Antibody-Radionuclide Conjugates for Cancer Therapy: Historical Considerations and New Trends

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Abstract

When delivered at a sufficient dose and dose rate to a neoplastic mass, radiation can kill tumor cells. Because cancer frequently presents as a disseminated disease, it is imperative to deliver cytotoxic radiation not only to the primary tumor but also to distant metastases, while reducing exposure of healthy organs as much as possible. Monoclonal antibodies and their fragments, labeled with therapeutic radionuclides, have been used for many years in the development of anticancer strategies, with the aim of concentrating radioactivity at the tumor site and sparing normal tissues. This review surveys important milestones in the development and clinical implementation of radioimmunotherapy and critically examines new trends for the antibody-mediated targeted delivery of radionuclides to sites of cancer. *Clin Cancer Res; 17(20); 6406–16. ©2011 AACR.*

Introduction

In 1975, the invention of hybridoma technology by Köhler and Milstein (1) enabled for the first time the production of rodent antibodies of single specificity (monoclonal antibodies). Antibodies recognize the cognate antigen with exquisite specificity, and this property triggered an intense development of preclinical and clinical projects based on the use of monoclonal antibodies as delivery vehicles for radionuclides (typically β-emitters), with the aim to achieve better imaging and therapy of cancer. These early approaches, which are summarized in many reviews (e.g., refs. 2–4), illustrate the unique theranostic (i.e., therapy + diagnostic) potential of radioimmunoconjugates, which is still valid today. In the ideal case, a cancer patient would first receive a diagnostic dose of an antibody labeled with a radionuclide compatible with imaging procedures [e.g., single photon emission computed tomography or positron emission tomography (PET); refs. 5, 6]. If adequate antibody localization at the site of disease is achieved, the patient could receive a therapeutic dose of the same antibody labeled with a radionuclide capable of inducing curative effects. Unfortunately, the majority of early clinical developments of radioimmunoconjugates failed to make an impact on cancer therapy. The problems were in part associated with the murine origin of monoclonal antibodies, which are immunogenic in humans and thus prevent repeated administration to patients [this limitation was subsequently overcome by the advent of chimeric, humanized, and fully human antibodies (7)]. Of more importance, most radioimmunotherapy approaches for the treatment of solid tumors failed because the radiation dose delivered to neoplastic masses was insufficient to induce objective responses and cures. Radioimmunotherapy represents one of the few areas of pharmacological intervention in which therapeutic performance can largely be predicted based on pharmacokinetic considerations (i.e., by analysis of the radiation dose delivered to tumors compared with the radiation dose delivered to normal tissues). These quantities are directly related to the area under the curve in graphs depicting the percent injected dose per gram (%ID/g) of tissue versus time, weighted with an exponential function that corrects for the radioactive decay of the therapeutic nuclide (Fig. 1). As far as toxicity is concerned, the total radiation dose delivered to normal organs can be used to calculate the maximum tolerated dose (8). However, the bone marrow reserve may vary among patients, making the precise prediction of hematological toxicity difficult (9).

Ideally, antibodies would rapidly accumulate at neoplastic sites and rapidly clear from the body; however, intact antibodies typically exhibit long circulation times in blood (which contributes to bone marrow toxicity) and a reduced diffusion into the tumoral mass, and may accumulate in critical organs, such as the liver (10, 11). The choice of the radionuclide largely depends on the size of the tumor to be treated, with high-energy β-emitters (e.g., ^{90}Y) being suitable for the therapy of larger tumors, and medium-energy β-emitters (e.g., ^{131}I and ^{177}Lu) being more effective for the treatment of smaller tumors (2). One of the main attractive features of radioimmunotherapy is the crossfire effect, i.e., the ability to damage

