Published in final edited form as:
Curr Opin HIV AIDS. 2013 May ; 8(3): 224–229. doi:10.1097/COH.0b013e32835ef0a1.

Curing HIV: lessons from cancer therapy

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Abstract

Purpose of review—Interest in finding a potential 'cure' for HIV has taken on greater interest and urgency since the report of an individual who underwent allogeneic stem cell transplant from a CCR5 delta 32 homozygote donor after high-dose chemotherapy for acute myeloid leukemia. The potential role of cancer chemotherapy and other cancer-directed treatment approaches is discussed in the context of their potential role in helping to eliminate HIV from the infected host.

Recent findings—Cancer chemotherapy and other cancer-targeted agents have been used successfully in treating a variety of malignancies in both HIV-infected and HIV-uninfected individuals. Lessons learned from these strategies may be of importance in helping to define more effective ways of controlling and eliminating HIV as well. Application of these anticancer strategies to patients with HIV are beginning to be explored and may help determine their potential usefulness in this disease as well.

Summary—Although cytotoxic chemotherapy is a crude and not particularly effective way of removing HIV latently infected cells and tissue reservoirs, several new approaches to targeting and controlling cancer proliferation may be of value in HIV cure research and may one day help to end this disease.

Keywords

adoptive cell therapy; chemotherapy; epigenetic manipulation; immunotoxin; stem cell transplant

INTRODUCTION

Although current antiretroviral therapy (ART) can greatly reduce the amount of proliferating and circulating HIV to very low 'undetectable' levels, can slow the progression of disease, and restore near normal life expectancies to HIV-infected individuals, HIV-infected cells are not eradicated from the host and rapid viral replication rebound occurs once ART is terminated, regardless of the duration of treatment. Recent interest in effecting a 'cure' for HIV has taken on greater interest with the report of the 'Berlin patient', an HIV-infected person with acute myeloid leukemia, who was found to have eliminated detectable HIV from all tissues examined after having undergone treatment for his leukemia with high-dose chemotherapy, monoclonal anti-myeloid leukemia (AML) antibody-toxin conjugate (gemtuzumab ozogamicin), and allogeneic stem cell transplant from an HIV-uninfected donor possessing the CCR5 delta 32 homozygous mutation [1■]. Although this case demonstrates the possibility of a cure for HIV, designing an effective, well tolerated, and

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Conflicts of interest The author acknowledges that he has contracts via the University of California for clinical trials with Sangamo Biosciences, Calimmune, Janssen and Bionor Immuno.

widely applicable treatment to eradicate HIV or to effect a means of controlling HIV without ongoing HIV therapy (functional cure), will likely require a multipronged approach using multiple strategies to both eliminate HIV latently infected cells as well as controlling HIV immunologically or genetically. Like many cancers, HIV can affect several cell types, which may or may not be directly susceptible to medications that target replicating viruses or infected cells and which may reside throughout the body, including many sanctuary sites. Several approaches to cancer treatment may have relevance to HIV for both understanding how we might go about better attacking HIV and may hold clues as to how we might develop new strategies for targeting HIV.

ELIMINATING INFECTED CELLS

A straightforward way of eliminated HIV-infected cells is killing cells that are already infected via the cytotoxic effect of chemotherapy alone. The rationale for this approach is based on the fact that anti-retroviral drugs, although extremely effective in blocking HIV replication, fail to directly kill cells that are already infected. Targeting killing of these cells with chemotherapy provides a complementary approach to ART that may help eradicate this infection. In the late 1980s and early 1990s, a small number of HIV-infected patients were treated with myeloablative chemotherapy followed by bone marrow transplants (BMTs) for a variety of hematologic malignancies while receiving antiretroviral suppressive therapy [2–5]. Although the antiviral therapy was what is now viewed as suboptimal, two patients after receiving cytotoxic chemotherapy, irradiation, and BMT were without detectable proviral DNA in their peripheral blood after successful transplants. These two patients subsequently died from other medical conditions not directly related to HIV; however, samples of their hematopoietic and lymphoid tissues as well as probes of other organs found no evidence of HIV in these patients. Since that time several cytotoxic drugs have been shown to be effective in depleting HIV-infected cells *in vivo* or *in vitro* including several alkylating agents, such as, cyclophosphamide, busulfan, and antimetabolites [6,7]. In addition, in mice infected with murine leukemia virus (a model of HIV infection), cyclophosphamide has been shown to reduce the number of virally infected cells to undetectable levels and to block the progression of disease [8]. More recent studies of bone marrow or peripheral stem cell transplants for hematologic diseases in HIV have demonstrated excellent antitumor outcome and good tolerance, but a general requirement for continued ART after transplant [9,10■].

