Abstract

The treatment strategies for chronic myeloid leukemia have changed dramatically with the advent of tyrosine kinase inhibitors. Since they provide an excellent opportunity for complete cytogenetic and molecular remissions, they are recommended as a first line therapy. Although a small fraction of patients has been reported to remain in molecular remissions after discontinuing of tyrosine kinase inhibitors, there is an increased likelihood of disease relapse after these drugs are discontinued. Therefore, allogeneic stem cell transplantation remains the only cure at present. However, toxicity of preparative regimens, development of graft versus host disease, infectious complications, and increased rates of relapse in advanced phases of the disease limit the safety and efficacy of this approach. This review highlights the major limitations of transplantation and the areas of studies required to improve the clinical outcomes.

Keywords: Allogeneic stem cells transplantation; Chronic myeloid leukemia; Tyrosine kinase inhibitors

Abbreviations: Chronic Myeloid Leukemia (CML); Chronic Phase (CP); Tyrosine Kinase Inhibitor (TKI); Accelerated Phase (AP); Blast Phase (BP); Allogeneic Stem Cells Transplantation (allo-SCT); Stem Cells Transplantation (SCT); Disease Free Survival (DFS); Human Leukocyte Antigen (HLA); First Generation TKIs (1G- TKIs; Second Generation TKIs (2G- TKIs); Graft Versus Host Disease (GVHD); T Cell Depletion (TCD); Disease Relapse (DR); Graft Versus Leukemia (GVL); Reduced Intensity Conditioning (RIC); Donor Lymphocyte Infusions (DLIs)

Introduction

Chronic Myeloid Leukemia (CML) is a hematological malignancy that arises from hematopoietic stem cells with abnormal BCR/ABL gene [1-4]. This oncogene is formed as a consequence of a reciprocal translocation between chromosomes 9 and 22, giving rise to the Philadelphia chromosome with abnormally high ABL1 kinase activity [5]. The gene is first acquired in a single primitive hematopoietic stem cell, after which it is called CML stem cell or leukemia stem cell. This stem cell proliferates with abnormal differentiation potential leading to uncontrolled expansion of seemingly normal myeloid cells [6].

1-2 CML cases per 100,000 population are reported each year. The disease is rare in children, and the median age of onset is 50-60 years. Common symptoms include fatigue, anemia, splenomegaly, weight loss without dietary changes, and sweats. However, 50% of the individuals in the developed countries do not experience any symptoms, and the disease is discovered when blood tests are performed for other medical reasons [3].

Chronic Phase (CP) is the early phase of the disease which is treated with imatinib mesylate, a Tyrosine Kinase Inhibitor (TKI) as a first line therapy [7,8]. The phase later progresses to a second; Accelerated Phase (AP) during which patients may respond to treatments for some months or even years [3]. The malignancy becomes very aggressive in the Blast Phase (BP) during which almost all of the treatment strategies fail [1,4]. Median survival at this stage is 6 months [3].

TKIs provide an opportunity for complete cytogenetic and molecular remissions. Although a small fraction of patients has been reported to remain in sustained molecular remissions after discontinuing TKIs [9-12], there is an increased likelihood of disease relapse after these drugs are discontinued [9,13-15]. A mathematical model based estimation by Horn et al. [11] predicts that 69% of the patients would relapse after stopping TKIs. This is due to the fact that these drugs do not eliminate the Philadelphia positive CML stem cells [9,13-20]. Moreover, TKI resistant BCR/ABL mutations are associated with a greater likelihood of disease progression [21]. A CML stem cell could also shift to a normal kinase pathway rather than BCR/ABL for its survival [13].

Therefore, allogeneic Stem Cell Transplantation (allo-SCT) remains the only cure at present [1,22-25]. However, it is associated with considerable rates of morbidity and mortality. New strategies involving the combination of TKIs with transplantation have provided opportunities to control relapse following allo-SCT [3,26-31], overcome chronic graft versus host disease [32-35], and to induce second chronic phase in the patients with advanced disease stages prior to transplantation [26,36].

This review focuses on the outcomes, risks and complications associated with allo-SCT and the areas of studies required to develop strategies for better prophylaxis.

