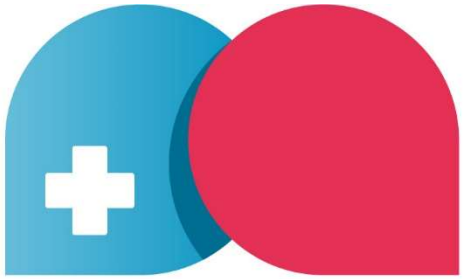
An evidence report on the treatment options for myelofibrosis in stage intermediate II or high risk: drug therapy (esp. JAKi) as definitive therapy vs. drug therapy as bridging followed by allogeneic stem cell transplantation



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CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AE	Adverse events
Allo-HSCT	Allogeneic hematopoietic stem cell transplantation
BAT	Best available treatment
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
FAQ	Frequently asked question
JAKi	Janus kinase inhibitors
MA	Meta-analysis
MF	Myelofibrosis
n.a.	Not applicable
NMA	Network meta-analysis
n.r.	Not reported
NRM	Non-relapse mortality
OS	Overall survival
PICOS	Participants, intervention, comparators, outcomes, and study design
PMF	Primary myelofibrosis
Post-ET-MF	Post essential thrombocythaemia myelofibrosis
Post-PV-MF	Post polycythaemia vera myelofibrosis
PV	Polycythaemia vera
QoL	Quality of life
RCT	Randomised controlled trial
RUX	Ruxolitinib therapy
SDM	Shared decision making
SR	Systematic review
UKA	University hospital Aachen

1. PROJECT OBJECTIVES

A key aim of the present project is to inform patients with primary or secondary myelofibrosis (MF) in stage intermediate II or high risk as part of shared decision making (SDM). In a teamwork with clinical experts from the UKA and patients we developed an evidence-based online decision aid.

For each of SHARE TO CARE's Decision Aids we prepare and regularly update evidence reports, that cover the relative effects of interventions defined in the inclusion criteria (PICOS) [1].

2. METHODS

2.1 INCLUSION CRITERIA

The frequently asked questions (FAQs) underpinning the literature searches were developed in collaboration with clinicians of the University Medical Center Aachen (UKA). These questions pertain to the relevant characteristics of participants, intervention, comparators, outcomes, and study design (PICOS), see Table 1.

Currently, allogeneic hematopoietic stem cell transplantation is the only treatment capable of inducing long-term remission of MF. However, most patients are ineligible for hematopoietic stem cell transplantation because of e.g. advanced age and/or the presence of comorbidities.

The decision for or against an allogeneic hematopoietic stem cell transplantation (allo-HSCT) which remains the only potentially curative treatment option for patients with MF, comes with a high risk of treatment related morbidity and mortality. For symptomatic treatment a broad range of drugs is used. This includes the relatively new drug class of Janus kinase inhibitors (JAKi) with promising results regarding reduction of constitutional symptoms and splenomegaly, and improvement of quality of life. Sometimes drug therapy is used as a bridging or prior approach towards allo-HSCT. However, many questions regarding the best treatment strategy, eligibility of patients, and timing are under debate. Therefore, careful patient selection and counselling is necessary.

This report primarily examines the question allo-HSCT versus drug therapy for patients with MF. It does not focus on the best allo-HSCT strategy (e.g. conditioning regimes, timing, donors) or best drug approach (e.g. best available treatment with or without JAKi, favourable JAKi).

Randomised controlled trials (RCTs) are the favoured study design to inform on relevant evidence relating to the treatment options for primary and secondary MF. However, since MF is an orphan disease and high-quality evidence from randomized clinical trials on allo-HSCT is scarce, we had to include several (prospective and retrospective) study designs (e.g. non-randomized comparative intervention studies, registries, or cohort studies).

Table 1: Inclusion and exclusion criteria

	Included	Excluded
Population	Patients > 18 years old with myelofibrosis - Intermediate-2 or high-risk primary myelofibrosis (pre-fibrotic or overt fibrotic PMF (PMF)) - Intermediate-2 or high-risk post polycythaemia vera myelofibrosis (post-PV-MF) or post essential thrombocythaemia myelofibrosis (post-ET-MF)) - Intermediate-1 risk PMF (after individual case evaluation) -> suitable for drug therapy and allogeneic stem cell transplantation	Patients < 18 years; with low risk or intermediate 1 risk PMF, PV, ET and other MPNs; existing contraindication for stem cell therapy
Intervention	Allogeneic hematopoietic stem cell transplantation (allo-HSCT) (w&w/o bridging drug therapy)	n.a.
Comparator	Drug therapy as definitive treatment. Approved treatment options: JAK inhibitors (ruxolitinib; fedratinib; momelotinib; Substances available in "off-label use" and other therapeutic approaches: interferon alpha, hydroxyurea, anagrelide, EPO, androgens, imides, busulfan; watch&wait	n.a.
Outcomes	• Mortality / survival / life expectancy • Consequences of the disease (eg. anaemia, symptomatic splenomegaly (/early feeling of satiety), constitutional symptoms (fever, weight loss, night sweats), itching, fatigue, bone, muscle and limb pain (see: MPN-SAF question.), transfusion independence / number of transfusions • quality of life (MPN-SAF questionnaire) • Adverse events: side effects of drug therapy, risks of allo-HSCT (transplant-associated mortality and morbidity (esp. GVHD)) • relapse and treatment failure • thromboembolic events, severe bleeding events • secondary acute leukaemia, MDS	n.a.
Study design	Systematic reviews, clinical practice guidelines (based on systematic searches), randomised controlled trials, observational studies, (prospective/retrospective) registry studies/analysis.	Narrative reviews; expert opinions; letters', overviews of reviews
n.a.= not applicable		

2.2 FREQUENTLY ASKED QUESTIONS

The following FAQs were identified:

