188×10^9/L, circulating blasts of 9%.

Case 1

- trisofmy 8, and *JAK2V617F* and *EZH2* mutations.
- Meanwhile, he became transfusion dependent. His risk was high according to MYSEC-PM (16.65 points).
- According to the MTSS, he was categorized as being at intermediate (if an HLA compatible donor was available) or high risk (with the availability of a mismatched unrelated donor).

Comment on case 1

- Is there an indication for HSCT in this 69-year-old man?
- If yes, what is the optimal preparation to reduce morbidity, risk of mortality, and relapse?

Disease- and treatment-specific scoring systems

HMR, high molecular risk; MIPSS70+ v. 2, MIPSS70-plus version 2; NR, not reached; RBC, red blood cell; RR6, ruxolitinib response; SMF, secondary MF (post-PV and –ET MF); VHR, very high risk.

* Model to predict survival according to response to ruxolitinib after 6 months.

† Moderate (<8 g/dL in women and <9 g/dL in men) and severe (8-9.9 g/dL in women and 9-10.9 g/dL in men).

‡ Complex karyotype: sole or 2 abnormalities, including +8, –7/7q-, i(17q), –5/5q-, 12p-, inv(3) or 11q23 rearrangement.

§ Unfavorable (chromosomal abnormalities except VHR or sole 13q-, +9, 20q-, chromosome 1 translocation/duplication or sex chromosome alterations including -Y), VHR (single/multiple abnormalities of –7, i(17q), inv(3)/3q21, 12p-/12p11.2, 11q-/11q23, +21, or other autosomal trisomies except +8/9).

‖ HMR (presence and number of *ASXL1*, *EZH2*, *SRSF2*, or *IDH1/2*).

¶ Original HMR and *U2AF1Q157*.

Our summary points for case 1

- Age, per se, is not a contraindication for HSCT, and we recommend transplantation in patients aged >65 years and even in those aged >70 years, depending on performance status and comorbidities after balancing disease-specific and transplant-specific risks.
- In general, we recommend transplantation for patients with DIPSS and MYSEC-PM intermediate-2/high and MIPSS70 high-risk scores, when patients have low/intermediate risk per the MTSS.

Our summary points for case 1

- We do not use blast reduction for chronic-phase MF.
- For accelerated- and blast-phase MF, investigational blast reduction with chemotherapy or with a combination of venetoclax and hypomethylating agents can be considered.
- Early HSCT is the most important factor for best outcome.

Our summary points for case 1

- We aim for our patients to undergo HSCT at the time of best spleen response to JAK inhibitor treatment.
- If JAK inhibitors fail and spleen size is extensive, we consider spleen irradiation for a few cases and splenectomy only for selected patients taking high complications of the procedure into account.

Management of cytopenia, iron overload, circulating blasts, and splenomegaly

Condition	Association with outcome	Management
Anemia	Most patients referred for HSCT are anemic and transfusion dependent, not prognostic for posttransplant outcomes	Ferritin <1000 µg/L: • Careful transfusion support Ferritin >1000 µg/L: • Deferasirox (14 mg/kg) from the start of conditioning until day 3 after transplantation, and monitor ferritin closely until at least day 14 • Pharmacological monitoring for busulfan AUC Peritransplant transfusion threshold: • <8 g/dL if patients usually achieved >8 g/dL before transplant referral • <7 g/dL if patients never achieved >8 g/dL before transplant referral and are not symptomatic (clinically adapted to anemia) Momelotinib is an investigational option for anemic and progressive disease while preparing for HSCT
Thrombocytopenia	Associated with worse survival and nonrelapse mortality	Peritransplant transfusion threshold: • $<10 \times 10^9$/L with no signs of bleeding • HLA-matched products in refractory cases and/or antiplatelet antibodies • Investigational eltrombopag or romiplostim in refractory cases, at high risk of and/or signs of bleeding Pacritinib is an investigational option for severe thrombocytopenia, and fedratinib for moderate thrombocytopenia and progressive disease while preparing for HSCT
Circulating blasts	Not associated with overall survival or nonrelapse mortality. Associated with increased risk of relapse in accelerated-phase MF.	No blast reduction in chronic-phase MF but close monitoring for relapse Venetoclax and/or azacitidine is an investigational option for accelerated and blast phase while preparing for HSCT but in need of treatment
Splenomegaly	Not associated with mortality. Associated with delayed engraftment, increased risk of graft failure, and relapse.	Start with JAK inhibitor (mostly ruxolitinib) and proceed directly to HSCT for eligible patients with spleen response or moderate or large spleen size with acceptable performance status and low or intermediate transplant-specific risk Fedratinib or investigational JAK inhibitors or clinical trials for patients with large spleen, cytopenia, and/or poor performance with high transplant-specific risk Splenic irradiation as part of HSCT preparation for patients with massive spleen, not responding to prior therapy, and no severe cytopenia Splenectomy only for very few selected patients with excellent performance

