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Successful Autologous Stem Cell Transplantation in a Severely Immunocompromised Patient with Relapsed AIDS-related B-cell Lymphoma

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Abstract
There is now evidence that the tolerability and response to systemic chemotherapy in HIV-infected patients with AIDS-related lymphoma (ARL) is significantly improved by highly active antiretroviral therapy. Here we report an severely immunocompromised AIDS patient with recurrent ARL who was successfully treated with autologous stem cell transplantation (ASCT). We also review the current literature of ASCT in HIV-infected patients.

Key words: HIV, AIDS, autologous stem cell transplantation, lymphoma, HAART

Introduction

Patients infected with the human immunodeficiency virus (HIV) are at high risk for developing hematological malignancies. Registry-linkage studies indicate that the relative risk is 100-400-fold for high-grade B-cell non-Hodgkin's lymphoma (NHL), compared to the general population [1, 2]. The effect of highly active antiretroviral therapy (HAART) on the incidence of lymphoma seems to be less pronounced than seen with other illnesses related to the acquired immune deficiency syndrome (AIDS) [2-4]. Thus, it seems likely that AIDS-related lymphoma (ARL) will remain a constant and relevant factor of morbidity and mortality in HIV-infected patients.

Since the onset of the AIDS epidemic, treatment of ARL has been a particular therapeutic challenge. The propensity towards advanced disease and the clinical aggressiveness of ARL would request intensive therapy. On the other hand, the reduced proliferative capacity of hematopoietic cells and the impaired immune function which are frequently observed in HIV-infected patients, lead to prolonged periods of myelosuppression and high rates of infectious complications [5]. Consequently, in the pre-HAART era, most therapeutic approaches focused on improving tolerability by reducing the dose of chemotherapeutic agents [6]. Not surprisingly, outcome of ARL patients was usually poor with a median overall survival of 6 to 7 months within larger cohorts of patients [6-8]. There is evidence that the tolerability and response to systemic chemotherapy is significantly improved by HAART [9-12]. This led investigators to explore the efficacy of more aggressive regimens, including autologous or allogeneic stem cell transplantation in patients with ARL. Hematopoietic stem cell transplantation (HSCT) is considered the treatment of choice for many hematological malignancies and transplant numbers of patients with lymphoma have increased five-fold during the last decade [13]. Data on HSCT in HIV-infected patients, especially in severely immunocompromised patients with ARL, are still limited. Here we report a severely immunocompromised AIDS patient successfully treated with autologous SCT, to our knowledge the first published case in Germany. We also review the current literature of stem cell transplantation in HIV-infected patients.

Case Report

A 23 year-old HIV-infected male presented in June 2004 with a severe pneumocystis pneumonia (PCP) and respiratory failure requiring mechanical ventilation. In addition, a large (more than 25 cm in diameter) tumour in the pelvis was found (see Fig. 1), which was classified histologically as to be diffuse-large B-cell lymphoma (immunoblastic subtype, $CD20^+$, $CD10^-$, $BCL\text{-}2^-$, proliferation rate 80 %). Lymphoma staging of the thorax, bone marrow and of the central nervous system yielded negative results.

The $CD4^+$ T cell count of the patient was 15/µl (2 %) and a plasma viremia of 714.000 RNA copies/ml was detected. Lactate dehydrogenase (LDH) level was 2.860 U/l. After treatment of PCP and cytoreductive pre-treatment, polychemotherapy was started. After 6 cycles of the CHOEP-14 regimen (cyclophosphamide, doxorubicine, vincristine, etoposide, prednison given every two weeks with granulocyte-colony stimulating factor (G-CSF) support), combined with the initiation of HAART (tenofovir, lamivudine, efavirenz), the patient achieved a complete remission (CR). However, three months later, a perianal relapse of his lymphoma was diagnosed. Consolidation immunochemotherapy with two cycles of R-ICE (rituximab, ifosfamide, carboplatin and etoposide) was given, followed by the administration of 10 µg/kg of G-CSF. A total of 4.4 x