In the late 1990s, cytotoxic therapy was at one time advanced as a means of reducing viral load in some patients [11,12]. The benefit of such therapy, however, has been very limited, perhaps because these treatments were not designed to eliminate the latently infected cells from reservoirs. For example, the ribonucleoside reductase inhibitor, hydroxyurea was combined with other antiretroviral medications and was shown to have a synergistic effect on suppressing HIV [13–16]. It was found to be helpful in some refractory patients not responsive to conventional HAART therapy and was also shown to reduce the mutation rate of HIV. However, because of the fact that hydroxyurea works by reducing the intracellular deoxyribonucleotide triphosphate pool, it had no effect on latently infected resting T cells with limited proliferation potential and, hence, had little effect on tissue reservoirs. Similarly a study exploring the effects of escalating doses of the cell-cycle nonspecific alkylating agent, cyclophosphamide, with antiretroviral drugs showed no change in the cellular reservoir of HIV [17]. More recent assessments of HIV patients with Hodgkin's disease or non-Hodgkin's lymphoma undergoing more contemporary cytotoxic combination chemotherapy with or without rituximab, an anti-CD20 monoclonal antibody, and using a more sensitive single-copy HIV RNA assay demonstrated persistence of low-level HIV viremia in individuals on continuous ART up to 3 years after achieving complete remission of their lymphomas [18■]. Similarly after high-dose, fully ablative chemo-therapy and autologous stem cell transplant for hematologic malignancies in HIV, continued low-level

viremia using single-copy assay could also be detected [19■], although the results of this study is limited by the retrospective nature of the study and the use of a convenience sample of participants. A prospective study of the effects of autologous stem cell transplant in HIV patients with hematologic malignancies with a focus on detection of low-level HIV pre-transplant and post-transplant is being conducted by the Bone Marrow Transplant Clinical Trials Network (BMT-CTN 0803) and the AIDS Malignancy Consortium (AMC 080) (clinicaltrial.gov/ct2/show/NCT01141712).

ALTERNATIVE MECHANISM FOR VIRAL CLEARANCE

In the now famous case of the 'Berlin Patient', other possible explanations for the ability to eradicate HIV from the host include the addition of other agents as part of the cancer chemotherapy regimen, including antithymocyte globulin, antimyeloid leukemia monoclonal antibody, the use of allogeneic cells resulting in a graft-versus-host effect against HIV latently infected cells and the use of donor cells protected against further HIV infection because of the presence of the CCR5 delta 32 homozygous mutation. Although it may not ever be possible to ascertain the relative contribution of these other factors to the cure, it is possible that the combination of these factors may have contributed to HIV elimination in this individual. To add some credence to the possible contribution of the allogeneic effect, a recent report from Boston [20■] demonstrated the inability to detect any evidence of HIV in two individuals after high-dose chemotherapy and allogeneic transplant for hematologic malignancies in individuals maintained on HAART for several years after transplant. A prospective study of high-dose chemotherapy and allogeneic stem cell transplant in HIV patients with hematologic diseases is currently in progress under sponsorship of the BMT-CTN (0903) and the AMC (081) (clinicaltrial.gov/ct2/show/NCT01410344).

OTHER USES OF CHEMOTHERAPY AS PART OF CURE STRATEGY

Although chemotherapy does have a direct effect on reducing the number of HIV-infected cells and can do so quite rapidly after its administration [21], another potential use of these drugs is as part of conditioning for cell transplant in gene therapy trials. Pretransplant conditioning with less than fully ablative chemotherapy has been used quite effectively in treating patients with leukemia and lymphoma, wherein the anticancer effect of the chemotherapy may be of secondary importance to the engraftment enhancing effects of low-dose chemotherapy and the subsequent graft-versus-leukemic effect of the transplanted cells. This strategy has been used effectively in HIV patients with non-Hodgkin's lymphoma who received partially ablative therapy with busulfan and cyclophosphamide [22]. More recently, in conjunction with genetic manipulation of autologous CD4 cells with CCR5R-directed zinc-finger nuclease, low-dose cyclophosphamide is being used as a means of further reducing the number of nongene-modified CD4 cells and promoting the engraftment of the gene modified cells (http://clinicaltrials.gov/ct2/show/NCT01543152). Similarly busulfan has been utilized effectively to 'make space' and facilitate engraftment of allogeneic $CD34^+$ hematopoietic stem cells in a variety of nonmalignant diseases [23–26] and is being considered for use with gene-modified $CD34^+$ cells in HIV (www.clinicaltrials.gov/ct2/show/NCT01734850).

