The Results of Allogeneic Stem Cell Transplantation in CML — the Experience of BMT Unit Tîrgu Mureș

Tunyogi Aliz-Beáta[1], Benedek I[2], Benedek Erzsébet[1], Köpeczi Judit Beáta[1], Kakucs Enikő[1], Istrati Monica[1]

[1] County Emergency Clinical Hospital Tîrgu Mureș, Clinical Hematology and BMT Unit
[2] University of Medicine and Pharmacy of Tîrgu Mureș

Introduction: Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder the molecular hallmark of the disease is the BCR-ABL gene rearrangement which occurs as the result of a reciprocal translocation between chromosomes 9 and 22. Imatinib, a small molecule, tyrosine kinase inhibitor (TKI) was the first drug that targeted BCR-ABL. Since the introduction of the first and second generation of TKI the role of allogeneic stem cell transplantation in chronic myeloid leukemia is being reevaluated. With this retrospective analysis our aim was to define the role of allogeneic stem cell transplantation for CML in the tyrosine kinase inhibitor era. The following is a general overview of the role of ASCT in the management of CML.

Material and methods: At the BMT Unit Tîrgu Mureș between 2005–2009 we performed five allogeneic transplantations of high risk CML patients with identical sibling donors.

Results: Two of the patients are at present in complete hematologic and cytogenetic remission with no or minimal immunosuppressive therapy after 6 and respectively 3 years of follow up time. Two of the patients had disease free survival but died from infectious complications appeared in the 3rd and 6th month after the allogeneic stem cell transplantation. One patient had an early relapse with treatment refractory disease and died from the evolution of the disease.

Conclusions: We perform allogeneic stem cell transplantation only in the cases in which we have resistance to first and second generation of tyrosine kinase inhibitors (TKI), intolerance to TKI and if we have a suitable donor.

Keywords: allogeneic transplantation, CML, RT-PCR

Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder that arises in the stem cell compartment [1, 2]. The molecular hallmark of the disease is the BCR-ABL gene rearrangement [3, 4], which usually occurs as the result of a reciprocal translocation between chromosomes 9 and 22 [5]. Historically, CML was treated with busulfan or hydroxyurea, and was associated with a poor prognosis. These agents controlled the hematologic manifestations of the disease, but did not delay disease progression. Treatment with interferon alpha (IFN-a) induced complete cytogenetic responses in 5–25% of patients with CML in CP, and improved survival. Combining IFN-alpha with cytarabine produced additional benefits [6]. Imatinib (previously STI571), a small molecule tyrosine kinase inhibitor (TKI), was the first drug that targeted BCR-ABL and it has become the standard frontline therapy for CML in early CP on the basis of the excellent response rates and favorable toxicity profile shown in numerous clinical trials [7]. Since the introduction of the first and second generation of TKI the role of allogeneic stem cell transplantation in chronic myeloid leukemia is being reevaluated. Only allogeneic stem cell transplantation is capable of eradicating the malignant clone and thus has curative potential, but it is applicable to only a fraction of CML patients due to the considerable treatment-associated mortality [8].

Indications for allogeneic stem cell transplantation:

- patients in chronic phase with a suitable donor are transplanted if they do not achieve a complete hematologic response with 3 months of imatinib if they are predominantly Ph positive at 6 months or still have >35% PH positive metaphases at 12 months.
- patients who had loss of a previous hematologic or cytogenetic response or had a 1 log increase in BCR-ABL transcripts in patients who had achieved a complete cytogenetic response.
- chronic phase up to age 45 years who have a sibling donor or up to the age of 35 years in those with a molecularly matched unrelated donor as initial treatment.
- resistance or intolerance to first and second generation of tyrosine kinase inhibitors (TKI) and we have a suitable donor [9].

With this retrospective analysis our aim was to define the role of allogeneic stem cell transplantation for CML in the tyrosine kinase inhibitor era. This article intends to bee a general overview of the role of ASCT in the management of CML.

