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Benefit of cabazitaxel in previously treated metastatic castration-resistant prostate cancer; CARD trial

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SUMMARY

The CARD trial,[1] was designed to compare cabazitaxel with androgen signaling inhibitors (abiraterone or enzalutamide) in patients with metastatic castration-resistant prostate cancer (mCRPC) who progressed after having received docetaxel for at least three cycles This trial was randomized and open labeled, spread over 62 sites across 13 countries in Europe. A total of 255 subjects were randomized to receive cabazitaxel (129) and androgen signaling inhibitor (126). None had received any prior therapy besides abiraterone/enzalutamide and docetaxel for carcinoma prostate.

The primary objective was to compare the radiographic progression-free survival (rPFS) with cabazitaxel versus enzalutamide or abiraterone. Progression was defined using Response Evaluation Criteria in Solid Tumors 1.1 for tumor lesions and Prostate Cancer Working Group 2 criteria for bone scan lesions or death. The secondary objectives were to compare the efficacy for prostate-specific antigen (PSA) response rate (fall of PSA of at least 50% from baseline), progression-free survival (PFS), overall survival (OS), and tumor response rate.

Cabazitaxel (25 mg) was administered intravenously over 1 h, every 3 weeks with oral prednisone 10 mg daily. The other arm received abiraterone (1000 mg daily with oral prednisone 5 mg twice daily) or enzalutamide (160 mg orally once daily). The treatment continued until there was an imaging-based progression of disease, unacceptable side effects, discontinuation, or start of a new therapy. The results of the trial are given in Table 1.

Cabazitaxel led to a significant longer OS (13.6 m vs. 11 m), PFS (4.4 m vs. 2.7 m), and rPFS (8 m vs. 3.7 m) than abiraterone or enzalutamide among patients with mCRPC in post-docetaxel setting. Cabazitaxel was also shown to improve other secondary end points.

COMMENTARY

Taxanes bind microtubules, promoting their stabilization and preventing cellular mitosis and division, and have a role in preventing androgen receptor (AR) nuclear translocation. The beneficial role of cabazitaxel in mCRPC in post-docetaxel setting is known.[2] The reason is because of its poor affinity for drug efflux pump, p-glycoprotein 1, which is a frequent cause of drug resistance in docetaxel. However, there is a dearth of studies comparing the efficacy of cabazitaxel versus abiraterone or enzalutamide in patients progressing on docetaxel or abiraterone or enzalutamide.

The results of the present trial are in agreement with previous studies that show poorer outcomes with a second androgen signaling targeted inhibitor probably because these agents target the same pathway and hence share the mechanism of resistance too.[3] Meanwhile, taxanes due to their different mechanism of action can overcome several mechanisms of resistance.[4] This may also be related to greater intra-tumoral penetration of cabazitaxel and retainment of its activity compared to docetaxel.[5] The AR variant-7 (AR-V7) immunohistochemical detection was not used in the study and would have been a useful addition, as taxanes are more efficacious than androgen signaling inhibitors for AR-V7-positive castration-resistant prostate cancer.

Access to cabazitaxel is low in India due to high cost and patient opting for the nonchemotherapy alternative of

Table 1: Result's of the card trial

Parameters	Cabazitaxel arm	Abiraterone/enzalutamide arm	*P*
Median imaging-based progression-free survival in months	8	3.7	<0.001
Median progression-free survival in months	4.4	2.7	<0.001
Fall of PSA of at least 50% from baseline (%)	35.7	13.5	<0.001
Tumor response (%)	37	12	0.004

PSA=Prostate-specific antigen

abiraterone/enzalutamide, which is easy to administer and requires less stringent monitoring. There is a need for more prospective trials in patients progressing on docetaxel therapy to to garner stronger evidence on whether to switch classes of drugs to an androgen pathway agent or a bone-targeted therapy versus stay on a cytotoxic chemotherapy.

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