OTHER CANCER TREATMENT STRATEGIES WHICH MAY BE USEFUL IN HIV

The past two decades have seen major advances in devising strategies to directly kill tumor cells based on their surface expression of tumor-associated antigens that can be targeted by antibodies alone or linked to cytotoxic payloads or alternatively by adoptive cell therapy with natural or genetically modified cytotoxic T lymphocytes (CTLs). These cancer

therapeutic developments have been paralleled by approaches against viruses including HIV, although the major problem of latently virally infected cells are that they are invisible to the targeted killing modality unless activated during treatment [27].

Antibodies chemically linked to low molecular weight-cytotoxic drugs offer a means for highly potent cell killing [28]. Antibody–drug conjugates (ADC) have been developed for a variety of cancers including the first such ADC approved by the Food and Drug Administration (FDA) in 2000 for relapsing acute myeloid leukemia, gentuzimab ozogamicin, a humanized anti-CD33 monoclonal antibody linked to calichemicin, which was one of the agents used to treat the 'Berlin patient' upon relapse of his AML. Another monoclonal antibody–toxin conjugate recently approved for use in refractory $CD30^+$ Hodgkin's lymphoma and $CD30^+$ anaplastic large T-cell non-Hodgkin's lymphoma is bentuximab vedotin, which is now also undergoing evaluation in HIV-associated Hodgkin's lymphoma in the AMC. The application of ADCs to viruses, including HIV, has been very limited so far. An antibody–doxorubicin conjugate was shown to kill cells infected with a laboratory-adapted HIV-1 and to protect mice from challenge with engineered infectious murine retrovirus encoding the corresponding HIV-1 envelope protein [29].

Similarly radioimmunotherapies that link a cytotoxic radionuclide to an antibody have been developed for non-Hodgkin's lymphoma [^{90}Y]-ibritimomab tiuxetan (Zevalin) and [^{131}I]-tositumomab (Bexxar). Recently a study [30] examined the effects of radioimmunotherapy [^{188}Re]-anti-gp41 monoclonal antibody in severe combined immunodeficient mice injected intrasplenically with HIV-infected PBMC and showed marked reduction in infected cells in the spleen at 72 h after infection whereas unlabeled antibody or irrelevant [^{188}Re]-labeled antibody had no effects.

Yet another approach is with immuntoxins, which have a long and somewhat checkered history in HIV therapy. An immunotoxin is a bifunctional protein containing a targeting moiety linked to a cytotoxic protein. Binding and internalization into target cells expressing the antigen or receptor leads to highly specific cell killing [31]. Denileukin difitox, a fusion protein containing interleukin-2 genetically linked to the effector domain of diphtheria toxin, is FDA approved for the treatment of persistent or relapsed CD25-positive cutaneous T-cell lymphoma. In HIV, potent specific in-vitro killing of CD4-targeted immunotoxins based on Pseudomonas exotoxin A, i.e. sCD4-PE40, underwent phase I clinical trials in the early 1990s prior to the advent of HAART, but these studies were halted because of dose-limiting reversible hepatotoxicity [32]. More recently, a different PE-based immunotoxin 3B3-PE38, containing a high-affinity anti-gp120 single chain variable fragment in place of sCD4 has shown no hepatotoxicity in rheseus macaques and is very effective in controlling HIV infection when used in conjunction with HAART [33]. Of concern is finding ways to lessen the immunogenicity of these immunotoxin proteins to allow more treatment cycles.

