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REVIEW PAPER

Hematopoietic stem cell transplantation in the treatment of HIV infection – comparison of "Berlin patient", "London patient" and "Dusseldorf patient"

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ABSTRACT

Introduction and aim. Human Immunodeficiency Virus-1 (HIV-1) remains one of the major issues in global public health. The standard therapy for HIV-1 positive patients includes using antiretroviral therapy (ART). These medications ensure suppression of viral replication but do not lead to a cure for the patient. The aim of this study was to present hematopoietic stem cell transplantation (HSCT) as a malignant treatment method which led to cure for three HIV-1 positive patients.

Material and methods. Literature available in April 2023 was searched by using the PubMed and Google Scholar databases. Articles were selected using the following words: HIV, AIDS, HSCT therapy, ART therapy.

Analysis of the literature. In each case of these described HSCT, the donor of hematopoietic stem cells had a homozygous mutation in the HIV co-receptor CCR5 (CCR5Δ32/Δ32). This mutation leads to a permanent lack of the protein and prevents penetration of virus by using this receptor. After transplantation, all of these 3 patients remained virus-free despite discontinuation of ART therapy.

Conclusion. More research is needed to reduce the risk of using HSCT and perhaps in the future be able to use this therapy in all HIV-infected people.

Keywords. AIDS, ART therapy, HIV, HSCT therapy

Introduction

According to data from the World Health Organization (WHO), at the end of 2021 there were 38,4 million people infected with Human Immunodeficiency Virus-1 (HIV-1) infection living worldwide. Since the beginning of the pandemic about 40.1 million people have died because of complications of HIV and this is why HIV remains one of the major issues in global public health.[1] Currently the standard treatment includes using antiretroviral therapy (ART). Rapid initiation of this therapy is very important to improve a patient's own health and to prevent their risk of HIV transmission to others.[2] Unfortunately, there are still cases of late detection of HIV infection. These patients are more likely to have comorbidities such as opportunistic infections and have a poorer response to ART than those who were previously diagnosed with HIV.[3] In addition, it is estimated that in 2021 as many as 25% of infected people were not using antiretroviral treatment.[4] ART can successfully suppress viral replication but must be used for the life of the patient which is associated with costs.[2] Also, some of the antiretroviral medications can demonstrate

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a long-term toxicity such as hepatic failure, lipodystrophy, and lactic acidosis.[5] Therefore, the new methods of treatment are still in search of. In recent years there have been described three patients who received allogeneic CCR5Δ32/Δ32 hematopoietic stem cell transplantation (HSCT) to treat hematological malignancy. In each case after transplantation and interruption of ART the plasma HIV-1 RNA and the immunological correlates of HIV-1 antigen were undetectable, which provides evidence for HIV cure.[6–8]

Aim

The aim of this article was to compare these three patients and present HSCT as a probably new method of treatment for HIV infections in the future.

Material and methods

In April 2023 scientific articles were reviewed by using Medeline (PubMed) and Google Scholar. Articles were searched using keywords: HIV, AIDS, HSCT therapy, ART therapy. The available scientific articles were analyzed and 24 were selected for final analysis. The collected knowledge was completed and systematized to achieve the final effect of the review.