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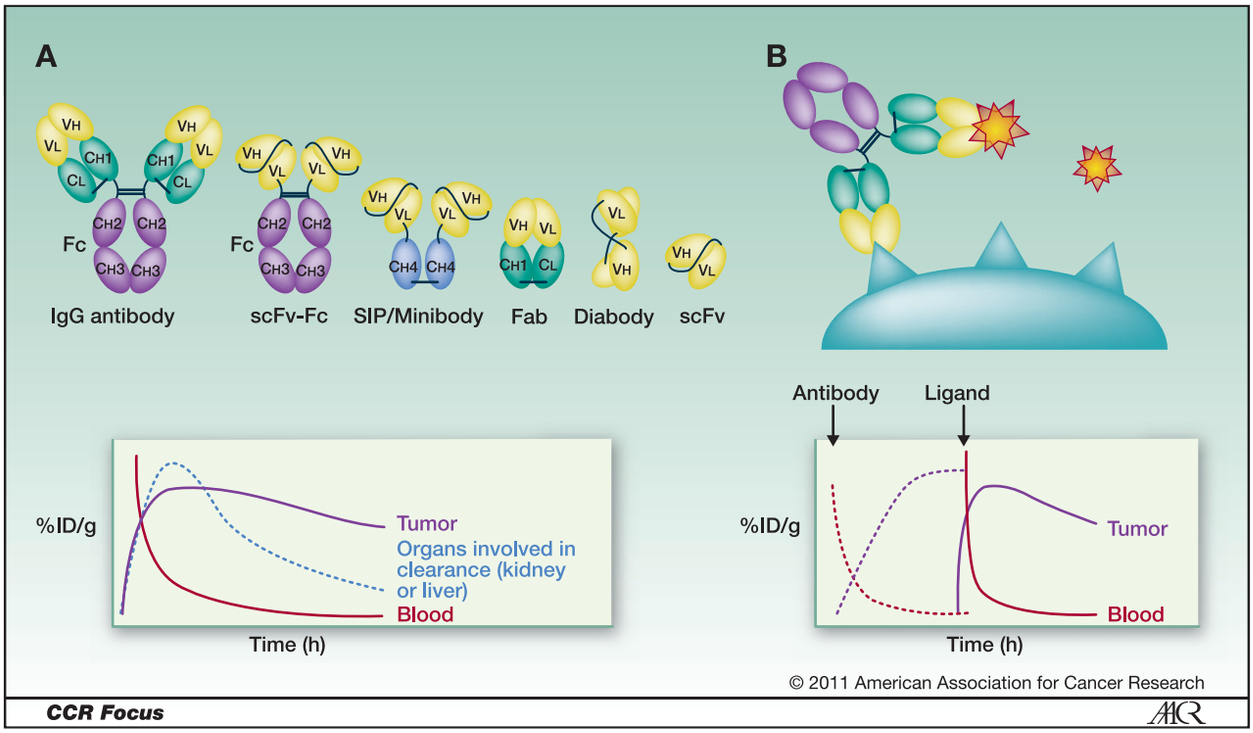

Figure 1. Schematic representation of antibody formats (A) and pretargeting strategies (B) for radioimmunotherapy applications. Targeting results are often expressed as % ID/g of tissue versus time; the curves show the relative accumulation of an antibody or antibody fragment in the tumor, excreting organs, and blood. The area under the curve for the tumor and normal organs is directly related to the dose of radioactivity delivered in a radioimmunotherapy procedure. In pretargeting strategies, the therapeutically relevant radioactivity dose is related to the one delivered by the small ligand (e.g., a radiometal chelator, schematically represented as a star), which is injected once the multifunctional antibody (dashed line) has reached adequate tumor/organ and tumor/blood ratios (2).

cells in close proximity to the site of antibody localization. In most cases, antibody radiolabeling is accomplished either by iodination of tyrosines or by conjugation of metal chelators [diethylenetriaminepentaacetic acid (DTPA) or 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)] to the antibody molecule (12).

The intrinsic radiosensitivity of tumor cells is a major determinant of a tumor's response to radiation (13). This may be a reason why the only 2 radioimmunoconjugates that have been approved and are commercially available (Table 1) are used for the treatment of non-Hodgkin's lymphoma—lymphoma cells are inherently sensitive to radiotherapy (14). ^{131}I-tositumomab (Bexxar) and ^{90}Y-ibritumomab tiuxetan (Zevalin) are both based on murine antibodies specific to CD20, an antigen that is present on normal B-cells and certain B-cell lymphomas. Although ^{90}Y-ibritumomab tiuxetan exhibited favorable results in the consolidation of first remission advanced-stage follicular lymphoma [prolonging progression-free survival by 2 years (15)], the superiority of radiolabeled drugs has not yet been shown in a clinical head-to-head comparison with rituximab-based protocols. This fact, together with challenges related to the use of radioactivity and the coordination between oncologists and nuclear medicine departments, may explain why the nonlabeled anti-CD20 antibody rituximab continues to be more widely used than Bexxar and Zevalin. Furthermore, other strategies for arming antibodies with active payloads have been pursued in the recent past (16–21).

