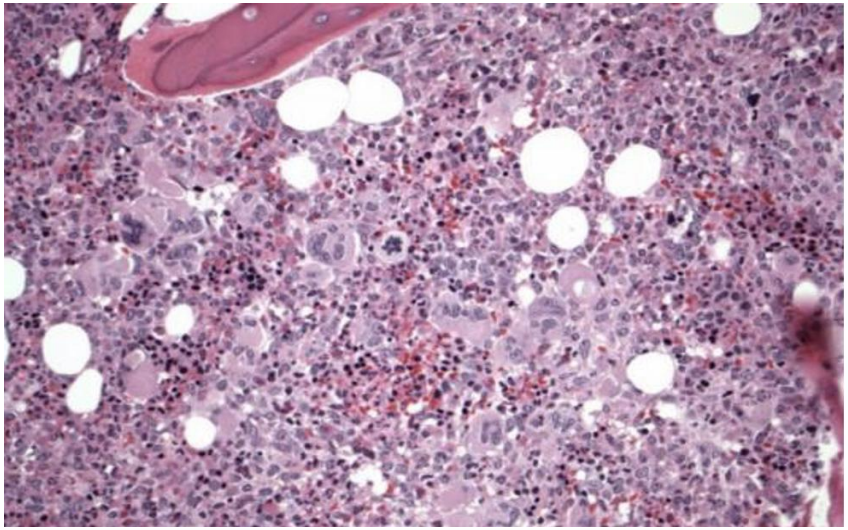
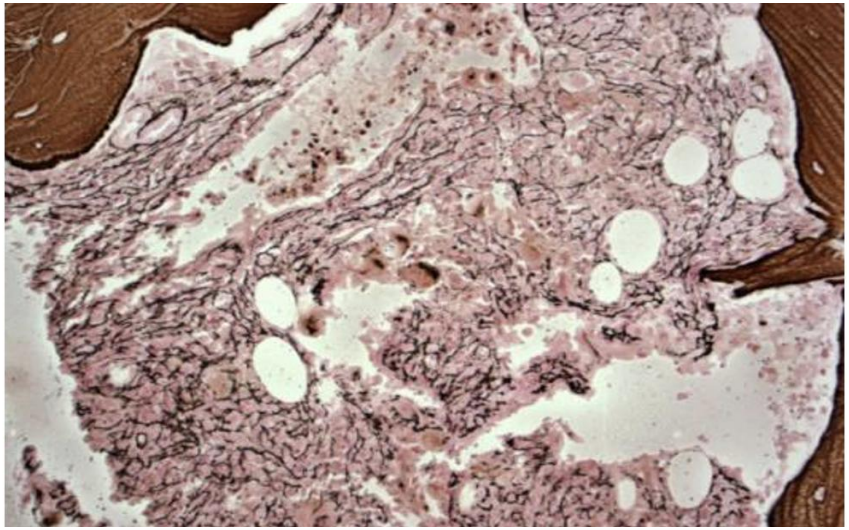




Challeges in myelofibrosis ALLO-HSCT

Davoud Babakhani,MD

Allogeneic hematopoietic stem cell transplantation (allo-HCT) still represents the only curative option for patients with myelofibrosis (MF).

A myeloproliferative neoplasm characterized by splenomegaly, constitutional symptoms, anemia, and a natural progression to acute leukemia.

Estimated median overall survival (OS) of approximately six years

The most commonly identified cause of death in patients with PMF:

transformation to acute leukemia accounted for 17 percent of deaths
progression of PMF (10 percent),
thrombosis and cardiovascular complications (7 percent),
infection (6 percent),
bleeding (3 percent),
portal hypertension (2 percent), and
second cancers (2 percent).

Transplant Indication

1.International Prognostic Scoring System (IPSS), which estimates survival at the time of MF diagnosis;

2. Dynamic IPSS (DIPSS), utilizing the same five factors of IPSS, but applicable at any stage during the disease course;

3. DIPSS-plus, which considers three additional adverse factors (transfusion dependency, thrombocytopenia <100 × 10 9 /L, and unfavorable cytogenetics)

RISK STRATIFICATION FOR PATIENTS WITH PMF

DYNAMIC INTERNATIONAL PROGNOSTIC SCORING SYSTEM (DIPSS)[1]

Prognostic Variable	Points		
	0	1	2
Age, y	≤65	>65	
White blood cell count, x10^9/L	≤25	>25	
Hemoglobin, g/dL	≥10		<10
Peripheral blood blast, %	<1	≥1	
Constitutional symptoms, Y/N	N	Y	

Risk Group	Points
Low	0
Intermediate-1 (INT-1)	1 or 2
Intermediate-2 (INT-2)	3 or 4
High	5 or 6

DIPSS-PLUS[2]

Prognostic Variable	Points
DIPSS low-risk	0
DIPSS intermediate-risk 1 (INT-1)	1
DIPSS intermediate-risk 2 (INT-2)	2
DIPSS high-risk	3
Platelets <100 x 10^9/L	1
Transfusion need	1
Unfavorable karyotype*	1

*Unfavorable karyotype: complex karyotype or sole or two abnormalities that include trisomy 8, 7/7q-, i(17q), 5/5q-, 12p-, inv(3), or 11q23 rearrangement.

Risk Group	Points
Low	0
Intermediate-1 (INT-1)	1
Intermediate-2 (INT-2)	2 or 3
High	4 to 6

Clinicohematologic-Based Prognostic Models of MF

Comparison of IPSS, DIPSS, and DIPSS-Plus[1]

Parameter	IPSS	DIPSS	DIPSS-Plus
Age >65 yr	**Yes (1 point)**	**Yes (1 point)**	**Yes***
Hgb <10 g/dL	Yes (1 point)	Yes (2 points)	Yes*
WBC >25 x 10^9/L	Yes (1 point)	Yes (1 point)	Yes*
PB blasts ≥1%	Yes (1 point)	Yes (1 point)	Yes*
Constitutional symptoms	**Yes (1 point)**	**Yes (1 point)**	**Yes***
Unfavorable karyotype	NA	NA	Yes (1 point)
RBC transfusion dependence	NA	NA	Yes (1 point)
Platelets <100 x 10^9/L	NA	NA	Yes (1 point)
Can be used at any time point	No (only at diagnosis)	Yes	Yes

*0-3 points for each based on DIPSS risk categories; features not individually weighted.