Imatinib Failure and Second Generation TKIs

The patients who fail to respond to imatinib or become intolerant to this drug are switched to second generation TKIs (2G- TKIs; nilotinib, etc.).

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dasatinib, bosutinib) [12]. However, they also have been approved for treatment in a first line setting in the United States, Europe and Japan [37]. 2G- TKIs (nilotinib, dasatinib, bosutinib) have been reported to be more potent BCR/ABL inhibitors than imatinib [37,38]. This has been demonstrated an open multicenter study by Saglio et al. [38]. The rates of major molecular response for nilotinib (in a first line setting) and imatinib were determined in 846 patients. The major molecular response rates at 12 months were significantly higher in the nilotinib group (43%) than in the imatinib group (22%). 93% of the patients achieved complete cytogenetic remission with nilotinib, while 76% of the patients could achieve it with imatinib. Moreover, 4% of the patients in the imatinib group progressed to advanced phases of the disease while less than 1% of the patients in the nilotinib group progressed to accelerated/blast phase [38].

Similarly, bosutinib has been reported to induce significantly higher molecular remissions (47%), compared with imatinib (33%) [39].

In another study by Kantarjian et al. [40] the cumulative rates of complete cytogenetic and molecular remissions at 12 months were significantly higher for the patients receiving dasatinib (46%), compared with imatinib (28%). The time period to achieve remissions was significantly shorter with dasatinib, compared with imatinib. Moreover, 1.9% of the patients progressed to advanced stages of the disease with dasatinib, while 3.5% progressed to CML-AP/BP with imatinib.

Despite the effectiveness of 2G-TKIs, secondary resistance to these drugs is often seen in the patients who initially fail imatinib [12]. Rate of complete cytogenetic remission is only 40-50% in the patients who switch to 2G-TKIs after imatinib failure, and some of these patients may also lose their response to 2G-TKIs [41]. In 2007, Kantarjian et al. [42] evaluated the response rates of 318 CML-CP patients with nilotinib after resistance/intolerance to imatinib. At 6 months, 31% of the patients could achieve complete cytogenetic remission. Moreover, patients with BCR/ABL kinase domain mutations had lower cytogenetic response rates (23%) than the patients who did not harbor mutations (35%). In a 24 months follow up of this study [43] only 41% of the imatinib resistant patients could achieve complete cytogenetic remission, and merely 28% of the imatinib resistant/intolerant patients achieved major molecular response with nilotinib.

Hochhaus et al. [44] described the outcomes of 186 CML-CP patients with dasatinib in a second line setting after imatinib failure. The rate of complete cytogenetic remission at 8 months was only 39%. In another study, Talpaz et al. [45] reported the response rates of 40 CML-CP, and 44 advanced phase patients with dasatinib after imatinib resistance/intolerance. The cumulative complete cytogenetic response rate was merely 30% at 8 months. Moreover, the responses were not durable in CML-CP/BP patients. Guilhot et al. [46] reported the outcomes of 107 CML-AP/BP patients with dasatinib after imatinib failure. Only 24% of the patients could achieve complete cytogenetic remission at 8 months.

Cortes et al. [47] demonstrated the response rates of 288 CML-CP imatinib resistant/intolerant patients with bosutinib. At a median follow up of 24 months, only 41% of the patients could achieve complete cytogenetic remission.

In a study by Garg et al. [41] the outcomes of 2-G TKIs in a third line setting were evaluated after failure of two TKIs (imatinib, dasatinib/ imatinib, nilotinib). Cytogenetic and molecular response rates of only 33% and 15% respectively, were observed in the patients who received a third line TKI (nilotinib/dasatinib) after failure of two prior TKIs. Out of 48 patients involved in the study, only 3 (all of three in CML-CP) could sustain cytogenetic response for more than 12 months [48].

The decreased effectiveness of 2G-TKIs in imatinib resistant patients, and the lack of durable responses can be attributed to the emergence of new BCR/ABL kinase domain mutations as the patients are exposed to 1G and 2G-TKIs [41]. Some of these mutations are highly sensitive to 2G-TKIs while others are less sensitive to these agents [48-51]. 2G-TKI resistant BCR/ABL kinase domain mutations lead to an increased risk of progression to advanced stages of the disease [49-53]. CML-AP/BP patients have worse outcomes even with 2G-TKIs and the responses are not durable [54]. Such patients should therefore, be considered for allo-SCT [41,48].