1. What does the treatment involve? (+ treatment related time and burden)
2. Will the treatment impact my life expectancy?
3. Will the treatment…
    a. reduce MPN-associated symptoms, like symptomatic splenomegaly (early feeling of satiety, pain) / spleen volume/constitutional symptoms (fever, weight loss, night sweats), itching, fatigue, bone, muscle and limb pain (MPN-SAF questionnaire)?
    b. affect risk of transformation in secondary AML?
4. How long will treatment effect last?
    a. relapse and treatment failure
5. How will treatment impact my quality of life? (MPN-SAF questionnaire)
6. What are the risks or side effects?
    a. Transplant-associated risks/side effects, e.g. mortality and morbidity (esp. GvHD)
    b. Drug-related side effects
7. (Additional information of interest
    a. What can I do to help myself?
    b. Where can I get additional information and/or a second opinion?
    c. Are there any other options? Register inclusion/ clinical trial participation?
    d. support/ self-help groups)

Questions categorized as “additional information of interest” (listed under 7) are not part of this report.

2.3 LITERATURE SEARCHES

Preliminary literature searches via PubMed, Onkopedia and international guideline resources were conducted to identify recently published (evidence-based) guidelines.

A search of studies of interest was carried out on PubMed, Cochrane Database of Systematic Reviews (CDSR), and Cochrane Central Register of Controlled Trials (CENTRAL), with language restrictions (English, German) from database inception until April 30, 2024. The search strategy used the keywords (myelofibrosis, "primary myelofibrosis", "post-polycythaemia vera myelofibrosis”, "secondary myelofibrosis", "post-essential thrombocythemia myelofibrosis") and “stem cell transplantation” (synonyms). The searches were without any limitations on study type, and collected studies were then manually checked for consistency with inclusion criteria.

3. Results

The preliminary literature search yielded two relevant guidelines on MF in general and one recommendation paper focused on indication and management on allo-HSCT in MF[2-4]. The methodological quality of the British as well as the German guideline couldn´t be assessed due to unavailable specific guideline reports. However, both guidelines were compiled according to a defined process and methodology including literature searches and consensus procedures by clinical experts in the field [3,4]. Recommendations are based on a review of the relevant myelofibrosis-related literature using diverse medical databases, e.g. PubMed.

Recommendations of the EBMT/ELN paper are based on an expert panel (Delphi process) without systematic searches or grading of evidence acknowledging the absence of randomised clinical trials directly investigating allo-HSCT in MF[2].

3.1 Overview of included studies

Table 2 summarises the sources of evidence used to answer the FAQs.

Table 2: Evidence sources

Publication (year/ reference)	Evidence source	Intervention(s)	FAQ1: What does the treatment involve?	FAQ2: Will the treatment impact my life expectancy?	FAQ3: Will the treatment affect (e.g. symptom reduction?	FAQ4: How long will treatment effect last?	FAQ5: How will treatment impact my quality of life?	FAQ6: What are the risks or side effects?
Maze et al. (2024) [5]	Retrospective observational study	Allo-HSCT vs. JAKi		✓				
Kröger et al. (2015a) [6]	Retrospective registry study	Allo-HSCT vs. BAT (non-transplant excl. JAKi)		✓				
Bewersdorf et al. (2021) [7]	SR & MA (incl. retrospective studies, prospective study, phase II clinical trials, registry studies)	Allo-HSCT		✓		✓		✓
Sureau et al. (2021) [8]	SR & NMA	JAKi (ruxolitinib, Momelotinib, fedratinib) vs. placebo/ BAT/BAT excl. JAKi		(✓)	✓			✓
COMFORT-I & -II [9-12]	RCT	RUX vs. placebo & RUX vs. BAT	(✓)	(✓)	✓	✓	✓	✓
JAKARTA [13,14]	RCT	Fedratinib vs. placebo		(✓)	✓			✓
MOMENTUM [15]	RCT	Momelotinib vs. danazol		(✓)	✓			✓

SIMPLIFY-2 [16]	RCT	Momelotinib vs. BAT (including ruxolitinib)		✓	✓			✓
SIMPLIFY-1 [17]	RCT	Momelotinib vs. ruxolitinib		✓	✓			✓
Onkopedia (2023) [4]	Guideline	Various treatments	✓	(✓)	(✓)	(✓)		(✓)
BHS guideline (2023) [3]	Guideline	Various treatments	✓	(✓)	(✓)	(✓)		(✓)
EBMT/ELN (2024) [2]	Recommendation paper	Allo-HSCT	✓	✓	(✓)	(✓)		(✓)

3.2 FAQ 1: What does the treatment involve?

This section covers the main treatment options for myelofibrosis. All treatment options alongside the purported mechanisms of action are described in Table 3 (below). This is partly a new and fast developing field of research.

Description of the disease:

Myelofibrosis (MF), which may occur de novo as primary MF (PMF) or following essential thrombocythemia (PET-MF) or polycythaemia vera (PPV-MF), is a chronic myeloproliferative neoplasm characterized by constitutional symptoms, hepatosplenomegaly, cytopenia, an increased risk of vascular complications, and a risk of transformation to acute leukaemia.

MF is a rare but serious disease affecting pluripotent hematopoietic stem and progenitor cells in the bone marrow. It is characterized by dysregulation of the JAK2 signaling pathway, leading to abnormal hematopoietic proliferation and a pathological increase in the release of cytokines and growth factors. As a result, the bone marrow is gradually replaced by fibrous scar tissue, impairing its ability to produce blood cells. In the EU, around 0,5 -1 in 100,000 people are diagnosed with myelofibrosis every year, with an equal sex incidence [3].

