

Radioimmunotherapy-based treatment of cancer

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ABSTRACT

The principle of cancer immunotherapy includes various methods of manipulations to influence immune responses against tumors in both humans and animals. This advanced technology of hybridoma production provided the necessary skills to efficiently produce highly specific monoclonal antibodies (mAb). Radioactively-tagged antibodies which are applied in radioimmunotherapy (RIT), can target adjacent cells and may not require immune function. This study highlights the mechanism and the effect of action of radioimmunotherapeutic agents, especially two applied agents including ⁹⁰Y-ibritumomab tiuxetan and ¹³¹I-tositumomab that are approved by Food and Drug Administration (FDA) for treatment of some cancers.

Key words: Radioimmunotherapy (RIT), Monoclonal antibodies (mAb), Cancer, ⁹⁰Y-Ibritumomab tiuxetan, ¹³¹I-Tositumomab.

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INTRODUCTION

Cancer is one of the most important causes of death in the world today. For decades, primary cancer therapy including chemotherapy and radiotherapy eliminate the bulk of tumor mass or metastatic cells. In history, the first successful cancer immunotherapy was carried out by William Coley in the 1890 using toxins derived from *Streptococcus erysipelatis* and *Bacillus prodigiosus*. The opening principle of cancer immunotherapy has been profoundly influenced by Paul Ehrlich's 'magic bullet', and confirmed by the development of antibiotics [1].

The principle of cancer immunotherapy including various methods of manipulations to hassle immune responses against tumors in both humans and animals [2, 3]. Therefore, the advent of the advanced technology of hybridoma production provided the necessary skills to efficiently produce highly specific

monoclonal antibodies (mAb) [4-6]. A variety of immunoglobulin-derived molecules were utilized in RAIT (Fig. 1) [7].

Monoclonal antibodies (mAb) may mediate its anti-tumor effects by using one of effector mechanisms, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity, and inducing or blocking intracellular signals, but the exact mechanisms of action of many of these clinically active antibodies remain unknown [8]. Antibodies targeting cell surface receptors that alter intracellular signaling pathways like as Rituximab bind to CD20, particularly when cross-linked, initiates a cascade of intracellular signals, many quite similar to signaling through the B cell receptor. The result of stimulation of these complex signaling pathways is cell cycle arrest or apoptosis [9].

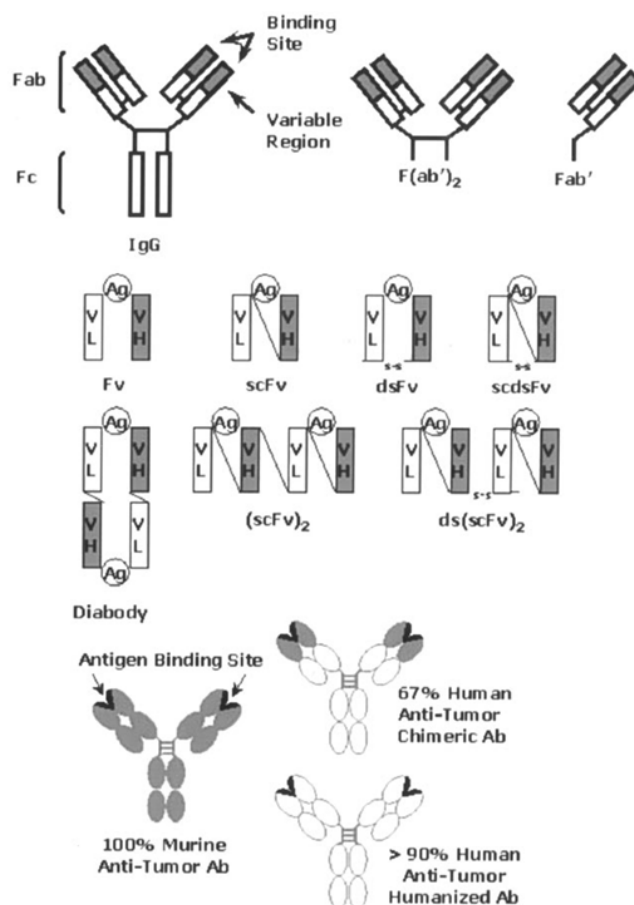


Fig 1. Schematic illustration of various antibody-derived targeting molecules being investigated in radioimmunotherapy (RAIT). (Reprinted by permission of the Society of Nuclear Medicine from [7]).

