First case of successful allogeneic stem cell transplantation in an HIV-patient who acquired severe Aplastic Anemia

We report on the first successful allogeneic stem cell transplantation (SCT) in an HIV-infected patient with severe aplastic anemia (SAA) performed at a tertiary care institution. Highly active antiretroviral therapy (HAART) was administered until transplantation and restarted 34 days later with sustained virological response. The patient did however develop a rapid rise in HIV load during the interruption of HAART associated with an acute febrile illness. Due to the extended period between the onset of SAA until SCT, the posttransplant course was complicated by bacterial infections. Stage two skin GvHD, but no AIDS-defining opportunistic diseases were experienced. Neutrophils recovered to >0.5/nL on day +18 and the CD4 count reached 250/μL on day +71 and >500/μL on day +182. The patient is in good condition with an ECOG score of 0 twelve months after transplantation. This report demonstrates the feasibility of allogeneic stem cell transplantation in the HIV setting.

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A 34 year-old HIV-infected man was referred to our hospital in July 2005 with a four week history of breathlessness on exertion, malaise, multiple hematoma and gingival bleeding. He was in CDC stage A3 with a nadir CD4 count of 192/μL. He had regularly taken HAART as an outpatient for 50 months, last with Tenofovir (TDF, 300 mg qd), Emtricitabine (FTC, 200 mg qd) and Ritonavir-boostered (100 mg bid) Fosamprenavir (FPV, 700 mg bid). His CD4 count hereunder was at 314/μL and the viral load below 400 copies/mL. He did not receive any other medication. His referring physician had found pancytopenia (hemoglobin 6.7 mg/dL, WBC 1.8/nL, neutrophiles 0.47/nL, platelets 12/nL) and stopped antiretroviral therapy as he suspected drug-induced toxicity. Bone marrow cytology and histology (Figure 1) showed a highly reduced hematopoiesis in all three lineages with a cellularity of 5%. The patient required erythrocyte and platelet transfusions and intravenous antibiotics for intermittent bacterial infections. Serologies were positive for CMV (IgG positive, IgM/IgA negative), but negative for hepatitis C, HHV-6, and parvovirus B19. Several blood samples were tested positive for HHV-8 by PCR. CT scans revealed multiple enlarged axillary, cervical, intrathoracic and intraabdominal lymph nodes all less than 2 cm in diameter. Biopsies of cervical and axillary lymph nodes showed only unspecific, HIV-associated lymphadenopathy, but no signs of either NHL or multicentric Castleman's disease. The patient was given *ex juvantibus* Cidofovir treatment, since a disseminated HHV8-infection was considered a possible explanation for the pancytopenia. HHV-8 PCR remained positive and pancytopenia persisted, thus Cidofovir was discontinued after 4 weeks. Two weeks later, the patient had to be readmitted due to sudden-onset fever of up to 40°C which was accompanied by diarrhoea, nausea and abdominal cramps. The C-reactive protein (CRP) peaked at 23 mg/dL. Empirical antibiotic therapy with Imipenem resulted in remission of fever and CRP within days without any specific finding in blood, urine, sputum and stool cultures. Eight weeks after the discontinuation of HAART, a new combination therapy was started with Abacavir (ABC), Lamivudin (3TC) and Ritonavir-boosted Saquinavir (SQV). Pausing the antiretrovirals for 2 months did not improve pancytopenia and thus a toxic genesis became increasingly unlikely, particularly because the patient had been on the same HAART regimen for many years before developing SAA. The renewed antiretroviral treatment reduced HIV load from 644.000 to 690 copies/mL within one month (Figure 2C).

Figure 1. Photomicrographs show hypocellular bone marrow before (a) bone marrow transplantation and regenerating hematopoeisis and normal cellularity after bone marrow transplantation (b).

