Indication and management of allogeneic haematopoietic stem-cell transplantation in myelofibrosis: updated recommendations by the EBMT/ELN International Working Group

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New options for medical therapy and risk scoring systems containing molecular data are leading to increased complexity in the management of patients with myelofibrosis. To inform patients' optimal care, we updated the 2015 guidelines on indications for and management of allogeneic haematopoietic stem-cell transplantation (HSCT) with the support of the European Society for Blood and Marrow Transplantation (EBMT) and European LeukemiaNet (ELN). New recommendations were produced using a consensus-building methodology after a comprehensive review of articles released from January, 2015 to December, 2022. Seven domains and 18 key questions were selected through a series of questionnaires using a Delphi process. Key recommendations in this update include: patients with primary myelofibrosis and an intermediate-2 or high-risk Dynamic International Prognostic Scoring System score, or a high-risk Mutation-Enhanced International Prognostic Score Systems (MIPSS70 or MIPSS70-plus) score, or a low-risk or intermediate-risk Myelofibrosis Transplant Scoring System score should be considered candidates for allogeneic HSCT. All patients who are candidates for allogeneic HSCT with splenomegaly greater than 5 cm below the left costal margin or splenomegaly-related symptoms should receive a spleen-directed treatment, ideally with a JAK-inhibitor; HLA-matched sibling donors remain the preferred donor source to date. Reduced intensity conditioning and myeloablative conditioning are both valid options for patients with myelofibrosis. Regular post-transplantation driver mutation monitoring is recommended to detect and treat early relapse with donor lymphocyte infusion. In a disease where evidence-based guidance is scarce, these recommendations might help clinicians and patients in shared decision making.

Introduction

In 2015, under the umbrella of the European Society for Blood and Marrow Transplantation (EBMT) and European Leukemia Net (ELN), we produced consensus-based guidelines for the indication and management of allogeneic haematopoietic stem-cell transplantation (HSCT) in myelofibrosis.[1] Since then, novel medications for the disease have been developed and synergistic combinations with standard JAK inhibitor therapy have been proposed. These treatments have the potential to reduce spleen size, and improve constitutional symptoms, quality of life, and maybe also survival outcomes. Furthermore, there have been substantial improvements in patient and donor selection, conditioning regimens, and post-transplantation supportive care, allowing for more patients to pursue potentially curative allogeneic HSCT.[2] The increase in options for medical therapy and the changing risk profile of allogeneic HSCT is leading to increased difficulty in counselling patients with myelofibrosis on their optimal management strategy.

In this project, as recommended by the Appraisal of Guidelines Research and Evaluation group,[3] we reviewed data from 2015–2022 regarding the results of allogeneic HSCT in myelofibrosis and revised the 2015-issued recommendations with the aim of optimising the use of allogeneic HSCT in myelofibrosis.

The consensus process and scope

According to the conceptual framework elements of the National Institutes of Health Consensus Development Program,[4] a six-member task force consisting of clinical experts in the treatment of myelofibrosis from the EBMT and European Hematology Association, and experts in clinical epidemiology and methodology (NK, BLS, DPM, MR, TB, and GB) appointed a 26-member expert panel from both the EBMT and ELN, who all hailed from Europe and the USA. A clinician with expertise in clinical epidemiology (GB) assured the methodological appropriateness of the process. The methodology of group discussion was followed with the intent to produce consensus-based recommendations (ie, not derived from a systematic review and grading of the evidence) acknowledging the absence of randomised clinical trials directly investigating allogeneic HSCT in myelofibrosis.

Through a Delphi process, the panel agreed on seven areas of major concern regarding allogeneic HSCT in myelofibrosis and generated and rank-ordered 18 key clinical questions using the criterion of clinical relevance (appendix pp 3–4) on the management of patients and risk of inappropriateness.[5]

17 panellists (URP, RBS, AB, AMV, TJ, TS, NK, NG, FP, NP, VG, AR, BLS, JCH-B, DPM, MR, and RT) drafted recommendations that addressed the identified key

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questions. The narrative literature review circulated among the experts and used for producing recommendations is in the appendix (pp 17–41). The list of produced recommendations was then circulated electronically to all participants through four iterations. In each iteration, all the panellists scored their agreement with the proposed statements by secret ballot and provided suggestions for rephrasing. For consensus we required 80% votes in favour. Overall, eight questionnaires were distributed, and all discussions were done electronically without any in-person meetings.

Recommendations

These recommendations primarily focus on the management of patients with primary myelofibrosis, the disease category on which haematologists have most experience and for which there is much literature-based evidence. Recommendations were also considered relevant to post-polycythaemia vera and post-essential thrombocythaemia myelofibrosis (secondary myelofibrosis). Due to differences in prognostic classifications of patients with primary myelofibrosis with respect to those with secondary myelofibrosis, specific consideration was given to these differences when developing the recommendations about the selection of patients for HSCT. A summary of the final, updated 2023 recommendations is in the panel. A comparison with the 2015 recommendations is in the appendix (pp 12–17).

Patient selection

Identifying candidates for transplantation

In the current molecular era, powerful prognostic tools for primary myelofibrosis have been developed (appendix pp 5–9). Mutations in genes such as *ASXL1, EZH2, IDH1, IDH2*, and *SRSF2* independently predicted poor survival in patients with primary myelofibrosis and were then designated as high-molecular-risk mutations.[6] The Mutation-Enhanced International Prognostic Score Systems (three-tiered MIPSS70 and four-tiered MIPSS70-plus) were developed using a cohort of patients aged 70 years or younger who were potentially eligible for allogeneic HSCT.[7,8] A further revision termed MIPSS70-plus version 2·0 incorporated the *U2AF1*Q157 variant as an additional high-molecular-risk mutation.[9] Refinement of risk categories was provided by defining new sex-adjusted and severity-adjusted haemoglobin thresholds for anaemia,[10] and by integrating a refined three-tiered cytogenetic risk distribution system.[11] The Myelofibrosis Secondary to PV and ET-Prognostic Model (MYSEC-PM) allocated patients with secondary myelofibrosis into four risk categories with different survival outcomes.[12]

