Radioimmunotherapy: From Current Clinical Success to Future Industrial Breakthrough?

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Radioimmunotherapy is a targeted molecular therapy that bears on radiobiologic and immunologic processes, without cross-resistance with other anticancer cytotoxic drugs. Since the first reports in the literature at the beginning of the 1980s, radioimmunotherapy techniques have significantly progressed because of advancements in recombinant humanized or human monoclonal antibodies, the synthesis of more stable chelates for radiolabeling, and pretargeting techniques that increase the therapeutic index. Several pivotal clinical studies demonstrated the efficacy of radioimmunotherapy in non-Hodgkin B-cell lymphoma (NHL), and 2 radioimmunotherapy-products targeting the CD20 antigen have been approved: ^{131}I-tositumomab (Bexxar; GlaxoSmithKline) and ^{90}Y-ibritumomab tiuxetan (Zevalin; Spectrum Pharmaceuticals). The marketing of ^{131}I-tositumomab is now discontinued. ^{90}Y-ibritumumab can be integrated in clinical practice using nonablative activities for the treatment of relapsed or refractory follicular lymphoma

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patients or as consolidation after induction chemotherapy in front-line treatment in follicular lymphoma patients (*1,2*). Numerous publications have also reported promising efficacy of anti-CD20 radioimmunotherapy in other more aggressive NHL subtypes (*3,4*) and of anti-CD22 radioimmunotherapy delivered as fractionated injections in different NHL subtypes (*5*). However, despite the safety and proven high clinical efficacy of radioimmunotherapy in NHL patients resistant to both chemotherapy and rituximab (probably the most effective treatment as a monotherapy in NHL), this outpatient treatment has not been widely adopted by the medical community. This is due to a combination of factors, including concerns about secondary myelodysplasia/acute leukemia risk, the lack of large randomized studies, the availability of many novel competing targeted agents such as ibrutinib or idelalisib, and the inability of oncohematologists to administer the therapy in their own departments (*6,7*).

Because solid tumors are more resistant to radiation and less accessible to large molecules such as antibodies, demonstrations of clinical efficacy of radioimmunoconjugates remain limited, and no large randomized study has been published. However, some radioimmunotherapy approaches have shown promising results in specific clinical settings, especially for small-volume tumors disseminated to bone marrow or at an early minimal residual disease stage. For example, adjuvant radioimmunotherapy using the anticarcinoembryonic antigen ^{131}I-labetuzumab delivered after salvage resection of liver colorectal metastases showed improved median overall survival and 5-y survival rates in a phase II study, compared with historic and contemporaneous controls not receiving radioimmunotherapy (*8*). However, these results need to be confirmed in multicenter randomized phase III trials.

In most cases, radioimmunotherapy is currently considered as a single-injection therapy agent, which is not realistic for the treatment of metastatic cancers. Fractionation of injected activity has been shown to reduce hematologic toxicity as a consequence of faster and more efficient bone marrow repair than tumor cell repair. Consequently, bone marrow should withstand the injection of higher cumulative activity, resulting in higher tumor dose and improved efficacy (*9*). Moreover, sequential doses of radioimmunoconjugate should favor a more uniform tumor dose distribution according to blood flow redistribution. The results of 2 clinical comparative studies are rather convincing and, importantly, involved a substantial number of patients. With ^{90}Y-ibritumomab tiuxetan, an increase of 32% of cumulative activity in fractionation with regard to a single dose brought about no significant change of hematologic toxicity but a real gain of progression-free survival from 26 to 40.2 mo (*10,11*). With the ^{177}Lu-labeled anti–prostate-specific membrane antigen huJ591, developed to treat metastatic prostate cancer, an increase of 14% of cumulative activity in fractionation with regard to a single dose brought about a slight decrease in hematologic toxicity and an improved clinical efficacy, with an improvement of 50% prostate-specific antigen decline rates from 12.5% to 29.2% and overall survival from 21.8 to 45.3 mo (*12,13*). In the future, fine tuning the most appropriate number of injections, activity per injection, and interval time between 2 sequential injections should also take into account bone marrow repair time and dose rates.

Low therapeutic index remains as a key problem for directly radiolabeled radioimmunoconjugates, especially in the treatment of macroscopic solid tumors. To reach significant antitumor efficacy, injected activities of radiolabeled antibodies must be close to toxic doses. To counter this, separation of the antigen-targeting component from the radioactivity vector in multistep pretargeting approaches has been proposed. Four major approaches using nonradioactive bispecific immunoconjugates and small-molecular-weight radiolabeled molecules have been investigated: the use of the avidin–biotin

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system, the use of bispecific antibodies and radiolabeled haptens, the use of antibody–DNA conjugates and radiolabeled small complementary DNA fragments, and the use of click chemistry for covalent pretargeting. Antibody–DNA conjugates or click chemistry are recent developments, and the immunogenicity of avidin is a well-known problem. Very promising are bispecific antibodies and bivalent radiolabeled haptens. These have been demonstrated to deliver improved tumor–to–normal-tissue activity ratios and potentially tumor-killing radiation doses in preclinical and clinical assays (*14*). Impressively, overall survival was improved in high-risk progressive metastatic medullary thyroid carcinoma patients, compared with historic controls not receiving radioimmunotherapy (*15*).

