

Stem cell transplantation for myeloproliferative diseases in the era of molecular therapy

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Summary

A sufficient part of allo-HSCT is now performed for myelodysplastic syndromes and myeloproliferative neoplasms (MPN), whereas chronic myeloid leukemia is mostly treated by tyrosine kinase inhibitors (TKI). In some special situations, the reasons for allo-SCT in CML are as follows: TKI toxicity; resistance to common drug therapy, and advanced disease (accelerated phase or blast crisis). However, an improvement in progression-free survival may be obtained in advanced CML after haploidentical allo-HSCT versus grafting from HLA-matched related/unrelated donors.

When planning therapy of primary myelofibrosis, one should take into account variable clinical course of the disease using, e.g., Lille scoring system which provides some prognostic criteria, molecular genetic markers, especially, overexpression of JAK2 gene thus allowing usage of ruxolitinib. Allo-SCT can cure myelofibrosis patients transformed to leukemia. In cases of relapse, a 2nd allo-HSCT or donor lymphocyte infusion may result into prolonged survival of the patients.

Results in chronic myelomonocytic leukemia patients treated with allo-HSCT depend on the pre-transplant risk scores. Patients transplanted in CR had significantly longer relapse-free survival and significantly longer overall survival. Early transplants were associated with higher survival rates. In cases of atypical CML, early allogeneic transplant should be performed. Allo-SCT is a method of choice in advanced systemic mastocytosis. It is performed in cases associated with non-mast cell involvement; in aggressive systemic mastocytosis, and in mast cell leukemia.

Keywords

Myeloproliferative disorders, allogeneic hematopoietic stem cell transplantation, tyrosine kinase inhibitors, chronic myeloid leukemia, primary myelofibrosis, chronic myelomonocytic leukemia, systemic mastocytosis.

Introduction

At the present time, WHO Classification of Myeloid Neoplasms includes a range of myeloproliferative Neoplasms (MPN). Of them, most common are: (1) chronic myeloid leukemia (CML, BCR-ABL1+); (2) chronic neutrophilic leukemia (CNL); (3) polycythemia vera (PV); (4) primary myelofibrosis (PMF); (5) essential thrombocythemia (ET), mastocytosis. A group of myelodysplastic/myeloproliferative Neoplasms (MDS/MPN) includes chronic myelomonocytic leukemia (CMML); atypical CML (aCML, BCR-ABL1-); juvenile myelomonocytic leukemia (JMML). Some MDS/MPN cases remain unclassifiable.

According to EBMT statistics 2015, 39% of allo HSCTs are performed in acute myeloid leukemia (AML), and 15%, for MDS/MPN (8000 transplants per year) [1]. Only 2% of BMTs are made in chronic myeloid leukemia (CML), mostly, in advanced clinical forms, thus showing increasing efficiency of tyrosine kinase inhibitors (TKI) therapy in chronic phase CML. Therefore, current challenges for allogeneic SCT in CML in the era of TK inhibitors are worth of discussion. The present review summarizes current strategies for treatment of different myeloid neoplasias.

Current strategies of CML treatment

Previously, allo-HSCT was the only curative treatment for CML, and CML was the most frequent indication for Allo SCT. With Imatinib, TKI became the frontline therapy for newly diagnosed CML. E.g. the IRIS Program “International Randomized Study of Interferon and STI571”, has demonstrated superiority of Imatinib *versus* interferon treatment in CML therapy [2]. Therefore, transplant activities in this field dropped quickly, and allo-SCT moved from frontline to second, third-line therapy. In some special situations, the reasons for allo-SCT are as follows: TKI toxicity; resistance to common drug therapy, and advanced disease (accelerated phase or blast crisis, BC).

Efficiency of allogeneic HSCT (Allo SCT) in chronic myeloid leukemia in the Imatinib era was evaluated in a subgroup of the Randomized German CML Study IV. Appropriate survival probability was evaluated showing that the patients with elective allo-SCT in first CP (n=20; group I) and those who underwent transplantation after Imatinib failure in first CP (n=36; group II) had a comparable 3-year survival probability of 88% and 94%, respectively (CI: 69.3-98.7 and 83.9-99.4). The patients who underwent transplantation in advanced disease (n=28; group III) had a 3-year survival probability of only 59% (CI: 38.6-77.5). Matched pair analysis for 53 patients who underwent transplantation compared to 106 matched Imatinib-treated patients also did not show any differences thus suggesting similar efficiency of the both treatment strategies [3].

