Journal of Carcinogenesis & Mutagenesis

ISSN: 2157-2518

Afreen and Safran, J Carcinogene Mutagene 2013, S14
DOI: 4172/2157-2518.S14-001

Review Article Open Access

Allogeneic Stem Cell Transplantation for Chronic Myeloid Leukemia in the Era of Tyrosine Kinase Inhibitors- What are the Limitations?

Sehar Afreen[1]* and Zakariya Al Safran[2]

[1]*Medical Imaging Department, King Fahad Specialist Hospital-Dammam, Dammam, Kingdom of Saudi Arabia*
[2]*King Fahad Specialist Hospital-Dammam, Dammam, Kingdom of Saudi Arabia*

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,

***Corresponding author:** Sehar Afreen, Research Assistant, Medical Imaging Department, King Fahad Specialist Hospital-Dammam, Dammam, Kingdom of Saudi Arabia, Tel: (+966) 5410 35255; Fax: (+966) 3 842 409; E-mail: seharafreen@yahoo.com or Afreen.Afreen@kfsh.med.sa

Received December 31, 2012; **Accepted** February 20, 2013; **Published** March 05, 2013

Citation: Afreen S, Safran ZA (2013) Allogeneic Stem Cell Transplantation for Chronic Myeloid Leukemia in the Era of Tyrosine Kinase Inhibitors- What are the Limitations? J Carcinogene Mutagene S14: 001. doi:10.4172/2157-2518.S14-001

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, dasanitib, 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] decsribed 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-BP patients. Guilhot et al. [46] reported the outcomes of 107 CML-AP 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/haploidentical 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-PBSCT 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. [24,91,99,102-105]. 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.

Acknowledgements

The authors are grateful to the Academic Affairs Training and Research administration of the King Fahad Specialist Hospital-Dammam (KFSH-D) for providing resources and funding for this manuscript. We also would like to thank the KFSH-D library staff for providing technical assistance in access to medical literature.