Role of the Antibody Format

The use of antibodies in immunoglobulin G (IgG) format for radioimmunotherapy is typically associated with high bone marrow toxicity (due to the long circulatory half-life of intact immunoglobulins) and high uptake in the liver (due to hepatobiliary clearance and FcRn-mediated recycling of these molecules). After early attempts to use proteolytically produced Fab or F(ab′)$_2$ antibody fragments (16), the advent of recombinant DNA technology enabled investigators to perform comparative evaluations of the biodistribution properties of a particular antibody in different formats, including monomeric scFv fragments, diabodies, mini-antibodies [or small immunoproteins (SIP)], and IgGs (refs. 17–20; Fig. 1). The general observation was that smaller antibody fragments (e.g., scFvs and diabodies) exhibit a rapid clearance via the renal route, whereas larger antibodies (e.g., SIPs and IgGs) are eliminated via the hepatobiliary route

Table 1. Radioimmunoconjugates in clinical trials for therapeutic applications under active development according to the Thomson Reuters Integrity database

Name	Brand name	Highest phase	Description	Condition	Organization	Study identifier
SHL-749 (Ibritumomab tiuxetan)	Zevalin	Launched 2002	Murine CD20 targeting antibody ibritumomab linked by the chelator tiuxetan to ^{90}Y (or ^{111}In for imaging purposes)	B-cell lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, non-Hodgkin's lymphoma	Bayer HealthCare Pharmaceuticals; Bayer Schering Pharma; Ben-Gurion University Negev; Biogen Idec; Nordion; Rigshospitalet; Spectrum Pharmaceuticals	IDEC 106-04 IDEC 106-06 PMID 12074764
		A phase III trial with 143 non-Hodgkin's lymphoma patients showed an overall response rate of 80% with ^{90}Y-ibritumomab tiuxetan, compared with 56% with rituximab (68). A second trial found an overall response rate of 74% in rituximab refractory patients (IDEC 106-06). These and other studies led to FDA approval in 2002 for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, including patients with rituximab refractory follicular non-Hodgkin's lymphoma. In 2008, Zevalin was approved as first-line consolidation for follicular lymphoma in the European Union.				
^{131}I-tositumomab	Bexxar	Launched 2003	Combination regimen consisting of the unlabeled and ^{131}I-labeled murine CD20 targeting antibody tositumomab	B-cell lymphoma, Hodgkin's lymphoma, diffuse large B-cell lymphoma, non-Hodgkin's lymphoma, multiple myeloma	Corixa; Fred Hutchinson Cancer Research Center; GlaxoSmithKline; Nordion	NCT00989664 NCT00996593
		In a pivotal study of 40 patients (69) that led to the approval for the treatment of rituximab-refractory, low-grade, follicular non-Hodgkin's lymphoma in 2003, a response rate of 65% with progression-free survival of 24.5 months for responders was measured. In 2004, the indication was expanded for the treatment of non-Hodgkin's lymphoma patients who have not received rituximab, after a study showed superiority to last qualifying chemotherapy in 60 patients (70).				
^{131}I ch-TNT-1/B	Cotara	Phase II	^{131}I-labeled chimeric monoclonal antibody chTNT-1/B for tumor necrosis therapy	Anaplastic astrocytoma, biliary cancer, colorectal cancer, liver cancer, pancreas cancer, glioblastoma multiforme, glioma, sarcoma	Peregrine Pharmaceuticals	NCT00004017
^{131}I-BC8		Phase II	^{131}I-labeled murine anti-CD45 monoclonal IgG1 antibody	Acute myeloid leukemia	Fred Hutchinson Cancer Research Center; National Cancer Institute; University of Washington	NCT00008177 PMID 19786617
^{111}In-J591, ^{177}Lu-J591		Phase II	^{111}In/^{177}Lu labeled humanized monoclonal antibody to prostate specific membrane antigen/extracellular domain (PSMAext)	Prostate cancer	BZL Biologics; Cornell University; Memorial Sloan-Kettering Cancer Center; Millennium Pharmaceuticals	NCT00859781

(Continued on the following page)

Table 1. Radioimmunoconjugates in clinical trials for therapeutic applications under active development according to the Thomson Reuters Integrity database (Cont'd)