Management of CML blast crisis and TKI usage could be dependent on some proven facts [4]:

- TKI moderately improves OS median survival for <1 year.
- Choice of TKI should be directed by mutational profile.
- Best prognosis is suggested in patients who achieve 2nd CP.
- In general, allo-SCT improved survival.

As shown by Hehlmann et al [4], the CML IV study with Imatinib treatment in patients with blast crisis CML has shown a survival of ca. 20% over 10 years, as compared to <5% survival in pre-Imatinib era. Distinct improvement in OS and event-free survival (EFS) was shown in BC CML patients when using combination of allo-SCT and TKIs compared to only TKIs. E.g., the median OS in the TKI+allo-HSCT group (20 months, 95% CI 1-74 months) was significantly longer than that in the TKIs group (4.5 months; 95% CI 3.5-5.5 months). Similarly, the 4-year OS rates in the TKIs+allo-HSCT group were significantly higher than those in the TKI group (50.0 vs 10.0%, P=0.016). (b) The median EFS in the TKIs+allo-HSCT group (18 months, 95% CI 1-72.7 months) was also significantly longer than in the TKIs group (3 months; 95% CI 1.9-4.0 months). The 4-year EFS rates in the TKIs+allo-HSCT group were significantly higher than those in the TKIs group (50.0 vs 10.0%, P=0.002) (Jiang H 2014). It should be noted that 2/3 of the donors were haploidentical.

Improved progression-free survival (up to 60%) was registered in the patients with advanced CML after haploidentical allo-HSCT *versus* grafting from HLA-matched related/unrelated donors [5]. Thus, the donor type may influence survival for transplanted patients with advanced CML.

Primary Myelofibrosis

To take into account variable clinical course of a myeloproliferative disorder, the Lille scoring system provides some prognostic criteria, as mentioned:

- The “low” group (Hb-level > 10 g/dL and WBC between 4 and 30 /nL (*median OS 93 months*);
- The “intermediate” group (Hb-level < 10 g/dL or WBC > 30/< 4 nL (*median OS 26 months*);
- The “high” group (Hb-level < 10 g/dL and WBC < 4 /nL or > 30 /nL (*median OS 13 months*).

Table 1. Summary of IPSS criteria

Risk Model	Risk Factor	Risk Stratification	Median Survival (months)
Dynamic IPSS	Age > 65 years Hgb < 10g/dL (2 pts) WBC > 25x10 ⁹ /L Circulating blasts ≥ 1% Constitutional symptoms	Low: 0 Intermed-1: 1-2 Intermed-2: 3-4 High: 5-6	Not reached 118 58 27
DIPSS-Plus	DIPSS Risk + Platelet < 100x10 ⁹ /L Unfavorable cytogenetics Transfusion requirement	Low: 0 Intermed-1: 1 Intermed-2: 2-3 High: 4-6	180 80 35 16

Table 2. Clinical outcomes of reduced-intensity conditioning (RIC) regimens in MF patients

Authors	n	Median age	NRM	OS
Rondelli et al. 2005	n=21	54 yrs	10% (1yr)	85% (2.5 yrs)
Kröger et al. 2005	n=21	53 yrs	16% (1yr)	84% (3yrs)
Bacigalupo et al. 2010	n=46	51 yrs	24% (5 yrs)	45% (5yrs)
Kröger et al. EBMT 2009	n=103	55 yrs	17% (1 yr)	67% (5yrs)

Reduced conditioning regimen when transplanting the MF patients yielded good results in terms of non-relapse-related mortality (NRM) and OS levels (Table 2).