However, bone any marrow aplasia persisted. The Neutrophile count at this stage was at 0.38 /nL, leaving the patient below 0.5 neutrophiles /nL for several months (Figure 2A). FACS-staining had excluded paroxysmal nocturnal hematuria (PNH). Thus, the diagnosis of severe aplastic anemia (SAA) was established.[1] There is no published experience with conventional immunosuppressive therapy (IT) using antilymphocyte globulin (ALG) in combination with cyclosporine (CsA) and/or steroids in HIV-infected patients, which is the standard therapy for AA. The young age, the good clinical condition before the development of SAA, the requirement for extended immunosuppression when applying IT, the possibility of a truly curative treatment with allogeneic BMT and decreased chances of success by delaying it let us to prefer the latter.[5] We consented with the patient to treat him with an allogeneic stem cell transplantation. He had no siblings, thus a search for an HLA-matched unrelated donor (MUD) was initiated (day –37). Two

weeks later (day –23), a 10/10 alleles HLA-matched, CMV-seropositive, male donor was identified and the transplant could be scheduled for November 2nd, 2005 (day 0). HAART was paused on day 0 to avoid potential drug interactions. The conditioning regimen included fludarabine (30 mg/m^2 on days –6 through –3) and cyclophosphamide (60 mg/kg on days -3, -2). The unmanipulated stem cell graft from G-CSF-mobilized peripheral-blood contained 7x10^6 CD34$^+$ cells/kg body weight. Graft-versus-Host-Disease (GvHD) prophylaxis included rabbit anti-thymocyte globulin (ATG) (10 mg/kg on days –5 through –2), cyclosporine A i.v. (target level 180 – 250 ng/mL), and methotrexate (MTX) (15 mg/m^2 day 1, 10 mg/m^2 days +3, +6). The first week after transplantation was clinically uneventful, however CRP increased to 25 mg/dL and the patient was given granulocyte transfusion on day +7 and day +9. On day + 11, he developed SIRS, atrial fibrillation, pericardial and bilateral pleural effusion as well as pulmonary edema necessitating mandatory ventilation on day +14. On day +18, neutrophils regenerated to >0.5/nL after an extensive period of neutropenia of total 70 days. On day +21 he developed a maculopapular rash compatible with a stage two skin GvHD, which promptly resolved to therapy with 100 mg prednisolone. The patient slowly improved clinically, but his CRP remained high around 10 mg/dL (Figure 2B). Interestingly, HIV viral load rapidly rose to 6.8x10^6/mL after transplantation (Figure 2 C). At that time, he developed an unclear neurological disease with remarkable myocloni, accompanied by high fever. After extubation on day +27, the patient presented dysphagia and a hoarse voice due to paresis of cranial nerves IX, X and XII. Repeated MRIs and lumbar punctures showed a high HIV load in the CSF without any other specific findings. We assumed critical illness polyneuropathy of the affected cranial nerves or HIV reactivation with an associated neurological disease as differential diagnosis. As a result of dysphagia, the patient had chronic aspiration and bronchiolitis which explained the elevated CRP. Antiretroviral therapy was reintroduced with Enfurvitide (T20) s.c., Zidovudine (AZT) i.v. on day + 34 (after a gastro-duodenal feeding tube was installed, this was changed to Zidovudine p.o. and later to Stavudine (d4T) p.o., Emtricitabine (FTC) and Abacavir solution) resulting in a prompt 4-log reduction of the viral load (Figure 2C). The normalization of blood counts as a result of the haematological recovery is shown in Figure 2A. Control bone marrow aspirations showed normal morphology and a 99% donor chimerism. The CD4 count reached >0.25/nL on day +71 and >0.5/nL on day +182 on continuing GvHD-prophylaxis/therapy. On day +120, the patient was transferred to rehabilitative care until day +158. He is currently being treated on an outpatient basis. No opportunistic infections were experienced so far, and HIV therapy can be administered effectively. The patient recovered from his cranial neuropathy is well 8 months after transplantation.

Discussion. There are only very few documented cases of BMT in HIV patients. In 1996, a patient with CML who successfully underwent allogeneic BMT[2] was later found HIV positive. He was reported to be alive and in complete remission 3 years later, but had progressed to less than 200/μL CD4-cells at that point. In 1992, a 16 year-old man received allogeneic BMT for SAA and was retrospectively found to have acquired HIV approximately 10 months earlier. The patient did not recover immunologically, developed severe opportunistic infections 8 months after transplantation and died from AIDS.[3] Interestingly, in an analysis of 29 patients with aplastic anemia from Brasil who received BMT, HIV infection was described as a major factor associated with poor immunological recovery.[4] Another report describes a 26 year-old patient who had AIDS and underwent allogeneic BMT apparently with the intention of treating HIV.[5] He died 48 days later due to hepatorenal failure. In neither of these cases, adequate HIV therapy was administered and the patients showed either immunological deterioration or short survival. There is one publication of two patients who had received an allogeneic transplantation of genetically modified stem cells.[6] One patient had refractory Hodgins's disease. He developed toxoplasmosis and died of a progression of the underlying disease. The other patient with acute myeloid leukaemia was alive 2 years after transplantation. Both patients had chronic GvHD and a non-myeloablative conditioning regimen was used. In our patient, we used a myeloablative conditioning regimen. AIDS-associated or HAART associated problems could be avoided through carefully timed administration of antiretroviral

