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

Saydam G *et al*. Allogeneic stem cell transplantation in CML

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**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

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**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.

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**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 MR4.0 (detectable disease with, 0.01% BCR-ABL1 IS or undetectable disease in cDNA with > 10.000 ABL1 transcripts) and MR4.5 (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].

**TREATMENT OF CML**

Imatinib, the first TKI, improved the 10-year survival rate from 10%-20% to 805-90%[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 versus 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.

***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/d 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 mcg/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. 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]. Pfirrmann *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 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% +/- 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 choice 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 manage with DLIs and TKIs.

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**Table 1 Calculation of relative risk**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Sokal score** | **Hasford score** | **EUTOS**  |
| Calculation  | 0.0116 × (age - 43.4) + 0.0345 × (spleen - 7.51) + 0.188 × [(platelet count/700)2 -0.563] + 0.0887 × (blast cells - 2.10) | 0.666 when age ≥ 50 + (0.042 × spleen) +1.0956 when platelet > 1500 × 109/L +(0.0584 × blast cells) +0.20399 when basophils > 3% + (0.0413 × eosinophils) + 100 | Spleen × 4 + basophils × 7 |
| Risk definition  | Exponential of the totalLow risk: < 0.8Intermediate risk: 0.8-1.2High risk: > 1.2 | Total × 1000Low risk: ≤ 780Intermediate risk: 781-1480High risk: > 1480 | TotalLow risk: ≤ 87High 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.

**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/orPh+ ≤ 35% | BCR-ABL1 > 10% and/or Ph+ 35%-95% | Non-CHRand/or Ph+ > 95% |
| 6 mo | BCR-ABL1 ≤ 1% and/orPh+ 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 CHRLoss of CCyRConfirmed loss of MMR mutations CCA/Ph+ |

In 2 consecutive tests, of which one with a BCR-ABL1 transcripts level ≥ 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.

**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 | 1st AP | 50 | Resistance to imatinib and clonal evolution | M |
| 2 | F | 51 | 2nd CP | 14 | Previous myeloid blastic phase | M |
| 3 | M | 25 | 2nd CP | 61 | Previous lymphoid blastic phase | M |
| 4 | M | 33 | 1st CP | 37 | Resistance to imatinib and dasatinib | M |
| 5 | F | 54 | 1st AP | 103 | Resistance to imatinib, nilotinib and dasatinib 1st accelerated phase  | F |
| 6 | M | 65 | 1st CP | 133 | Resistance to imatinib and nilotinib | F |
| 7 | F | 49 | 1st CP | 62 | Resistance to imatinib | M |
| 8 | M | 53 | 2nd CP | 63 | Previous myeloid blastic phase | M |
| 9 | M | 41 | 1st CP | 51 | Resistance to imatinib | M |
| 10 | M | 61 | 1st CP | 75 | Resistance to imatinib, nilotinib and dasatinib | F |

ASCT:Allogeneic stem cell transplantation.

**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.