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

Charles B. Simone, II, MD, Stephen M. Hahn, MD

Department of Radiation Oncology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

Corresponding Author:
Stephen M. Hahn, MD

Address:
Hospital of the University of Pennsylvania
Perelman School of Medicine at the University of Pennsylvania
Perelman Center for Advanced Medicine
3400 Civic Center Blvd.
Department of Radiation Oncology, TRC 2 West
Philadelphia, PA 19104
Phone: 215-662-7296
Fax: 215-349-5923
Email: steve.hahn@uphs.upenn.edu

Running Head: Radioimmunotherapy for Prostate Cancer

Conflicts of Interest: None
Summary

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 Tawaga et al. support the continued clinical and preclinical development of radioimmunotherapy for solid tumors.

In this issue of Clinical Cancer Research, Tagawa and colleagues report their findings of a phase II study of lutetium-177-labeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody J591 (177Lu-J591) for metastatic castration-resistant prostate cancer (mCRPC) [1]. This is one of the few reported phase II studies of disease-specific single-agent radioimmunotherapy for solid malignancies and significantly advances this new era of targeted radiotherapy using disease-specific monoclonal antibodies.

Brachytherapy and external beam radiation therapy have well-established roles for definitive therapy of localized prostate adenocarcinoma [2]. However, radiotherapy for mCRPC has historically been solely for palliation. This role is expanding with recent interest in radionuclide and radioimmunotherapy. Although radioimmunotherapy is most established for non-Hodgkin’s lymphoma, its applications to solid malignancies have been limited. Prostate cancer, however, allows for a highly tumor-restricted antigen in PSMA, and mCRPC patients often have limited-volume disease confined to bone marrow and lymph nodes that is more easily accessed by circulating antibodies.

In the study by Tagawa et al., among 47 patients with PSA progression after hormonal therapies with or without chemotherapy treated at two centers with single administration of 177Lu-J591, 15 initially received 65mCi/m² and 32 subsequently received the maximum tolerated dose (MTD) of 70mCi/m². Overall, 10.6% experienced >50% PSA decline and 36.2% experienced >30% decline. This included 46.9% with >30% PSA decline among those treated at the MTD (n=32). Furthermore, 9/12 (75%) patients with radiographically measurable disease had some measure of disease control (1=partial response, 8=stable disease) and 8/12 (67%) assessed for circulating tumor cells (CTCs) had >50% decline in tumor cell counts 4-6 weeks after treatment.

Importantly, Tagawa et al. used post-administration imaging of 177Lu-J591 to assess tumor targeting. Also, 111In-J591 imaging was performed prior to 177Lu-J591 administration in selected patients. Overall, 93.6% had accurate targeting of known sites of disease compared to pre-treatment CT, MRI, and/or bone scans based on planar gamma camera imaging 3-7 days after 177Lu-J591 infusion. Furthermore, patients with imaging densities suggesting low PSMA expression were somewhat less likely to have PSA responses.

In an ad hoc analysis, median overall survival was significantly greater for patients receiving 70mCi/m² than 65mCi/m² (21.8mo vs. 11.9mo, p=0.03). This is similar to historical median survival of mCRPC of <2 years [3], and recent phase III trial reports for mCRPC [4-5]. Furthermore, patients with PSA declines had improved median survivals (22.2mo vs. 11.4mo, p<0.01). Notably, only a minority of patients had measurable disease, yet radioimmunotherapy still impacted survival compared to historical controls. The authors suggest that immune mechanisms may impact clinical outcomes independent of immediate tumor response; however, this mechanism cannot be confirmed with the current study.
Systemic radioisotope therapy with unsealed radiation sources like samarium-153 (β-emitter), strontium-89 (β-emitter), and radium-223 (α-emitter) can decrease PSA, reduce pain, improve quality of life, and even improve overall survival in mCRPC patients with bone metastasis [6-8]. In a groundbreaking radionuclide study, patients with mCRPC and multiple or painful bone metastases needing external beam radiotherapy were randomized to radium-223 or placebo. Radium-223 reduced bone-alkaline phosphatase concentration (p<0.0001), increased time to PSA progression (p=0.048), resulted in numerically fewer skeletal-related events (p=0.065), and increased median overall survival (65.3wks vs. 46.4wks, p=0.066; hazard ratio adjusted for baseline covariates 2.12 [1.13-3.98]) [9].