References

1. Calabretta B, Perrotti D (2004) The biology of CML blast crisis. Blood 103: 4010-4022.
2. Swords R, Alvarado Y, Cortes J, Giles FJ (2007) Second-generation tyrosine kinase inhibitors as therapy for chronic myeloid leukemia. Curr Hematol Malig Rep 2: 83-88.
3. Perrotti D, Jamieson C, Goldman J, Skorski T (2010) Chronic myeloid leukemia: mechanisms of blastic transformation. J Clin Invest 120: 2254-2264.
4. Zhu X, Song Y, Zhang H, An G (2010) Biological characteristics and regulatory effects of bone marrow mesenchymal stem cells on hematopoietic stem cells in patients with chronic myelocytic leukemia. CRTER 14: 8377-8381.
5. Cross NC, Daley GQ, Green AR, Hughes TP, Jamieson C, et al. (2008) BCR-ABL1-positive CML and BCR-ABL1-negative chronic myeloproliferative disorders: some common and contrasting features. Leukemia 22: 1975-1989.
6. Bruns I, Czibere A, Fischer JC, Roels F, Cadeddu RP, et al. (2009) The hematopoietic stem cell in chronic phase CML is characterized by a transcriptional profile resembling normal myeloid progenitor cells and reflecting loss of quiescence. Leukemia 23: 892-899.
7. Peggs K, Mackinnon S (2003) Imatinib mesylate--the new gold standard for treatment of chronic myeloid leukemia. N Engl J Med 348: 1048-1050.
8. Hochhaus A, O'Brien SG, Guilhot F, Druker BJ, Branford S, et al. (2009) Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. Leukemia 23: 1054-1061.
9. Chu S, McDonald T, Lin A, Chakraborty S, Huang Q, et al. (2011) Persistence of leukemia stem cells in chronic myelogenous leukemia patients in prolonged remission with imatinib treatment. Blood 118: 5565-5572.
10. Gado K, Matolcsy A, Csomor J, Kicsi D, Bodor C, et al. (2012) Long lasting complete molecular remission after suspending dasatinib treatment in chronic myeloid leukemia. Exp Hematol Oncol 1: 17-3619-1-17.
11. Horn M, Glauche I, Muller MC, Hehlmann R, Hochhaus A, et al. (2013) Model-based decision rules reduce the risk of molecular relapse after cessation of tyrosine kinase inhibitor therapy in chronic myeloid leukemia. Blood 121: 378-384.
12. Cortes J, Goldman JM, Hughes T (2012) Current issues in chronic myeloid leukemia: monitoring, resistance, and functional cure. J Natl Compr Canc Netw 10 Suppl 3: S1-S13.
13. Perl A, Carroll M (2011) BCR-ABL kinase is dead; long live the CML stem cell. J Clin Invest 121: 22-25.
14. Rohon P (2012) Biological therapy and the immune system in patients with chronic myeloid leukemia. Int J Hematol 96: 1-9.
15. Graham SM, Jørgensen HG, Allan E, Pearson C, Alcorn MJ, et al. (2002) Primitive, quiescent, Philadelphia-positive stem cells from patients with chronic myeloid leukemia are insensitive to STI571 in vitro. Blood 99: 319-325.
16. Holtz MS, Slovak ML, Zhang F, Sawyers CL, Forman SJ, et al. (2002) Imatinib mesylate (STI571) inhibits growth of primitive malignant progenitors in chronic myelogenous leukemia through reversal of abnormally increased proliferation. Blood 99: 3792-3800.
17. Copland M, Hamilton A, Elrick LJ, Baird JW, Allan EK, et al. (2006) Dasatinib (BMS-354825) targets an earlier progenitor population than imatinib in primary CML but does not eliminate the quiescent fraction. Blood 107: 4532-4539.
18. Jørgensen HG, Allan EK, Jordanides NE, Mountford JC, Holyoake TL (2007) Nilotinib exerts equipotent antiproliferative effects to imatinib and does not induce apoptosis in CD34+ CML cells. Blood 109: 4016-4019.
19. Konig H, Holtz M, Modi H, Manley P, Holyoake TL, et al. (2008) Enhanced BCR-ABL kinase inhibition does not result in increased inhibition of downstream signaling pathways or increased growth suppression in CML progenitors. Leukemia 22: 748-755.

20. Corbin AS, Agarwal A, Loriaux M, Cortes J, Deininger MW, et al. (2011) Human chronic myeloid leukemia stem cells are insensitive to imatinib despite inhibition of BCR-ABL activity. J Clin Invest 121: 396-409.

21. Soverini S, Martinelli G, Rosti G, Bassi S, Amabile M, et al. (2005) ABL mutations in late chronic phase chronic myeloid leukemia patients with up-front cytogenetic resistance to imatinib are associated with a greater likelihood of progression to blast crisis and shorter survival: a study by the GIMEMA Working Party on Chronic Myeloid Leukemia. J Clin Oncol 23: 4100-4109.

22. Visani G, Rosti G, Bandini G, Tosi P, Isidori A, et al. (2000) Second chronic phase before transplantation is crucial for improving survival of blastic phase chronic myeloid leukaemia. Br J Haematol 109: 722-728.

23. Radich JP, Gooley T, Bensinger W, Chauncey T, Clift R, et al. (2003) HLA-matched related hematopoietic cell transplantation for chronic-phase CML using a targeted busulfan and cyclophosphamide preparative regimen. Blood 102: 31-35.

24. Crawley C, Szydlo R, Lalancette M, Bacigalupo A, Lange A, et al. (2005) Outcomes of reduced-intensity transplantation for chronic myeloid leukemia: an analysis of prognostic factors from the Chronic Leukemia Working Party of the EBMT. Blood 106: 2969-2976.

25. Weisser M, Ledderose G, Jochem Kolb H (2007) Long-term follow-up of allogeneic HSCT for CML reveals significant improvement in the outcome over the last decade. Ann Hematol 86: 127-132.