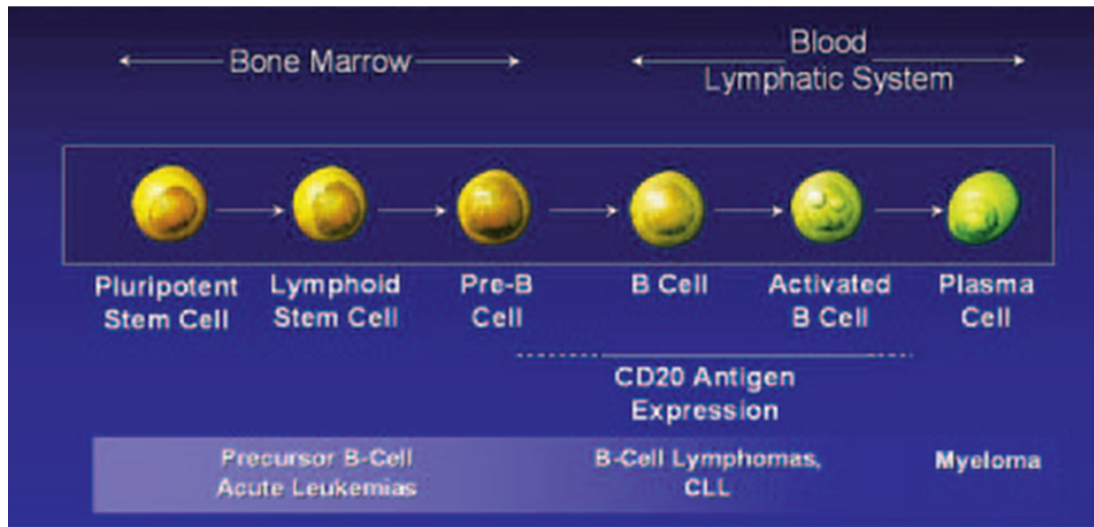


Fig 2. CD 20 antigen expression. (Reprinted by permission of the Society of Nuclear Medicine from [18]).

Unlabeled antibodies may not reach to all cancer cells to kill them. Therefore, using antibody–drug conjugates may overcome low antigen density and lack of necessary local immune cells. Accordingly, radioactively-tagged antibodies or radioimmunotherapy (RIT) can target adjacent cells and may not require immune functions [8]. This study reviews the mechanism and the effect of action of radioimmunotherapeutic agents, ^{90}Y -ibritumomab tiuxetan and ^{131}I -tositumomab approved by Food and Drug Administration (FDA) effective in treatment of in some cancers.

DISCUSSION

General features of radioimmunotherapy

Advances in cancer diagnosis and therapy require improvements in the agents used to image and treat disease [10]. RIT has the potential to deliver radiation therapy to tumor or metastatic cells throughout the body while maintaining a high therapeutic index [11]. On the other hand, RIT represents a novel therapeutic approach that combines the tumor-targeting attributes of lymphocyte-specific monoclonal antibodies with therapeutic radioisotopes [12]. Therefore, RIT has been used to consolidate remissions after chemotherapy with good results in future [13, 14].

There are a number of radiopharmaceuticals are used in RIT e.g ^{67}Cu -21T-BAT-Lym-1 for Non-Hodgkin's Lymphoma(NHL) [15], ^{131}I -Labeled Chimeric Monoclonal Antibody MOv18 in patients with ovarian cancer [16] and solid tumors [17]. The most extensively studied, Yttrium-90 (^{90}Y)-ibritumomab tiuxetan (Zevalin®) and Iodine-131 (^{131}I)-

tositumomab (Bexxar®) are both directed against CD20 [12] which is found on the surface of pre–B lymphocytes, mature B lymphocytes and more than 90% of B-cell NHL (Fig. 2) [18-24]. Both radioimmunotherapeutic agents recognize epitopes in the extracellular domain of the CD20 antigen, and formation of the antibody–antigen complex induces apoptosis, complement-dependent cytotoxicity, and antibody-dependent cytotoxicity [25, 26]. The radioisotopes also contribute to the mechanism of action of the drugs by emitting β -particles, which deposit enough energy in the tumor to result in cell death [27-29].

