

Allogeneic stem cell transplantation in chronic myeloid leukemia patients: Single center experience

Nur Soyer, Ayse Uysal, Murat Tombuloglu, Fahri Sahin, Guray Saydam, Filiz Vural

Nur Soyer, Ayse Uysal, Murat Tombuloglu, Fahri Sahin, Guray Saydam, Filiz Vural, Department of Hematology, Ege University Medical Faculty, 35100 Izmir, Turkey

Author contributions: Soyer N, Uysal A, Tombuloglu M, Sahin F, Saydam G and Vural F have been involved equally and have read and approved the final manuscript; Soyer N, Uysal A, Tombuloglu M, Sahin F, Saydam G and Vural F meet the criteria for authorship established by the International Committee of Medical Journal Editors and verify the validity of the results reported.

Conflict-of-interest statement: No.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Nur Soyer, MD, Department of Hematology, Ege University Medical Faculty, Ankara Blvd, Bornova, 35100 Izmir, Turkey. drakadnur@yahoo.com
Telephone: +90-232-3904541
Fax: +90-232-3738797

Received: August 23, 2016

Peer-review started: August 24, 2016

First decision: October 20, 2016

Revised: October 21, 2016

Accepted: January 2, 2017

Article in press: January 3, 2017

Published online: February 6, 2017

Abstract

Chronic myeloid leukemia (CML) is a myeloproliferative disease which leads the unregulated growth of myeloid

cells in the bone marrow. It is characterized by the presence of Philadelphia chromosome. Reciprocal translocation of the *ABL* gene from chromosome 9 to 22 t (9; 22) (q34; q11.2) generate a fusion gene (*BCR-ABL*). BCR-ABL protein had constitutive tyrosine kinase activity that is a primary cause of chronic phase of CML. Tyrosine kinase inhibitors (TKIs) are now considered standard therapy for patients with CML. Even though, successful treatment with the TKIs, allogeneic stem cell transplantation (ASCT) is still an important option for the treatment of CML, especially for patients who are resistant or intolerant to at least one second generation TKI or for patients with blastic phase. Today, we know that there is no evidence for increased transplant-related toxicity and negative impact of survival with pre-transplant TKIs. However, there are some controversies about timing of ASCT, the optimal conditioning regimens and donor source. Another important issue is that BCR-ABL signaling is not necessary for survival of CML stem cell and TKIs were not effective on these cells. So, ASCT may play a role to eliminate CML stem cells. In this article, we review the diagnosis, management and treatment of CML. Later, we present our center's outcomes of ASCT for patients with CML and then, we discuss the place of ASCT in CML treatment in the TKIs era.

Key words: Chronic myeloid leukemia; Allogeneic stem cell transplantation; Tyrosine kinase inhibitors; Graft vs host disease; Survival

© **The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Tyrosine kinase inhibitors (TKIs) have changed the fatal outcomes of chronic myeloid leukemia (CML). Many studies showed that TKIs provided rapid response, few serious adverse event and impressive survival outcomes. Although, allogeneic stem cell transplantation (ASCT) is only curative treatment option for CML, since 1999, the numbers of ASCT have dropped. Currently, ASCT is offering for patients who are resistant or intolerant

to at least one second generation TKI or for patients with blastic phase. Here, we present our center's outcomes of ASCT for patients with CML and then, we discuss the place of ASCT in CML treatment in the TKIs era.

Soyer N, Uysal A, Tombuloglu M, Sahin F, Saydam G, Vural F. Allogeneic stem cell transplantation in chronic myeloid leukemia patients: Single center experience. *World J Hematol* 2017; 6(1): 1-10 Available from: URL: <http://www.wjgnet.com/2218-6204/full/v6/i1/1.htm> DOI: <http://dx.doi.org/10.5315/wjh.v6.i1.1>

INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm that characterized by the presence of Philadelphia chromosome^[1]. The incidence of CML is 1-2 cases per 100000. Reciprocal translocation of the *ABL* gene from chromosome 9 to 22 t (9; 22)(q34;q11.2) generate a fusion gene (*BCR-ABL*). *BCR-ABL* oncoprotein had constitutive tyrosine kinase activity that is a primary cause of chronic phase of CML^[2].

Approximately 50% of patients are asymptomatic that they diagnosed incidentally after their routine laboratory tests. If they are symptomatic, symptoms are left upper quadrant pain or early satiety, fatigue, night sweats, symptoms of anemia, and bleeding due to platelet dysfunction. Splenomegaly is the main physical finding, in slightly > 50% of patients^[3].

Characteristic feature of complete blood cell count is leukocytosis with basophilia and with immature granulocytes (metamyelocytes, myelocytes and promyelocytes and few myeloblasts). Thrombocytosis is frequent but severe anemia is rare^[4]. Bone marrow aspirates and biopsy with conventional cytogenetics is taken from untreated patients at diagnosis. Cytogenetics must be performed by chromosome banding analysis (CBA). Fluorescence *in situ* hybridization (FISH) for t (9; 22) (q34;q11.2) and quantitative reverse transcriptase PCR (qRT-PCR) for *BCR-ABL* can be performed on peripheral blood^[3].

The disease is classified into chronic phase (CP, most patients at presentation), accelerated phase (AP), and blast phase (BP)^[4]. Clinical and hematologic criteria for the definition of AP according to World Health Organization (WHO) is the presence of one or more of the following: Persisting or increasing splenomegaly and/or white blood cells (> 10 × 10⁹/L) unresponsive to therapy, 10%-19% blast cells and/or > 20% basophils in peripheral blood or bone marrow, platelet counts > 1000 × 10⁹/L uncontrolled by therapy or < 100 × 10⁹/L unrelated to therapy or clonal chromosome abnormalities in Ph⁺ cells. Clinical and hematologic criteria for the definition of BP according to WHO is the presence of one or more of the following: Blast cells ≥ 20% and/or extramedullary involvement excluding liver and spleen, including lymph nodes, skin, CNS, bone, and lung^[4]. European LeukemiaNet (ELN) criteria for the definition of

AP and BP slightly differ from WHO criteria. According to ELN, the definition of AP is the presence of one or more of the following: 15%-29% blast cells and/or > 20% basophils in peripheral blood or bone marrow, platelet counts < 100 × 10⁹/L unrelated to therapy or clonal chromosome abnormalities in Ph⁺ cells. The definition of BP is blast cells ≥ 30% in peripheral blood or bone marrow and/or clonal chromosome abnormalities in Ph⁺ cells^[5].

The differential diagnosis of CML includes Ph⁻ negative chronic myeloproliferative neoplasms, leukemoid reactions, Ph-negative CML or chronic myelomonocytic leukemia.

At the diagnosis, there are several prognostic scoring systems to assess the risk of poor outcome: The Sokal score, Hasford score and the European Treatment and Outcome Study score (Table 1)^[6-8]. Additionally, the stage of disease and response to tyrosine kinase inhibitor (TKI) are important factors for prognosis.

According to ELN response criteria, the complete hematologic response (CHR) is defined as white blood cell < 10 × 10⁹/L, no immature granulocytes, basophils < 5%, platelet count < 450 × 10⁹/L, and non-palpable spleen. The complete cytogenetic response (CCyR) is defined as no Ph (+) metaphases by CBA or < 1% *BCR-ABL1*-positive nuclei of at least 200 examined nuclei by FISH of peripheral blood. The partial, minor, minimal and no CyR is defined as 1%-35% Ph⁺ metaphases, 36%-65% Ph⁺ metaphases, 66%-95% Ph⁺ metaphases and > 95% Ph⁺ metaphases by CBA, respectively. Molecular response is assessed with the international scale (IS) as the ratio of *BCR-ABL1* transcripts to *ABL1* transcripts. Major molecular response (MMR) is defined as < 0.1% *BCR-ABL1* expression. Deep molecular responses are defined as MR^{4.0} (detectable disease with, 0.01% *BCR-ABL1* IS or undetectable disease in cDNA with > 10000 *ABL1* transcripts) and MR^{4.5} (detectable disease with, 0.0032% *BCR-ABL1* IS or undetectable disease in cDNA with > 32.000 *ABL1* transcripts in the same volume of cDNA used to test for *BCR-ABL1*). Molecularly undetectable leukemia is defined as undetectable *BCR-ABL* with assay sensitivity ≥ 4.5 or 5.0 logs^[9].