26. Pavlu J, Szydlo RM, Goldman JM, Apperley JF (2011) Three decades of transplantation for chronic myeloid leukemia: what have we learned? Blood 117: 755-763.

27. Kröger N (2011) Approaches to relapse after allogeneic stem cell transplantation. Curr Opin Oncol 23: 203-208.

28. Olavarria E, Siddique S, Griffiths MJ, Avery S, Byrne JL, et al. (2007) Post transplantation imatinib as a strategy to postpone the requirement for immunotherapy in patients undergoing reduced-intensity allografts for chronic myeloid leukemia. Blood 110: 4614-4617.

29. Klyuchnikov E, Kröger N, Brummendorf TH, Wiedemann B, Zander AR, et al. (2010) Current status and perspectives of tyrosine kinase inhibitor treatment in the posttransplant period in patients with chronic myelogenous leukemia (CML). Biol Blood Marrow Transplant 16: 301-310.

30. Hayat A, McCann SR, Langabeer S, Irvine S, McMullin MF, et al. (2009) Effective use of imatinib-mesylate in the treatment of relapsed chronic myeloid leukemia after allogeneic transplantation. Haematologica 94: 296-298.

31. Savani BN, Montero A, Kurlander R, Childs R, Hensel N, et al. (2005) Imatinib synergizes with donor lymphocyte infusions to achieve rapid molecular remission of CML relapsing after allogeneic stem cell transplantation. Bone Marrow Transplant 36: 1009-1015.

32. Magro L, Mohty M, Catteau B, Coiteux V, Chevallier P, et al. (2009) Imatinib mesylate as salvage therapy for refractory sclerotic chronic graft-versus-host disease. Blood 114: 719-722.

33. Olivieri A, Locatelli F, Zecca M, Sanna A, Cimminiello M, et al. (2009) Imatinib for refractory chronic graft-versus-host disease with fibrotic features. Blood 114: 709-718.

34. Nakasone H, Kanda Y, Takasaki H, Nakaseko C, Sakura T, et al. (2010) Prophylactic impact of imatinib administration after allogeneic stem cell transplantation on the incidence and severity of chronic graft versus host disease in patients with Philadelphia chromosome-positive leukemia. Leukemia 24: 1236-1239.

35. Alho HS, Maasilta PK, Vainikka T, Salminen U (2007) Platelet-Derived Growth Factor, Transforming Growth Factor-?, And Connective Tissue Growth Factor In A Porcine Bronchial Model Of Obliterative Bronchiolitis. Exp Lung Res 33: 303-320.

36. Lee SJ, Kukreja M, Wang T, Giralt SA, Szer J, et al. (2008) Impact of prior imatinib mesylate on the outcome of hematopoietic cell transplantation for chronic myeloid leukemia. Blood 112: 3500-3507.

37. Ferdinand R, Mitchell SA, Batson S, Tumur I (2012) Treatments for chronic myeloid leukemia: a qualitative systematic review. J Blood Med 3: 51-76.

38. Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, et al. (2010) Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 362: 2251-2259.

39. Cortes JE, Kim DW, Kantarjian HM, Brümmendorf TH, Dyagil I, et al. (2012) Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. J Clin Oncol 30: 3486-3492.

40. Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, et al. (2010) Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 362: 2260-2270.

41. Garg RJ, Kantarjian H, O'Brien S, Quintás-Cardama A, Faderl S, et al. (2009) The use of nilotinib or dasatinib after failure to 2 prior tyrosine kinase inhibitors: long-term follow-up. Blood 114: 4361-4368.

42. Kantarjian HM, Giles F, Gattermann N, Bhalla K, Alimena G, et al. (2007) Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. Blood 110: 3540-3546.

43. Kantarjian HM, Giles FJ, Bhalla KN, Pinilla-Ibarz J, Larson RA, et al. (2011) Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results. Blood 117: 1141-1145.

44. Hochhaus A, Kantarjian HM, Baccarani M, Lipton JH, Apperley JF, et al. (2007) Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. Blood 109: 2303-2309.

