Case Study of Co-morbidities --- HIV/AIDS and Blood Cancer

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Abstract. HIV/AIDS is considered an uncurable disease today, and patients have to take medicine uninterrupted for their whole life to control the viral load. However, there have been five special cases possibly cured --- the Berlin patient (HIV-1 and AML), the London patient (HIV-1 and Hodgkin's Lymphoma), the Düsseldorf patient (HIV-1 and AML), the New York patient (HIV-1 and high-risk AML monosomy 7), and the City of Hope patient (HIV-1 and AML). They were infected with HIV and blood cancer concurrently and received allogeneic hematopoietic stem cell transplant (allo-HSCT). By comparing the Düsseldorf patient and the New York patient who are in relatively similar conditions, umbilical cord blood (UCB) is very likely to be the better source for transplant based on the severity of graft versus host disease (GvHD) after transplant. A possible future treatment which is to combine the haematopoietic stem cell transplant (HSCT) and gene therapy with the help of CRISPR-Cas9, is suggested.

1. Introduction

This case study summarises the conditions and treatment procedures of the five patients, in order to provide integrated clinical information for future research in finding cures for HIV-1/AIDS. It also aims to stress the importance so as to promote broader use of UCB in transplantation. Some research has revealed that UBC can act as an alternative to bone marrow (BM) and is quite promising as new therapies. [27] Considering the low frequency of Delta 32 mutation on CCR5 gene among populations, the study also offers an artificial way to achieve this through gene editing. This means that the problem of lacking appropriate donors is predicted to be addressed effectively as the request will be healthy HSC instead of that with homozygous CCR5Δ32/Δ32. In this case, not only the number of patients with cured co-morbidities (HIV and blood cancer) might increase, HIV/AIDS might be curable in the future. Much research is expected to be done on traditional and prospective HSCT, or other treatments that can lead to complete remission of HIV/AIDS.

2. Theoretical Background

Acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV) which is a class VI retrovirus. It is currently no cure or vaccine. The approved treatment uses antiretroviral drugs in combination. For instance, tenofovir disoproxil fumarate (TDF), emtricitabine (FTC) and dolutegravir (DTG)[11]. HIV-1 enters and infects the cells by binding to receptor CD4 and co-receptor CCR5 on the cell surface membrane of macrophages or CD4+ T cells. This mechanism is the key to developing possible treatment other than using multiple antiretroviral drugs. Interfering with CD4 causes dangerous side effects because of its many important functions in cells[1][2], like binding to class II MHC molecules on antigen-presenting cells[12], while it is safer to mask CCR5 to block HIV-1 entry[3]. People who are homozygous for Delta 32 mutation on CCR5 gene are resistant to HIV-1 infection as a result of disabling CCR5 protein[16]. (To note that HIV-1 uses CD4 and CCR5 while HIV-2 can infect either CCR5(+) or CXCR4(+) cells without CD4[14].)

Take acute myeloid leukaemia (AML) as an example of a blood cancer. AML is due to the large number of immature white blood cells (WBCs) derived from myeloid stem cells. These abnormal WBCs take up space in the bone marrow and metastasise to the central nervous system (brain and spinal cord), skin, and gums. As a result of this, infection, anaemia, or easy bleeding may occur. Chemotherapy, radiation therapy and stem cell transplants are used for treatment today[13]. Among AML patients, those who have high-risk AML may experience failure of induction chemotherapy and early relapse. This also makes allogeneic transplantation an intervention feasible only for a fraction of patients with high-risk disease[17].

3. The Berlin Patient

The Berlin patient (1966-2020) is a Caucasian male called Timothy Ray Brown; the first case cured for HIV. He was diagnosed as HIV-1 positive in 1995. He took low-dose zidovudine and then changed to take protease inhibitors (antiretroviral drugs) since 1996. He was diagnosed with AML in the early 2006 through a bone marrow biopsy. The first-round chemotherapy (each round takes a week) went well. After several weeks break, the patient developed fungal pneumonia in the second round, but that passed

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with antifungal treatment. After another few weeks' break, he got a dangerous infection during the third round and was put into an induced coma. Then the doctor ceased the chemo treatment and told him to go on vacation. AML was in remission after his trip to Italy but rebounded at the end of 2006. So he received stem cell transplant which was adult donor CCR5Δ32/Δ32 bone marrow cells (10/10 HLA match)[6], on February 6th, 2007, when he also stopped Antiretroviral therapy (ART) immediately after transplant. He received a second transplant in February 2008 for the second recurrence of AML (at the end of 2007, when he was also infected with pneumonia) from the same donor and had severe GvHD this time. The patient became delirious, nearly went blind, was almost paralyzed and eventually learned to walk again and had almost fully recovered in 2014, whereas no HIV was found in his blood three months after the first transplant (May, 2007)[4]. However, Timothy Ray Brown died on September 30th, 2020 after a five-month battle with leukaemia relapsed again[21].

