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An Update on Allogeneic Hematopoietic Progenitor Cell Transplantation for Myeloproliferative Neoplasms in the Era of Tyrosine Kinase Inhibitors

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Abstract

Myeloproliferative neoplasms are a category of diseases which has been traditionally amenable to allogeneic hematopoietic progenitor cell transplantation. Current developments in drug therapy have delayed transplantation for more advanced phases of the disease, especially for patients with chronic myelogenous leukemia, while transplantation remains a mainstream treatment modality for patients with advanced myelofibrosis and chronic myelomonocytic leukemia. Reduced-intensity conditioning has decreased the treatment-related mortality and advances in the use of alternative donors for transplantation could extend the use of this procedure to an increasing number of patients with improved safety and efficacy. Here we review the current knowledge about allogeneic transplantation for myeloproliferative neoplasms and discuss the most important aspects to be considered when contemplating transplantation for patients with these diseases. JAK2 inhibitors offer the promise to improve spleen size and performance of patients with myelofibrosis and extend transplantation for patients with more advanced disease.

Keywords

Myeloproliferative neoplasms; myelofibrosis; chronic myelogenous leukemia; chronic myelomonocytic leukemia; polycythemia vera; essential thrombocythemia; allogeneic stem cell transplantation

Introduction

Myeloproliferative neoplasms (MPN) generally refer to a group of clonal chronic hematologic disorders with both distinct and overlapping features. The 2008 WHO classification divides these diseases into two broad categories – Classical and Atypical MPNs(1). The Classical MPNs are Chronic Myeloid Leukemia (CML), Idiopathic/Primary Myelofibrosis (MF), Polycythemia Vera (PV), Essential Thrombocythemia (ET), systemic mastocytosis, chronic neutrophilic leukemia (CNL) and chronic eosinophilic leukemia

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(CEL)(2), while atypical MPNs are Chronic MyeloMonocytic Leukemia (CMML), Juvenile Myelomonocytic leukemia (JMML) and atypical Chronic Myeloid Leukemia (aCML) BCR-ABL negative. The discovery of the BCR-ABL inhibitor imatinib (Gleevec) has revolutionized the treatment of CML and has made allogeneic hematopoietic progenitor cell transplantation (AHPCT) a second choice for patients who failed treatment with tyrosine kinase inhibitors (TKIs), or have progressed to accelerated or blast phase. More recently, several JAK2V617F inhibitors have shown activity in idiopathic myelofibrosis, primarily related to reduced symptoms and decrease in spleen size. These effects appear to be independent of the presence of this mutation and, clearly, only partially recapitulate the great success for imatinib for treatment of CML. Nevertheless, the advent of novel agents hold the promise to further improve the medical treatment for these diseases, and will pose a continuous challenge to the alternative treatment option which is allogeneic transplantation. This article will focus on the treatment of myeloproliferative neoplasms using hematopoietic progenitor cell transplantation in the era of novel tyrosine kinase inhibitors.

Chronic Myeloid Leukemia

CML, which could currently be described as the “golden” MPN, is characterized by an abnormal proliferation of mature myeloid cells propagated by fusion of Abelson gene on chromosome 9 with the break point cluster region gene on chromosome 22, resulting in the BCR-ABL fusion gene and protein (3). Prior to the 21st century AHPCT was the treatment of choice for this disease and the most common indication for transplantation. AHPCT was replaced for patients in first chronic phase by treatment with TKIs, and their success reverberated to other malignancies. While AHPCT remains the only curative modality available (4) it was unfortunately fraught with significant morbidity and mortality. Hehlmann et al. initially reported on patients with chronic phase CML who were randomized based on donor availability, to allogeneic transplantation versus the drug treatment (5). This group observed that patients on the drug treatment arm had better survival in the first 8 years due to very small treatment related mortality in this group (5). However, after the 8-year follow-up survival appeared better with transplant because of continued relapse in the non-transplant group (5). The randomized clinical trial of Interferon versus STI-571 (IRIS trial) showed that, for the patients who were on imatinib, the event free survival (EFS) and overall survival (OS) were 81% and 85% respectively, and when only CML-related deaths prior to allogeneic transplantation were taken in to consideration the OS increased to 93% (6). Prior to the approval of imatinib, CML was the most common indication for AHPCT in the first chronic phase, with an overall survival of 50% at 10 years (7). Since imatinib became available, several second (nilotinib and dasatinib), and third (ponatinib) generation TKIs have been developed. A few drugs specifically target resistant mutations like T315I present in a subgroup of patients with CML. These mutations may develop at the time of resistance to imatinib or other TKIs, and the development of such mutations may signal the imminent need for AHPCT.