45. Talpaz M, Shah NP, Kantarjian H, Donato N, Nicoll J, et al. (2006) Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. N Engl J Med 354: 2531-2541.

46. Guilhot F, Apperley J, Kim DW, Bullorsky EO, Baccarani M, et al. (2007) Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase. Blood 109: 4143-4150.

47. Cortes JE, Kantarjian HM, Brümmendorf TH, Kim DW, Turkina AG, et al. (2011) Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood 118: 4567-4576.

48. Jabbour E, Kantarjian H, O'Brien S, Shan J, Garcia-Manero G, et al. (2011) Predictive factors for outcome and response in patients treated with second-generation tyrosine kinase inhibitors for chronic myeloid leukemia in chronic phase after imatinib failure. Blood 117: 1822-1827.

49. Branford S, Melo JV, Hughes TP (2009) Selecting optimal second-line tyrosine kinase inhibitor therapy for chronic myeloid leukemia patients after imatinib failure: does the BCR-ABL mutation status really matter? Blood 114: 5426-5435.

50. O'Hare T, Eide CA, Deininger MW (2007) Bcr-Abl kinase domain mutations, drug resistance, and the road to a cure for chronic myeloid leukemia. Blood 110: 2242-2249.

51. Bradeen HA, Eide CA, O'Hare T, Johnson KJ, Willis SG, et al. (2006) Comparison of imatinib mesylate, dasatinib (BMS-354825), and nilotinib (AMN107) in an N-ethyl-N-nitrosourea (ENU)-based mutagenesis screen: high efficacy of drug combinations. Blood 108: 2332-2338.

52. Champlin R, Jabbour E, Kebriaei P, Anderlini P, Andersson B, et al. (2011) Allogeneic stem cell transplantation for chronic myeloid leukemia resistant to tyrosine kinase inhibitors. Clin Lymphoma Myeloma Leuk 11 Suppl 1: S96-100.

53. Cortes J, Kim DW, Raffoux E, Martinelli G, Ritchie E, et al. (2008) Efficacy and safety of dasatinib in imatinib-resistant or -intolerant patients with chronic myeloid leukemia in blast phase. Leukemia 22: 2176-2183.

54. Oyekunle A, Klyuchnikov E, Ocheni S, Kröger N, Zander AR, et al. (2011) Challenges for allogeneic hematopoietic stem cell transplantation in chronic myeloid leukemia in the era of tyrosine kinase inhibitors. Acta Haematol 126: 30-39.

55. Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H, et al. (2006) Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 355: 2408-2417.

56. de Lavallade H, Apperley JF, Khorashad JS, Milojkovic D, Reid AG, et al. (2008) Imatinib for Newly Diagnosed Patients With Chronic Myeloid Leukemia: Incidence of Sustained Responses in an Intention-to-Treat Analysis. J Clin Oncol 26: 3358-3363.

57. Léger CS, Nevill TJ (2004) Hematopoietic stem cell transplantation: a primer for the primary care physician. CMAJ 170: 1569-1577.

58. Huang XJ, Liu DH, Liu KY, Xu LP, Chen YH, et al. (2008) Modified donor lymphocyte infusion after HLA-mismatched/haploidentical T cell-replete hematopoietic stem cell transplantation for prophylaxis of relapse of leukemia in patients with advanced leukemia. J Clin Immunol 28: 276-283.

59. Speiser DE, Hermans J, van Biezen A, Starobinski M, Jeannet M, et al. (1997) Haploidentical family member transplants for patients with chronic myeloid leukaemia: a report of the Chronic Leukaemia Working Party of off European Group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant 19: 1197-1203.

60. Drobyski WR, Klein J, Flomenberg N, Pietryga D, Vesole DH, et al. (2002) Superior survival associated with transplantation of matched unrelated versus one-antigen–mismatched unrelated or highly human leukocyte antigen–disparate haploidentical family donor marrow grafts for the treatment of hematologic malignancies: establishing a treatment algorithm for recipients of alternative donor grafts. Blood 99: 806-814.