After these encouraging results, a prospective phase II multicenter trial studied progressive medullary thyroid carcinoma patients, confirming pretargeted radioimmunotherapy efficacy with 76% disease control (*16*). Tumor uptake assessed by postradioimmunotherapy immunoscintigraphy was a significant predictor of response. Preradioimmunotherapy biomarker doubling time and impact of radioimmunotherapy on biomarker doubling time predicted survival, confirming the value of serum biomarkers in selecting patients and monitoring therapy. Recently, recombinant bispecific antibodies produced by the dock-and-lock technique have been introduced in early clinical trials (*17*). Interestingly, pretargeting 2 tumor antigens was proposed many years ago, and increased uptake of activity by cells expressing both target antigens was observed in animal models (*18,19*).

The study in this issue of *The Journal of Nuclear Medicine* by Razumienko et al. (*20*) presents another interesting and promising application of bispecific radioimmunoconjugates. Razumienko et al. initiated xenograft tumors using trastuzumab-sensitive or insensitive human epidermal growth factor receptor-2 (HER2)–positive breast cancer cell lines. Next, they targeted both HER2 and epidermal growth factor receptor (EGFR) using a bispecific radioimmunoconjugate and compared tumor uptake and cytotoxic effects of this bispecific radioimmunoconjugate against monospecific ^{177}Lu-labeled trastuzumab Fab or epidermal growth factor in the 2 HER2-positive breast tumors. Both cell lines had a moderate and comparable expression of HER2 and EGFR. The authors showed that the tumor uptake of bispecific radioimmunoconjugate was 2- to 3-fold greater than monospecific ^{177}Lu-labeled trastuzumab Fab or epidermal growth factor in the trastuzumab-sensitive tumor. Interestingly, trastuzumab-resistant tumors responded to treatment with bispecific radioimmunoconjugates even if the response was lower than that of trastuzumab-sensitive tumors. The relative resistance of trastuzumab-resistant tumors was due to a higher expression of insulin growth factor-1 receptors, which is associated with radiation resistance. These preclinical results could open a new therapeutic window for treatment of trastuzumab-resistant tumors if they are confirmed in upcoming clinical studies.

Combination therapy is the rule in chemotherapy and combination of radioimmunotherapy, especially fractionated radioimmunotherapy, with radio-sensitizing agents also represents an attractive option in poor prognostic metastatic solid tumors. Indeed, fractionated ^{90}Y-clivatuzumab tetraxetan and low-dose gemcitabine demonstrated promising therapeutic activity and manageable myelosuppression in a phase I trial performed in patients with advanced pancreatic ductal carcinoma (*21*). As a result, an international multicenter phase III clinical trial has been designed, and patient recruitment is in progress.

New antibodies that target the key immune checkpoint receptors such as CTLA4 and PD-1, or its ligand PD-L1, also offer an exciting opportunity (*22*). Indeed, tumors can proliferate in part because immune surveillance is blocked by regulatory immune cells such as Tregs and tumor-associated macrophages. Anti-CTLA-4, anti–PD-1, or anti–PD-L1 antibodies relieve blockade of immune effector cells and show antitumor effects. Radiation-induced tumor cell death results in the provision of antigens for immune cross-presentation as well as immune-activating cytokine release, inflammatory signals, and upregulation of important antigens on surviving tumor cells such as class I MHC and Fas. However, these effects that could boost antitumor immune responses are blocked by the immune regulatory cells infiltrating the tumor. Thus radioimmunotherapy and immune checkpoint inhibitors could act synergistically in metastatic tumors, in a way similar to that which is already observed in some preliminary studies with external-beam radiation therapy and anti–CTLA-4 or PD-1 antibodies (*23*).

All of these perspectives suggest that radioimmunotherapy, used as stand-alone or in combination with other synergistic modalities, is highly promising and could contribute to substantial gains in overall survival for patients with solid tumors, who currently have a dismal prognosis. Despite this, not all patients could respond to radioimmunotherapy equally because it is dependent on the level of expression of tumor-surface target receptors. Radioimmunotherapy may be rather expensive, and, for a minority of patients, it can have severe side effects. This is why there is a need for a preselection of patients who are likely to respond. Nuclear medicine is perfectly suited to this situation inasmuch as the same molecule can be labeled first with a positron-emitting radionuclide for PET imaging and selection of patients with high tumor uptake and second with an electron (or α-)-emitting radionuclide for treatment. This is the theranostic concept (*24*). The estimation of target antigenic molecule expression in all tumors is necessary to predict the therapeutic effect. Biopsy samples are not sufficient because tumor tissue is heterogeneous, and these samples may not be representative of the whole-body tumor antigen expression and accessibility. Moreover, expression levels of antigenic molecules can change during treatment and repetitive biopsies are invasive, expensive, and onerous on patients.

CONCLUSION

Innovative radioimmunotherapy methods and development of novel radioimmunoconjugates remain relevant in the era of personalized medicine, especially in the context of multimodality strategies for treatment of poor-prognosis cancer that is resistant to conventional therapies. However, to convince the oncohematologist community, randomized clinical trials have to be designed and patients should be stratified for response to radioimmunotherapy. Moreover, PET molecular imaging, especially immuno-PET, should be considered in theranostic approaches to estimate the antigenic expression level and mutation status allowing patient stratification.

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