The new molecular findings in primary myelofibrosis prompted the development of a Genetically Inspired Prognostic Scoring System (GIPSS), which was exclusively based on molecular and cytogenetic variables.[13,14] To accurately predict patient outcome following allogeneic HSCT, the Myelofibrosis Transplant Scoring System (MTSS) was formulated for patients with primary and secondary myelofibrosis.[15] MTSS identifies patient risk level after allogeneic HSCT by including transplantation-specific risk factors, such as donor source and Karnofsky index or the Dynamic International Prognostic Scoring System (DIPSS). However, the evidence base determining the level of risk of transplantation stems from retrospective comparative studies that are not prospectively validated.[16,17]

A very high-risk group of patients who present with *TP53* mutations (including multi-hit constellation with complex karyotype) at the time of allogeneic HSCT was recently described, showing substantial mortality due to high rates of leukaemic transformation for those patients with multi-hit constellation. However, patients with single-hit mutation showed similar outcomes when compared with wild-type patients.[18] In terms of patient selection for transplantation, our recommendation is that patients with DIPSS intermediate-2-risk or high-risk or MIPSS70 or MIPSS70-plus high-risk or MYSEC-PM high-risk or intermediate-2-risk (for secondary myelofibrosis) and MTSS low-risk or intermediate-risk should be considered candidates for allogeneic HSCT. Patients with DIPSS intermediate-1-risk or MIPSS70 or MIPSS70-plus intermediate-risk and MTSS low-risk should be offered allogeneic HSCT, balancing patient preferences, actual treatment options, including clinical trials, and other risk features (including presence of *TP53* mutations).

In older patients (ie, over 70 years), several studies show promising outcomes after allogeneic HSCT in the presence of good performance status and other low-risk features such as an HLA-identical donor.[19–22] Our recommendation in patients older than 70 years is that allogeneic HSCT can be offered on an individual basis, balancing patient preferences and disease-associated and patient-associated features.

Optimal timing to undergo allogeneic HSCT in candidate patients

Optimal timing to undergo allogeneic HSCT in patients with myelofibrosis who are candidates for transplantation is difficult to establish in the absence of an ad-hoc prospective clinical trial. Cipkar and colleagues developed a Markov cohort model in patients with myelofibrosis to predict the optimal timing of transplantation.[23] Months of survival after transplantation peaked at 9·7 months (95% CI 9·5–9·9 months) from diagnosis in patients with DIPSS high-risk disease and at 16·6 months (95% CI 16·4–16·8 months) from diagnosis in patients with intermediate-2 disease. Patients with intermediate-1 risk had a delayed peak in net gain in life expectancy at 20·5 months (95% CI 20·2–20·7 months). Patients with low-risk disease had a greater net gain in life expectancy with a plateau at 29–45 months. According to this decision model, we recommend that transplantation is indicated

upfront for patients diagnosed with DIPSS intermediate-2-risk and high-risk disease, whereas the procedure can be delayed for those with a low-risk or intermediate-1-risk disease.

Most high-risk myelofibrosis candidates for allogeneic HSCT receive a JAK inhibitor. The response to ruxolitnib after 6 months (RR6) model based on simple variables, such as dose, palpable spleen size, and number of red

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See Online for appendix

For more on the **Mutation-Enhanced International Prognostic Score Systems** see http://www.mipss70score.it/

For more on the **Myelofibrosis Secondary to PV and ET-Prognostic Model** see http://www.mysec-pm.eu/

For more on **both the Myelofibrosis Transplant Scoring System and the Dynamic International Prognostic Scoring System** see https://pmfscorescalculator.com/

For more on **RR6** see http://www.rr6.eu/

Panel: **Summary of European Society for Blood and Marrow Transplantation (EBMT) and European LeukemiaNet 2023 recommendations for allogeneic hematopoietic stem-cell transplantation (HSCT) in myelofibrosis**

Patient selection for allogeneic HSCT

- Patients with primary myelofibrosis and an intermediate-2 or high-risk dynamic International Prognostic Scoring System (DIPSS) score, or a high-risk mutation-enhanced IPSS for patients younger than 70 years (MIPSS70) or MIPSS70-plus score, and a low or intermediate risk myelofibrosis transplant scoring system (MTSS) score
- Patients with secondary myelofibrosis and a high or intermediate-2 secondary myelofibrosis prognostic model score
- Patients with primary myelofibrosis and an intermediate-1 risk DIPSS score, or intermediate risk MIPSS70 or MIPSS70-plus score, with low risk MTSS score, balancing patient preferences, actual treatment options, including clinical trials, and other risk features (ie, *TP53* mutations)
- Patients over 70 years of age can be offered allogeneic HSCT on an individual basis, balancing patient preferences and disease-associated and patient-associated features

Optimal timing for allogeneic HSCT

- Immediate for patients with intermediate-2-risk and high-risk DIPSS score, whereas allogeneic HSCT can be delayed for low-risk or intermediate-1-risk disease
- Transplantation-eligible patients on JAK inhibitors should be assessed for response and after 6 months of therapy patients falling into the high-risk category of the response to ruxolitnib after 6 months (RR6) model should receive timely evaluation for transplantation

Pre-transplantation management

- All patients with splenomegaly greater than 5 cm below the lower costal margin or splenomegaly-related symptoms who are candidates for allogeneic HSCT should receive a spleen-directed treatment, ideally with a JAK-inhibitor
- JAK-inhibitor weaning with drug stop at the time of, or after, the start of the conditioning regimen seems to be safe to reduce cytokine rebound syndrome and cardiac complications
- In case of splenomegaly response (less than 5 cm below lower costal margin), proceed with allogeneic HSCT; in other circumstances, second-line options are recommended (alternative JAK inhibitors or novel agents, splenectomy, or splenic irradiation), particularly when spleen is palpable more than 15 cm below the lower costal margin
- Patients with increased peripheral blood blasts (up to 10%) and those with accelerated phase or blast phase disease are not excluded from allogeneic HSCT and should be referred for timely evaluation
- Patients in chronic phase with less than 10% blasts in peripheral blood or bone marrow do not require any additional therapy directed at blast reduction before transplantation
- Blast reduction therapy should be considered in blast phase; the choice of acute myeloid leukaemia-type intensive induction chemotherapy versus non-intensive options, such as hypomethylating agents alone or in combination with venetoclax, should be individualised by careful assessment of patient-related factors and disease-associated genetic factors
- Evidence is insufficient to make recommendations on the potential benefit of reducing the blast count in patients with accelerated phase disease
- In patients in accelerated phase or blast phase of disease, participation in clinical trials or co-operative group registries is highly recommended
- Splanchnic vein thrombosis is not necessarily a contraindication to allogeneic HSCT—in these patients thrombosis should be evaluated for portal hypertension and for liver cirrhosis; pre-transplantation interventions, if effective, might revert the contraindication to transplantation