61. van Rood JJ, Loberiza FR, Zhang M, Oudshoorn M, Claas F, et al. (2002) Effect of tolerance to noninherited maternal antigens on the occurrence of graft-versus-host disease after bone marrow transplantation from a parent or an HLA-haploidentical sibling. Blood 99: 1572-1577.

62. Ottinger HD, Ferencik S, Beelen DW, Lindemann M, Peceny R, et al. (2003) Hematopoietic stem cell transplantation: contrasting the outcome of transplantations from HLA-identical siblings, partially HLA-mismatched related donors, and HLA-matched unrelated donors. Blood 102: 1131-1137.

63. Federmann B, Bornhauser M, Meisner C, Kordelas L, Beelen DW, et al. (2012) Haploidentical allogeneic hematopoietic cell transplantation in adults using CD3/CD19 depletion and reduced intensity conditioning: a phase II study. Haematologica 97: 1523-1531.

64. Lu D, Dong L, Wu T, Huang X, Zhang M, et al. (2006) Conditioning including antithymocyte globulin followed by unmanipulated HLA-mismatched/haploidentical blood and marrow transplantation can achieve comparable outcomes with HLA-identical sibling transplantation. Blood 107: 3065-3073.

65. Radich J (2010) Stem cell transplant for chronic myeloid leukemia in the imatinib era. Semin Hematol 47: 354-361.

66. Devergie A, Reiffers J, Vernant JP, Herve P, Guyotat D, et al. (1990) Long-term follow-up after bone marrow transplantation for chronic myelogenous leukemia: factors associated with relapse. Bone Marrow Transplant 5: 379-386.

67. Martin PJ, Clift RA, Fisher LD, Buckner CD, Hansen JA, et al. (1988) HLA-identical marrow transplantation during accelerated-phase chronic myelogenous leukemia: analysis of survival and remission duration. Blood 72: 1978-1984.

68. Clift RA, Buckner CD, Thomas ED, Bryant E, Anasetti C, et al. (1994) Marrow transplantation for patients in accelerated phase of chronic myeloid leukemia. Blood 84: 4368-4373.

69. Saussele S, Lauseker M, Gratwohl A, Beelen DW, Bunjes D, et al. (2010) Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. Blood 115: 1880-1885.

70. Copelan EA, Crilley PA, Szer J, Dodds AJ, Stevenson D, et al. (2009) Late mortality and relapse following BuCy2 and HLA-identical sibling marrow transplantation for chronic myelogenous leukemia. Biol Blood Marrow Transplant 15: 851-855.

71. Bacher U, Klyuchnikov E, Zabelina T, Ottinger H, Beelen DW, et al. (2009) The changing scene of allogeneic stem cell transplantation for chronic myeloid leukemia--a report from the German Registry covering the period from 1998 to 2004. Ann Hematol 88: 1237-1247.

72. Thomas ED, Clift RA, Fefer A, Appelbaum FR, Beatty P, et al. (1986) Marrow transplantation for the treatment of chronic myelogenous leukemia. Ann Intern Med 104: 155-163.

73. Goldman JM, Gale RP, Horowitz MM, Biggs JC, Champlin RE, et al. (1988) Bone marrow transplantation for chronic myelogenous leukemia in chronic phase. Increased risk for relapse associated with T-cell depletion. Ann Intern Med 108: 806-814.

74. Shimoni A, Leiba M, Schleuning M, Martineau G, Renaud M, et al. (2009) Prior treatment with the tyrosine kinase inhibitors dasatinib and nilotinib allows stem cell transplantation (SCT) in a less advanced disease phase and does not increase SCT Toxicity in patients with chronic myelogenous leukemia and philadelphia positive acute lymphoblastic leukemia. Leukemia 23: 190-194.

75. Kottaridis PD, Milligan DW, Chopra R, Chakraverty RK, Chakrabarti S, et al. (2001) In vivo CAMPATH-1H prevents GvHD following nonmyeloablative stem-cell transplantation. Cytotherapy 3: 197-201.

