Radioimmunotherapy as a Novel Approach in HIV, Bacterial, and Fungal Infectious Diseases

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Abstract

In the past several decades, many antimicrobial agents have been used in treating different fungal, bacterial, and viral infections. However, these agents have faced challenges such as pronounced side-effect profiles and pathogen resistance. In addition, a cure for many chronic infections such as human immunodeficiency virus (HIV) has not been achieved, and the incidence of opportunistic infections in immunocompromised patients has increased significantly in the past decades. Therefore, an alternative strategy for combating these infections is needed. Radioimmunotherapy (RIT) has been proposed to be a valuable tool in the management of such infections. The side-effects associated with RIT are minimal as the targeted antigens are only expressed on microbial or infected cells. RIT demonstrated impressive potency in eradicating pathogens in animal models and patient samples. *Cryptococcus neoformans*, HIV, and *Bacillus anthracis* are few examples of infections for which RIT has been an effective treatment using radionuclides such as bismuth-213 (^{213}Bi) or rhenium-188 (^{188}Re).

Keywords: radioimmunotherapy, HIV, monoclonal antibody, fungal infections, bacterial infections

Introduction

The available antipathogenic medications have been used for several decades to treat a wide range of infectious diseases. However, they have suffered from low potency, resistance development, and high toxicity in certain cases.^{1–3} There is no cure^{4,5} for many infectious diseases, including AIDS, fungal, and parasitic diseases, and this creates the urgent need for curative agents. Radioimmunotherapy (RIT) has been successful in treating certain cancers such as non-Hodgkin's lymphoma.^{6,7} Recently, RIT has been proposed as a potential breakthrough therapeutic approach for infectious diseases. The therapy involves administration of a radionuclide-labeled monoclonal antibody (mAb) that selectively binds to a cell surface antigen delivering a sufficient amount of radiation to kill the cell.⁸ Since the targeted antigen is presumed to be only found on targeted microbes or infected cells and absent on other cells, minimal side-effects are anticipated.

The significance of RIT over naked antibody strategies is the direct physical destruction of targeted cells caused by delivering cytotoxic radiation, which induces apoptosis or even necrosis.⁹ RIT effectiveness is not affected by immunological status of the host receiving the therapy.¹⁰ In addition, drug resistance to conventional treatments does not affect the potency of RIT. Higher potency and effectiveness of RIT may also reduce the time required for treatment. These reasons have

encouraged researchers to continue evaluating the efficacy of RIT in treating infectious diseases. As many pathogenic microorganisms divide much faster than mammalian cells, with the former doubling times being minutes or 2–3 h, the radionuclides chosen for RIT of infection need to be able to deliver high-energy radiation in short periods of time to match the fast division of microbial cells. In this regard, the α emitter bismuth-213 (^{213}Bi) and a powerful β^- -emitter rhenium-188 (^{188}Re) with 46-min and 16.9-h physical half-lives, respectively, were chosen. Another feature of ^{213}Bi and ^{188}Re that might be beneficial for RIT of infections is the safety of these radionuclides: ^{213}Bi α emissions have a very short track in tissue and will not affect healthy nontargeted tissues, and ^{188}Re is not a bone-seeking radionuclide that quickly oxidizes to inert perrhenate, which is excreted through the kidneys. Safety aspects are important for RIT of infectious diseases in which tolerance toward side-effects will be lower than in oncology. In this review, evidence of the RIT potential in treatment of invasive infectious diseases will be presented.

Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) affects 1.2 million individuals in the United States. The number increases by 50,000 new HIV diagnoses each year.¹¹ Currently, the combination of different antiretroviral therapies (ARTs)

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used in treating HIV is proving to be highly effective. However, no curative treatment for HIV infection has been discovered yet. The purpose of these ARTs is to reduce viral replication and viral load, but they do not target intracellular HIV. This allows the virus to replicate when therapy is interrupted, therefore requiring continuation of a lifelong treatment. Additionally, toxicity and resistance emerge during the therapy.¹² Hence, RIT provides a strategy by delivering cytotoxic radiation to virally infected cells. mAbs that specifically target viral proteins such as gp120 and gp41 were labeled with ²¹³Bi or ¹⁸⁸Re to test their cytotoxic activity against HIV-infected cells.¹³ ²¹³Bi-labeled mAb 246-D (mAb to gp41) demonstrated significantly higher cytotoxicity against human peripheral blood mononuclear cells (hPBMCs) infected by the HIV-1 strain JR-CSF when compared with either the ²¹³Bi-labeled irrelevant control mAb 1418 or cold antibody 246-D.¹³