Survival by Risk Group and Prognostic Model

Risk Group ▪ Points	Median OS, Yr		
	IPSS[2]	DIPSS[3]	DIPSS-Plus[4]
Low ▪ 0	11.3	NR	15.0
Intermediate-1 ▪ IPSS/DIPSS-Plus: 1 ▪ DIPSS: 1-2	7.9	14.2	6.6
Intermediate-2 ▪ IPSS: 2 ▪ DIPSS: 3-4 ▪ DIPSS-Plus: 2-3	4.0	4.0	2.9
High ▪ IPSS: ≥3 ▪ DIPSS: ≥5 ▪ DIPSS-Plus: ≥4	2.3	1.5	1.3

1. Bose. Cancer. 2016;122:681. 2. Cervantes. Blood. 2009;113:2895. 3. Passamonti. Blood. 2010;115:1703. 4. Gangat. JCO. 2011;29:392.

intermediate-2- and high-risk disease according to the IPSS, DIPSS, or DIPSS-plus and age <70 years should be considered potential candidates for allo-HCT.

patients with intermediate-1-risk disease and age <65 years should be considered as candidates if:

- they present with either transfusion-dependent anemia, or
- a significant percentage of peripheral blasts (>2%), or
- adverse cytogenetics or
- high-risk mutations

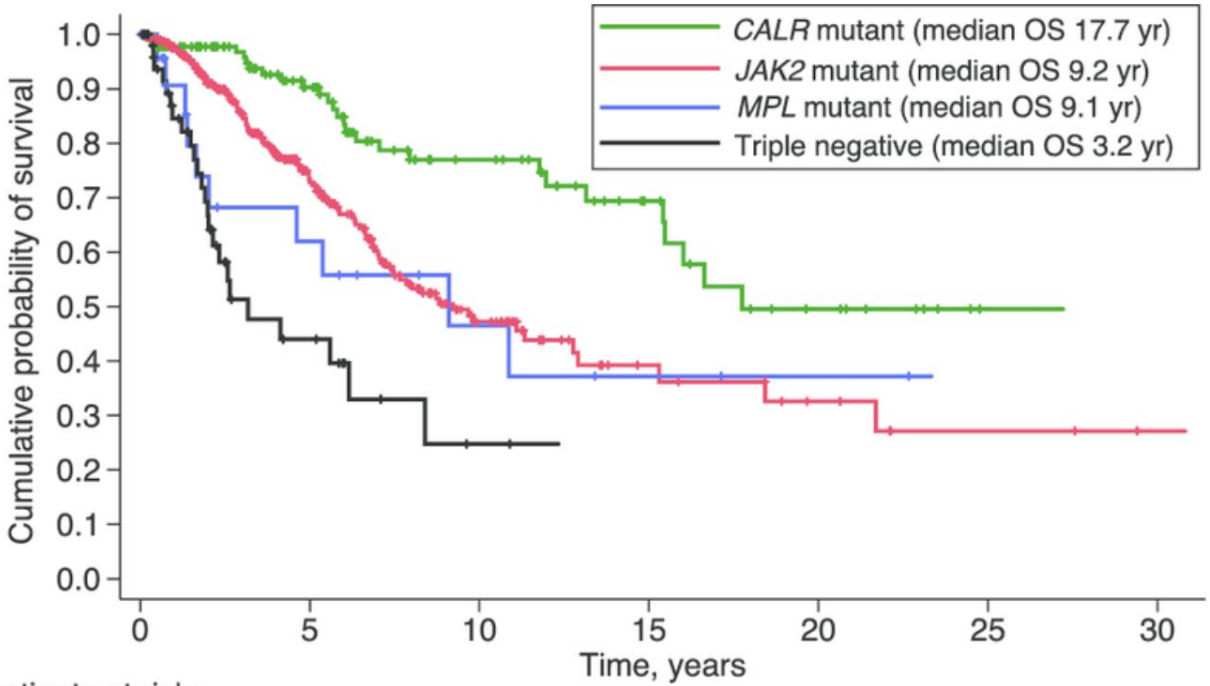
Patients who are triple negative (JAK2/CALR/MPL) or CALR wild type and ASXL1 mutated, irrespective of DIPSS risk scores, should be considered for HSCT

Median OS for patients with a mutation of JAK2, CALR, MPL, or triple-negative disease were 5.9, 15.9, 9.9, and 2.3 years, respectively.

More than 80 percent of patients with PMF harbor a variant of at least one of the following genes.

- ASXL1 (38 percent)
- SRSF2 (14 percent)
- U2AF1Q157 (8 percent)
- EZH2 (7 percent)
- IDH1/2 (4 percent)

Median survivals for those with none, one, or two or more mutations in these genes, were 12.3, 7.0, and 2.6 years, respectively



No. of patients at risk:

CALR mutant	140	72	37	19	9	1
JAK2 mutant	396	135	39	13	7	3
MPL mutant	25	10	5	3	2	0
Triple negative	53	11	2	0	0	0

Kaplan-Meier analysis of survival of PMF patients stratified according to their driver mutation. Vertical tick marks indicate right-censored patients. In univariate analysis, CALR-mutant patients had a better OS than JAK2-mutant (HR 2.3, P , .001), MPL-mutant (HR 2.6, P 5 .009), and triple-negative patients (HR 6.2, P , .001). Three JAK2-mutant patients had short follow-up and were not included in the analysis.

Allo-HCT was able to overcome the prognostic value of several of these mutations in a cohort of 101 patients, supporting the value of early transplantation in such a high-risk population

In order to integrate the modern molecular information, the mutation-enhanced IPSS “MIPSS70” and “MIPSS70-plus” (including cytogenetics) scoring systems have been developed as decisional tools for transplant indication in patients less than 70 years old.

Contemporary Prognostic Scoring Systems: MIPSS70 Plus 2.0

Variable
Severe anemia (Hgb: women <8 g/dL, men <9 g/dL) (2 pts)
Moderate anemia (Hgb: women 8-9.9 g/dL, men 9-10.9 g/dL) (1 pt)
Leukocytes >25 x 10^9/L
Platelets <100 x 10^9/L
Bone marrow fibrosis ≥2
Circulating blasts ≥2% (1 pt)
*Constitutional symptoms (2 pts)
*Absence of *CALR* type 1/like mutation (2 pts)
*1 high molecular risk mutation (2 pts)
≥2 high molecular risk mutations (3 pts)
Unfavorable karyotype (3 pts)
Very high–risk karyotype (4 pts)

Score	Risk Grouping	10-yr Survival, %	Median OS, yr
0	Very low	86	NR
1-2	Low	50	10.3
3-4	Intermediate	30	7
5-8	High	10	3.5
9-14	Very high	<3	1.8

HMR: *ASXL1*, *EZH2*, *SRSF2*, *IDH1/2*, *U2AF1*
VHR karyotype: -7, i(17q), inv(3)/3q21, 12p-/12p11.2, 11q-/11q23, other trisomies not including +8 or +9
Favorable: normal, or 13q-, +9, 20q-, chromosome 1 trans/dup, sex chromosome abnormality including -Y
Unfavorable: all other

Tefferi. JCO. 2018;17:1769.

