The Future of Radioligand Therapy: α, β, or Both?

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Endoradiotherapy approaches are experiencing growing interest with the increase in the number of carrier molecules becoming available for different targets. The cross-fire effect has been described as an important mechanism for the efficacy of radioligand therapies by particle-induced destruction of multiple cells in the neighborhood of a tracer-accumulating cell, which at least partially compensates for the heterogeneity seen in malignant tumors. This is in contrast to nonradioactive targeting treatment, in which usually only the cells binding the therapeutic molecule are destroyed (one hit, one kill). Therapeutic effects are further enhanced by the radiation-induced bystander effect (RIBE). RIBE describes a situation in which cells that are not directly exposed to the ionizing radiation, but are in the neighborhood of exposed cells, behave as if they have been exposed (Fig. 1): they die or show chromosomal instabilities or other abnormalities. Although the exact mechanism of RIBE is not fully understood, there is evidence that stress signal factors transmit information from irradiated cells to neighboring cells.

The cross-fire effect seems to be higher in large tumor masses and with isotopes that have a long range, such as β-emitters (*1*). This effect may also compensate for the intralesional heterogeneity of a specific target. Therefore, at first glance it seems counterintuitive that in patients with large tumor masses, a particle with a shorter range, such as an α-emitter, is more efficient than (or at least equally as efficient as) a particle with a longer range. Advantages of α-emitters are double-strand breaks of DNA, severe chromosomal damage such as shattered chromosomes at mitosis and complex chromosomal rearrangements, destruction of cells independently of cell cycle and oxygenation of the lesion, and the potential to overcome resistance toward β- or γ-irradiation and toward chemotherapy (*1,2*). α-emitters have been applied using DOTATOC for neuroendocrine tumors and a prostate-specific membrane antigen (PSMA) ligand for prostate cancer (*2–4*). Before this work, tracers with α-emitting isotopes were—because of their high-linear-energy transfer and limited range in tissue—rather seen as an appropriate therapy for disseminated disease, micrometastases, and elimination of single tumor cells (*5,6*). However, clinical experience has demonstrated that α-emitters can also be efficient in controlling large, bulky disease (*2*). The limited range in tissue ensures a highly controlled irradiation that can be targeted to tumor cells while having only low to moderate effects on normal tissues. Nevertheless, in a study on cynomolgus monkeys with an ^{225}Ac-labeled antibody against CD33, renal toxicity and anemia were observed at high doses (*7*). This effect was partly explained by the long half-life of the antibody in the blood and lack of the target in cynomolgus monkeys. Similar results were found in tumor-bearing mice treated with a PSMA-targeted small molecule labeled with ^{211}At (*8*). Although significantly improved survival was seen in mice with micrometastases, uptake in renal proximal tubules was noted, resulting in late nephrotoxicity.

Besides the reaction at the area under treatment, radiation therapy induces responses also in remote lesions (Fig. 1)—coined the "abscopal effect" (*9*). This phenomenon has been observed in a variety of tumors and is attributed to irradiation-induced immune mechanisms such as exposure of tumor antigens, increased maturation of antigen-presenting cells taking up antigen released by dying cells, production of proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-α, and changes in the tumor microenvironment for improved recruitment of effector T-cells. The phenomenon was originally described for external radiation but may also occur during endoradiotherapy and may be used for combinations of endoradiotherapy with α-emitters and immune therapy (*10,11*). α-therapy may lead to the release of antigenic molecules from the tumor and induce systemic T cell–dependent antitumor immunologic reactions. In a study on immunocompetent mice, tumor cell irradiation using a ^{213}Bi-labeled antibody induced a protective antitumor response mediated by tumor-specific T cells against a secondary tumor cell injection (*11*).

Bearing in mind the high toxicity expected not only in the tumor but possibly also in benign tissues, the carrier molecule that transports the radioactivity to the tumor site is of high importance. This importance relates not only to the moiety responsible for binding to the target but also to the chelator trapping the isotope. Isotopes with multiple decays, such as ^{225}Ac, may change their affinities and detach from the chelator. This detachment may not be a problem if the carrier molecule is internalized and the radioactivity is trapped in intracellular compartments, as determined largely by the target structure. But elution of the isotope from the chelator is a challenge if the carriers remain extracellular. In such a case, the development of suitable conjugation chemistry that would securely sequester α-emitters is needed (*6*). Concerning the target-binding moiety of the tracer, the format of the ligand is critical. Antibodies may have a higher hematotoxicity than small molecules or peptides because of their longer circulation time (*12*). In contrast, differences in the biodistribution may be in favor of antibodies with respect to the lower accumulation in specific benign tissues. This favoring of antibodies has been seen in the salivary glands, where the PSMA-specific antibody J591 shows only low uptake whereas small-molecule inhibitors of PSMA lead to high local doses with associated damage of the glands when α-particle emitters are used (*3,4*). The difference in accumulation between antibody and small molecule may best be explained by trapping of the small molecule because of PSMA binding and an additional, at present unknown, salivary-gland blocking strategy by which the incidence and severity of xerostomia is