**Allo-SCT in TKI Era**

One of the major downsides of TKIs is that allo-SCT is recommended only when patients develop resistance or intolerance to these drugs. As a result high risk patients with co-morbidities, and advanced CML are referred for transplantation. This leads to increased rates of relapse, and transplant related mortality [54]. Approximately 10-20% of the patients die as a result of treatment related toxicity, and GVHD occurs in almost half of the patients who undergo transplantation [52].

The probability of remaining in complete cytogenetic remission for five years with imatinib is 60-65% [55,56], which declines to 40-45% when the patients are switched to 2G-TKIs after imatinib resistance or intolerance [26,41]. Therefore, allo-SCT should always be considered for such patients, and donor search should immediately begin in order to avoid delay that could result in fatal progression of the disease. An ideal donor is Human Leukocyte Antigen (HLA) matched sibling [57,58]. Since the probability of having such a donor is only 25-30% [58], HLA- mismatched/haploidentical related donor allografts are used. But this approach is associated with increased rates of fatal Graft Versus Host Disease (GVHD), graft rejection, delayed immune reconstitution, and complications that arise with the strategies to overcome HLA barrier and relapse [59- 63].

**Impact of Disease Phase on Allo-SCT**

The effectiveness of allo-SCT in CML patients largely depends on the disease phase at the time of transplantation [22,26,64]. CML-CP patients benefit the most from transplantation, with a Disease Free Survival (DFS) rate of 80%, and overall survival rates of more than 80% [52,65]. However, CML advance phase patients have a very poor prognosis [52,66,67]. The overall survival and DFS rates for advanced phase patients are 50% and 40% respectively, which are almost half of those for chronic phase [68]. In a recent subgroup analysis of the German CML study IV by Saussele et al. the overall survival rate at three years for the patients who underwent transplantation in the chronic phase was 91%, while that for the patients in advanced phase was 59% [69].

Copelan et al. [70] demonstrated the allo-SCT outcomes of 335 CML patients. 229 of them were in CML-CP and 106 patients were in advanced phase at the time of transplantation. Overall survival rates were 70.5% for chronic, 38% for accelerated, and 16% for blast phase patients. At three years, DFS rates were 68.8%, 38%, and 13.6% for chronic, accelerated and blast phase patients respectively. Relapse rates at three years in advanced phase were higher (32.5%) than the patients who were in chronic phase (21.4%) at the time of allo-SCT [70].
Bacher et al. [71] analyzed transplantation outcomes of 716 CML patients. 66.7% of the patients were in first chronic phase while 21% were in advanced phase of the disease. 12.4% of the patients were in second or third chronic phase at the time of allo-SCT. The five year overall survival rates for chronic and advanced phase patients were 70% and 34% respectively [71].

Blast phase patients have even worse outcomes due to increased likelihood of relapse, and transplant related mortality [65]. It has been demonstrated that the overall transplantation survival rates for CML-BP patients are only 10-20% [72,73]. Nonetheless a better clinical outcome can be achieved with the induction of a second chronic phase [26]. This was demonstrated in a study by Visani et al. in 2000 [22], in which CML-BP patients were given fludarabine/ ara C regimen prior to allo-SCT. The strategy was successful in re-inducing chronic phase in CML-BP patients and contributed to an increased survival rate after the transplantation. Similarly, TKI administration prior to allo-SCT can result in a less advance disease phase, which can be beneficial for the accelerated or blast phase CML patients who are referred for transplantation [74]. For CML-BP patients who are able to achieve a second chronic phase (with TKIs for example), the transplantation outcomes are similar to the accelerated phase patients [65].

