Cancer and human immunodeficiency virus (HIV) are both scary things to have in your body, but a new treatment is successfully using the latter against the former. Recent news reports, among others in the New York Times, talked about this new cure for leukemia by using HIV. This mini-review puts this news in perspective and provides a broader view as there appear to be several areas where clinical research on HIV and leukemia seem to connect. The topics covered range from antiviral gene therapy approaches using HIV-based lentiviral vectors to the risk of leukemia induction by these integrating vectors, and from an anti-leukemia transplantation strategy that turned out to provide a functional cure for HIV, to novel vaccination approaches.

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Introduction

Much recent progress has been reported in the field of gene therapy. Immunotherapy based on chimeric antigen receptor molecules that are directed against surface markers on cancer cells is one of the promising approaches. In this procedure, the T cells of a leukemia patient are modified with a HIV-based lentiviral vector to deliver the anti-leukemia transgene. We will discuss the ins and outs of recent publications in this field and discuss the confusion in the media about the use of HIV was used to fight leukemia.

Retroviral and lentiviral vectors and the risk of leukemia induction

γ-Retroviral vectors were frequently used to obtain robust and stable genetic modification of human T lymphocytes because these vectors can efficiently integrate within the genome and ensure that the inserted transgene is passed to the progeny of the transduced cells. Subsequently, lentiviral vectors were developed, which are in fact largely based on the human immunodeficiency virus (HIV) genome. HIV is also a member of the Retroviridae family and the lentiviral vectors share the unique property of being able to integrate into the host cell genome, which makes them the...
delivery vehicle of choice when a durable therapeutic effect is needed. Additional benefits of the lentiviral over retroviral vector system include the ability to transduce non-dividing cells.

However, genome integration is also considered a potentially unsafe property of gene therapy vectors. Several insertions next to a proto-oncogene were linked to leukemia induction in patients treated with the first-generation retroviral vectors. Such serious adverse effects were observed using stem and progenitor cell therapies, but the safety profile of retroviral vectors in T cells is so far excellent. Furthermore, the third-generation “self-inactivating” lentiviral vectors were specifically designed to avoid such insertional oncogenesis events, and the initial clinical results with stem cells are reassuring.

**HIV-based vectors for gene therapy against leukemia**

The recent news reports concerned the effective treatment of a 6-year-old girl by a research team of the Abramson Cancer Center at the University of Pennsylvania led by Dr Carl June. This clinical success was presented at the American Society of Hematology (ASH) annual meeting in Atlanta, Georgia (8–11 December, 2012). She was selected as a patient for the experimental technique after 2 years of battling with lymphoblastic leukemia, where chemotherapy failed to either cure the disease or result in a period of remission long enough to consider a bone marrow transplant. Testing, 2 months after the procedure, revealed no sign of cancer and 6 months later she is still in remission and is now back at school. What is the experimental therapy about, does it really use HIV, and how novel is this news?

In fact, the same approach had already been used by the same team on several adult patients and these results were published in 2011, but she was the first child to undergo this experimental adoptive T cell transfer procedure. The pursuit of tumor-reactive T cells as a cancer therapy was originally spurred by the discovery of the graft-versus-leukemia effect in patients undergoing allogeneic hematopoietic stem cell transplantation. Chronic lymphocytic leukemia (CLL) is the most common type of this blood disease that strikes some 15,000 people in the United States and kills 4300 each year. Chemotherapy and radiation can hold this form of leukemia at bay for years, but until now the only cure has been a bone marrow transplant, which is effective only half the time, requires a matching donor, and often causes life-threatening effects such as opportunistic infections.

The T cells of patients were modified to express a chimeric antigen receptor (CAR) with specificity for the B cell antigen CD19, which has expression limited to normal and malignant B cells. The HIV link comes from the use of a lentiviral vector for gene therapy against leukemia induction in patients treated with the first-generation retroviral vectors. The initial patient received a low dose of 1.5 × 10^9 modified T cells/kg 4 days after receiving chemotherapy for depletion of lymphocytes. Tumor lysis syndrome with fever, aches and pains was apparent at 22 days after treatment, which coincided with the induction of the cytokines interferon-γ and interleukin-6. The number of circulating CAR-positive T cells vigorously increased nearly 1000 times compared with the level detected the day after infusion. Engineered T cells persisted at high levels for 6 months in the blood and bone marrow, accompanied by a profound loss of normal B cells and leukemia cells that express CD19. Remission was ongoing 10 months after treatment.

Such prominent anti-leukemia activity points to sustained effector functions of the CAR-modified T cells, which is likely attributed to the replicative capacity of the transferred cells. This poses a major advantage over previous attempts in which the re-injected T cells killed a few cancer cells and then died out. This durable therapeutic effect also provides a major advantage over other therapeutic options, e.g., using antibodies. The two studies reported tumor responses in three patients with advanced CLL, now followed by the first treatment of a child. The news reports indicate that up to 12 patients were treated in total (http://rt.com/news/girl-leukemia-treatment-hiv-702/). Three adults had complete remissions, four had improved conditions, but did not beat the disease completely, one is still in a too-early stage to evaluate, and two patients saw no effect from the treatment. Apparently, a second child was treated who showed an initial response, but eventually relapsed. Thus, T cell therapy appears to be a promising medical breakthrough that may replace bone marrow transplants, but there is a need to conduct additional trials and to optimize the method as several previous breakthroughs in the cancer field have shown initial success and subsequent failure. Whereas funding of the initial trial turned out to be difficult, likely because the approach was too novel and/or risky, the new results may accelerate the fundraising process. In the future, attempts should tackle the commercialization of this type of genetic medicine, which remains challenging given the complex biology involved and will require significant scrutiny from regulatory bodies, such as the Food and Drug Administration before coming to the market.