It is recommended that either a molecular or cytogenetic test or both can be used for monitoring of CML. It's depends on local conditions of center. Routine blood counts with differentials are recommended every 1-2 wk until complete hematological response. Then, every three months, it should be evaluated to assess any side effects of TKIs. Every three months, molecular monitoring with qRT-PCR is recommended until major molecular response. Then, it can be performed every 3-6 mo. CBA of marrow cell metaphases was used for cytogenetic analysis at 3, 6 and 12 mo until CCyR. Then, it can be performed every twelve months. FISH on blood cells can be used for monitoring when the CCyR has been achieved. If patients fail to achieve therapeutic targets, progress to accelerate or blastic phase or show dysplastic changes, bone marrow biopsy and cytogenetic tests are recommended. Mutational analysis should be performed in case of progression or treatment failure^[9].

Table 1 Calculation of relative risk

| | Sokal score | Hasford score | EUTOS |
|-----------------|---|---|---|
| Calculation | $0.0116 \times (\text{age} - 43.4) + 0.0345 \times (\text{spleen} - 7.51) + 0.188 \times [(\text{platelet count}/700)^2 - 0.563] + 0.0887 \times (\text{blast cells} - 2.10)$ | 0.666 when age $\geq 50 + (0.042 \times \text{spleen}) + 1.0956$ when platelet $> 1500 \times 10^9/\text{L} + (0.0584 \times \text{blast cells}) + 0.20399$ when basophils $> 3\% + (0.0413 \times \text{eosinophils}) + 100$ | Spleen $\times 4 + \text{basophils} \times 7$ |
| Risk definition | Exponential of the total Low risk: < 0.8 Intermediate risk: 0.8-1.2 High risk: > 1.2 | Total $\times 1000$ Low risk: ≤ 780 Intermediate risk: 781-1480 High risk: > 1480 | Total Low risk: ≤ 87 High risk: > 87 |

Age is given in years. Spleen is given in centimeters below the costal margin (maximum distance). Blast cells, eosinophils, and basophils are given in percent of peripheral blood differential. All values must be collected before any treatment. EUTOS: European Treatment and Outcome Study.

TREATMENT OF CML

Imatinib, the first TKI, improved the 10-year survival rate from 10%-20% to 80%-90%^[10]. Since its approval, two other TKIs, nilotinib and dasatinib, were approved first for second line then also for first line treatment for CML^[11,12]. TKIs are now considered standard therapy for patients with chronic myelogenous leukemia.

First line treatment of CP-CML

Currently, imatinib (400 mg once daily), nilotinib (300 mg twice daily), and dasatinib (100 mg once daily) are recommended in first line therapy of CP-CML^[9].

The main study of imatinib is International Randomized Study of Interferon and STI571 (IRIS). Patients with CML were randomized to receive imatinib 400 mg/d or INF- α plus low-dose subcutaneous cytarabine in this study. After a median follow-up of 19 mo, CCyR rate was 74% in imatinib arm and 9% in INF- α plus low-dose subcutaneous cytarabine ($P < 0.001$)^[13]. In 8-year follow-up of the IRIS study, 53% of patients who treated with imatinib still had CCyR, although estimated event free survival (EFS) and overall survival (OS) rate were 81% and 93%, respectively^[10].

The Dasatinib vs Imatinib Study in Treatment-Naive CML Patients (DASISION) and the Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients study (ENEST-nd) are randomized, prospective studies that showed superiority of dasatinib and nilotinib vs imatinib in newly diagnosed CML patients. In DASISION study, CCyR rate at 12 mo was 77% in dasatinib arm and 66% in imatinib arm ($P = 0.007$)^[11,14]. In 3-year follow-up, responses were deeper and faster than imatinib arm. The 3-year OS and progression free survival (PFS) rates were similar both arms, but transformation to AP-CML and BP-CML was lesser than imatinib arm^[15]. In ENEST-nd study, MMR rates at 12 mo were 44% in the arm of nilotinib 300 mg orally twice daily, 43% in the arm of nilotinib 400 mg orally twice daily, and 22% in the arm of imatinib ($P < 0.001$). The CCyR rates at 12 mo were significantly higher for nilotinib (80% for the 300-mg dose and 78% for the 400-mg dose) than for imatinib (65%) ($P < 0.001$)^[12]. In 3-year follow-up, responses were deeper and faster than imatinib arm and transformation to AP-CML and BP-CML was lesser than imatinib arm^[16].

Widespread using of TKIs is associated with drug resistance. One of the most common mechanisms of resistance involves point mutations in the kinase domain of BCR-ABL. The optimal treatment for patients failing imatinib treatment is imatinib dose escalation, a second-generation TKI or allogeneic stem cell transplantation (ASCT)^[1]. Recently, there are some experimental studies using combination of TKIs to overcome the drug resistance^[17-19]. They reported that combination of TKIs could overcome and prevent resistance. Combined TKIs approach should be investigated in further clinical trials in the subset of patients with TKI resistance.

Patients should be followed up according to definition of ELN response criteria (Table 2). If patients do not achieve a CHR by 3 mo, switching to a second TKI should be considered. If patients had $> 10\%$ BCR-ABL1 transcript level at 3 mo, it is recommended that serial molecular monitoring should be performed for 3 mo. If patients had $> 10\%$ BCR-ABL1 transcript level at 6 mo, therapy should be changed. If patients do not achieve CCyR by 12 mo, it requires a change in therapy. At any time, therapy should be changed, if patients loss of CHR or CCyR or PCyR or confirmed loss of MMR or determined new mutations and/or CCA/Ph^{+9]}.

Second line treatment of CP-CML

For patients who had intolerance to first line TKI, anyone of the other TKIs approved first line therapy can be used. Patient's comorbidities and toxicity profile of TKIs are considered in the choice of therapy^[9].

For patients who had failure of TKI in first line, other TKIs approved first line therapy that patient did not use, bosutinib or ponatinib were recommended. Bosutinib was studied in patients that were resistant to or intolerant of imatinib. The CHR and CCyR rates were 86% and 41%, respectively. The 2-year PFS and OS rates were 79% and 92%, respectively^[20]. Ponatinib is the only TKI with activity in patients with the T315I mutation. In phase II Ponatinib Ph ALL and CML Evaluation study, among 267 patients with chronic-phase CML, 56% had a major cytogenetic response, 46% had a complete cytogenetic response, and 34% had a major molecular response^[21]. So, bosutinib (500 mg once daily) and ponatinib (45 mg once daily) have been approved for patients resistant to prior therapy.

Table 2 European LeukemiaNet response criteria to tyrosine kinase inhibitors at first line

| | Optimal | Warning | Failure |
|-----------------------|---|--|---|
| Baseline | NA | High risk or CCA/Ph ⁺ , major route | NA |
| 3 mo | BCR-ABL1 ≤ 10% and/or Ph ⁺ ≤ 35% | BCR-ABL1 > 10% and/or Ph ⁺ 35%-95% | Non-CHR and/or Ph ⁺ > 95% |
| 6 mo | BCR-ABL1 ≤ 1% and/or Ph ⁺ 0 | BCR-ABL1 1%-10% and/or Ph ⁺ 1%-35% | BCR-ABL1 > 10% and/or Ph ⁺ > 35% |
| 12 mo | BCR-ABL1 ≤ 0.1% | BCR-ABL1 > 0.1%-1% | BCR-ABL1 > 1% and/or Ph ⁺ > 0 |
| Then, and any at time | BCR-ABL1 ≤ 0.1% | CCA/Ph ⁻ (-7 or 7q-) | Loss of CHR Loss of CCyR Confirmed loss of MMR mutations CCA/Ph ⁺ |

In 2 consecutive tests, of which one with a BCR-ABL1 transcripts level $\geq 1\%$. This table was originally published in Baccarani *et al*^[5]. CCA/Ph⁺: Clonal cytogenetic abnormalities in Ph-positive cells; CCA/Ph⁻: Clonal cytogenetic abnormalities in Ph-negative cells; Ph: Philadelphia chromosome; CCyR: Complete cytogenetic response; MMR: Major molecular response; NA: Not applicable.