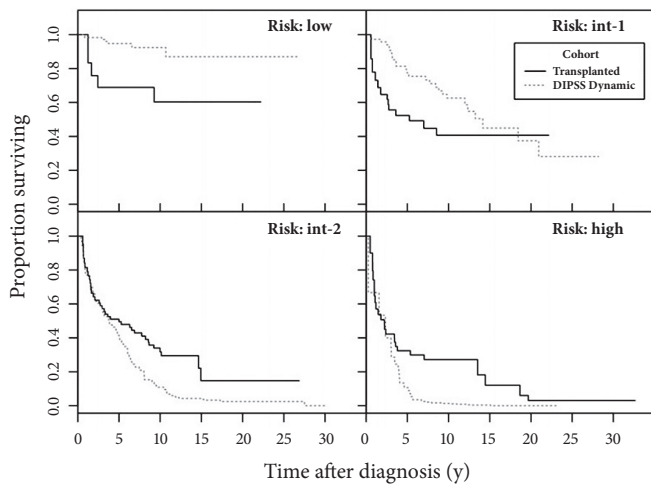


Figure 1. Survival probabilities for the 4 risk subgroups in MF (DIPSS risk: low, int-1, int-2, high). DIPSS score is taken at stem cell transplant (solid, transplant cohort) or at the indicated time (dotted, nontransplant cohort). Time (horizontal axis) elapses from diagnosis [10].

Efficiency of SCT proved to depend on initial risk score, e.g., assessed by DIPSS. As seen from Fig. 1, SCT in advanced disease prolongs survival in high-risk patients.

Allogeneic SCT option for myelofibrosis with leukemic transformation was evaluated in EBMT study. This involved 1048 cases in allo SCT; 46 patients, with leukemic transformation [11]. The cumulative incidence of treatment-related mortality at 1 year was 28%, and of relapse at 3 years was 47%. The 3-year progression-free (PFS) and overall survival (OS) rates were 26% and 33%, respectively. Hence, allogeneic SCT can cure myelofibrosis patients transformed to leukemia.

Molecular genetic markers, i.e., multiple gene expression profile of leukemic cells may be predictive for the outcome in myelofibrosis patients after allogeneic transplantation, especially overexpression of JAK2 and ASXL1 gene, as shown by Kröger et al. [12].

Our previous studies concerned treatment of the myelofibrosis patients who relapsed after first allo-SCT [13]. The following treatment consisted of either donor lymphocyte infusions, or second allo-SCT from an alternative donor. A group of 30 patients with relapsed myelofibrosis treated by donor lymphocyte infusions and/or second allo-SCT showed good 5-year overall survival rates. I.e., 2nd SCT caused complete remission in 14 out of 17 patients (82%).

Ruxolitinib, a JAK2 inhibitor, is a promising therapeutic option for MF patients during peritransplant period [14]. Feasibility and safety of Ruxolitinib treatment was tested in Hamburg-Eppendorf clinic and Ruxolitinib was used in 12 patients at a dose of 10+10 mg. Severe GVHD was observed only in 1 case of 12; overall survival was 100% after short follow-up (a mean of 163 days) [15].

Chronic Myelomonocytic Leukemia (CMML)

CMML is another chronic myeloproliferative disorder. Different prognostic scores for CMML were developed in MD Anderson, Mayo Clinics, a Düsseldorf scoring etc. CMML-specific prognostic scoring system was the subject to external validation being tested in 578 patients, as seen from Table 3.

Progression-free survival (PFS) in CMML was assessed by a group from the MD Anderson Cancer Center [17]. The study was performed in 83 CMML patients. In 78 cases a pre-transplant induction treatment was applied, with 37 patients receiving hypomethylating agents and cytotoxic chemotherapy in 41 cases. Patients treated with a hypomethylating agent had a lower cumulative incidence of relapse at 3 years post-transplant (22%) than those treated with other agents (35%; P=.03), improved progression-free survival (PFS), with no detectable difference in treatment-related mortality at 1 year post-HST. In summary, their data support the value of hypomethylating agents administered before allo-SCT, in order to achieve morphologic remission.

Results in CMML patients treated with allo-HSCT depend on the pre-transplant risk scores (HCT-specific CPSS), as shown by IBMTR group in 209 patients [16]. I.e., adjusted disease-free survival, starting at the time of transplant, at a median follow-up of 51 months. CPSS score, Karnofsky per-

Table 3. Prognostic scales in CMML, a summary of different studies [16]