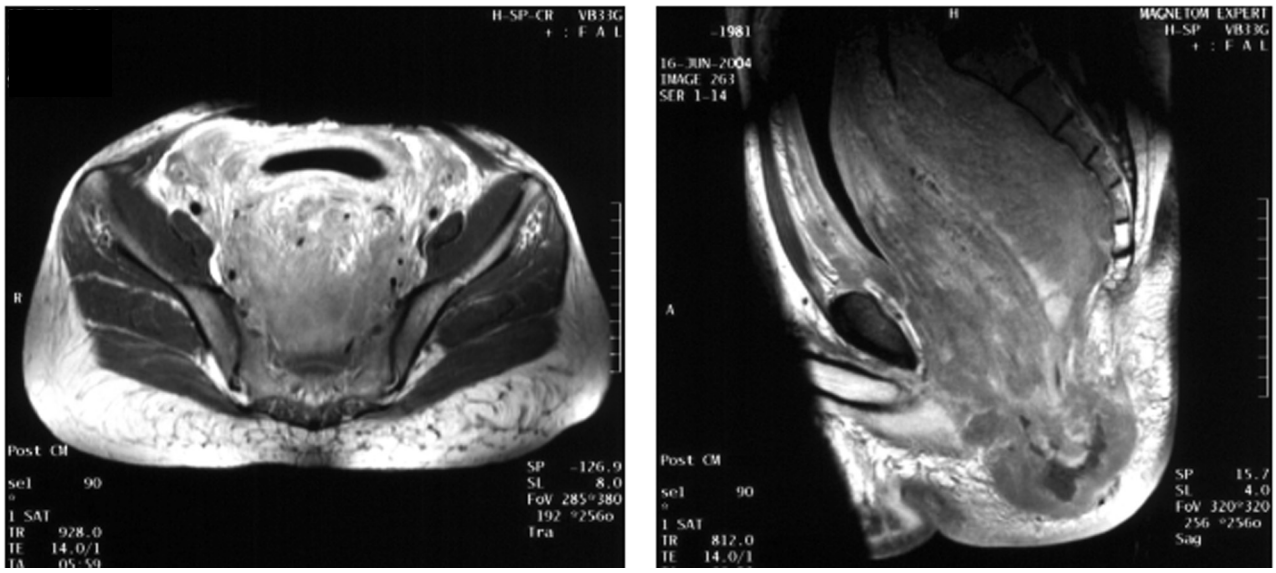

Fig.1. MRT of pelvis at initial diagnosis, showing a large tumour (> 25 cm in diameter).

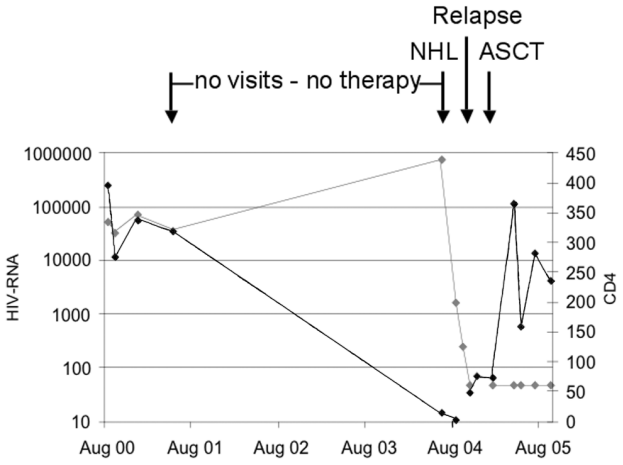

Fig. 2. CD4+ T cell counts/µl (dark line) and HIV-RNA (viral load, copies/ml) over time.

10^6 CD34+ positive cells/kg could be collected. At that time, HIV-RNA was less than 50 copies/ml and the CD4+ cell count had increased modestly from 5 to 73 cells/µl (6 %) under HAART.

Six weeks later, the patient who had achieved CR underwent ASCT using BEAM conditioning (total doses: BCNU 600 mg, etoposide 1800 mg, cytarabine 3200 mg, melphalan 280 mg). Prompt engraftment occurred, with leucocytes of more than 1.000/nl at day 12 and more than 20.000 platelets/µl without transfusion support at day 13. The only transplant-related complications were mucositis grade I allowing continuous HAART, and a short febrile episode. The patient recovered quickly, and at the last follow-up at 6 months post transplantation, the patient remained in CR and in a good condition. CD4+ cells had increased to 238/µl (10 %) and plasma viremia remained constantly below the limit of detection (details are shown in Fig. 2).

Discussion

To our knowledge, this is the first case of a successful ASCT in a severely immunocompromised HIV-infected patient suffering from recurrent NHL in Germany. This case shows that autologous SCT can be effective in HIV-infected patients with lymphoma, confirming small series [14-20] with a total of approximately 75 HIV-infected patients, mainly suffering from B-cell NHL but also from Hodgkin's Lymphoma (Table 1). There have been also anecdotal reports on syngeneic [21] or allogeneic SCT [22] in HIV-infected patients.