Treatment of AP-CML

The therapeutic approach in AP-CML differs according to whether the patient is TKI naive or has progressed from CP while taking a TKI. All recommendations are based on results of single-arm, retrospective and prospective studies. For TKI naive patients; it is recommended a TKI (imatinib 400 mg twice daily or dasatinib 70 mg twice daily or 140 mg once daily). Allogeneic donor search should be done. ASCT is recommended for the AP patients who do not achieve an optimal response with TKI^[9]. Response rate was reported higher with second generation TKIs than imatinib^[22].

For patients who progressed from CP to AP-CML while taking a TKI; it is recommended anyone of the TKIs that were not used before progression. Allogeneic donor search and ASCT should be performed all patients^[9].

Treatment of BP-CML

It is recommended combinations of induction chemotherapy and TKIs for patients with BP-CML. ASCT is recommended for all BP-CML patients who are eligible^[9].

ASCT

ASCT is a highly effective treatment for CML. Since TKIs were used routinely in first line treatment and were safe and highly effective at controlling CP-CML, the numbers of allografts performed for CML have dramatically decreased^[23]. Although outcomes of ASCT improved over years, HSCT is still limited to patients with an available donor and remains associated with significant morbidity and mortality^[24]. However, ASCT remains an important therapeutic option for CML, especially for patients who are resistant or intolerant to at least one second generation TKI or for patients with blastic phase^[9]. Another issue is keep in mind that BCR-ABL signaling is not necessary for survival of CML stem cell and TKIs were not effective on these cells^[25,26]. ASCT is still had the potential for cure.

In this report, we present our single center experience of the outcomes of ASCT for patients with CML. Then, we will review our data with the literature of ASCT for CML.

CASE SERIES

Ten patients (3 female and 7 male) with CML were

treated with ASCT in our center between October 2000 and December 2015. The median age at the transplantation was 50 (range 22-65) years. All patients were in chronic phase at diagnosis. Only one patient did not receive imatinib, this patient treated with interferon and hydroxyurea. Others received at least imatinib. One patient had primary imatinib resistance and 8 had lost their response. Four patient who had lost their response to imatinib received second-line TKIs. At the time of transplantation, 5 of all were in first CP, 3 were in 2nd CP and 2 was in AP. Time from diagnosis to ASCT was 61.5 (range 14-133) mo. Nine of all transplantation were matched sibling donor and one was an antigen mismatched (HLA A antigen) unrelated donor transplantation. Patient's characteristics are shown in Table 3.

Seven patients received myeloablative conditioning regimens (busulfan 3.2 mg/kg per day 4 d and cyclophosphamide 60 mg/kg per day 2 d) and 3 patients were received non-myeloablative regimens (fludarabine 30 mg/m² per day 5 d and busulfan 3.2 mg/kg per day 2 d; fludarabine 30 mg/m² per day 5 d, busulfan 3.2 mg/kg per day 2 d and, cyclophosphamide 350 mg/m² per day 3 d). Cyclosporine (2 mg/kg per day day -1, levels maintained at 200-300 μ g/L until dose reduction) and methotrexate (15 mg/m² on day +1, 10 mg/m² on day +3, +6, +11 for myeloablative regimens and 10 mg/m² on day +1, +3 and +6 for non-myeloablative regimens) were used for graft vs host disease (GVHD) prophylaxis. In all patients, peripheral blood stem cell grafts were used.

All patients were engrafted. The median neutrophil and platelet engraftment times were 13 (10-25) d and 14.5 (10-30) d, respectively (Table 4). The median follow-up was 16.5 (3-117) mo. Only 3 patients are still alive without disease. The median follow-up of these patients were 87 (50-117) mo. Five patients died of complications after ASCT including acute GVHD ($n = 3$), and infection ($n = 2$). Two of all patients relapsed at 19 (molecular relapse) and 6 (hematological relapse) months from the date of ASCT.

Although our cohort is small, most of patients achieved molecular remission after transplantation. Only 2 patients died because of blastic crises and granulocytic sarcoma.

Table 3 Patients characteristics

| Patient | Sex | Age at ASCT (yr) | Disease phase at ASCT | Time from diagnosis to ASCT (mo) | Indication for ASCT | Donor sex |
|---------|-----|------------------|-----------------------|----------------------------------|--|-----------|
| 1 | M | 22 | 1 st AP | 50 | Resistance to imatinib and clonal evolution | M |
| 2 | F | 51 | 2 nd CP | 14 | Previous myeloid blastic phase | M |
| 3 | M | 25 | 2 nd CP | 61 | Previous lymphoid blastic phase | M |
| 4 | M | 33 | 1 st CP | 37 | Resistance to imatinib and dasatinib | M |
| 5 | F | 54 | 1 st AP | 103 | Resistance to imatinib, nilotinib and dasatinib 1 st accelerated phase | F |
| 6 | M | 65 | 1 st CP | 133 | Resistance to imatinib and nilotinib | F |
| 7 | F | 49 | 1 st CP | 62 | Resistance to imatinib | M |
| 8 | M | 53 | 2 nd CP | 63 | Previous myeloid blastic phase | M |
| 9 | M | 41 | 1 st CP | 51 | Resistance to imatinib | M |
| 10 | M | 61 | 1 st CP | 75 | Resistance to imatinib, nilotinib and dasatinib | F |

ASCT: Allogeneic stem cell transplantation; AP: Accelerated phase; CP: Chronic phase; M: Male; F: Female.

Others died because of acute GVHD and infection. However, only 3 patients achieved long term survival, ASCT has a place for treatment of CML.

DISCUSSION

As we mentioned above, ASCT is still important therapy for CML patients. In 1982, different groups were reported ASCTs with bone marrow graft from HLA-matched siblings^[27-29]. Then, it was shown that CML patients who received T-cell depleted transplants with or without GVHD had higher probabilities of relapse than recipients of non-T-cell depleted allografts without GVHD. These data support graft-vs-leukemia (GVL) effect independent of GVHD^[30]. Other reports showed that donor leukocyte infusions (DLI) for treatment of recurrent CML after ASCT could achieve stable remissions^[31-33].

Outcomes of ASCT for CP-CML patients continued to improve with general improvements in transplant management and powerful GVL effect of DLI. In the post-TKIs era, there are some reports evaluating outcomes of ASCT and potential negative effect of TKIs^[34-38].

According to European Society for Blood and Marrow Transplantation (EBMT) data, the 2-year OS, transplantation-related mortality (TRM) and relapse rate in patients transplanted between 2000 and 2003 were 61%, 30% and 22%, respectively^[34]. Eighty-four patients with CML who underwent ASCT were evaluated in 3 groups according to the reason of ASCT: Group I (early transplantation in low-risk patients, EBMT scores 0-1), group II (imatinib failure in first CP), and group III (advanced disease). At a median follow-up of 30 mo, the 3-year OS was 88% in group I, 94% in group II and 59% in group III. TRM was 8%^[35]. In a cohort study, it was compared the outcomes of imatinib vs ASCT for AP-CML. In ASCT arm, median follow-up was 51 mo, and the 6-year OS, EFS, and PFS were 83.3%, 71.8% and 95.2%, respectively. In imatinib arm, median follow-up was 32 mo, and the 6 year OS, EFS and PFS were 51.4%, 39.2% and 48.3%, respectively. Patients treated with ASCT were significantly higher OS ($P = 0.023$), EFS ($P = 0.008$) and PFS ($P = 0.000$) than patients treated with imatinib^[36]. Pfirmann *et al*^[37] compared two consecutive

German studies III (recruitment from 1995 to 2001) and IIIA (recruitment from 1997 to 2004) on chronic myeloid leukemia. They reported that HLA matching, age of transplantation ≤ 44 and time from diagnosis to ASCT ≤ 1 year had a significant association with improved survival. They also reported that improvement of transplantation practice over years was associated with better survival. These findings suggested that the timing of ASCT is an important factor on survival outcomes.