Although no comparative clinical trial has been performed between ^{90}Y -ibritumomab tiuxetan and ^{131}I -tositumomab, published results suggest that the two compounds achieve similar response rates and response durations [12, 30-32]. Also, RIT utility may be improved by re-treatment, radiosensitizing agents and pre-targeting [33-35]. For example, RIT responses in rituximab-refractory patients suggest a different mechanism of action, i.e. targeted radiation therapy, rather than antibody-dependent killing [8].The efficacy of RIT is usually assed with positron emission tomography (PET) scan [36]. It should be mentioned that subsequent chemotherapy following RIT in NHL is tolerable [36-38].

Clinical using of radioimmunotherapy in the treatment of cancers

The FDA approved radioimmunotherapeutic agents (Zevalin and Bexxar) are recommended for the treatment of patients with follicular and transformed NHL who failed to respond to or relapsed after prior

therapies, including rituximab and standard chemotherapy [39, 40]. Initial interesting data were confirmed this application in a phase II trial by multicenter studies [41]. The efficacies reported thus far for therapeutic regimens containing ^{90}Y -ibritumomab tiuxetan and ^{131}I -tositumomab are similar in patients with previously treated and chemotherapy-refractory low-grade relapsed NHL, with overall response rates in the 60%–83% range and complete response rates ranging from 15% to 52% (M4, 8–15). ^{131}I -tositumomab has a higher overall response rate (95%) and complete response rate (75%) when applied as initial therapy for follicular NHL [42]. In total, the safety of both agents is confirmed. The most common adverse events for these radioimmunotherapies in patients previously treated with chemotherapy are serious cytopenias, which are experienced by most patients receiving either ^{90}Y -ibritumomab tiuxetan or ^{131}I -tositumomab [21].

In untreated patients with advanced-stage Follicular Lymphoma (FL), the second most common histological subtype of NHL, ^{131}I -tositumomab showed an overall response rate of 95%, with a rate of complete remission of 74%. In this study, the 5-y progression-free survival was 59%, the toxicity was moderate myelosuppression, and no cases of myelodysplastic syndrome or acute leukemia had been observed at the time of the report [42]. Some other studies reported that ^{90}Y -ibritumomab tiuxetan has been effective in relapsed or refractory patients with CD20-positive FL [29, 43, 44]. Also, providing low-dose radiation to enhance the expression of CD20 in B-cell malignancies, together with its geographically selective cytotoxic effects, warrant further exploration of the use of focal low doses of radiation and CD20-targeted radioimmunotherapy in patients with CD20-positive B cell malignancies [45]. According to the same studies, ^{90}Y -ibritumomab tiuxetan has been approved for consolidation treatment as a part of first-line therapy in both Europe and now the United States [39]. Overall, about 60% of oncologist believed that ^{90}Y -ibritumomab tiuxetan or ^{131}I -tositumomab as a suitable second- or first-line treatment for patients with NHL. As it seems, the future growth of RIT with ^{131}I -tositumomab or ^{90}Y -ibritumomab tiuxetan was judged to be positive by most oncologist [39].

Another research field utilizes RIT prior to stem cell transplant [46, 47]. There is a strong rationale for using RIT as a part of preconditioning treatment for stem cell transplantation (SCT). This is especially pertinent because the majority of patients with relapsed or refractory B-cell NHL are more than 60 years old, and yet are often denied potentially curative high-dose chemotherapy and/or total-body irradiation because of the risk for excessive treatment

related morbidity and mortality [48, 49]. In contrast to total-body irradiation, and by virtue of its targeted activity, RIT (conventional and high dose) can be used in elderly patients with comorbidities undergoing SCT, making it appropriate as a pretransplant regimen for a wider patient population [50]. In two studies, ^{90}Y ibritumomab tiuxetan was used to treat patients with NHL who were not eligible for high-dose chemotherapy and/or total-body irradiation containing therapies prior to SCT.

