

Molecular therapy of prostate carcinoma

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SUMMARY

Molecular imaging and therapy is based on a radiolabeled molecule that binds to a unique feature of a cell. Prostate Specific Membrane Antigen [PSMA] is a complex antigen with an extra-cellular, transmembrane and intra-cellular component that is uniquely expressed on prostate tissue and has a greater degree of expression on prostate carcinoma. The degree of PSMA expression increases with the degree of aggressiveness of the prostate carcinoma. A murine monoclonal antibody [termed J591] has been developed that binds to the extra-cellular epitope of PSMA with a high degree of affinity and specificity. It has been "humanized" and radiolabeled with the radionuclides Indium-111 [useful for imaging], Yttrium-90 [a radiometal that emits a beta particle which is potentially useful for targeted radionuclide therapy], and Lutetium-177 [which also emits a beta particle that is useful for targeted therapy as well as a gamma photon that can be imaged]. Over several years, physicians and scientists in nuclear medicine, urology and medical oncology have evaluated radiolabeled forms of hJ591 for therapy. In general, serum PSA has been used as evidence of recurrent and progressive disease in men with proven prostate carcinoma. The Maximum Tolerated Dose [MTD] for a single administration has been identified as 2.6 GBq (70 mCi)/m². At this dose, PSA responses have been seen in many patients. The response is very dose-dependant with fewer responses observed at 2.25 GBq/m². Accordingly, a dose fractionation protocol has been evaluated in which patients receive 2 doses, 2 weeks apart. The MTD for the fractionated protocol is 1.5 GBq/m² for a total dose of 3.0 GBq/m². Initial studies were performed in patients with advanced metastatic disease. More recently, additional protocols 1) to evaluate the potential efficacy of this therapy in patients with initial evidence of biochemical failure (i.e. rising PSA after initial therapy) and 2) to evaluate the incremental value of radiolabeled J591 as a supplement to Docetaxel chemotherapy.

Key words: Prostatic Neoplasms; Molecular Targeted Therapy; Prostate-Specific Antigen; Antibodies, Monoclonal; Diagnostic Imaging; Radioisotopes

The development of a radioimmunotherapy regimen for the treatment of any tumor begins with the identification of a target protein that can serve as an antigen. Some years ago, a transmembrane protein termed Prostate Specific Membrane Antigen [PSMA], which appears to be specific to the prostate gland, was identified. PSMA is a surface antigen expressed on all prostate cancer cells. PSMA is distinct from Prostate Specific Antigen [PSA] which is a prostate derived protein that is shed into the circulation. Serum PSA is elevated in benign prostatic enlargement as well as in prostate carcinoma. Despite this non-specific feature, PSA is useful as a biomarker for the detection and monitoring of prostate carcinoma. PSMA expression increases progressively in higher grade tumors, as well as metastatic disease and hormone-refractory prostate cancer and hence provides a target for molecular imaging and therapy. A variety of antibodies were developed by the murine hybridoma monoclonal antibody production method. Some time ago, physicians and medical scientists at the New York Presbyterian Hospital-Weill Cornell Medical Center identified one of these antibodies, J591, for further evaluation as a vehicle for radioimmunotherapy of prostate carcinoma. J591 binds to the **extra**cellular domain of PSMA of viable PSMA positive cells and is rapidly internalized following antibody-antigen interaction. PSMA is expressed on the neo-vasculature of other solid tumors but not on normal tissue. For trials in patients, the immunoglobulin was rendered "non-immunogenic", that is 90-95% of the murine backbone was replaced with human immunoglobulin while retaining the immunorecognition portion, preserving the immunoreactivity (binding to PSMA) of the modified molecule.

CHOICE OF RADIOLABEL

Since the PSMA-J591 antigen-antibody complex is rapidly internalized, a radiometal was chosen as the radiolabel. A radiometal, if digested from the immunoglobulin, is insoluble in the intracellular environment and will remain within the cell. Amongst the radiometals, Lutetium-177 [¹⁷⁷Lu] was chosen over Yttrium-90 since the longer half life (6.7 days vs 64 hrs) was advantageous as the biologic half life of the immunoglobulin was at least 7 days and the lower β -energy of ¹⁷⁷Lu might afford an advantage in the treatment of micrometastatic disease. (0.49 Mev vs 2.3 Mev). DOTA was used as a chelating moiety. In addition, ¹⁷⁷Lu has a γ emission that can be imaged with traditional nuclear medicine equipment to demonstrate targeting (Figure 1).

