HSCT FOR CHRONIC MYELOPROLIFERATIVE DISEASES

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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 summary of the recommendations of the Brazilian Society of Bone Marrow Transplantation Consensus Panel in 2020 for these areas.

PHILADELPHIA-POSITIVE MYELOPROLIFERATIVE DISEASE

CHRONIC MYELOID LEUKEMIA: SUMMARY OF RECOMMENDATIONS

1. Imatinib mesylate, nilotinib, or dasatinib are the treatment of choice for newly diagnosed chronic phase (CP) chronic myeloid leukemia (CML) (level 1b).[2-9]

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

a. Children: there are no currently available studies comparing TKI and HSCT in this population. The therapeutic approach is similar to that in adults and is based on the use of first or second generation TKIs. Hematopoietic Stem Cell Transplantation (HSCT) should be considered after failure of a second generation TKI or in advanced phase (AP and BC) CML. Data on the primary efficacy and safety of ponatinib are still lacking in children, for which further studies are awaited. Likewise, ongoing studies are still assessing the adverse effects of the long-term use of TKIs in this population. Adherence to TKI therapy should also be taken into account when deciding upon the best treatment strategy in children and adolescents (level 2b). [10-15]

b. Advanced phase disease: in AP, HSCT should be indicated if the response to second generation TKI therapy (dasatinib or nilotinib) is suboptimal, or in case of a T315I mutation when ponatinib is unavailable.[16-20] In BC, it should always be considered, preferably after a preliminary course of TKI therapy with or without chemotherapy (level 2b). [21,22]

c. 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) or HSCT, if the former is unavailable (level 2b). [20, 23]

d. T315I mutation, if ponatinib is unavailable (level 2b). [18,19]

3. For young patients with an HLA-identical related or unrelated donor, myeloablative conditioning should be used. Reduced intensity or non-myeloablative conditioning should be reserved for patients over 60 years of age and/or with significant comorbidities (level 1b). [24-27]

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 (level 1b). [28,29]

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), or haploidentical transplants are acceptable in the absence of an HLA-identical BM (or PBSC) donor (level 1a). [30-33]

6. 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 (level 2b). [34-37]

7. Molecular relapse is defined as progressively increasing BCR-ABL/ABL1 gene transcripts in at least two consecutive results (level 2b). [36,37]

8. Use of imatinib mesylate and of second generation TKIs (dasatinib and nilotinib) 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 (level 2b). [38-40]

9. 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 imatinib mesylate. 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 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 imatinib mesylate, at a dose of 400mg per day, or a combination of these. In case of hematologic relapse in AP or BC, consider the use of a TKI plus DLI (level 1b). [41-46]

10. Imatinib mesylate, nilotinib, 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 (level 2b). TKIs may also be combined with DLI in the management of such cases, with better overall responses (level 2b). Prompt and long-lasting responses are usually seen under TKI therapy for CML relapsing in CP (level 2b). Response tends to be worse and less durable in AP or BC relapse (level 2b). [47,48]

11. In patients previously resistant or intolerant to imatinib mesylate, consider using a second generation TKI (nilotinib or dasatinib), when deciding upon use of a TKI alone or in combination with DLI (level 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 (level 2b). [47,48]

12. Consider using post-transplant TKI prophylaxis in patients at a high risk for relapse (>1 st CP and AP/BC) (level 2b). [49-53]

13. 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 (level 2b). [54]

14. 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 (level 2b). [55]

TABLE 1 – Response to TKI definitions.[31]

Time	Optimal Response	Failure	Warning
Diagnosis	-	-	High risk (ELTS)* additional clonal abnormalities in Ph+ cells (ACA)
3 months	RTQPCR (EI) ≤10%	>10%, confirmed in-3 months	RQPCR>10%
6 months	RTQPCR (EI) ≤1%	RQPCR>10%	RQPCR 1 a 10%
12 months	RTQPCR(EI) ≤0,1%	RQPCR>1%	RQPCR 0,1 a 1%
Any moment	MMR sustained RTQPCR (EI) ≤0,1%	RQPCR>1%, resistant mutation, additional clonal abnormalities in Ph+ cells (ACA) **	RQPCR 0,1 a 1%; loss of MMR