Table 3: Description of treatments

Primary and secondary myelofibrosis
Primary myelofibrosis (pre-fibrotic or overt-fibrotic myelofibrosis) is usually treated similar to secondary myelofibrosis (post-ET-MF and post-PV-MF). Current management approaches are based upon clinical phenotype, prognostic group, patient age and performance status with consideration of comorbidities. Conventional treatments such as hydroxyurea, glucocorticoids, androgens, and most recently, janus kinase inhibitors (JAKi), facilitate symptom control, spleen size reduction, and control of myeloproliferation. However, they have no clear disease-modifying effect. The only curative treatment for suitable patients with intermediate-2 or high risk (primary/secondary) myelofibrosis is allogeneic hematopoietic stem cell transplantation (allo-HSCT). Drug therapy might be used as definitive therapy or as bridging to allo-HSCT [[2,3] Guidelines recommend that patients should be informed about available clinical trials and should be offered participation [3,4].
Drug therapy with JAK-Inhibitors (ruxolitinib, fedratinib, momelotinib (= only for patients with anaemia))
The janus kinase inhibitors (JAKi) Ruxolitinib, Fedratinib, and Momelotinib are approved by the EMA. JAK inhibitors are indicated for the treatment of symptoms or disease-related splenomegaly. JAK inhibition cannot be considered as curative treatment. However, JAK inhibitors are used to manage symptoms or as a bridging treatment to HSCT as it may decrease spleen size and improve constitutional symptoms to reduce therapy-related complications after stem cell transplantation.

Ruxolitinib (Jakavi®)
Ruxolitinib was the first JAK Inhibitor approved for the treatment of MF in 2012. It is an inhibitor of the JAK1 and JAK2 protein kinases and works by competitively inhibiting the ATP-binding catalytic site on JAK1 and JAK2. The result of this inhibition is disruption of cytokine and growth factor signaling pathways, leading to a decrease in pro-inflammatory cytokines and chemokines, which are usually elevated in MF and other inflammatory conditions. Furthermore, JAK1 is involved in regulating interleukin 2 and 6 and TNF alpha, while JAK2 is involved with many cellular functions that include proliferation and differentiation.
Ruxolitinib is taken orally and is available in 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg tablets. The dosing regimen is based on the patient's individual situation as well as blood results. (In rare cases, discontinuation of ruxolitinib has been associated with severe, life-threatening AEs attributed to MF symptom rebound and cytokine storm.) [11,18]

Fedratinib (Inrebic®) is approved for the treatment of disease-related splenomegaly (enlargement of the spleen) or symptoms in adult patients who have not been pretreated with a Janus-associated kinase (JAK) inhibitor or who have been treated with ruxolitinib. Fedratinib is a kinase inhibitor with activity against wild-type and mutation-activated Janus-associated kinase 2 (JAK2) and FMS-like tyrosine kinase 3 (FLT3). The recommended dose is 400 mg (orally) once a day [4].

Momelotinib (Omjjara®) is a JAK1/JAK2 and activin A receptor type I (ACVR1) inhibitor used to treat disease-related enlargement of the spleen (splenomegaly) or symptoms in adult patients with moderate to severe anemia, who have primary MF, post-PV MF or post-ET MF and who have not been pretreated with a JAK inhibitor or who have been treated with ruxolitinib. The drug is available as tablets (recommended dose 200mg once a day) [3].
In addition to its effect on JAK1 and JAK2, momelotinib shows activity against ACVR1 (Activin A Receptor Type I), another signaling pathway involved in the regulation of erythropoiesis. This additional inhibition may contribute to the efficacy of momelotinib in the treatment of the anemic component of myelofibrosis by supporting erythropoiesis and thus improving anemia.

Additional substances available in "off-label use" and other therapeutic approaches [2-4]

Some other drugs are used as problem-orientated strategies, e.g. interferon alpha, hydroxyurea, anagrelide, EPO, androgens, imides, busulfan.
Hyperproliferation: If platelet counts are very high (>1.5 million/µl) over a longer period, leucocytes are significantly elevated or there are circulatory disorders, treatment with cytoreductive (cell-reducing) drugs may be considered. Various studies have shown that these can prevent the risk of thromboembolic complications. Hydroxyurea (HU) is a so-called cell division toxin (cytostatic) that restricts the function of the bone marrow and thus reduces the number of blood cells. However, HU not only affects the platelets, but also inhibits the production of white blood cells (leukocytes) and red blood cells (erythrocytes). If the erythrocytes are already in decline and anemia is apparent, this can be exacerbated by HU. Interferon-alpha is a hormone-like messenger substance (cytokine) is another option - off-label use - that can be used to treat PMF.
Supportive treatment options for declining haematopoiesis: Blood transfusions (erythrocyte concentrates); Androgens counteract anemia requiring treatment by promoting the formation of new erythrocytes.
Watch&wait: The guidelines recommend watch&wait only for symptom-free patients in the low-risk group. This includes initially only follow-up observation, but no drug treatment.
This should include quarterly blood count checks and an annual comprehensive examination including ultrasound of the liver and spleen. A new bone marrow puncture is usually only necessary if the course of the disease changes significantly. However, patients have always the right/choice to watch&wait or even doing nothing.

Hematopoietic stem cell transplantation following drug therapy as bridging
Hematopoietic stem cell transplantation (HSCT) is the only curative therapeutic modality for primary and secondary MF at present. As part of the stem cell transplantation procedure, the patient undergoes conditioning therapy to eradicate malignant cells residing in the bone marrow. After transplantation, the donor's immune cells recognize and destroy any remaining malignant cells, a process known as the graft-versus-leukemia effect. However, the new immune system can also attack healthy cells, such as those in the skin, intestines, or liver. This adverse reaction is known as graft-versus-host disease (GvHD), an undesirable side effect of transplantation. To manage graft-versus-host disease (GvHD), patients receive prophylaxis with immunosuppressive therapy, commonly involving a combination of calcineurin inhibitors (CNI) and an antimetabolite. This therapy is typically tapered or discontinued approximately six months post-transplantation, although the exact duration may vary among patients. Due to the strong suppression of the immune system during the transplantation and the slow build-up of the new immune system after the actual transplantation, certain precautions are required to protect the patient from infections. (Optimal) Timing of HSCT is difficult to establish in absence of prospective clinical trials[2]. Based on prediction models a HSCT is considered for patients with intermediate-2 and high-risk disease (and if they are in a transplantable condition and have a biological age of up to around 70 years)[4]. Patients over 70 years of age can be offered HSCT on an individual basis (acknowledging patient preferences, disease- and patient-related features). Patients may receive JAK inhibitors and/or other supportive medications as a bridging strategy until hematopoietic stem cell transplantation (HSCT). In some cases, additional procedures or drug interventions may be required in the pre-transplant phase to enhance transplantation outcomes, such as addressing splenomegaly or a high number of peripheral blood or bone marrow blasts. HSCT donation can be from a HLA-matched sibling or HLA-matched unrelated person. However, matched sibling donors are the preferred donor source for allogeneic HSCT (considering factors like age or comorbidities). Peripheral blood is the predominant stem-cell source for transplantation in MF.

