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COMMENTARY

Combination of Radioligand Therapy and Immunotherapy: How to Make It Work in Clinic?

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Abstract: Combining external beam radiation therapy (EBRT) with immunotherapy showed promise pre-clinically by inducing immunogenic cell death (ICD) thus releasing damage-associated molecular patterns (DAMPs) and cytokines to activate the immune system. Clinical results, however, have often been disappointing. Radioligand therapy (RL), which uses targeted radionuclides to deliver cytotoxic radiation, offers advantages over EBRT by treating multiple tumors simultaneously. Combining RL with immunotherapy faces challenges, as prolonged radiation exposure can damage immune cells, and the "cross-fire" and "bystander" effects may harm incoming effector cells. Current RL therapies require multiple doses, further complicating immune cell viability. To optimize RL-immunotherapy combinations, timing is critical. Administering immunotherapy weeks after RL therapy may reduce radiation-induced immune cell damage. Additionally, selecting radionuclides with shorter half-lives could minimize immune cell toxicity while maintaining tumor-killing efficacy. Future RL therapies should prioritize radionuclides with optimal emission profiles and half-lives to enhance synergy with immunotherapy and improve clinical outcomes.
Keywords: immunotherapy, radioligand therapy, combination therapy, clinical outcomes, radiobiology

Introduction

Introduction of immunotherapy into the clinic in 2011 in the form of anti-CTLA4 immune checkpoint inhibitors has drastically changed the landscape of oncology, producing spectacular results in some patients with metastatic melanoma.[1] Those initial successes were followed by immune anti-PD1 and PD-L1 checkpoint inhibitors,[2–4] with further developments seeing approval of more complex versions of immunotherapy such as CAR T cells.[5,6] However, it soon became clear that the objective response was observed in a minority of treated patients, often accompanied by severe immune-related side effects, and the responses could be short-lived. One of the major reasons for that is the immunologically "cold" nature of many tumors, which does not allow the immune system, such as CD8+ T cells or natural killer (NK) cells, to unleash their anti-tumoral abilities.[7–9] The need to perturb tumors to make them immunologically "hot" encouraged combining external beam radiation therapy (EBRT), which is a widely used modality in cancer treatment with immunotherapy.[10] Initial pre-clinical results were very encouraging and demonstrated that such combination works through a variety of mechanisms, such as immune-activating process of cellular destruction, commonly referred to as immunogenic cell death (ICD).[11] This process, taking place within the tumor microenvironment (TME), is characterized not only by the emission of diverse damage-associated molecular patterns (DAMPs), such as calreticulin expressed on the plasma membrane surface, along with extracellular adenosine triphosphate (ATP) and high mobility group protein B1 (HMGB1), but also by the release of multiple immune-stimulating or chemotactic cytokines, including type I interferons and C-X-C motif chemokine ligand 10 (CXCL10).[11–13] However, clinical implementation of radiotherapy–immunotherapy combinations often produces disappointing results. In this regard, simultaneous administration of immune checkpoint inhibitor nivolumab and adjuvant EBRT with temozolomide to patients with newly diagnosed glioblastoma did not demonstrate any therapeutic advantage over standard of care EBRT and chemotherapy in a placebo-controlled Phase III clinical trial.[14] In the same vein, no synergistic or additive effects were observed in patients with locally advanced head

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and neck cancer when treated with a combination of checkpoint inhibitor avelumab and EBRT in the course of two randomized clinical trials.[15,16]

Radioligand therapy (RL) utilizes receptor or antigen-specific molecules to direct radionuclides emitting cytotoxic particles, such as beta- or alpha-particles, or Auger electrons to cancer cells for destruction.[17,18] Within the last decade three RL agents for the treatment of metastatic prostate cancer and neuroendocrine tumors have been approved, with multiple clinical trials for other cancers currently on-going.[19–21] While EBRT in some cases results in a systemic anticancer response known as the abscopal effect linked to the immune activation initiated by radiation-induced DNA damage,[22] the potential advantage of internally administered radiation in the form of RL therapy over EBRT is its capability to treat simultaneously multiple tumors, including even small clusters of malignant cells.[17] Realization of RL potential to immune activate multiple tumor sites in the body for combination with immunotherapy (Figure 1) provided the impetus for pre-clinical investigations, which started shortly after approval of 223Radium (223Ra) chloride (Xofigo) for treatment of prostate cancer metastatic to the bone.[23] The outcomes of resulting pre-clinical and clinical combinations of RL therapy and immunotherapy are discussed in three recent excellent reviews on the topic, to which we refer readers.[23–25] Importantly, similar to the situation with EBRT-immunotherapy combinations, the data emanating from clinical trials does not often demonstrate synergy. For example, there was no statistically significant difference in progression-free survival between patients with metastatic prostate cancer receiving 153Sm-EDTMP (Quadramet) and its combination with a therapeutic vaccine.[26] In another example, in a Phase II trial patients with metastatic prostate cancer who received combination therapy of $223RaCl_2$ (Xofigo) and the immune checkpoint inhibitor pembrolizumab did not demonstrate improvement in either overall survival or progression-free survival when compared to the Xofigo-only group.[27] Some encouraging results are primarily emanating from different case reports at this stage.