Donor selection criteria

- HLA-matched sibling donors remain the preferred donor type, except when the potential donor is deemed too old or has comorbidities that will exclude them
- In the absence of an HLA-matched sibling or HLA-matched unrelated donor, alternative donor sources should be considered: outcomes are similar for haploidentical HSCT and 7/8 matched HSCT from an unrelated donor; cord blood transplantation is generally not recommended

Stem-cell source and dose

- Peripheral blood is the recommended stem-cell source for HLA-matched sibling and unrelated donor transplants, and preliminary data suggest that it might also be for haploidentical transplantation using post-transplantation cyclophosphamide (PTCY)
- A high dose of CD34+ stem cells (>$7{\cdot}0 \times 10^6$ cells per kg) is recommended for HLA-matched sibling and unrelated donor transplants; due to a scarcity of data, a preferred stem-cell dose cannot be recommended for haploidentical transplants

Conditioning regimen

- Reduced intensity conditioning and myeloablative conditioning are both valid options

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- For older patients or those with clinically significant comorbidities, or both, a reduced intensity conditioning regimen is more appropriate, whereas for younger patients with a good performance status, a myeloablative conditioning regimen can be selected
- Current data suggest no benefit to adjusting intensity on the basis of genomic risk
- Optimal regimen doses and schedules for reduced intensity conditioning regimens are to be determined; registry data suggest that fludarabine–busulfan is associated with better outcomes

Prophylaxis for graft-versus-host disease (GVHD)

- For HLA-matched unrelated donor HSCT, calcineurin inhibitors and methotrexate with anti-thymocyte–globulin (ATG) or anti-T-lymphocyte globulin (ATLG) is a valid anti-GVHD prophylaxis; an alternative approach could be calcineurin inhibitor with mycophenolate mofetil, and either ATG or ATLG, especially in reduced intensity conditioning
- For mismatched unrelated donor HSCT, PTCY with calcineurin inhibitors could be used as alternative to an ATG-based or ALTG-based GVHD prophylaxis
- For matched related donor HSCT, adding ATG to the usual calcineurin inhibitor-based GVHD prophylaxis could decrease acute GVHD
- For haploidentical donor HSCT, PTCY-based prophylaxis is recommended

Post-transplantation management

Poor graft function

- The use of erythropoietin for anaemia and granulocyte-colony stimulating factor for neutropenia is recommended and can serve as a bridge to a definitive treatment
- Thrombopoietin analogues to treat post-transplantation thrombocytopenia should be used in a controlled setting (registries or clinical trials) or on an individual case-based decision
- In patients with poor graft function and persistent splenomegaly with complete donor cell chimerism, splenectomy might be an option; JAK2 inhibitors could reduce the spleen size and persistent constitutional symptoms, however, this treatment has not been tested for the indication of poor graft function
- The most definitive treatment for poor graft function is a $CD34^+$ selected boost from the original donor (either fresh or cryopreserved), without further conditioning, and should be considered in patients without active GVHD
- Since the time for donor recruitment can be delayed, especially if using an unrelated donor, attempts to reach the donor and obtain the boost product should start early after making the diagnosis of primary graft failure

Primary graft failure

- Needs to be identified early (before day +28) and requires a fast decision of whether to proceed with a second transplantation
- Prevention of primary graft failure includes the preferential use of an HLA-matched donor, a high dose of $CD34^+$ cells at the time of transplantation, and the control of bulky splenomegaly

Molecular monitoring after transplantation

- Molecular monitoring after transplantation is indicated and should be performed at 1 month and at 3-month intervals thereafter, for up to 1 year; however, late relapses support the need for continued monitoring (annual testing might be reasonable)
- It is recommended that minimal or measurable residual disease (MRD) assays are performed in accredited laboratories undertaking quality controls with reference materials
- There is no evidence supporting a preference of bone marrow versus peripheral blood as source of DNA
- Highly-sensitive assays for the driver mutations are recommended to be used, in particular digital droplet PCR-based assays for $JAK2^{V617F}$; assays for *MPL* and *CALR* are less standardised but should have a sensitivity of less than 1%
- The use of myeloid gene-associated mutations for MRD cannot be recommended; experiences with ad-hoc developed digital droplet assays for selected mutations in *IDH1*, *IDH2*, and *DNMT3A* remain largely investigational

Preventing relapse after transplantation

- The EBMT definitions of relapse should be used in clinical practice and clinical trials to standardise clinical approaches and research initiatives
- A finding that indicates potential molecular relapse should be confirmed by a consecutive analysis within 28 days
- Pre-emptive therapy with donor lymphocyte infusion should be initiated after cessation of immunosuppression at the stage of persistent MRD and pursued until complete remission or MRD clearance is achieved; in case of molecular or haematological relapse, donor lymphocyte infusion is indicated
- Prophylactic donor lymphocyte infusion is currently not recommended
- There is insufficient evidence to support the use of JAK inhibitors post-transplantation as maintenance therapy to prevent relapse

Second allogeneic HSCT

- Data suggest that the majority of patients who relapse more than 5 years post-transplantation can be successfully salvaged by second allogeneic HSCT
- Patients who relapse within 1 year or have early graft failure are poor second transplant candidates

blood cell transfusions, evaluated during the first 6 months of ruxolitinib treatment, were able to identify a group of patients with a shorter expected survival (appendix p 9).[24] These patients did not show a reduction in spleen size and required more red blood cell transfusions. The model was recently validated in a retrospective cohort of 140 patients with myelofibrosis, which confirmed that RR6 can be used for early identification of patients with poor prognosis and potential candidates for allogeneic HSCT.[25] Based on these results, we recommend that transplantation-eligible patients who received JAK inhibitors should be carefully and systematically assessed for response, and after 6 months of therapy, patients falling into the high-risk category of the RR6 model should be evaluated for allogeneic HSCT.