Slide credit: clinicaloptions.com

Such scores have been proven to poorly predict patients' outcome for patients with secondary myelofibrosis (sMF; post-Polycythemia Vera (PPV-MF) or postEssential Thrombocythemia myelofibrosis (PET-MF)),

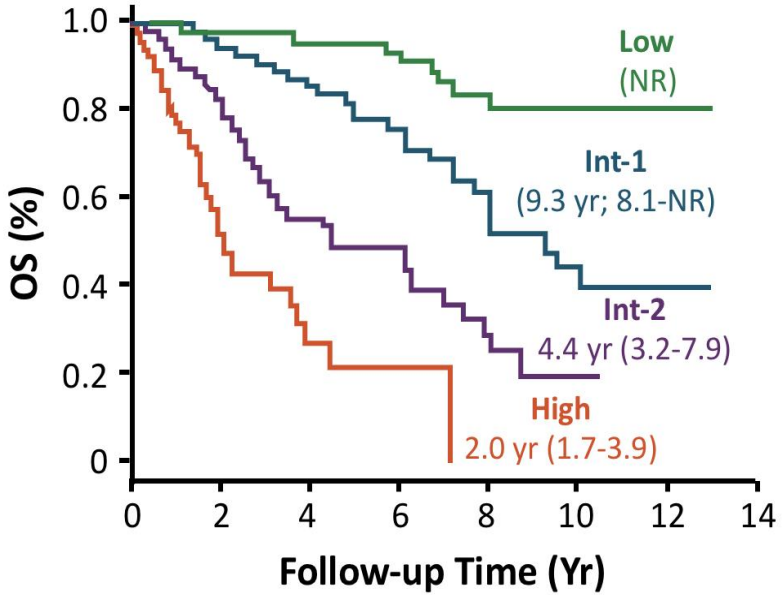
As they present a better survival compared to primary myelofibrosis .

For those patients with sMF, the so-called Myelofibrosis SECondary to PV and ET-Prognostic Model (MYSEC-PM) was developed and documented better prognostic ability.

Post-ET and Post-PV MF: MYSEC

Variable	Points
Age at secondary MF diagnosis (multiplier)	0.15
Hgb <11 g/dL	2
Platelets <150 x 10^9/L	1
Circulating blasts ≥3%	2
CALR-unmutated	2
Constitutional symptoms	1

- Low-risk: <11
- Intermediate-1 risk: 11-13.99
- Intermediate-2: 14-15.99
- High: 16 or more



Passamonti. Leukemia. 2017;31:2726. mysec-pm.eu.

Risk Score		IPSS	DIPSS	DIPSS-Plus	MYSEC-PM	MIPSS70	MIPSS70-Plus v2.0	GIPSS
Applicability		PMF at diagnosis	PMF at any time	PMF at any time	sMF at diagnosis	PMF at any time	PMF at any time	PMF at any time
Features		Clinical	Clinical	Clinical & Molecular	Clinical & molecular	Clinical & molecular	Clinical & molecular	Genetical only
Items (points)	Age	>65 y (1)	>65 y (1)	>65 y (1)	Age (0.15/y)	–	–	–
	Leucocytes	>25 × 10^9/L (1)	>25 × 10^9/L (1)	>25 × 10^9/L (1)	–	>25 × 10^9/L (1)	–	–
	Blasts	≥1% (1)	≥1% (1)	≥1% (1)	≥3% (2)	≥2% (2)	≥2% (2)	–
	Constitutional symptoms	Yes/No (1)	Yes/No (1)	Yes/No (1)	Yes/No (1)	Yes/No (1)	Yes/No (2)	–
	Hemoglobin	<10 g/dL (1)	<10 g/dL (2)	<10 g/dL (2)	<11 g/dL (2)	<10 g/dL (1)	<8 g/dL (F)/<9 g/dL (M) (2) 8–9.9 g/dL (F)/9–10.9 g/dL (M) (1)	–
	TD-anemia	–	–	Yes/No (1)	–	–	–	–
	Cytogenetics	–	–	Unfavorable [£] (1)	–	–	very high risk [§] (4) unfavorable [§] (3)	very high risk [§] (2) unfavorable [§] (1)
	Platelets	–	–	<100 × 10^9/L (1)	<150 × 10^9/L (2)	<100 × 10^9/L (2)	–	–
	Molecular	–	–	–	No CALR (2)	No CALR type-1 (1) HMR [%] mutation (1) >1 HMR [%] mutations (2)	No CALR type-1 (2) HMR [$] mutation (2) >1 HMR [$] mutations (3)	No CALR type-1 (1 ASXL1 (1) SRSF2 (1) U2AF1Q (1)
	BM fibrosis	–	–	–	–	Grade ≥2 (1)	–	–
Higher risk Categories (score) Median OS		Int-2 (2): 4 y High (3–4): 2.3 y	Int-2 (3–4): 4 y High (5–6): 1.5 y	Int-2 (2–3): 2.9 y High (4–6): 1.3 y	Int-2 (>14 < 16): 4.4 y High (≥16): 2 y	Int (2–4): 7.1 y High (>4): 2.3 y	High (5–8): 4.1 y Very high (≥9): 1.8 y	Int-2 (2): 4.2 y High (≥3): 2 y