Changes in Transplantation for CML

Several reports have documented a decline in annual transplantation rates for CML. The German Registry of Stem Cell Transplantation (DRST) group observed a 28% reduction in

annual transplant rates between 1998–2004 (8), similar to reports form the CIBMTR and EBMT (9). This reduction was seen across the board in patients in first chronic phase. However, an increase in the number of transplants was seen in more advanced CML patients, like those in second chronic phase or beyond (accelerated or blast phase), with the CIBMTR documenting an increase from 21% to 41% from 1999 to 2003 (10). Allogeneic transplantation is thus now reserved for patients who have progressed to accelerated or blast phase, chronic phase CML patients that have failed at least second-generation TKIs, and those who have developed resistant mutations to TKI, such as T315I mutation, with limited drug treatment options.

An important question is whether treatment with TKIs affects transplant outcomes or not. In a recent CIBMTR study, Lee and colleagues showed on 1309 patients (409 treated with imatinib prior to transplant) that patients who had received a TKI prior to undergoing an allogeneic transplant did not have worse outcomes (11). The three-year OS was 72% versus 65% (P=0.07) in patients with prior TKI vs. no TKI, suggesting that transplant outcomes were not compromised by the use of drug therapy prior to transplantation (11).

The German CML group published an interim analysis of patients who were transplanted early for high risk disease, those that had failed imatinib and those that had advanced disease. A total of 84 patients received an allogeneic transplantation (12). This group observed a complete molecular remission rate of 88% after AHPCT, and a treatment related mortality of 8% (12). The 3 year OS in patients with imatinib failure was 94%, while those with advanced disease had an OS of 59% (12). In the original IRIS study secondary resistance was deemed to occur at a rate of 4% annually, and was associated usually with a mutation in the BCR-ABL1 kinase domain (6, 13, 14).

Second and third generation TKIs have shown responses in patients with resistant mutations (14, 15). Recently, ponatinib has been approved for patients with T315I mutation based on a phase II study which showed a 57% major cytogenetic response (15). Allogeneic transplantation has been shown to be of benefit in patients who harbor BCR-ABL1 KD mutations, including the T315I mutation (14, 16). A retrospective analysis of patients transplanted with this mutation compared to a historical cohort, showed that these patients appear to fare better with 2-year OS rates for chronic phase, accelerated phase, blast phase and Ph^+ ALL of 59%, 67%, 30% and 25% (16, 17).

Only a few studies have analyzed transplant outcomes of patients who transformed to accelerated or blast phase. Jiang Q et al. showed that patients with accelerated phase disease, had superior outcomes with transplantation, compared to patients who received imatinib only with a 6-year PFS of 71.7% versus 39.2% (P=0.035) and 6-year OS and of 83.3% versus 51.4% (P=0.023), with factors such as increased percentage of peripheral blasts and longer CML disease durations as adverse risk factors (18). It was has also been reported that in patients with advanced phase disease (AP or BP), the outcomes are worse post-transplant in patients with BCR-ABL1 mutations (14). Jabbour et al. reported a 2-year OS of 46% versus 72% (P=0.12) in patients with BCR-ABL1 mutations versus no mutations (14). Our group evaluated the outcomes of patients in second chronic phase after they progressed to lymphoid or myeloid blast phase CML and observed a long term survival of 42% with no

significant differences in outcomes for patients who progressed with lymphoid versus myeloid blast crisis (19).

Alternative donor transplantation for CML

More recently, alternative donors are increasingly used for patients without a matched donor with good results. Haploidentical donors may expand the use of transplantation for patients with advanced disease. Huang XJ and colleagues initially reported results on 93 patients treated with unmanipulated haploidentical transplantation for patients with CML who lack a matched related donor. All patients received BuCy2 regimen. The treatment-related mortality at day 100 and 1 year post transplant were only 8.7% and 20.7%, while 4-year PFS for patients in CP2, AP and BP were 85%, 73% and 61.5%, respectively(20). Our recent experience with haploidentical transplantation is also very encouraging. We have recently reported results of the first 10 treated patients with advanced CML (7 progressed to BP, 3 to AP) with a haploidentical transplant using post-transplantation cyclophosphamide, at our institution. All 10 patients engrafted promptly the donor cells and none died of treatment-related mortality. Four patients subsequently relapsed, 3 who were not in second chronic phase at the time of transplant. Overall 6 patients survived, 5 in molecular remission after a median follow-up of 22 months (21).