Analysis of the literature

Antiretroviral therapy

In the mid-1990s, therapy based on a combination of several drugs acting at different stages of the viral replication cycle began to be used to treat HIV infection. It has been successful in reducing the deaths of HIV patients by half. Currently, combination therapies consisting of at least 3 antiretroviral drugs are a routine method of fighting HIV used by 27.5 million people infected with HIV. Approved pharmaceuticals include: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, entry and fusion inhibitors and integrase chain transfer inhibitors.[9] According to the latest recommendations, it is suggested that antiretroviral therapy be started immediately after the diagnosis of virus infection. Initially, oral drugs containing an integrase chain transfer inhibitor are used. They are characterized by high safety and tolerability and cause rapid suppression of the virus. What is more, they have a high barrier to the development of resistance and a low potential for interactions with other drugs. If virus suppression is successful, patients may be offered bi-monthly injection therapy consisting of cabotegravir and rilpivirine. Typically, injections are started after oral medication to ensure tolerance. In a situation where, despite treatment, the viral load is high (RNA>200 copies/mL), it is necessary to modify the therapy individually for the patient, based on genotypic resistance testing.[10] Despite the great success of antiretroviral therapy, specifically reducing mortality and disease progression, virus reservoirs remain present in the body. It is necessary to use treatment for the rest of the patient's life, otherwise the virus will start to replicate and spread, which will definitely worsen the patient's clinical condition.[8,11] Additional motives to look for a different method of treatment are: long-term toxicity of drugs, the emergence of both acquired and transmissible drug resistance and possible interaction of antiretroviral drugs with drugs taken permanently by infected patients, whose number is increasing due to greater survival and thus aging population of HIV-positive patients. Some drugs may also cause metabolic complications such as weight gain, most commonly seen in females, black people and Latinos one year after starting treatment. Drugs causing weight gain include integrase inhibitors and tenofovir alafenamide. Weight gain may occur: in patients starting antiretroviral therapy with integrase inhibitors or tenofovir alafenamide, in patients switching to the above-mentioned agents due to viral suppression, and in those taking integrase inhibitors or tenofovir alafenamide as a consequence of pre-exposure prophylaxis.[10] For this reason, it is necessary to control BMI and perform annual tests to detect diabetes and vascular diseases. For years, the goal of scientists has been to find a treatment that would eliminate the virus from the body permanently and thus make it possible to resign from the use of antiretroviral therapy.[9,10]

Hematopoietic stem cell transplantation (HSCT) for HIV treatment

CCR5 coreceptor

HIV-1 can be transmitted through the bloodstream or through unprotected sexual contact. Entering the body, the virus infects cells that have the CD4 receptor on their surface. It exists mainly on the surface of Th lymphocytes, but also on other cells of the immune system, for example on monocytes. The viral glycoprotein gp120 binds to the receptor via coreceptors: CCR5 and CXCR4. Once the virus has entered the host cell, it uses the enzyme reverse transcriptase to create viral DNA. After being transported to the cell nucleus, the genetic material of the virus is translated and an infectious virion is formed, which leaves the cell by lysing it.[12] The vast majority of viruses use the CCR5 co-receptor during acute and early infection. As the disease progresses untreated, variants using CXCR4 emerge. Studies have shown that in some untreated patients infected with HIV-1 type B, 81-88% are 'R5-tropic' viruses. In people receiving treatment, "R5-tropic" viruses account for 49-78%, mixed variants are 22-48%, while "X4-tropic" viruses are only 2-5%. The emergence of virus variants using the CXCR4 co-receptor results in drug resistance to CCR5 inhibitors. One such drug is maraviroc, approved in 2007.[13] A natural deletion of the 32nd base pair in frame (CCR5Δ32) introduces a premature stop codon

and generates a shortened protein that does not appear on the cell surface, rendering the virus unable to enter it. The CCR5Δ32/Δ32 homozygous genotype leads to a permanent lack of the protein and grants natural resistance to HIV viruses that use the CCR5 receptor to enter the cell. People who are heterozygous for this gene have a 2-3 year lower disease progression.[11,14,15] In the Caucasian race, the frequency of the CCR5Δ32 allele (heterozygous form) is 10-20%, while homozygotes are only 1–2%. In contrast, in people of Mongoloid and Negroid races, this mutation is almost absent.[16] During the emergence of "X4-tropic" variants, a natural deletion of the 32 base pair in-frame reads (CCR5Δ32) will not prevent the virus from entering the body.[13]

HIV and malignant tumors of the hematopoietic system

The HIV-1 virus leads to cell lysis, resulting in the progressive destruction of the immune system. The effect of this is the occurrence of immunosuppression, which is responsible for the appearance of opportunistic infections or malignant tumors.[17] A study has shown that HIV-positive people are twice as likely to develop cancer as the general population.[18] In both high-income and low- or middle-income countries, the most common malignancy associated with AIDS is non-Hodgkin's lymphoma (NHL). Prior to the introduction of ART, the most common NHLs were: diffuse large B-cell lymphoma, Burkitt's lymphoma, and primary central nervous system lymphoma. They occurred more frequently in patients with more severe immunodeficiency. After the introduction of multidrug antiretroviral therapy, the incidence of NHL especially in developed countries has decreased but is still higher than in the general population.[17,18] In addition, thanks to the high effectiveness of ART therapy, HIV-infected patients live longer, which makes them more likely to suffer from malignant tumors unrelated to the disease, such as: acute leukemia, Hodgkin's lymphoma, myelodysplastic syndromes or multiple myeloma.[19] Studies have shown a significant disproportion in oncological care between the HIV-negative population and the infected population. Moreover, research into new cancer drugs usually does not include HIV-positive patients. This is due to the specific clinical picture of these patients, possible interactions between drugs included in ART, and chemotherapeutic agents and the expected number of post-treatment complications, including increased mortality in this group of oncological patients.[18,19]

