Theranostic radioimmunotherapy (RIT) combined with immunotherapy: The best way to go?

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The clinical efficacy of radioimmunotherapy has been clearly documented in non-Hodgkin B-cell lymphoma (NHL) even if, due to a combination of factors, it has not been widely adopted by the oncologist community particularly because of the competitive maintenance treatment using rituximab [1].

Some quite promising results have been also obtained in solid tumors despite their relative radioresistance. For treatment of metastatic cancers, single-injection RIT is not realistic for a substantial efficacy. Fractionation of injected activity allows to reduce hematologic toxicity due to a faster bone marrow repair than tumor cell repair. It results that bone marrow can support the injection of higher cumulative activity allowing a higher tumor dose and better efficacy especially for small-size tumors [2].

RIT with anti-PMSA-177Lu-J591 antibody has clearly shown the interest of fractionation in treatment of patients with metastatic castration resistant prostate cancer. An increase of 14% of fractionated cumulative activity with regard to a single injection led to a slight decrease in hematologic toxicity and an impressive overall survival gain from 21.8 to 45.3 mo with respectively low dose and maximal tolerated dose, even if such improvement should be cautiously considered due to the small number of patients [3].

Another promising approach is the use of pretargeting technology. In a clinical study, anti-carcinoembryonic antigen (CEA)/anti-diethyleneetriamine pentaacetic acid (DTPA) -indium bispecific antibody, followed 4 days later by a 177Lu-labeled bivalent hapten were injected in patients with advanced, progressive medullary thyroid cancer. Forty-seven percent of patients, defined as biologic responders by a more than 100% increase in calcitonin doubling time, experienced a significant increase in Progression Free Survival (PFS) was found with evidence of serum PSA decline only in the combination arm [8]. This was the first clinical trial combining a radiopharmaceutical agent with an immunotherapy modality. Another ongoing randomized clinical trial combines Sipuleucel-T, another vaccine designed to induce activation of T cells specific against prostate-specific antigen (PSA) has been combined with samarium-153-EDTMP (Quadramet®) in a randomized phase 2 trial in patients with metastatic castration-resistant prostate cancer without visceral metastases. Interestingly a significant increase in Progression Free Survival (PFS) was found with evidence of serum PSA decline only in the combination arm [8]. This was the first clinical trial combining a radiopharmaceutical agent with an immunotherapy modality. Another ongoing randomized clinical trial combines Sipuleucel-T, another vaccine designed to induce activation of T cells specific against prostate-specific antigen PAP (Prostatic Acid Phosphatase) with radium-223 (Xofigo®) vs Sipuleucel-T alone and is currently recruiting for a completion date in 2020.

Other clinical trials combining RIT and immunotherapy are planned for the coming years.

In conclusion, for the last 2 or 3 decades a lot of clinical studies performed with different antibodies in hundreds of patients have shown chances of efficient RIT but they do not allow whole-body mapping of tumor antigenic expression and thus their capacity to predict efficient treatment remains limited.

Immuono-PET with antibodies labeled with positron-emitting radionuclides such as zirconium-89 or iodine-124, offers a non invasive quantitative imaging for evaluation of tumor antigenic expression in all metastases in a patient and thus can help select patients for an efficient RIT [6]. Immuno-PET, using 89Zr-anti-HER2 antibody (trastuzumab) proved to be useful in selecting patients HER2+ in accordance with immunohistochemistry and to predict response to trastuzumab therapy [7].

Large multicentre randomized clinical trials need to be implemented before stating that immuno-PET is really useful for patients stratification before RIT.

Need for combination therapy

It is well established that ionizing radiation can stimulate the immune system in several ways. As a result, radiotherapy and especially targeted radiotherapy including RIT can contribute to shift an immunosuppressive tumor microenvironment to a more favorable immune stimulatory effect. As a result it makes sense to combine targeted radiotherapy with immunotherapy for a better efficacy.

A therapeutic vaccine, PSA-TRICOM (PROSTVAC) designed to induce activation of T cells specific against prostate-specific antigen (PSA) has been combined with samarium-153-EDTMP (Quadramet®) in a randomized phase 2 trial in patients with metastatic castration-resistant prostate cancer without visceral metastases. Interestingly a significant increase in Progression Free Survival (PFS) was found with evidence of serum PSA decline only in the combination arm [8]. This was the first clinical trial combining a radiopharmaceutical agent with an immunotherapy modality. Another ongoing randomized clinical trial combines Sipuleucel-T, another vaccine designed to induce activation of T cells specific against prostate-specific antigen PAP (Prostatic Acid Phosphatase) with radium-223 (Xofigo®) vs Sipuleucel-T alone and is currently recruiting for a completion date in 2020.

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Received: July 20, 2017; Accepted: August 17, 2017; Published: August 21, 2017
a clinical efficacy in sensitive lymphomas and solid tumors especially in the situation of small-size tumors [9]. In the near future it will be useful to select patients for RIT on the basis of immune-PET imaging using the same antibody labeled with a positron-emitting radionuclide. Finally the efficacy of RIT could be substantially improved when combined to immunotherapy.

References


3. Batra JS, Karir BS, Vallabhajosula S (2015) Fractionated dose radiolabeled antiprostate specific membrane antigen (PSMA) radioimmunotherapy (177Lu-J591) with or without docetaxel for metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 33: 194. [Crossref]


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