Meanwhile, minimal cytotoxicity against noninfected cells was observed, demonstrating specificity of the radiolabeled mAb 246-D. When tested in an *in vivo* setting, eradication of infected cells was also observed.¹³ However, ¹⁸⁸Re-246-D showed higher potency than ²¹³Bi-246-D *in vivo* in eradicating HIV-1 due to longer half-life of ¹⁸⁸Re, which allowed more radiolabeled antibody molecules to reach the infected cells. A small reduction in platelet count was observed after 1 week. This provides further evidence of the low toxicity of these mAbs due to the gp41 protein expression only on HIV-1-infected hPBMCs.

The transmembrane glycoprotein gp41 has recently been characterized and is found to be expressed on the virus and on the surface of virally infected human cells.¹⁴ However, the expression of this glycoprotein is reduced during HIV treatment regimens. Since majority of HIV patients receive antiretroviral medications, the effect of such treatments on RIT, which targets this glycoprotein, had to be determined. *In vitro* experiments showed that 0.74 MBq (20 μ Ci) ²¹³Bi-2556 and 2.96 MBq (80 μ Ci) ²¹³Bi-2556 were able to kill a significantly higher number of infected cells when combined with antiretroviral agents compared with the killing ability of antiretroviral alone (Fig. 1).¹⁵

The highly specific mAb 2556 used in these experiments targets the conserved domain of gp41. The mAb showed high affinity and reactivity to gp41. These characteristics minimized the competitiveness between the mAb and the patient's own anti-gp41 antibodies. Flow cytometry results confirmed the ability of mAb ²¹³Bi-2556 to completely eradicate HIV-1-infected cells compared with the ²¹³Bi-1418 control mAb and cold mAb 2556.

SCID mice were injected in the spleen (IS) or intraperitoneally (IP) with hPBMCs infected with the HIV-1 strain JR-CSF.¹⁶ These administrations were followed by the IP injection of cold 2556, ²¹³Bi-2556, ²¹³Bi-1418, or saline 2 days after infection. In both models (IP and IS), injection of ²¹³Bi-2556 at the highest dose significantly reduced infected hPBMCs.¹⁶ Importantly, ²¹³Bi-2556 mAb was also shown to cross the blood-brain barrier in an *in vitro* study and kill hPBMCs and monocytes infected with HIV without affecting the barrier (Fig. 2). This provides another advantage over conventional treatments that lack the ability to enter the brain, which limit the ability of ART to treat HIV-associated neurocognitive disorders.¹⁷ Drug resistance in HIV treatment is known to be a crucial drawback of avail-

able therapies. Targeting of the highly conserved domain of gp41 increases the likelihood that RIT will retain its effectiveness when viruses have mutated.

Bacterial Infections

The use of RIT in bacterial infection treatments has also been well investigated. Due to rapid replication of bacteria in the tissues of the host, extensive damage to organs is likely, often with fatal consequences. *Streptococcus pneumoniae* and *Bacillus anthracis* are two examples that cause severe life-threatening infections.¹⁸ The use of RIT may, therefore, provide a good therapeutic choice for treatment of such aggressive infections. *S. pneumoniae* is a major cause of community-acquired pneumonia and, in some cases, meningitis, bacteremia, and sepsis. Human MAb D11, which binds to pneumococcal capsular polysaccharide 8 (PPS8), was labeled with ²¹³Bi.¹⁹ *In vitro* experiments showed that ²¹³Bi-D11 mAb had significantly more bactericidal activity than the irrelevant isotype control IgM antibody. *In vivo* experiments also showed that mice infected with *S. pneumoniae*, followed by radiolabeled mAb injections, had significantly improved survival rates and no bacteremia compared with those injected with radiolabeled irrelevant control mAb and unlabeled mAbs. In addition, treatments were well tolerated with no statistical difference in the platelet count between the RIT-treated and control groups.

