Strategies for Developing Effective Radioimmunotherapy for Solid Tumors

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Abstract
Single-agent radioimmunotherapy (RIT) has proven efficacy as a treatment for hematological malignancies, particularly non-Hodgkin’s lymphoma. Although promising, RIT has been less effective for solid tumors, in part because they are less radiosensitive. Bone marrow transplantation permits the administration of larger radiopharmaceutical doses, but the results of bone marrow transplantation-supported RIT for solid tumors have been marginal. The purpose of this publication is to provide an overview of promising RIT strategies for solid tumors. It is apparent that combination therapy is required, but optimization of the radiopharmaceutical should be the first step. Metallic radioisotopes provide higher tumor radiation doses but not necessarily an improved therapeutic index, that is, the ratio of tumor: normal tissue radiation doses. Biodegradable peptide linkers between the chelated metal and the antibody improve the therapeutic index. Further improvements depend on identification of synergistic therapies which recognize that: (a) continuous, low-dose radionuclide therapy acts through apoptosis; and (b) apoptosis is often blocked because most tumors have ineffective p53 and increased Bcl-2. Taxanes are particularly attractive as synergistic agents for RIT because they induce cell cycle arrest in the radiosensitive G2-M phase and p53-independent apoptosis. Optimal sequence and timing for combined modality RIT are critical to achieve synergy. Data from preclinical and clinical studies will be reviewed to illustrate the potential of these strategies.

Introduction
Combinations of surgery, radiotherapy, and chemotherapy cure as many as 85% of patients when the tumor is localized. Unfortunately, most patients present with advanced disease associated with regional and often distant metastases. Under these circumstances, conventional therapy is less effective, and about 50% of all patients with cancer remain incurable. Alternative therapeutic approaches, among which is the use of biological agents such as MoAbs, are required. Because of encouraging partial response rates, immunotherapy has begun to fulfill its promise, as corroborated by United States Food and Drug Administration approval of Rituxan and Herceptin for follicular NHL and Her2-neu-positive breast cancer, respectively (1, 2).

Several RPs are close to approval for RIT in patients with NHL, where therapeutic responses, including complete responses, are quite common (3). Remissions in solid tumors, such as breast, prostate, and colon cancer, are less frequent, partial, and of short duration (4-8). Although half of patients with advanced breast cancer who failed all conventional therapies responded to radiolabeled chimeric L6 (which has unique biological properties that facilitate RIT), these remissions were not sustained (9). Consequently, it seems appropriate to assess the situation to evolve future RIT strategies for solid tumors.

Single-agent RIT has not proven sufficiently effective in patients with advanced, solid tumors and large tumor burdens. However, agents less than ideal with respect to the radionuclide, antibody, and conjugation method have been used in many clinical trials, primarily for reasons of a practical and proprietary nature (10). This has led to a compromised clinical and dosimetric therapeutic index because of decreased targeting and increased normal tissue uptake (10). The therapeutic index, that is, the relationship between the antitumor effect and normal tissue toxicity, determines the utility of an anticancer therapy. Antibody constructs provide a remarkable opportunity to enhance the therapeutic index in a variety of ways. Most directly, the antibody provides specific targeting by which a radionuclide can be selectively targeted to the tumor. A variety of strategies have been shown to alter the therapeutic index of radiolabeled antibodies by either increasing the tumor uptake of radiation or decreasing the radiation delivered to normal tissues. The foremost consideration for a RIT strategy must be the development and use in clinical trials of the best RPs. Methods for improving the therapeutic index, total radiation dose and its uniformity of distribution, and the radiation dose rate need to be addressed. Additionally, it is essential to bear in mind that a major mechanism of the antitumor effect of RIT is apoptosis from continuous, low dose rate radiation. The molecular aberrations common in tumors represent obstacles to both chemotherapy and RIT, but focusing on the mechanism of apoptosis provides significant opportunities for improvement in therapy. RIT can be combined with agents that overcome the molecular obstacles to apoptosis.

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3 The abbreviations used are: MoAb, monoclonal antibody; RIT, radioimmunotherapy; BMT, bone marrow transplantation; RP, radiopharmaceutical; NHL, non-Hodgkin’s lymphoma; DOTA, 1,4,7,10-tetra-azacyclododecane N,N',N",N"-tetraacetic acid.
Radiopharmaceuticals

RPs have three elements: (a) the antibody with unique pharmacokinetic and potential biological properties for targeting; (b) the radionuclide that provides a radiation source; and (c) the chelate-linker that combines the antibody and radionuclide and influences the pharmacokinetic behavior. Each of these elements can profoundly alter the character of the RP, as can the radiochemistry required to prepare the RP.