In summary, allogeneic transplantation for patients with CML in now performed for patients with more advanced disease, who progressed to accelerated of blast phase, are resistant or intolerant to TKIs. Alternative donor transplantation can now be performed safely for these patients and will likely extend this form of treatment to virtually all patients in need.

Idiopathic/Primary Myelofibrosis

Myelofibrosis (MF) is a Philadelphia-chromosome negative myeloproliferative neoplasm or unclear etiology. Whether there is a primary causal mutation leading to myelofibrosis is yet to be determined; however, a number of mutations have been found to be associated with this condition among which are Janus kinase 2 (JAK2) and MPL mutations (22–24). While drug therapy is currently being explored, and despite recent FDA approval of ruxolitinib, a JAK1/2 inhibitor which has been shown to improve MF symptoms, and spleen size (25). However, the only curative treatment modality for myelofibrosis remains allogeneic transplantation.

Scoring Systems

Prognostic scoring systems have long helped the decision to proceed with transplant and have been recently refined. A detailed list of scoring systems used to decide which patients should be considered for transplantation is provided in Table 1. The International Prognostic Scoring System (IPSS) for primary myelofibrosis, and subsequent improvements most recently with the Dynamic IPSS Plus allowed a better discrimination of the risk category and helped the treating physician make decisions with regards to observation, initiation of drug therapy and help guide timing of allogeneic transplantation (26–28). The DIPSS-Plus classifies patients into low-risk, intermediate 1, intermediate 2 and high risk disease (27). This scoring system utilizes specific patient risk factors to predict leukemia-free survival and

overall survival. The DIPPS-Plus was an improvement on IPSS and DIPSS by incorporating patient's platelet count, transfusion status and karyotype into the model, and was found to better predict the patient outcomes. The current recommendation is that patients in the intermediate-risk 2 and high-risk group be evaluated for allogeneic transplantation as soon as possible as the median survival in these 2 groups was reported to be 35 months and 16 months, respectively (27). This scoring system also appreciates the risk of leukemic transformation, with the 5-year risk of transformation of 6% in the low-risk group and 18% in the high-risk group category. The 10-year leukemia free survival was 12% and 31%, in the low-risk and high-risk group (27).

Only a few reports have attempted to investigate scoring systems to predict outcomes for patients with myelofibrosis after allogeneic transplantation. Bacigalupo et al. reported on a scoring system based on transfusion requirement (>20 units of PRBCs), spleen size (>22cm) and donor type (matched sibling versus alternative donor)(29). Patients were subsequently categorized into 2 groups; low and high-risk. These investigators observed a higher transplant-related mortality (TRM) in those with high-risk (41%) versus the low risk group (8%) and a relapse-related death of 12% versus 41% in the low risk versus high-risk group ($P = 0.02$) (29). The 5-year overall survival for all patients was 45%, ranging from 77 % in the low-risk group to only 8% in the high-risk group of patients ($P < 0.001$). Although based on a relatively small number of patients and not validated, this scoring system appears to discriminate well between the proposed risk groups and could be a useful tool to better select candidates for allogeneic transplantation.

Allogeneic transplantation for patients with MF is usually limited by the more advanced age of the patients and the fact that they have associated co-morbidities, which are known risk factors for increased morbidity and mortality in ASCT. The three-year overall survival in patients with MF post-transplant was reported to be in the range of 30–50%, while transplant related mortality can be as high as 40% (30). There have been different factors attributed to this variation, one of which is the intensity of the conditioning regimen employed. In a recent retrospective report from the United Kingdom, outcomes of 51 patients who received either a myeloablative (MA) or reduced-intensity conditioning (RIC) AHPCT for MF were compared; they observed no significant difference in 3-year OS or PFS, (OS 44% versus 31%, PFS 44% versus 24%) in the myeloablative versus RIC group (31). Interestingly, there was no significant difference in non-relapse mortality rate (NRM) between the 2 groups; however, the relapse rate was lower (12%) in the MA group versus RIC (46%) with a strong trend towards significance ($P=0.06$), likely not reached due to the relatively small number of patients. These results were almost similar to the results reported by the CIBMTR study group, in which a 3-year disease free survival (DFS) of 39%, and 1-year transplant related mortality (TRM) of 15% in patients with matched sibling donors who received RIC transplantation was found. However, patients who had an unrelated donor appeared to have worse transplant outcomes with a DFS and TRM of 17% and 49%, respectively (32). In a multicenter study of RIC prior to allogeneic stem cell transplantation showed that in patients who had a fully matched unrelated donor there was no significant difference in non-relapse mortality when compared to HLA matched sibling donors, 13% versus 10% (33). For mismatched donors, the NRM was significantly higher at 38% (33). These results were comparable with preliminary results from the Phase II MPD-RC 101 prospective clinical

trial, where the investigators observed a higher transplant related mortality due to a higher rate of primary or secondary graft failure in patients who had unrelated donor transplants and received RIC with fludarabine and melphalan-based conditioning (34).