Pre-transplantation management

Patients with splenomegaly before transplantation

A publication from 2021 by the EBMT showed that 401 (73%) of 546 patients with myelofibrosis referred for transplantation in Europe between 2000 and 2017 had splenomegaly palpable more than 5 cm below the left costal margin.[26] Importantly, the proportion of subjects with massive palpable splenomegaly, as defined by a spleen length equal to or greater than 15 cm, was 135 (25%). This report confirmed the prognostic role of an enlarged spleen in influencing transplantation outcome.[26] Two independent studies reinforced the evidence that larger spleen size is significantly associated with higher rates of post-transplantation relapse.[21,27]

The first option for managing splenomegaly in myelofibrosis is using JAK inhibitors. In an EBMT study, relapse incidence and event-free survival were significantly improved in ruxolitinib responsive patients compared with non-responders, those who lost response before allogeneic HSCT, or a population unexposed to ruxolitinib.[28]

Alternative JAK inhibitors (eg, fedratinib, pacritinib, and momelotinib) have shown efficacy in reducing splenomegaly, even though information on their use before transplantation is scarce.

The optimal strategy for drug withdrawal before transplantation remains unknown. In this regard, JAK inhibitor weaning with medication cessation at the time of, or after, the start of the conditioning regimen for allogeneic HSCT seems to be safe and can reduce the occurrence of cytokine rebound syndrome and systemic complications.

The benefit of splenectomy in this setting is under discussion. In the previously mentioned EBMT study,[26] splenectomy was associated with improved engraftment and better non-relapse mortality with consequent superior overall survival compared with patients undergoing transplantation with progressive disease and splenomegaly greater than 15 cm. However, a possible increase in post-transplantation relapse could not be completely ruled out. Splenic irradiation could be a suitable option in patients with surgical contraindications in experienced centres, but more systematic data are needed to recommend its use.[29]

We recommend that all patients who are candidates for allogeneic HSCT with splenomegaly greater than 5 cm below the left costal margin or splenomegaly-related symptoms should receive a spleen-directed treatment before transplantation, preferentially with a JAK inhibitor. JAK-inhibitor weaning with drug stop at the time of, or after, the start of conditioning regimen seems to be safe to reduce the occurrence of cytokine rebound syndrome and systemic complications. In case of splenomegaly response (<5 cm below the left costal margin), the Panel agreed on recommending to proceed with transplantation. In other circumstances, second-line treatment options are recommended, particularly when the spleen is palpable more than 15 cm below left costal margin. Alternative JAK inhibitors or novel drugs, splenectomy, or splenic irradiation can be used, taking into account local practice and experience. The Panel highlighted that the high risk of relapse and early hepatotoxicity in these patients is an unmet clinical need for more systematic data.

Higher number of blasts before transplantation

Patients with chronic phase myelofibrosis who have peripheral blood blasts equal to or greater than 4% have a poorer prognosis compared with those with peripheral blood blasts between 1% and and 3%.[30] Blasts greater than 3% in peripheral blood is also a risk factor for blast phase transformation.[31]

There are no data to support whether patients in chronic phase myelofibrosis with peripheral blood or bone marrow blasts equal to or greater than 4% should be treated differently to those with lower blasts before allogeneic HSCT. A 2022 multicentre retrospective study showed similar overall survival for patients with chronic phase myelofibrosis and those with accelerated phase myelofibrosis receiving homogenous reduced-intensity conditioning allogeneic HSCT, whereas increased risk for relapse was observed for accelerated phase myelofibrosis compared with chronic phase myelofibrosis.[32]

Based on several retrospective studies, blast reduction treatment strategies used against acute myeloid leukaemia are recommended in patients with accelerated phase or blast phase myeloproliferative neoplasms.[33] The purpose of these strategies is to reduce the burden of disease by achieving complete or partial remission or reversion to the chronic phase of the disease. A 2023 study from EBMT showed that patients with blast phase myeloproliferative neoplasms undergoing transplantation in complete remission had superior overall survival compared with those with active disease at transplantation.[34] Another study from Center for International Blood and Marrow Transplant Research (CIBMTR) showed that genetic factors of the disease rather than blast reduction play an important part in determining the outcomes of allogeneic

HSCT in patients with blast phase myeloproliferative neoplasms.[35] Outcomes in patients with blast phase myeloproliferative neoplasms who received allogeneic HSCT were worse if mutated TP53 or adverse risk cytogenetics was present, irrespective of blast counts.[35]

There is a lack of prospective data on optimal blast reduction strategies in myelofibrosis. Retrospective studies have reported the use of acute myeloid leukaemia intensive induction therapy consisting of daunorubicin and cytarabine, and high-dose cytarabine-containing protocols, such as FLAG-Ida (fludarabine, cytarabine, granulocyte-colony stimulating factor and idarubicin) or others.[33,36,37] Use of low-intensity approaches with hypomethylating agents such as azacytidine and decitabine, in combination with venetoclax[38] or with ruxolitinib,[39] have been reported. Biological factors such as *TP53* mutation could weigh against intensive induction chemotherapy. In addition, targeted therapy such as *IDH1/2* inhibitors can be considered, depending on access and resources.

We recommend that patients with increased blast counts in the peripheral blood (up to 10%) and those with accelerated or blast phase disease are not excluded from allogeneic HSCT. They should be referred for transplantation evaluation. Patients in chronic phase with blasts in peripheral blood or bone marrow at less than 10% do not require any additional therapy directed at blast reduction before transplantation.

The Panel also concluded that blast reduction therapy should be considered in patients in blast phase. Current evidence is insufficient to make recommendations on the potential benefit of reducing the blast count in patients with accelerated phase myelofibrosis, although an increased risk of relapse after transplantation has been observed. The choice of intensive induction chemotherapy versus non-intensive options, such as hypomethylating agents alone or in combination with venetoclax, should be individualised by careful assessment of patient-related factors and disease-associated genetic factors.