According to Center for International Bone Marrow Transplantation Research (CIBMTR) data in TKI era, 3-year OS and disease free survival (DFS) rates were 36% and 27% in second CP, 43% and 37% in AP, and 14% and 10% in BP. Pre-transplant imatinib had no association with transplant outcomes, including acute and chronic GVHD^[38]. In a study with CIBMTR data, they reported that pre-transplant imatinib therapy was associated with improved survival after transplantation and, they showed similar acute GVHD rates both using and not using imatinib before transplantation^[39]. Fifty-one patients with CML underwent ASCT for advanced disease at diagnosis or for treatment failure with TKIs. At a median follow-up of 71.9 mo, the 8-year OS, EFS, relapse, and non-relapse mortality (NRM) were 68%, 46%, 41% and 23%, respectively^[40]. Another study demonstrated that OS, DFS, relapse and NRM rates were similar between pre-transplant imatinib arm and no imatinib arm. On the other hand, mortality was higher in CP patients with suboptimal response than in CP patients with CCyR or major CyR on imatinib^[41]. In a retrospective study, it was demonstrated that there was no evidence for increased transplant-related toxicity with pre-transplant dasatinib and nilotinib therapy^[42]. In a small study, they showed that using dasatinib and nilotinib before ASCT did not increase transplant-related toxicity or GVHD^[43]. According to these data, there is no evidence for increased transplant-related toxicity and negative impact of survival with pre-transplant TKI.

Goldman *et al*^[44] reported that 15-year OS and relapse rates were 88% and 8% for sibling donor ASCT and 87% and 2% for unrelated donor ASCT, respectively. Recent randomized, prospective study evaluated differences between early allogeneic HSCT (group A) and best drug

Table 4 Transplantation outcomes

| Patient | PNL engraftment (d) | PLT engraftment (d) | Acute GVHD | Chronic GVHD | Post-transplant disease status | Last status |
|---------|---------------------|---------------------|------------|--------------|--|-------------|
| 1 | 12 | 18 | No | No | Molecular relapse and granulocytic sarcoma | Died |
| 2 | 15 | 16 | No | No | Blastic crises | Died |
| 3 | 18 | 30 | No | No | Remission | Died |
| 4 | 14 | 14 | Yes | No | Remission | Died |
| 5 | 25 | 21 | Yes | Yes | Remission | Alive |
| 6 | 19 | 15 | Yes | No | Remission | Died |
| 7 | 10 | 10 | No | No | Remission | Alive |
| 8 | 10 | 10 | Yes | No | Remission | Died |
| 9 | 11 | 14 | Yes | No | Remission | Alive |
| 10 | 12 | 13 | Yes | No | Remission | Died |

GVHD: Graft vs host disease; PNL: Neutrophil; PLT: Platelet.

treatment (group B) in patients eligible for both strategies. The 10-year OS was not different between group A (76%) and group B (69%). Patients of group A with low risk EBMT score (10-year OS 85%) had significantly higher survival (median $P < 0.001$) compared with patients with high-risk (10-year OS 41%) and non-high-risk Euro score in group B (median $P = 0.047$; 10-year OS 73%)^[45]. The studies demonstrated that ASCT is still an option for selected CML patients.

Myeloablative vs non-myeloablative regimens

The curative effect of ASCT in CML is largely associated with the immune effect (GVL) mediated by alloreactive donor T cells. Reduced intensity conditioning (RIC) regimens provided reduced toxicity and rapid engraftment for elderly patients or those with comorbidities. In a small study was demonstrated that GVL effect may be insufficient and cytoreduction is required to provide cure with ASCT for CML^[46]. The 5-year OS and DFS was 85% \pm 8% with fludarabine, low-dose busulfan, and anti-T-lymphocyte globulin containing non-myeloablative (NMA) regimen^[47]. In a study which was evaluated ASCT with RIC regimen for CML, after a median follow-up of 30 mo, 35.3% of patients were still alive^[48]. Kebriaei *et al.*^[49] evaluated outcomes of 64 CML patients with advanced-phase disease who were treated with fludarabine-based RIC regimens. The 5-year OS and PFS were 33% and 20%, respectively. TRM was 33% at 100 d and 48% at 5 years after ASCT. In a study that were compared outcomes of MA conditioning regimen (56 patients) vs RIC regimen (28 patients), the 5- and 10-year leukemia-free survival and OS were similar. On the other hand, relapse rate was higher in patients receiving RIC regimen, whereas mortality rate was higher in patients receiving MA regimen^[50]. In a large multicenter CIBMTR analysis compared RIC regimens with NMA regimens, relapse risk was lower and DFS was higher with RIC regimens than NMA regimens^[51]. According to all these data, RIC regimens have had a place for elderly patients and patients who had comorbidities, but NMA regimens were inferior to RIC regimens.

In a study that was used data from the CIBMTR, they compared outcomes in patients who treated with ASCT following MA conditioning with cyclophosphamide (Cy) in

combination with TBI, oral busulfan (Bu) or intravenous (IV) busulfan^[52]. They concluded that Cy in combination with IV Bu was associated with less relapse than TBI or oral Bu. NRM and OS were similar.

GVHD prophylaxis

Another important issue is GVHD prophylaxis for ASCT. In CML, GVHD prophylaxis can influence the outcomes. T-cell depletion was associated with higher relapse rate, but DLIs were controlled the disease relapse in CML^[30-33]. Zuckerman *et al.*^[53] evaluated 38 patients who treated with ASCT using partial T cell depletion (TCD) and preemptive DLI, without post-transplant GVHD prophylaxis. The 5-year LFS and OS were 78.95% and 84.2%, respectively. Acute GVHD rate was 18% in post-transplant patients and 24% in patients receiving DLI. They concluded that partial TCD and preemptive DLI was reduced the GVHD risk. In a small study, the CCyR was induced in 8 of 9 CML patients who treated with ASCT using an alemtuzumab-based RIC regimen. GVHD incidence was low but disease relapse was frequent^[54].

Post-transplantation relapse

DLIs, TKIs, chemotherapy and second ASCT can be used for treatment of relapse CML after ASCT^[55-59]. Olavarria *et al.*^[55] reported response to imatinib in 128 patients with CML relapsing after ASCT. The CCyR rate was 58% for patients in CP, 48% for AP and 22% for patients in BC. The CyR rates were 63% for CP or AP and 43% for BP in a small study that evaluated response to imatinib in 28 relapse CML patients after ASCT^[58]. They concluded that imatinib is highly effective treatment for relapse CML after ASCT. A retrospective study was evaluated pre-DLI factors associated with prolonged survival in remission without secondary GVHD. They reported that approximately 50% of responding patients treated with DLI had GVL effect without secondary GVHD. Prolonged survival in remission without secondary GVHD was observed in patients who were given DLI beyond 1 year from ASCT for molecular and/or cytogenetic relapse^[60].

Donor source

Transplantation from HLA-matched sibling donor (MSD) has been associated with the most favorable outcomes^[61-64].

In a study from China, they compared the long-term outcomes of HLA-MSD with mismatched related donor (MRD) and unrelated donor (URD) ASCT for CML. They concluded that OS is similar between HLA allele-matched URD and MSD transplantation, but OS is lower in MRD and mismatched URD transplantation than MSD transplantation^[64].

Although MSD transplantation has favorable outcomes, MSD is available for only one third of the patients. So, we can choose MRD, URD or haploidentical donor for ASCT. Previously, haploidentical donor transplantation has had inferior outcomes than MSD. These results are related to higher GVHD and TRM rates. Post-transplantation cyclophosphamide improved the outcomes of haploidentical transplantation. Ma *et al*^[65] compared outcomes of 67 haploidentical ASCT and 23 MRD ASCT for patients with BP-CML or CP-CML from blast crisis. The 3-year OS and RFS rates were 60.0% and 51.1 for haploidentical transplantation and 55.3% and 47.8% for MRD transplantation, respectively. They concluded that haploidentical transplantation is an option for BP-CML with comparable survival to MRD transplantation.