The activity of RIT in targeting *B. anthracis*, the causative organism of anthrax, was also reported. The infection is caused by a toxin produced by the pathogen and consists of a protective antigen (PA), lethal factor (LF), and edema factor (EF). mAbs for PA 7.5G and 10F4 and mAb for LF 14FA were labeled with ¹⁸⁸Re or ²¹³Bi and tested *in vitro* for their killing of *B. anthracis* cells.²⁰ mAb 14FA had the highest affinity and the lowest number of binding sites than 7.5G and 10F4 mAbs. The same mAbs were radiolabeled with ²¹³Bi and injected into A/JCr mice after infecting them with *B. anthracis*. Results showed that the groups that received 3.7 MBq (100 μ Ci) ²¹³Bi-labeled mAbs had prolonged survival rates compared with groups that received irrelevant mAbs.²⁰ In another study, RIT was employed to target *B. anthracis* spores that are highly resistant to therapeutics, and infection with spores is indicative of poor prognosis. These spores express a collagen-like glycoprotein BclA on their surface. A mAb targeting BclA labeled with ²¹³Bi was able to kill a significant number of *B. anthracis* spores compared with the control groups.²¹

Fungal Infections

The majority of fungal infection cases caused by the encapsulated pathogen *Cryptococcus neoformans* occur in immunocompromised patients and only occasionally in healthy individuals. mAb 18B7 was developed to target this pathogen and showed good binding to all four serotypes of *C. neoformans*.²² The *C. neoformans* mouse model was also developed to assess the effectiveness of mAb 18B7 against the pathogen.²³ Significant improvement in A/JCr mouse survival was recorded when compared with control groups.²²⁻²⁴ In addition, mAb 18B7 was also evaluated in a clinical trial in patients with *C. neoformans* infection.²² Results showed that this mAb potentiates the antifungal activity of human and mouse effector cells, which activates

FIG. 1. Survival of infected cells when treated with different antiretroviral agents with or without ^{213}Bi -labeled mAbs. Results show that using ^{213}Bi -labeled mAbs with all retroviral agents significantly enhanced the cytotoxicity of agents against HIV-infected cells. ATZ, atazanavir; FTC, emtricitabine; TFV, tenofovir; EFV, efavirenz; mAb, monoclonal antibody; HIV, human immunodeficiency virus. *statistically significant difference.

the complement pathways leading to disposition of complement component 3 (C3) on the cryptococcal capsule.²²

The availability of *C. neoformans* animal models and organism-specific antibodies encouraged the testing of the potency of radiolabeled mAb 18B7. Results showed that injecting 18B7 radiolabeled with 3.7 MBq (100 μCi) ^{213}Bi enhanced the survival of A/Cr mice by 60% on day 75 post-therapy compared with the radiolabeled isotype control IgG1 and phosphate-buffered saline-treated group.²⁵ The radionuclide ^{188}Re was used for radiolabeling of the same mAb and tested for its activity against *C. neoformans* in the same mouse model. ^{188}Re -18B7 administration resulted in 40% survival on day 75 post-therapy. The experiments

involved injecting C57BL6 mice with 3.7 MBq (100 μCi) ^{213}Bi -18B7 24 h postinfection; 3.7 MBq (100 μCi) ^{188}Re -18B7 24 h postinfection; 3.7 MBq (100 μCi) ^{188}Re -18B7 48 h postinfection; or left untreated and then sacrificing the animals 75 days post-treatment. In another study, differences in the activities of radiolabeled antibodies in the brain and lungs were observed.¹⁰ The brain colony-forming unit (CFU) count was not lowered by ^{188}Re -18B7 24 h postinfection. However, a significant reduction in brain CFUs was observed when ^{188}Re -18B7 was injected 48 h postinfection. In contrast, the lung CFUs were significantly lowered by ^{188}Re -18B7 24 h postinfection and 3.7 MBq (100 μCi) ^{188}Re -18B7 48 h postinfection. Interestingly, administering the same mAb, but radiolabeled with ^{213}Bi -18B7, 24 h postinjection caused an eradication of fungal cells in the lungs and brains.¹⁰ Since most *C. neoformans* infection cases are detected in immunocompromised patients, the effect of the immune status on RIT was tested. Results showed that the immunity status had no effect on RIT.¹⁰ These results are encouraging for the translation of RIT to immunocompromised patients with this opportunistic infection.

A comparison between the therapeutic potency of RIT and the conventional treatment, amphotericin, was performed.²⁶ In this report, A/JCr mice were infected with melanized or nonmelanized *C. neoformans* cells followed by IP injection with 3.7 MBq (100 μCi) ^{213}Bi -18B7 mAb or amphotericin. Despite using the high dose of amphotericin (1 $\mu\text{g/g}$ body weight), it failed to reduce the lung and brain CFUs. However, the RIT group showed complete eradication of the fungus in the brain and lungs.²⁶ These findings were confirmed by other reports that observed the lack of ability of amphotericin B in short periods of incubation to sterilize the cerebrospinal fluid and blood of patients infected with *C. neoformans*.²⁷