Here, we comment on the probable reasons for this lack of synergy between two therapies and on possible ways to change this situation with the goal of improving clinical outcomes.

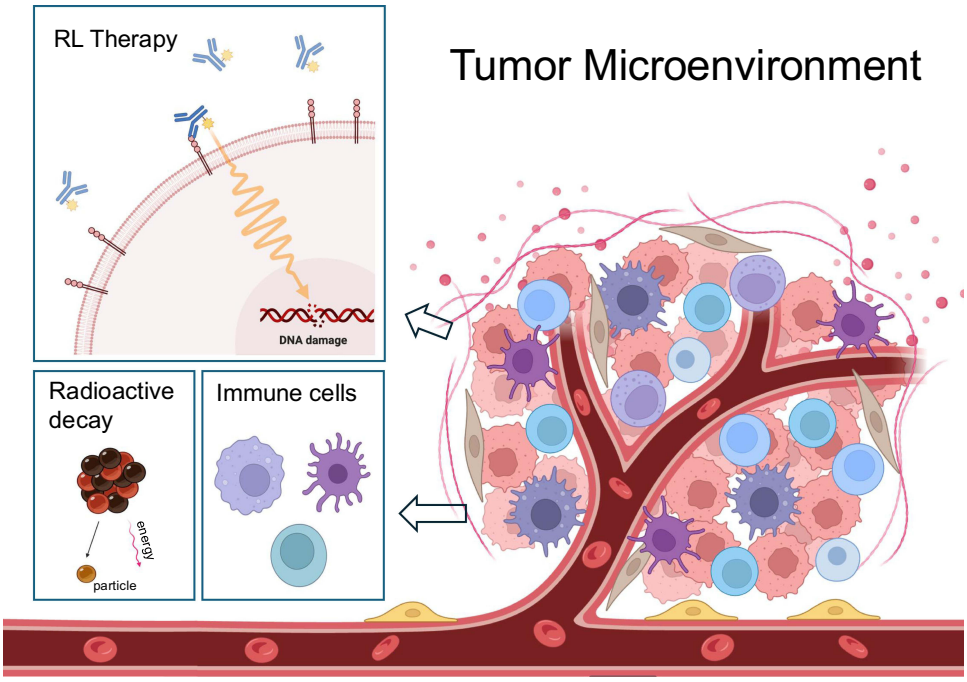

Figure 1 Radioligand (RL) therapy utilizes tumor cells targeting molecules to carry radionuclides to tumors, causing damage to tumor cells resulting in the immunogenic cell death. Radiation also affects resident immune cells in the tumor microenvironment. Future combinations of RL therapy and immune therapy should be calibrated based on type of radioactive decay of atoms, dosage and half-life of radionuclides, and the timing of immune therapy administration, to maximize their synergistic effects.

Reasons for Reduced Efficacy of RL Therapy and Immunotherapy Combinations in Clinic

The overwhelming majority of clinical studies of RL therapies and immunotherapy involved application of three approved by the regulatory agencies overseeing radiopharmaceuticals: the already mentioned alpha particles emitting 223Ra chloride (Xofigo); beta particles emitting 177Lutetium (177Lu)-labeled somatostatin receptors binding peptide (Lutathera); and 177Lu-labeled prostate-specific membrane antigen (PSMA)-binding small molecule PSMA-617 (Pluvicto).[19–21] Both 223Ra and 177Lu radionuclides have relatively long physical half-lives of 11.4 and 6.9 days, respectively. On the other hand, one of the mechanisms behind RL efficacy as an anti-cancer therapy is that, once the radionuclides-carrying radiopharmaceuticals are bound to their respective targets on the tumor cells, they tend to stay there for prolonged periods of time, "showering" tumor cells with cytocidal high energy particles. This is one of the advantages of RL therapy in comparison with EBRT, whereby radiation is delivered from outside of the tumor and does not present after an irradiation session is completed. However, a prolonged radiation dose of RL agents might be damaging to the immune cells that it is supposed to "invite" into the tumor as lymphocytes, such as cytotoxic CD8+ T cells, which are some of the most radiosensitive cells in the body.[28] Shea et al describe variable effects of RL therapy on different cohorts of immune cells such as abrogation of regulatory T cells in tumors and decrease in number of NK cells.[24] In addition, beta emitters such as 177Lu are effective due to the so-called "cross-fire" effect, which is irradiation at a distance from the original RL agent binding site in the tumor due to long-range (hundreds of cell diameters) beta particles in tissue.[29] Again, this advantage of RL therapy, which ensures homogeneous irradiation of tumor volume, reverses the disadvantage when it is combined with immunotherapy because incoming tumor-fighting immune cells will be irradiated irrespective of the direction from which they are entering the tumor. Another radiobiological effect that is observed for both EBRT and RL therapy but is more prominent for RL therapy is "bystander" effect, which takes place when irradiated tumor cells are sending death signals to the tumor cells nearby that might not have been affected by radiation directly.[30,31] The latter cells will, in turn, start sending death signals to neighboring cells, thus initiating a chain reaction of cell signaling leading to cell death. This powerful mechanism is responsible for tumor stabilization or even continuous shrinkage days or months after the RL therapeutic agent has decayed and/or effluxed from the tumor. Obviously, receiving such death signals will negatively affect the immune cells residing in or entering TME. Finally, all three currently approved RL therapies are administered to patients multiple times to increase the efficacy: Xofigo is given up to 6 times every 4 weeks; Lutathera, 4 doses every 8 weeks; and Pluvicto, 6 doses every 6 weeks.[19–21] This means that, for several months while a patient is undergoing their treatment with one of these RL agents, there will be a continuous presence of "hard-hitting" alpha- or beta-particles emitting radionuclides in the tumors, which might be compromising the viability and anti-tumor action of immune cells.