3.3 FAQ 2: Will the treatment impact my life expectancy?

As mentioned above no (randomised) controlled studies with direct comparisons between drug therapy with JAK inhibitors (and/or other substances) or allo-HSCT are available today. Only retrospective observational or registry studies were identified [2,5,6]. Additional data on overall survival (OS) were extracted from a meta-analysis based on various study designs for allo-HSTC [7] and from RCTs comparing a JAKi (ruxolitinib, fedratinib, momelitinib) vs. placebo/best available treatment (BAT) [9-11,13-17].

The natural history of MF is predicted with a median OS of 4 years for intermediate-2 and 1.5 years for high risk based on Dynamic International Prognostic Scoring System (DIPSS) [19].

Prospective, comparative studies

Maze et al. analysed MF patients from Canadian and US centres who received two upfront treatment strategies: JAKi vs. allo-HSCT (including JAKi up to six months as a bridge) [5]. Of the 302 patients with one of these two initial treatment strategies, Dynamic International

Prognostic Scoring System (DIPSS) score was intermediate-1 in 126 patients (42%), intermediate-2 in 150 (50%), and high in 26 (9%). Due to small numbers of intermediate-2 and high-risk patients (n=176), these groups were analysed together. The upfront treatment was Jaki (n=115) and allo-HSCT (n=61).

The median OS of patients with intermediate-2 and high-risk disease was 55 (95% CI: 36–72) months in the upfront JAKi group vs. 36 (95% CI: 20–not reached; NR) months in the upfront HCT group (p = 0.27). The median OS of the full cohort (including intermediate 1) of MF patients was longer in those who were managed with an upfront JAKi strategy: 69 (95% CI: 57–89) months for patients in the upfront JAKi group vs. 42 (95% CI: 20–NR) months in the upfront HSCT group (p = 0.01).

In the first twelve months after initiation of treatment, 43 patients of the full cohort died (allo-HSCT n= 31; JAKi n=12). In the allo-HSCT group, 24 (77%) deaths were treatment-related, 2 (7%) were due to disease progression or relapse, and 5 (16%) were considered to be due to other causes, including cardiovascular events, bleeding, and other malignancies. In the JAKi group, 6 (50%) deaths were attributed each to disease progression and other events.

At 36 and 60 months, no significant survival differences were observed for the combined int-2 and high-risk group.

	36-month survival, median (95% CI)			60-month survival, median (95% CI)		
	JAKi	HCT	*P* value	JAKi	HCT	*P* value
Total cohort ($n = 302$)	0.69 (0.63-0.76)	0.53 (0.43-0.65)	0.01	0.56 (0.48-0.65)	0.50 (0.48-0.65)	0.41
Int-1 ($n = 126$)	0.79 (0.71-0.89)	0.57 (0.40-0.80)	0.04	0.68 (0.57-0.80)	0.57 (0.40-0.80)	0.34
Int-2, High ($n = 176$)	0.60 (0.35-0.62)	0.51 (0.40-0.71)	0.28	0.43 (0.31-0.58)	0.46 (0.35-0.62)	1.00

MF myelofibrosis, *JAKi* JAK inhibitor therapy, *HCT* allogeneic hematopoietic cell transplantation, *PMF* primary myelofibrosis, *DIPSS* dynamic international prognostic scoring system, *CI* Confidence interval.

Tab.: Survival of patients with MF who received upfront HCT vs. JAKi in DIPSS-stratified categories (Maze et al. 2024 [5])

Maze et al. did not observe a benefit of a universal upfront HSCT approach in any DIPSS-stratified category in patients with MF aged 70 years or less [5].

Retrospective, comparative studies

Earlier retrospective studies have shown a survival advantage of allo-HSCT compared to non-transplant therapy. The EBTM/ETL guideline summarised that the median overall survival (OS) for DIPSS intermediate-2- and high-risk patients after allo-HSCT was superior to that after non-transplant management [20]. The 5-year OS after HSCT ranged from 38-83% (depending on donor and/or conditioning regime) [20].

Kröger et al. [6] carried out a retrospective study including patients stratified by DIPSS risk who received allo-HSCT (American and European multicenter collection = the transplant cohort) and patients who did not (independent European multicenter collection = the nontransplant cohort). 438 patients <65 years old at diagnosis who received allogenic SCT (n=190) or conventional therapies (n=248, no patient was treated with Ruxolitinib) were

included and analysed. Patients with postpolycythemia vera MF and postessential thrombocythemia MF were excluded.

DIPPS categories were reported for different time points. In the nontransplant cohort (conventional therapy) at diagnosis and in the transplant cohort at transplantation. Therefore, the transplant cohort had higher numbers of patients with intermediate-2-risk and high risk. The medium time from diagnosis to transplant was 1.2 years (0.0-22.2).

The 1-year proportions surviving in the transplant and nontransplant cohorts were 82% and 77% for int-2, and 65% and 67% for high-risk patients.

The 5-year proportions surviving in the transplant and nontransplant cohorts were 50% and 41% for int-2, and 32% and 11% for high-risk patients.