RIT that targets antigens found in many invasive fungal infections was investigated.²⁸ This approach can eliminate

FIG. 2. Graph showing the potency of ^{213}Bi -2556 in killing HIV cells located in the brain. ^{213}Bi -2556 was able to cross the blood-brain barrier (*in vitro*) and kill only HIV-infected cells at lower doses. However, when higher doses of radiation were used (50.0 μCi), RIT killed noninfected cells as well. RIT, radioimmunotherapy. *statistically significant difference.

the need for a specific mycological diagnosis before therapy is initiated. For this reason, many common cell wall-associated antigens were evaluated as potential targets; β -glucan is one such antigen that is expressed by many fungi on their cell surface. mAbs to this antigen were produced and tested in *Candida albicans* and *C. neoformans* animal models.^{29–31} Heat shock protein 60 (Hsp60) is another antigen found on the surface of different fungi, including *Histoplasma capsulatum*.³² Importantly, the mAb targeting Hsp60 on *H. capsulatum* was also able to react with the same antigen expressed by other pathogenic fungi, but did not cross-react with human Hsp60.³² In addition, the mAb targeting melanin was found to react and bind to many pathogenic fungi that have this antigen in their cell walls.³³ These fungi included *Blastomyces dermatitidis*, *C. neoformans*, *H. capsulatum*, *Coccidioides posadasii*, *Aspergillus spp.*, *Scytalidium dimidiatum*, *C. albicans*, *Sporothrix schenckii*, and *Paracoccidioides brasiliensis*.²⁸

For testing the RIT targeting such universal antigens, mAbs 4E12, an IgG2a to fungal Hsp60; 2G8, an IgG 2b to β -(1,3)-glucan; and 6D2, an IgM to melanin; were radiolabeled with ²¹³Bi and evaluated for their cytotoxic activity against *C. neoformans* and *C. albicans*.²⁸ A wide difference in their cytotoxic activity was observed. ²¹³Bi-labeled mAbs to HSP60 and to β -(1,3)-glucan were both able to reduce the viability of both fungi in the 80%–100% range. However, ²¹³Bi-6D2 mAb to melanin was able to kill only 50% of *C. neoformans* cells and was not effective in killing *C. albicans*. All therapies were compared with unlabeled mAbs and radiolabeled isotype-matching control mAbs. These experiments showed promising results for the use of RIT, which targets common fungal antigens, in treating invasive fungal pathogens.

Pharmacokinetics of Anti-Infectious RIT

The pharmacokinetics and binding characteristics of different antibody isotypes and forms for use in anti-infectious RIT were investigated.³⁴ The intention was to determine the most suitable delivery vehicle for RIT to treat human pathogen *C. neoformans* and other fungal pathogens. IgG1 and IgM isotypes and IgG1-derived F(ab')₂ and Fab fragments were tested for this purpose. The pharmacokinetics of any specific mAb depends on many factors: antibody affinity/avidity for the antigen, its molecular weight, and $t_{1/2}$ in the blood. The results showed that the affinity of 13F1 IgM toward its antigen in the polysaccharide capsule of *C. neoformans* was significantly lower than that of the 18B7 IgG1 mAb. This lower binding affinity caused a significant reduction in the dose delivered by ¹⁸⁸Re-13F1 to *C. neoformans* compared with ¹⁸⁸Re-18B7. This rendered 13F1 IgM unable to kill *C. neoformans* cells in *in vitro* RIT studies.³⁵ In addition, the 18B7 mAb has higher affinity toward capsule polysaccharides than the soluble polysaccharide.³⁶ Because the *C. neoformans* capsule has several-fold higher concentration of polysaccharide than the soluble polysaccharide in blood,³⁷ the mAb accumulated on the surface of the pathogen rather than forming polysaccharide-antibody complexes in blood. These observations provide evidence of the importance of high-affinity mAbs for RIT.

The biodistribution of ¹¹¹In-labeled 18B7 and its F(ab')₂ and Fab fragments was investigated to evaluate the effect of

molecular weight on the biodistribution pattern of antibodies in *C. neoformans*-infected mice.³⁴ The results showed that the uptake in lungs for 18B7 and its F(ab')₂ differed. Intact ¹¹¹In-18B7 was taken up by lungs to a higher extent than ¹¹¹In-F(ab')₂ at 24 h postadministration. Lung uptake of ¹¹¹In-Fab was significantly lower than both ¹¹¹In-labeled 18B7 and its F(ab')₂ at the same time point. However, the uptake of these mAbs in other organs showed variable results. For example, the uptake of ¹¹¹In-F(ab')₂ and ¹¹¹In-Fab by the kidneys was significantly higher than the whole ¹¹¹In-18B7. Other organs such as the spleen and brain showed no difference in the uptake of the different mAb forms when given 24 h postinfection. Similar patterns in different organ uptake values were observed when mAbs were given 48 h after infection. Although more research is needed on this particular mAb to draw more definitive conclusions, it is clear that not only do molecular weights of the mAb influence the organ uptake but also its physiological nature and progression of infection in the targeted organs.