Figure 2. Haematology, clinical chemistry and HIV-therapy. A: Hematological work up shows successful engraftment and improvement of pancytopenia. Neutrophiles reached values < 0.5/nL on day +18 and finally were 10-fold higher than before BMT. Platelets recovered concurrently. B: Clinical chemistry before and after BMT. C: HIV-PCR, CD4 count, HHV-8 PCR and HIV-therapy. HIV load was rapidly elevated in the therapy-free interval day 0 until day +14. After reintroduction of HAART, HIV load was under the limit of detection from day +138. CD4 count reached pretransplant level after the neutropenic period. Qualitative HHV-8 PCR became negative after BMT.
Abbreviations: Nucleoside reverse transcriptase inhibitors: ABC = Abacavir, AZT = Zidovudine, D4T = Stavudin, TDF = Tenovovir;
Protease inhibitors: SQV = Saquinavir, rtv = Ritonavir;
Fusion inbitor: T20 = Enfuvirtide;
68-2 = inpatient; O = outpatient; BMT = day 0 of allogeneic bone marrow transplant, ICU = Intensive care; Reha = rehabilitative care.

therapy. The patient experienced one episode of skin GvHD that spontaneously resolved and did not reoccur. There were no further episodes of GvHD. Altogether, the course after transplantation and the problems experienced did not differ crucially from what can be expected in a non HIV-infected patient with SAA undergoing this procedure. Formerly, attempts have been made to influence HIV disease in a positive manner by BMT[5] or baboon bone-marrow xenotransplantation,[7] but no long-term improvement of viremia or immunological status could be seen. In contrast, we had to learn in this case that HIV viral load rapidly rose after BMT when HAART was interrupted. A discontinuation of HAART causes acute symptoms associated with HIV load increase in approximately 5% of HIV patients with a CD4 count larger than 350/µL.8 It would be interesting to further examine whether this was merely a result of HAART interruption and immunosuppression, or whether there was an acute HIV disease with the donor bone marrow innate to HIV. This is raising the question whether HAART should be administered throughout the immediate peritransplant period with non-myelotoxic agents. However, this will have to be weighed against the risk of influencing engraftment in a negative manner by applying HAART, and more data will have to be collected on this particular aspect. The drop in CD4 counts after the transplantation paralleled the lymphopenia. After lymphocyte recovery, the CD4 count reached the pre-transplantation levels again. Thus it is more a result of myeloablation and not of a progress of the HIV infection. Little is known for instance about a possible association between HHV-8-infection and AA. In HIV patients, HHV-8 was found to be associated with Kaposi's Sarcoma, primary effusion lymphoma (PEL) and multicentric Castleman's disease (MCD).[9] HHV-8 has also been shown to rarely cause a relapsing inflammatory and lymphoproliferative syndrome in non-HIV-infected patients.[10] The role of HHV-8 in Multiple Myeloma is more controversial.[9,11] In hindsight, we do think that it is not possible to decide whether or not HHV-8 was responsible for the AA in this case, at least not in a scientifically sound manner. HHV-8 has never been demonstrated in the bone marrow of our patient, it could only be found in PCRs from peripheral blood. It must however be mentioned that all except two follow-up PCR after the transplantation had been negative for HHV-8 (Figure 2 C). In the context of a successful engraftment, we do believe that the hypothesis of an HHV-8 related genesis of the AA cannot be completely dismissed.

Over the last three years, an increasing amount of data on autologous stem cell transplantation in cases of HIV-associated lymphoma[12-14] has been published. Also, there is a considerable number of HIV-patients with leukemia.[15] This case has demonstrated the feasibility of allogeneic BMT in an HIV-infected patient.

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