HSCT scheme

The basis for qualifying HIV-positive patients with hematological malignancies for transplantation is the long-term use of ART therapy to significantly reduce and weaken virus populations. The first step is to search for an human leukocyte antigen (HLA)-matching donor who will also have the CCR5Δ32/Δ32 mutation, which gives a chance to completely eliminate the virus from the body.[20] Allogeneic stem cell transplantation begins with conditioning (myeloablative therapy). It involves high-dose chemotherapy and/or radiotherapy to kill cancer cells. Then, hematopoietic cells are transfused into the peripheral blood. Stem cells adhere to the endothelial cells of the bone marrow, followed by cell migration past the endothelium and extracellular matrix into the marrow niche. The bone marrow initiates the production of new cells.[21] After 12-16 months after transplantation, the number of lymphocytes returns to normal, which means that their number is within the range of 1-5 thousand/mm^3. The functional recovery of cells takes longer. After transplantation, it is necessary to use immunosuppressive drugs to weaken the immune response of the recipient to reduce the risk of graft-versus-host disease (GvHD). Supportive therapy involves the administration of drugs to prevent infections and eliminate the side effects of chemotherapy and radiotherapy.[22]

History of HSCT

Allogeneic stem cell transplantation is not a new concept in the fight against HIV-1. It was known that as a result of a transplant, the recipient's hematopoietic cells, including those carrying the HIV virus, are replaced by the donor's cells. With complete chimerism, the HIV-1 virus would be eliminated from the recipient's body. Two patients (known as Boston patients) with malignant tumors who had been HIV-positive for more than 30 years underwent a hematopoietic stem cell transplant in 2013. The donors were not carriers of the CCR5Δ32 mutation. Full past chimerism was established, and post-transplant viral DNA was not detectable in peripheral blood mononuclear cells or plasma. It is worth noting that the patients were treated with ART before, during and after the transplantation. Treatment was discontinued to determine whether drug-free, lasting HIV remission was possible. Viral relapse in the form of acute retroviral syndrome occurred after 3 and 8 months. Without transplantation, discontinuation of antiretroviral drugs resulted in relapse within 2-3 weeks. In addition, both patients developed an anti-host reaction.[11,20] Possibly latent proviruses remained in the bodies of the Boston patients and could multiply in the donor's cells without treatment.[11,22] Another case of a failed HSCT attempt in an HIV-positive patient is a patient from Essen. The patient was diagnosed with anaplastic large cell lymphoma. Decisions were made for HSCT from a donor who was homozygous for the allele CCR5Δ32. The recipient's ART therapy was discontinued 7 days prior to the transplantation. Post-transplant viral load was undetectable. The virus remission lasted 20 days followed by a viral rebound.[23]

Another HIV-positive patient with T-cell lymphoma received a transplant in 2019 from a donor homozygous for the CCR5Δ32 allele. The doctors hoped for a great success and complete elimination of the HIV virus from the patient's body. Unfortunately, the emergence of CXCR4-tropic viruses that could enter cells and were responsible for repopulation of the virus after transplantation was observed. Sequencing of the genetic material showed that viruses with this tropism were present 3 months before the HSCT was performed.[20] Detection of "X4-tropic" virus variants before starting treatment is therefore an important criterion when considering HSCT in HIV-positive patients, because if they are detected, a transplant from a donor with the CCR5Δ32 mutation will not be effective.