The 10-year proportions surviving in the transplant and nontransplant cohorts were 32% and 11% for int-2, and 27% and 1% for high-risk patients.

The results indicate that non-transplant-treated PMF patients 65 years of age or younger at diagnosis with int-2 or high-risk disease are likely to benefit from HSCT on a longer range.

Systematic Reviews / Meta analyses

Bewersdorf et al. identified 43 studies with 8.739 patients on allo-HSCT and showed rates of 1-year, 2-year, and 5-year OS of 66.7%, 64.4%, and 55.0%, respectively [7].

Non-relapse-mortality (NRM) is a major driver of mortality especially in the first year after allo-HSCT for MF. Rates of 1-year, 2-year, and 5-year NRM were 25.9% (95% CI, 23.3%-28.7%), 29.7% (95% CI, 24.5%- 35.4%), and 30.5% (95% CI, 25.9%-35.5%) [7].

Results of RCTs on ruxolitinib and momelotinib showed comparable long-term OS rates as reported by Maze et al. [5,10,15]. OS at 5-years were 57,5% for ruxolitinib (COMFORT-I and –II pooled analysis) [10]. In the SIMPLIFY-1 trial the 4- and 6-year OS rates were 62.9% and 56.5% for patients randomized to momelotinib and 64.4% and 52.7% for patients randomized to ruxolitinib [17,21].

Certainty of included studies:

Certainty of the results by Kröger et al. is low, due to small sample sizes, confounding factors and restricted to patients with primary MF. In addition, the impact of ruxolitinib (or another JAK inhibitors) compared to allo-HSCT could not be assessed [7].

Maze et al. included patients with PPV- and PET-MF and the non-HSCT-cohort was treated with JAKi. However, the results are limited to the retrospective, non-randomised study design – confounding and selection bias may be present [5]. Results by Bewersdorf et al. are limited due to possible confounding and selection bias as well as the variable characteristics [7].

Conclusion for the decision aid:

The median overall survival (OS) for patients without treatment (natural course of disease) is about 48 months for intermediate-2 and 18 months for high risk based on DIPSS. Results from an observational study combining both risk groups showed a median OS of 55 months for an upfront JAKi-treatment and 36 months for upfront allo-HSCT treatment. The rates of OS at 5-years were comparable with 43% and 46% for JAKi and allo-HSCT, respectively.

Other allo-HSCT studies showed a 5-year survival rate of about 55%; JAKi-RCTs showed 5-6 years survival rates ranging from 52.7 to 57.5%.

3.4 FAQ 3: What are the benefits of the treatment options regarding various symptoms, e.g. spleen volume, constitutional symptoms?

No comparative, controlled studies matching the PICO were identified.

Benefits of drug treatment with JAKi were extracted from RCTs comparing one JAKi vs. placebo/BAT/another JAKi. Various drug options are available for symptomatic therapy. However, targeted oral therapy with JAK1 inhibitors has become the established treatment for myelofibrosis. The focus here is therefore on the results of JAKi. JAKi therapy can be supplemented with other active substances. The drug therapy regime is based on the individual patient characteristics.

No publication with general results on spleen size/volume after allo-HSCT were identified. Allo-HSCT has a large risk of non-relapse mortality (NRM), which varies considerably due to patient-, myelofibrosis-, and donor-specific characteristics. One of these characteristics might be a (massive) splenomegaly at transplantation time. Therefore, management of splenomegaly prior to allo-HSCT is important. Despite this knowledge, recommendations on best treatment strategies varies in specialised centers. The pretransplant spleen management has impact on the results of the allo-HSCT. The various management options, e.g. medical strategies (JAKi, conventional non-JAKi cytoreductive strategies), splenectomy, splenic irradiation, are not the focus of this report. Depending on the individual spleen volume/splenomegaly and the selected pretransplant management, effects on spleen volume or other symptoms due to splenomegaly/enlarged spleen size will differ after allo-HSCT. Recently published guidelines and recommendation papers refer to the existing evidence on different strategies, based on retrospective and prospective study designs [2-4,22].

The outcome **spleen size** (35% or more reduction in spleen volume at week 24) was assessed in RCTs on the three JAKis ruxolitinib, fedratinib and momelotinib: The proportion of patients – who were treated with ruxolitinib – with a reduction of spleen size was 41.9% (compared to placebo) [11]. The mean reduction was 31.6% and almost all patients treated with ruxolitinib had some degree of reduction in spleen volume. Compared to BAT (0% at week 24 + 48) a total of 32% of the patients with ruxolitinib had at least a 35% reduction in spleen volume at week 24 and 28% at week 48 [9]. Proportions with fedratinib were 36% and 55% in

JAKARTA I +II, respectively [13]. Spleen size was reduced in 26.5% (SIMPLIFY-1), 7% (SIMPLIFY-2) and 23.1% (MOMENTUM) of patients with momelotinib treatment [12,15-17].

Around 80% of ruxolitinib-patients experienced >10% reduction in spleen volume; primary resistance is rare. Nearly 40-50% of patients were achieving a 50% reduction in symptom burden within eight weeks, if the dose is adequate [3].

Symptom response (total symptom score reduction ≥ 50% at week 24): The proportion of patients with a symptom response (e.g. appetite loss, dyspnea, fatigue, insomnia, and pain) with ruxolitinib was 45.9% [11], with fedratinib 36% in JAKARTA-I and 26% in JAKARTA-II, and with momelotinib ranging from 24.6% to 28.4% [15-17].

A systematic review and network meta-analysis by Sureau et al. confirms ruxolitinib place as the reference JAK inhibitor, closely followed by fedratinib, for reducing splenomegaly and improving disease-related symptoms [8]. The study suggests that the choice of a JAK inhibitor could depend on the line of treatment and to the risk of onset of severe anemia and/or thrombocytopenia. In this regard, momelotinib could be confirmed as a valuable option in case of anemia and fedratinib in case of thrombocytopenia [8].