DOSE ESCALATION TRIAL AND SELECTION OF MAXIMAL TOLERATED DOSE

The initial clinical trial with ¹⁷⁷Lu-DOTA-J591 was a Phase I dose escalation trial performed in patients with metastatic castrate resistant prostate cancer. A total of 35 patients received a dose of 370 MBq-2.78 Gbq/m² with a total of 20 mg immunoglobulin. Dose limiting toxicity was observed at the highest dose level resulting in selecting 2.6 GBq/m² as the maximal tolerated dose [MTD]. Overall, 6 patients had a greater than 50% decline in serum PSA. In 31% (10 of 31 patients), there was at least a 30% decline in PSA. 34% of the patients had stabilization of previously rising PSA values. Accurate targeting of known sites of disease was observed in 94% (30/32) of patients. Human anti-human antibody [HAHA] was not observed in any patient.

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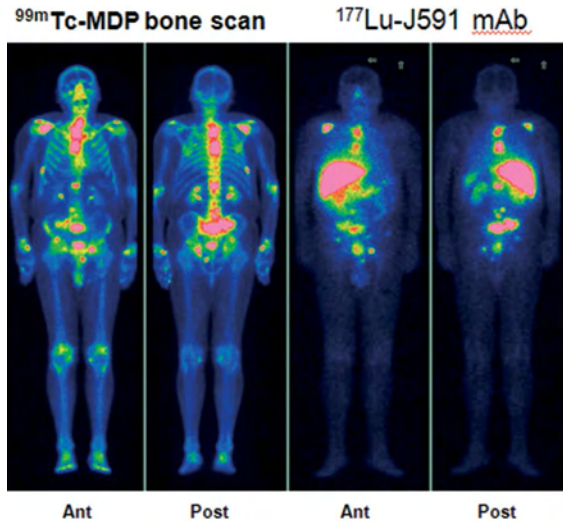


Figure 1. ^{99m}Tc -MDP bone and ^{177}Lu -J591 scintigraphy demonstrating multiple sites of osseous metastases on bone imaging as well as degenerative and arthritic changes in the upper and lower extremities. The ^{177}Lu -J591 image is obtained 3-5 days after the infusion of the therapy dose. Targeting of metastatic disease by the radiolabeled antibody is identified in multiple osseous sites as well as areas of soft tissue involvement. Degenerative osseous lesions are not seen but there is non-specific uptake in the hepatic parenchyma, the usual site of metabolism of globulin.

In a follow-up Phase II study at the 2 highest tolerated dose levels, the overall favorable results were again observed but with a greater fraction of patients achieving evidence of response at the MTD. Accordingly, it was decided to evaluate whether a fractionated dose schedule would permit a greater total dose administered and possibly a more sustained response (Figure 2).

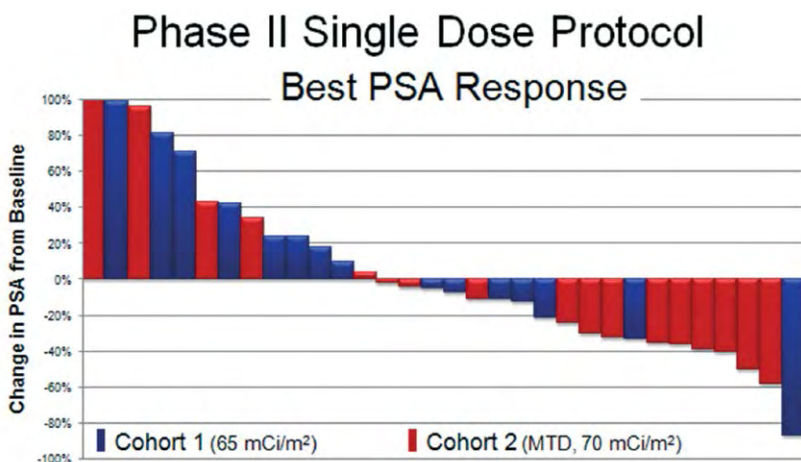


Figure 2. So-called “water-fall” plot demonstrating change in serum PSA from baseline in 32 patients receiving 65 or 70 mCi/m^2 in a single dose administration protocol. Although a prior Phase I study had demonstrated that 70 mCi/m^2 was the Maximal Tolerated Dose, the investigators were asked to evaluate 15 patients at the slightly lower dose level (65 mCi/m^2) to confirm safety before going on to the previously determined MTD of 70 mCi/m^2 . The PSA responses vary but the overall impression is that the higher dose is more effective as assessed by PSA response. This finding provoked the conclusion that the tumor response was quite sensitive to the radiation absorbed dose and suggested 2 points for further study. 1. Would a fractionated dose schedule allow for a greater total dose administered? 2. Are the differences in the responses observed a consequence of variable degrees of targeting?