Material and methods

At the BMT Unit Tîrgu Mureș between 2005–2009 we performed five allogeneic transplantations of high risk CML patients with identical sibling donors. High resolution HLA typing was performed both for the patient and for the donors. All patients received Imatinib and presented intolerance or resistance to the treatment. The hematological assessment was done at the first presentation to our clinic. For the patients in advanced phase of the disease flow cytometry was performed from bone marrow to de-

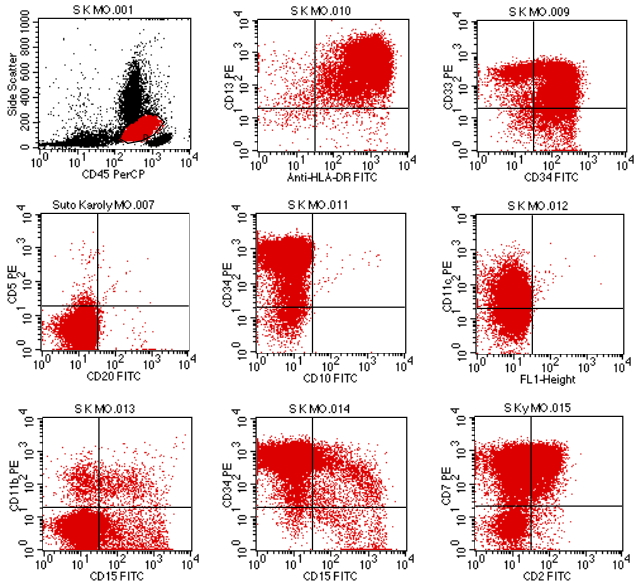

Fig. 1. Case 5: Flow cytometry before transplantation. SK, CML in blastic transformation, 41% blasts.

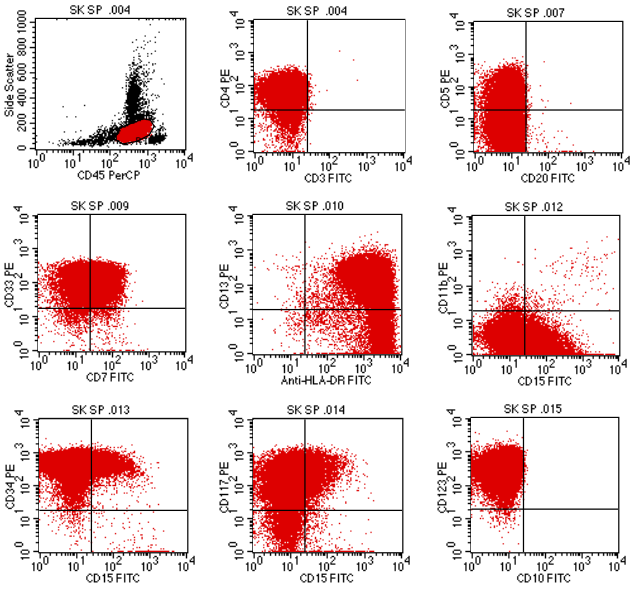

Fig. 2. Case 5: Flow cytometry performed in may 2009. SK, PB, 80% blasts.

termine the percent and the phenotype of the blast cells. For the assessment of the patient post transplantation we used the detection of BCR-ABL transcript with RT-PCR, cytogenetic with conventional G banding, complete blood count and flow cytometry in case of relapse.

Results

The characteristics of the patients are presented in Table I.

The 1st patient is a 24 year old male patient with a HLA identical sibling diagnosed in 2003 with CML. He received imatinib (Glivec®) 400 mg/day with intolerance (hematological toxicity – grade 3 thrombocytopenia). The imatinib (Glivec®) was reduced to 300 mg/day. The BCR-ABL transcript levels were increasing.

The 2nd patient is a 41 year old female with a HLA identical sibling diagnosed in 1998 with CML. First treated with hydroxyurea and then with imatinib (Glivec®) 400 mg/day. In 2006 under the imatinib treatment the disease progressing to accelerated phase. The patient received escalated doses of imatinib (600 mg/day), with progression of the disease to blastic transformation.

The 3rd patient is a 48 year old female with a HLA identical sibling diagnosed with CML in 1996. First treated with hydroxyurea and then with imatinib (Glivec®) 400 mg/day. In 2006 under the imatinib treatment the disease progressing to accelerated phase. These patient although received escalated doses of imatinib (600 mg/day).

The 4th patient is a 38 year old female diagnosed in 2003 with CML. She was treated with imatinib (Glivec®) 400 mg/day the disease progressing to accelerated phase. At presentation she received imatinib (Glivec®) 600 mg/day.