Name	Brand name	Highest phase	Description	Condition	Organization	Study identifier
^{131}I-Metuximab	Licartin	Phase II	^{131}I-labeled murine monoclonal antibody HAb18 F(ab')2 fragment against the HCC-associated antigen HAb18G/CD147	Liver cancer	Eastern Hepatobiliary Surgery Hospital; Fourth Military Medical University	NCT00819650 NCT00829465
^{177}Lu-DOTA-cG250		Phase II	Chimeric monoclonal antibody G250 conjugated to DOTA and radiolabeled with ^{177}Lu	Kidney cancer (renal cell carcinoma)	Ludwig Institute for Cancer Research; Radboud Universiteit Nijmegen	NCT00142415
^{131}I-3F8		Phase II	^{131}I-labeled anti-GD2 ganglioside murine IgG3 monoclonal antibody	Cancer, medulloblastoma, neuroblastoma	Memorial Sloan-Kettering Cancer Center; National Cancer Institute; National Cancer Institute	NCT00003022 PMID 18048828
^{131}I-L19	Radre-tumab	Phase II	^{131}I-labeled SIP composed of L19 that binds to the ED-B domain of human fibronectin	Non–small cell lung cancer, solid tumors, hematologic/blood cancer	Philogen	NCT01125085
^{131}I-F16	Tena-Rad	Phase II	^{131}I-labeled human monoclonal antibody against the A1 domain of tenascin-C	Hematological cancer, solid tumors	Philogen	NCT01240720
^{177}Lu-J591		Phase II	^{177}Lu-labeled humanized monoclonal antibody J591 targeting prostate-specific membrane antigen (PSMA)	Metastatic prostate cancer	Cornell University; Memorial Sloan-Kettering Cancer Center	NCT00195039 NCT00859781
^{90}Y-hLL2 IgG; (Epratuzu-mab-^{90}Y)	LymphoCide ^{90}Y	Phase I/II	^{90}Y/^{111}In-labeled human-mouse monoclonal IMMU-hLL2 targeting CD22	Follicular lymphoma, non-Hodgkin's lymphoma, acute lymphoblastic leukemia	Garden State Cancer Center; Immunomedics	NCT00421395 NCT00061425 PMID 16033839
Pretargeted antibody-guided radioimmunotherapy		Phase I/II	Pretargeted antibody-guided radioimmunotherapy using biotinylated anti-tenascin antibody (BC4), avidin, and ^{90}Y-biotin	Glioma, non-Hodgkin's lymphoma	Sigma-Tau	
^{90}Y-hPAM4 (^{90}Y Clivatuzumab tetraxetan)	hPAM4-Cide	Phase I/II	Human-mouse monoclonal hPAM4 IgG1 targeting human Mucin-1 conjugated to DOTA and radiolabeled with ^{90}Y	Pancreas cancer	Garden State Cancer Center; Immunomedics	NCT00603863 NCT00597129

Phase I drugs ^{177}Lu-CYT-500, ^{188}Re-6D2, ^{90}Y-cG250, ^{131}I-huA33, ^{225}Ac-HuM195, ^{131}I-CHT-25, F16-^{131}I are not listed in the table. Important studies are referenced with their ClinicalTrials.gov identifier; for selected publications, the PubMed ID (PMID) is given.

(6, 17, 19). It appears that the slow extravasation of the antibody molecule into tissue may limit the efficiency of tumor targeting, and that a rapid diffusion of binding molecules into the neoplastic mass may only be achieved by the use of much smaller compounds [probably <2000 Dalton (21, 22)].

Pretargeting

Pretargeting is a promising approach to increase the therapeutic index of radioimmunotherapy strategies (2, 3, 23). In a pretargeted setup, the radionuclide is administered separately from the antibody vehicle and displays more favorable tumor-targeting properties. Most pretargeting approaches have so far relied on 1 of the 2 following approaches:

1. The use of radioactive biotin derivatives for selective localization on antibody-streptavidin conjugates (24, 25) or noncovalent biotinylated antibody-streptavidin complexes, termed 3-step pretargeting (26).
2. The use of chelators of radioactive metals for selective localization on multispecific antibodies that are capable of simultaneously binding to a tumor-associated antigen and the metal chelator (27, 28).

Both approaches rely on the fact that an artificial tumor-associated antigen is created upon binding of the antibody derivative at the tumor site, and on the favorable pharmacokinetic properties associated with the small size of the radiolabeled compound, which rapidly distributes in the neoplastic mass while being rapidly eliminated from the rest of the body via the urinary excretion route (ref. 23; Fig. 1). Indeed, in spite of the short time needed for excretion, the kidneys may become the dose-limiting organ for toxicity, as is often the case for peptide-based radiopharmaceuticals (29).

Antibody-based pretargeting strategies have produced spectacular biodistribution results in tumor-bearing animals [with tumor uptake as high as 278 ± 130%ID/g and tumor/blood ratios > 30 at 1 hour postinjection (30)] and promising results in cancer patients (31, 32).

It could be argued that pretargeting approaches would not be needed if medicinal chemistry were more efficient in finding low-molecular-weight binders for tumor-associated antigens, making targeting proteins obsolete.

