DOI: 10.46765/2675-374X.2023V4N1P191

CONSENSUS UPDATE

HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR CHRONIC MYELOPROLIFERATIVE NEOPLASMS

Marcos Paulo Colella[1], Antonio Vaz de Macedo[2], Gustavo Machado Teixeira[3], Andreza Alice Feitosa Ribeiro[4], Afonso Celso Vigorito[5], Vaneuza Araújo Moreira Funke[6]

1 Hematopoietic Stem Cell Transplant Unit Member, HEMOCENTRO /UNICAMP; PhD in Internal Medicine, UNICAMP, SP, Brazil. 2 Hematology Clinic Coordinator, Hospital da Polícia Militar, MG; Bone Marrow Transplant Unit Member, Hospital Luxemburgo, Instituto Mário Penna, MG; Teaching Assistant, PPCR/ECPE, Harvard T.H. Chan School of Public Health, USA; Master's Degree in Health Sciences: Infectious Diseases and Tropical Medicine, School of Medicine, Federal University of Minas Gerais (UFMG), MG, Brazil. 3 Bone Marrow Transplant Unit Coordinator, Hospital das Clínicas, UFMG; Hematologist, Hospital Alberto Cavalcanti, FHEMIG, MG; Master's Degree in Sciences Applied to Adult Health Care, School of Medicine, UFMG, MG, Brazil. 4 Bone Marrow Transplant Unit Member, Hospital Israelita Albert Einstein, SP, and Instituto Nacional de Câncer, RJ; Bone Marrow Transplant Unit Coordinator, Hospital Maternidade Brasil, SP; PhD in Health Sciences, USP, SP, Brazil. 5 Bone Marrow Transplant Inpatient Unit Coordinator, UNICAMP; PhD in Internal Medicine, UNICAMP, SP, Brazil; Post-Doctoral Researcher, Seattle- Washington, USA. 6 Head of Adult Bone Marrow Transplant Center, Complexo Hospital de Clínicas, Federal University of Paraná (UFPR); Assistant Professor of Hematology, UFPR; Master's Degree in Hematology, UFPR, PR, Brazil; Fellow at the Long Term Follow Up Division - Seattle- Washington, USA.

Corresponding author: Marcos Paulo Colella (mpc@unicamp.br)

Received: 13 Dec 2022 • Revised: 15 Dec 2022 • Accepted: 13 Jan 2023.

INTRODUCTION

According to the World Health Organization, myeloproliferative neoplasms (MPN) are defined as clonal diseases caused by proliferating hematopoietic progenitor cells. They can be divided into Philadelphia-positive - chronic myeloid leukemia (CML) – and Philadelphia-negative disorders - primary myelofibrosis (PMF), polycythemia vera (PV), and essential thrombocythemia (ET)[1]. This document is a 2022 update and summary of the recommendations of the Brazilian Society of Bone Marrow Transplantation Consensus Panel convened in 2020 for this field.

PHILADELPHIA-POSITIVE MYELOPROLIFERATIVE DISEASE

Chronic Myeloid Leukemia: Summary of Recommendations

1. Imatinib mesylate, nilotinib, bosutinib or dasatinib are the treatments of choice for newly diagnosed chronic phase (CP) chronic myeloid leukemia (CML)[2-10] (1B).

2. The main indications for hematopoietic stem cell transplantation (HSCT) for adult CML patients in the tyrosine kinase inhibitor (TKI) era:

a. Advanced phase disease: In accelerated phase (AP), HSCT should be indicated if the response to second generation TKI therapy (dasatinib, nilotinib or bosutinib) is suboptimal, or in case of a T315I mutation when ponatinib or asciminib is unavailable[11-17]. In blast crisis (BC), it should always be considered, preferably after a preliminary course of TKI therapy with or without chemotherapy[18,19] (2B).

b. Chronic Phase: in case of failure of imatinib, in accordance with the European LeukemiaNet 2020 recently updated criteria, in the absence of a T315I mutation, a second generation TKI should be started. In case of TKI failure, consider third generation TKI therapy (ponatinib, asciminib) or HSCT, if the former is unavailable[19] (19) (1B).

d. T315I mutation, if ponatinib or asciminib is unavailable[15,18,19] (1B).

