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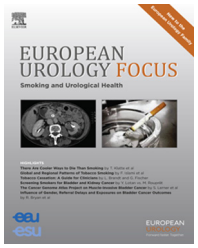

Review – Prostate Cancer

Optimal Treatment Sequence for Metastatic Castration-resistant Prostate Cancer

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Abstract

Context: Unprecedented development of therapeutics for prostate cancer in recent years has left clinicians with the challenge of adequately sequencing therapeutic agents to optimise patient benefit. No clear guidelines exist on optimal treatment sequences.
Objective: To summarise the evidence on first-line activity, cross-resistance, and potential combinations of agents approved for metastatic castration-resistant prostate cancer (mCRPC).
Evidence acquisition: A nonsystematic literature search of articles on agent sequencing in mCRPC in PubMed and relevant cancer conferences up to June 2016 was performed.
Evidence synthesis: No definitive evidence on the optimal mCRPC treatment sequence exists. Hormonal agents are preferred for first-line treatment on the basis of favourable toxicity, but no evidence of superiority over chemotherapy exists. Evidence suggests significant cross-resistance between agents in first- and second-line settings. The impact of prior chemotherapy in metastatic hormone-sensitive disease is unknown. No combinations have proven benefit to date. Molecular biomarker assessment in liquid biopsies may aid selection of treatment in the near future.
Conclusions: It is unlikely that a single sequence will be adequate for all mCRPC patients. An individualised strategy that assesses the biological mechanisms of the disease and monitors molecular drivers of progression and resistance to treatment is required to maximise benefit for each patient and bring us closer to the goal of best care.
Patient summary: In this review we summarise evidence on the optimal sequence of anticancer drugs for metastatic castration-resistant prostate cancer. No agent has proven superior to another as front-line treatment, and the exact impact of prior treatments on drug efficacy is unknown. Better biomarkers for treatment selection and evaluation of response to treatment will be needed to personalise the optimal sequence for each individual patient.

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1. Introduction

Advanced prostate cancer is a major cause of cancer morbidity and mortality worldwide. Although initially sensitive to androgen deprivation therapy (ADT), progression despite castrate levels of testosterone eventually occurs, and patients enter the lethal castration-resistant (CRPC) phase of the disease. Since its approval in 2004, docetaxel was the only agent until 2010 that had proven survival benefit in metastatic CRPC (mCRPC) [1]. After 2010, however, the

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approval of five new agents with survival benefit revolutionised the therapeutic landscape for the disease (Table 1) [2–8]. Most of the trials evaluating novel agents were developed in patient populations that had only received docetaxel, and no evidence on their clinical activity when given sequentially is available. Furthermore, trials evaluating the activity of some of these agents in earlier stages of the disease could significantly change the landscape in the near future.

Adequate evidence on how to effectively sequence and combine therapies in CRPC is necessary to optimise benefit to patients suffering from this disease. There is a need to develop predictive biomarkers for treatment selection based on disease biology, and treatment response biomarkers to assess therapeutic benefit and allow early changes in treatment for nonresponding patients.

Here we synthesise current evidence on the optimal sequence of agents in CRPC, as well as the potential role of

Table 1 – Phase 3 trials in metastatic castration-resistant prostate cancer

Trial	Experimental arm	Control arm	Primary endpoint	Secondary endpoints	Comments
Hormonal agents					
COU-301 [3] (n = 1195)	Abiraterone 1000 mg OD + prednisone 5 mg BD	Prednisone 5 mg BD + placebo	OS 14.8 vs 10.9 mo (HR 0.65; $p < 0.001$)	Time to PSA progression; PSA response rate; rPFS	Post-docetaxel
AFFIRM [5] (n = 1199)	Enzalutamide 160 mg OD	Placebo	OS 18.4 vs 13.6 mo (HR 0.63; $p < 0.001$)	PSA response rate; pain response rate; quality of life (EQ-5D); PSA-PFS; rPFS; time to first SRE	Post-docetaxel population; patients with risk factors for seizures excluded
COU-302 [4] (n = 1088)	Abiraterone 1000 mg OD + prednisone 5 mg BD	Prednisone 5 mg BD + placebo	rPFS (PCWG2) 16.5 vs 8.3 mo (HR 0.53; ($p < 0.001$) OS NR vs 27.2 mo (HR 0.75; $p = 0.01$)	Time to opiate use; time to initiation of cytotoxic chemotherapy; time to ECOG PS decline; PSA response rate; radiographic response rate; quality of life	Co-primary endpoints OS + rPFS; chemotherapy-naïve patients; no visceral metastases included; OS did not meet prespecified significance criteria
PREVAIL [6] (n = 1715)	Enzalutamide 160 mg OD	Placebo	32.4 vs 30.2 mo (HR 0.7; $p < 0.0001$)	Time to initiation of cytotoxic chemotherapy; time to first SRE	Chemotherapy-naïve patients; 11% with visceral disease; patients with risk factors for seizure were excluded
Chemotherapy					
TAX 327 [1] (n = 1006)	Docetaxel 75 mg/m^2 every 3 wk (D75)	Mtx 12 mg/m^2 every 3 wk (M) Docetaxel 30 mg/m^2 weekly (D30)	OS - D75 18.9 mo - D30: 17.4 mo - M: 16.5 mo	PSA response rate; pain response; quality of life (FACT-P)	45% with pain at baseline; D75 superior toD30 and M; D30 not superior to M
SWOG 99-16 [61] (n = 674)	Docetaxel 60 mg/m^2+ estramustine 260 mg days 1–5 every 3 wk	Mtx 12 mg/m^2 every 3 wk	OS 17.5 vs 15.6 mo ($p = 0.02$)	PSA response; radiologic response rate	33% with pain at baseline; significant toxicity associated with estramustine
TROPIC [2] (n = 755)	Cabazitaxel 25 mg/m^2 every 3 wk	Mtx 12 mg/m^2 every 3 wk	OS 15.1 vs 12.7 mo (HR 0.7; $p = 0.0001$)	PFS; PSA response rate; radiographic response rate; pain response	Post-docetaxel; significant haematologic toxicity with cabazitaxel; no difference in pain response
FIRSTANA [16] (n = 1168)	Cabazitaxel 25 mg/m^2 (C25) Cabazitaxel 20 mg/m^2 (C20)	Docetaxel 75 mg/m^2 (D75)	OS (C25 vs D75) 25.2 vs 24.3 mo (HR 0.97) OS (C20 vs D75) 24.5 vs 24.3 mo (HR 1.01)	PFS; PSA response rate; radiographic response rate; pain response; quality of life	No significant benefit of cabazitaxel over docetaxel in first-line treatment; tumor response rate higher in the C25 arm
PROSELICA [32] (n = 1200)	Cabazitaxel 20 mg/m^2 (C20)	Cabazitaxel 25 mg/m^2 (C25)	OS (noninferiority) 13.4 vs 14.5 mo (HR 1.01)	PFS; PSA response rate; radiographic response rate; pain response; quality of life	Noninferiority of C20 established; PSA and RECIST response rates higher in the C25 arm; lower toxicity rates in the C20 arm

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