Considerations Regarding the Choice of the Radionuclide

To date, the majority of radioimmunotherapy clinical development programs have involved the use of β-emitting radionuclides. A discussion about the relative merits of different isotopes for therapeutic purposes is beyond the scope of this article and has been reviewed elsewhere (2). The choice of a β-emitting radionuclide for radioimmunotherapy involves considerations about the physical properties and availability of the radionuclide, the labeling methods used, the possibility of imaging, and the safety of the patient (either with the same nuclide or with chemically related nuclides). β-emitters such as ^{131}I, ^{177}Lu, and ^{90}Y can deposit their energy within 1–10 mm depending on their physical properties, and thus may compensate for heterogeneous antibody uptake within the tumor mass (ref. 33; Figs. 1 and 2). Auger electron emitters, such as ^{111}In and ^{125}I, have been shown to be suitable for radioimmunotherapy of small solid tumors. ^{111}In- and ^{125}I-labeled antibodies have both been shown to significantly increase survival rates in xenograft experiments compared with unlabeled antibodies (34–36). In Auger electron emission, most of the energy is delivered within a sphere of several nanometers around the decay site, and thus dosimetry is limited in accuracy due to heterogeneity of the tumor tissue and radiation delivery (34). This strategy appears to be ideally suited for internalizing antibodies, because cells expressing a tumor-associated antigen on their surface would receive the most damage from this radioimmunotherapy approach; however, experimental data suggest that Auger electron emitters may also be used for noninternalizing antibodies (34).

Up to now, Auger electron emitters have not been widely used, possibly due to the large radioactivity doses that are required and the resulting costs for radioprotection and radioactive waste disposal.

There is a strong rationale for the antibody-based pharmacodelivery of α-emitting radionuclides to well-defined tumor-associated structures (e.g., individual leukemia cells in blood or vascular structures within the neoplastic mass), in consideration of the high-energy and short path length of α radiation associated with radionuclides such as ^{211}At, ^{213}Bi, ^{225}Ac, and ^{227}Th. Fig. 2 schematically illustrates the implications of using β-emitters or α-emitters for antibody-based targeting of the tumor neovasculature (37). With the use of a β-emitting radionuclide, it should be possible to irradiate tumor cells that are not adjacent to the tumor blood vessels with a crossfire effect spanning several millimeters. However, the efficacy of this therapeutic modality may be limited by the fact that new blood vessels represent only a small percentage of the total tumor mass. By contrast, the high energy and short tissue penetration of α-emitters concentrate tissue damage around tumor blood vessels, leading to a highly selective killing of tumor endothelial cells (37, 38). There is growing evidence that a selective destruction of the tumor neovasculature may lead to an avalanche of tumor cell death (39–41).

Vascular Tumor Targeting

Blood vessels represent the most accessible structure within the tumor for pharmaceutical agents coming from the blood stream. The formation of new blood vessels is a rare event in the healthy adult [largely confined to the female reproductive system (42, 43)] but a characteristic feature of many aggressive cancer types. Therefore, the use

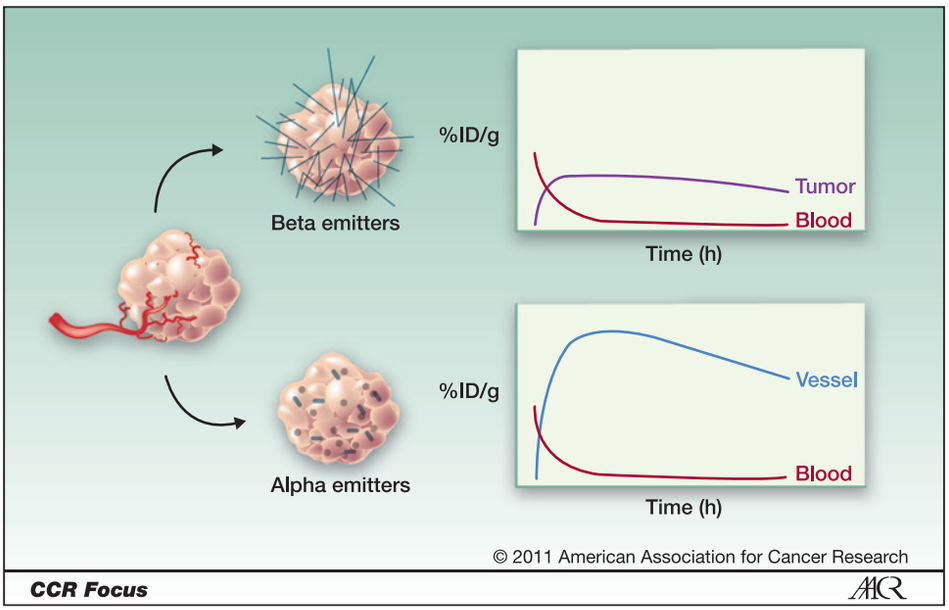

Figure 2. A vascular targeting antibody deposits energy in different tumor locations depending on the type of radionuclide used. An α-emitting radionuclide (e.g., ^{211}At) has a higher energy than β-emitting radionuclides and a tissue penetration range of only 50–80 μm, confining the toxic effects to a volume of a few cell diameters, i.e., to the tumor vasculature (37). In this case, vessel/blood radioactivity ratios may be predictive of the relative damage caused by α particles to endothelial cells and blood cells.

