The role of 225Ac-PSMA-617 in chemotherapy-naive patients with advanced prostate cancer: Is it the new beginning

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SUMMARY

The treatment of metastatic castrate-resistant prostate cancer (mCRPC) includes abiraterone acetate, enzalutamide or docetaxel chemotherapy along with androgen ablation. However, the response to these agents is often short lived and not complete. Prostate-specific membrane antigen (PSMA) is overexpressed in metastatic prostate cancer and has been found to be a suitable target for imaging and therapy. The ^{225}Actinium labeled derivative, ^{225}Ac-PSMA-617, has shown a remarkable therapeutic efficacy in mCRPC patients.

Sathekge *et al.*[1] performed a study with a treatment group consisting of patients who relapsed after the initial therapy and presented with metastatic prostate carcinoma. Inclusion criteria included Eastern Cooperative Oncology Group score 2 or lower, a life expectancy of 6 months or more, widespread metastatic disease precluding treating with radiotherapy, patients' refusal of chemotherapy or hormonal therapy, and lack of access to second-generation anti-androgen therapy (abiraterone and enzalutamide). All patients underwent ^{68}Ga-PSMA-11 positron-emission tomography/computed tomography (PET/CT) before ^{225}Ac-PSMA-617 treatment to look if the lesions were PSMA avid.

The initial administered activity was 8 MBq. Administered activity was de-escalated in subsequent treatment cycles to 7, 6, or 4 MBq based on the response to earlier administered treatment and repeated after every 8 weeks. Response to the treatment was seen by serum prostate-specific antigen (PSA) and ^{68}Ga-PSMA-PET/CT imaging. PSA was obtained at the beginning and then monthly, and ^{68}Ga-PSMA-PET/CT was repeated every 8 weeks (before each subsequent cycle of treatments was administered) and every 12 weeks after completion of the treatment until disease progression.

Good antitumor activity as assessed by serum PSA level, and ^{68}Ga-PSMA-PET/CT was seen in 16/17 patients. In 14/17 patients, PSA decline ≥ 90% was seen after treatment, including seven patients with undetectable serum PSA following two (2/7) or three cycles (5/7) cycles of ^{225}Ac-PSMA-617. Fifteen of 17 patients had a >50% decline in lesions avidity for tracer on ^{68}Ga-PSMA-PET/CT including 11 patients with complete resolution (PET-negative and either stable sclerosis on CT for bone or resolution of lymph node metastases) of all metastatic lesions.[1] There were side effects in the form of xerostomia, bone marrow toxicity, and renal toxicity.

COMMENTS

The treatment of mCRPC is still evolving. This study gives options of using receptor-targeted therapy. Various agents used till date are tabulated in the following Table 1.[2]

PSMA-617 had been labeled with radioisotope Lu-117 (beta emitter) and Ac-225 (alpha emitter) for radioligand therapy. 225Ac-PSMA-617 is more effective for chemotherapy naïve mCRPC. These patients need to be under close scrutiny during treatment due to its toxicity to the liver, kidney, and bone marrow. In a similar earlier study by Kratochwil *et al.*,[3] 24 (63%) men had a PSA decline of more than 50% and 33 (87%) had a PSA response of any degree. The median duration of tumor control under 225Ac-PSMA-617 last-line therapy was 9.0 months, and five patients had an enduring response of more than 2 years.

Remission could be achieved with ^{225}Ac-PSMA-617 (targeted alpha therapy) receptor ligand therapy in chemotherapy-naïve patients with advanced metastatic prostate carcinoma. Remarkable therapeutic efficacy could be achieved with reduced toxicity to salivary glands due to a strategy of de-escalation of administered activities in the second and third treatment cycles. There is only a limited amount of presently available isotope and that too produced by only a few centers in the world.[4] The availability of the treatment and the cost is an issue.

Table 1: Various studies and agents/drugs in the treatment of mCRPC

Study	Drug used	Comparison	Selection criterion	OS in months	PFS	PSA reduction
COU-AA-302 Ryan CJ *et al*., 2013	Abiraterone + prednisone	Placebo + prednisone	No previous docetaxel ECOG 0-1 PSA or radiographic progression No or mild symptoms No visceral metastases	34.7 versus 30.3	16.5 versus 8.3	>50% in 62%
PREVAIL Beer TM *et al*., 2014	Enzalutamide	Placebo	No previous docetaxel ECOG 0-1 PSA or radiographic progression No or mild symptoms 10% had visceral metastases	32.4 versus 30.2	20.0 versus 5.4	>50% in 78%
Kantoff PW *et al*., 2010	Sipuleucel-T	Placebo	Some with previous docetaxel ECOG 0-1 Asymptomatic or minimally symptomatic	25.8 versus 21.7	3.7 versus 3.6	>50% in 26%
Parker *et al*., 2013	Radium-223	Placebo	Previous or no previous docetaxel ECOG 0-2 Two or more symptomatic bone metastases No visceral metastases	14.9 versus 11.3	NA	>30% in 16%
deBono *et al*., 2010	Cabazitaxel + prednisone	Mitoxantrone + prednisone	Previous docetaxel ECOG 0-2	15.1 versus 12.7	2.8 versus 1.4	NA
Kratochwil *et al*.[3]	225Ac-PSMA-617		chemotherapy naïve mCRPC			>50% in 63%

mCRPC=Metastatic castrate resistant prostate cancer, PSA=Prostate-specific antigen, OS=Overall survival, PSMA=Prostate-specific membrane antigen, NA=Not available, ECOG=Eastern Cooperative Oncology Group

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