**GVHD and T Cell Depletions**

Poor engraftment and GVHD are mediated by donor T cells in HLA-mismatched allo-SCT [59]. T cell depletion (TCD) strategies were thus developed [75]. TCD/CD34+ stem cell selection followed by a mega dosage of CD34+ cells can overcome GVHD, but results in delayed immune reconstitution [26,63,76], non-relapse mortality rate of up to 57% due to toxicity and infectious complications [77]; with cytomegalovirus [78] and invasive fungal infections [79] being the most fatal ones. Hence, therapeutic regimens to control and manage post HLA-mismatched allo-SCT complications are required to make it a feasible approach. There is also a need for development and optimization of better TCD alternatives. One such study by Huang et al. in 2008 [58] described a HLA mismatched/haploidentitical allo-SCT strategy without in vitro TCD. A combination of Granulocyte Colony Stimulating Factor mobilized peripheral blood stem cells and Granulocyte Colony Stimulating Factor primed bone marrow was used for allo-SCT. The study was designed based on the observation that Granulocyte Colony Stimulating Factor in vivo recruited peripheral blood stem cells have ten times more T cells, and two to three times more CD34+ stem cells [80]. Also, bone marrow and peripheral blood stem cells mobilized in this manner lose some of their ability to induce acute GVHD and chronic GVHD [81,82]. The approach facilitated engraftment, faster immune reconstitution and reduced the probability of Disease Relapse (DR). Improved clinical outcomes were observed even for the patients with advanced phases of CML, with 4-years overall survival rates of 76.5%, 73.3%, and 61.5% in CP, AP, and BP respectively [58].

**TKIs and GVHD**

Imatinib mesylate has been investigated to overcome chronic GVHD [32,33]. It also has been demonstrated to induce immunomodulatory effect that can decrease the probability and severity of chronic GVHD [34]. This might be due to the fact that the drug inhibits the proliferation of T cells in vitro and blocks the platelet derived growth factor and transforming growth factor β pathways that lead to the development of chronic GVHD [35]. A retrospective study by Nakasone et al [34] demonstrated lower incidence and severity of chronic GVHD in the patients who did not receive T cell depleted grafts, and were administered imatinib for more than three months for controlling DR after transplantation. However, large multicenter prospective studies are required to confirm this observation. Whether 2G-TKIs have the same immunomodulatory effect also needs to be determined.

**Disease Relapse and Donor Lymphocyte Infusions**

Another major limitation of allo-SCT is DR due to which success rate of allo-SCT declines to 20-30% [83,84], 5-20% of the chronic phase patients relapse following allo-SCT while the rate is as high as 30-60% for the patients who are in advanced phase at the time of transplantation [85]. Moreover, recurrence can occur even years after transplantation [26]. This necessitates a careful monitoring of minimal residual disease to control DR related mortality. Increased incidences of DR are observed with SCT strategies involving TCD, decreased quantity of donor T cells in allografts, and Reduced Intensity Conditioning (RIC) regimens [86,87]. This can be attributed to the lack of a GVHD response that, despite of being associated with considerable morbidity and mortality, might play a role in facilitating GVL effect [56,57].

Donor Lymphocyte Infusions (DLIs) were developed to overcome DR, and have been very effective in CML patients [58,87-89]. Donor lymphocyte infusions have been very effective for the patients who relapse with CML-CP [88-90]. Complete remission rates of 70-90% have been observed in CML-CP relapsed patients even with incremental doses of DLIs [90]. The efficacy of DLI in inducing remissions is the result of GVL effect that is mediated by the donor lymphocytes against residual malignant cells of the host [91-93]. However, the outcome may only be seen several months after the infusions [90]. The approach is also not without risk since it can lead to severe GVHD [94]. The likelihood of life threatening GVHD is greater even if incremental doses of donor lymphocytes are infused within 12 months after allo-SCT [92,94-96]. Donor lymphocytes cannot also be infused if the original donor is unavailable or if the recipient develops severe GVHD. Moreover, advanced phases of the disease are least responsive to DLIs [91]. Therefore, there is a need for development of treatment strategies that reduce the probability of DR and eliminate or at least delay the need for DLIs [28].