of antibodies specific to tumor neovascular antigens represents an attractive avenue for the selective delivery of therapeutic payloads to the tumor site (ref. 42; Fig. 3). Also, unlike antibodies that are specific to antigens expressed on the surface of tumor cells, vascular tumor-targeting antibodies could be used for many different tumor types. Over the years, vascular tumor antigens have been discovered by serendipity (i.e., analyzing antibodies by

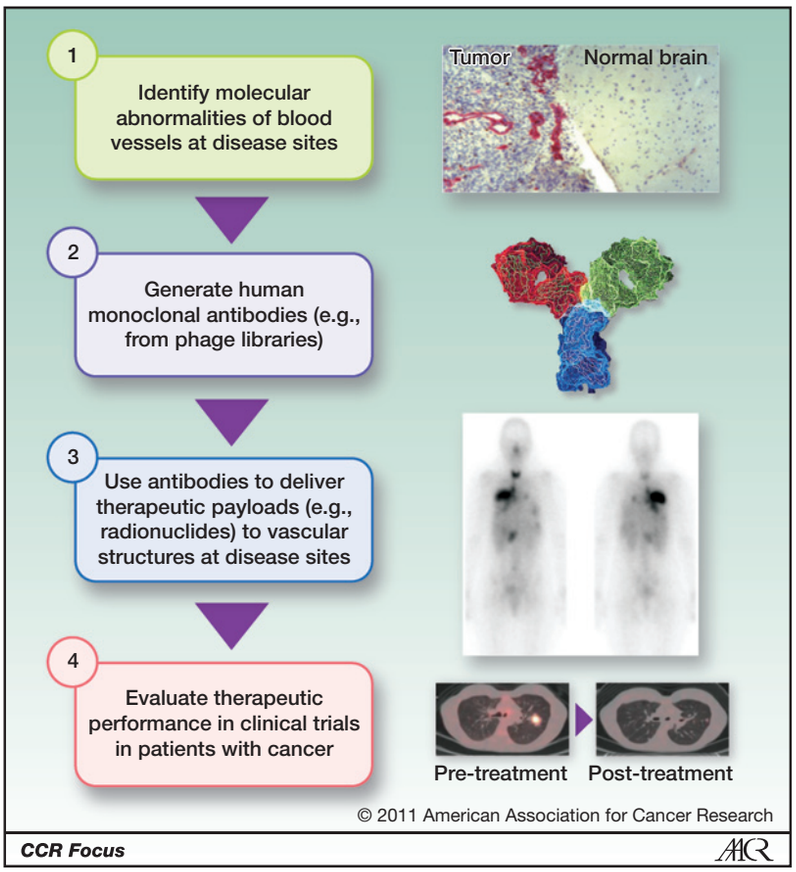

Figure 3. Schematic representation of the 4 basic steps in the implementation of a vascular targeting strategy for the therapy of cancer. The immunohistochemical picture corresponds to a section containing both glioblastoma multiforme and normal brain, in which only the tumor blood vessels were selectively stained in red by an antibody specific to the EDB domain of fibronectin. In general, the identification of markers that are specifically expressed on tumor blood vessels represents the starting point for the development of an antibody-based vascular targeting strategy.

immunohistochemistry), transcriptomic studies, *in vivo* phage library panning (44), and perfusion-based mass spectrometry–assisted techniques (45–47).

We have developed human monoclonal antibodies (L19, F8, and F16) specific to splice isoforms of fibronectin and tenascin-C, which represent some of the most extensively characterized markers of tumor angiogenesis known so far (42). The tumor-targeting properties of several derivatives of the L19, F8, and F16 antibodies have been studied by quantitative biodistribution analysis, revealing promising *in vivo* tumor targeting results for a variety of different tumors (18, 48, 49). Some of these antibody derivatives have been moved to clinical trials, mainly as radionuclide conjugates or cytokine-based fusion proteins. These agents include the L19 and F16 antibodies labeled with ^{131}I for radioimmunotherapy applications (50) or with ^{124}I for immuno-PET (6).

Of interest, it was recently discovered that fibronectin and tenascin-C isoforms are abundant not only in the majority of solid tumors but also around the neovasculature of most lymphoma types (47, 50, 51). The L19 antibody in SIP format and labeled with ^{131}I has shown promising results for the radioimmunotherapy of refractory Hodgkin's lymphoma patients, and more than 100 cancer patients have already been treated with this agent (Fig. 4).