Due to a lack of prospective data to guide the optimal transplantation-driving strategies in patients in accelerated and blast phase disease, participation in clinical trials or co-operative group registries is highly recommended.

Splanchnic vein thrombosis before transplantation

To our knowledge, no study has specifically addressed the effects of splanchnic vein thrombosis on the outcomes of allogeneic HSCT in patients with myelofibrosis. The presence of portal hypertension is associated with an increased risk of hepatotoxicity, development of hyperbilirubinemia, and sinusoidal obstruction syndrome.[40] The Panel concluded that splanchnic vein thrombosis per se is not a contraindication to allogeneic HSCT. Patients with splanchnic vein thrombosis should be evaluated for portal hypertension and for liver cirrhosis, under the consideration that transplantation-related mortality is unacceptably high in case of uncontrolled portal hypertension or liver cirrhosis. In case of Budd-Chiari syndrome, transjugular intrahepatic portosystemic shunt positioning should be discussed with hepatologists and interventional radiologists.

Pre-transplantation interventions, if effective in correcting portal hypertension, might revert the contraindication to allogeneic HSCT.

Donor selection

The CIBMTR reported the transplantation outcomes of 233 patients with myelofibrosis on the basis of donor type.[41] The probability of 5-year overall survival was 56% (95% CI 44–67%) for patients with an HLA-matched sibling and 48% (95% CI 37–58%) for patients with an HLA-matched unrelated donor. Donor type was also a significant predictor of transplantation-related mortality, with a 4-times increased risk of transplantation-related mortality for patients with an HLA-matched unrelated donor compared with those who had HLA-matched sibling donors. Few studies have evaluated alternative donor outcomes in myelofibrosis. A retrospective analysis from the EBMT reported on the outcomes of 35 patients with myelofibrosis who received cord blood transplantation.[42] The 2-year overall survival was 44%, and the 2-year event free survival was 30%. A multicentre retrospective analysis evaluated haploidentical HSCT with post-HSCT cyclophosphamide in 69 patients with myelofibrosis.[27] At 3 years, the overall survival was 72% (95% CI 59–81%) and the relapse-free survival was 44% (95% CI 29–59%). The cumulative incidence of transplantation-related mortality was 23% (95% CI 14–34%). To date, to our knowledge, no prospective study has evaluated donor age as a factor for donor selection.

With the available evidence, we concluded that matched sibling donors remain the preferred donor source for allogeneic HSCT except when the potential donor is of an age deemed too old to be a potential donor or has comorbidities which will exclude them. In the absence of an HLA-matched sibling or HLA-matched unrelated donor, alternative donor sources should be considered.

Available evidence indicates similar outcomes with haploidentical HSCT and 7/8 HLA-matched unrelated donors. Cord blood transplantation is generally not recommended in patients with myelofibrosis.

Stem-cell source and dose

Peripheral blood is the predominant stem-cell source for transplantation in myelofibrosis.[43] However, to our knowledge, no randomised comparisons between peripheral blood and bone marrow grafts in myelofibrosis have been reported. In retrospective studies, peripheral blood was associated with a higher probability of engraftment than bone marrow, with no significant effect on overall survival.[44] In haploidentical transplantation, the use of bone marrow grafts has been associated with an increased incidence of graft failure[45] and of relapse.[21,27] In a recent EBMT study of 657 patients with myelofibrosis

undergoing reduced-intensity conditioning transplantation from HLA-matched siblings or unrelated donors with peripheral blood as the stem-cell source, infusion of more than $7·0\times10^6$ CD34$^+$ cells per kg was associated with higher rates of neutrophil and platelet recovery than lower infusion doses.[46] In HLA-matched sibling donor recipients, a higher CD34$^+$ dose correlated with improved overall survival and progression-free survival, and reduced non-relapse mortality. Consistent with this finding, in a single-centre series from Canada, a higher dose of CD34$^+$ peripheral blood progenitors ($\leq5\times10^6$ cells per kg *vs* $5–9\times10^6$ cells per kg *vs* $\geq9\times10^6$ cells per kg) was associated with improved overall survival and progression-free survival, and reduced non-relapse mortality.[47] Of note, no detrimental effect of a high CD34$^+$ dose on the risk of acute or chronic graft-versus-host disease (GVHD) was documented in these studies. In a multicentre, retrospective study of 69 haploidentical blood or marrow transplantations, the CD34$^+$ cell dose ($>6\times10^6$ cells per kg *vs* $<6\times10^6$ cells per kg) correlated with overall survival and non-relapse mortality outcomes and relapse risk.[48]

Few data are available on transplant outcomes in myelofibrosis according to stem-cell source. The Panel concluded that peripheral blood is the recommended haematopoietic stem cell source for HLA-matched sibling and unrelated donor transplantation, and preliminary data suggest that it might also be the preferred source for haploidentical transplantation using post-transplantation cyclophosphamide. A high dose of CD34$^+$ cells ($>7·0\times10^6$ CD34$^+$ cells per kg) is recommended for HLA-matched sibling and unrelated donor transplantations. Due to insufficient data, a preferred stem-cell dose cannot be recommended for haploidentical transplantation.

Conditioning regimen

Given the scarcity of direct evidence from prospective trials, optimal conditioning intensity and regimen choice are difficult to ascertain. A large retrospective analysis performed on behalf of the EBMT compared outcomes between myeloablative conditioning and reduced-intensity conditioning for allogeneic HSCT in patients with myelofibrosis between 2000 and 2014.[48] In the myeloablative conditioning cohort, 5-year overall survival was 53% (95% CI 49–57%). The cumulative incidence of non-relapse mortality and relapse at 5-years were 35% and 20%, respectively. In the reduced-intensity conditioning cohort, 5-year overall survival was 51% (95% CI 48–54%) (ie, it did not significantly differ from the myeloablative conditioning cohort). Importantly, regarding unadjusted 5-year estimates of GVHD-free or relapse-free survival, this study did suggest a benefit for myeloablative conditioning over reduced intensity conditioning regimens, which should be taken into consideration with young, fit, myeloablative conditioning-eligible patients.