The role of JAK2V617F Mutation in Allogeneic Transplantation for MF

JAK2V617F mutation is found in up to 50% of patients with myelofibrosis (24). JAK2V617F mutation has been suggested to be an adequate biomarker to detect residual disease and monitor for disease relapse post-transplant (35, 36). In a recent study Alchalby et al. observed that the 5–year overall survival was improved in those that were JAK2-wild type versus those who had the mutation, 44% versus 70% (P=0.007), suggesting that patients with JAK2V617F mutation could have worse outcomes after AHPCT (36). This group also evaluated JAK2 mutational status at 3-month intervals post-transplant and observed that clearance of JAK2 mutation was associated with a decreased risk of relapse(36). Patients who had cleared JAK2V617F had a 5% risk of relapse versus 31% for those who were still positive at 3 months. This risk was also shown to increase at 6 months (36). Moreover, reappearance of JAK2V617F mutation post-transplant was very likely to be associated with relapsed disease, unless rapid taper of immune suppression or donor-lymphocyte infusion was employed.

It has become clear that patients with MF do not tolerate very intense conditioning due to more advanced age and associated comorbidities. Our group has explored RIC transplantation for patients with myelofibrosis using busulfan-based conditioning. Patients received higher (AUC 4000 μmol.min or 100mg/m2 for 4 days), and lower (130mg/m2 for 2 days) busulfan doses. Fludarabine dose was the same in both groups at 40mg/m2 for 4 days. We observed that patients who received higher busulfan doses had a better 3-yr OS survival of 75% vs. 60% in the low busulfan dose group (37). Event-free survival (EFS) was also significantly better at 61% vs. 27% owing to a lower cumulative incidence of relapse of 29% in the high-dose busulfan versus 53% in the low-dose busulfan group (37). Interestingly, the incidence of non-relapse mortality was not increased with higher doses of busulfan, suggesting that a reduced toxicity conditioning sufficient enough to achieve sustained engraftment of donor cells could be most effective in producing long term remissions with low treatment-related mortality in patients with myelofibrosis (37).

Transplantation for Myelofibrosis with Leukemic Transformation

The outcomes for patients with myelofibrosis with leukemic transformation (LT) have been particularly poor with conventional therapy, with single institutional studies reporting a median OS of approximately 3 months, whether patients received treatment with chemotherapy or no treatment at all (38). Leukemic transformation occurs in 8 to 23% of patients with MF in the first 10 years after a diagnosis, with a median of 31 months (38, 39). We have shown that patients with MF and leukemic transformation can achieve durable long term remission after transplant (39). Our group initially reported the MD Anderson experience on 14 patients who had progressed to acute leukemia. Most patients received fludarabine-melphalan RIC conditioning. All patients achieved remission after transplant and long term survivors also received cytotoxic chemotherapy prior to transplant. After a median follow-up of 31 months, OS and PFS were 49% and 33% (39). Kennedy et al.

recently reported results of a retrospective study for patients with MPNs with leukemic transformation, who received induction therapy followed by allogeneic transplantation (40). The two-year OS survival was 47% for the cohort of patients who received a transplant, compared to an overall survival of 15% for those who did not receive a transplant (40). Factors significantly associated with worse outcomes in patients who were treated with the intent of a cure were patient's poor performance status, percentage of bone marrow blast > 50% and the presence of three or more cytogenetic abnormalities (40). These two studies suggest that there is a benefit to transplanting patients with MF and other MPNs that have transformed to acute leukemia and selected patients may benefit from this procedure after adequate cytoreduction (39,40).

In summary, transplantation for myelofibrosis should probably be performed with an ablative yet reduced-intensity conditioning regimen, although the optimal type and intensity remains unclear. JAK2 inhibitors offer the promise to improve symptoms of patients with this disease and make more patients eligible for transplantation.

Chronic Myelomonocytic Leukemia

CMML is one of the more rare and atypical MPNs which under the most recent WHO 2008 criteria is classified in the Myeloproliferative/Myelodysplastic Syndrome category(41). It is divided in 2 groups based on the percentage of bone marrow and peripheral blood blasts: CMML type 1 has < 10% bone marrow and < 5% peripheral blood blasts, and CMML type 2 which has 10%−19% bone marrow and 5–19% peripheral blood blasts(42). CMML has been notoriously resistant to medical therapy and there are few studies designed exclusively for treatment of this disease. Multiple therapeutic approaches have been employed and various pharmacotherapeutics agents have been tried, like cytotoxic chemotherapy, TKIs (imatinib), immunomodulating agents such as lenalidomide, hypomethylating agents, histone deacetylase inhibitors and farnesyl transferase inhibitors, all with modest results (43, 44).