Adoptive cell therapy with engineered T cells or stem cells may also play an important role in both cancers and HIV. Antigen specificity can be provided by natural T-cell receptor (TCR) or a chimeric antigen receptor (CAR), typically composed of a ligand against the desired surface antigen linked to a suitable transmembrane region and one or more cytoplasmic domains containing signaling motifs critical for CTL effector function. The CAR gene can be introduced into the patient's lymphocytes *ex vivo* using a retroviral or lentiviral vector, the cells expanded and infused back into the patient, with or without myeloablative lympho-depletion. The CAR binds to the intact antigen expressed on the target cell surface independent of MHC, thus, circumventing tumor or viral immune evasion strategies and, thus, also not requiring use of autologous cells. Recently these CAR-modified cells have been effectively used in the treatment of refractory chronic lymphocytic leukemia and progressive follicular lymphoma (using a second-generation CAR recognizing the B-

cell antigen CD19 [34■]). Adoptive cell therapy is the principle behind the use of CCR5 delta 32 homozygous donors for stem cell or BMT and for the recently revived interest in adoptive gene therapy for HIV (http://clinicaltrials.gov/ct2/show/NCT01734850). Also work continues to engineer CD8 T cells to express the TCR from HIV-1 gag-specific CTL from hematopoietic stem cells [35,36■].

Yet another lesson learned from new therapeutic approaches being used to treat refractory malignancies is to try to enhance the host's immunity against malignant cells via overcoming inhibitory immune effects that may prevent better immunologic tumor control. The recent approval for use in malignant melanoma of ipilimumab, a monoclonal antibody to CTLA-4, that regulates antitumor responses by blocking the interaction of CTLA-4 with its ligands, CD80/CD86, and thus, augments T-cell activation and proliferation, suggests that this drug may also be useful in enhancing the anti-HIV effects of cytotoxic T cells as well. Similarly, a new antibody against programmed death-1 (PD-1), a cell surface membrane protein that may negatively regulate TCR signaling and may broadly effect immune responses in a variety of immune cells, is being investigated in a variety of cancers [37■] and may have a role in the control of HIV-1 as well [38■].

Finally, the growing field of epigenetic manipulation of cancer or virally-infected cells via drugs such as histone deacetylase inhibitors and proteo-some inhibitors have results in new cancer therapies, for example vorinostat for lymphoma [39] and other solid tumors, romidepsin for peripheral T-cell lymphoma [40,41], and bortezomib for multiple myeloma and mantle cell lymphoma, and may prove to be another means of activating HIV as well as other oncogenic viruses, such as Epstein–Barr virus and Human Herpes Virus-8 from latently infected cells, thus, making them more likely to undergo apoptosis or more amenable to direct cytotoxic targeting by other means. Indeed, bortezomib may have additional anti-HIV effects through its proteosome inhibitor effects reversing the effects of the HIV-1 virion infectivity factor by slowing the degradation of APOBEC3G, allowing it to be incorporated into budding HIV virions. In support of this mechanism, in-vitro studies inhibiting the 26S proteasome have been shown to impair HIV viral budding and infectivity [42].

CONCLUSION

Advances in the field of cancer therapeutics may provide additional strategies and approaches for someday affecting a functional cure for HIV. By combining our currently very effective means of inhibiting viral replication (i.e. with HAART) with nonselective or preferably selective killing of HIV-infected cells. Although cytotoxic chemotherapy is a crude and not particularly effective way of removing HIV-infected cells from the host, it does provide us with clues as to how we might attack HIV latently infected cells and tissue reservoirs. Of the approaches described here, several are now under active clinical investigation, including adoptive cell therapy and activating and subsequently selectively targeting latently infected cells. If recent advances in new treatments for cancers may foretell the future for HIV cure research, we may indeed one day see the end of this disease as we know it.

Acknowledgments

R.M. is the Group Chair and PI of the NIH/NCI-funded AIDS Malignancy Consortium (CA 121947) and an investigator on the following NIH grants (AI 069424, AI 28697, MH 087222, UL1TR000124 and DHHS award 2946SC8.

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KEY POINTS

- Several approaches to treating malignancies have relevance to both understanding the mechanisms by which HIV may be ‘cured’ and, perhaps, how we might better target and eliminate HIV-infected cells.
- Cancer chemotherapy may have a role in removing HIV-infected cells and may be important to the engraftment of naturally resistant or gene-modified cells that can halt the further spread of HIV.
- Novel means of targeting malignant cells via immunologic (i.e. antibodies or antibody–toxin conjugates, gene-directed cellular or abrogation of immune inhibitory mechanisms) as well as via epigenetic manipulations have recently resulted in new cancer therapies and may also show the way to better means of eliminating HIV virally infected cells as well.