The indications for ASCT in the citated series [14-20] were very heterogeneous, including relapse, refractory disease after first line chemotherapy, CR with poor-risk features or the presence of unfavorable lymphoma subtypes in previously untreated patients. This may explain why the outcome differed markedly in these series, with an overall survival (OS) at two years ranging from 39 % to 79 %. For example, in the two series reporting the highest CR rates and the best OS [18, 19], there was a considerable number of patients who were transplanted in first CR, whereas the other studies included only patients with relapse or refractory disease [14-17]. There is also evidence that advanced stage may be an important predictor for poor outcome in HIV-infected patients undergoing ASCT. In one study [17], the projected OS at two years was 12 % versus 90 % ($p = 0.001$) for patients with stage IV disease versus patients with less than stage IV, respectively.

Our patient was considered high-risk not only because of early relapse but also the severity of immunosuppression with less than 100 CD4+ T cells/µl at the time of ASCT, including history of a life-threatening AIDS-defining illness (PCP). The number of patients with less than 100 CD4+ T cells/µl at the time of

Table 1. Series of patients with AIDS-related B-cell lymphoma or Hodgkin's disease, undergoing ASCT.

Ref.	n (HL)	Median $CD4^+$ cells/μl at BL (range)	Conditioning regimen	Median $CD34^+$ x 10^6 cells/kg (range)	ANC > 500/μl (days)	Platelets > 20.000 /μl (days)	Outcome
14, 15	14 (6)	113 (5-572)	BEAM or C/TBI	5.8 (2.8-20)	12 (7-14)	11 (5-21)	10/14 CR, 5 alive (mo 14-49, 4 in CR). 7 died of L (mo 1-11), 2 died in CR (mo 16, 28)
16, 17	26* (10)	181 (88-365)	BEAM	6.8 (4.1-8.3)	10 (8-11)	12 (8-18)	14/15 CR, 13 alive (mo 2-28, 11 in CR). OS 51 % at 17 mo
18	20 (2)	175 (25-1064)	CBV	10.6 (n.s.)	11 (9-23)	15 (n.s.)	17/20 CR, 17 alive (mo 6-70, 17 in CR). 1 died of L (mo 2, 4), 1 Tx-related death
19	14* (3)	186 (72-364)	BEAM	4.7 (1.8-21.2)	16 (9-33)	20 (11-445)	10/11 CR, 9 alive (mo 7-36, 7 in CR). 1 died of L (mo 1), 1 in CR (mo 15)
20	13*	200	BC	n.s.	n.s.	n.s.	preliminary data (ongoing AMC 020 trial). 3/5 CR.

Abbreviations: BEAM = BCNU/carmustine, etoposide, cytarabine, melphalan. CY/TBI = Cyclophosphamide (plus/minus thiothepa) with total body irradiation. CBV = cyclophosphamide, BCNU, etoposide. BC = busulfan, cyclophosphamide. ANC = Absolute Neutrophil Counts. HL = Hodgkin Lymphoma. OS = Overall Survival. CR = Complete Remission, mo = Months, n.s. = not stated, L = Lymphoma. *Discrepancies in the numbers of patients and in the CR rates are due to incomplete follow up or to the fact that some patients died from lymphoma progression before ASCT could be conducted.

ASCT reported to date is low. Of note, the collection of hematopoietic stem cells was successful in our patient despite his severe immune suppression. This seems remarkable since a decreased proliferative capacity of the bone marrow is a common consequence of late stages of HIV infection [5, 23]. Our case supports the notion that there is no evidence for a relationship between $CD4^+$ T cell counts and the number of $CD34^+$ cells harvested. Except for one study in which 10 % of the patients failed to achieve an adequate peripheral blood mononuclear cell collection [17] and of patients receiving a zidovudine-based HAART [18], cell collection was successful in most HIV patients (14, 15, 18, 19].

As in our patient, engraftment occurred in all patients published to date. Only in one series engraftment appeared to be slower than in uninfected patients [19]. This observation may be consistent with the lower numbers of $CD34^+$ cells collected in this trial. Toxicity of the conditioning regimen with BEAM was acceptable in our patient, also confirming the results of other studies [14-20]. The only toxic death reported to date was a 68-years old patient who developed cardiomyopathy and subsequently died from multiorgan failure [18]. As in our patient, HAART could be maintained throughout the transplant procedure in most series, except for short interruptions because of mucositis.

The indication for stem cell transplantation in HIV-infected patients remains debatable as is the optimal regimen for stem cell mobilization and conditioning. Based on the experience reported to date, one may assume that in the HAART era, collection and transplantation of hematopoietic stem cells in HIV-infected patients is possible even in severely immunocompromised patients. As ARL will remain a relevant factor of morbidity and mortality, there is an urgent need for defining the role of ASCT not only for relapsed ARL but also for patients with poor-risk features of ARL and agreements on the key modalities of such treatment. To this end, international cooperative studies are warranted.

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