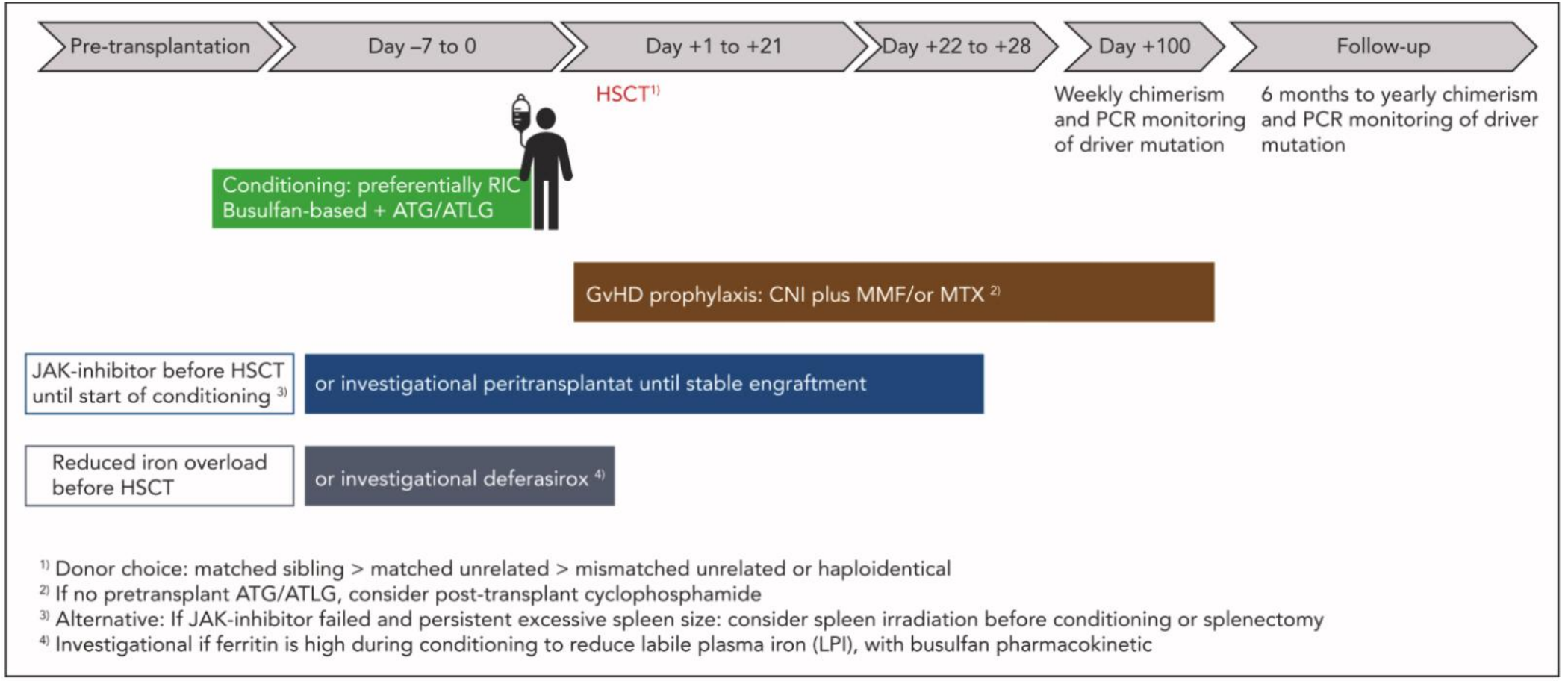
Case 2

- A 51-year-old male patient with *JAK2*-, *ASXL1*-, and *EZH2*-mutated PMF, with a DIPSS intermediate-2 score (score 3: hemoglobin level at 8 g/dL and leukocytes at 30 × 10^9/L).
- High risk per the MIPSS70 (score 6: non-*CALR* type 1, high molecular risk, hemoglobin level at 8 g/dL, and leukocytes at 30 × 10^9/L), was referred for HSCT.
- He had a younger 47-year-old HLA-identical brother.
- According to MTSS, he was at intermediate risk (score 4: leukocytes at 30 × 10^9/L, and *ASXL1* and *JAK2* mutation).