HSCT success- description of three cases

The first HIV-infected patient to see viral remission after allogeneic hematopoietic stem cell transplantation (allo-HSCT) was a 40-year-old man known as the "Berlin patient". He was diagnosed with acute myeloid leukemia (AML) in 2007, 10 years after being diagnosed with HIV-1 and 4 years after starting ART treatment. During AML treatment with induction chemotherapy, the patient developed severe adverse outcomes such as hepatotoxicity and renal failure. For this reason, ART therapy was discontinued, leading to a viral rebound. Treatment was resumed immediately before the virus reached a steady state. Despite the treatment, AML recurred after 7 months. The next stage of treatment was the transplantation of hematopoietic stem cells from a donor identical in terms of HLA (10/10), with a homozygous mutation in the HIV co-receptor CCR5 (CCR5Δ32/Δ32). Grade I graft-versus-host cutaneous disease was only observed within the first year after transplantation. AML recurrence was observed 332 days after transplantation. Before a second transplant of stem cells obtained from the same donor was performed, the patient underwent a single dose of whole-body irradiation. The patient was also treated with chemotherapy with an anti-CD33 monoclonal antibody conjugate (gemtuzumab ozogamicin). The second procedure led to remission of AML. In this patient the transplantation resulted in complete chimerism, and the patient's peripheral blood monocytes changed from heterozygous to homozygous genotype for the CCR5 delta32 allele. After just 159 days, no HIV-1 DNA could be detected in the rectal mucosa. During a 20-month ART-free follow-up, HIV-1 was undetectable in peripheral blood, bone marrow, and rectal mucosa as assessed by PCR tests.[24] 3 years after HSCT, while the patient was still off antiviral drugs, no evidence of viral replication was shown. The patient's CD4 cell count increased to over 800/μL and all hematopoietic stem cell-derived cells tested, including intestinal macrophages, became CCR5-negative.[6] The patient did not use ART and remained HIV-free until his death of a recurrence of AML in 2020.[8,25]

The second patient in whom the virus rebound was not observed after treatment for a hematological malignancy was a person known as the "London Patient".[26] Infection with the virus was detected in 2003, and ART treatment was started in 2012. Also in 2012, the patient was diagnosed with Hodgkin's lymphoma Stage IVB (nodular sclerosing). The patient received first-line chemotherapy and was given alemtuzumab (anti-CD52 antibody) before the transplantation in order to destroy T lymphocytes. The donor of hematopoietic stem cells was HLA 9/10 and CCR5Δ32 homozygous person. Full donor chimerism was obtained in fractions of all leukocytes and CD3+ T cells as early as day 30 post-transplantation and persisted in both cell fractions throughout. The host genotype was homozygous wild-type CCR5 before allogeneic HSCT and became CCR5Δ32/Δ32 after transplantation, with loss of CCR5 surface expression from circulating CD4 and CD8 T cells. On day 77 post-transplant, the patient developed fever and gastrointestinal symptoms. These were symptoms of GvHD grade I. However, they resolved without any intervention. Weekly analyses of plasma viral load were performed for the first three months and monthly thereafter. The plasma HIV-1 RNA remained undetectable with a detection limit of less than one RNA copy per ml. HIV-1 DNA associated with complete peripheral blood mononuclear cells also fell below the limit of detection. According to the treatment protocol, ART was interrupted 16 months after transplantation. Total DNA in CD4 T cells at posttransplant day 876 was undetectable in all replicates by ultrasensitive qPCR.[27]

The last HIV-free patient to date to stop taking ART after allo-HSCT therapy is the 'Düsseldorf patient'. The man, who was diagnosed with HIV-1 in 2008 and started ART in 2010, is now 53 and has not used treatment since 2018. In 2011, he was diagnosed with AML, which went into complete remission as a result of chemotherapy. However, after AML relapsed, the search for a donor began. A systematic search identified a 10/10 HLA-matched stem cell donor with a homozygous CCR5Δ32 mutation. After chemotherapy with antithymocyte globulin conjugate, the first transplant was performed in February 2013. After another relapse of AML and 34 days after the second HSCT, full donor chimerism was established and maintained. Following donor lymphocyte infusions, the patient developed mild chronic GvHD of the eyes with bilateral keratoconjunctivitis sicca, which persists to this day. ART was continued throughout, and HIV-1 proviral DNA and HIV-1 RNA remained undetectable. Negative in vivo growth tests using two different humanized mouse models confirmed the absence of replication-competent virus in the samples tested. ART was discontinued in November 2018, 69 months after

HSCT. After discontinuation of ART, the patient had no clinical or laboratory evidence of acute retroviral syndrome. Plasma HIV-1 RNA was still undetectable 48 months after treatment discontinuation.[28]