Several models have been proposed to determine prognosis of this disease, most recent one was based on registry data from the Spanish database. In this CMML specific prognostic scoring system, patients were stratified based on cytogenetics, patient characteristic, LDH and hematologic indices (45). In regards to cytogenetics, three cytogenetic risk categories were identified, with significant differences in 5-year survival (P<0.001); low-risk were patients with normal karyotype, or loss of Y chromosome with 35% survival at 5-years, high-risk composed of patients with trisomy 8, chromosome 7 anomalies and patients with complex karyotype (4% survival at 5-years), while intermediate-risk were patients were who did not belong to any of the two groups with 26% survival at 5-years (45). The MD Anderson group analyzed outcomes of approximately 200 patients with CMML treated at our institution and described a new prognostic scoring system for this disease, subsequently validated in other studies (46). The factors significantly associated with outcome were Hgb<12g/dL, presence of circulating immature myeloid cells, absolute lymphocyte count >2.5×10^9/L, and marrow blasts ≥10%. Four prognostic groups were identified based on the number of factors present, with median survival of 24, 15, 8 and 5 months. Because overall very poor outcomes (median survival 12 months for the whole cohort) and no good

alternative treatment options, we currently advocate allogeneic stem cell transplantation in almost all patients eligible for transplantation.

While medical treatment has been generally ineffective, allogeneic transplantation, similar to other MPNs, can cure this disease. However, transplant outcomes for these patients are, in general, worse than other MPDs. Several reports described outcomes of patients with CMML. Results of a multicenter study were reported by Kroger et al. in 2002. This group studied 50 patients with CMML (18 with >5% blasts at transplantation), 43 had a matched related donor transplant, and 40 had bone marrow as stem cell source (47). All patients received myeloablative conditioning with or without total body irradiation. The 5-year estimated OS and DFS were only 21% and 18%, respectively, while relapse rate was 49%. This high relapse rate suggested that more intense conditioning might be needed for these patients (47). Factors which appeared to improve DFS (while did not reach statistical significance) were the development of acute GVHD, male donor, early transplantation in disease course and the use of unmanipulated grafts (47).

Krishnamurthy and colleagues reported a smaller retrospective study of 18 patients, majority of who had received RIC (17 patients), with T-cell depletion (48). In their cohort, the 3-year overall survival and NRM were both 31% with a relapse rate of 47% (48). A large retrospective study analyzed 283 CMML patients from the European Bone Marrow Transplantation (EBMT) database and evaluated factors that affected patient outcomes(49). The NRM overall was 37%, reportedly lower in those transplanted after 2002 and who had a peripheral blood stem cell transplant (P=0.015 and 0.023 respectively)(49). There were no significant differences in OS and relapse-free survival (RFS) with regards to conditioning regimen used, type of the donor/stem cell source, or the use of T-cell depletion (49). This group observed that most patients (61%) died of transplant related complications, and 32% were related to the underlying disease (Table 2).

The Fred Hutchinson Cancer Research Center initially reported results of 21 patients with CMML treated with myeloablative conditioning, predominantly TBI-based(50). This group reported a DFS of 39% at 3 years and relapse rate of only 25%. The probability of survival was improved if patients were transplanted earlier in course of their disease (50). The same group updated results and reported long term outcomes on 85 patients with CMML (51). They observed a DFS of 40% at 10 years, with median time to relapse of 183 days. The non-relapse mortality was 33% at 2 years and 34% 10 years post-transplant. The probability of disease progression was only 24% at 2 years and 27% at 10 years. Predictors of better RFS were good-risk cytogenetic category, low comorbidity index, high pre-transplant hematocrit and lower age. Although grades 3–4 acute GVHD occurred in 21 patients (26%), and chronic GVHD in 37 patients (44%) at 2 years, only 2 patients died as a result of GVHD (51). Encouraging, conditioning with targeted busulfan was associated with better outcomes, although this was not statistical significant.