Comment on case 2

- How should the transplant be performed considering graft-versus-host disease (GVHD) prophylaxis and donor platform in this relatively young patient with high molecular genetic risk?

Optimized general pre and peritransplant approach.



Our summary points for case 2

- We use ATLG as GVHD prophylaxis for all patients and a reduced dose (30 mg/kg) for patients with a matched related donor.
- If available, we prefer matched related donor whereas most of our HSCTs are on basis of matched unrelated donors. Haploidentical transplants remain investigational but can be used in environments with limited access to matched unrelated donors.
- We usually perform transplantation with >5 × 10^6 $CD34^+$/kg cells and use peripheral blood for almost all procedures, if available.

Case 3

- A 53-year-old male patient was diagnosed with PMF 4 years ago.
- He presented with fibrosis grade 3, hemoglobin level of 11.8 g/dL, leukocytes at 34 × 10^9/L, 1% circulating blasts, platelets at 480 × 10^9/L, and a spleen size of 2 fingers below the left costal arch.
- Molecular analyses revealed *JAK2V617F* and *ASXL1* mutations. He had 1 HLA-identical brother (aged 53 years). Risk was classified as DIPSS intermediate-1, MIPSS70 intermediate, and MTSS intermediate.

Case 3

- At that time, balancing risks and benefits were in favor of postponing HSCT. Two years later, he presented with similar blood levels, increased spleen size, and constitutional symptoms.
- Molecular genetics showed increased variant allele frequency.
- Now, the patient was classified as being DIPSS intermediate-2 risk, MIPSS70 high risk, and MTSS intermediate risk.
- He received ruxolitinib and HSCT indication.