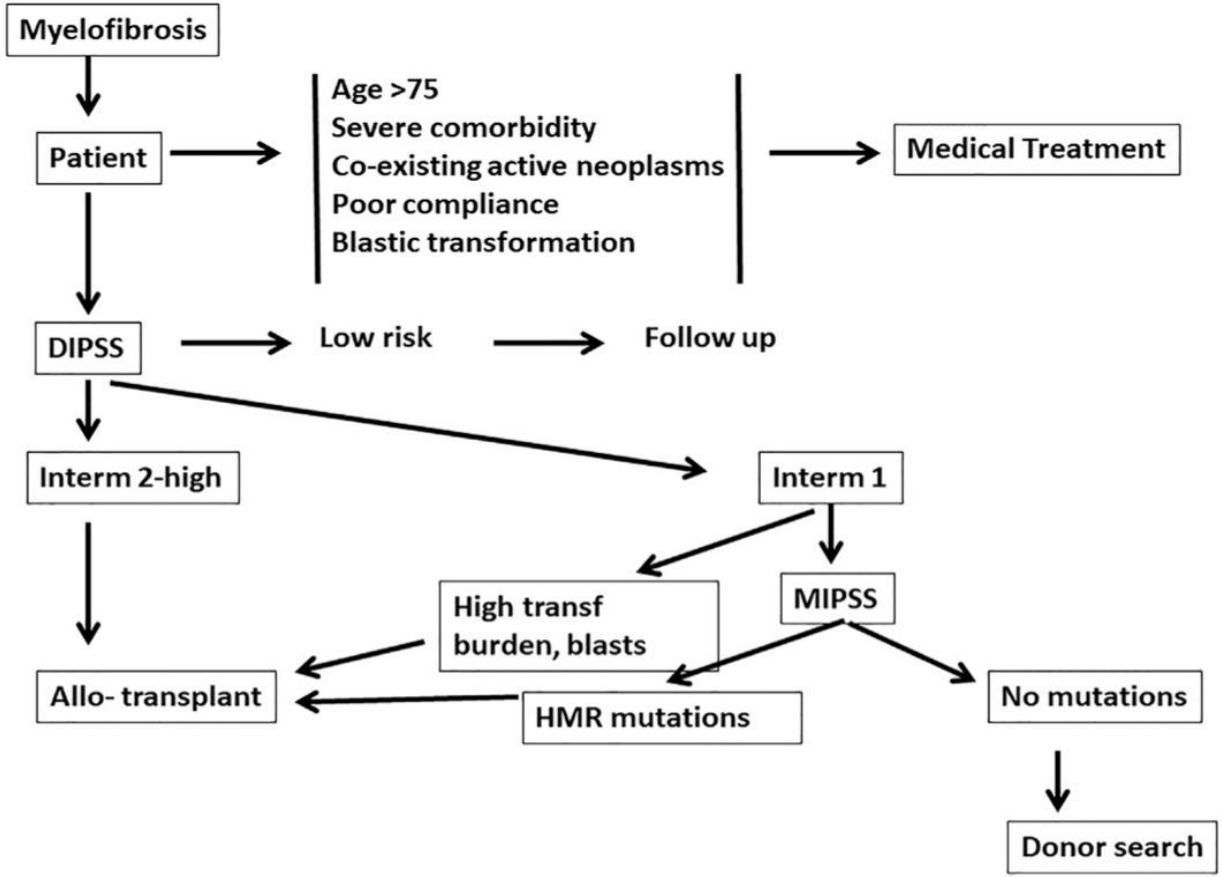


FIGURE 1 | Eligibility for a transplant procedure in patients with myelofibrosis: medical treatment should be offered for older patients (>75 years) and/or patients with comorbidities. Dynamic international prognostic scoring system (DIPSS) will then identify patients low risk patients, who should be followed. DIPSS-intermediate 2 and high risk patients are who are strong candidates for an allogeneic transplant. DIPSS-Intermediate 1 patients with a high transfusion burden and blasts counts are also strong candidates for an allogeneic transplant. Patients may also be studied with a molecular international prognostic scoring system (MIPSS), and may be eligible for transplantation if high risk mutations (HMR) (see text) are identified.

Patient Selection

One of the easiest tools for the evaluation of patients' eligibility for a transplant is represented by Karnofsky performance status (KPS).

On the basis of a simple scale from 0 (death) to 100 (normality), according to subject well-being, KPS has been invariably associated with transplant outcomes, including myeloablative and reduced intensity conditioning platforms.

Patients with scores lower than 90 are generally projected to a worse transplant result, due to increased non-relapse mortality

The most used tool for patients' evaluation and selection is represented by the hematopoietic cell transplantation-specific comorbidity index (HCT-CI). Developed by Sorror et al. and published in 2005,

This score includes the presence and severity of 15 comorbidities.

HCT-CI classifies patients at low (0), intermediate (1–2), and high (≥ 3) risk, correlating with worse survival due to increased non-relapse mortality

Myelofibrosis-specific Transplant Scoring System (MTSS)

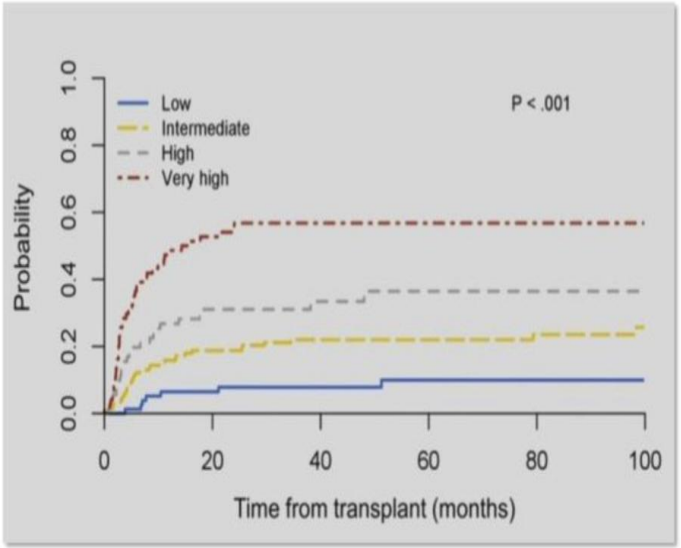
has been proposed with specific aim to predict outcome after alloHSCT

leukocytes >25 × 10 9/L,	1 point
platelets <150 × 10 9/L,	1 point
Karnofsky scale <90%,	1 point
age >57 years,	1 point
ASXL1 mutation.	1 point
JAK2-mutated	2 points
triple negative status	2 points
MMUR donor	2 points

	5-year OS
low	90%.
intermediate	77%.
high	50%.
very high	34%.

Myelofibrosis Transplant Scoring Systems (MTSS)

- **Non-relapse mortality**
- **Low (score of 0 to 2)**
  - 5y NRM: 10%
- **Intermediate (score of 3 to 4)**
  - 5y NRM: 22%
- **High (score of 5)**
  - 5y NRM: 36%
- **Very High (score of 6 to 9)**
  - 5y NRM: 57%



Role of blast

Found to be not significant for posttransplant outcome.

Furthermore, accelerated-phase MF,(circulating blasts 10–19%) usually confers very high risk for progression and poor outcome.

We identified 35 patients with accelerated phase MF undergoing reduced intensity alloHSCT. In comparison with 349 chronic-phase patients (< 10% blasts), the estimated 5-year overall survival was 65% compared with 64%, and median overall survival was not reached.

In terms of relapse, 5-year cumulative incidence was 30% for the accelerated-phase group in comparison with 15% for the chronic-phase group.

Donor Choice

An HLA-matched donor, either sibling or unrelated, is associated with a better outcome.

HLAmismatched unrelated donor transplantations showing significantly worse outcome.

Use of HLA-mismatched unrelated donors have been reported to be an independent risk factor for both disease-free and overall survival in several reports.

No comparative studies on the outcomes of matched unrelated donor and haploidentical donors in PMF have been published to date.

The use of cord blood was reported only for a minority of patients. increased risk of graft failure and higher NRM. 40% of engraftment failure ,remains experimental.

Donor type is an important predictor of outcome in myelofibrosis:a study from the Center for International Blood and Marrow Transplant Research (CIBMTR) on 233 transplants for myelofibrosis showed that donor type was an independent risk factor for TRM, with a relative risk of death of 3.92 for matched unrelated donor (MUD) and 9.37 for mismatched unrelated donor (MMUD), when compared to matched related donor (MRD).

The 5 year overall survival was 56% for MRD, 48% for MUD and 34% for MMUD.

The main causes of death were GvHD, infections and organ failure, in particular among MMUD grafts

CIBMTR shows a higher risk of GvHD for patients receiving MUD(RR1.98) and MMUD(RR1.52) as compared to MRD

Haploidentical donors have been increasingly employed over time.
Evidence is increasing in favor of this option that seems to offer similar results compared to HLA-matched donors also in MF setting.

One EBMT study showed feasibility of haploidentical alloHSCT, timely neutrophil engraftment in over 80% of cases, and acceptable overall and progression-free survival rates with relapse rates not dissimilar to the unrelated donor setting. However, strategies to minimize the risk of graft failure and the relatively high nonrelapse mortality of 38% at 2 years need to be evaluated.