* ELTS: *EUTOS long term survival score*
Adapted from: Hochaus, A, et al. Leukemia 2020;34(4):966-984 [23].
** Two results exhibiting the same abnormality in at least two Ph+ cells are necessary to fulfill this criterion: TKI: tyrosine kinase inhibitor; MMR: major molecular response; ACA: additional chromosome abnormalities in Ph+ cells; RTPCR: real-time quantitative polymerase chain reaction; IS: International Scale (BCR-ABL/ABL1 control gene ratio).

*** Risk scores can be calculated directly by accessing the following site: http:/leukemia- et.org/content/leukemias/cml/cml_score/index_eng.html.

TABLE 2 - European LeukemiaNet 2020 chronic myeloid leukemia treatment recommendations31

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-SCT)
Blast Crisis at diagnosis	Start with imatinib, change to a 2nd generation TKI according to mutation 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 BCP (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 22.
TKI: tyrosine kinase inhibitor; ACA: additional chromosomal aberrations: 2CP: second chronic phase; BC: blast crisis; allo- HSCT: allogeneic hematopoietic stem cell transplant; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; FLAG-IDA: fludarabin + cytarabin + granulocyte-colony stimulating factor + idarubicin; HiperCVAD: hyperfractionated CVAD: cyclophosphamide + vincristin + doxorubicin + dexamethasone.
Figure 1: Treatment algorithm for chronic phase (CP), accelerated phase (AP), and blasts crisis (BC) chronic myeloid leukemia (CML).31

FIGURE 1 - Treatment algorithm for chronic phase (CP), accelerated phase (AP), and blasts crisis (BC) chronic myeloid leukemia (CML).31
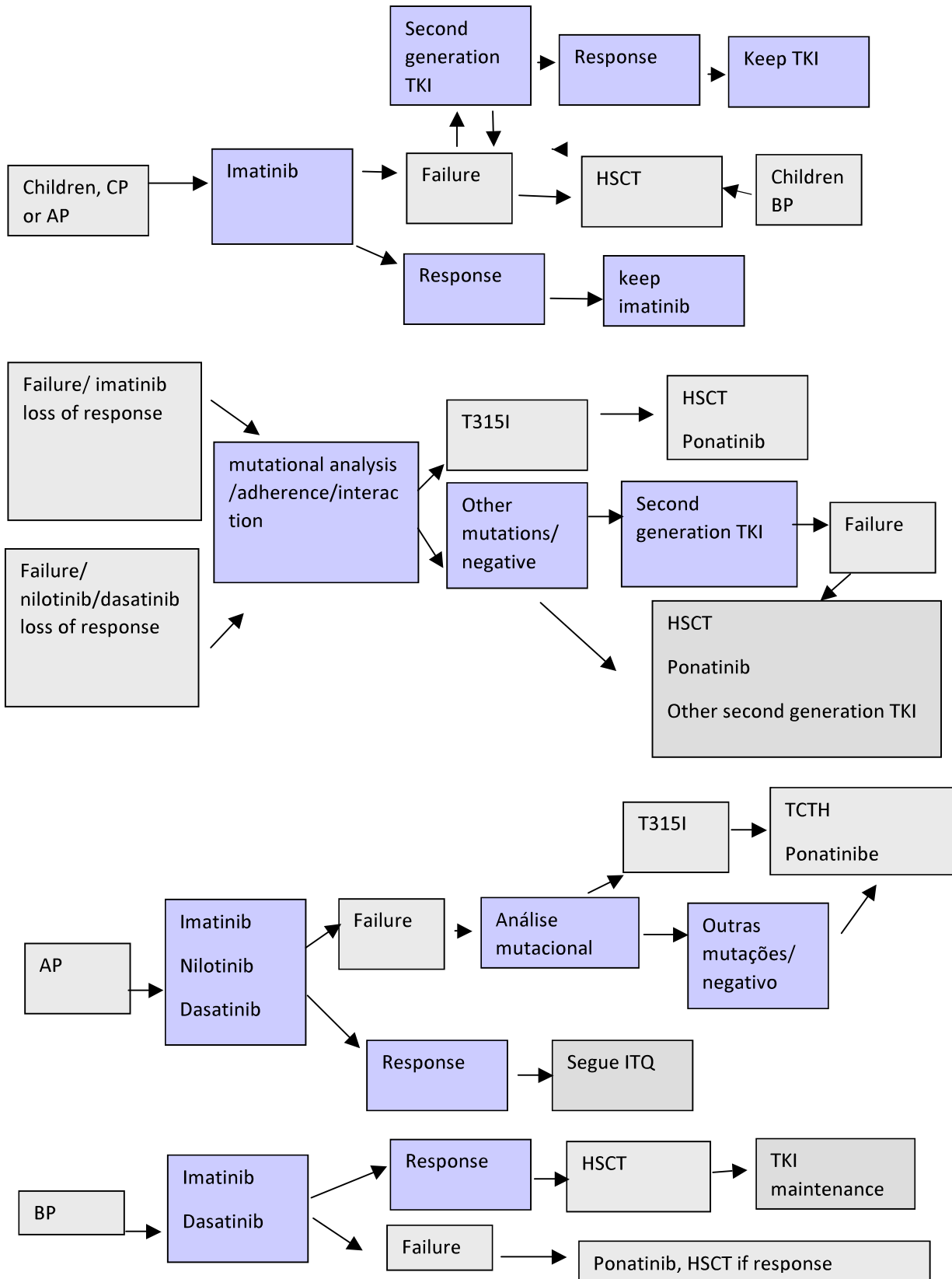
TABLE 3 - Recommendations for post HSCT monitoring and relapse therapy in CML patients 41-46