4. The London Patient

The London patient is a Latino male named Adam Castillejo. He is 40 years old (2022)[6]. The patient was diagnosed with HIV-1 infection in 2003 and his ART was initiated with TDF, FTC and efavirenz (EFV) in 2012. In December 2012, he was diagnosed with nodular sclerosing Hodgkin's lymphoma (NSHL) [22] which is the most common type of HL. NSHL usually starts in B-cells in lymph nodes located in the neck or in an area of the chest between the lungs. These B-cells change into much larger, cancerous cells called Reed Sternberg cells [23] that have two nuclei[24]. ABVD chemotherapy (doxorubicin hydrochloride, bleomycin sulfate, vinblastine sulfate, and dacarbazine) is prescribed. Also, a number of salvage regimens including ESHAP, anti-CD30 monoclonal antibody (Brentuximab) and mini-LEAM were used. During the first-line chemotherapy, ART was switched to TDF, FTC and raltegravir (RAL) and there was a 5-day episode of ART interruption in late 2015. Based on resistance mutations K65R and M184V in reverse transcriptase as well as E157Q in integrase, ART was changed into DTG, rilpivirine (RPV) and lamivudine (3TC), with viral suppression subsequently achieved. A complete metabolic remission was achieved with second-line chemotherapy (IGEV, which includes ifosfamide, gemcitabine, vinorelbine, and prednisolone) in March 2016. In May 2016, he received CCR5Δ32/Δ32 homozygous peripheral blood stem cells (9/10 HLA match) transplant from an unrelated adult donor. 77 days after transplant, the patient presented with a fever and gastrointestinal symptoms. Gastric, duodenal and colonic biopsies were consistent with grade 1 GvHD. He stopped ART in September 2017 (18 months after transplant) and HIV had been undetectable in his blood for 18 months off ART (February 2019)[22].

5. The Düsseldorf Patient

The Düsseldorf patient is a 42-year-old (2010) male from Düsseldorf. He was diagnosed with HIV infection in October 2010. He received darunavir, ritonavir, TDF and FTC as ART. He was diagnosed with AML in January 2011 and his ART was changed into RAL, TDF and FTC. To note that RAL is integrase inhibitor. Most of this class of drugs have few interactions with other medicines, particularly compared to darunavir and ritonavir, which belong to protease inhibitors. He had five courses of chemotherapy and went into remission, but AML relapsed in 2012. And then, three courses of new combinations of chemo were prescribed but still failed to treat AML[10]. In February 2013, the patient received a bone marrow transplant from a 10/10 CCR5Δ32/Δ32 donor[9]. Some degree of GvHD developed after the transplant[15]. In the mid 2014, he changed to take DTG, abacavir and 3TC for ART and all three drugs were in one pill called Triumeq, taken once daily[10]. ART was stopped in November 2018 (69 months after transplant) and there was no viral rebound 14 months later[7][10].

6. The New York Patient

The New York patient is a middle-aged U.S. woman of mixed race. This is the first known case in a woman of mixed race, and the first known case with haplo-cord CCR5Δ32/Δ32 stem cell transplant (SCT). The woman developed high-risk AML in 2017 while on ART for acute HIV-1 infection in 2013. After chemotherapy, in 2017, the patient received CCR5Δ32/Δ32 Haplo-cord transplant which included 5/8 matched cord blood units and relative's peripheral blood mononuclear cells (lymphocytes & monocytes) which are in BM and derived from HSCs. She remained clinically well with no GvHD. ART was stopped 37 months after transplant and there was no viral rebound 14 months off ART[6].

Comparing the Düsseldorf patient and the New York patient who were in the similar conditions; they were both middle-aged and infected with HIV-1 and AML, as well as received a transplant. Whereas, the Düsseldorf patient developed GvHD after the bone marrow transplant which means that the T-cells from bone marrow transplanted react immunologically against his antigens thus attacking his cells and tissues, but the New York patient didn't after the haplo-cord transplant.

7. The City of Hope Patient

The City of Hope patient is a 66-year-old (2022) Caucasian male[25]. He is the oldest patient with HIV and blood cancer to undergo a transplant and achieve remission from both conditions[5]. He was diagnosed with HIV-1 in 1988 and his CD4 count fell below 100 at one point at which he was diagnosed with AIDS. In the mid-1990s when ART became available, he started to take ART. In 2018, he was diagnosed with AML [26] and then received three different courses of chemotherapies to get into remission so as to reduce the chance of serious

complications resulting from the intensive transplant process[5], especially for older and less fit patients. In early 2019, he received stem cell transplant from an unrelated HLA-matched CCR5Δ32/Δ32 homozygous donor and developed mild GvHD[26]. He continued ART with tenofovir alafenamide (TAF), FTC and DTG 25 months post-transplant[25]. The patient stopped taking ART in March 2021[5]. No viral rebound was detected 17 months after stopping ART (August 2022)[26].