We reported outcomes of patients with CMML treated at our institution. A total of 279 patients were evaluated with 9% of patients undergoing an ASCT (52). We have found that the patients who received an allogeneic transplant survived longer with overall survival at 2 and 5 years of 40.5%, and 24.3% respectively, compared to 34.3% and 8.9% for patients

who did not receive a transplant. Predictors of worse outcomes after transplant were the presence of splenomegaly, poor-risk cytogenetics and a high IPSS score of ≥ 1.5. Preliminary analysis of the first 83 patients treated with allogeneic transplantation at MD Anderson Cancer Center, showed, in multivariate analysis, that factors significantly associated with better survival were the use of a matched related donor and the development of cGVHD, while severe grade 3–4 aGVHD and ≥20% blasts at transplant negatively impacted outcomes. In our analysis, cytogenetic risk category did not have a significant impact on transplant outcomes (unpublished data).

In summary, while allogeneic transplantation remains the only treatment modality which ensures long-term survival for patients with CMML, results are far from optimal. It appears that persistent high treatment-related mortality (although improved over the past years) and higher relapse rates remain important limitations. Available data suggests that myeloablative conditioning, probably busulfan-based, and early transplantation is likely needed to successfully treat this disease. Novel approaches which will minimize treatment-related mortality are needed for these patients.

Polycythemia Vera/Essential Thrombocythemia

PV and ET are relatively indolent myeloproliferative diseases which usually have a prolonged course spanning many years, as patients do well on multiple treatment modalities such as phlebotomy, hydroxyurea and more recently on JAK2 inhibitors. Up to 95% of patients with PV harbor the JAK2V617F compared with approximately half the patients with ET (24, 53). Despite their relatively long course, these diseases have the ability to potentially transform into myelofibrosis and acute myeloid leukemia, making them candidate diseases for allogeneic transplantation. Patients with PV or ET transformed to MF may have better outcomes than those with primary/idiopathic MF (54, 55). There are very few reports on the use of HPCT for advanced PV or ET. Platzbecker et al. reported transplant outcomes for 25 patients with PV (n=12) and ET (n=13) (55). Approximately two thirds of patients were alive after a median follow-up of 57 months. The median duration of disease was 150 months in patients who survived versus 252 months is those who died, which suggested, again, that increase in the interval from diagnosis to transplant was associated with an increased risk of dying (HR = 1.87)(55).

Another study reported transplant outcomes for patients with post-ET (n=18), and post-PV (n=12) myelofibrosis and other MPNs (56). This group showed that patients with post-PV, and post-ET MF had a significantly lower rate of treatment-related mortality and higher probability of survival compared to patients with other MPNs (P=0.03) (56).

A large retrospective CIBMTR analysis confirmed these very good outcomes and analyzed 117 patients who received an allogeneic transplantation for advanced PV and ET between 1990 – 2007 (57). This study also included patients whose disease had transformed to myelofibrosis; however, 52% of ET and 50% of PV patients did not have transformed disease. Most patients received MA conditioning (n=80), while a subgroup received RIC and non-myeloablative transplants (n=37). The 1-year and 5-year OS for ET were 69% and 55%, respectively, while for PV were both 71%. The treatment-related mortality at 100 days for

patients with ET and PV was 16% and 22%, respectively. The most common causes of death were organ toxicity (50% for ET and 38% for PV patients). Relapse rates at 1-year for the ET and PV patients were only 11% and 25%, respectively (57).

In summary, transplantation for advanced PV and ET is feasible and should probably be performed with a reduced-intensity conditioning regimen before leukemic transformation, “spent phase” or major organ dysfunction is encountered.

Conclusions and Future Directions

Although allogeneic hematopoietic progenitor cell transplantation remains the only curative option for patients with myeloproliferative diseases, and, despite improvement in outcomes due to advancements in HLA-typing, management peri-transplant infectious complications, immunosuppression and GVHD prevention and therapy, this procedure is still fraught with significant morbidity and mortality, especially in older patients with advanced disease. Thus the decision to proceed with an allogeneic stem cell transplant should be individualized and a more rigorous selection of candidates for transplant is required. It is important to stratify patients and take into consideration existing data for each specific disease, patient’s treatment goals, and expected quality of life when making the recommendation to proceed with an allogeneic stem cell transplant in an individual with a myeloproliferative neoplasm. While CML patients are younger and would tolerate more intense conditioning, patients with myelofibrosis are older and transplantation using a fully intense myeloablative conditioning is associated with unacceptable treatment-related mortality. For these patients, reduced-intensity conditioning appears to be better tolerated; however, the least toxic conditioning which achieves elimination of the disease to ensure optimal long-term outcomes remains to be determined. Transplantation in the early stages of the disease, before significant organ damage and certainly before transformation to acute leukemia is important, as a more advanced disease is associated, in general, with increase toxicity, higher treatment-related mortality and worse outcomes.