Antibody. MoAb targeted treatment is based on the presumption that differences in cell surface protein expression between cancerous and normal tissues facilitates selective targeting of tumors based on the unique specificity of the mAbs for the tumor-associated antigens. Major mechanisms by which mAbs kill tumor cells include: (a) activating the immune system to lyse the tumor cells (e.g., complement and antibody-dependent cellular cytotoxicity); (b) triggering or interfering with the function of a physiologically important receptor; (c) targeting agents to tumor cells (e.g., toxins, isotopes, drugs, and cytokines); and (d) eliciting an antitumor response indirectly by inducing autoantibodies.

Antibodies with higher affinity and greater specificity can be generated; they have been shown to have increased tumor uptake and decreased normal tissue uptake (11). RPs that require the administration of a large mass of antibody to obtain a favorable biodistribution should be viewed as evidence of cross-reactivity with antigen on normal cells, it seems to be advantageous for the anti-CD20 and chimeric L6 antibodies because of their biological activity in vivo. In these circumstances, it is important to establish that the advantages of biological activation are warranted, essential to the success of the therapy, and not achievable by simpler means.

Radionuclide. The preferred radionuclide for use in RIT is one that deposits a large amount of energy at a high dose rate and with as long a range as possible to adequately address the nonuniformity of antibody penetration incident to the large size of solid tumors. $^{131}$I, the most commonly used radionuclide in trials thus far, is like the proverbial “utility infielder” in baseball. It is readily available, inexpensive, and does not complicate assessment of the pharmacokinetics of the RP. $^{131}$I is valuable for therapy, but its use is complicated by the added radiation burden to the patient and others incident to the great abundance of energetic penetrating radiations. $^{131}$I is useful for imaging but only for dosimetric data and high-contrast, large-target sources. In contrast to $^{131}$I, a variety of metallic radionuclides, such as $^{90}$Y, an energetic β emitter, have been shown to be retained in the tumor even after degradation of the RP, thereby increasing the radiation dose (Fig. 1). The nonpenetrating energy per transition is about 5.1 (1.99:0.41 rad g/µCi h) for $^{90}$Y when compared to $^{131}$I. $^{90}$Y has a range of 5 mm (approximately 500 cell diameters), which provides more uniform distribution of radiation as compared with $^{131}$I, which has a range of 1 mm. Early chelates permitted escape of the radiometal to normal tissues, thus decreasing the advantage of the metallic RP by reducing the tolerated dose (10). Chelators, such as the macrocycle DOTA, bind yttrium with extraordinary stability. Also important, $^{90}$Y can be used in high doses without the need for hospitalization. A disadvantage of $^{90}$Y is that it cannot be readily imaged, resulting in the need for a surrogate, e.g., $^{111}$In. DOTA also binds indium with considerable kinetic stability (13), so that DOTA chelates of γ-emitting $^{111}$In can be used to trace the pharmacokinetics and estimate the radiation dosimetry of the corresponding $^{90}$Y RP. Studies of both blood and urine clearance and measurement of radiation in tissue biopsies indicate that the pharmacokinetics of $^{111}$In and $^{90}$Y RPs closely parallel each other in individual patients (14, 15). Therefore $^{111}$In can be used to track $^{90}$Y in the same formulation. In addition, we have found that normal organ doses determined from $^{111}$In imaging are very similar in individual patients over time (14). When considering adjuvant therapy for minimal residual disease, $^{90}$Y is useful, although a caveat is that the range of $^{90}$Y emissions can become disadvantageous when diffuse malignancy exists in normal tissues, such as the bone marrow (unless BMT is implemented). Even when macrocyclic chelates such as DOTA are used in the RP, radiometals present a problem because they are retained in the liver (16). $^{90}$Y retention in the liver causes a lower therapeutic index than that of the equivalent radioiodinated MoAb (Fig. 2; Ref. 17). The liver can be dose limiting when BMT is incorporated into the RIT strategy. The need for a biodegradable linker between the chelated $^{90}$Y and the mAb to release the chelated $^{90}$Y is apparent.

Chelate-Linker. On the basis of evidence that intrahepatoctye cathepsins (endopeptidases) are responsible for most of the protein metabolism in hepatic lysosomes, a biodegradable linker (glycylglycylglycyl-L-(p-isothiocyanato)-phenylalanine amide) that is susceptible to endopeptidase activity has been developed (18). DOTA-peptide RPs are novel because the peptide linker can be catabolized in the liver, thereby reducing the radiation dose to normal tissues and improving the therapeutic index. The peptide linker has been shown in mice and in patients
compared with an equivalent RP (2-iminothiolane-2-[p-(bromoacetamido)benzyl]-DOTA), and 90Y-DOTA-peptide-ChL6 in a human xenograft mouse model reflect the slower liver clearance of the metallic RPs. Comparison of the two metallic RPs indicates that the RP containing the peptide linker had a liver radiation dose one-half that of the nonbiodegradable linker. Radiation doses to other organs and the tumor were similar for the two metallic RPs.