76. Ho VT, Soiffer RJ (2001) The history and future of T-cell depletion as graft-versus-host disease prophylaxis for allogeneic hematopoietic stem cell transplantation. Blood 98: 3192-3204.

77. Koh LP, Rizzieri DA, Chao NJ (2007) Allogeneic hematopoietic stem cell transplant using mismatched/haploidentical donors. Biol Blood Marrow Transplant 13: 1249-1267.

78. Craddock C, Szydlo RM, Dazzi F, Olavarria E, Cwynarski K, et al. (2001) Cytomegalovirus seropositivity adversely influences outcome after T-depleted unrelated donor transplant in patients with chronic myeloid leukaemia: the case for tailored graft-versus-host disease prophylaxis. Br J Haematol 112: 228-236.

79. Wingard JR (2005) The changing face of invasive fungal infections in hematopoietic cell transplant recipients. Curr Opin Oncol 17: 89-92.

80. Körbling M, Anderlini P (2001) Peripheral blood stem cell versus bone marrow allotransplantation: does the source of hematopoietic stem cells matter? Blood 98: 2900-2908.

81. Morton J, Hutchins C, Durrant S (2001) Granulocyte–colony-stimulating factor (G-CSF)–primed allogeneic bone marrow: significantly less graft-versus-host disease and comparable engraftment to G-CSF–mobilized peripheral blood stem cells. Blood 98: 3186-3191.

82. Huang X, Chang YJ, Zhao XY (2007) Maintaining hyporesponsiveness and polarization potential of T cells after in vitro mixture of G-CSF mobilized peripheral blood grafts and G-CSF primed bone marrow grafts in different proportions. Transpl Immunol 17: 193-197.

83. Gratwohl A, Hermans J, Niederwieser D, Frassoni F, Arcese W, et al. (1993) Bone marrow transplantation for chronic myeloid leukemia: long-term results. Chronic Leukemia Working Party of the European Group for Bone Marrow Transplantation. Bone Marrow Transplant 12: 509-516.

84. Horowitz MM, Rowlings PA, Passweg JR (1996) Allogeneic bone marrow transplantation for CML: a report from the International Bone Marrow Transplant Registry. Bone Marrow Transplant 17 Suppl 3: S5-6.

85. Kantarjian HM, O'Brien S, Cortes JE, Giralt SA, Rios MB, et al. (2002) Imatinib mesylate therapy for relapse after allogeneic stem cell transplantation for chronic myelogenous leukemia. Blood 100: 1590-1595.

86. Eapen M, Giralt SA, Horowitz MM, Klein JP, Wagner JE, et al. (2004) Second transplant for acute and chronic leukemia relapsing after first HLA-identical sibling transplant. Bone Marrow Transplant 34: 721-727.

87. Kröger N (2011) Approaches to relapse after allogeneic stem cell transplantation. Curr Opin Oncol 23: 203-208.

88. Huang XJ, Liu DH, Liu KY, Xu LP, Chen H, et al. (2007) Donor lymphocyte infusion for the treatment of leukemia relapse after HLA-mismatched/haploidentical T-cell-replete hematopoietic stem cell transplantation. Haematologica 92: 414-417.

89. Kolb H, Schattenberg A, Goldman J, Hertenstein B, Jacobsen N, et al. (1995) Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. European Group for Blood and Marrow Transplantation Working Party Chronic Leukemia. Blood 86: 2041-2050.

90. Kolb HJ, Schmid C, Barrett AJ, Schendel DJ (2004) Graft-versus-leukemia reactions in allogeneic chimeras. Blood 103: 767-776.

91. Thepot S, Zhou J, Perrot A, Robin M, Xhaard A, et al. (2010) The graft-versus-leukemia effect is mainly restricted to NIH-defined chronic graft-versus-host disease after reduced intensity conditioning before allogeneic stem cell transplantation. Leukemia 24: 1852-1858.