3. For young patients with an HLA-identical related or unrelated donor, myeloablative conditioning (MAC) should be used. Reduced intensity (RIC) or non-myeloablative conditioning should be reserved for patients over 60 years of age and/or with significant comorbidities[20-23](1B).

4. Graft-versus-host disease (GVHD) prophylaxis should be based on a calcineurin inhibitor (cyclosporin, tacrolimus) plus methotrexate. In a long-term follow-up analysis, triple immunosuppressant-based prophylaxis with methylprednisolone resulted in better overall survival, but these results are yet to be confirmed in larger, prospective studies (1B)[24,25]. Post-transplantation cyclophosphamide should be used for mismatched unrelated and haploidentical donors (26) (1B).

5. Bone marrow, if available, is the preferred stem cell source in patients with CP CML. Patients with advanced disease should receive peripheral blood stem cells (PBSC). Alternative stem cell sources, such as umbilical blood cord (UBC), can be used in the absence of other available sources[27–30]we conducted an individual-patient data meta-analysis using data from nine randomized trials enrolling 1,111 adult patients. Results: Compared with BMT, PBSCT led to faster neutrophil (odds ratio [OR] = 0.31; 95% CI, 0.25 to 0.38; P < .00001 (1B).

6. Matched or mismatched unrelated donors or haploidentical transplants are acceptable in the absence of an HLA-identical sibling donor[26,31] (1A).

7. Post-transplant monitoring of BCR-ABL using real time quantitative polymerase chain reaction (RT-qPCR) should be performed every three months, during the first two years, and every six months, up to five years post-transplant. This should be followed by yearly monitoring from then onwards[32–34] (2B).

8. Molecular relapse is defined as progressively increasing BCR-ABL/ABL1 gene transcripts in at least two consecutive results and loss of major molecular response (>0,1%)[34] (2B).

9. Use of imatinib mesylate and of second generation TKIs (dasatinib, nilotinib or bosutinib) does not seem to affect the occurrence of early transplant-related toxicity, nor to delay engraftment. Similarly, it does not seem to affect survival, relapse, or non- relapse mortality[35–38](2B).

10. In case of molecular relapse, consider donor lymphocyte infusions (DLI) at escalated doses (1 x 10^6, 5 x 10^6, 1 x 10^7, 5 x 10^7, 1 x 10^8 CD3+ cells/kg) at three-month intervals. In case of cytogenetic or hematologic relapse, consider DLI at escalated doses at three-month intervals, starting at 1 x 10^7 CD3+ cells/kg, or consider use of TKI. Subsequent DLI doses should not be administered if a satisfactory response is obtained or in case chronic GVHD ensues. In case of unrelated or haploidentical related donors, start at a DLI dose 1-2 log lower than that depicted above (1B). In case of hematologic relapse in CP or cytogenetic relapse, consider DLI, starting at higher escalated doses (1 x 10^7, 5 x 10^7, 1 x 10^8 CD3+ cells/kg), or TKI, or a combination of these. In case of hematologic relapse in AP or BC, consider the use of a TKI plus DLI[39–44](1B).

11. Imatinib mesylate, nilotinib, bosutinib or dasatinib are currently acceptable alternatives to DLI for the treatment of post-transplant relapse of CML, or in cases where relapse occurs in the setting of chronic GVHD (2B). TKIs may also be combined with DLI in the management of such cases, with better overall responses (2B). Prompt and long-lasting responses are usually seen under TKI therapy for CML relapsing in CP (2B). Response tends to be worse and less durable in AP or BC relapse[45,46] (2B).