FRACTIONATED DOSE TRIAL

The trial consisted of 3-6 patients per cohort receiving 2 doses of 74 MBq/m^2 of ^{177}Lu -DOTA-J591 2 weeks apart. After confirming safety at each level, the dose was escalated in subsequent patients by 16 MBq/m^2 increments. The primary goal was to determine the MTD with secondary goals to determine the pharmacokinetics, biodistribution and dosimetry as well as to assess targeting on images and any clinical or biomarker response. Twenty-eight patients with a median age of 72 years (range 57 to 86) were studied. The median PSA value was 49 (range 2.0-766.5). 85% of the patients had skeletal involvement and 46% had soft tissue lesions. All had progressed despite hormonal therapy and approximately half had progressed despite chemotherapy (docetaxel or docetaxel plus other agents). Grade 4 thrombocytopenia was observed in 21% of the patients but no patient had significant bleeding. Two patients required platelet transfusions. Grade 4 neutropenia was observed in only 11% of the patients. There were no febrile consequences. Mild transaminitis was seen in 29%. Approximately one in 3 patients had a mild reaction to the infusion itself (flushing, chills) but most were transient and all were reversible. The patients had not been premedicated with anti-histamines or anti-pyretic medication. A decline of the serum PSA was observed in 58% of the patients (Figure 3).

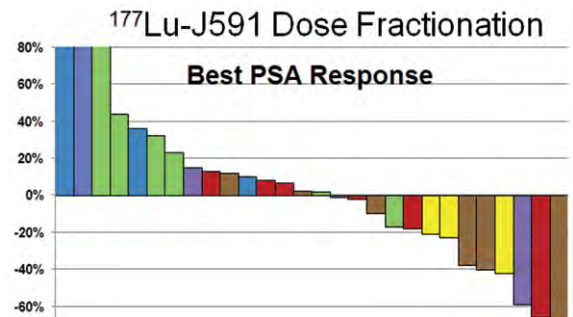


Figure 3. “Water-fall” plot of PSA response in a Phase I Fractionated Dose Escalation Trial. Patients received 2 doses 2 weeks apart at a fixed level, initially set at 20 mCi/m^2 incrementing by 5 mCi/m^2 in subsequent cohorts of 3 patients after demonstration of safety at the preceding dose level. As expected, trend toward better responses at the higher cumulative dose. 40 $\text{mCi}/\text{m}^2 \times 2$ (Total: 80 mCi/m^2) was determined to be MTD. A Phase II trial at this level is currently underway.

SUMMARY AND CONCLUSION

Fractionated therapy with ^{177}Lu -DOTA-J591 is well-tolerated and allows administration of a greater total amount of radioactivity than a single dose protocol. Dose fractionation of ^{177}Lu -J591 monoclonal antibody demonstrates reduced bone marrow toxicity and has the potential to increase the total cumulative dose that can be administered for radioimmunotherapy. Some myelosuppression is observed but it is readily managed and is reversible. In the fractionated dose scheme, the cumulative dose of radioactivity exceeds the single dose MTD of ^{177}Lu -DOTA-J591. Successful targeting of known sites of metastatic disease occurs in the majority of patients. Overall, decline of serum PSA values have been seen despite a potentially suboptimal ^{177}Lu -J591 dose administered to a significant fraction of the patient population with bulky metastatic disease in the single and divided dose escalation trial.

A phase I study of ^{177}Lu -J591 fractionated radioimmunotherapy in combination with docetaxel has begun enrollment based on improved tolerability of fractionated dose radioimmunotherapy scheme plus the radiosensitizing and debulking properties of docetaxel. Currently, ^{90}Y -DOTA-J591 which has a higher energy β emission than ^{177}Lu -DOTA-J591 is being considered for treatment of larger masses.

Conflict of interest

We declare no conflicts of interest.

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