92. Collins RH Jr, Goldstein S, Giralt S, Levine J, Porter D, et al. (2000) Donor leukocyte infusions in acute lymphocytic leukemia. Bone Marrow Transplant 26: 511-516.

93. Dazzi F, Szydlo RM, Craddock C, Cross NC, Kaeda J, et al. (2000) Comparison of single-dose and escalating-dose regimens of donor lymphocyte infusion for relapse after allografting for chronic myeloid leukemia. Blood 95: 67-71.

94. Collins RH, Shpilberg O, Drobyski WR, Porter DL, Giralt S, et al. (1997) Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation. J Clin Oncol 15: 433-444.

95. Peggs KS, Thomson K, Hart DP, Geary J, Morris EC, et al. (2004) Dose-escalated

donor lymphocyte infusions following reduced intensity transplantation: toxicity, chimerism, and disease responses. Blood 103: 1548-1556.

96. Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, et al. (2009) Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol 27: 6041-6051.

97. Bornhäuser M, Thiede C, Platzbecker U, Kiani A, Oelschlaegel U, et al. (2011) Prophylactic transfer of BCR-ABL–, PR1-, and WT1-reactive donor T cells after T cell–depleted allogeneic hematopoietic cell transplantation in patients with chronic myeloid leukemia. Blood 117: 7174-7184.

98. Sloand E, Childs RW, Solomon S, Greene A, Young NS, et al. (2003) The graft-versus-leukemia effect of nonmyeloablative stem cell allografts may not be sufficient to cure chronic myelogenous leukemia. Bone Marrow Transplant 32: 897-901.

99. Giralt S, Estey E, Albitar M, van Besien K, Rondon G, et al. (1997) Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. Blood 89: 4531-4536.

100. McSweeney PA, Niederwieser D, Shizuru JA, Sandmaier BM, Molina AJ, et al. (2001) Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. Blood 97: 3390-3400.

101. Maloney DG, Sandmaier BM, Mackinnon S, Shizuru JA (2002) Non-myeloablative transplantation. Hematology Am Soc Hematol Educ Program .

102. Tauro S, Craddock C, Peggs K, Begum G, Mahendra P, et al. (2005) Allogeneic Stem-Cell Transplantation Using a Reduced-Intensity Conditioning Regimen Has the Capacity to Produce Durable Remissions and Long-Term Disease-Free Survival in Patients With High-Risk Acute Myeloid Leukemia and Myelodysplasia. J Clin Oncol 23: 9387-9393.

103. Ringhoffer M, Harsdorf Sv, Schmitt M, Wiesneth M, Zenz T, et al. (2007) Reduced-intensity conditioning followed by T-cell depleted allogeneic stem cell transplantation for patients with chronic myeloid leukaemia and minimal residual disease at the time of transplant: high risk of molecular relapse. Br J Haematol 136: 127-130.

104. Warlick E, Ahn KW, Pedersen TL, Artz A, de Lima M, et al. (2012) Reduced intensity conditioning is superior to nonmyeloablative conditioning for older chronic myelogenous leukemia patient undergoing hematopoietic cell transplant during the tyrosine kinase inhibitor era. Blood 119: 4083-4090.

105. Luo Y, Lai XY, Tan YM, Shi JM, Zhao YM, et al. (2009) Reduced-intensity allogeneic transplantation combined with imatinib mesylate for chronic myeloid leukemia in first chronic phase. Leukemia 23: 1171-1174.

106. Faber E, Koza V, Vitek A, Mayer J, Sedlacek P, et al. (2007) Reduced-intensity conditioning for allogeneic stem cell transplantation in patients with chronic myeloid leukemia is associated with better overall survival but inferior disease-free survival when compared with myeloablative conditioning - a retrospective study of the Czech National Hematopoietic Stem Cell Transplantation Registry. Neoplasma 54: 443-446.

This article was originally published in a special issue, **Cancer Diagnosis, Treatment and Therapy** handled by Editor(s). Dr. Said Dermime , King Fahad Specialist Hospital Dammam, Saudi Arabia