Comparing these 3 cases, it can be seen that cell therapy with allogeneic hematopoietic stem cell transplantation from donors with the homozygous CCR5Δ32 mutation may prove to be a breakthrough discovery in the treatment of HIV infection. So far, this therapy has been used in each of the patients to treat hematological cancer. The "Berlin patient" and the "Düsseldorf patient" required 2 transplants to achieve full recovery, while the "London patient" achieved remission after the first HSCT. There are more differences between these patients, the most important of which are listed in Table 1.[6,24,26–29]

Table 1. Differences between Berlin, London and Düsseldorf patients*

	Berlin patient	London patient	Dusseldorf patient
HIV diagnosed	1997	2003	2008
Years of ART treatment (pre-transplantation)	4	4	3
Hematological malignancy	Acute myeloid leukemia	Hodgkin's lymphoma	Acute myeloid leukemia
CCR5 genotype pre-transplantation	Heterozygous for 32 bp deletion	wild-type	wild-type
Donor HLA match	10/10	9/10	10/10
Conditioning regimen	1 HSCT: FLAMSA, CTX, ATG, TBI 2 HSCT: Ara-C, GO, TBI	LACE, anti-CD52	Flu, Treo
First transplantation	2007	2016	2013
Number of transplantations	2	1	2
GVHD	Yes	Yes	Yes
ART interruption post transplantation	Day of transplantation	16 months	69 months
Viral remission	Over 12 years	6 years	Over 4 years

* FLAMSA – fludarabine, arabinofuranosil citidina and amsacrine; CTX – cyclophosphamide; ATG – antithymocyte globulin; TBI – total body irradiation; Ara-C – arabinofuranosil citidina; GO – gemtuzumab; LACE – lomustine, arabinofuranosil citidina, cyclophosphamide and etoposide; Flu – fludarabine; Treo – treosulfan

Disadvantages of the method

Unfortunately, despite the great potential of HSCT, the complete recovery of patients from HIV infection has many limitations. First of all, hematopoietic stem cell transplants are very risky because mortality is between 40 and 55%.[16] In addition, baseline immunosuppression in HIV patients significantly increases the risk of opportunistic infections after transplantation.[19] Another difficulty of the method is the low frequency of CCR5Δ32/Δ32 homozygotes in the general population. Furthermore, a donor who is homozygous must be histocompatibility match to the recipient.[16] A way to avoid problems with HLA matching may be a haplo-cord blood transplant. Recently, the first case of HIV-1 remission and possible cure has been reported in a woman who received a CCR5Δ32/Δ32 haplo-core transplant (cord blood cells combined with haploidentical stem cells from an adult) for the treatment of AML. After 18 months without antiretroviral therapy there was still no viral rebound, however, this is a new method that needs more research.[30] There is also the possibility that the virus uses the CXCR4 co-receptor, chances of which increase with the duration of the infection. This will result in the repopulation of the virus after transplantation.[11] Finally, the side effects of conditioning regimens and the high risk associated with the development of GvHD mean that currently this therapy is used only in patients with hematological malignancy.[26]

Conclusion

Widespread use of antiretroviral therapy has resulted in increased survival, quality and life expectancy for HIV-infected people. The result is a growing number of HIV-positive patients with malignant neoplasms, especially hematological ones. Hematopoietic stem cell transplantation from a donor who is homozygous for the CCR5Δ32 allele not only causes tumor remission but can also cause permanent viral remission and the associated resignation from ART therapy. Currently, three such transplants have been successfully performed in the world. In the first patient, known as the "Berlin patient", virus load was undetectable for 12 years until the patient's death. However, this method is associated with numerous complications such as high mortality, toxicity, the low incidence of the CCR5Δ32 allele and the small chance of finding an appropriate donor. Currently, the use of this method is associated with more side effects than the use of ART therapy. To reduce the risk of HSCT treatment failure research is underway on autologous transplants using genetically engineered cells. Gene therapy is currently based mainly on the elimination of CCR5 in CD4+ T Cells or HSCs, which may contribute to the natural resistance to HIV and the lack of rebound. More research is needed to reduce the risk of using HSCT and perhaps in the future be able to use this therapy in all people living with HIV.

Declarations

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Author contributions

Conceptualization, A.B. and J.B.; Methodology, A.B.; Software, J.B. and M.B.; Validation, J.B., M.B., and N.D.;

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Conflicts of interest

The authors declare no conflict of interest.

Data availability

Not applicable.

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