Uroscan

VISION trial: ^{177}Lu-PSMA-617 for progressive metastatic castration-resistant prostate cancer

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SUMMARY

The VISION trial[1] evaluated the advantages of ^{177}Lu-PSMA-617 over best supportive care in improving the overall survival and image-based progression-free survival in patients with progressive metastatic castration-resistant prostate cancer (mCRPC). This was an international, multi-centric, phase three, open-label, randomized trial that recruited mCRPC patients who progressed even after receiving both androgen-receptor-pathway inhibitors (abiraterone or enzalutamide) and either one or two taxane regimens.

A total of 831 patients were included in the study. Subjects were assigned randomly into either ^{177}Lu-PSMA-617 + standard care or standard care alone in 2:1 ratio. Five hundred and fifty-one patients were allotted to the ^{177}Lu-PSMA-617 group and 280 patients to the standard care group. 7.4GBq of ^{177}Lu-PSMA-617 was given every 6 weeks in 4–6 cycles to the patients in the first group. The primary outcome initially was only overall survival. Image-based progression-free survival was added as the second primary outcome after amending the initial protocol. Secondary outcome measures were objective response (based on RECIST, version 1.1), the safety profile of the drug, and health-related quality-of-life (Functional Assessment of Cancer Therapy–Prostate score), pain scores (Brief Pain Inventory Short Form [BPI-SF] score), and prostate-specific antigen (PSA) response. Adverse reactions were recorded from the day of initiation of the intervention to 30 days' poststoppage of the drug or initiation of a second-line drug. All the patients randomized in the study had a positive PSMA gallium-68–labeled PSMA-11 PET scans.

There was a significant improvement in the overall survival in the patients who received ^{177}Lu-PSMA-617 and standard care compared to standard care alone (15.3 months vs. 11.3 months; hazard ratio [HR] - 0.62; 95% confidence interval [CI] - 0.52–0.74; $P < 0.001$). The second primary endpoint, image-based progression-free survival, also showed significant improvement in the patients who received ^{177}Lu-PSMA-617 (HR - 0.40; 95% CI - 0.29–0.57; $P = 0.008$). Although a higher incidence of adverse effects was seen in the intervention group (52.7% vs. 38%), the quality of life remained the same with no significant changes. The longer treatment duration (7.6 months vs. 2.1 months) might have influenced this. Adverse effects such as fatigue (43%) and dry mouth (38%) were most commonly seen in the treatment group. There was a higher incidence of complications (grade three and above in severity) in the patients who had received ^{177}Lu-PSMA-617. Around 46% (vs. 7.1% in control group) of the patients had >50% reduction and >33% (vs. 2% in control group), patients had >80% reduction in the PSA levels.

COMMENTS

With a large sample size (n = 831) and long follow-up (20.9 months), a significant improvement in the overall survival and radiographic progression-free survival was noted with ^{177}Lu-PSMA-617 in this study. Although several prospective trials and small randomized trials tried to establish this, they were limited by their study design and small sample size.[2,3] Seminal research was conducted in mCRPC patients using ^{177}Lu-PSMA-617 in the Indian population, which demonstrated its effectiveness and better safety profile [Table 1].[3-5] However, this can be utilized only in mCRPC patients with positive PSMA scans, and nearly 85% of the mCRPC patients have PSMA-positive scans. The degree of positivity correlates with reduced overall survival. Thus, ^{177}Lu-PSMA-617 has the potential to be invaluable in the treatment of this patient subset.

Ninety percent of the patients with mCRPC will have bone metastasis, and nearly half of the cases will develop a critical skeletal event within 2 years.[1] ^{177}Lu-PSMA-617 showed a significant delay in the occurrence of symptomatic bone lesions. There was significant delay in the worsening of FACT-P (5.7 months vs. 2.2 months) and BPI-SF (5.9 months vs. 2.2 months) scores which demonstrates better quality of life despite the higher incidence of adverse events.

The study population is very heterogeneous, including patients with a wide range of treatment histories for varied durations. Although the control group had received

Table 1: Various trials on ^{177}Lu-PSMA617 in metastatic castration resistance prostate cancer

Study	VISION trial[1]	TheraP trial[2]	Yadav *et al*.[3]
Interventional drug	^{177}Lu-PSMA617	^{177}Lu-PSMA617	^{177}Lu-PSMA617
Control	Standard therapy alone	Cabazitaxel	-
Study population	Progressive mCPRC who already received ADT along with taxane regimen	mCRPC patients who already received ADT	Progressive mCRPC patients on ADT and/or taxane chemotherapy
Study design	Phase 3, RCT	Phase 2 unblinded RCT	Single-arm prospective study
Sample size	831	200	90
Allotment	2:1	1:1	-
Primary outcome	OS IB-PFS	PSA response	OS
IB-PFS	8.7 months versus 3.4 months		
OS	15.3 months versus 11.3 months	Yet to report	14 months
PSA response rate	46% versus 7.1% (>50% response) 33% versus 2% (>80% response)	66% versus 37%	45% at the end of assessment
Adverse events (Grade 3-4)	52.7% versus 38%	33% versus 45%	No adverse events

IB-PFS=Imaging-based progression-free survival, OS=Overall survival, RCT=Randomized control trial, ADT=Androgen deprivation therapy, mCRPC=Metastatic castration resistance prostate cancer, PSA=Prostate-specific antigen

supportive care, most of the patients received anti-cancer therapies, including glucocorticoids and androgen deprivation therapy. The lack of standardization of the standard treatment regimens in both the arms and the heterogeneous patient treatment profiles can be considered additional limitations. Furthermore, patients received varied number of lutetium cycles (4 + 2 cycles in a few patients and four cycles in few patients) in the treatment arm, which were not mentioned in the results section.

The mean survival rate of patients with mCRPC is only 9–36 months, with the cancer-specific mortality being driven by the resistance to hormonal therapy.[1] Thus, there is an imperative need for formulating an effective intervention for this population subset. With this largest prospective randomized trial till date showing favorable results, ^{177}Lu-PSMA-617 stands as a new ray of hope in patients with progressive PSMA-positive mCRPC. Nevertheless, the agent's availability and the associated costs with the treatment are a significant hindrance for its extensive utilization in progressive mCRPC.

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Received: 04.07.2021, **Revised:** 18.09.2021,
Accepted: 22.09.2021, **Published:** 01.10.2021
Financial support and sponsorship: Nil.
Conflicts of interest: There are no conflicts of interest.

Access this article online	
Quick Response Code:	**Website:** www.indianjurol.com
	DOI: 10.4103/iju.iju_292_21

How to cite this article: Rohith G. VISION trial: ^{177}Lu-PSMA-617 for progressive metastatic castration-resistant prostate cancer. Indian J Urol 2021;37:372-3.