Time after HSCT	MONITORIZATION	RESULT	INTERVENTION
Two 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: 10 6®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; 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 and 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 6 years after diagnosis. 56 Even so, the clinical course is highly heterogeneous, and survival may vary from a few months to more than 10 years. 57 Therefore, prognosis may be better estimated by a number of scoring systems, among which the Dynamic International Prognostic Scoring System plus (DIPSS plus)58 is one of the most commonly 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.58 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 (level 2b).

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) 59 and the Clinical-Molecular Myelofibrosis Transplant Scoring System (MTSS) 60 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 (level 2b).

INDICATION

No therapeutic agents have thus far been shown to improve the overall survival of patients with PMF; allogeneic HSCT remains the only curative option for such patients to date. Not all patients, however, benefit from this procedure. Hence, we recommend that transplant indication be based on the DIPPS plus score, whereby allogeneic HSCT should be performed in intermediate-2 and high- risk patients.61 HSCT may sometimes be indicated for patients classified as intemediate-1 risk 62 , 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 (level 2b).

CONDITIONING REGIMEN INTENSITY

It is not defined what is the ideal conditioning regimen in transplantation for myelofibrosis patients, given the patients' average age of diagnosis, most regimens will be of reduced intensity, however the ideal dose is not established. For patients under the age of 50, we recommend myeloablative conditioning; for those over 50 years old, reduced intensity conditioning 63, which is usually fludarabine associated with busulfan or melphalan. There is no superiority between conditioning regimens, the melphalan regimen seems to obtain greater control of the disease, but with higher mortality unrelated to relapse than the regimen with busulfan, resulting in similar overall survival 64.

The MD Anderson group recently published a non-randomized, phase II study comparing 2 different levels of intravenous busulfan associated with fludarabine: 15 patients using low busulfan (130 mg / m2 for 2 days) and 31 patients with high busulfan (100mg / m2 for 4 days), with 27 patients with a serum level adjusted to AUC of 4000. In an average follow-up of 3 years, patients using busulfan with a higher dose had an event-free survival of 58% against 27% of those who used low doses. In conclu-

sion, the use of fludarabine regimen with busulfan with serum level control seems to reduce relapse without increasing transplant-related mortality.65 Non-myeloablative conditions have a higher rate of grafting failure 66 (level 2b).