Conclusion for the decision aid:

No comparative, controlled studies on symptoms are available.

No publication with general results on spleen size/volume after allo-HSCT was identified. Depending on the individual spleen volume/splenomegaly and the selected pretransplant management, effects on spleen volume or other symptoms due to splenomegaly/enlarged spleen size will differ after allo-HSCT.

Drug therapy with JAKi is very likely to reduce splenomegaly and improve disease-related symptoms in a majority of patients. Different JAKis are available and choice of JAKi depends on individual situation, e.g. due to anemia or intolerance, (and/or prior therapy regimes).

3.4.2 What are the benefits regarding need for treatment, e.g. blood transfusion

No prospective controlled studies directly comparing transfusion-independence of patients treated with drug therapy versus allo-HSCT were identified.

Regarding haematological reconstitution after allo-HSCT a (very) slow recovery, as compared to other diagnoses, is reported with a significant number of patients remaining transfusion-dependent months after allo-HSCT.

In COMFORT-I 60% of RUX-patients received red blood cell transfusions (mean 1.7 transfusion per month) COMFORT-II During the treatment period, more patients in the ruxolitinib group than in the best-available-therapy group received at least one transfusion of packed red cells

(51% vs. 38%). The mean number of transfusions per month was similar in the two treatment groups (0.86 and 0.91, respectively) [9,11].

At baseline 68.4% patients in the momelotinib and 70% in the ruxolitinib group were transfusion independent [SIMPLIFY-1; [17]. At week 24, more patients who received momelotinib were transfusion independent (66.5%) compared with the ruxolitinib group (49.3%; nominal P <.001). Fewer patients who received momelotinib were transfusion dependent at week 24 (30.2%; 24.7% at baseline) compared with those who received ruxolitinib (40.1%; nominal P = .019; 24% at baseline). The median rate of red blood cells transfusion through week 24 was 0 units per month in the momelotinib group compared with 0.4 units per month in the ruxolitinib group (nominal P < .001) [17].

Conclusion for the decision aid:

Comparative studies on allo-HSCT versus drugs are not available.

A successful transplantation is not necessarily accompanied by immediate transfusion independence. Depending on the individual initial situation, transfusion independence can be maintained or achieved with JAKi-treatment.

3.4.3. Will the treatment affect the occurrence of a secondary disease?

No prospective controlled studies directly comparing occurrence of secondary diseases, e.g. AML, of patients treated with drug therapy versus allo-HSCT were identified.

The overall risk of leukemic transformation in patients with overt-fibrotic primary MF is reported around 20% (natural course). Patients with post-PV and post-ET myelofibrosis have a similar risk of leukemic transformation [23-25]. Reported frequencies for post-PV acute myeloid leukemia (AML) are 2.3–14.4% at 10 years and 5.5–18.7% at 15 years and for post-ET AML are 0.7–3% at 10 years and 2.1–5.3% at 15 years [26].

Bewersdorf summarised the rates of patients with progression to AML prior to their allo-HSCT ranging from 0% to 27% [7]. The broad range with a highest rate, which is higher than the predicted rate, might be due to selective study populations, e.g. the proportion of high-risk patients (exclusively) included.

In the two RCTs on ruxolitinib was no indication of a leukemogenic effect and the risk of leukemic transformation was similar in the treatment, placebo, and best available therapy arms [9,11]. AML (leukemic transformation) occurred in 3% in the momelotinib-trials [15].

Conclusion for the decision aid:

Disease transformation into secondary AML is one of the disease-related complications affecting survival prognosis. Leukemic transformation is reported in about 20% of MF-patients (PMF, post-PV-MF, post-ET-MF). The different treatment strategies may affect the occurrence of leukemic transformation/AML. Due to the different populations in and between the studies and the treatment groups, no estimate of the treatment effects is given.

3.5 FAQ 4: How long will treatment effect last?

No prospective controlled studies directly comparing treatment failures/relapses of patients treated with drug therapy versus allo-HSCT were identified.

Cohort study or registry data:

Regarding relapse after allo-HSCT, published rates vary between 10-30% within five years across retrospective studies [27,28].

However, Bewersdorf et al. synthesized data on relapse-free survival (RFS) and progression-free survival (PFS) for patients after allo-HSCT [7][6].

Rates of 1-year, 2-year, and 5- year RFS were 65.3% (95% CI, 56.5%-73.1%), 56.2% (95% CI, 41.6%-69.8%), and 53.6% (95% CI, 39.9%-66.9%), respectively.

Rates of 1-year, 2-year, and 5-year PFS were 56.9% (95% CI, 41.4%-71.2%), 50.6% (95% CI, 39.7%-61.4%), and 43.5% (95% CI, 31.9%-55.8%), respectively. The meta-analyses had to rely on the definitions of RFS and PFS in the primary studies. The used term relapse might include different categories of relapse, e.g. molecular relapse only, cytogenetic relapse or morphological/clinical relapse. Data were not available for all time points and study heterogeneity was significant and substantial for most timepoints.

JAKi: Progression or progression-free survival rates for JAKi were assessed in COMFORT-II [9], JAKARTA [13], and JAKARTA-2 [29]. Progression at 1-year were reported in 30% of patients with ruxolitinib and 26% with BAT [9]. 1-year PFS rates with fedratinib compared to placebo were 83% and 67%, respectively [13]; in JAKARTA2 (a single arm trial) a 1-year PFS of 59% was reported [29].

For ruxolitinib the median time of response is 3.2 years [10]. Around half of patients (with JAKi) remain on therapy at 3 years. The leading causes of discontinuation being disease progression, other adverse events or death. Loss of response can be heralded by e.g. worsening symptoms, sustained increased in spleen size, worsening cytopenia [3].

Guidelines suggest that ruxolitinib might be discontinued if there is no response or no improvement in symptoms/spleen size after six months despite dose optimisation [3].

