Syngeneic Graft-Versus-Chronic-Myeloid-Leukemia-Effect?

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Summary

Fefer et al first suggested in 1979 that the Ph1-positive clone in chronic myeloid leukemia (CML) can be eradicated by chemotherapy, and that the marrow can be repopulated by stem cells from identical twins. Since then, there have been increasing reports of a graft-versus-leukemia-like effect following syngeneic stem cell transplantation (SCT) in CML. This case report describes three CML patients who achieved complete hematological, cytogenetic and molecular remission following syngeneic SCT. We suggest that syngeneic SCT should be included in the treatment decisions for CML patients with available identical twins, considering the reduced incidence of morbidity and mortality compared to allogeneic SCT.

Keywords: syngeneic stem cell transplantation, chronic myeloid leukemia, graft versus leukemia effect

Report

Chronic myeloid leukemia (CML) is a malignant disorder of hematopoietic cell origin that, for a variable period of time, retains the capacity to differentiate, leading to marked marrow hyperplasia and increased numbers of myeloid cells and platelets in the peripheral blood [1]. The hallmark of this disorder is the Philadelphia (Ph) chromosome genetic abnormality t (9; 22) (q34; q11) in which there is a reciprocal translocation between the long arms of chromosomes 9 and 22 resulting in the BCR-ABL fusion, and it is present in about 90% of patients with CML [2]. There have been several treatment strategies for this disorder including busulfan, hydroxyurea, and alpha interferon (α-IFN), resulting in varying degrees of hematological and cytogenetic remission. The introduction of the tyrosine kinase inhibitor imatinib had a major impact and brought a dramatic change to the management of CML. It induces a high number of complete cytogenetic remissions, but molecular remission is rarely observed. While imatinib is a highly effective therapy for CML, both de novo and acquired resistance have been observed. In those cases where it has been studied, resistance has been associated with BCR-ABL gene amplification in some, and mutations in BCR-ABL that prevent imatinib from inhibiting the kinase in others [1,3]. In some patients, point mutations in BCR-ABL can be found at diagnosis and, with imatinib treatment, cells bearing these mutations may undergo positive selection [1,4]. The long-term benefits of imatinib are currently unknown and although efforts should be made to control the problem of resistance [5], alternative cure strategies have to be developed.

Currently, allogeneic stem cell transplantation (allo-SCT) remains the only curative treatment approach, but due to its high treatment-related morbidity and mortality, the timing of allo-SCT in the “tyrosine kinase era” remains to be determined. Allo-SCT is currently reserved for poor responders to imatinib and its derivatives as well as high-risk patients [6]. The curative potential of allo-SCT in leukemias has been demonstrated from various clinical data to be partly due to its graft-versus-leukemia (GvL) effect. Currently, very little data exists to support the concept of GvL effect in syngeneic SCT. The pioneers in the use of syngeneic SCT in CML have been Dr. A. Fefer and his colleagues of the Seattle Marrow Transplant Team at the Fred Hutchinson Cancer Research Center, University of Washington. In 1979 [7], they published the results of identical twin transplants in four patients with chronic phase CML treated with dimethyl busulfan, cyclophosphamide (CY), and a single 920 rads exposure of total body irradiation (TBI). All four recovered with Ph-negative normal hematopoiesis. The same group also reported in 1982 [8] on twelve patients in the chronic phase of Ph1 (Philadelphia)-positive chronic granulocytic leukemia (CGL) who received chemoradiotherapy and marrow from their healthy identical twins. All achieved complete remission, with disappearance of all Ph1-positive cells. In 1986 [9], they published another report of syngeneic marrow transplan-
tation in hematological cancers including sixteen patients who received transplantation in the chronic phase of Ph1+ chronic granulocytic leukemia (CGL). All showed disappearance of all Ph1+ cells. Other authors who have shown that the Ph1-positive clone in CML can be eradicated by chemotherapy and the marrow repopulated by stem cells from normal twins include Mackinnon et al [10], Fujii et al [11], Littleton et al [12] and Pelosini et al [13].

Several groups such as the European LeukemiaNet have developed a treatment algorithm in the management of chronic myeloid leukemia [14]. To this detailed treatment algorithm we would like to add the possibility of syngeneic stem cell transplantation in patients with chronic myeloid leukemia (CML) if an identical twin is available. This constellation occurs rarely—in about 1 out of 300 patients—but it offers a curative therapeutic option with low treatment-related mortality.

