



Bombesin antagonist based radiotherapy of prostate cancer combined with WST-11 vascular targeted photodynamic therapy

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Kim *et al.* (1) from Memorial Sloan-Kettering Cancer Center investigated the possibility to enhance the effect of radionuclide therapy by vascular-targeted photodynamic (VTP) therapy in an experimental prostate cancer animal model. They used bombesin-antagonist peptide as a targetor which is binding gastrin releasing peptide receptor (GRPr) and it was labeled with high energy beta-emitting radionuclide ⁹⁰Y and the radionuclide was linked with DOTA-chelate. This peptide receptor radionuclide therapy (PRRT) compound, ⁹⁰Y-DOTA-AR (bombesin antagonist) radiopeptide was followed by therapy with WST-11 (Weizmann STeba-11 drug; a negatively charged water-soluble palladium-bacteriochlorophyll derivative, Tookad[®] Soluble) application. This VTP approach generates reactive oxygen/nitrogen species within tumor blood vessels, resulting in their instantaneous destruction and causes rapid tumor necrosis. Radionuclide emitting charged particle forms Cherenkov luminescence imaging (CLI) which can be used to monitor the retention of the accumulated ⁹⁰Y-PRRT. In this work, they demonstrated that the instantaneous arrest of tumor vasculature trapped radiopharmaceuticals in the vicinity of the tumor and thus improved the efficacy of targeted radiotherapy (1).

They used two GRPr positive prostate cancer xenograft models derived from PC-3 and VCaP cell lines. The animals were randomly assigned to four different groups, including sham control (saline and illumination only), VTP, ⁹⁰Y-DOTA-AR, and combination of ⁹⁰Y-DOTA-AR and VTP (the design is shown in *Figure 1*). The uptake of

radioisotopes was monitored by CLI. CLI of ⁹⁰Y-PRRT demonstrated statistically significant longer retention of radiotracer within the VTP treated PC-3 xenografts compared with the non-VTP treated ones, and similar results were observed with VCaP xenografts. Also, when ⁹⁰Y-PRRT was combined with VTP, tumor growth delay was significantly longer than for the control or the other therapy groups (*Figure 2*). This means, that tumor vascular arrest by VTP improves ⁹⁰Y-DOTA-AR retention in the tumor microenvironment thereby enhancing therapeutic efficacy.

VTP is a new non-thermal ablation method involving systemic administration of the photosensitizing agent WST-11. Conventional photodynamic therapy agents are extravasated to the surrounding tissues mainly affecting the tumor cells (2), while WST-11 non-covalently binds to albumin and mainly targets the tumor vasculature (3). Permanent vascular arrest is limited to vessels smaller than 40 μm, which is well suited to the tumor microenvironment (3).

GRPr, i.e., bombesin receptor subtype 2, is overexpressed in multiple human cancers at a high incidence rate (4), and all prostate cancers demonstrated receptor specific binding of radiolabeled bombesin in all tumors (n=30), whereas normal prostate and benign prostate hyperplasia displayed only minimal binding of bombesin (5). Radiolabeled bombesin analogs have been developed as targeting vectors for imaging and radionuclide therapy of tumors via specific binding to GRPr (6) and have been applied to

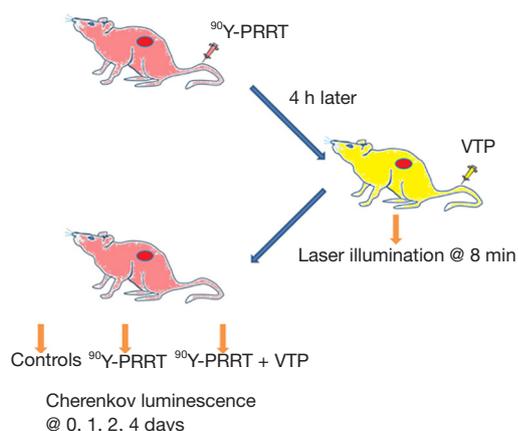


Figure 1 Schematic illustration of experimental set-up. PRRT, peptide receptor radionuclide therapy; VTP, vascular targeted photodynamic therapy. Modified with permission from Kim *et al.* (1).

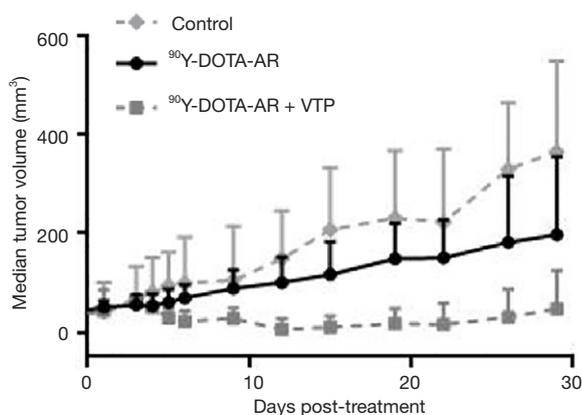


Figure 2 Tumor growth curves in control animals (control), in animals treated with peptide receptor radionuclide therapy (PRRT)-compound (^{90}Y -DOTA-AR) and in animals treated with PRRT and vascular targeted photodynamic therapy (^{90}Y -DOTA-AR + VTP). Reprinted with permission of the American Association for Cancer Research from Kim *et al.* (1).

clinical studies with radiolabeled bombesin based peptides in the imaging of metastasized prostate tumors with success (7). Importantly, one bombesin antagonist peptide, ^{111}In -DOTA-AR (^{111}In -DOTA-PEG4-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH₂), has demonstrated favorable affinity to GRPr and optimal uptake at 1–4 hours in PC-3 human prostate cancer xenografts (8).

This peptide DOTA-AR used here is a high-energy beta emitter ^{90}Y ($t_{1/2}$ =64 hours) which makes it suitable for non-invasive CLI, ^{90}Y -DOTA-AR could act as a surrogate to

investigate whether the arrest of tumor microvasculature in the target tissue enhances the radionuclide retention.

In summary, the initial experience with combinatorial sequential therapy using VTP with PRRT demonstrates very promising results. This has potential to improve cytotoxic effects in prostate cancers, because VTP does not show any serious photo-toxicity and its interval between drug injection and laser illumination is short. VTP provides an attractive option to decrease of fast washout of the accumulated radiopharmaceuticals from tumors.

Radionuclide therapies are effective in the treatment of prostate cancer, and they are part of current clinical practice especially in Europe and Australia. Two rather new methods, Lu-177-PSMA-617 and Ra-223 are shown to effectively improve survival (9,10). Combination of these with Cherenkov luminescence and vascular targeted therapy may improve therapy efficacy in metastatic tissues which are more radiation resistant.

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Footnote

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