Transplantation time

There are some reports that time from diagnosis to ASCT less than 12 mo is associated with better outcomes for patients advanced phase CML^[36,37]. Xu *et al*^[66] reported that for T315I mutation positive CML patients, haploidentical ASCT is highly curative treatment and immediate ASCT could result in promising survival for patients in CP/AP. There are different suggestions about patients in CP CML who failed second-line TKI. These patients could receive a third-line agent or be considered for SCT. Patients in BP should receive intensive chemotherapy with or without a TKI. If patients achieved second chronic phase, ASCT should be considered^[9].

CONCLUSION

ASCT is still an important option for treatment of CML. There are some questions about timing of transplantation, optimal conditioning regimen and optimal GVHD prophylaxis. Some reports indicate that using TKI before ASCT is not associated with inferior ASCT outcomes. Non-myeloablative ASCT seems to be feasible for older and medically infirm patients. Relapse after ASCT can be managed with DLIs and TKIs.

REFERENCES

- 1 **Jabbour E**, Kantarjian H. Chronic myeloid leukemia: 2014 update on diagnosis, monitoring, and management. *Am J Hematol* 2014; **89**: 547-556 [PMID: 24729196 DOI: 10.1002/ajh.23691]
- 2 **Quintás-Cardama A**, Cortes J. Molecular biology of bcr-abl1-positive chronic myeloid leukemia. *Blood* 2009; **113**: 1619-1630 [PMID: 18827185 DOI: 10.1182/blood-2008-03-144790]
- 3 **Baccarani M**, Pileri S, Steegmann JL, Muller M, Soverini S, Dreyling M. Chronic myeloid leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; **23** Suppl 7: vii72-vii77 [PMID: 22997458 DOI: 10.1093/annonc/
- 4 **Swerdlow SH**, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, editors. World Health Organization classification of tumors of haematopoietics and lymphoid tissues. Lyon, France: IARC Press, 2008
- 5 **Baccarani M**, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J, Cervantes F, Deininger M, Gratwohl A, Guilhot F, Hochhaus A, Horowitz M, Hughes T, Kantarjian H, Larson R, Radich J, Simonsson B, Silver RT, Goldman J, Hehlmann R. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. *J Clin Oncol* 2009; **27**: 6041-6051 [PMID: 19884523 DOI: 10.1200/JCO.2009.25.0779]
- 6 **Sokal JE**, Cox EB, Baccarani M, Tura S, Gomez GA, Robertson JE, Tso CY, Braun TJ, Clarkson BD, Cervantes F. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. *Blood* 1984; **63**: 789-799 [PMID: 6584184]
- 7 **Hasford J**, Pffirmann M, Hehlmann R, Allan NC, Baccarani M, Kluin-Nelemans JC, Alimena G, Steegmann JL, Ansari H. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. *J Natl Cancer Inst* 1998; **90**: 850-858 [PMID: 9625174]
- 8 **Hasford J**, Baccarani M, Hoffmann V, Guilhot J, Saussele S, Rosti G, Guilhot F, Porkka K, Ossenkoppele G, Lindoerfer D, Simonsson B, Pffirmann M, Hehlmann R. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. *Blood* 2011; **118**: 686-692 [PMID: 21536864 DOI: 10.1182/blood-2010-12-319038]
- 9 **Baccarani M**, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF, Cervantes F, Clark RE, Cortes JE, Guilhot F, Hjorth-Hansen H, Hughes TP, Kantarjian HM, Kim DW, Larson RA, Lipton JH, Mahon FX, Martinelli G, Mayer J, Müller MC, Niederwieser D, Pane F, Radich JP, Rousselot P, Saglio G, Saubele S, Schiffer C, Silver R, Simonsson B, Steegmann JL, Goldman JM, Hehlmann R. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood* 2013; **122**: 872-884 [PMID: 23803709 DOI: 10.1182/blood-2013-05-501569]
- 10 **Deininger M**, O'Brien SG, Guilhot F, Goldman JM, Hochhaus A, Hughes TP, Radich JP, Hatfield AK, Mone M, Filian J, Reynolds J, Gathmann I, Larson RA, Druker BJ. International randomized study of interferon vs STI571 (IRIS) 8-year follow up: sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase treated with imatinib. *ASH Annual Meeting Abstracts* 2009; **114**: 1126
- 11 **Kantarjian HM**, Shah NP, Cortes J, Baccarani M, Agarwal MB, Undurraga MS, Wang J, Ipiña JJ, Kim DW, Ogura M, Pavlovsky C, Junghans C, Milone JH, Nicolini FE, Robak T, Van Droogenbroeck J, Vellenga E, Bradley-Garelik MB, Zhu C, Hochhaus A. Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). *Blood* 2012; **119**: 1123-1129 [PMID: 22160483 DOI: 10.1182/blood-2011-08-376087]
- 12 **Saglio G**, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C, Pasquini R, Clark RE, Hochhaus A, Hughes TP, Gallagher N, Hoeneckopp A, Dong M, Haque A, Larson RA, Kantarjian HM. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med* 2010; **362**: 2251-2259 [PMID: 20525993 DOI: 10.1056/NEJMoa0912614]
- 13 **O'Brien SG**, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, Cornelissen JJ, Fischer T, Hochhaus A, Hughes T, Lechner K, Nielsen JL, Rousselot P, Reiffers J, Saglio G, Shepherd J, Simonsson B, Gratwohl A, Goldman JM, Kantarjian H, Taylor K, Verhoef G, Bolton AE, Capdeville R, Druker BJ. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2003; **348**: 994-1004 [PMID: 12637609 DOI: 10.1056/NEJMoa022457]
- 14 **Kantarjian H**, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, Moiraghi B, Shen Z, Mayer J, Pasquini R, Nakamae H, Huguet F, Boqué C, Chuah C, Bleickardt E, Bradley-Garelik MB, Zhu C, Sztatowski T, Shapiro D, Baccarani M. Dasatinib versus imatinib

