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# 225Ac-PSMA-617 in chemotherapy-naive patients with advanced prostate cancer

Purpose: 225Ac- Prostate-specific membrane antigen (PSMA)-617 is a highly promising novel compound for therapy of prostate cancer. A remarkable therapeutic efficacy has been demonstrated in heavily pre-treated metastatic castration-resistant prostate cancer (mCRPC) patients, with xerostomia as the main side effect. A promising strategy for minimization of side effects is based on optimization of the dosing regime while maintaining sufficient therapeutic efficacy for several cohorts of patients, including chemotherapy-naïve patients.

Subjects & Methods: Fifty-seven patients with progressive advanced prostate cancer that had exploited established first-line or second line therapies available in South Africa or that were not eligible or refused certain established therapies were selected for treatment with 225Ac-PSMA-617 on the basis of compassionate use. Therapy was performed in 2 months intervals, with initial dose of 8 MBq (or 10 MBq in case of very advanced disease, superscan), then de-escalation to 6 or 4 MBq in case of good response. The patients were divided into two groups: A: patients that have undergone standard therapy (surgery, radiation therapy and androgen deprivation) and some second line therapies (N=17). B: patients that have undergone only standard therapy or only parts (N=40), while some patients were completely treatment naïve (n=10). Prostate-specific antigen (PSA) and blood cell count were measured every 4 weeks. Monitoring and follow-up included Eastern Cooperative Oncology Group score, pain symptoms, treatment-related toxicity, PSA-response and ALP-response. 68Ga-PSMA-PET/CT was used for baseline staging and imaging follow-up every 8weeks.

Results: Good antitumor activity by means of objective radiologic response or tumor marker decline was observed in 71% of patients in group A while a remarkable 92% response rate was observed in group B. Chemotherapy-naïve patients exhibited significantly increased rate of response, and of complete response. Both groups presented with significant palliation of bone pain and reduced toxicity to salivary glands due to de-escalation. These interim results also show a favourable hematological and renal toxicity profile and quality of life improvements.

Conclusion: The remarkable therapeutic efficacy of 225Ac-PSMA617 reported earlier is confirmed with even better clinical outcomes in chemotherapy-naive advanced prostate cancer patients treated. Reduced toxicity to salivary glands due to de-escalation should be further explored for informing clinical practice and clinical trial design.

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