DONOR

HLA-matched unrelated donors are an acceptable alternative for patients without an HLA-identical sibling donor. 67 HLA-mismatched related donors may also be acceptable, but further studies are needed to better address this issue (level 2b). [68]

STEM CELL SOURCE

Both BM and PBSCs are acceptable stem cell sources in this scenario (level 2b).[69]

SPLENECTOMY

Routine splenectomy prior to transplant is not recommended in patients with splenomegaly, except in cases with a spleen size greater than 22cm 70. Splenic radiation, in turn, may be considered within the context of clinical trials (level 2b).

RUXOLITINIB

Ruxolutinib 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.

The use of ruxolitinib in most patients with myelofibrosis (MF) results in a reduction in the size of the spleen, which could decrease the time of grafting in the transplant, in improving constitutional symptoms and therefore in performance status, which could result in improvement of survival, and given the immunomodulatory action on T lymphocytes, it could decrease the incidence and severity of graft disease against the host. There are some concerns regarding the use of ruxolitinib in pre-transplantation: cytopenias, increased incidence of viral infections such as CMV, increased immunosuppression could interfere with the graft versus disease effect, the withdrawal syndrome: fever, recurrence of symptoms, splenomegaly of rebound, cytokine release syndrome, the latter being more common when the interruption is made abruptly and / or long before the conditioning regime starts.

A prospective study that studied the use of ruxolitinib for 56 days, started 60 days before conditioning, gradually decreased in 4 days and interruption 1 day before conditioning, showed that its use was safe. However, in this group of 21 patients, no significant reduction was seen in the rate of graft failure or in the incidence of GVHD 71. Another prospective study, phase II, this one using ruxolitinib for at least 8 weeks, with a gradual reduction of 5 mg every 4 days and interruption 4 days before the infusion also showed that the use of pre-HSCT ruxolitinib is safe: none patient had cytokine release syndrome and the overall 2-year survival was 86%, suggesting a benefit in overall survival 72. Level of evidence 2b. In addition studies have shown that ruxolitinib use is well tolerated during conditioning and others investigate its use in low doses until grafting: in a study with a small number of patients maintained low dose ruxolitinib until D + 28: 2 out of 12 patients had to cease on medication, the average grafting time was 12 days, no grafting failure, low incidence of acute GVHD and about 40% reactivation of CMV. [73]

We recommend it be used at the highest tolerated dose, with gradual tapering every four days and complete withdrawal by one to two days prior to transplant. 70 According to a recent phase II study published this year, its use prior to HSCT seems to be safe and to improve overall survival in patients who are referred for transplantation (level 2b) [71]

HAPLOIDENTICAL TRANSPLANTATION IN MYELOFIBROSIS

The results of haploidentical transplantation in myelofibrosis still lack published data. One of the first reports was published in 2016 analyzing the use of alternative donors from 2000 to 2014, unrelated and haploidentical, with related donors compatible in myelofibrosis 74. Although it was an analysis of a few patients: 23 haploidentical transplants, without which 20 in the last 5 years, the study showed a significant improvement in the survival of transplanted patients with myelofibrosis who used alternative donors: when analyzed the period of 2011 to 2014 the transplant survival curve with compatible related donor and haploidentical donors are comparable.

In 2019, the EBMT group published the retrospective report of 56 patients, median age of 57 years 75. Myeloablative conditioning was chosen in 70% of the cases and 59% of the cases used thiotepa + fludarabine + busulfan with cyclophosphamide in PT; 2/3 used bone marrow as a source of progenitor cells. The grafting rate was 82%. The cumulative incidence of acute GVHD up to D + 100 was 28% (grade II-IV)

and 9% (grade III / IV) and chronic GVHD in 1 year was 45%. In 2 years, overall survival was 56%, the incidence of relapse 19% and unrelated mortality 38%. This study showed that haploidentical trans-

plantation is feasible, with good rates of grafting and overall survival and relapse not unlike unrelated transplants, however approaches must be instituted to decrease the considerable transplant-related mortality rate.

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