The 5th patient is a 41 year old male with identical sibling diagnosed in 2007 under imatinib treatment 400 mg/day presented blastic transformation of the disease (Flow cytometry performed).

All the patients had an HLA identical sibling donor. The donors age, sex, and the number of CD34+ and CD3+ cells are presented in Table II.

We used conventional conditioning regimen with Busulfan + Cyclofosfamid with one exception. In the second case we used reduced intensity conditioning regimen

Table I. Characteristics of the patients

Patient	Age (years)	Sex	Disease phase	Date of diagnosis	Treatment
B.C.	24	M	Chronic faze (CF)	2003	Glivec 400 mg/day Intolerance to imatinib → Glivec 300 mg/day (Bcr-Abl ↑ – 2005)
S.A.	41	F	Blastic transformation (BT)	1998	Hydreea + IFN (1998) Glivec 400 mg/day (1999–2005) → AF Glivec 600 mg →↑ BT
A.M.	47	F	Accelerated phase (AF)	1996	Hydreea + IFN (2001) Glivec 400 mg/day (2002–2007) → AF Glivec 600 mg/day
V.I.	38	F	Accelerated phase (AF)	2003	Glivec 400 mg/day (2003–2005) → AF Glivec 600 mg/day
S.K.	41	M	Blastic transformation (BT)	2007	Glivec 400 mg/day (04/2008) → BT Cytosar + Glivec

Table II. The caracteristics of the donors. Number of cells harvested

Patient	Donor type	Donor sex	Donor age	CD34+ stem cells	CD3+ cells
B.C.	Identical sibling	M	17 years	1.76 × 10^6/kg	91.89 × 10^6/kg
S.A.	Identical sibling	F	55 years	4.44 × 10^6/kg	137.9 × 10^6/kg
A.M.	Identical sibling	M	50 years	6.26 × 10^6/kg	433.17 × 10^6/kg
V.I.	Identical sibling	M	42 years	5.57 × 10^6/kg	278.9 × 10^6/kg
S.K.	Identical sibling	F	40 years	4.13 × 10^6/kg	367.9 × 10^6/kg

(RIC) due to the bad physical condition of the patient (weight 39 kg!). The immunosuppression was performed with Cyclosporine 3 mg/kg + MTX 15 mg/m^2 D1+, 10 mg/m^2 D3+, 6+, 11+. In the second case due to sever neurological toxicity (hallucinations) we need to change the immunosuppressive treatment (Tacrolimus 0.02 mg/kg) (Table III).

Table IV contains the presence of graft versus host disease (GVHD) in patients. Three patients presented mild or moderate acute GVHD. One patient presents chronic GVHD. Two patients presented no GVHD at all.

In Table V we present the survival of the patients after transplant in correlation with other factors.

Two of the patients are in complete hematologic and cytogenetic remission with no or minimal immunosuppressive therapy (Medrol 4 mg/day – mild chronic GVHD) after 6 and respectively 3 years of follow-up time. Two of the patients had a good disease free survival but died from infectious complications appeared in the 3rd and 6th month after the allogeneic stem cell transplantation (bronchopneumonia, sepsis). One patient had an early relapse (2 months after the transplant). The immunosuppressive treatment was stopped and donor lymphocyte infusion was administered with no response.

January 2009: Flow cytometry: peripheral blood (PB): 30% blasts, RT-PCR: BCR-ABL: 142%. Treatment: High dose (HD) chemotherapy + Dasatinib: 2 × 70 mg/day.

May 2009: Flow cytometry: PB: 80% blasts (fig. 2), RT-PCR: BCR-ABL: 188%. Treatment: HD-chemotherapy + Nilotinib: 2 × 400 mg/day.

September 2009: Flow cytometry: PB: 70% blasts. Treatment: HD-chemotherapy + Nilotinib 2 × 400 mg/day. After the HD-chemotherapy the patient presented left lobar pneumonia, septicemia and died due to multiple organ failure. We suspected the T351I mutation but we did not have the possibility to perform the analysis.