Some patients are intolerant of ruxolitinib due to side effects. AEs led to ruxolitinib discontinuation in approximately one-third of patients who were randomized or crossed over to ruxolitinib, a rate that was substantially higher than the 12.6% AE-related discontinuation rate with placebo [9,11].

Conclusion for the decision aid:

Relapse rates after allo-HSCT within 5 years vary between 10-30% based on retrospective studies. Rates of relapse-free survival after allo-HSCT may range from around 65.3% at 1-year

to 53.6% at 5-years. The rates of progression-free survival are lower with around 56.9% at 1-year and 43.5% at 5-years.

Study results indicate that JAKi can reduce symptoms/spleen size of some degree for a longer period (3 years or longer) in int-2 or high-risk patients. 1-year progression-free survival ranges from 59% to 83% for different drug therapies (with/without JAKi). Some patients must stop or interrupt the medication due to adverse effects. Medication regimes may be changed (e.g. from ruxolintinib to fedratinib as a second line therapy) when symptoms increase, or intolerance is given.

3.6. FAQ 5: How will treatment impact my quality of life?

No studies directly comparing QoL of patients treated with drug therapy versus allo-HSCT were identified.

The symptom burden of MF has been well explored. Symptoms such as fatigue, abdominal pain, weight loss, pruritis, anorexia, bone pain, fever, and night sweats are very common in myeloproliferative neoplasms (MPNs) and appear to be worse in patients with MF. Surveys and other single arm trials assessed burden of symptoms and QoL with various assessment forms and for different MF populations/treatments, e.g. allo-HSCT. A systematic review/meta-analysis of these studies has not been conducted, yet.

QoL of patients after allo-HSCT (any indication) has shown that QoL declines in the first 30 to 100 days after transplant and improves by 1 to 2 years compared to baseline.

A study with MF patients on QoL following allo-HSCT has shown that there is very little change in symptom burden over the first year following transplant in general. However, significant improvement was observed in MF specific symptoms, and in patients who had a high symptom burden at baseline. By one year 61% felt that their QoL was better than it was prior to transplant. These findings suggest that many of the patients do not experience a significant decline in QoL at 1 year after alloSCT, and more than half of them actually report that their QoL improves [30].

RCTs on JAKi treatment showed (compared to baseline) improved quality of life by noticeably alleviating constitutional symptoms such as chronic fatigue and night sweats (reduced total symptom score (TSS) as measured by the modified Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)).

In JAKARTA-2 overall HRQoL and functional status were evaluated using the QoL Questionnaire Core 30 (QLQ-C30), a self-administered questionnaire that measures HRQoL in patients with cancer. The mean [±SD] baseline global health status/QoL score in JAKARTA2 was 44.6 [20.1], > 20 points lower than the mean score of 66.1 [21.7] in the age- and gender-matched general population. Mean global health status/QoL domain score was significantly ($P < 0.01$) improved from baseline at all visits, exceeding the +10-point threshold for clinically meaningful improvement at three timepoints. At the sixth medication circle, mean QLQ-C30

global health status/QoL domain score had increased by 11.1 points from baseline (mean 57.5 points).

Conclusion for the decision aid:

The medication reduces the symptoms, and this is accompanied by an improvement in QoL. With allo-HSCT, the QoL still appears to be poor/not improved sometime after the procedure. Compared to before the procedure, the majority (61%) state that QoL is better after one year.

3.7. FAQ 6: What are the risks or side effects?

a. Transplant-associated risks/side effects, e.g. morbidity (esp. GVHD)

A systematic review and meta-analyse by Bewersdorf et al presents data on graft failure, and acute and chronic graft-versus-host-disease (GvHD) [7].
Due to a long-time span of included studies with heterogenous reporting and grading of adverse events, rates of adverse events could not be assessed.
100-day mortality serving as a surrogate for transplant-related complications ranged from 0% to 20%.
The combined rate of graft failure was 10.6% (95% CI, 8.9%-12.5%) with primary and secondary graft failure occurring in 7.3% (95% CI, 5.7%-9.4%) and 5.9% (95% CI, 4.3%-8.0%) of patients, respectively.

Variable prophylactic regimens were used for GVHD or even not reported in the included studies. Rates of acute and chronic graft-versus-host disease were 44.0% (95% CI, 39.6%-48.4%; grade III/IV: 15.2%) and 46.5% (95% CI, 42.2%-50.8%; extensive or moderate/severe: 26.1%), respectively. Affected organs included skin, liver, and lower gastrointestinal tract [7].

Quality of the evidence is restricted by the absence of randomised trials and the retrospective designs of the studies. In addition, the heterogeneity of patient and transplant characteristics is another limitation.

b. Drug-related side effects

Cytopenias, in particular anemia and thrombocytopenia, are the most frequent adverse events (AEs) with JAKi in patients with MF. A systematic review and network meta-analysis by Sureau et al. on anemia and thrombopenia events showed significantly less grade 3/4 anemia with momelotinib than with ruxolitinib, fedratinib, or pacritinib [8].
Grade 3/4 anemia in patients treated with RUX ranged from 42-45% [9,11]. Rates for momelotinib patients of anemia with grade ≥3 were 14.8%] (any grade, 23.4%).
Analysis did not show any statistically significant difference between ruxolitinib, fedratinib, and pacritinib.

Fewer occurrence of thrombocytopenia with fedratinib compared to ruxolitinib, momelotinib, and pacritinib. Analysis did not highlight any statistically significant difference between ruxolitinib, momelotinib, and pacritinib. Thrombocytopenia was (any grade, 25.0%

and grade ≥3, 16.4%) with momelotinib and ranged with RUX for grade 3/4 thrombocytopenia from 8-13% [8].