12. In patients previously resistant or intolerant to imatinib mesylate, consider using a second generation TKI (nilotinib, bosutinib or dasatinib), when deciding upon use of a TKI alone or in combination with DLI (2B). In patients previously resistant or intolerant to more than one TKI, consider using a previously unused TKI, or opt for DLI without a TKI, in the absence of chronic GVHD[45,46] (2B).

13. Consider using post-transplant TKI prophylaxis for two years in patients at a high risk for relapse (>1st CP and AP/BC)[47–51] (2B).

14. In case a post-transplant BCR-ABL fusion gene mutation is detected, the mutational profile should be taken into account when choosing the most appropriate TKI for prophylaxis or preemptive therapy in this setting[52](2B).

15. A second allogeneic HSCT may be considered in case of TKI- and/or DLI- resistant relapse following a first transplant, if a suitable donor is available, in the absence of contraindications to transplant[53] (2B).

TABLE 1. European LeukemiaNet 2020 chronic myeloid leukemia treatment recommendations

Prevention by elimination of BCR-ABL1	Assurance of effective TKI treatment
Early: emergence of high-risk ACA	Observe closely, consider intensification of treatment (ponatinib, early allo-HSCT)
Blast crisis at diagnosis	Start with imatinib, change to a 2nd generation TKI according to mutational profile.
Resistance to second generation TKI	Ponatinib or clinical trial, consider HSCT, donor search.
Ponatinib failure	High risk of progression, early allo-HSCT recommended.
Accelerated phase	Treat as high-risk patients; proceed to allo- HSCT if response to TKI is not optimal.
Progression to blast phase	Poor outcome with currently available TKIs. Add chemotherapy based on AML regimens for myeloid BC (such as dasatinib or ponatinib + FLAG-IDA) or ALL regimens for lymphoid B CP (such as imatinib or dasatinib + hyperCVAD). Choice of TKI based on prior therapy and mutational status. Proceed to allo-HSCT soon after CP2 is achieved.

Adapted from: Hochaus, A, et al. Leukemia 2020;34(4):966-984 (19).

ACA: additional chromosomal aberrations; ALL: acute lymphoblastic leukemia; allo- HSCT: allogeneic hematopoietic stem cell transplant; AML: acute myeloid leukemia; BC: blast crisis; CVAD: cyclophosphamide + vincristin + doxorubicin + dexamethasone; 2CP: second chronic phase; FLAG-IDA: fludarabin + cytarabin + granulocyte-colony stimulating factor + idarubicin; HiperCVAD: hyperfractionated CVAD; TKI: tyrosine kinase inhibitor.

TABLE 2. Recommendations for post-HSCT monitoring and relapse therapy in CML patients (32-46)

TIME AFTER HSCT	MONITORING	RESULT	INTERVENTION
2 years	Quantitative RT-PCR every 3 months (level 2b)	Molecular relapse: increasing BCR-ABL/ABL ratio in two measures: relapse cutoff defined by local lab (2B)	Consider escalated dose DLI. For related transplants: CD3+/Kg: 106®5 x 10 6 ®10 7® 5 X 107 ® 108 every 3 months. For unrelated transplants: 1 log less: 105 ® 5 X 105 ®106 ® 5 X 106 ® 107 Hold dose if chronic GVHD signs or symptoms (1B)
3-5 years	Quantitative RT-PCR every 6 months (level 2b)		
After 5 years	Quantitative RT-PCR every year (level 2b)		
Any time	Cytogenetics if positive PCR (level 2b)	Cytogenetic relapse	Consider DLI as above (1B) and imatinib (2B)
Any time	Complete blood count	Hematologic relapse	Consider DLI as above (1B) and imatinib (2B)

DLI = donor lymphocyte infusions; GVHD = graft-versus-host disease; RT-PCR = real time polymerase chain reaction

PRIMARY MYELOFIBROSIS, POLYCYTHEMIA VERA, ESSENTIAL THROMBOCYTHEMIA

INTRODUCTION

According to the World Health Organization, myeloproliferative neoplasms (MPN) are defined as clonal diseases caused by proliferating hematopoietic progenitor cells. The most common Philadelphia-negative disorders are primary myelofibrosis (PMF), polycythemia vera (PV), and essential thrombocythemia (ET)[1].