The first prospective EBMT reduced-intensity conditioning allogeneic HSCT trial in myelofibrosis enrolled 103 patients using a fludarabine plus busulphan and rabbit antithymocyte globulin-based platform.[49] The cumulative incidence of non-relapse mortality at 1-year was 16% (95% CI 9–23%), with an estimated 5-year overall survival of 67% (95% CI 55–79%). Age played an important role in outcome determination. Popat and colleagues reported long-term results from a prospective phase 2 trial of fludarabine plus busulphan in 46 patients, where intensifying the regimen with pharmacokinetic monitoring of busulphan appeared to reduce relapse without increased non-relapse mortality.[50] Robin and colleagues directly compared outcomes for reduced-intensity conditioning allogeneic HSCT for myelofibrosis using fludarabine plus busulphan or fludarabine plus melphalan in a retrospective evaluation.[51] The results showed no difference between both cohorts for progression-free survival, with a lower relapse rate in the fludarabine plus melphalan group.[51] Comparing fludarabine plus busulphan, melphalan plus fludarabine, and fludarabine plus carmustin plus melphalan resulted in similar non-relapse mortality, relapse, and overall survival, but more mixed chimerism in the fludarabine plus busulphan group.[52] Using the CIBMTR database, Murthy and colleagues identified adults aged 18 years or older with myelofibrosis undergoing allogeneic HSCT between 2008 and 2019 and analysed the outcomes separately in reduced-intensity conditioning and myeloablative conditioning cohorts.[53] Among 872 eligible patients, 493 underwent allogeneic HSCT using reduced-intensity conditioning (fludarabine plus busulphan or fludarabine plus melphalan) and 379 using myeloablative conditioning (fludarabine plus busulfan or busulfan plus cyclophosphamide). The results suggest that fludarabine plus busulfan is associated with better outcomes compared with the other compunds in both reduced-intensity conditioning (better overall survival, lower early non-relapse mortality, and lower acute GVHD) and myeloablative conditioning (lower acute GVHD and better relapse-free survival) in myelofibrosis. Lastly, reduced-intensity conditioning outcomes were explored in 556 patients aged 65 years or older. Estimated 5-year overall survival in this cohort was 40% and busulphan-based conditioning was associated with decreased mortality compared with a non-busulphan-based regimen (hazard ratio 0·7 [95% CI 0·5–0·9]).[22]

Regarding changing conditioning intensity on the basis of disease risk, an international collaborative analysis of 645 genomically-annotated patients who underwent allogeneic HSCT showed a 6-year overall survival of 59% (95% CI 52–66%) for myeloablative conditioning and 63% (95% CI 58–68%) for reduced-intensity conditioning.[19] In the era of molecular risk profiling, higher-intensity conditioning, compared with reduced-intensity conditioning, did not appear to improve outcomes for high-risk myelofibrosis as

determined by mutational and cytogenetic profiles. Kunte and colleagues published results on 69 patients with chronic phase myelofibrosis who underwent haploidentical allogeneic HSCT using mostly reduced-intensity conditioning or non-myeloablative conditioning with post-transplant cyclophosphamide and reported a 3-year overall survival of 72% (95% CI 59–81%) and relapse-free survival of 44% (95% CI 29–59%).[27]

Based on this data, the Panel agreed that both reduced-intensity conditioning and myeloablative conditioning are valid options for myelofibrosis. For older patients or those with substantial comorbidities, or both, a reduced-intensity conditioning regimen is more appropriate, whereas for suitably aged younger patients with a good performance status, a myeloablative conditioning regimen can be selected. The optimal intensity of the conditioning regimen still needs to be defined for specific situations, but current data suggest no benefit to adjusting intensity on the basis of genomic risk.

A spectrum of reduced-intensity conditioning regimens and protocols has shown acceptable transplantation-related mortality and overall survival. There is no direct evidence to recommend which reduced intensity conditioning regimens should be preferentially adopted. Recent registry data suggest that fludarabine–busulphan treatment is associated with better outcomes in reduced intensity conditioning.[53] The Panel agreed that further studies are needed to derive more detailed information on optimal regimen doses and schedules.

GVHD prophylaxis

In the setting of myeloablative conditioning, the usual GVHD prophylaxis is a combination of calcineurin inhibitors and a short course of methotrexate, which has shown greater efficacy than cyclosporine alone in randomised trials.[54,55] In the setting of myeloablative conditioning and unrelated donors, rabbit antithymocyte globulin has been reported to decrease acute and chronic GVHD in two studies, which translated to a significantly longer overall survival.[56–58] In the setting of myeloablative conditioning and matched related donors, two trials enrolling patients with myeloid diseases testing ATG have been reported.[59,60] Improved GVHD relapse-free survival was reported in these two studies using ATG. There are less data in the setting of reduced-intensity conditioning—one randomised trial included patients who received myeloablative conditioning or reduced-intensity conditioning after transplantation from an unrelated donor.[61] In this study, antithymocyte globulin treatment was predictive of a reduced duration of immunosuppressive therapy and less acute GVHD, without any differences in terms of chronic GVHD or non-relapse mortality. Adding post-transplant cyclophosphamide to standard immunosuppression protocols after reduced intensity conditioning in HLA-matched related and matched and mismatched unrelated donors resulted in significantly improved GVHD-free and relapse-free survival.[62] All these randomised studies were not focused on myelofibrosis and in most cases did not include any patients with myelofibrosis. A retrospective, EBMT registry study has analysed the role of antithymocyte globulin in patients with myelofibrosis who received a matched related donor transplantation, reporting that the incidence of acute GVHD was lower when antithymocyte globulin was added.[63] Chronic GVHD incidence was similar with or without antithymocyte globulin (>50% in both groups), and non-relapse mortality was lower with antithymocyte globulin.