The therapeutic indices of tumor:liver for 125I-ChL6, 90Y-DOTA-ChL6 (2-iminothiolane-2-[p-(bromoucxetamido)benzyl]-DOTA), and 90Y-DOTA-peptide-ChL6 in a human xenograft mouse model reflect the slower liver clearance of the metallic RPs. Comparison of the two metallic RPs indicates that the RP containing the peptide linker had a liver radiation dose one-half that of the nonbiodegradable linker. Radiation doses to other organs and the tumor were similar for the two metallic RPs.

Bone Marrow Transplantation

BMT has been used to facilitate dose intensification of chemotherapy in patients; doses of the chemotherapeutic agents can be increased by 5–10 times those used conventionally (23). With regard to RIT, BMT enables the transfer of dose-limiting toxicity from the radiosensitive hematopoietic cells to the more radioresistant cells of the liver, kidney, or lung. Press et al. (12) have demonstrated that a single large dose of 131I-labeled mouse B1 antibody (anti-CD20) was remarkably effective therapy for NHL when BMT was used. Doses of 131I approaching a curie, much larger than those possible for nonmyeloablative RIT (except perhaps when fractionated into multiple doses; Ref. 24), were possible. Although morbidity and mortality were greater than those usually encountered in nonmyeloablative RIT, toxicity was much less than that associated with chemotherapy and BMT, apparently because of the absence of effects on the epithelial barriers to infection and the endothelial barriers to bleeding. The dose-limiting organ for 131I was the lung when BMT was used. Encouraging results in patients with breast cancer have also been observed when the biologically active chimeric L6 antibody was used for RIT in association with BMT. Others have similarly reported encouraging early results for trials of RIT with BMT (25, 26).

Synergistic Radioimmunotherapy

It has been evident for some time that novel, synergistic, multimodality therapy is needed for solid tumors to combat the molecular mechanisms, genetic mutations, and epigenetic abnormalities that protect the cancer from therapeutic interventions. With dose intensification and BMT, meaningful remissions seem possible, but cures seem unlikely, even when maximum doses of the RP are reached. The increased radiation dose and dose rate made possible by BMT addresses the relative radioresistance of solid tumors but fails to address molecular aberrations common in cancer, particularly those that have failed conventional therapy. These molecular aberrations are often responsible for the failure to respond to chemotherapy.

Several strategies can be used to select a potentially synergistic agent for RIT. An obvious one is to select one or more chemotherapeutic agents that have been effective as therapy for a specific type of cancer. By the time that RIT is introduced, patients have usually become resistant to the chemotherapeutic drugs proven effective in their specific cancer. Others have proposed that an agent be selected because of differing toxicities; this approach leads to a relatively restricted list of possibilities but does emphasize the attractiveness of biological agents that tend to have different and often minimal toxicities. Cytokines and antibodies fall into this category of possibilities. Others have proposed that the agent should be chosen because it operates through a mechanism different than that of the primary therapeutic agent.

RIT involves a continuous, low dose rate form of radiotherapy in which a major mechanism of action is the induction of apoptosis (27–29). Taxanes are radiosensitizers in the broad sense of the term because they cause G2-M-phase cell cycle arrest; they stabilize microtubule formation, resulting in a mitotic block, and activate apoptosis (30). Taxanes promote apoptosis through bypass of the p53 pathway that is often nonfunc-
tonal in tumor cells; taxanes also create Bcl-2 dysfunction, overriding the Bcl-2 block of apoptosis. Bcl-2 is increased in many cancers. These molecular aberrations are common in human tumor cells and have been implicated in chemotherapy and radiotherapy failure. The potential synergy between taxanes and RIT was assessed in the HBT3477 breast cancer and the PC3 prostate cancer mouse models. In the low doses used in these studies, taxane did not act as a classic antineoplastic agent but as a cell cycle-specific radiation sensitizer (31, 32). Synergy between the taxane and RIT was demonstrated in both the breast and prostate cancer models, providing a strong rationale for evaluating this synergy in clinical trials. A recently reported Phase I clinical trial in ovarian cancer patients shows that Taxol (in doses up to 100 mg/m²) with RIT did not increase toxicity, providing additional support for the combined modality RIT strategy (33).

To recapitulate, there are opportunities for substantial improvement in the RPs used for RIT. Trials thus far have been disadvantaged by the use of inferior RPs. The utilization of radiometals, stable chelators, and biodegradable linkers with BMT will allow a maximum RP dose to be administered. RIT in conjunction with additional synergistic agents is likely to have a great impact on therapy for solid tumors.

References


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Clin Cancer Res 1999;5:3219s-3223s.

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