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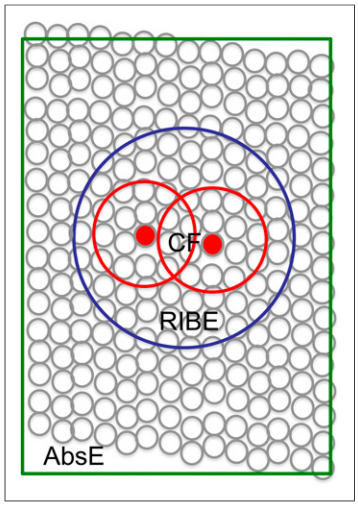

FIGURE 1. Mechanisms enhancing efficacy of endoradiotherapy: cross-fire effect (CF, overlap of red circles) may compensate for target heterogeneity, RIBE (blue circle) leads to death of neighboring cells not directly exposed to irradiation, and abscopal effect (AbsE, green rectangle) induces responses also on remote lesions outside RIBE area and depends on induction of immune reactions.

decreased. However, despite its higher side effects with respect to the salivary glands, the α-labeled small-molecule inhibitor of PSMA shows the advantages of a better penetration of the tumor and a faster clearance, with benefit for bone marrow dose. Especially in patients with diffuse bone marrow infiltration, the α-labeled small molecule may have better therapeutic efficacy and lower hematotoxicity. In this situation, a reliable stratification strategy for patients with multiple metastases is needed to decide whether a patient is to receive a radiopharmaceutical labeled with a β-emitting isotope or a molecule with an α-emitter (Fig. 2).

Coming back to the question of α, β, or both, we opt for both, but *both* has two possible interpretations. The first interpretation is that a carrier labeled either with a β-emitter or with an α-emitter may be used for therapy. This strategy is used at our institution for patients with castration-resistant prostate cancer. An α-emitter is applied for patients in whom ^{177}Lu therapy has failed or who have disseminated disease of the bone marrow, and the strategy has been shown to be highly effective in both situations (*3*). Meanwhile, a dosimetric analysis has revealed that a treatment activity of 100 kBq of ^{225}Ac-PSMA-617 per kilogram per cycle repeated every 8 wk presents a reasonable trade-off between toxicity and biochemical response (*4*). As mentioned above for this strategy, a stratification procedure such as PSMA ligand PET/CT is needed. The second interpretation is the use of cocktails. This strategy could involve one carrier molecule labeled with a β-emitter and an α-emitter. At present, it is unclear whether this strategy is better than that of giving only one isotope. Another and more promising approach would be the administration of two different carriers addressing two different targets. In this setting, the carrier labeled with the β-emitter may be used for debulking of large tumor masses and the carrier labeled with the α-emitter may target critical subpopulations in a tumor such as cells with stem cell properties.

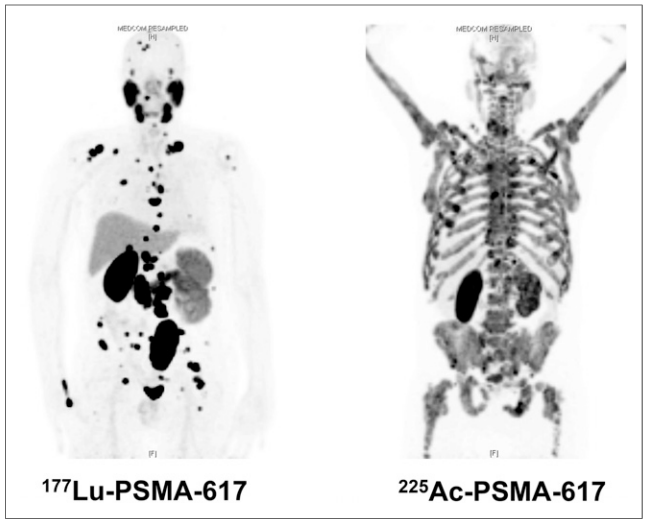

FIGURE 2. Stratification of therapy according to bone marrow involvement. Maximum-intensity-projection PSMA ligand PET/CT in 2 patients. Patient lacking diffuse bone marrow infiltration (left) is candidate for treatment with ^{177}Lu-PSMA ligand, whereas patient with infiltration of bone marrow (right) should be treated with ^{225}Ac-PSMA ligand.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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