STRATIFICATION

Patients with PMF often have a dismal prognosis, with a mean overall survival of only six years after diagnosis[54]. Even so, the clinical course is highly heterogeneous, and survival may vary from a few months to more than 10 years[55]. Therefore, prognosis may be better estimated by several scoring systems, among which the Dynamic International Prognostic Scoring System plus (DIPSS plus)[56] is one of the most applied. According to this prognostic model, patients stratified as low risk present a median survival of 185 months, which decreases to 78 months in intermediate-1 risk patients, 35 months in the intermediate-2 subgroup, and 16 months in the high-risk category[56]. Polycythemia vera and essential thrombocythemia, in turn, have a more favorable prognosis, and patients should only be referred for allogeneic HSCT in case myelofibrosis or leukemic transformation has developed (2B). At fibrotic phase PV or ET, the MYSEC prognostic index can be used (http://www.mysec-pm.eu). It has been shown to be able to stratify these patients into four categories: low risk (median survival not reached; intermediate-1: median survival 9.3 years), intermediate-2 (median survival 4.4 years) and high risk (median survival two years) [57].

MUTATIONS

Mutational profiling, including CALR, MPL, JAK2, ASXL1, EXH2, SRSF2, IDH1/2 and U2AF1 mutations, should be performed, whenever possible, to allow for the Mutation Enhanced International Prognostic Scoring System 70+ v2.0 (MIPSS70+ v2.0) [58] and the Clinical-Molecular Myelofibrosis Transplant Scoring System (MTSS)[59] to be applied, given their ability to estimate post-transplant outcomes based on disease-, patient-, and transplant-related factors. This may aid in the clinical decision-making process when assessing eligibility for transplantation. Such prognostic models should not, however, replace the DIPSS plus score when assessing these patients (2B).

INDICATION

Allogeneic HSCT remains the only curative option for myelofibrosis patients to date. Not all patients, however, benefit from this procedure. Hence, we recommend that transplant indication be based on the DIPPS or DIPPS plus score, whereby allogeneic HSCT should be performed in intermediate-2 and high-risk patients[60–63]. HSCT may sometimes be considered for patients classified as intemediate-1 risk[63], particularly in younger patients and those with high transfusion dependency, more than 2% blasts in peripheral blood, or with an unfavorable karyotype. Other scoring systems, namely the MIPSS70+ v2.0 and the MTSS, may further assist in the clinical decision-making process[63] (2B).

CONDITIONING REGIMEN INTENSITY

It has not yet been defined what the ideal conditioning regimen is in transplantation for PMF patients. Given the patients' average age at diagnosis, most regimens will be of reduced intensity, the ideal dose of which is not established. For patients under the age of 50, we recommend MAC; for those over 50 years old, RIC[64-66], which usually consists of fludarabine associated with busulfan or melphalan sometimes associated to thiotepa[67]. Despite no evidence of superiority between conditioning regimens, the melphalan regimen seems to obtain greater control of the disease, albeit with higher non relapse mortality than the regimen with busulfan, resulting in similar overall survival[64].

The MD Anderson group recently published a non-randomized, phase II study comparing two different levels of intravenous busulfan associated with fludarabine: 15 patients using low-dose busulfan (130 mg/m^2 for two days) and 31 patients with high-dose busulfan (100mg/m^2 for four days), including 27 patients with a serum level adjusted to an AUC of 4000. In an average follow-up of three years, patients using busulfan at a higher dose had an event-free survival of 58% against 27% of those who used low doses. In conclusion, the use of conditioning regimens containing fludarabine and busulfan with serum level control seems to reduce relapse without increasing transplant-related mortality[65]. Non-myeloablative conditioning has also a higher rate of graft failure[66] (2B).