In summary, when considering allo-HCT in MF, sibling donors and *high stem cells doses* should be considered as the best options.
Matched-unrelated or haploidentical donors might be a second preferred choice.

Conditioning Regimen

MAC should be preferred in young patients with advanced disease and good performance without comorbidities and with an HLA-matched sibling donor.

Usually, the conditioning regimen was based on busulfan plus cyclophosphamide and total body irradiation with or without cyclophosphamide,

but transplant related mortality (NRM) and GvHD rates were high,

especially in older individuals, ranging from 20 to 48% at 1 year.

RIC may be preferred in patients older than 50 years.

(FLU-BU): busulfan (10 mg/kg) orally (or equivalent IV dose) plus fludarabine (180 mg/m 2) and in vivo T-cell depletion with anti-thymocyte globulin at a dose of 3 x 10 mg/kg (for related) or 3 x 20 mg/kg (for unrelated donor)1-year nonrelapse mortality of 16%, and an estimated 5-year overall survival of 67%

(FLU-MEL):Fludarabine 90 mg/m 2, combined with melphalan 140 mg/mincreased early toxicity ,acute GVHD ,NRM, but relapse was lower ,inferior survival.

A randomized GITMO study comparing fludarabine in combination with busulfan 10 mg/kg i.v. or thiotepa 12 mg/kg failed to identify significant differences in terms of clinical outcome.

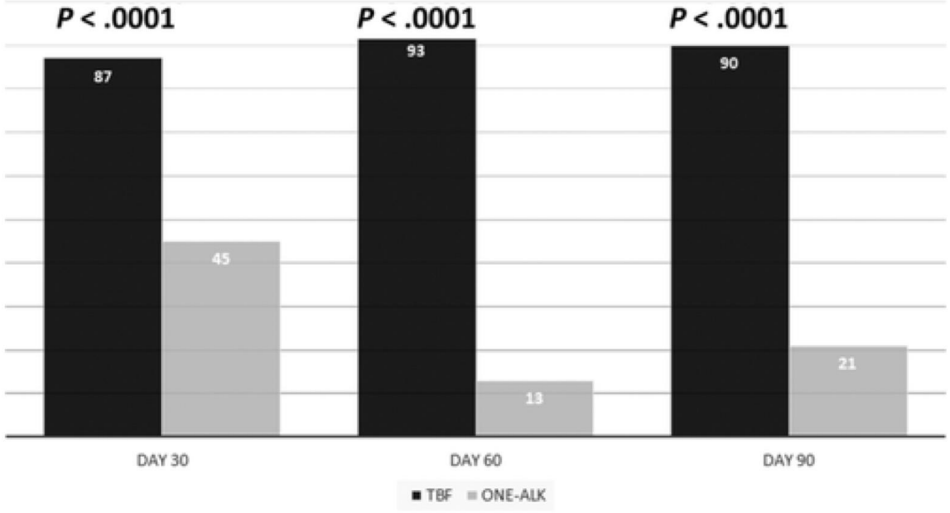
TBF patients received thiotepa (5 mg /kg/dayx2), fludarabine (50 mg/m 2× 3) and 3 days of intravenous BU 3.2 mg/kg/day

The proportion of patients with F-DC on day +30, in the TBF vs the ONE-ALK group, was respectively 87% vs 45% ($P < .001$).

The 5-year cumulative incidence of relapse was 9% in the TBF group, vs 43% for the ONE-ALK group ($P < .001$).

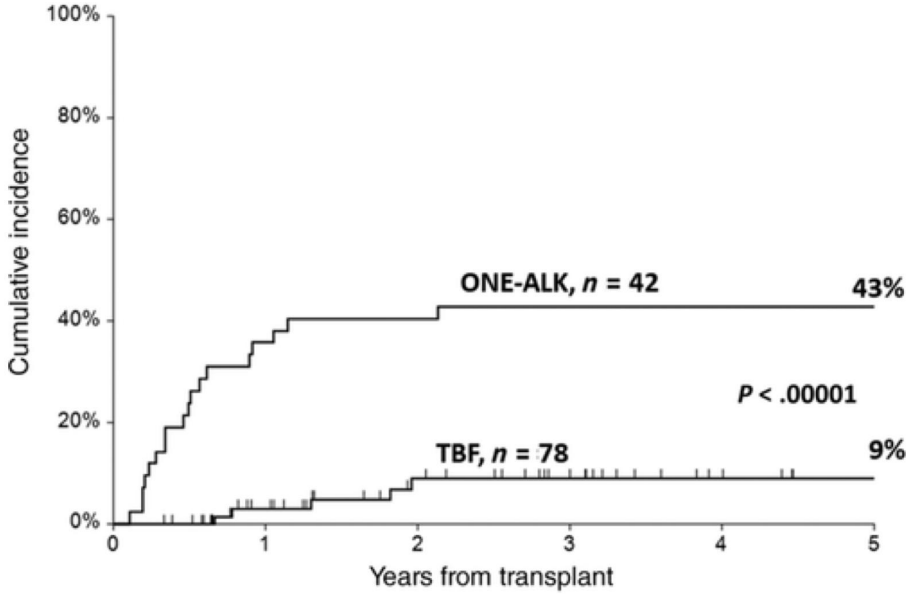
The 5-year disease-free survival was 63% for TBF and 38% for the ONE-ALK group ($P = .004$)

% of patients with full donor chimerism



n = 120 *n* = 97 *n* = 93

RELAPSE in myelofibrosis: the effect of the conditioning regimen



Splenomegaly Management

In a recent European multicenter study reporting 546 patients with available information on spleen size at the time of transplant, patients undergoing a transplant with a spleen palpable below 5 cm from left costal margin presented the best transplant outcome compared to patients with a spleen between 5 and 14 and more than 15 cm, respectively.

The increasing risk of death was found to be related to non-relapse mortality, with patients belonging to the lower category presenting a significantly shorter time to engraftment. This report confirmed a prior observation by Bacigalupo et al., who reported a higher NRM in patients with splenomegaly diameter >22 cm by ultrascan evaluation

Ruxolitinib

first drug which was approved for myelofibrosis management
ruxolitinib reducing constitutional symptoms and splenomegaly,
improvement of pro-inflammatory status typical of MF may favor a positive graft function , decreasing the risk of graft failure and poor graft function,

A most recent EBMT study in 551 who received alloHSCT without (n = 274) or with (n = 277) ruxolitinib pretreatment. The overall leukocyte engraftment on day 45 was 92% and significantly higher in ruxolitinib responsive patients than those who had no or lost response. The 1-year nonrelapse mortality was 22% without significant difference between the arms.

In a multivariate analysis, ongoing spleen response under ruxolitinib at time of alloHSCT was significantly associated with lower risk of relapse (8% compared with 19%) and better 2-year event free survival (69% compared with 54%) in comparison to patients without ruxolitinib pretreatment. No significant difference was found for OS.