- in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2010; **362**: 2260-2270 [PMID: 20525995 DOI: 10.1056/NEJMoa1002315]
- 15 **Jabbour E**, Kantarjian HM, Saglio G, Steegmann JL, Shah NP, Boqué C, Chuah C, Pavlovsky C, Mayer J, Cortes J, Baccarani M, Kim DW, Bradley-Garelik MB, Mohamed H, Wildgust M, Hochhaus A. Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). *Blood* 2014; **123**: 494-500 [PMID: 24311723 DOI: 10.1182/blood-2013-06-511592]
 - 16 **Larson RA**, Hochhaus A, Hughes TP, Clark RE, Etienne G, Kim DW, Flinn IW, Kurokawa M, Moiraghi B, Yu R, Blakesley RE, Gallagher NJ, Saglio G, Kantarjian HM. Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. *Leukemia* 2012; **26**: 2197-2203 [PMID: 22699418 DOI: 10.1038/leu.2012.134]
 - 17 **Komarova NL**, Katouli AA, Wodarz D. Combination of two but not three current targeted drugs can improve therapy of chronic myeloid leukemia. *PLoS One* 2009; **4**: e4423 [PMID: 19204794 DOI: 10.1371/journal.pone.0004423]
 - 18 **Hiwase DK**, White D, Zrim S, Saunders V, Melo JV, Hughes TP. Nilotinib-mediated inhibition of ABCB1 increases intracellular concentration of dasatinib in CML cells: implications for combination TKI therapy. *Leukemia* 2010; **24**: 658-660 [PMID: 20010623 DOI: 10.1038/leu.2009.242]
 - 19 **Zhu Y**, Pan L, Hong M, Liu W, Qiao C, Li J, Qian S. The combination therapy of imatinib and dasatinib achieves longterm molecular response in two imatinib-resistant and dasatinibintolerant patients with advanced chronic myeloid leukemia. *J Biomed Res* 2014 Sep 7; **30**: Epub ahead of print [PMID: 27346465 DOI: 10.7555/JBR.28.20130172]
 - 20 **Cortes JE**, Kantarjian HM, Brümmendorf TH, Kim DW, Turkina AG, Shen ZX, Pasquini R, Khoury HJ, Arkin S, Volkert A, Besson N, Abbas R, Wang J, Leip E, Gambacorti-Passerini C. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. *Blood* 2011; **118**: 4567-4576 [PMID: 21865346 DOI: 10.1182/blood-2011-05-355594]
 - 21 **Cortes JE**, Kim DW, Pinilla-Ibarz J, le Coutre P, Paquette R, Chuah C, Nicolini FE, Apperley JF, Khoury HJ, Talpaz M, DiPersio J, DeAngelo DJ, Abruzzese E, Rea D, Baccarani M, Müller MC, Gambacorti-Passerini C, Wong S, Lustgarten S, Rivera VM, Clackson T, Turner CD, Haluska FG, Guilhot F, Deininger MW, Hochhaus A, Hughes T, Goldman JM, Shah NP, Kantarjian H. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med* 2013; **369**: 1783-1796 [PMID: 24180494 DOI: 10.1056/NEJMoa1306494]
 - 22 **Ohanian M**, Kantarjian HM, Quintas-Cardama A, Jabbour E, Abruzzo L, Verstovsek S, Borthakur G, Ravandi F, Garcia-Manero G, Champlin R, Pierce S, Alattar ML, Trinh LX, Luthra R, Ferrajoli A, Kadia T, O'Brien S, Cortes JE. Tyrosine kinase inhibitors as initial therapy for patients with chronic myeloid leukemia in accelerated phase. *Clin Lymphoma Myeloma Leuk* 2014; **14**: 155-162.e1 [PMID: 24332214 DOI: 10.1016/j.clml.2013.08.008]
 - 23 **Giralt SA**, Arora M, Goldman JM, Lee SJ, Maziarz RT, McCarthy PL, Sobocinski KA, Horowitz MM; Chronic Leukemia Working Committee, Center for International Blood and Marrow Transplant Research. Impact of imatinib therapy on the use of allogeneic haematopoietic progenitor cell transplantation for the treatment of chronic myeloid leukaemia. *Br J Haematol* 2007; **137**: 461-467 [PMID: 17459051 DOI: 10.1111/j.1365-2141.2007.06582.x]
 - 24 **Gratwohl A**, Baldomero H, Passweg J. The role of hematopoietic stem cell transplantation in chronic myeloid leukemia. *Ann Hematol* 2015; **94** Suppl 2: S177-S186 [PMID: 25814084 DOI: 10.1007/s00277-015-2313-3]
 - 25 **Hamilton A**, Helgason GV, Schemionek M, Zhang B, Myssina S, Allan EK, Nicolini FE, Müller-Tidow C, Bhatia R, Brunton VG, Koschmieder S, Holyoake TL. Chronic myeloid leukemia stem cells are not dependent on Bcr-Abl kinase activity for their survival. *Blood* 2012; **119**: 1501-1510 [PMID: 22184410 DOI: 10.1182/blood-2010-12-326843]
 - 26 **Copland M**, Hamilton A, Elrick LJ, Baird JW, Allan EK, Jordanides N, Barow M, Mountford JC, Holyoake TL. Dasatinib (BMS-354825) targets an earlier progenitor population than imatinib in primary CML but does not eliminate the quiescent fraction. *Blood* 2006; **107**: 4532-4539 [PMID: 16469872 DOI: 10.1182/blood-2005-07-2947]
 - 27 **Clift RA**, Buckner CD, Thomas ED, Doney K, Fefer A, Neiman PE, Singer J, Sanders J, Stewart P, Sullivan KM, Deeg J, Storb R. Treatment of chronic granulocytic leukaemia in chronic phase by allogeneic marrow transplantation. *Lancet* 1982; **2**: 621-623 [PMID: 6125772 DOI: 10.1016/S0140-6736(82)92735-0]
 - 28 **Goldman JM**, Baughan AS, McCarthy DM, Worsley AM, Hows JM, Gordon-Smith EC, Catovsky D, Batchelor JR, Goolden AW, Galton DA. Marrow transplantation for patients in the chronic phase of chronic granulocytic leukaemia. *Lancet* 1982; **2**: 623-625 [PMID: 6125773 DOI: 10.1016/S0140-6736(82)92736-2]
 - 29 **McGlave PB**, Arthur DC, Kim TH, Ramsay NK, Hurd DD, Kersey J. Successful allogeneic bone-marrow transplantation for patients in the accelerated phase of chronic granulocytic leukaemia. *Lancet* 1982; **2**: 625-627 [PMID: 6125774 DOI: 10.1016/S0140-6736(82)92737-4]
 - 30 **Horowitz MM**, Gale RP, Sondel PM, Goldman JM, Kersey J, Kolb HJ, Rimm AA, Ringden O, Rozman C, Speck B. Graft-versus-leukemia reactions after bone marrow transplantation. *Blood* 1990; **75**: 555-562 [PMID: 2297567]
 - 31 **Kolb HJ**, Mittermüller J, Clemm C, Holler E, Ledderose G, Brehm G, Heim M, Wilmanns W. Donor leukocyte transfusions for treatment of recurrent chronic myelogenous leukemia in marrow transplant patients. *Blood* 1990; **76**: 2462-2465 [PMID: 2265242]
 - 32 **van Rhee F**, Lin F, Cullis JO, Spencer A, Cross NC, Chase A, Garicochea B, Bungey J, Barrett J, Goldman JM. Relapse of chronic myeloid leukemia after allogeneic bone marrow transplant: the case for giving donor leukocyte transfusions before the onset of hematologic relapse. *Blood* 1994; **83**: 3377-3383 [PMID: 8193375]
 - 33 **Mackinnon S**, Papadopoulos EB, Carabasi MH, Reich L, Collins NH, Boulad F, Castro-Malaspina H, Childs BH, Gillio AP, Kernan NA. Adoptive immunotherapy evaluating escalating doses of donor leukocytes for relapse of chronic myeloid leukemia after bone marrow transplantation: separation of graft-versus-leukemia responses from graft-versus-host disease. *Blood* 1995; **86**: 1261-1268 [PMID: 7632930]
 - 34 **Gratwohl A**, Brand R, Apperley J, Crawley C, Ruutu T, Corradini P, Carreras E, Devergie A, Guglielmi C, Kolb HJ, Niederwieser D. Allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia in Europe 2006: transplant activity, long-term data and current results. An analysis by the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). *Haematologica* 2006; **91**: 513-521 [PMID: 16533723]
 - 35 **Saussele S**, Lauseker M, Gratwohl A, Beelen DW, Bunjes D, Schwerdtfeger R, Kolb HJ, Ho AD, Falge C, Holler E, Schlimok G, Zander AR, Arnold R, Kanz L, Dengler R, Haferlach C, Schlegelberger B, Pffirmann M, Müller MC, Schnittger S, Leitner A, Pletsch N, Hochhaus A, Hasford J, Hehlmann R. 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* 2010; **115**: 1880-1885 [PMID: 19965667 DOI: 10.1182/blood-2009-08-237115]
 - 36 **Jiang Q**, Xu LP, Liu DH, Liu KY, Chen SS, Jiang B, Jiang H, Chen H, Chen YH, Han W, Zhang XH, Wang Y, Qin YZ, Liu YR, Lai YY, Huang XJ. Imatinib mesylate versus allogeneic hematopoietic stem cell transplantation for patients with chronic myelogenous leukemia in the accelerated phase. *Blood* 2011; **117**: 3032-3040 [PMID: 21252092 DOI: 10.1182/blood-2010-09-308510]
 - 37 **Pffirmann M**, Saussele S, Hochhaus A, Reiter A, Berger U, Hossfeld DK, Nerl C, Scheid C, Spiekermann K, Mayer J, Hellmann A, Lechner K, Falge C, Sayer HG, Bunjes D, Ganser A, Beelen