DONOR

HLA-matched unrelated donors are an acceptable alternative for patients without an HLA-identical sibling donor[66]. HLA-mismatched related donors may also be acceptable, but further studies are needed to better address this issue[67] (2B).

The results of haploidentical transplantation in PMF still lack published data. One of the first reports was published in 2016, comparing the use of alternative donors (unrelated and haploidentical) with HLA-matched related donors in 95 patients with PMF between 2000 and 2014[68]. Although it was an analysis of a relatively few numbers of patients, including 23 haploidentical transplants, 20 of which in the last five years, the study showed a significant improvement in the survival of transplanted patients with PMF who used alternative donors during the period of 2011 to 2014 as compared to that of 2000 to 2010[68].

In 2019, the EBMT group published a retrospective report of 56 patients, with a median age of 57 years[67]. Myeloablative conditioning was chosen in 70% of the cases, 59% of which used thiotepa + fludarabine + busulfan with post-transplant cyclophosphamide; two thirds used bone marrow as stem cell source. The engraftment rate was 82%. The cumulative incidence of acute GVHD up to D + 100 was 28% (grade II-IV) and 9% (grade III / IV) and of chronic GVHD at 1 year was 45%. At two years, overall survival was 56%, the incidence of relapse was 19%, and non-relapse mortality was 38%. This study showed that haploidentical transplantation is feasible, with a comparable overall survival with that of unrelated transplants; however, efforts should be made toward decreasing the considerable transplant-related mortality rate found in this study.

STEM CELL SOURCE

PBSCs are the preferred stem cell source, but BM is also acceptable in this scenario[69](2B).

SPLENECTOMY

Routine splenectomy prior to transplant is not recommended in patients with splenomegaly, except in cases with a spleen size greater than 20cm[70,71]. Splenic radiation, in turn, may be considered within the context of clinical trials (2B).

RUXOLITINIB

Ruxolitinib is a Janus kinase (JAK) 1/2 inhibitor known to be involved in the pathophysiology of PMF. Despite its effectiveness in controlling many of the symptoms presented by PMF patients, it should not be regarded as an alternative to HSCT, since it does not affect the natural history of the disease. Hence, though we do recommend it for symptomatic control, it should not delay referral for transplantation[72].

In a prospective study evaluating the use of ruxolitinib prior to transplant, it was started 60 days before conditioning, gradually decreased in four days, until complete withdrawal one day before conditioning. Despite being shown to be safe in this group of 21 patients, no significant reduction was seen in the rate of graft failure or in the incidence of GVHD[72]. Another prospective phase II study investigated ruxolitinib use for at least eight weeks, with a gradual reduction of 5 mg every four days and withdrawal four days before stem cell infusion. This study also showed that the use of pre-HSCT ruxolitinib is safe: none of the patients had cytokine release syndrome, and the 2-year overall survival was 86%, suggesting a benefit in overall survival[73] (2B). In addition, other studies have shown that ruxolitinib is well tolerated during conditioning, and others have investigated its use at low doses until engraftment. In a study with a small number of patients who were kept under low dose ruxolitinib until D + 28, in two out of 12 patients this medication had to be discontinued. The average engraftment time was 12 days, there was no graft failure, and there was a low incidence of acute GVHD. However, the incidence of cytomegalovirus reactivation was 40%[74].

Robin et al.[75] published a phase II study evaluating the use of ruxolitinib six months before HSCT. Among the 76 patients included, 64 had a donor, 18 of whom were matched-sibling donors, 32 matched-unrelated donors and 14 mismatched-unrelated donors. Among the 64 patients who received ruxolitinib, 92% were transplanted at three months, 26% had a complete response, 20% had a partial response, and 54% had no response. All patients received RIC (fludarabine/melphalan) and GVHD immunoprophylaxis with cyclosporine and mycophenolate mofetil +/- antithymocyte globulin. Overall survival at 12 months was 68%, and disease-free survival was 55%. The cumulative incidence of grade II-IV acute GVHD was 66%, and non-relapse mortality was 42%[75].