Radioimmunotherapy offers distinct advantages over other radionuclide therapies. PSMA, a non-secreted cell membrane protein, has expression highly restricted to prostate epithelium and is expressed in nearly all prostate cancers. J591 is a deimmunized monoclonal antibody against the extracellular domain of PSMA (Figure 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 anti-tumor effects from radiopharmaceutical accumulation adjacent to malignant cells or stroma and, therefore, do not appreciably treat extra-osseous 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 et al., may prove the superior option since it has a longer half-life, higher activity at the MTD, and is both a short-range (0.2-0.3mm) beta particle and gamma particle emitter, allowing for lower radiation dose to bone marrow.

Radionuclide therapy for prostate cancer is generally well tolerated, with reversible hematologic toxicities from samarium-153, strontium-89, and radium-223. Since a larger fraction of administered activity remains in various organs and body spaces, radioimmunotherapy has the potential of increased toxicity compared to radionuclide therapy. The specificity of tumor-specific PSMC monoclonal antibody is likely to mitigate this risk. Nonetheless, in the study by Tagawa et al., all 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. Higher rates were recorded in patients treated at 70mCi/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 2013 American Urologic Association guidelines, symptomatic mCRPC patients with good performance statuses are recommended to receive docetaxel chemotherapy, or otherwise mitoxantrone (evidence level grade B), ketoconazole (grade C), or radionuclide therapy (grade C). Additionally, radionuclides should be considered in mCRPC patients with poor performance statuses 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 United States Food and Drug Administration approval of radium-223 to treat mCRPC patients with symptomatic bony metastasis, it is expected that future mCRPC guidelines will recommend an even larger role for radionuclide and radioimmunotherapy.

Tagawa et al. should be commended for their work demonstrating 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 177Lu-J591 on mCRPC natural history. As the authors suggest, randomized Phase III data using 177Lu-J591-targeted radiotherapy are required to further develop this agent.

Although Tagawa et al. have reasonably demonstrated safety of 177Lu-J591 in a heavily pre-treated patient population, there are concerns regarding hematological toxicity with radioimmunotherapeutic use. Safety and efficacy data combining 177Lu-J591 with other therapies or administering it sequentially or in the salvage setting after docetaxol should be assessed. Rational selection of patients based on PSMA expression perhaps using quantitative pre-treatment imaging is likely to prove desirable if PSMA expression level is found to correlate with response to PSMA-targeted therapy.

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 5-10 years to treat this disease that are improving the outlook for this patient population. The results of Tagawa et al. suggest that radioimmunotherapy with targeted agents such as 177Lu-J591 is a promising new therapeutic strategy to explore.
References

Figure Legend

**Figure 1. Mechanism of cytotoxicity for 177Lu-J591.** Prostate-specific membrane antigen (PSMA) is a non-secreted cell membrane protein upregulated in nearly all prostate cancers. **Left** J591 is a deimmunized monoclonal antibody against the extracellular domain of PSMA. **Middle** J591 anti-PSMA is radiolabeled with lutetium-177 linked via a DOTA chelate to J591. **Right** When 177Lu-J591 binds to PSMA, lutetium-177 comes into close contact with prostate cancer cells and can achieve cytotoxic effects to both bone and soft tissue and visceral metastases via short-range beta and gamma emission.
Figure 1:

J591 anti-PSMA deimmunized monoclonal antibody

J591 anti-PSMA radiolabeled with lutetium-177

Beta and Gamma emission

Prostate cancer cell

PSMA molecule

© 2013 American Association for Cancer Research
Clinical Cancer Research

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

Charles B. Simone II and Stephen M. Hahn

Clin Cancer Res Published OnlineFirst August 7, 2013.

Updated version

Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-13-1540

Supplementary Material

Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2013/09/17/1078-0432.CCR-13-1540.DC1

Author Manuscript

Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts

Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions

To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.