Ruxolitinib [9-11]
Cytopenias, in particular anemia and thrombocytopenia, are the most frequent adverse events (AEs) with RUX in patients with MF.
Grade 3/4 anemia in patients treated with RUX ranged from 42-45%. Ranges for grade 3/4 thrombocytopenia were 8-13%. About the half of the grade 3 or 4 anemia and thrombocytopenia AEs occurred during the first 8 (-12) weeks of treatment. These AEs, which are to be expected given the mechanism of action as a JAK1/JAK2 inhibitor, were generally manageable with dose reductions, brief interruptions or transfusions. Although mean hemoglobin and platelet levels decreased during the first 8–12 weeks of treatment, both stabilized thereafter, with hemoglobin levels increasing toward baseline before stabilizing.

Non-hematologic AEs, e.g. diarrhoea, nausea, vomiting, fatigue, headache, dizziness, bruising, were generally observed at a grade 1 and 2 and at a similar rate to placebo or best available therapy in the COMFORT trials. [9-11]

Risk of overall infection was not elevated with ruxolitinib treatment [9,11]. However, a 5-year analysis of data from COMFORT-I reported that rates of grade 3/4 sepsis were 1.7 and 1.5 events/100 patient-years of exposure (PYE) in the ruxolitinib randomized and ruxolitinib crossover groups, respectively, and 1.0/100 PYE during the 24-week placebo treatment period [10].
Herpes zoster infections have been reported with ruxolitinib. In the 5-year COMFORT-I analysis, most cases of herpes zoster were single episodes that were grade ≤ 2 and resolved without long-term sequelae. (Use of non-live, varicella zoster subunit vaccine to prevent herpes zoster should be considered for patients receiving ruxolitinib). In addition, serious bacterial, mycobacterial, fungal, viral and other opportunistic infections have occurred in patients treated with RUX.

Fedratinib
Gastrointestinal (GI) symptoms, including diarrhea, nausea, and vomiting, are the most common non-hematological AEs observed with fedratinib therapy.
Very common serious side effects are anaemia, thrombocytopenia and diarrhoea.
Encephalopathy has also been observed with the use of the JAK2 inhibitor fedratinib for MF: four cases (2%) of confirmed or suspected Wernicke encephalopathy were observed in the phase 3 JAKARTA trial in patients treated with fedratinib 500 mg/d. In later analysis of patients with lower doses (up to 400mg/d) no additional cases were reported [20].

Momelotinib
The most common any-grade nonhematologic AE was diarrhea (n = 194; 26.8%), followed by nausea (n = 141; 19.4%), fatigue (n = 127; 17.5%), and cough (n = 126; 17.4%). Most gastrointestinal AEs were grade 1 or 2. Peripheral sensory neuropathy was reported in 89 patients (12.3%), with grade ≥3 events in 5 (0.7%). The most common grade ≥3 nonhematologic AE was pneumonia (n = 61; 8.4%). Hematologic AEs included thrombocytopenia (any grade, n = 181 [25.0%] and grade ≥3, n = 119 [16.4%]), anemia (any grade, n = 170 [23.4%] and grade ≥3, n = 107 [14.8%]), and neutropenia (any grade, n = 49

[6.8%] and grade ≥3, n = 38 [5.2%]). Serious hematologic AEs occurred in <5% of patients (anemia, 4.6% and thrombocytopenia, 1.0%) [15].

Conclusion for the DA:
Transplant-associated risks/side effects: The combined rate of graft failure was 10.6% with primary and secondary graft failure occurring in 7.3% and 5.9% of patients, respectively. Variable prophylactic regimens were used for GVHD or even not reported in the included studies. Rates of acute and chronic graft-versus-host disease were 44.0% (grade III/IV: 15.2%) and 46.5% (extensive or moderate/severe: 26.1%), respectively. Affected organs included skin, liver, and lower gastrointestinal tract.

Drug-related side effects: The JAK inhibitors currently available are immunmodulatory by nature and have numerous side effects that require careful use.
Anemia and thrombocytopenia are the most frequent adverse events, which are to be expected given the mechanism of action as a JAK1/JAK2 inhibitor. They are generally manageable with dose reductions, brief interruptions or transfusions.

4. DISCUSSION

4.1 SUMMARY OF MAIN FINDINGS

This evidence review we aimed at presenting the benefits and risks of treatment options for the orphan diseases primary and secondary myelofibrosis. Survival in MF is reduced, especially for the target population of intermediate-2 and high-risk patients. Allogeneic stem cell transplant is a treatment option (the only curative approach) and carries a significant risk profile but can result in long-term disease-free survival. Drug therapy with JAKi is (compared to other drug approaches) effective in decreasing splenomegaly, improving patients' symptom and quality of life, with increased risk for anemia and thrombocytopenia.

4.2 STRENGTH, LIMITATIONS AND UNCERTAINTIES

The strengths of this report are the searches of the most recent evidence summarized in the clinical practice guidelines, and various study designs as well as coverage of a wide range of FAQs and outcomes of interest.

However, no evidence from randomised trials on patients with MF comparing allo-HSCT versus drug therapy (JAKi) was available for consideration. Thus, the quality of the evidence that informed this report is limited by the trials and retrospective analyses available.

Therefore, some limitations should be mentioned. Firstly, because of the absence of randomized controlled trials, confounding and selection bias cannot be excluded. Secondly, the target group for the planned decision aid was defined as relatively broad. Many characteristics that are relevant with regard to the choice of treatment or even exclude certain treatment options could not be taken into account, e.g. performance status, and disease characteristics, known mutations.

Moreover, improvement in GvHD prophylaxis strategies and decrease in NRM post allo-HSCT in recent years has been reported. In parallel to mechanistic drug discoveries the number of allo-HSCTs performed for MF continues to increase resulting in better evidence-based knowledge about conditioning regimes, prophylactic approaches and improvement in supportive care.

The results of this report highlight the need for an individualized approach to patient selection, timing of allo-HSCT and discussion of non-transplantation strategies in the treatment of MF. To make an informed decision, patients should be aware of the potential benefits but also of the risks and uncertainties of the different options (due to missing evidence of high-quality study designs and very different treatment regimens).

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