Data demonstrated better disease control in relapsed and refractory FL and transformed B-cell NHL with no unexpected additional toxicities [32, 51]. Because RIT delivers targeted radiation, it is feasible that any additional therapeutic benefit would be delivered without adding to the high-dose chemotherapy associated toxicity, which could increase the treatment options for older and frailer patients [52].

Also, ^{90}Y -ibritumomab tiuxetan has been used in phase II trials in relapsed and refractory mantle cell lymphoma (MCL). Overall response rates were about 30%, but with only moderate event-free survival of 6 months (median) in relapsed MCL [53]. However, the efficacy of RIT as a member of multimodal strategies might be more efficient. RIT may be applied as part of the induction therapy, consolidation therapy or part of high-dose regimen followed by autologous transplantation [54]. Accordingly, this study suggest that consolidating RIT results in impressively improved complete response rates (from 13% to 55%) and a prolonged progression-free survival of 31 months in first line therapy [46].

Furthermore, advanced prostate cancer is attractive for RIT since metastases from prostate cancer are almost exclusively located in bone marrow and lymph nodes (good access to antibodies) and the metastases are often small enough to ensure good antibody penetration [55, 56].

Goldenberg et al, were the first to demonstrate that a prostate-associated marker could be targeted and imaged by antibodies labelled with radionuclides [57]. Later Meredith et al. treated prostate cancer patients with ^{131}I -labelled CC49 monoclonal antibodies to TAG 72 [58]. Six of 10 symptomatic patients had bone pain relief, but no patients met the radiographic or prostate specific antigen (PSA) criteria for objective response [59].

The other radioimmunotherapeutic agent, ^{131}I -A5B7, is a carcinoembryonic antigen (CEA)-specific mouse monoclonal antibody that has been shown to localize to human colon carcinoma xenografts [60]. A previous phase I rial of single-agent ^{131}I -A5B7, done in patients with advanced colorectal cancer, defined bone marrow suppression as the dose-limiting toxicity at a maximum tolerated dose of 2,400 MBq/m². One out of ten subjects showed a partial response.