Other cancers may also be targeted with this new approach, e.g., hard-to-treat cancers such as mesothelioma and pancreatic cancer. In order to attack large tumors with adoptive cellular therapy, it seems pivotal that the T cells proliferate to achieve an appropriate effector-to-target cell ratio in vivo. Thus, approaches to safely increase the proliferative potential of T cells and their trafficking to tumors are needed.

The treated patients may exhibit B cell depletion and hypogammaglobulinemia, which is an expected toxic effect that is manageable. Targeting of B cells with rituximab through the CD20 molecule is an effective and relatively safe strategy for patients with B cell neoplasm. However, B cell loss may cause substantial problems in the future treatment of non-CLL tumor types. Safety measures may range from simple protocol modifications (e.g. infusion of a lower number of T cells) to intricate novel strategies (e.g. incorporation of an inducible cellular suicide switch).

**HIV virotherapy for leukemia**

In a laboratory setting, replication-competent HIV variants have also been proposed as therapeutic agents against
leukemias. This so-called virotherapy forms a relatively novel strategy that is based on the selective replication of modified viruses in cancer cells, e.g., the use of an engineered adenovirus in the treatment of head and neck cancer. We explored the possibility of generating leukemia-specific HIV variants based on the observation that several accessory viral proteins are not needed for HIV replication in transformed T cell lines, yet are important for virus replication in primary cells. A minimized derivative of HIV with five gene deletions (vif, vpr, vpu, nef and U3) was demonstrated to replicate in several leukemic T cell lines, but not in normal peripheral blood mononuclear cells. To improve the safety of such a therapeutic agent, a drug-inducible control switch was subsequently incorporated.

Live, attenuated HIV as a vaccine approach

Similar safety concerns relate to the use of live, attenuated HIV variants as vaccine candidates to protect against a future infection. Such variants can completely protect rhesus macaques from subsequent challenge with the highly pathogenic, wild-type virus. Although this degree of efficacy is in sharp contrast to that achieved with a wide variety of alternative vaccination strategies, safety concerns remain. Protection is inversely correlated to the degree of virus attenuation, such that the most effective designs retain considerable pathogenic potential. Even if the vaccine strain can be tuned to be safe, one cannot preclude that pathogenic variants arise via spontaneous virus evolution. Insertional oncogenesis and leukemia induction also remains a possibility. Despite the incorporation of safety features, such as drug-controlled gene switches, these concerns have precluded the further development of live, attenuated HIV strains as human vaccines.

HIV-induced leukemia

Untreated HIV infection causes acquired immune deficiency syndrome (AIDS) and this major impairment in the immune system is — not surprisingly — associated with an increased risk of cancer, including a number of "solid tumor" cancers and non-Hodgkin lymphoma, but also Hodgkin lymphoma, myeloma and leukemia. Research continues on how to fine tune the therapeutic regimens in these patients, which range from different combinations of chemotherapy and antiretroviral therapy to stem cell transplants. Perhaps surprisingly, there is little evidence that active HIV replication and the numerous integration events into the host cell genome that occur during the lifetime of an HIV-infected individual is directly linked to these HIV-associated cancers via insertional oncogenesis. A likely explanation is that the infected cells have a very short half life because they are recognized and removed by the immune system.

A functional HIV cure due to leukemia treatment

Several new antiviral strategies have been proposed and were recently reviewed. Then there is that remarkable therapeutic success that connects HIV and leukemia. For the first time in medical history, an HIV patient seems to have been cured from the disease. The patient underwent a stem cell transplant in the hopes of treating his leukemia, but ended up being cured of both the leukemia and HIV. The stem cells used for the transplant came from a donor who carried the â-32 deletion in the CCR5 gene that disrupts the expression of this major receptor for HIV entry into cells. Once the patient received the transplant, he stopped taking the antiretroviral drugs that had been managing his virus infection. The virus did not reappear in his blood, although one may suspect that it is still lurking somewhere in his body.

Now some 5 years later, the doctor has declared him HIV-free, as the patient’s CD4 cell count falls within the range of an uninfected person. Functional cure is perhaps the best description and one should realize that such a transplant is too risky and taxing to offer to HIV-infected individuals. Nevertheless, this clinical result has spurred many alternative gene therapeutic approaches to inactivate the CCR5 gene, to silence CCR5 gene expression or to inhibit HIV by other means. An attractive vehicle to deliver the antiviral payload is again the lentiviral vector.

Summary

Several preclinical studies and clinical successes were presented, demonstrating that there is much progress in the field of molecular medicine. This has been facilitated by the delineation of molecular pathways and the detailed dissection of disease processes. Progress is particularly obvious for the field of gene therapy, which shows — after a difficult initial phase — that therapeutic efficacy and safety can go hand in hand. HIV research led to the discovery of many new molecular mechanisms and this insight has spurred several original therapeutic strategies. HIV is not only the target for therapeutic intervention, this virus has also provided one of the favorite tools for efficient gene therapy in the form of lentiviral vector systems. Using this molecular knowledge base, novel tailor-made therapeutic strategies can be designed that will eventually change the way we treat patients. The recent progress in molecular medicine has been spectacular, and it seems only a matter of time before some approaches will translate to improvements in patient care.

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References