Scoring System	No. Patients	External Validation	Variables Included in Final Scoring System
MD Anderson prognostic score	213	No	1. Hemoglobin <12g/dL 2. Circulating immature myeloid cells 3. Absolute lymphocyte count >2.5 × 10 ⁹ /l 4. BM blasts ≥10%
Dusseldorf score	288	No	1. BM blasts ≥5% 2. LDH >200 u/l 3. Hemoglobin ≤9g/dL 4. Platelets ≤100 × 10 ⁹ /l
Spanish cytogenetic risk stratification system	414	No	1. Low risk: normal karyotype or loss of Y chromosome as single anomaly 2. High risk: presence of trisomy 8 or abnormalities of chromosome 7, or complex karyotype 3. Intermediate risk: all other abnormalities
CMML-specific prognostic scoring system	578	Yes	1. CMML FAB type 2. CMML WHO type 3. CMML-specific cytogenetics* 4. RBC transfusion dependence
Mayo prognostic model	226	Yes	1. Absolute monocyte count > 10 × 10 ⁹ /l 2. Presence of circulating blasts 3. Hemoglobin <10g/dL 4. Platelet count < 100 × 10 ⁹ /l

formance status, and graft source proved to be significant predictors of survival. The patients with intermediate-2/high risk had a nearly 2-fold increased risk of death after relapse compared to those with low/intermediate-1 CPSS scores.

An EBMT study of relapse-free survival (left) and overall survival (right) according to disease stage (CR *versus* no-CR) at transplantation was performed in a group of 513 CMML patients. The subjects transplanted in CR had lower probability for non-relapse death (P=0.002) and longer relapse-free and OS (P=0.001 and P=0.005, respectively). In multivariate analysis the only significant prognostic factor for survival was the presence of CR at transplantation (P= 0.005). Hence, patients transplanted in CR had significantly longer relapse-free survival and significantly longer overall survival [18].

Moreover, both RFS and OS differed according to transplantation within 12 months or after 12 months after diagnosis of CMML. Early transplant was associated with significantly higher survival rates.

Systemic mastocytosis

Systemic mastocytosis (SM) is a myeloproliferative disorder with clonal expansion of mast cell precursors in various organs [19]. It is a heterogeneous group by the clinical course and malignant precursor biology: it may indolent do not shorten life expectancy. Advanced SM may proceed as Mast Cell Leukemia (MCL), SM with associated hematologic non-mast cell lineage diseases, or aggressive systemic mastocytosis (ASM).

Survival rates from months to a few years despite cytoreductive therapy were not too high.

I.e., the 3-year OS and PFS in the total group of mastocytic malignancies are about 50-60% etc. [20]. Allo-SCT is a method of choice in advanced systemic mastocytosis. However, some somatic mutations predispose for inferior clinical outcome in this disorder, i.e., ASXL1 or CBL mutations (Fig. 2). These molecular markers comprise a distinct risk factor when treating ASM [21].

Atypical chronic myeloid leukemia (aCML) with BCR-ABL1-negativity is considered a special clinical entity characterized by leukocytosis, affected granulocyte myeloid precursors, dysgranulopoiesis, PH-negativity, SETBP1 expression. Mutated RAS was found in some cases (7/20 [35%] vs 4/29 [14%]) and less JAK2p.V617F (3/42 [7%] vs 10/52 [19%]). Compared with unclassified MDS/MPN-U, patients with aCML showed a significant inferior OS (12.4 months, 95% CI [9.0-16.1] vs 21.8 months, 95% CI [17.6-28.8]) and ACL-free survival (11.2 months, 95% CI [7.0-13.5] vs 18.9 months, 95% CI [12.3-26.3]), as reported by Wang et al. [22].

Age- and risk-score dependent survival in atypical CML were assessed as five-year overall survival following allogeneic transplantation in 42 patients from an EBMT study [23]. As expected, the older age of aCML patients (<45 years) was associated with sufficiently lower 5-year survival (<40%) as compared to younger patients.

