Current status of hematopoietic stem cell transplant in chronic myeloid leukemia

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ABSTRACT

Indications for hematopoietic stem cell transplant (HSCT) in chronic myeloid leukemia (CML) have changed over time. This change has largely been influenced by the advent of tyrosine kinase inhibitors, increased understanding of the mechanisms underlying disease phase progression as well as drug resistance, refinement of transplant techniques and exploitation of graft versus leukemia effect in this disease. Here, we have discussed the status of HSCT in CML in the present era with regards to the current indications, factors determining outcome and management strategies for posttransplant relapse.

Key words: *Chronic myeloid leukemia, hematopoietic stem cell transplant, posttransplant relapse*

INTRODUCTION

Over last three decades, the role of hematopoietic stem cell transplant (HSCT) in chronic myeloid leukemia (CML) has seen several phases and continues to be defined. In 1980's, HSCT came as a revolutionary concept that offered cure from CML.[1] In 1990's, transplant methodologies were refined, which resulted in increased cure rates and decreased transplant-related mortality. Survival outcomes improved significantly in chronic phase patients with 3 years survival rate of more than 80%.[2] Allogeneic HSCT, thus became treatment of choice in CML. Thirty years later, it is still the only treatment that offers cure in CML. The ability of allogeneic HSCT to cure CML is related to the antileukemic effects of both the conditioning regimen and the graft versus leukemia (GVL) effect of the donor lymphocytes. However, with the advent of imatinib in early 2000's the natural history of CML was changed and so did the way we treated CML.[3] With the excellent response rates and minimal toxicity imatinib soon became the treatment of choice for chronic phase CML, and it was thought that HSCT was no longer needed at least in chronic phase.[4,5] However, as our experience with imatinib increased, issues of resistance/intolerance in chronic phase emerged. At 18 months of treatment, imatinib resistance was seen in 15% of chronic phase patients.[6] Also, the treatment of advanced phase disease (accelerated and blast phases) with imatinib proved to be inadequate.[7] Second-generation tyrosine kinase inhibitors (TKIs) including dasatinib and nilotinib were able to achieve <50% complete cytogenetic response (CCyR) in imatinib resistant/intolerant cases.[8] Thus, transplantation still has a definite, though more limited, role in the treatment of CML.

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CURRENT INDICATIONS OF HEMATOPOIETIC STEM CELL TRANSPLANT IN CHRONIC MYELOID LEUKEMIA

In advanced phase disease, treatment with TKIs can achieve initial good response (second chronic phase). However, such responses are usually short lived and do not appear to be associated with long-term survival.[9,10] In one study, the rate of major CyR and CCyR in accelerated phase patients treated with imatinib at 600 mg/day was only 24% and 17%, respectively.[9] In another analysis of three phase II studies of CML patients in blast crisis treated with 600 mg/day imatinib, at 36 months only 7% were disease free and only 14% were alive.[11] Allogeneic HSCT is the treatment of choice in such cases. However, it would be prudent to start the patient on a TKI for two reasons. First, it tides over the time period required to find human leukocyte antigen (HLA) matched unrelated donor if HLA-matched sibling is not available. Second, cure rates in advanced phase disease are better if transplanted in second chronic phase.[12]

Among patients in chronic phase treated with imatinib as first line TKI therapy, approximately 20% will fail primary therapy, either from intolerance, relapse or progression to advanced phase disease.[6,13] It is reasonable to consider

HSCT at the time of first-line failure. However, secondary TKI therapy should be started at the time of resistance for two reasons-first, a CCyR on secondary therapy is achieved in approximately 50% patients[14] second, a donor search may take months. Patients who relapse with a T315I mutation should proceed to transplant at the earliest, given the low-response rate to secondary therapy. Similarly, those who have a mutation within the P loop region, which is known to be associated with an increased risk of progression to advance phase disease, transplant is a reasonable option.

Thus, current indications for transplant in CML include [Figure 1]:

1. Advanced phase disease (accelerated phase and blast crisis)
2. Resistance/intolerance to TKIs
3. Relapse on TKIs.

FACTORS DETERMINING OUTCOME FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT IN CHRONIC MYELOID LEUKEMIA

Several factors influence the outcome of allogeneic HSCT in CML, most importantly the phase of the disease,[15,16] but also, the type of donor used,[17,18] the nature of the stem cell product,[19-21] and the age of the patient.[1,22] The European Group for Blood and Marrow Transplantation (EBMT) devised a risk score based on five separate characteristics, which predicted treatment-related mortality and 5 years overall survival following allogeneic hematopoietic cell transplantation.[23] This system uses HLA matching, stage, age, sex of donor/recipient and time from diagnosis to transplant as risk factors. Survival at 5 years varied from 72% for the best score to 22% for the worst score. The EBMT risk score was later validated using separate data from the International Bone Marrow Transplant Registry.[24] However, the value of this prognostic scoring system is largely for prognostication rather than decision-making.

