Editorial Commentary

Nanoparticles as theranostic vehicles in prostate cancer

Rafael Morales-Barrera, Cristina Suárez, Joaquín Mateo, Macarena González, Joan Carles

Vall d'Hebron Institute of Oncology, Vall d' Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain

Correspondence to: Joan Carles, MD, PhD. Director GU, CNS and Sarcoma Program, Department of Medical Oncology, Vall d'Hebron University Hospital, Passeig Vall d'Hebron 119-129, 08035-Barcelona, Catalonia, Spain. Email: jcarles@vhio.net.

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Prostate cancer (PCa) is the second most common tumor in men with more than 1.3 million cases diagnosed and more than 350,000 deaths estimated to occur in 2018 (1). Androgen deprivation therapy (ADT) is the cornerstone in the management for metastatic PCa. However, ADT is not curative and most of the patients will develop metastatic castration-resistant prostate cancer (mCRPC) during the next two years after ADT. Approved drugs for mCRPC include second-generation androgen receptor inhibitors (abiraterone acetate and enzalutamide) (2-5), immunotherapy like sipuleucel-T (6), alpha-emitting radiotherapeutic drug (Radium 223) (7) and chemotherapies including docetaxel and cabazitaxel (8-10).

Docetaxel, a cytotoxic taxane, is an antimicrotubule agent that promotes and stabilizes microtubule assembly, disrupting microtubule dynamics, which are sufficient to induce mitotic arrest in G2/M (8). Also, it has been reported that docetaxel is able to modulate androgen receptor (AR) expression and modulate its trafficking from the cytoplasm to the nucleus (11). In 2004, docetaxel plus prednisone was the first FDA approved therapy for the treatment of mCRPC improving overall survival (OS) and pain palliation compared with mitoxantrone plus prednisone in two large phase III studies. (8,9). Also in the last years, it has been demonstrated the survival benefit when docetaxel is added to ADT in patients with metastatic hormone-sensitive PCa patients (12,13).

Over the last decades, the nanothecnology in cancer therapy is providing significant opportunities to develop novel and effective treatments, particularly improving drug delivery and tumor drug-exposure. Among a wide variety of nanosystems, Doxil®, Myocet®, Depocyt®, Genexol-PM® are approved for use in the treatment of cancer (14). BIND-014 is a targeted nanoparticle (NP) with diameter of 100nm improving the delivery of docetaxel in cancer cells. BIND-014 binding to prostate-specific membrane antigen (PSMA), a cell-surface protein that is overexpressed on PCa cells (15).

Nanothecnology is an emerging and promising field for PCa. Autio *et al.* conducted a phase II clinical trial among patients with mCRPC treated with BIND-014, the first targeted polymeric nanoparticle containing docetaxel (16). The median radiographic progression free survival (rPFS) was 9.9 months (mo) (95% CI, 7.1–12.6 mo) that was better than the prespecified in the trial design (rPFS ≥6 mo). Despite the potential benefits of nanoparticles, the safety profile of BIND-014 is similar to docetaxel in terms of rates of grade 3/4 hematoxicity, fatigue and neuropathy, and no unexpected toxicities were observed (8,16). However, BIND-014 is associated with less nonhematological (diarrhea, decreased appetite). Tumor responses were higher with BIND-014 (32%) compared with docetaxel every three weeks (12%), whereas PSA response observed with BIND-014 were lower (30% *vs.* 45%) (8,16). The role of circulating tumor cells (CTCs) as independent adverse prognostic factor of OS in mCPRC has been demonstrated in two prospective phase 3 studies evaluating docetaxel (17,18). Autio *et al.*, reported a conversion from unfavorable CTC (≥5 cells per 7.5 mL) counts to favorable counts (<5 cells per 7.5 mL) in 50% of the patients, which is comparable to data from the SWOG S4021 trial. Interestingly, they evaluated

18 patients with CTCs that expressed PSMA (based on the Epic Sciences platform), 61% of those patients had PSMA-positive CTCs. High PSMA-positive CTC counts at 3 and 9 weeks were associated with worse rPFS (1.84 *vs.* 5.82 mo). These findings suggest the potential role of PSMA-positive CTCs in identifying patients who are not getting benefit of BIND-014.

This study provides an excellent clinical utility of nanoparticle therapeutics for PCa therapy specifically PSMA overexpression on the surface on PCa cells. On the other hand, the characterization of PSMA-positive CTCs can be a useful tool for the identification of patients who respond or not to PSMA-targeted therapies. However, the lower prevalence of PSMA expression in CTC (16), the intrapatient heterogeneity (14) and the effect of ADT on PSMA PET/CT is highly dependent on the castration sensitivity (19) are the main challenges for the development of this diagnostic test that can provide useful information about treatment decision in real life evaluations.

The implementation of radiolabelled compounds targeting (PSMA) for diagnostic and therapeutic approaches is a key challenge to overcome in the management for PCa patients. Recently, the correlation between PSMA PET/CT in metastatic PCa patients and clinical response to chemotherapy showed promising results for evaluation of treatment response (20,21).

Expression of PSMA is an important prerequisite for future prospective clinical trials in mCRPC patients and opens a window of opportunity of how we should evaluate the clinical impact of PSMA expression in CTC for patients with advanced PCa and/or early stage of the disease.

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Footnote

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