Vascular targeting applications may extend to leukemia, in consideration of the fact that extensive formation of new blood vessels has been documented in the bone marrow of patients with acute myeloid leukemia (52).

Locoregional Approaches

Some tumors (e.g., astrocytomas, liver, head, and neck) tend to grow in a defined compartment and are therefore suitable for locoregional administration of radiolabeled antibodies.

Pemtumomab (Theragyn), a murine monoclonal antibody (HMFG1) that is specific to an epitope of the *MUC1* gene product and labeled with ^{90}Y, was developed as a product for the locoregional treatment of patients with epithelial ovarian cancer. Although promising results were obtained in phase II clinical trials, the product failed to extend survival or time to relapse in a trial of 447 patients with a negative second-look laparoscopy (53).

Riva and colleagues (54) treated >200 glioblastoma patients by administering a ^{131}I-labeled antibody specific to tenascin-C into the postoperative cavity, with the aim of sterilizing tumor cells in the immediate surroundings of the original tumor mass and, ideally, distant tumor cells. Similar approaches have been implemented for the pharmaceutical development of Neuradiab (another radiolabeled antibody specific to tenascin-C) by Reardon and colleagues (55), Zalutsky and colleagues (56), and Bradmer Pharmaceuticals (57), but phase III clinical trials have been suspended.

Another approach for locoregional treatment is the intravesical administration of radiolabeled antibodies, which may provide a benefit to patients with bladder cancer by taking advantage of the natural access to the bladder via the urethra (58).

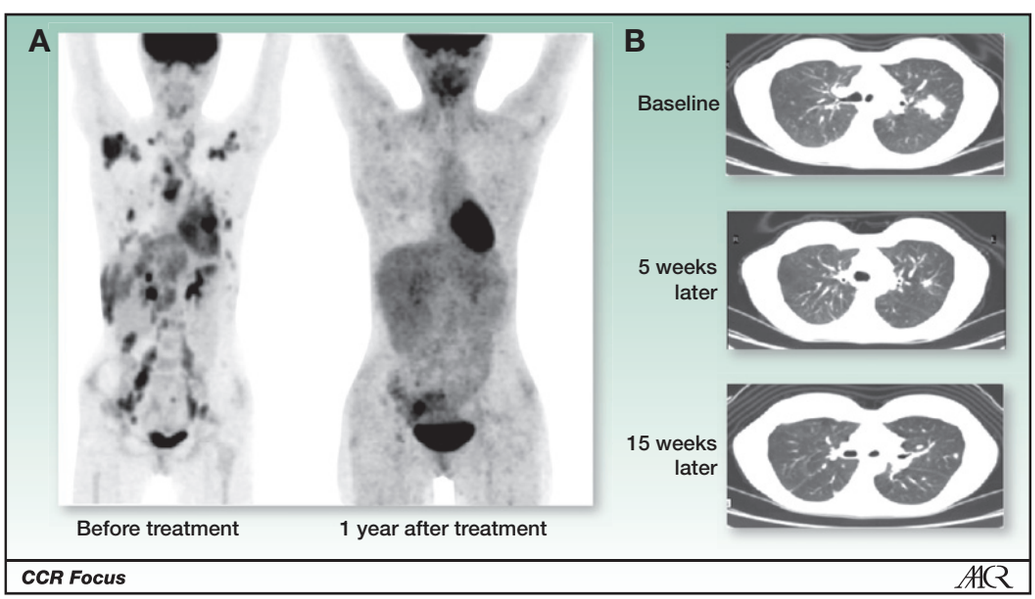

Figure 4. Response observed in a patient with Hodgkin's lymphoma after treatment with SIP(L19) labeled with ^{131}I. A, fluorodeoxyglucose PET analysis of the patient at presentation [courtesy of Prof. G. Mariani and Dr. P. Erba; adapted from Sauer et al. (50)] and 1 year after treatment with the radioimmunotherapeutic drug (at higher sensitivity). B, computed tomography analysis of a pulmonary lesion responding to treatment.

Combination Therapy

Radioimmunotherapy can confer a clinical benefit to cancer patients even when administered as a single agent. However, cancer pharmacotherapy mostly makes an impact when a combination of multiple therapeutic agents is used. The combination of radiolabeled antibodies with cytotoxic drugs has been studied preclinically and clinically (59, 60), but may ultimately suffer from the fact that both therapeutic modalities are often associated with substantial bone marrow toxicity. However, clinical and preclinical studies indicate that certain compound classes (e.g., vascular disrupting agents and cytotoxic agents with favorable myelotoxicity profiles) may indeed potentiate radioimmunotherapy (61).