**TKIs Following Allo-SCT for Relapse**

Post allo-SCT administration of both 1G and 2G-TKIs can also overcome DR and prolong disease free survival in CML-CP and AP patients [3,27,29]. Olavarria et al. [28] demonstrated improved outcomes of CML patients with imatinib administration post allo-SCT. 22 CML patients were involved in the study that underwent RIC regimen. They were subsequently treated with imatinib mesylate as a maintenance therapy. 21 patients completed it for one year during which DR did not occur and the drug was well tolerated. 15 patients relapsed following the discontinuation of imatinib who were then treated with DLIs, and 10 out of them achieved molecular remission. A similar finding was reported by Hayat et al. [30], in which CML-CP relapsed patients were treated with imatinib who underwent allo-SCT in pre-imatinib era. These studies suggest that imatinib can be used to minimize the risk of early relapse and improve clinical outcomes. Also, the use of imatinib is feasible both with and without DLIs in controlling CML-AP relapse [29]. However, wide scale prospective studies are required to compare the efficacy of these approaches. Since the outcome is poor for CML-BP patients, optimum time and dosage of both 1G and 2G-TKI therapy following allo-SCT need to be determined [29].

In the present TKI era, most of the patients have already been...
exposed to imatinib, and therefore, they may be unresponsive to its therapy for controlling DR after transplantation [29,30]. 2G-TKIs provide a hope for such patients. However, resistance to all TKIs which is mainly due to T315I mutation is a concern [97]. Newer strategies will be required to overcome DR in such cases. A novel approach to overcome DR was developed by Bornhäuser et al. [97] that involved the infusion of in vitro stimulated CD8+ T cells against leukemic peptide antigen following allo-PB SCT in four CML-CP/AP patients. None of the patients relapsed or developed GVHD. Three of them achieved molecular remission and retained it for more than three years of follow up. The study provided a hope to deal with DR for the patients who are resistant or intolerant to TKIs. However, large scale studies are required to confirm the safety and efficacy of this strategy.

Reduced Intensity Conditioning

The anti-leukemic effect of allo-SCT is ascribed to GVL and intense myeloablative preparative regimens [98]. Such regimens are high in toxicity and contraindicated in the co-morbid or intensely pre-treated patients, the elderly and young adults who wish to preserve fertility [99]. Hence less toxic, RIC/ non-myeloablative preparative regimens without total body irradiation are recommended for these patients [64,99-101]. These preparative strategies can also be used for the grafts that are low in CD34+ stem cells. Since RIC/ non-myeloablative strategies lead to faster immune reconstitution and reduce the duration of neutropenia, less infectious complications are observed following allo-SCT [64,80]. The risk of GVHD also declines due to the reduced secretion of pro-inflammatory cytokines [80]. However, the entire burden of leukemia eradication is shifted to GVL effect, which alone might not be enough to overcome the malignancy. [24,91,102-105]. Increased rates of relapse have been observed with RIC regimens [24,106]. Approximately 32-35% of the chronic phase RIC conditioned patients relapse following allo-SCT [24,106]. In an analysis of a Czech study by Faber et al. [106], it was reported that the relapse rate for RIC conditioned advanced phase CML patients was significantly higher (45%) than the patients who received myeloablative conditioning (0%).

Luo et al. [105] reported the transplantation outcomes of 28 CML-CP patients who underwent RIC regimen. 60.8% of the patients achieved major cytogenetic remission, and 32% relapsed within one year of allo-SCT. These relatively high relapse rates can be attributed to the use of fludarabine in reduced conditioning regimen, which has a limited anti- tumor effect [24]. Optimization of RIC regimens with low dosages of total body irradiation and 1G, 2G-TKI/ DLI combination strategies are thus required to effectively overcome/prevent relapse and ensure prolonged disease free survival.

Conclusion

Although allo-SCT still remains the only cure for CML, it is not without significant risks of morbidity and mortality. Time required for donor search, preparatory regimen related toxicity, advanced disease stages, delayed immune restoration, severe GVHD and DR are the major limitations in its safety and efficacy. Early donor search and transplantation, induction of chronic phase in patients with advanced disease stages prior to allo-SCT, less toxic preparative regimens, intensive supportive care, TCD alternatives, and optimized TKI and allo-SCT combination strategies can result in improved clinical outcomes. Large scale prospective studies are required for development and optimization of interventions that can benefit the patients with aggressive disease progression and TKI resistant BCR/ABL kinase domain mutations.

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