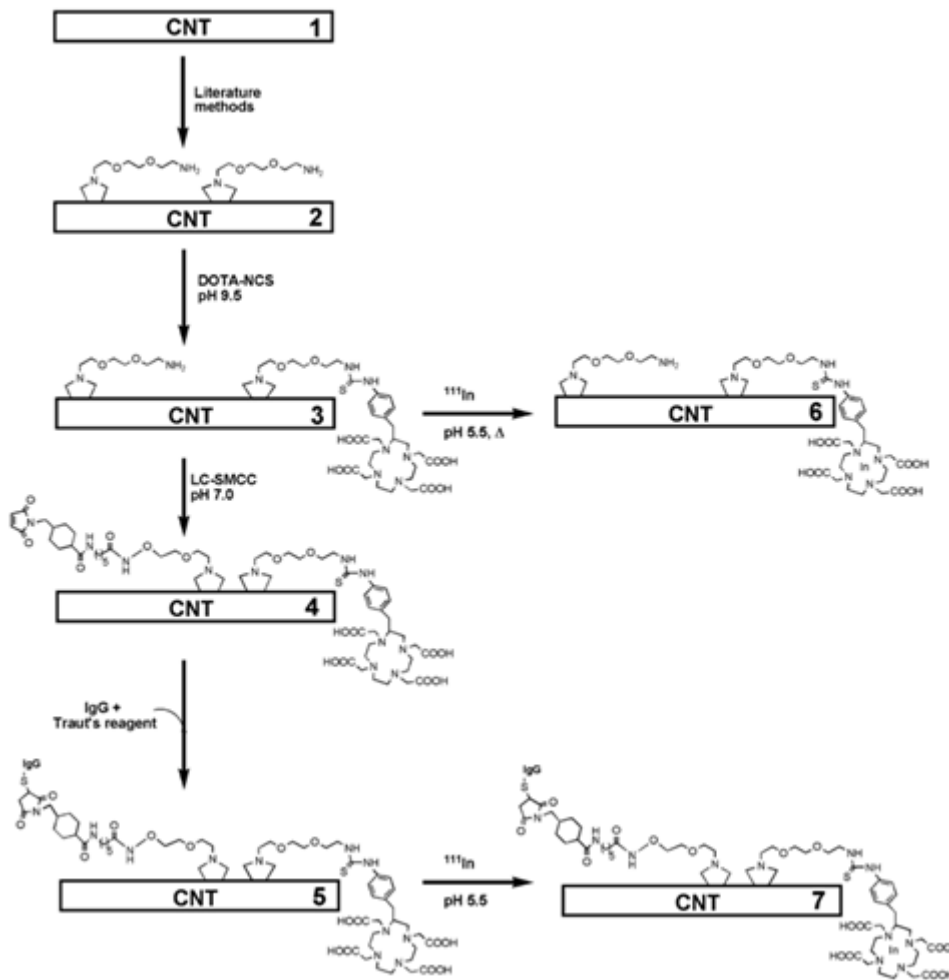


Fig 3. Reaction plot for all carbon nanotubes (CNT) assemblies. (Reprinted by permission of the Society of Nuclear Medicine from [62]).

However, the efficacy of radioimmunotherapy in solid tumors is limited by low tumor penetration into the poorly perfused central tumor areas and relative radioresistance of hypoxic tissue [61].

On other hand, novel nanotechnological discoveries can pave the way for nuclear medicine to achieve remarkable therapeutic value. In this query, single-walled carbon nanotubes (CNT) as a nanoparticle with specific characteristics such as high aspect ratio, having highly regular structures with defined periodicity were used in animal model [62]. Carbon nanotubes also showed exceptional mechanochemical features that can be utilized as specific drug delivery platforms [62].

McDevitt et al tested CNT in vitro by flow cytometry and cell-based immunoreactivity methods and in vivo in a murine xenograft model of lymphoma and achieved to encouraging results (Fig. 3) [62]. Table-1

shows some main studies of the radioimmunotherapy in the treatment of cancers.

CONCLUSION

In an ideal condition, the choice of cancer therapy for a specific patient should be based on the most effective therapy for that patient, and perhaps on its cost-effectiveness, without any influence from its profitability to the treating physician. It seems crucial for the future of RIT not only to demonstrate that these radiolabeled antibodies are effective and safe for treatment of patients with cancers in multiple clinical settings, but also to rationalize the process to provide easy referrals and better collaboration among specialists and to ensure that appropriate safeguards are developed. Also, seems that novel approaches promise to increase the durability of remissions achieved with radiolabeled antibody therapy.

Table 1. some main studies of the radioimmunotherapy in the treatment of cancers.

RIT Agent	Used Tumor	Efficacy	Reference
¹³¹ I-anti-B1 (anti-CD20) antibody	B-cell lymphoma	Four of the ten patients with complete remissions	[63]
¹³¹ I-tositumomab	Low-grade B-cell non-Hodgkin's lymphomas (Multicenter phase II study)	One third of patients had a complete remission	[64]
¹³¹ I-tositumomab	Follicular Lymphoma	Prolonged clinical and molecular remissions	[42]
⁹⁰ Y-ibritumomab tiuxetan	Follicular, or transformed B-cell non-Hodgkin's lymphoma	Well tolerated and produces statistically and clinically significant higher overall response rate and complete remission	[29]
⁹⁰ Y-ibritumomab tiuxetan	relapsed or refractory non-Hodgkin lymphoma	Safe and well tolerated	[43]
⁹⁰ Y-ibritumomab tiuxetan	advanced follicular lymphoma (Phase III trial)	Highly effective with no unexpected toxicities	[65]
⁹⁰ Y-ibritumomab tiuxetan and ¹³¹ I-tositumomab	non-hodgkin lymphoma (a phase II multicenter trial)	(40.9%) had treated patients	[66]
⁹⁰ Y-ibritumomab Tiuxetan	non-Hodgkin's lymphoma	Confirmed to be useful in assessing treatment response	[67]

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