Although molecular weights of mAbs seem to play a significant role in organ/pathogen uptake, the loss of binding affinity should be a concern if low-molecular-weight antibody forms are intended for use in anti-infectious RIT. F(ab')₂ and Fab fragments had a significantly lower %ID/g than intact mAbs.³⁴ Monovalent Fab fragments have lower affinity than intact antibodies toward targeted antigens after the loss of polyvalence, while for polyvalent F(ab')₂ fragments, the loss of Fc region's contribution to avidity might also result in less binding to target antigens.³⁸ In this regard, the influence of various Fc regions on binding to target antigens for antibody families with an identical complementary determining region, but different Fc region, has been demonstrated.³⁹ When considering the best delivery vehicle for the RIT of infection with α - or β -emitting radionuclides, one has to choose molecules that have the highest possible binding to the microbial target to ensure killing of fast dividing microbial cells.³⁵

In addition, the chemistry of radionuclides attached to the same mAb had significant effect on biodistribution of antibodies. ¹⁸⁸Re- and ¹¹¹In-labeled 18B7 mAbs revealed similar infected lung uptake patterns after 24 h. However, ¹⁸⁸Re-18B7 cleared fivefold faster from the blood than ¹¹¹In-18B7. ¹¹¹In-labeled 18B7 showed significantly higher hepatic uptake (35% ID/g at 48 h) compared with ¹⁸⁸Re-labeled 18B7 (<2% ID/g). The high hepatic uptake of ¹¹¹In and other trivalent metal radiolabels is due to their tendency to accumulate in the liver after mAb catabolism. On the other hand, ¹⁸⁸Re bound to mAbs by SH groups is metabolized to perhenate anion, which is rapidly excreted in urine. For this reason, ¹⁸⁸Re is considered a safe and viable radionuclide for RIT when attached to a whole antibody compared with trivalent radiometals such as ⁹⁰Y and ¹⁷⁷Lu. Interestingly, ¹¹¹In-F(ab')₂ fragments showed more stability in pulmonary uptake and less hepatic uptake compared with whole ¹¹¹In-18B7.³⁴ ¹¹¹In-F(ab')₂ accumulated to significantly higher levels in the liver than ¹⁸⁸Re-labeled whole 18B7.

In summary, higher affinity mAbs are essential for targeting pathogenic fungal infections *in vivo*. In addition, whole IgG mAbs and F(ab')₂ fragments are considered better options as RIT vehicles when compared with IgM mAbs and Fab fragments. The whole IgG labeled with the nonresidualizing radionuclide (¹⁸⁸Re) had less hepatic and

renal uptake than ^{111}In -labeled whole mAb or F(ab')_2 fragments. This is believed to provide the crucial safety feature for RIT.

Conclusions

RIT was developed for the treatment of cancer decades ago. It is currently approved by FDA and marketed under different trade names such as Zevalin[®] and Bexxar[®] (mAbs labeled with 90-yttrium (^{90}Y) and 131-iodine (^{131}I), respectively, which target CD20 in cancer cells). Experimental results repeatedly provide strong evidence of the potential usefulness of RIT in different microbial infections. In fact, since microbes express antigens that are unique and different from host antigens, simplicity in targeting them with high specificity and low cross-reactivity may potentially be achievable with fewer complications. In addition, increase in the incidence of infectious pathologies is causing exhaustion of antimicrobial therapeutic possibilities and increase in drug-resistant microbes. Therefore, the need for an alternative therapeutic option is highly warranted and RIT may be the future tool for combating these infections. In terms of translating this approach into clinical practice, RIT of infection will most likely encounter the same challenges as RIT of cancer—issues of radionuclide supply, need for cold chain in handling antibodies, and necessity of dealing with nuclear regulatory issues. However, recent approval of several targeted radionuclide therapies in the cancer arena both in Europe and in the United States demonstrates that the medical community has become much more willing to utilize such therapies in patient care.

Disclosure Statement

No competing financial interests exist.

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