There is preclinical and clinical evidence that JAK signaling plays a major role in graft-versus-host disease (GVHD), suggesting a potential role of JAK inhibition in the prevention and treatment of GVHD. The hypothesis for peritransplant use may be that ruxolitinib may reduce the cytokine storm after ATG and prevent acute GVHD.

A small report on 12 patients investigated the impact on GVHD prevention when ruxolitinib (5 mg twice daily) was continued throughout the peritransplantation period until stable engraftment occurred . No graft failure was observed. Only one patient developed fever of unknown origin after discontinuation of ruxolitinib. Overall, only one patient each experienced acute GVHD grade I or II, with no nonrelapse mortality.

The cytokines rebound after ruxolitinib withdrawal may have induced some cases of cardiac shock and tumor lysis syndrome recorded in those experiences .

These reports have induced researchers to extend the use of ruxolitinib to the conditioning regimen phase, or even until engraftment.

Table 2. List of studies investigating the role of ruxolitinib (RUX) in the pre- or peri-transplant period.

Author	Year	N	Study Design	Conditioning Regimens	RUX Use	Spleen Response	RUX Tapering Strategy	Discontinuation Syndrome	GF (%)	G2-4 aGVHD (%)	NRM (%)	OS (%)
Jaekel, N. [78]	2014	14	Retro	RIC (Flu-Bu/TBI) MAC (NA)	Pre	64%	Stop at conditioning	None	7%	14%	7% at 9 m	50% at 1 y
Stübig, T. [79]	2014	22	Retro	RIC (Flu-Bu/Mel/Treo)	Pre	45% (>50%) 24% (<50%)	Stop at conditioning	None	0%	36%	14% at 1 m	81% at 1 y
Shanavas, M. [44]	2016	100	Retro	RIC (Flu-Bu/Mel/Cy/BCNU/TBI) MAC (Flu-Bu/Mel or Bu-Cy)	Pre	23%	Not defined	10%	8%	37%	28% at 2 y	61% at 2 y
Kroger, N. [84]	2018	12	Prosp	RIC (Flu-Bu)	Peri	100%	Stop at day +28 post-transplant	None	0%	8%	0% at 17 m	100% at 17 m
Kadir, S.S.S.A. [87]	2018	46	Retro	RIC (Flu-Bu/ FLAMSA-Flu-Bu)	Pre	39%	Not defined	None	4%	37%	23% at 2 y	73% at 2 y
Gupta, V. [88]	2019	21	Prosp	RIC (Flu-Bu)	Pre	45%	Tapering off at conditioning (4 days before)	None	16%	47%	28% at 2 y	66% at 2 y
Salit, R.B. [82]	2020	28	Prosp	RIC (Flu-Mel) MAC (Bu-Cy±Flu)	Pre	NA	During Conditioning (day-4)	None	0%	78%	7% at 13 m	86% at 2 y
Ali, H. [89]	2021	18	Prosp	RIC (Flu-Mel)	Peri	NA	Day +30 post-transplant	None	0%	17%	23% at 1 y	77% at 1 y
Kroger, N. [77]	2021	277	Retro	RIC (NA) MAC (NA)	Pre	56%	Not defined	6%	NR	29%	26% NR at 1 y 15% R at 1 y	66% at 2 y
Robin, M. [90]	2021	59	Prosp	RIC (Flu-Mel)	Pre	46%	Variable	15.8%	3%	66%	42% at 1 y	68% at 1 y

When ruxolitinib fails ???

second generation JAK-inhibitors can be considered;

fedratinib: has received FDA and EMA approval (JAKARTA-2 trial)

Momelotinib: (SIMPLIFY-2 trial)

pacritinib: 20–30% in spleen volume reduction and/or symptoms response in the subset of patients with low-platelet counts (<100 × 10 9/L)

Novel classes of drugs (e.g., BH3-mimetics, CDK-6-inhibitors, BET-inhibitors, telomerase inhibitors,…), alone or in combination with JAK-inhibitors, have proven initial efficacy in MF, with relevant biological effects (reduction of BM fibrosis, molecular burden decrease) in a significant proportion of patients. Unfortunately, almost all ongoing studies exclude transplant candidates.

Splenectomy

Retrospective study including 1195 MF allo-HCT patients was conducted with the aim to give a conclusive answer to the question whether to perform splenectomy before transplantation could affect long term transplant outcome.

202 (17%) patients were submitted to splenectomy prior to transplant.

The proportion of surgical procedures tended to decrease over time, probably thanks to the availability of novel treatments (e.g., ruxolitinib).

Splenectomy was confirmed to be associated to a faster neutrophil and platelet engraftment and lower non-relapse mortality with an increased relapse risk.

Splenectomized patients had a 54% decrease in death risk compared to subjects with progressive splenomegaly over 15 cm below left costal margin.

A higher than two-fold increase in blast evolution was observed among splenectomized subjects.

For this concern, it should be considered to proceed early to transplantation after splenectomy, ideally within 1–3 months, if feasible.

The current evidence, therefore, suggests the use of splenectomy in all suitable patients with progressive splenomegaly, while on any medical treatment, palpable over 15 cm below left costal margin.

Splenomegaly in patients with primary or secondary myelofibrosis who are candidates for allogeneic hematopoietic cell transplantation: a Position Paper on behalf of the Chronic Malignancies Working Party of the EBMT

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Splenomegaly is a hallmark of myelofibrosis, a debilitating haematological malignancy for which the only curative option is allogeneic haematopoietic cell transplantation (HCT). Considerable splenic enlargement might be associated with a higher risk of delayed engraftment and graft failure, increased non-relapse mortality, and worse overall survival after HCT as compared with patients without significantly enlarged splenomegaly. Currently, there are no standardised guidelines to assist transplantation physicians in deciding optimal management of splenomegaly before HCT. Therefore, the aim of this Position Paper is to offer a shared position statement on this issue. An international group of haematologists, transplantation physicians, gastroenterologists, surgeons, radiotherapists, and radiologists with experience in the treatment of myelofibrosis contributed to this Position Paper. The key issues addressed by this group included the assessment, prevalence, and clinical significance of splenomegaly, and the need for a therapeutic intervention before HCT for the control of splenomegaly. Specific scenarios, including splanchnic vein thrombosis and COVID-19, are also discussed. All patients with myelofibrosis must have their spleen size assessed before allogeneic HCT. Myelofibrosis patients with splenomegaly measuring 5 cm and larger, particularly when exceeding 15 cm below the left costal margin, or with splenomegaly-related symptoms, could benefit from treatment with the aim of reducing the spleen size before HCT. In the absence of, or loss of, response, patients with increasing spleen size should be evaluated for second-line options, depending on availability, patient fitness, and centre experience. Splanchnic vein thrombosis is not an absolute contraindication for HCT, but a multidisciplinary approach is warranted. Finally, prevention and treatment of COVID-19 should adhere to standard recommendations for immunocompromised patients.