For patients with myelofibrosis, treatment with JAK2 inhibitors prior to transplant may ameliorate splenomegaly and improve patient’s performance status, while maintenance post transplant for CML with TKIs and with JAK2 inhibitors for MF should be investigated in an attempt to prevent disease relapse post-transplant.

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Key points

- A differential approach should be undertaken for patients with different MPNs requiring allogeneic transplantation
- Busulfan-based conditioning appears to be associated with improved transplant outcomes for patients with MPNs
- Patients with myelofibrosis are older and benefit from the reduced-intensity conditioning while patients with CML and CMML may require more intense (myeloablative) conditioning
- Patients with advanced PV/ET have better outcomes and should be considered for transplantation before progression to acute leukemia or advanced phases of the disease
- For patients with known mutations, novel targeted approaches to decrease disease burden prior transplant and prevent disease relapse post-transplant are warranted

Table 1:

Current indications for allogeneic hematopoietic stem cell transplantation for myeloproliferative neoplasms.

Disease	Prognostic Factors	Scoring System	Median Survival (mo)	Indications for Transplantation	Comments
Myelofibrosis					
Lille	Hb < 10 g/dL WBC < 4 or >30×10^9/L	0 Low 1 Intermediate 2 High	93 26 13	Score ≥ 1	
Dupriez	Hb < 10 g/dL WBC 4 or >30×10^9/L Thrombocytopenia < 100 × 10^9/L	0-1 Low 2-3 High	176 33	Score ≥ 2	
Mayo PSS	Hb < 10 g/dL WBC 4 or >30×10^9/L Thrombocytopenia < 100 × 10^9/L Monocytosis > 1 × 10^9/L	0 LOW 1 Intermediate ≥2 High	173 61 26	Score ≥ 1	
IPSS	Age > 65 Hb < 10 g/dL WBC >25×10^9/L Circulating blasts >1% Constitutional symptoms present	0 Low 1 Intermediate-1 2 Intermediate-2 ≥3 High	11.3 7.9 4 2.3	Score ≥ 2	Used at diagnosis
Dynamic IPSS	Age > 65 Hb < 10 g/dL WBC >25×10^9/L Circulating blasts >1% Constitutional symptoms present	0 LOW 1-2 Intermediate-1 3-4 Intermediated-2 5-6 High	NR 14.2 4 1.5	Score ≥ 3	Used throughout disease course. Hb< 10g/dl is given 2 points
DIPSS plus[#]	**DIPSS + Red cell transfusion need Thrombocytopenia < 100 × 10^9/L Unfavorable karyotype**	**0 LOW 1 Intermediate-1 2-3 Intermediate-2 >4 High**	**15.4 6.9 2.9 1.3**	**Score ≥ 2 (≥1 should be considered as survival very poor)**	**Unfavorable karyotype − complex, 1 or 2 abnormalities that include +8,7q-, 5q-, 11q23, 12p-, 17q, inv(3), monosomal karyotype**
CML	**Progression to AP/BP Intolerance to TKIs Resistant mutations Failure to respond or loss of response to TKIs**	**N/A**		**Progression to AP/BP Intolerance to TKIs Resistant mutations Failure to respond or loss of response to TKI BCR-ABL negative CML**	**Presence of any of these factors**
CMML					
Modified Bournemouth	Hgb<10g/dL ANC<2500/>16000 PLT<100,000 BM blasts>5%	0-1 Low 2-4 High	32 8.9	Score ≥ 1	
CMML-specific cytogenetic risk	Normal; loss of Y All other +8, CRS 7 abn., complex	Low Intermediate High	37 18 11	Intermediate or high-risk	
MDAPS	**Hgb<12g/dL ALC>2.5×10^9/L PB IMCs>0% BM Blasts>10%**	**0-1 Low 2 Intermediate-1 3 Intermediate-2 4 High**	**24 15 8 5**	**Transplant should be considered in all patients**	**Median survival 12 mo for the whole group**
PV/ET	**N/A**	**N/A**		**Progression to AP/BP**	

Disease	Prognostic Factors	Scoring System	Median Survival (mo)	Indications for Transplantation	Comments
				Progression to SMF Advance disease (“spent phase”)	

MF – myelofibrosis; CML – chronic myeloid leukemia; CMML – chronic myelomonocytic leukemia; PV – polycythemia vera; ET – essential thrombocythemia; AP – accelerated phase; BP – blast phase; N/A – not applicable; TKI – tyrosine kinase inhibitors; IPSS- international prognostic scoring system; SMF – secondary myelofibrosis; MDAPS – MD Anderson Prognostic Score; Hgb – hemoglobin; ALC – absolute lymphocyte count; ANC – absolute neutrophil count; PLT –platelet count; PB – peripheral blood; BM – bone marrow; IMCs – immature myeloid cells; abn. - abnormalities.