We report on three patients with a median age of 42 years [range 25 to 58] who were transplanted from an identical twin between 1997 and 2001 at the University Hospital Hamburg/Germany. All patients were at the chronic phase and had received pre-treatment with hydroxyurea with or without interferon. At time of transplantation all patients still had Philadelphia chromosome positive metaphase and detectable BCR-ABL transcripts. In two of the patients the conditioning regimen consisted of an intensified regimen with total body irradiation 12 Gray, Busulfan 8 mg/kg, and Cyclophosphamid 60 mg/kg, while the third patient was conditioned with Busulfan [14 mg/kg] and Cyclophosphamid [120 mg/kg]. All patients received peripheral blood stem cells with a median dose of 4.3 x 10⁶ CD34+ cells/kg (range 3.5–8.2) The toxicity consisted mainly of mucositis grade II according to the Bearman scale. There was a rapid engraftment of the leukocytes >1.0/nl at a median of 9 days [range 8–10]. Two patients developed a mild maculopapulous exanthem of the skin, which was verified by histological examination as acute graft-versus-host-disease.

With a median follow-up of 5 years [range 4–7.5], all patients are in complete hematological, cytogenetic, and molecular remission [table 1]. Molecular remission was determined by highly sensitive methods as described recently [15]. This long lasting molecular remission suggests a syngeneic graft-versus-chronic myeloid leukemia-effect, since in the German CML study none of the 23 patients who received autologous transplantation achieved a molecular remission during follow-up. The results in these patients support other published data [6-13] in which a GvL effect has been induced in syngeneic SCT in CML patients. The possible targets for the syngeneic graft-versus-leukemia effect in CML might be proteinase 3 or PRAME and to a lesser extent BCR/ABL transcript [16]. The observation of mild acute graft-versus-host disease of the skin after syngeneic stem cell transplantation has been reported by others [13,17,18]. In the case of Pelosini et al [13], their patient has remained in complete hematological and molecular remission and in good clinical condition three years after syngeneic SCT. In a syngeneic mice model it has been shown that interleukin-2 and Cyclosporin after twin transplantation reduces the relapse rate via graft-versus-leukemia effect without graft-versus-host disease [19].

The pathophysiological mechanisms of graft-versus-host-disease (GvHD)-like syndromes in syngeneic SCT in humans are yet to be fully understood. In 2003, Latif et al [20] summarized all 17 cases of severe GvHD previously reported in the literature following syngeneic SCT in addition to detailed reports of their own two patients. Postulated mechanisms include mediation by auto reactive lymphocytes directed at MHC class II proteins and the use of cyclosporin A [21]. The role of cyclosporin A (CsA) itself is poorly understood. The fact that some of the patients did not receive CsA means that other mechanisms may exist which should be further studied [20]. Another possibility that might contribute to the lower risk of relapse in comparison to autologous stem cell transplantation is the fact that the stem cell graft from a syngeneic donor is not contaminated with CML cells.

In conclusion, we suggest that if an identical twin is available, syngeneic stem cell transplantation should be included in the treatment decisions in CML since it has a lower treatment-related mortality than allogeneic stem cell transplantation, taking into account the increasing reports of a GvL-like syndromes following syngeneic SCT in this disorder, and the fact that it induces long-lasting molecular remission in contrast to imatinib mesylate. Further studies should be carried out to determine the mechanisms that promote GvHD-like effects in recipients of syngeneic stem cell transplantation.

References

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<table>
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Table 1. Patients’ characteristics
Сингенный эффект „трансплантат против хронического миелоидного лейкоза“?

Очени С., Шаффхаузен Ф., Бахер У., Фезе Б., Крепег Н.

Резюме

Fefer и соавт. впервые предположили в 1979 г., что Ph1-позитивный клон при хроническом миелоидном лейкозе (ХМЛ) может быть устранен посредством химиотерапии, и что костный мозг может быть заселен стволовыми клетками от идентичного близнеца. С тех пор публиковалось все большее число сообщений об эффекте, сходном с эффектом „трансплантат против лейкоза“ после сингенной трансплантации стволовых клеток (ТСК) при ХМЛ. В данном сообщении описаны три больных с ХМЛ от 25 до 58 лет (средний возраст - 42 года), которым проведена сингенная ТСК на фоне хронической фазы заболевания и лечения гидроксимочевиной и/или интерфероном. Кондиционирующая терапия включала применение бусульфана и циклофосфамида у одного больного, и, у двух пациентов, кроме того - общее облучение тела в суммарной дозе 12 Гр. Токсические эффекты терапии были умеренными, и восстановление числа лейкоцитов до >1.0 в нл наблюдалось через 8-10 суток. У двух больных отмечена кожная реакция "трансплантат против хозяина" в легкой форме. Дальнейшее наблюдение этих больных до 5-летнего срока показало, что у них достигнута полная гематологическая, цитогенетическая и молекулярная ремиссия после ТСК от сингенного донора. Эта долгосрочная молекулярная ремиссия предполагает наличие сингенного эффекта "трансплантат против хронического миелоидного лейкоза". Мы предполагаем, что сингенная ТСК может быть включена в число возможностей лечения больных ХМЛ, имеющих идентичных близнецов, принимая во внимание сниженную частоту осложнений и смертности, по сравнению с аллогенной ТСК.

Ключевые слова: Сингенная трансплантация стволовых клеток, хронический миелоидный лейкоз, эффект „трансплантат против лейкоза“