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Splenomegaly exceeding 15 cm by palpation or 22 cm of longitudinal diameter according to ultrasound scan evaluation might be associated with:

delayed engraftment, increased risk of graft failure, and poor graft function, resulting in an increased risk of NRM and shorter OS.

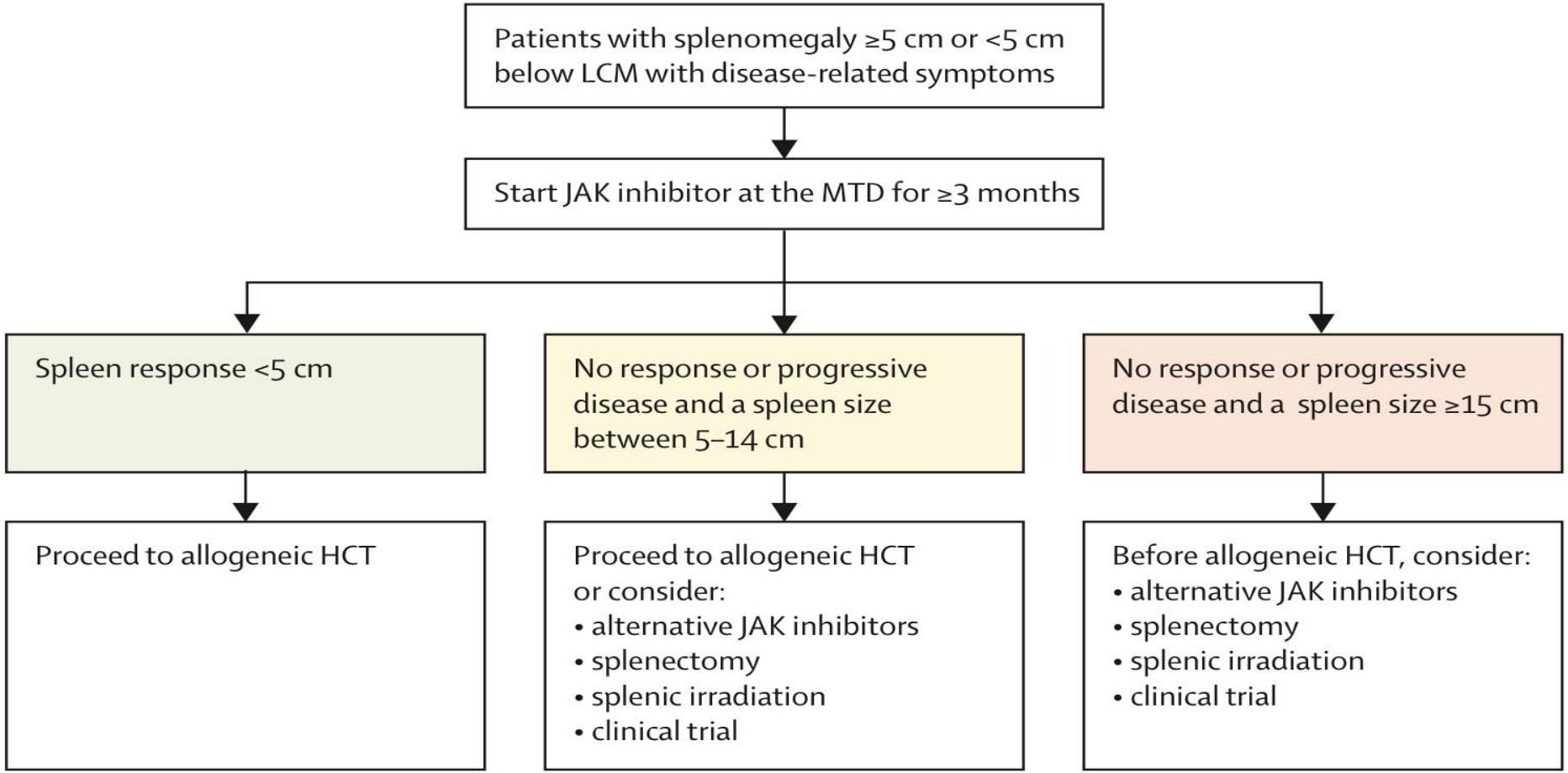

Figure 2: **Flowchart for managing myelofibrosis candidates for transplantation with splenomegaly**
HCT=haematopoietic cell transplantation. LCM=left costal margin. MTD=maximum tolerated dose.

Splenic Irradiation(SI)

has been used in the past for splenomegaly-related symptoms
in those patients with high surgical risk,
particularly before the advent of JAK-inhibitors.
benefit of splenic irradiation is usually short-lived, median duration of response of 6 months
and worsening of cytopenias is frequently observed

The most frequent schedules consist of 6–10 Gy delivered in 0·5–1 Gy fraction daily, on alternate days, or even weekly

In the largest study available, reporting 23 MF patients submitted to SI due to symptomatic splenomegaly, the response rate on splenomegaly was 93.9%, with a median maximal decrease in spleen length of 5 cm.

Symptom relief was documented in 95.6% of patients; however, the benefit duration was limited to a median of 6 months. Significant cytopenias were recorded in around one half of the study cohort, with life-threatening events in 26% of patients.

To date, splenic irradiation could be offere to those MF patients with massive splenomegaly and surgical contraindications only in experienced Centers.

Timing of Transplant

Whether to proceed to transplant early or after treatment failure is a controversial.

Some data support the idea of not waiting for the transplant at the time of disease progression.

1.A progressive splenomegaly may induce a delayed engraftment and increased risk of non-relapse mortality after transplant.

2. it is well recognized that JAK-inhibitors do not affect the risk of leukemic evolution.

3.For patients evolving in accelerated or blastic phase of MF, the prognosis is poorer. 2-fold increase in relapse incidence in accelerated phase of disease (blast cells 10–19%). In the overt blast phase, the probability to achieve a long-term disease control after transplant is severely reduced, even in pre-transplant complete remission.

As a consequence, our approach is ***to proceed to the transplant as soon as possible***, given the time of best disease response.

