What’s in a Label? Radioimmunotherapy for Metastatic Prostate Cancer

Charles B. Simone II and Stephen M. Hahn

Prostate cancer has a highly tumor-restricted prostate-specific membrane antigen (PSMA) and may be the ideal solid-organ malignancy for treatment with radioimmunotherapy. Encouraging results using lutetium-177–labeled anti-PSMA monoclonal antibody J591 from a phase II study by Tagawa and colleagues support the continued clinical and preclinical development of radioimmunotherapy for solid tumors. Clin Cancer Res; 19(18); 4908–10. ©2013 AACC.
Radioimmunotherapy offers distinct advantages over other radionuclide therapies. PSMA, a nonsecreted cell membrane protein, has expression highly restricted to prostate cancers. J591 is a deimmunized monoclonal antibody against the extracellular domain of PSMA (Fig. 1). Agents like samarium-153, strontium-89, and radium-223 target sites of increased bone metabolism but do not target tumor directly. They instead impart antitumor effects from radiopharmaceutical accumulation adjacent to malignant cells or stroma and, therefore, do not appreciably treat extraosseous visceral metastases. By radiolabeling tumor-specific PSMA monoclonal antibody, delivering cytotoxic therapy to both bone and soft tissue and visceral metastases is achievable. Yttrium-90 and lutetium-177 have both been used for radiolabeling in clinical trials. Lutetium-177, used in the study by Tagawa and colleagues, may prove the superior option because it has a longer half-life, higher activity at the MTD, and is both a short-range (0.2–0.3 mm) beta particle and gamma particle emitter, allowing for lower radiation dose to bone marrow (1).

Radioimmunotherapy for prostate cancer is generally well tolerated, with reversible hematologic toxicities from samarium-153, strontium-89, and radium-223. Because a larger fraction of administered activity remains in various organs and body spaces, radioimmunotherapy has the potential of increased toxicity compared with radionuclide therapy. The specificity of tumor-specific PSMA monoclonal antibody is likely to mitigate this risk. Nonetheless, in the study by Tagawa and colleagues, all the patients experienced hematologic toxicities, including grade 4 thrombocytopenia in 46.8% lasting a median of 7 days and grade 4 neutropenia in 25.5% lasting a median of 5 days (1). Higher rates were recorded in patients treated at 70 mCi/m². Myelosuppression, although typically transient, was of concern, as 7 patients did not recover a normal platelet count. Such bone marrow suppression is significant and may limit the ability to deliver other subsequent therapies or combine 177Lu-J591 with other cytotoxic agents. Therefore, careful consideration is required when determining integration of radioimmunotherapy with other therapies for mCRPC.

In the 2013 guidelines from the American Urologic Association, symptomatic mCRPC patients with good performance status are recommended to receive docetaxel chemotherapy, or otherwise mitoxantrone (evidence level grade B), ketoconazole (grade C), or radionuclide therapy (grade C). In addition, radionuclides should be considered in patients with mCRPC with poor performance status treated with prior docetaxel or if they have not had prior docetaxel but are unable or unwilling to receive abiraterone plus prednisone (3). In the months since these guidelines were devised, with May 2013 U.S. Food and Drug Administration approval of radium-223 to treat patients with mCRPC with symptomatic bony metastasis, it is expected that future mCRPC guidelines will recommend an even larger role for radionuclide and radioimmunotherapy.

Tagawa and colleagues should be commended for their work showing that 177Lu-J591-targeted radiotherapy has a measurable response rate in mCRPC. Prospective assessment of tumor targeting with radioimmunotherapy agents is also promising and should be further developed to better select patients and perhaps improve the therapeutic index of these agents. Survival was not the primary
endpoint of this study, and therefore, limited conclusions can be made regarding the impact of $^{177}$Lu-J591 on mCRPC natural history. As the authors suggest, randomized phase III data using $^{177}$Lu-J591–targeted radiotherapy are required to further develop this agent (1).

Although Tagawa and colleagues have reasonably shown the safety of $^{177}$Lu-J591 in a heavily pretreated patient population, there are concerns regarding hematologic toxicity with radioimmunotherapeutic use. Safety and efficacy data combining $^{177}$Lu-J591 with other therapies or administering it sequentially or in the salvage setting after docetaxel should be assessed. Rational selection of patients based on PSMA expression, perhaps using quantitative pretreatment imaging, is likely to prove desirable if PSMA expression level is found to correlate with response to PSMA-targeted therapy (1).

Although mCRPC remains an incurable condition and is projected to result in up to 29,720 deaths in the United States this year (10), several new agents have been developed over the past 5 to 10 years to treat this disease that are improving the outlook for this patient population. The results of Tagawa and colleagues suggest that radioimmunotherapy with targeted agents such as $^{177}$Lu-J591 is a promising new therapeutic strategy to explore (1).

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No potential conflicts of interest were disclosed.

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References
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