Table III. Conditioning regimen, date of transplant, immunosupression

Patient	Conditioning regimen	Date of transplant	Immunosupresion
B.C.	Busulfan 16 mg/kg Cyclofosfamid 200 mg/kg	10/2005	Cyclosporine 3 mg/kg + MTX 15 mg/m^2 D1+, 10 mg/m^2 D3+,6+,11+
S.A.	Busulfan 10 mg/kg Fludara 150 mg/m^2 (RIC)	07/2006	Cyclosporine 3 mg/kg + MTX 15 mg/m^2 D1+, 10 mg/m^2 D3+,6+,11+ → Tacrolimus 0.02 mg/kg
A.M.	Busulfan 16 mg/kg Cyclofosfamid 200 mg/kg	03/2008	Cyclosporine 3 mg/kg + MTX 15 mg/m^2 D1+, 10 mg/m^2 D3+,6+,11+
V.I.	Busulfan 16 mg/kg Cyclofosfamid 200 mg/kg	09/2008	Cyclosporine 3 mg/kg + MTX 15 mg/m^2 D1+, 10 mg/m^2 D3+,6+,11+
S.K.	Busulfan 16 mg/kg Cyclofosfamid 200 mg/kg	09/2008	Cyclosporine 3 mg/kg + MTX 15 mg/m^2 D1+, 10 mg/m^2 D3+,6+,11+

Table IV. The presence of GVHD

Patient	GVHD
B.C.	No GVHD
S.A.	Day 3+, BiT: 5.2 mg/dl aGVHD grade II
A.M.	Day 15+ Skin: maculo-papular rash <25%, aGVHD grade I → cGVHD bulosus epidermiolysis, BiT: 3.2 mg/dl
V.I.	Skin: maculo-papular rash 25–50% aGVHD grade II
S.K.	No GVHD

Discussion

Allogeneic stem cell transplantation can cure up to 80–85% of patients with CML but can be associated with significant morbidity and mortality [10]. There have been attempts to define risk factors associated with failure to assist in the decision of timing allogeneic stem cell transplantation for an individual patient with CML [11]. The risk factors for overall survival and transplant related mortality according to EBMT risk assessment score is the donor type, disease stage, recipient age, gender of donor, time from diagnosis to HSCT [12]. The status of disease at transplantation is a powerful predictor of outcome. Patients in accelerated phase or in blast crisis have a very bad prognosis. Most of the patients were in advanced phase of the disease, four of them with high EBMT risk score. Only two of the five patients survived. Although HSCT might be the only treatment able to cure patients in advanced phase, only a few patients in this subgroup achieve a long and stable remission or definitive cure.

Despite improvement of treatment with new generation of TKI, allogeneic stem cell transplantation remains the only curative treatment for patients with CML [13].

Conclusions

- CML is a very complex disease in which we perform allogeneic stem cell transplantation only in the cases in which we have resistance to first and second generation of tyrosine kinase inhibitors (TKI), intolerance to TKI and if we have a suitable donor.
- The results of transplant depend on the disease phase, age and physical condition of the patient, the suitability of the donor and the complications that appear after the transplantation (infections, GVHD).
- We need to identify the high risk patients with the suitable donor to perform the transplant in time when the patient is still in CF.

Table V. Correlations of the survival with other risk factors

Patient	EBMT risk score	GVHD	Complications	Follow-up time Diseas status	Survival status	Cause of death
B.C.	2	No GVHD	Bronchopneumonia Urinary tract infection (Escherichia coli) Esophagitis (Candida albicans)	6 years CCyR	Alive	NA
S.A.	5	aGVHD liver grade II	Acute bronchitis Esophagitis (Candida albicans) Neurological complications (Halucinations)	6 months DFS	Death	Infection
A.M.	4	aGVHD skin grade II >cGVHD	Febrile neutropenia Oral infection (Candida glabrata)	3 years CCyR	Alive	NA
V.I.	4	aGVHD skin, grade I	Urinary tract infection (Pseudomonas aeruginosa), Sepsis	3 months DFS	Death	Infection
S.K.	6	No GVHD	Esophagitis (Candida krusei) Acute pyelonephritis (Pseudomonas aeruginosa) Ocular herpes zoster	1 year Early relapse	Death	Disease progression

NA – not applicable, aGVHD – acute graft versus host disease, cGVHD – chronic graft versus host disease, DFS – disease free survival, CCyR – complete cytogenetic remission

- Allogeneic stem cell transplantation is the only known method with which we can obtain real cure of CML, the TKI need to be taken lifelong.
- In the case of performing allogeneic transplantation in CML we have to be aware in each case of the risks and benefits of this method.

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