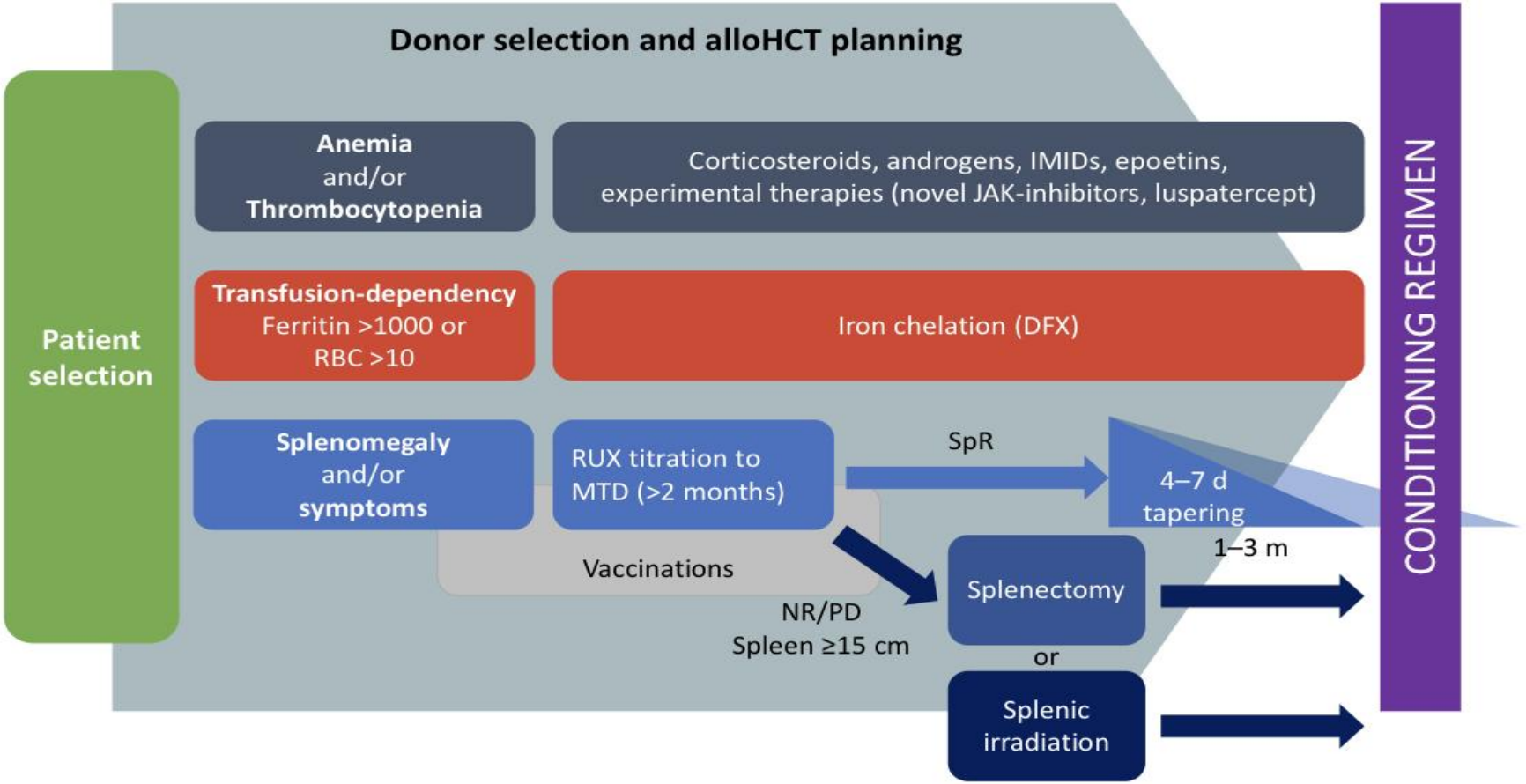

Figure 1. Proposed pre-transplant management of MF candidates to allogeneic stem cells transplantation. IMIDs: immunomodulating agents; RUX: ruxolitinib; MTD: maximum tolerated dose; RBC: red blood cells; SpR: spleen response; NR: no response; PD: progressive disease.

Anemia

corticosteroid (prednisone 0.5 to 1 mg/Kg/day)

androgen therapy (testosterone enanthate 400 to 600 mg weekly, fluoxymesterone 10 mg po TDS, or danazol 600 mg/day)

thalidomide (50 mg/day) as single agent or in combination with corticosteroids (prednisone 15 to 30 mg/day)

lenalidomide (5–10 mg/d), in the presence of del(5)(q31)

Immunomodulating agents have also been associated with responses on thrombocytopenia

epoetin treatment has been reported in 45–50% of MF patients, mainly in the context of inadequate endogenous erythropoietin level (<125 U/L) and non-transfusion-dependent anemia: female sex, leukocyte count ≥ 10 × 10 9 /L, and serum ferritin < 200 ng/mL

activin receptor ligand traps (e.g., luspatercept), currently approved for refractory anemia with ring sideroblasts (RARS-MDS);

recombinant pentraxin-PRM-151 with anti-fibrotic activity;

and new generation JAK-inhibitors (momelotinib, pacritinib),

iron overload

Hepato-cirrhosis, cardiomyopathy, endocrinologic disturbances,Infection ,acute and chronic GHVD, sinusoidal obstruction syndrome ,graft failure and poor graft function

deferoxamine (short half-life and prolonged infusion)

deferiprone (risk for agranulocytosis) have a minimal role in chelation of such patients,

deferasirox,has proven its efficacy in reducing iron burden with manageable toxicity (mainly creatinine increase)

Ideally, all patients receiving support with more than 10 units of blood and/or serum ferritin >1000 ng/mL should receive irondirected treatment.

(DONOR CHIMERISM AND MUTATIONS)

Alchalby et al. has shown that JAK2 negativity after allogeneic HSCT significantly reduces the risk of relapse.

Similar results have been obtained with MPL and CALR mutations as MRD markers.

A recent retrospective single-center study has shown that patients with detectable mutations on day +100 or at day +180 after allogeneic HSCT have a significant higher risk of clinical relapse at 5 years, as compared to molecular-negative patients (62% vs 10%, $P<0.001$ and 70% vs 10%, $P<0.001$, respectively)

However, 10% to 15% of patients are triple negative and cannot be followed after transplantation with a molecular marker: in these patients chimerism studies can be helpful to identify early signs of relapse.

Early (+30) full donor chimerism is highly predictive of long-term disease control. The cumulative incidence of relapse at 5 years, was 14% vs 40% for patients with or without full donor chimerism .

We found that a conditioning regimen including *two alkylating agents* (busulfan and thiotepa) induces a significantly higher rate of complete donor chimerism on day +30, as compared to patients prepared with one alkylating agent (either busulfan, melphalan or thiotepa) (87% vs 45%, $p<0.0001$).

MRD positive patients or patients with declining donor chimerism, who still are receiving immunosuppressive therapy, may discontinue immunosuppressive drugs and/or receive donor lymphocyte infusions (DLI)

POOR GRAFT FUNCTION (PGF)

poor graft function :cytopenia with full donor chimerism

incidence :11%

1.inappropriate function of engrafted donor stem cells and can be treated with the infusion of selected CD34+ cells from the same donor, without a preparative regimen

2.high dose eltrombopag

Klyuchnikov et al. reported on outcomes following CD34+ selected stem cell boost without further conditioning in 32 MF patients, with a median interval of 5 months between alloHSCT and infusion of the boost (median CD34+ cell dose was 3.4 × 106 /kg).

Hematological improvement was observed in 81% of patients, occurring within a median of 30 days.

The cumulative incidence of grades II–IV acute GVHD was 17% and chronic GVHD 26%.

RELAPSE AFTER ALLOGENEIC TRANSPLANT

the most common cause of death (41-61%) was relapse of MF, for all time periods (2-5years, 5-10 years)

1.ruxolitinib

2.donor leukocytes infusion (DLI)

3.second allogenic HSCT