Table 2.

Selected studies evaluating outcomes of MPNs after allogeneic hematopoietic stem cell transplantation.

DX	N	Median age (yrs)	Disease stage	Disease at SCT	Graft source/ Donor	Regimen intensity	Conditioning type	TRM	RR	OS/PFS	Ref #
CML	47	44	CP, AP/BP	66% AP/BP	49% MRD	RIC 68%	NR	13%@2yrs	38%	EPS 67% MA, 35%RIC at 2 yrs EPS 36% with, 58% without mutations at 2 yrs	14
	64	46	CP, AP/BP	33% CP	6l% MRD +MUD	NR	NR	18.2%@1yr in CP	NR	OS 56%, 67% and 30% for CP. AP and BP at 2 yrs	16
	63	40	BP	100% CP2	94% MRD +MUD	MA 66%	NR	23.8%	22%	OS 55% myelod BP, 39% lymphoid BP at 3 yrs	19*
	93	29	CP, AP. BP	70% CP 30% AP +BP	100% HAPLO; 100% 8M+P8	MA 100%	BuCy 100%	20.7% at 2 years	3.3% CP; 31.5% AP/BP at 4 years	DFS 76% CP1;85.7% CP2; 73% AP; 61.5% BP at 4yrs	20
MF	289	45-MRD 49-MUD	CP, AP	NR	56% MRD; 35% MUD BM 63%	MA 79.2% (BuCy 53%)	Multiple	MRD-24%, 38% at 1 and 5 yrs MUD-43%,50% at 1 and 5yrs	35% at 5yrs MRD 38% Sat 5yrs MUD	DFS 33% MRD, 27% MUD at 5 yrs DFS 39% at 3 yrs tor RIC	32
	103	55	CP, AP	NR	68% MUD: PB 96%	RIC	Bu 10mg/kg	16% at 1 yr	22% at 5 years	DFS 51% at 5 yrs	33
	46	58	NR	NR	50% MUD; 4l % MRD	RIC	Bu 100%	37% at 3yrs	37% at 3 yrs	OS 69% and DFS 50% at 3 yrs	37*
	14	55	BP	43% CP	57% MRD; 7l % PB	RIC 64%	Flu/Mel 64%	29% at 2 yrs	23% at 2 yrs	DFS 49% at 2 yrs; 33% at last f/u	39
	17	57	BP	100% CP	70% MRD; 82% PB	RIC 53%	NR	41%	33%	OS 47% at 2 yrs; DFS 29.4% at 4 yrs	40
CMML	50	44	N/A	76%CMML-1	76% MRD; 80% BM	NR	TBI 52%	35% at 1yr; 55% at 5 yrs	42% at 2 yrs	OS 21%, DFS 18% at 5 yrs	46
	85	52	N/A	57%CMML-1	46% MUD;62% PB	MA 82%	Bu-48%	33% at 2yrs	24% at 2yrs	PFS 38% at 10 yrs;	50
PV/ET	25	43	CP; 28% AML	16% AML	48% MRD; 32% MUD 76% BM	MA96%	BuCy 46%	36%	8%	OS 64% and DFS 56% at 4.7 yrs; BvCy 13/14 (93%) survived at last f/u	54
	117	50	NR	NR	70% MUD: PB 63%	MA68%	Bu 72% ET	27% for ET at 1 yr	13% for ET at 5yrs	PFS 62% and 47% at 1 and 5 yrs for ET	56

							Bu 74% PV	22% for PV at 1 yr	30% for PV at 5 yrs	PFS 54% and 48% st 1 and 5 yrs for PV	

*Abstracts

DX – diagnosis; CML – chronic myeloid leukemia, MF – myelofibrosis; CMML – chronic myelomonocytic leukemia; PV/ET – polycythemia vera, ET – essential thrombocythemia; NR – not reported; N/A – not applicable; CP – chronic phase; AP – accelerated phase; BP – blast phase; MRD – matched related donor; MUD – matched unrelated donor; HAPLO – haploidentical; SCT – stem cell transplant; MA – myeloablative; RIC – reduced-intensity conditioning; Bu – busulfan; Cy – cyclophosphamide; Flu – fludarabine; Mel – melphalan; TBI – total body irradiation; BM – bone marrow; PB – peripheral blood; EFS – event-free surviva; DFS – disease-free survival; OS – overall survival; f/u – follow-up