In patients with myelofibrosis, haploidentical transplantation using post-transplant cyclophosphamide has also been reported from retrospective studies showing encouraging results.[27,64] An approach for reduced-intensity conditioning using cyclophosphamide, fludarabine, total-body irradiation with post-transplant cyclophosphamide, and tacrolimus and sirolimus as GVHD prophylaxis in patients with myelofibrosis transplanted from matched or mismatched related or unrelated donor showed low chronic GVHD but a high relapse rate at 3 years (40% [95% CI 20–60%]).[21] There are no available phase 3 trial data showing the superiority of ruxolitinib-based GVHD prophylaxis over a ruxolitinib-free regimen.

The Panel agreed on indicating calcineurin inhibitors and methotrexate with ATG or ATLG as a valid anti-GVHD prophylaxis when the donor is HLA-matched unrelated. The alternative could be including calcineurin inhibitors, mycophenolate mofetil, and antithymocyte globulin–ATLG, especially in reduced-intensity conditioning regimens. In the setting of mismatched unrelated donors, post-transplantation cyclophosphamide with calcineurin inhibitors can be used as alternative to antithymocyte globulin–ATLG-based GVHD prophylaxis. In the setting of matched related donors, adding antithymocyte globulin to the usual calcineurin inhibitor-based GVHD prophylaxis might decrease acute GVHD.

In the setting of haploidentical donors, post-transplantation cyclophosphamide-based GVHD prophylaxis is recommended. Ruxolitinib as GVHD prophylaxis can be tested in the setting of prospective protocols, as well as calcineurin inhibitor-free GVHD prophylaxis or a de-escalated dose of post-transplantation cyclophosphamide.

More studies including patients with myelofibrosis are needed to give more accurate recommendations on specific situations.

Post-transplantation management

Poor graft function and graft failure

Cytopenia, or pancytopenia, comes in two distinct and very different forms after an allogeneic HSCT: primary graft failure and poor graft function, as summarised in the appendix (p 10).[65]

There is no consistent evidence about management strategies to either reduce the risk or treat established poor graft function in patients with myelofibrosis post-allogeneic HSCT. The use of thrombopoietin analogues is

growing in the post-transplantation setting. However, data are limited in patients with myelofibrosis. Klyuchnikov and colleagues reported on outcomes following a CD34+ selected stem-cell boost in 32 patients with poor graft function, 14 of whom had myelofibrosis, with a median interval of 5 months between allogeneic HSCT and infusion of the CD34+ stem cells (median CD34+ cell dose $3{\cdot}4 \times 10^6$ per kg).[66] Haematological improvement was observed in 26 (81%) patients, occurring at a median of 30 days. The cumulative incidence of grades 2–4 acute GVHD was 17% (95% CI 3–31%) and chronic GVHD 26% (95% CI 16–46%). The use of a CD34+ stem-cell boost in this setting has additionally been reported by other groups.[67]

A high dose of CD34+ stem cells appears particularly effective in HLA-identical sibling transplantations.[50] CD34+ grafts selected for allogeneic HSCTs, usually associated with a greater risk of primary graft failure when compared with unmanipulated grafts, have been shown to be very successful in a small group of patients with myelofibrosis (n=27), following double alkylator conditioning with no primary graft failure.[68]

Regarding poor graft function, the Panel recommends the use of growth factors for anaemia (erythropoietin) or neutropenia (granulocyte colony-stimulating factor). These agents are unlikely to reverse poor graft function but can serve as a bridge to a definitive treatment. Although there has been some use of thrombopoietin analogs postallogeneic HSCT for treatment of post-transplantation thrombocytopoenia, data on the use of these agents in patients with myelofibrosis who underwent allogeneic HSCT are scarce, and the drug should be used in a controlled setting (registries or clinical trials) or on an individual case-based decision.

In patients with poor graft function and persistent splenomegaly with complete donor cell chimerism, splenectomy might be an option, but it is not without risks. JAK2 inhibitors might reduce the spleen size and persistent constitutional symptoms; however, JAK2 inhibitors have not been tested been tested for the indication of post-transplantation poor graft function and potential negative effects on haematopoiesis should be taken into consideration.

The most definitive treatment for poor graft function is a CD34+ stem-cell boost from the original donor, either fresh or cryopreserved, without further conditioning. This treatment should be considered in patients without active GVHD. Since the time for donor recruitment can be delayed, especially if using an unrelated donor, attempts to reach the donor and obtain the boost product should start early after making the diagnosis of poor graft function.

Primary graft failure needs to be identified early (before day 28 following stem cell transplantation) and requires a fast decision of whether to proceed to a second transplantation. Prevention of this complication in patients with myelofibrosis includes the preferential use of an HLA-matched donor, a high dose of CD34+ cells at the time of transplantation, and the control of bulky splenomegaly.

Molecular monitoring after transplantation

A driver mutation in *JAK2*^{V618F}, *MPL*^{W516}, and *CALR* occurs in about 90% of patients with myelofibrosis, representing ideal markers for response monitoring after allogeneic HSCT. In 40–50% of patients with myelofibrosis additional myeloid geneassociated mutations, identified through next-generation sequencing, are present. Mutations with low variant allele frequency might be associated with the myelofibrosis clone or represent independent clonal haemopoiesis of indeterminate potential.

A *JAK2*^{V618F} VAF of greater than 1% as early as day 28 after HSCT or mixed chimerism on day 100 was associated with an increased risk of relapse.[69] Detectable minimal or measurable residual disease (MRD) at day 180 for any driver mutation predicted an 8-times higher risk of relapse in multivariate analysis than those without detectable MRD.[70]

The Panel recommends molecular monitoring after transplantation, since detection MRD might drive timely immunotherapy interventions. Monitoring should be performed at 1 month and at 3-month intervals thereafter, up to 1 year; however, late relapses support continued monitoring (annual testing might be reasonable), since the majority of these late relapses are sensitive to donor lymphocyte infusion or early second allogeneic stem cell transplantation. We recommend the use of highly-sensitive assays for the driver mutations, in particular digital droplet PCR-based assays for *JAK2*^{V618F} with a sensitivity of less than 0·01%. Assays for *MPL* and *CALR* are less standardised but should have a sensitivity of less than 1%. There is no evidence supporting a preference of bone marrow versus peripheral blood (which remains the most convenient) as source of DNA.

