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# Safety of cabazitaxel in senior adults with metastatic castration-resistant prostate cancer: Results of the European compassionate-use programme

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Supportive care

**Abstract** ***Background:*** Cabazitaxel/prednisone has been shown to prolong survival versus mitoxantrone/prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) that has progressed during or after docetaxel. Subsequently, compassionate-use programmes (CUPs) and expanded-access programmes (EAPs) were established worldwide, allowing access to cabazitaxel before its commercial availability. Preliminary results of the European CUP/EAP, focusing on the elderly population (aged $\geqslant$70 years), are reported.
***Patients and methods:*** Enrolled patients with progressive mCRPC received cabazitaxel (25 mg/m$^2$) plus 10 mg oral prednisone/prednisolone every 3 weeks until disease progression, death, unacceptable toxicity or physician/patient decision. Safety was analysed by age group (<70, [70–75] and $\geqslant$75 years). The influence of selected variables on grade $\geqslant$3 neutropenia and/or neutropenic complications was analysed in multivariate analysis.
***Results:*** 746 men were enrolled (<70 years, $n = 421$; [70–75], $n = 180$, $\geqslant$75 years, $n = 145$). Number of cabazitaxel cycles, dose reductions for any cause, dose delays possibly related to

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cabazitaxel adverse events, and tolerability were similar in the three age groups. Prophylactic granulocyte colony-stimulating factor (G-CSF) use was more common in men aged ⩾70 years. In multivariate analysis, age ⩾75 years, treatment cycle 1, and neutrophil count <4000/mm$^3$ before cabazitaxel injection were associated with increased risk of developing grade ⩾3 neutropenia and/or neutropenic complications. Prophylactic use of G-CSF at a given cycle significantly reduced this risk by 30% (odds ratio 0.70, $p = 0.04$).

***Conclusion:*** The results suggest that cabazitaxel has a manageable safety profile in everyday clinical practice. Prophylactic use of G-CSF, especially at cycle 1 and in men aged ⩾75 years, is important and improves tolerability in senior adults treated with cabazitaxel.



## 1. Introduction

The past 4 years have seen significant advances in the management of metastatic castration-resistant prostate cancer (mCRPC), with five novel therapies (abiraterone, cabazitaxel, enzalutamide, radium-223, and sipuleucel-T) demonstrating a survival benefit in phase III clinical trials [1–5].

Taxanes have an important role in this broad armamentarium. Their anti-tumour activity has been shown to promote assembly and stabilisation of microtubules, blocking tumour cell division [6], and inhibiting tumour cell trafficking, including nuclear translocation of the androgen receptor, a key driver of prostate cancer growth [7,8]. In 2004, the results of two pivotal phase III studies (TAX 327 and SWOG 99-16) demonstrated, for the first time, a significant improvement in overall survival (OS) with docetaxel/prednisone and docetaxel/estramustine compared with mitoxantrone/prednisone [9–11]. Moreover, 19% of patients treated in TAX 327 and receiving docetaxel every 3 weeks (q3w) survived for at least 3 years, versus only 14% with mitoxantrone [11]. Based on these results, docetaxel plus prednisone became the standard of care for mCRPC, recommended by many international guidelines [12–17].

Cabazitaxel is a next generation taxane, selected for clinical development based on its ability to overcome docetaxel resistance and its ability to cross the blood–brain barrier in preclinical animal models [18–20]. In the phase III TROPIC trial, median survival was 15.1 months (95% confidence interval [CI] 14.1–16.3) with cabazitaxel/prednisone, and 12.7 months (95% CI 11.6–13.7) with mitoxantrone/prednisone [1]. Updated results showed a long-term survival benefit, with almost twice as many patients alive at 2 years with cabazitaxel compared with the active control arm mitoxantrone (15.9% versus 8.2%; odds ratio [OR] 2.11; 95% CI 1.33–3.33) [21].

Cabazitaxel is now considered an effective treatment option for mCRPC for patients progressing during or after docetaxel [12,13,15,16]. In TROPIC, however, cabazitaxel was associated with some clinically important adverse events (AEs)—mainly an increased risk of ⩾grade 3 febrile neutropenia (cabazitaxel 8% versus mitoxantrone 1%) and grade ⩾3 diarrhoea (cabazitaxel 6% versus mitoxantrone <1%) [1]. Overall, 5% of patients in the cabazitaxel group and 2% of those in the mitoxantrone group died within 30 days of the last infusion—the most frequent cause of death in the cabazitaxel group was neutropenia and its clinical consequences. This toxicity might have, at least in part, been because patients were heavily pretreated and had very advanced disease, prophylactic G-CSF at the first cabazitaxel cycle was not allowed (it was only allowed at first occurrence of either neutropenia lasting ⩾7 or neutropenia complicated by fever or infection) and because in this worldwide study, some centres lacked expertise in pro-active management of AEs [22]. The crucial role of adequate patient care was highlighted by a post hoc analysis limited to French TROPIC centres (90 patients in total) where proactive management of side-effects was required [23]. In this sub-study, the discontinuation rate due to AEs with cabazitaxel was lower than in the global TROPIC population (11% versus 18%) and there was no death due to toxicity, resulting in a greater OS benefit versus mitoxantrone (18.0 months versus 14.3 months).

The TROPIC results led to the establishment of compassionate-use programmes (CUPs) and early-access programmes (EAPs) in 30 countries worldwide, allowing access to the drug before its commercial availability. An awareness programme for physicians and nurses on the pro-active management of AEs related to cabazitaxel was implemented in each centre. Results from the German CUP and the Italian EAP have already been published [24,25]. Compared to TROPIC, there was a consistently lower rate of febrile neutropenia (Germany 1.8%; Italy 5% versus 8% in TROPIC) and grade ⩾3 diarrhoea (Germany 0.9%; Italy 2.8% versus 6% in TROPIC) [1,24,25], demonstrating the benefits of pro-active measures to reduce the incidence and severity of cabazitaxel-related AEs. In this paper, we report the preliminary safety results of the European CUPs/EAPs. In the interest of patients, the safety analysis focuses particularly on the senior adult patients (aged [70–75] and ⩾75 years) as this population is at increased risk of chemotherapy-induced AEs due to associated comorbidities [26].

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