It has been demonstrated that after HSCT, allele burden of JAK2-V617F is related to relapse. In such scenario, ruxolitinib has been investigated as preemptive therapy[76].

Therefore, we recommend ruxolitinib to be used at the highest tolerated dose, with gradual tapering every four days and complete withdrawal by one to two days prior to transplant[72]. According to a recent phase II study, its use prior to HSCT seems to be safe and to improve overall survival in patients who are referred for transplantation[72].

However, in the absence of randomized controlled trials, we recommend that all patients with interme-

diate-2 or high risk PMF and high-risk myelofibrosis secondary to PV or ET be referred for HSCT as soon as possible[73] (2B).

SUMMARY OF RECOMMENDATIONS:

• Allogeneic HSCT is indicated for high or intermediate-2 risk PMF patients and for high-risk myelofibrosis secondary to PV or ET. Intermediate-1 patients and those with severe thrombocytopenia, peripheral blasts or having high risk mutations can also be candidates for allogeneic HSCT (2B).

• The DIPSS plus classification is recommended. When possible, MIPSS70+ v2.0 or MTSS should also be used (2B).

• It seems reasonable to offer MAC for patients under 50 years old and RIC for those above this age or with comorbidities. When possible, levels of busulfan should be monitored (2B).

• In the absence of a matched sibling donor, alternative donors can be used (unrelated and haploidentical, in this sequence) (2B).

• Peripheral blood is the preferred source, but bone marrow can also be acceptable (2B).

• Pre-transplant splenectomy is not routinely recommended. It can be considered if splenomegaly is above 20 cm (2B).

• Relapse after HSCT should be managed with donor lymphocyte infusions[74] (2B).

• Monitoring of the JAK-V617F mutation should be performed after HSCT, since it is correlated with relapse[76] (2B).

• Pre-transplant ruxolitinib can improve both clinical condition and survival, but referral for HSCT should not be deferred, since this is the only curative procedure. When ruxolitinib is used, we recommend it at the highest tolerated dose (20mg BID), with gradual tapering every four days and complete withdrawal by one to two days prior to transplant (2B).

• Driver mutations and an NGS panel should be performed whenever possible, which might strengthen the indication for HSCT, particularly in intermediate-1 PMF patients (2B).

TABLE 3. HSCT indications for Myeloproliferative Neoplasms

DISEASE	MSD	MUD	MMUD	MMSD
PMF/DIPSS-PLUS				
Low Risk	GNR	GNR	GNR	GNR
Intermediate-1	CO*/2C	CO*/2C	CO */2C	CO*/2C
Intermediate-2 and high risk	S/2B	S/2B	S/2C	CO/2C
CML				
CP				
TKI failure (second or third line)	S/2B	S/2B	CO/2C	CO/2C
AP	S/2B	S/2B	CO/2C	CO/2C
BP	S/2B	S/2B	CO/2C	CO/2C
>1st CP	S/2B	S/2B	CO/2C	CO/2C

AP: Accelerated phase CML; BP: Blast phase CML; CML: Chronic myeloid leukemia; CO: clinical option; CP: chronic phase CML; DIPSS-PLUS: Dynamic International Prognostic Scoring System Plus; GNR: generally not recommended; HSCT: hematopoietic stem cell transplantation; MSD: matched-sibling donor; MMSD: mismatched-sibling donor; MUD: matched-unrelated donor; MMUD: mismatched-unrelated donor; PMF: primary myelofibrosis; S: standard; TKI: tyrosine kinase inhibitor.

*CO: circulating blasts, high risk mutations

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