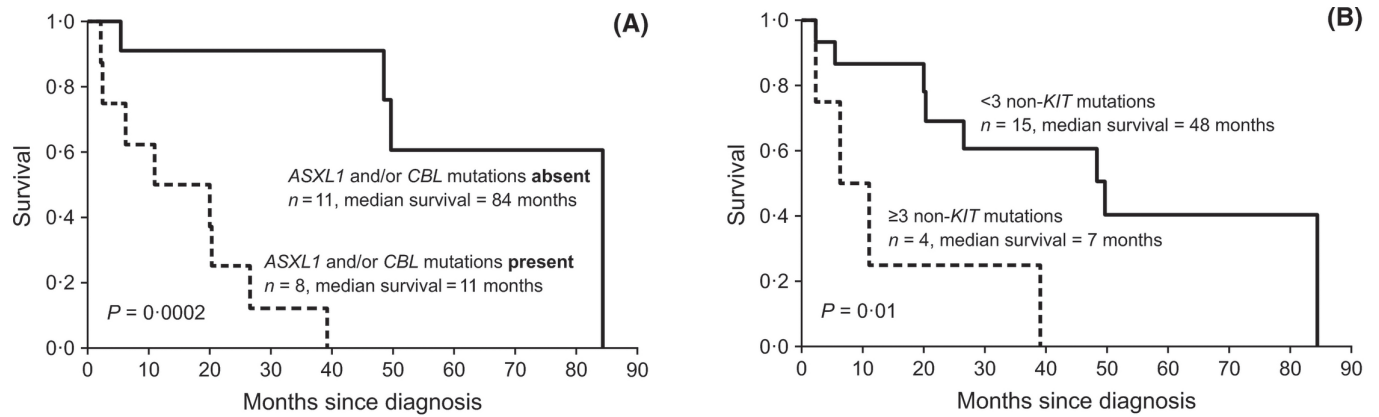


Figure 2. Molecular risk factors determine survival rates in systemic mastocytosis

Summary

As based on clinical experience and current multicentric studies, some recommendations may be given on WHOM and WHEN to transplant, as follows:

In CML:

HSCT: in 1st complete remission – TKI failure, TKI intolerance, acceleration phase, blast crisis:

TKI ± chemoinduction is performed

In Myelofibrosis:

HSCT at DIPPS INTERMED 2 and high risk scores at INTERMED 1 and with high risk features

In CMML:

Early HST, pre-treatment with hypomethylating agents

In Mastocytosis:

HSCT: in systemic mastocytosis, AHNMD (SM with associated non-mast cell)

in ASM (Aggressive Systemic Mastocytosis)

in MCL (Mast Cell Leukemia)

Conflict of interest

No conflict of interest is declared.

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Трансплантация стволовых клеток при миелопролиферативных заболеваниях в эру молекулярной терапии

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Резюме

Значительная часть аллогенных трансплантаций гемопоэтических стволовых клеток (алло-ТГСК) сейчас проводится по поводу миелодиспластического синдрома или миелопролиферативных заболеваний, тогда как хронический миелоидный лейкоз (ХМЛ) лечат, в основном, ингибиторами тирозинкиназ (ИТК). В некоторых особых ситуациях, есть следующие причины для алло-ТГСК при ХМЛ: токсичность препаратов ИТК, резистентность к обычной лекарственной терапии и прогрессия болезни (фаза акселерации или бластный криз). Однако повышения выживаемости без прогрессии можно добиться в продвинутой фазе ХМЛ после гаплоидентичной ТГСК, по сравнению с пересадкой от HLA-совместимого родственного или неродственного донора.

При планировании терапии первичного миелофиброза (ПМФ) следует учитывать различия в клиническом течении заболевания, применяя, например, Лилльскую систему оценок, которая дает прогностические критерии, а также молекулярно-генетические маркеры, в особенности, гиперэкспрессию гена JAK2, что дает основания к применению руксолитиниба. Алло-ТГСК может излечивать больных с ПМФ при трансформации его в лейкоз. В случаях рецидива, вторая алло-ТГСК или инфузия лимфоцитов донора может привести к удлинению продолжительности жизни пациентов.

Результаты терапии больных с хроническим миеломоноцитарным лейкозом, леченных алло-ТГСК, зависят от оценок их клинического риска до пересадки. Пациенты, трансплантированные в полной ремиссии, имеют большую длительность общей и безрецидивной выживаемости. Раннее выполнение трансплантации коррелирует с более высокими цифрами выживаемости пациентов. В случаях атипичного ХМЛ следует проводить раннюю трансплантацию. Алло-ТГСК является методом выбора при обширном системном мастоцитозе. Она проводится в случаях, ассоциированных с вовлечением других клеток, кроме мастоцитов, при агрессивном системном мастоцитозе и при мастоцитарной форме лейкоза.

Ключевые слова

Миелопролиферативные заболевания, аллогенная трансплантация гемопоэтических стволовых клеток, ингибиторы тирозинкиназ, хронический миелоидный лейкоз, первичный миелофиброз, хронический миеломоноцитарный лейкоз, системный мастоцитоз.