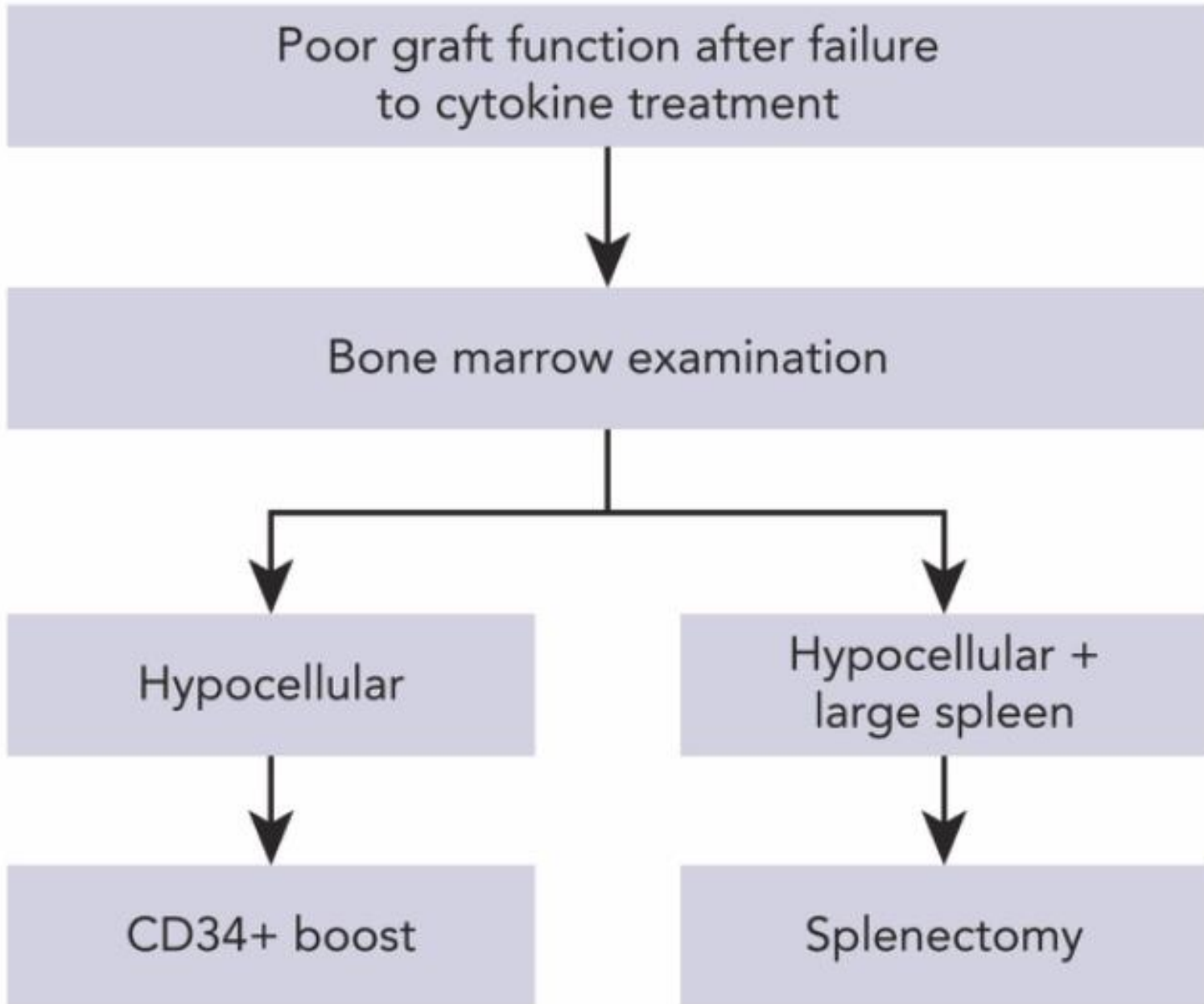
Comment on case 3

- Because HSCT indication is given, what type of conditioning should we use, and how can the risk of relapse and complications be reduced?

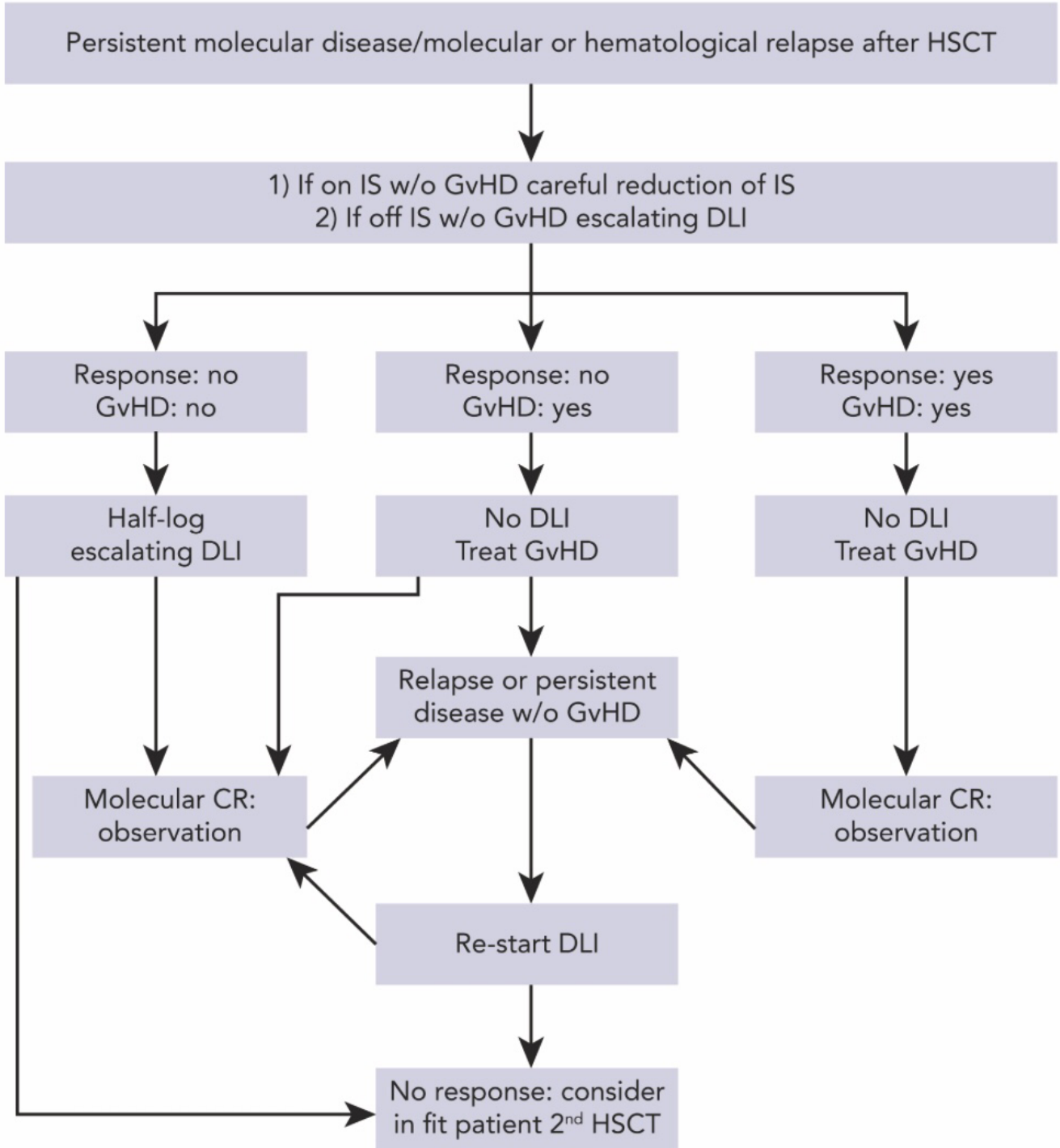
Selected studies investigating conditioning regimens and intensities in MF