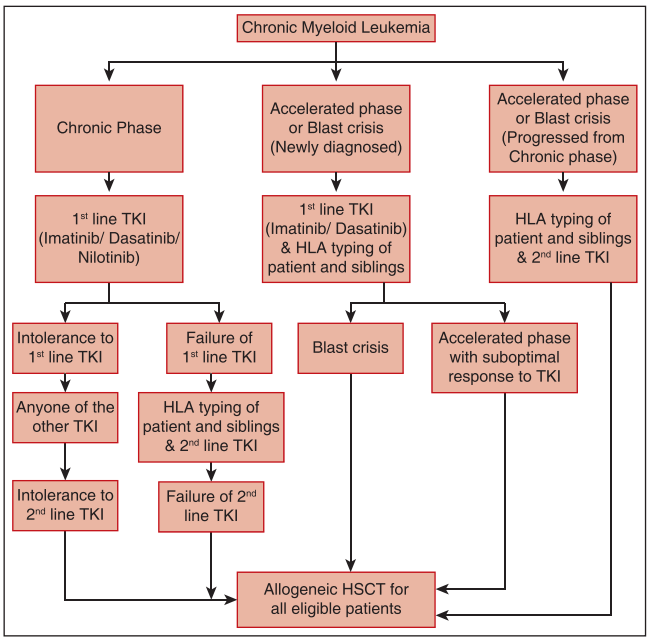

Figure 1: Algorithm for consideration of hematopoietic stem cell transplant in chronic myeloid leukemia

As mentioned, the most important prognostic factor for survival posttransplant is disease phase. Five years disease-free survival varies from 90% in chronic phase to 40-50% in accelerated phase to 10-20% in blast crisis.[15,16] Outcome of patients in blast crisis who achieve a second chronic phase with TKI therapy is similar to that of patients in accelerated phase. Advances in HLA typing and graft versus host disease (GVHD) therapy has improved transplant outcomes in CML.[17] Results with a fully matched unrelated donor are quite similar to that achieved with a matched-related donor.[18] Bone marrow harvest has been replaced by peripheral blood mobilization for stem cell collection making the procedure more donor compliant. Two randomized trials involving patients with various hematologic malignancies, including CML, concluded that use of granulocyte colony-stimulating factor mobilized peripheral blood stem cells lead to faster myeloid and platelet recovery, no significant difference in acute or chronic GVHD and an overall survival advantage compared with bone marrow.[19,20] However, another study in chronic phase CML showed no significant difference in the outcome between the bone marrow and peripheral blood groups.[21] In earlier studies, younger age has been shown to improve survival after HSCT in CML,[1] however, better supportive care, better donor selection and use of reduced intensity conditioning regimens have dampened the effect of age on survival outcome.[22] Some studies had suggested that increased interval from diagnosis to transplant was associated with a worse transplant outcome, higher relapse rate and an increase in nonrelapse mortality.[17,25] This was attributed to the development of resistant clones associated with a longer delay to transplantation. Another factor implicated in affecting outcome in earlier studies was the use of prior imatinib, which was shown to be associated with an increase in regimen-related toxicity and mortality, especially from hepatic causes.[26] However, larger studies have shown that there is no deleterious effect of the pretransplant imatinib on outcome.[27] Furthermore, patients with Abl mutations have similar outcomes compared with those with no mutations following transplantation.

POST-TRANSPLANT RELAPSE

On average 5-20% of the chronic phase patients and 30-60% of advanced phase patients relapse following allo-HSCT.[28] Increased incidence of relapse is seen with HSCT strategies involving T-cell depletion and use of reduced intensity conditioning regimens.[29] Careful monitoring of minimal residual disease should be done to prevent disease relapse posttransplant. An increasing level of BCR-Abl transcript measured by quantitative polymerase chain reaction is predictive of impending disease relapse and needs intervention. Modalities available to prevent and/or treat posttransplant relapse include donor lymphocyte infusion (DLI) therapy, TKI therapy, interferon therapy and infusion of *in vitro* stimulated $CD8^+$ T cells.[30-32] DLI have been very effective (70-90% complete remission rate) for patients who relapse with chronic phase.[33,34] The efficacy of DLI is the result of GVL effect which is highly pronounced in CML. However, the drawbacks of DLI are (1) advanced phases of the disease are least responsive to DLIs, (2) effect of DLI may last for few months and repeat DLI may be required and (3) it may be complicated by life-threatening GVHD. TKI therapy with imatinib is highly effective in treatment of posttransplant relapse.[28,30] In a study of 28 CML patients who were treated with imatinib for posttransplant relapse, 74% and 35% patients achieved complete hematological remission and CCyR, respectively.[28] Longer follow-up of similar patients had shown that these responses are quite durable.[35] Response rates are higher in patients who relapse in chronic phase compared to those who relapse in advanced phase disease.[28] Furthermore, there is some evidence that imatinb maintenance therapy posttransplant is effective in preventing relapse in high-risk cases.[36]

CONCLUSION

Allogeneic HSCT remains the only curative treatment for CML. However, considering the morbidity and mortality associated with HSCT and efficacy and favorable toxicity profile of TKIs, CML chronic phase patients should be initially treated with TKI. For patients with advanced phase disease and those with chronic phase disease who are resistant or intolerant to TKI or relapse on TKI, HSCT is the treatment of choice.

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