Ideally, radiolabeled antibodies should be combined with pharmaceutical agents that display nonoverlapping toxicities. For example, the combination of radioimmunotherapy with intact immunoglobulins (such as the epidermal growth factor receptor inhibitor cetuximab) has exhibited promising results in animal models (20).

The combination of external beam radiation and radioimmunotherapy has been proposed for more than a decade. This therapeutic strategy is particularly appealing in the context of brain malignancies, in consideration of the fact that external beam irradiation of the brain typically should not exceed 30 Gy, and monoclonal antibodies exhibit extremely low uptake in the healthy portion of the brain as a result of the blood-brain barrier function. Vascular tumor-targeting antibodies may efficiently target high-grade astrocytomas *in vivo* (62, 63). The ^{131}I-labeled antibody L19, which is specific to the alternatively spliced EDB domain of fibronectin, is currently being investigated in combination with whole-brain external beam radiation for the treatment of patients with brain metastases, with encouraging results.

Conclusions

After many years of intense research activities, the opportunities and challenges associated with the development of radiolabeled antibodies for cancer therapy strategies are beginning to be better understood. Undoubtedly, the marketing authorization of Zevalin and Bexxar for the therapy of patients with certain types of lymphoma represents a success for the field. However, the limited number of approved products and the limited market penetration of these products indicate that radioimmunotherapy still needs to make an impact on cancer therapy.

Technical and logistical challenges associated with the use of radioimmunotherapy (e.g., antibody radiolabeling, logistics, radioprotection issues, and disposal of radioactivity) have contributed to preventing a broader use of this therapeutic approach. However, these reasons alone do not justify the limited use of radiolabeled antibodies. Indeed, one could argue that central labeling procedures could dramatically simplify the implementation of radionuclide-based therapies, and that other logistical problems could be solved if the therapeutic performance were comparable to that observed in patients with thyroid cancer, in whom radiometabolic therapy with ^{131}I has been practiced for decades with excellent safety and activity (64).

From the patients' perspective, radioimmunotherapy has often been described as a "walk in the park," because treatment is typically not associated with the discomfort and side effects that are characteristic of conventional chemotherapy. Obviously, excessive radiation to critical organs [e.g., the bone marrow, due to its intrinsic radiosensitivity and the rapid equilibration of radiolabeled antibodies within its extracellular fluid volume (65)] may give rise to substantial toxicity, which may not always be managed by growth factors and transfusions (e.g., platelets), or may require reinfusion of peripheral blood stem cells. However, what ultimately matters most is the fine balance between the quality of life during and after treatment and the therapeutic effect (e.g., as measured in terms of survival benefit).

The success of radioimmunotherapy in lymphoma is largely related to the intrinsic radiosensitivity of hematological malignancies. Indeed, dramatic results from the use of Bexxar and Zevalin in other lymphoma types [e.g., CD20-positive Hodgkin's lymphomas (66)] have been reported, although regulatory approval has not been sought to date.

For the treatment of solid tumors, it appears that only the advent of breakthrough technologies (e.g., better tumor targeting with novel antibody formats, different radionuclides, more accessible targets, and/or innovative pretargeting strategies) may lead to a sufficient improvement in the tumor radiation dose in comparison with normal organs. Investments in this field will crucially rely on clinical and industrial success. In the absence of positive results, a vicious (rather than virtuous) circle is likely to continue delaying innovation in radionuclide-based treatment strategies.

How often can radioimmunotherapy be administered to patients? When fully human antibodies are used, treatment can be repeated without immunogenicity concerns. In such cases, the risk-benefit analysis must take into consideration the cumulative damage to critical organs (e.g., bone marrow, liver, and kidney) and the probability of developing secondary tumors years after treatment (19) [in analogy to the slightly increased risk of secondary primary malignancies in patients treated with radioactive iodine for thyroid cancer (67)]. The myelotoxicity induced by radioimmunotherapy treatment and the subsequent slow recovery from the nadir in platelet and leukocyte counts may prevent the administration of alternative therapeutic agents (e.g., cytotoxic drugs) for a substantial period of time (i.e., 2–3 months).

The next few years will tell us whether the radiolabeled antibodies that have been approved for the treatment of lymphomas are more efficacious than nonradiolabeled anti-CD20 antibodies for the management of patients (a direct comparison in a realistic setting, such as consolidation therapy, is still lacking), and whether radioimmunotherapy can provide competitive advantages compared with other intervention modalities for patients with solid cancer. The excellent acceptance of radioimmunotherapy by patients, together with the opportunity to rationally develop products based on imaging and dosimetric data, suggests that there may be a second renaissance in the development of radiolabeled antibodies.

Disclosure of Potential Conflicts of Interest

D. Neri is a shareholder of and consultant for Philogen. M. Steiner disclosed no potential conflicts of interest.

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