Possible Ways to Improve Clinical Outcomes of RL Therapy and Immunotherapy Combinations

In their pivotal review on EBRT and immunotherapy combinations, Galuzzi et al called for adapting EBRT to immunotherapy by improving radiotherapy regimens in target volumes.[32] How would such adaptation work for RL therapy and immunotherapy combinations? If currently approved RL therapies are considered, the timing of immunotherapy administration has to be carefully calibrated to avoid, as much as possible, compromising the effector cells with radioactivity in the tumors. In this regard, it might be prudent to provide the immunotherapy component of combination treatment from 2 to 4 weeks after the RL dose to ensure that, while a lot of cells have already undergone ICD and released DAMPs, the bulk of radioactivity is already gone from the tumor. In regards to the development and approval of novel RL agents that will be combined with immunotherapy, the radionuclides nuclear emission schemes and half-lives have to be taken into consideration. The informed choice of radionuclide with an optimal emission scheme is important for coming up with effective combinations of RL therapy and immunotherapy as the current dogma in the field of RL agents is that alpha-emitters are always more efficacious than beta emitters, and the long-lived alpha-emitters have more advantages than short-lived ones. Contrary to this dogma, pre-clinical work has demonstrated that long-lived alpha-emitters, such as 223Ra or 225Actinium (225Ac) with its 9.9 days physical half-life, are killing a significant number of effector cells, which can negatively affect the

efficacy of combination therapies.[33,34] Pre-clinical studies comparing side by side the combination of radioimmunotherapy with 225Ac- versus 177Lu-labeled antibody to melanin and anti-PD-1 immune checkpoint inhibitor (ICI) revealed a significant synergistic effect between 177Lu-labeled antibody and ICI, and an absence of any synergistic or additive effect for 225Ac-labeled antibody and ICI.[34] Along the same lines of investigation, an antibody to melanin labeled with short-lived (46 minutes physical half-life) alpha-emitter 213Bismuth (213Bi), which is an 225Ac daughter in combination with ICI, was very effective in the same experimental melanoma; a 225Ac-labeled antibody and ICI combo, however, did not have any effect on the tumor.[35] As several new RL therapies based on 225Ac-labeled molecules will be entering the clinic in the next several years, any combination of such agents with immunotherapy will have to be carefully calibrated to avoid disappointing outcomes. If the current positive momentum in the RL therapy field continues, more of the short-lived alpha- and beta emitting radionuclides such as 211Astatine, 212Lead/212Bismuth, 213Bismuth, 166Holmium etc. will become available. Such short-lived radionuclides have a very profound effect on tumor cells due to their high decay rate and, because of this high decay rate, they disappear from the tumors very fast, thus giving an opportunity to incoming effector cells to kill tumor cells in synergistic fashion. In addition, more personalized clinical treatment could possibly minimize radiation-induced damage, such as real-time monitoring of biomarkers in response to RL and dynamic adjustment of treatment protocols due to immune activity.

Conclusion

The field of RL therapy and immunotherapy combination is still very new and will, undoubtedly, experience a lot of productive development in the next decade. It will require the conserted efforts of radiopharmaceutical scientists, nuclear medicine physicians and oncologists to adapt current and future RL therapeutic agents to those combinations by taking into consideration the pharmacokinetics and radiobiology of RL agents. Timing between the administration of RL agents and immunotherapy, half-life of the radionuclides, nature of radioactive emissions, immune status of tumors and individualized radiation dosimetry should be carefully evaluated in clinical trials of combination therapies.

Abbreviations

RL, radioligand; EBRT, external beam radiation therapy; ICD, immunogenic cell death; DAMPs, damage-associated molecular patterns; TME, tumor microenvironment; ATP, adenosine triphosphate; HMGB1, high mobility group protein B1; CXCL10, C-X-C motif chemokine ligand 10; NK, natural killer.

Disclosure

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