8. Comparisons Between Bone Marrow Transplant and Umbilical Cord Blood Transplant

All the patients received allo-HSCT and HSCs are found in both bone marrow and umbilical cord blood. They can develop into all types of blood cells, whereas umbilical cord blood might be more desirable than bone marrow in terms of source of HSCs for transplant.

Table 1. Comparisons between BM and UCB as source of transplant(Edited by the author)

	SC from BM	SC from UCB
Collection	BM aspiration.	From cut UC after birth.
Availability	Last minute consent refusal.	Rapid.
HLA	Perfect match.	Perfect match isn't required.
GVHD	Higher chance	Lower chance
Cell dose	Higher	Lower
Engraftment time	Shorter	longer

Social perspective
Medical perspective
Take precedence

Social perspective includes collection and availability, while the medical includes human leukocyte antigen (HLA), GvHD, success isolating rate and time taken for engraftment. Analysis is carried out by taking these two perspectives into consideration. Bone marrow aspiration is needed for the collection of stem cells from bone marrow and this can be harmful to the donor. But umbilical cord blood stem cells are from the cut umbilical cord after birth and this is not invasive or painful to the donor. There might be the risk of last-minute consent refusal in bone marrow transplant while stem cells from umbilical cord blood will be rapidly available when transplant is needed as they are stored in advance. It is also true for bone marrow transplant that HLA has to be perfectly matched between donor and recipient when perfect match is not required for umbilical cord blood transplant which is particularly crucial to patients who have mix-raced ancestry. This is because HLA is protein on most cells that immune system uses to distinguish self and foreign. In this case, unmatched HLA will make the transplant be recognised as foreign and patient will reject it. What is more, umbilical cord blood transplant has lower chance of causing GvHD. But regarding cell dose and engraftment time, bone marrow is more likely to be preferable. Since stem cell dose is higher in bone marrow than in umbilical cord blood[6], and it takes less time for bone marrow transplant in comparison[18].

In light of these facts, the broader use of CCR5Δ32/Δ32 haplo-cord transplant should be considered to achieve HIV-1 remission and cure for people living with HIV-1 requiring SCT for other diseases.

9. CCR5 Gene-edited HSC Transplantation as Future Treatment

Homozygous Delta 32 deletion of CCR5 gene is very rare among populations. In this case, haematopoietic stem cell (HSC) with CRISPR-Cas9 edited CCR5 transplant may be a possible treatment for not only patients have HIV-1 and AML but also for those who only infected with HIV-1. This approach was proved to have high cleavage efficiency, low off-target effect, and long-term repopulating HSCs in an animal study. Firstly, using CRISPR-Cas9 to edit a few base pairs on CCR5 gene of isolated HSCs. And then transplanting these edited HSCs to the patient. After proliferation and differentiation of HSCs, ideally, robust CCR5 ablation can be achieved and the patient will be HIV resistant as a result. While there are still some safety concerns. The high-throughput whole-genome sequencing result showed one potential non-specific site located in a nonsense region which still may lead to off target effects. [19] Also, there might be potential risks for CCR5-edited babies in bone development because osteoclasts are derived from HSCs and their function may be affected by the deficiency of CCR5 gene of HSCs. [20] But overall, CCR5-edited HSC transplant is promising for future clinical use and is worth further research.

10. Discussion

Data such as medicine used for ART, cell (CD4, CD8, etc.) volume before and after transplant, HIV-1 RNA and HIV-1 DNA copy number, might be missing or not be detailed enough due to the limited published resources on individual cases. Although comparisons between the Düsseldorf patient and the New York patient provide some evidence for UCB in reducing GvHD, it is hard to rule out the possibility that other factors (gender, ART, chemotherapy before transplant, etc.) may have an influence on the presence and severity of GvHD. More research is needed to reveal the upsides and downsides of UCB along with the possible reasons.

11. Conclusion

The investigations into the five patients give us insight that UCB had the potential to be used more widely in the future when transplant is needed. In order to achieve this, the public should raise the awareness of UCB donation and the subsidise for banking is advised. HIV/AIDS is not a curable disease except for a small number of patients in

particular conditions, which stem cell transplant is necessary as treatment for infection other than HIV/AIDS. Stem cell transplant has substantial risks and high mortality, so it is not suggested to be the conventional treatment for HIV/AIDS yet, especially for those who only infected with HIV/AIDS. As further research and evaluation on safer and more effective cures for HIV/AIDS continues, investment is important as well.

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