Study	Regimen		Survival	Nonrelapse mortality	Relapse
McLornan et al[82] (RIC vs MAC)	Busulfan/fludarabine (57%)	Busulfan/fludarabine (47%)	5 y: 53% vs 51%	3 y: 32% vs 33%	3 y: 17% vs 20%
Patriarca et al[90] (RIC)	Busulfan/fludarabine	Thiotepa/fludarabine	2 y: 54% vs 70%	2 y: 21% vs 21%	2 y: 36% vs 24%
Kröger et al[58] (RIC)	Busulfan/fludarabine		5 y: 56%	1 y: 21%	5 y: 25%
Gupta et al[80] (RIC)	Busulfan/fludarabine (38%), fludarabine/melphalane (28%), fludarabine/TBI (22%)		5 y: 47%	3 y: 22%	3 y: 47%
Gagelmann et al[29] (RIC vs MAC)	Busulfan/fludarabine (63%)	Busulfan/cyclophosphamide (59%)	6 y: 63% vs 59%	2 y: 26% vs 29%	2 y: 10% vs 9%
Murthy et al[75]	Fludarabine/melphalane (66%), busulfan/fludarabine (34%)	Busulfan/fludarabine (65%), busulfan/cyclophosphamide (35%)	2 y: 57% vs 72%*	1 y: 20% vs 16%	1 y: 49% vs 41%

Graft failure and poor graft function


Poor graft function after failure to cytokine treatment
Bone marrow examination
Hypocellular
Hypocellular + large spleen
CD34+ boost
Splenectomy

Donor lymphocyte infusion (DLI)


Persistent molecular disease/molecular or hematological relapse after HSCT
1) If on IS w/o GvHD careful reduction of IS
2) If off IS w/o GvHD escalating DLI
Response: no
GvHD: no
Response: no
GvHD: yes
Response: yes
GvHD: yes
Half-log
escalating DLI
No DLI
Treat GvHD
No DLI
Treat GvHD
Relapse or persistent
disease w/o GvHD
Molecular CR:
observation
Molecular CR:
observation
Re-start DLI
No response: consider
in fit patient 2nd HSCT

Relapse monitoring, prevention, and management

- Approximately 10% to 30% of patients experience relapse after HSCT within a median of 7 months.
- However, also late relapse can occur, and we observed a 14% cumulative incidence of relapse after 5 years.

Relapse monitoring, prevention, and management

- Molecular monitoring by sensitive polymerase chain reaction analysis for 1 of the driver mutations (*JAK2*, *CALR*, or *MPL*) or highly sensitive chimerism for triple-negative MF after HSCT are able to detect minimal measurable disease, which has been shown to precede hematological relapse. This enables early intervention.