We cannot recommend the use of myeloid gene-associated mutations to measure MRD, considering that the current sensitivity of NGS platforms varies and a threshold of less than 1% can be rarely obtained in routine laboratories. Experiences with ad-hoc developed digital droplet assays for selected mutations in IDH1, IDH2 and DNMT3A remain largely investigational. It is recommended that MRD assays are performed in an accredited laboratory that does quality controls with reference materials.

Preventing relapse after transplantation

Aiming to provide practical management recommendations, the EBMT proposed working definitions of molecular, cytogenetic, and morphological or clinical relapse (appendix p 11).[65] Donor lymphocyte infusion to harness the graft-versus-myelofibrosis effect has been successfully reported for patients with haematological relapse after allogeneic HSCT.[71,72]

In the case of relapse, which is still present following weaning of immunosuppression, donor lymphocyte

infusions with an escalating dose scheme in the absence of concurrent GVHD was shown to be an effective strategy;[73,74] donor lymphocyte infusions should ideally be given at the stage of molecular relapse, acknowledging the higher likelihood for success when initiated preemptively.[73,74]

Donor lymphocyte infusions given for molecular relapse induced a higher rate of molecular remission (88%) than donor lymphocyte infusions for haematological relapse (60%), with a corresponding lower incidence of GVHD.[73,74] In about half of patients, molecular remission could be achieved without causing GVHD.

The Panel recommends the use of the proposed EBMT definitions of relapse in clinical practice, as well as in clinical trials, to standardise clinical approaches and research initiatives in the field of relapsed myelofibrosis after transplantation. Disease-specific markers, such as driver mutations or cytogenetics, should be serially monitored in combination with myeloid chimerism analyses. Interpretation of results should consider the variable course of chimerism, mutational clearance, and regression of fibrosis and splenomegaly. A finding suspicious for molecular relapse should be confirmed by a consecutive analysis within 28 days. To prevent relapse, the Panel recommends that after cessation of immunosuppression, pre-emptive therapy with donor lymphocyte infusions alone is initiated at the stage of persistent MRD and pursued until complete remission or MRD clearance is achieved. In case of molecular or haematological relapse, donor lymphocyte infusions are indicated. Prophylactic donor lymphocyte infusions are currently not recommended. There is insufficient evidence to support use of JAK inhibitors as maintenance therapy post-transplantation to prevent relapse.

Considering a second transplantation

Data regarding the outcome of a second transplantation in patients with myelofibrosis are scarce and exclusively from retrospective studies, as feasibility prevents randomised controlled trials. Since the EBMT and ELN 2015 recommendations,[1] two studies have addressed the issue of second transplantation.

The EBMT retrospectively analysed 216 patients with myelofibrosis undergoing a second allogeneic HSCT between 2010 and 2017.[75] The study included patients receiving a second HSCT for either relapse (56%) or graft failure (31%). The median time from first to second HSCT was 8 months, with 132 (61%) patients being within 12 months of their first transplantation. The same donor as the first transplant was chosen in 31% of patients, whereas a different donor was chosen for 54% of patients. 3-year non-relapse mortality was 36% (95% CI 28–43%) and the relapse rate was 25% (95% CI 17–32%). Grade 2–4 acute GVHD occurred in 25% (95% CI 19–31%) of patients and grade 3–4 acute GVHD in 11% (95% CI 6–15%) of patients. The 3-year incidence of chronic GVHD was 33% (95% CI 26–40%), including 14% (95% CI 9–19%) with extensive grade. Graft failure incidence at 1 year was 14% (95% CI 8–19%). The 3-year overall survival was 42% (95% CI 34–49%), and relapse-free survival was 39% (95% CI 31–48%). Survival was negatively affected by poor performance status and a short interval from the time of first allogeneic HSCT, and was worse in patients being transplanted after graft failure due to increased non-relapse mortality.

Late relapse was investigated in a cross-sectional study including 227 patients with myelofibrosis who underwent an allogeneic HSCT between 1994 and 2015. Among 94 evaluated patients who were alive and in remission at 5 years after HSCT, 13 (14%) had a late molecular or haematological relapse at a median of 7·1 years postallograft. Patients who relapsed received donor lymphocyte infusions, either alone or in combination with a second HSCT, and 8 (73%) had full donor cell chimerism and molecular remission. After a median follow-up of 45 months, the 3-year overall survival for relapsed patients was 91% (95% CI 77–100%) compared with 99% (95% CI 96–100%) for those who did not relapse.[76] Data suggest that the majority of patients who relapse 5 years after transplantation can be successfully salvaged by a second allogeneic HSCT. Patients who relapse within 1 year or have early graft failure are poor second transplantation candidates. Candidates for a second transplantation should be chosen carefully or given additional pre-transplantation therapy.

Conclusion

No evidence from randomised trials on patients with myelofibrosis was available for consideration in this project; thus, the quality of the evidence that informed this iteration of the recommendations is limited by the trials and retrospective analyses available. However, given that the expert Panel represents the practice from large and experienced centres and has an implicit and comprehensive mastery of scientific and practical information to guide decision making, we believe these consensus recommendations might help clinicians and patients where evidence-based guidance is unavailable. We hope that these recommendations will not only contribute to improving outcomes but also to enabling data collection to inform future practice.

Contributors

NK and GB designed the project. All other authors participated in the discussion, the formulation of the recommendations, and approved the final manuscript.

Declaration of interests

NK has received honoraria for lectures and advisory boards from Kite, Jazz, Merck Sharp & Dohme, Neovii Biotech, Alexion, Takeda, Novartis, Riemser, Pfizer, and Bristol Myers Squibb. NK has also received research support from Neovii, Riemser, Novartis, and Deutsche Knochenmarkspender Datei, and research grants from Neovii, Jazz, Celgene, and Novartis. AMV has received honoraria for lectures from Novartis, Incyte, AbbVie, GlaxoSmithKline, Bristol Myers Squibb, and AOP Orphan Pharmaceutical GmbH. CH has received honoraria for lectures from AbbVie, AOP Orphan Pharmaceutical GmbH, Bristol Myers Squibb, CTIBioPharma, Imago Biosciences, Incyte, Novartis, Galacteo, Geron, Gilead, GlaxoSmithKline, Janssen, Keros, Promedior, Roche, Shire,

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