- DW, Baldomero H, Schanz U, Heimpel H, Kolb HJ, Hasford J, Gratwohl A, Hehlmann R. Explaining survival differences between two consecutive studies with allogeneic stem cell transplantation in patients with chronic myeloid leukemia. *J Cancer Res Clin Oncol* 2014; **140**: 1367-1381 [PMID: 24718719 DOI: 10.1007/s00432-014-1662-y]
- 38 **Khoury HJ**, Kukreja M, Goldman JM, Wang T, Halter J, Arora M, Gupta V, Rizzieri DA, George B, Keating A, Gale RP, Marks DI, McCarthy PL, Woolfrey A, Szer J, Giralt SA, Maziarz RT, Cortes J, Horowitz MM, Lee SJ. Prognostic factors for outcomes in allogeneic transplantation for CML in the imatinib era: a CIBMTR analysis. *Bone Marrow Transplant* 2012; **47**: 810-816 [PMID: 21986636 DOI: 10.1038/bmt.2011.194]
- 39 **Lee SJ**, Kukreja M, Wang T, Giralt SA, Szer J, Arora M, Woolfrey AE, Cervantes F, Champlin RE, Gale RP, Halter J, Keating A, Marks DI, McCarthy PL, Olavarria E, Stadtmauer EA, Abecasis M, Gupta V, Khoury HJ, George B, Hale GA, Liesveld JL, Rizzieri DA, Antin JH, Bolwell BJ, Carabasi MH, Copelan E, Ilhan O, Litzow MR, Schouten HC, Zander AR, Horowitz MM, Maziarz RT. Impact of prior imatinib mesylate on the outcome of hematopoietic cell transplantation for chronic myeloid leukemia. *Blood* 2008; **112**: 3500-3507 [PMID: 18664621 DOI: 10.1182/blood-2008-02-141689]
- 40 **Nair AP**, Barnett MJ, Broady RC, Hogge DE, Song KW, Toze CL, Nantel SH, Power MM, Sutherland HJ, Nevill TJ, Abou Mourad Y, Narayanan S, Gerrie AS, Forrest DL. Allogeneic Hematopoietic Stem Cell Transplantation Is an Effective Salvage Therapy for Patients with Chronic Myeloid Leukemia Presenting with Advanced Disease or Failing Treatment with Tyrosine Kinase Inhibitors. *Biol Blood Marrow Transplant* 2015; **21**: 1437-1444 [PMID: 25865648 DOI: 10.1016/j.bbmt.2015.04.005]
- 41 **Oehler VG**, Gooley T, Snyder DS, Johnston L, Lin A, Cummings CC, Chu S, Bhatia R, Forman SJ, Negrin RS, Appelbaum FR, Radich JP. The effects of imatinib mesylate treatment before allogeneic transplantation for chronic myeloid leukemia. *Blood* 2007; **109**: 1782-1789 [PMID: 17062727 DOI: 10.1182/blood-2006-06-031682]
- 42 **Jabbour E**, Cortes J, Kantarjian H, Giralt S, Andersson BS, Giles F, Shpall E, Kebriaei P, Champlin R, de Lima M. Novel tyrosine kinase inhibitor therapy before allogeneic stem cell transplantation in patients with chronic myeloid leukemia: no evidence for increased transplant-related toxicity. *Cancer* 2007; **110**: 340-344 [PMID: 17559140 DOI: 10.1002/cncr.22778]
- 43 **Shimoni A**, Leiba M, Schleuning M, Martineau G, Renaud M, Koren-Michowitz M, Ribakovski E, le Coutre P, Arnold R, Guilhot F, Nagler A. 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* 2009; **23**: 190-194 [PMID: 18596746 DOI: 10.1038/leu.2008.160]
- 44 **Goldman JM**, Majhail NS, Klein JP, Wang Z, Sobocinski KA, Arora M, Horowitz MM, Rizzo JD. Relapse and late mortality in 5-year survivors of myeloablative allogeneic hematopoietic cell transplantation for chronic myeloid leukemia in first chronic phase. *J Clin Oncol* 2010; **28**: 1888-1895 [PMID: 20212247 DOI: 10.1200/JCO.2009.26.7757]
- 45 **Gratwohl A**, Pffirrmann M, Zander A, Kröger N, Beelen D, Novotny J, Nerl C, Scheid C, Spiekermann K, Mayer J, Sayer HG, Falge C, Bunjes D, Döhner H, Ganser A, Schmidt-Wolf I, Schwerdtfeger R, Baurmann H, Kuse R, Schmitz N, Wehmeier A, Fischer JT, Ho AD, Wilhelm M, Goebeler ME, Lindemann HW, Bormann M, Hertenstein B, Schlimok G, Baerlocher GM, Aul C, Pfreundschuh M, Fabian M, Staib P, Edinger M, Schatz M, Fauser A, Arnold R, Kindler T, Wulf G, Rosselet A, Hellmann A, Schäfer E, Prümmer O, Schenk M, Hasford J, Heimpel H, Hossfeld DK, Kolb HJ, Büsche G, Haferlach C, Schnittger S, Müller MC, Reiter A, Berger U, Saußebe S, Hochhaus A, Hehlmann R. Long-term outcome of patients with newly diagnosed chronic myeloid leukemia: a randomized comparison of stem cell transplantation with drug treatment. *Leukemia* 2016; **30**: 562-569 [PMID: 26464170 DOI: 10.1038/leu.2015.281]
- 46 **Sloand E**, Childs RW, Solomon S, Greene A, Young NS, Barrett AJ. The graft-versus-leukemia effect of nonmyeloablative stem cell allografts may not be sufficient to cure chronic myelogenous leukemia. *Bone Marrow Transplant* 2003; **32**: 897-901 [PMID: 14561990 DOI: 10.1038/sj.bmt.1704231]
- 47 **Or R**, Shapira MY, Resnick I, Amar A, Ackerstein A, Samuel S, Aker M, Naparstek E, Nagler A, Slaviv S. Nonmyeloablative allogeneic stem cell transplantation for the treatment of chronic myeloid leukemia in first chronic phase. *Blood* 2003; **101**: 441-445 [PMID: 12393604 DOI: 10.1182/blood-2002-02-0535]
- 48 **Das M**, Saikia TK, Advani SH, Parikh PM, Tawde S. Use of a reduced-intensity conditioning regimen for allogeneic transplantation in patients with chronic myeloid leukemia. *Bone Marrow Transplant* 2003; **32**: 125-129 [PMID: 12838275 DOI: 10.1038/sj.bmt.1704107]
- 49 **Kebriaei P**, Detry MA, Giralt S, Carrasco-Yalan A, Anagnostopoulos A, Couriel D, Khouri IF, Anderlini P, Hosing C, Alousi A, Champlin RE, de Lima M. Long-term follow-up of allogeneic hematopoietic stem-cell transplantation with reduced-intensity conditioning for patients with chronic myeloid leukemia. *Blood* 2007; **110**: 3456-3462 [PMID: 17652620 DOI: 10.1182/blood-2007-04-085969]
- 50 **Topcuoglu P**, Arat M, Ozcan M, Arslan O, Ilhan O, Beksac M, Gurman G. Case-matched comparison with standard versus reduced intensity conditioning regimen in chronic myeloid leukemia patients. *Ann Hematol* 2012; **91**: 577-586 [PMID: 21971669 DOI: 10.1007/s00277-011-1349-2]
- 51 **Warlick E**, Ahn KW, Pedersen TL, Artz A, de Lima M, Pulsipher M, Akpek G, Aljurf M, Cahn JY, Cairo M, Chen YB, Cooper B, Deol A, Giralt S, Gupta V, Khoury HJ, Kohrt H, Lazarus HM, Lewis I, Olsson R, Pidala J, Savani BN, Seftel M, Socié G, Tallman M, Ustun C, Vij R, Vindeløv L, Weisdorf D. Reduced intensity conditioning is superior to nonmyeloablative conditioning for older chronic myelogenous leukemia patients undergoing hematopoietic cell transplant during the tyrosine kinase inhibitor era. *Blood* 2012; **119**: 4083-4090 [PMID: 22408257 DOI: 10.1182/blood-2012-02-409763]
- 52 **Copelan EA**, Avalos BR, Ahn KW, Zhu X, Gale RP, Grunwald MR, Hamadani M, Hamilton BK, Hale GA, Marks DI, Waller EK, Savani BN, Costa LJ, Ramanathan M, Cahn JY, Khoury HJ, Weisdorf DJ, Inamoto Y, Kamble RT, Schouten HC, Wirk B, Litzow MR, Aljurf MD, van Besien KW, Ustun C, Bolwell BJ, Bredeson CN, Fasan O, Ghosh N, Horowitz MM, Arora M, Szer J, Loren AW, Alyea EP, Cortes J, Maziarz RT, Kalaycio ME, Saber W. Comparison of outcomes of allogeneic transplantation for chronic myeloid leukemia with cyclophosphamide in combination with intravenous busulfan, oral busulfan, or total body irradiation. *Biol Blood Marrow Transplant* 2015; **21**: 552-558 [PMID: 25528388 DOI: 10.1016/j.bbmt.2014.12.010]
- 53 **Zuckerman T**, Katz T, Haddad N, Fineman R, Dann EJ, Avivi I, Ofra Y, Gavish I, Faibish T, Sahar D, Hertz E, Sabo E, Reisner Y, Rowe JM. Allogeneic stem cell transplantation for patients with chronic myeloid leukemia: risk stratified approach with a long-term follow-up. *Am J Hematol* 2012; **87**: 875-879 [PMID: 22847303 DOI: 10.1002/ajh.23263]
- 54 **Poiré X**, Artz A, Larson RA, Kline J, Odenike O, Rich E, Godley L, Stock W, van Besien K. Allogeneic stem cell transplantation with alemtuzumab-based conditioning for patients with advanced chronic myelogenous leukemia. *Leuk Lymphoma* 2009; **50**: 85-91 [PMID: 19142796 DOI: 10.1080/10428190802626624]
- 55 **Olavarria E**, Ottmann OG, Deininger M, Clark RE, Bandini G, Byrne J, Lipton J, Vitek A, Michallet M, Siegert W, Ullmann A, Wassmann B, Niederwieser D, Fischer T. Response to imatinib in patients who relapse after allogeneic stem cell transplantation for chronic myeloid leukemia. *Leukemia* 2003; **17**: 1707-1712 [PMID: 12970768 DOI: 10.1038/sj.leu.2403068]
- 56 **Kim YJ**, Kim DW, Lee S, Kim YL, Hwang JY, Park YH, Kim HJ, Lee JW, Min WS, Kim CC. Cytogenetic clonal evolution alone in CML relapse post-transplantation does not adversely affect response to imatinib mesylate treatment. *Bone Marrow Transplant* 2004; **33**:

- 237-242 [PMID: 14628081 DOI: 10.1038/sj.bmt.1704332]
- 57 **DeAngelo DJ**, Hochberg EP, Alyea EP, Longtine J, Lee S, Galinsky I, Parekkedon B, Ritz J, Antin JH, Stone RM, Soiffer RJ. Extended follow-up of patients treated with imatinib mesylate (gleevec) for chronic myelogenous leukemia relapse after allogeneic transplantation: durable cytogenetic remission and conversion to complete donor chimerism without graft-versus-host disease. *Clin Cancer Res* 2004; **10**: 5065-5071 [PMID: 15297408 DOI: 10.1158/1078-0432.CCR-03-0580]
- 58 **Kantarjian HM**, O'Brien S, Cortes JE, Giralt SA, Rios MB, Shan J, Giles FJ, Thomas DA, Faderl S, De Lima M, Garcia-Manero G, Champlin R, Arlinghaus R, Talpaz M. Imatinib mesylate therapy for relapse after allogeneic stem cell transplantation for chronic myelogenous leukemia. *Blood* 2002; **100**: 1590-1595 [PMID: 12176876]
- 59 **Savani BN**, Montero A, Kurlander R, Childs R, Hensel N, Barrett AJ. Imatinib synergizes with donor lymphocyte infusions to achieve rapid molecular remission of CML relapsing after allogeneic stem cell transplantation. *Bone Marrow Transplant* 2005; **36**: 1009-1015 [PMID: 16205732 DOI: 10.1038/sj.bmt.1705167]
- 60 **Radujkovic A**, Guglielmi C, Bergantini S, Iacobelli S, van Biezen A, Milojkovic D, Gratwohl A, Schattenberg AV, Verdonck LF, Niederwieser DW, de Witte T, Kröger N, Olavarria E. Donor Lymphocyte Infusions for Chronic Myeloid Leukemia Relapsing after Allogeneic Stem Cell Transplantation: May We Predict Graft-versus-Leukemia Without Graft-versus-Host Disease? *Biol Blood Marrow Transplant* 2015; **21**: 1230-1236 [PMID: 25797175 DOI: 10.1016/j.bbmt.2015.03.012]
- 61 **Weisdorf DJ**, Anasetti C, Antin JH, Kernan NA, Kollman C, Snyder D, Petersdorf E, Nelson G, McGlave P. Allogeneic bone marrow transplantation for chronic myelogenous leukemia: comparative analysis of unrelated versus matched sibling donor transplantation. *Blood* 2002; **99**: 1971-1977 [PMID: 11877268]
- 62 **Ringden O**, Pavletic SZ, Anasetti C, Barrett AJ, Wang T, Wang D, Antin JH, Di Bartolomeo P, Bolwell BJ, Bredeson C, Cairo MS, Gale RP, Gupta V, Hahn T, Hale GA, Halter J, Jagasia M, Litzow MR, Locatelli F, Marks DI, McCarthy PL, Cowan MJ, Petersdorf EW, Russell JA, Schiller GJ, Schouten H, Spellman S, Verdonck LF, Wingard JR, Horowitz MM, Arora M. The graft-versus-leukemia effect using matched unrelated donors is not superior to HLA-identical siblings for hematopoietic stem cell transplantation. *Blood* 2009; **113**: 3110-3118 [PMID: 19059878 DOI: 10.1182/blood-2008-07-163212]
- 63 **Arora M**, Weisdorf DJ, Spellman SR, Haagenson MD, Klein JP, Hurley CK, Selby GB, Antin JH, Kernan NA, Kollman C, Nademane A, McGlave P, Horowitz MM, Petersdorf EW. HLA-identical sibling compared with 8/8 matched and mismatched unrelated donor bone marrow transplant for chronic phase chronic myeloid leukemia. *J Clin Oncol* 2009; **27**: 1644-1652 [PMID: 19224849 DOI: 10.1200/JCO.2008.18.7740]
- 64 **Liu QF**, Xu XJ, Chen YK, Sun J, Zhang Y, Fan ZP, Xu D, Jiang QL, Wei YQ, Huang F, Feng R, Liu XL, Xu B, Meng FY. Long-term outcomes of HLA-matched sibling compared with mismatched related and unrelated donor hematopoietic stem cell transplantation for chronic phase chronic myelogenous leukemia: a single institution experience in China. *Ann Hematol* 2011; **90**: 331-341 [PMID: 20872002 DOI: 10.1007/s00277-010-1081-3]
- 65 **Ma YR**, Huang XJ, Xu ZL, Liu KY, Chen H, Zhang XH, Han W, Chen YH, Wang FR, Wang JZ, Wang Y, Chen Y, Yan CH, Xu LP. Transplantation from haploidentical donor is not inferior to that from identical sibling donor for patients with chronic myeloid leukemia in blast crisis or chronic phase from blast crisis. *Clin Transplant* 2016; **30**: 994-1001 [PMID: 27292967 DOI: 10.1111/ctr.12779]
- 66 **Xu LP**, Xu ZL, Zhang XH, Chen H, Chen YH, Han W, Chen Y, Wang FR, Wang JZ, Wang Y, Yan CH, Mo XD, Liu KY, Huang XJ. Allogeneic Stem Cell Transplantation for Patients with T3151 BCR-ABL Mutated Chronic Myeloid Leukemia. *Biol Blood Marrow Transplant* 2016; **22**: 1080-1086 [PMID: 26995693 DOI: 10.1016/j.bbmt.2016.03.012]

P- Reviewer: Fukuda S, Liu L, Tanabe S S- Editor: Gong XM

L- Editor: A E- Editor: Li D





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