Our summary points for case 3

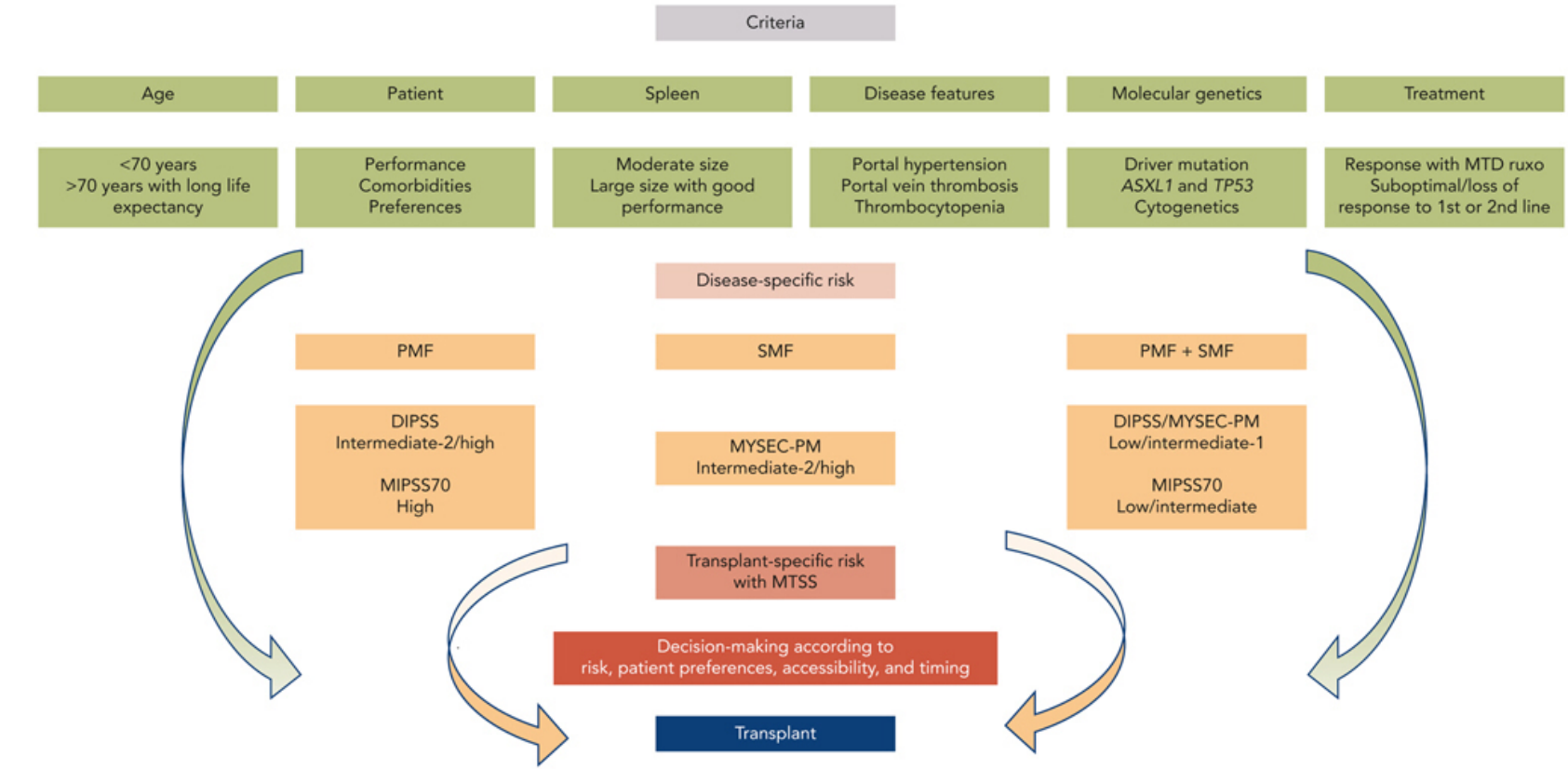
- All our patients who receive first HSCT, receive RIC with busulfan (area under the curve targeted) and fludarabine.
- Currently, we invesitgate to continue JAK inhibition throughout transplantation and taper up to day 28 or to engraftment in patients with spleen response and/or on ruxolitinib before HSCT.

Our summary points for case 3

- $CD34^+$-selected boost is a valid option for poor graft function if the bone marrow is hypocellular, whereas in case of hypercellularity and persistent splenomegaly, posttransplant splenectomy can be considered.
- Long-term molecular monitoring using polymerase chain reaction analysis for driver mutations and/or high-sensitivity chimerism analysis is crucial to adequately monitor patients for relapse.
- DLI should be administered for molecular persistence and target molecular remission. A second HSCT can be considered for fit patients after DLI failure.

How I Treat Transplant-Eligible Patients with Myelofibrosis

Criteria used to determine if a patient is a candidate for transplantation:



Conclusion: **With the introduction of JAK inhibitors and promising new developments, it becomes even more important to identify the right moment and to design the right platform for curative treatment.**

*Kröger et al. DOI: 10.1182/**blood**.2023021218*

Blood Visual Abstract

Conclusion

- MF remains a challenging disease, especially in this intensive treatment setting, and therefore complex networks of patient-, disease-, and transplant-related factors need to be considered.
- Patients should be carefully assessed for treatment response and ideally undergo HSCT at time of response to JAK inhibition.