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Perspective

CABAZITAXEL: MEDICAL USES, MECHANISM OF ACTION AND COMMON SIDE EFFECTS

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PERSPECTIVE

Cabazitaxel is a chemotherapeutic medication used to treat cancer. This drug is a "taxane derivative" as well as a "anti-microtubule agent." Cabazitaxel is an antineoplastic drug used to treat hormone-refractory metastatic prostate cancer that has progressed after treatment with a docetaxel-based regimen. Cabazitaxel is an anti-neoplastic drug that is combined with the steroid prednisone (Kommineni et al., 2019). Cabazitaxel is a drug that is used to treat prostate cancer that has progressed after docetaxel treatment. Cabazitaxel is made using a precursor taken from yew needles in a semi-synthesis process (10-deacetylbaccatin III). On June 17, 2010, the US Food and Drug Administration (FDA) authorised it.

Until 2010, there were no effective life-prolonging medicines for men with docetaxel-resistant prostate cancer. The FDA approved cabazitaxel, a second-generation taxane drug, in 2010 for the treatment of docetaxel-pretreated mCRPC based on the results of a key randomised phase III (TROPIC) trial. Cabazitaxel is a tubulin-binding taxane that varies from docetaxel and paclitaxel in that it has a low affinity for P-glycoprotein, the ATP-dependent drug efflux pump. Cabazitaxel was proven to be active in docetaxel-sensitive cancers as well as those with natural or acquired docetaxel resistance in preclinical investigations using cancer cell lines and animal xenograft models (Rzeszotarska et al., 2019).

During phase I testing, cabazitaxel was given by intravenous infusion every three weeks at ascending doses of 10 to 25 mg/m, giving the first indication of its safety and efficacy in males with prostate cancer. Neutropenia was the primary dose-limiting toxicity (DLT) in the study. A phase III trial was undertaken to examine its activity due to the lack of cross-resistance between this drug and docetaxel, as well as early reports of good responses in men with CRPC from this phase I trial.

The TROPIC trial, which enrolled 755 men with mCRPC who had progressed after docetaxel-based treatment and was conducted in 146 institutions across 26 countries, determined the safety and efficacy of cabazitaxel in patients with advanced prostate cancer. Three hundred and seventy-seven patients were randomly assigned to receive mitoxantrone 12 mg/m² intravenously every three weeks (along with oral prednisone 10 mg daily) and three hundred and eighty-seven patients were randomly assigned to receive cabazitaxel 25 mg/m² intravenously every three weeks (plus prednisone). Overall survival in men getting cabazitaxel was 15.1 months after a median follow-up of 12.8 months, compared to 12.7 months in those receiving mitoxantrone (HR 0.70, P 0.0001).

Cabazitaxel significantly improved PFS (2.8 months vs. 1.4 months, P = 0.0001), time to PSA progression (6.4 months vs. 3.1 months, P = 0.001), radiographic tumour response rates (14.4 percent vs. 4.4 percent, P = 0.0005), and PSA response rates (39.2 percent vs. 17.8 percent, P = 0.0002). There were no changes in pain responses or time to pain progression between the two treatment arms. The FDA approved cabazitaxel with prednisone for the second-line treatment of docetaxel-refractory mCRPC in June 2010 based on the findings of this trial.

Medical uses

Cabazitaxel is indicated in combination with prednisone for the treatment of metastatic castration-resistant prostate cancer following docetaxel-based treatment.

Mechanism of action

Taxanes enhance microtubule stabilization and inhibit cellular mitosis and division. Moreover, taxanes prevent androgen receptor (AR) signaling by binding cellular microtubules and the microtubule-associated motor protein dynein, thus averting AR nuclear translocation.

Cabazitaxel is a microtubule inhibitor. Cabazitaxel binds to tubulin and promotes its assembly into microtubules while simultaneously inhibiting disassembly. This leads to the stabilization of microtubules, which results in the interference of mitotic and interphase cellular functions. The cell is then unable to progress further into the cell cycle, being stalled at metaphase, thus triggering apoptosis of the cancer cell.

Cabazitaxel is extensively metabolised in the liver (>95%), primarily by the CYP3A4/5 isoenzyme (80–90%), and to a lesser amount by CYP2C8, yielding 20 distinct metabolites. The active demethylated derivatives of cabazitaxel RPR112698 and RPR123142, respectively, are two of these metabolites. Another metabolite of cabazitaxel is docetaxel. In human plasma, the primary circulating moiety is capazitaxel. Cabazitaxel has the potential to induce major adverse effects such as neutropenia, hypersensitivity responses, gastrointestinal problems, and renal failure (Thibault et al., 2018). Exacerbation of unfavourable reactions such as bone marrow suppression and gastrointestinal issues are among the potential side effects of an overdose. Cabazitaxel is able to pass across the blood-brain barrier. Rat LD₅₀ = 500 mg/kg

Common side effects

These side effects happen in more than 10 in 100 people (more than 10%). You might have one or more of them. They include:

Risk of infection

Increased risk of getting an infection is due to a drop in white blood cells. Symptoms include a change in temperature, aching muscles, headaches, feeling cold and shivery and generally unwell. You might have other symptoms depending on where the infection is (Chen et al., 2020).

Infections can sometimes be life threatening. You should contact your advice line urgently if you think you have an infection.

Breathlessness and looking pale

You might be breathless and look pale due to a drop in red blood cells. This is called anaemia.

Bruising and bleeding

This is due to a drop in the number of platelets in your blood. These blood cells help the blood to clot when we cut ourselves. You may have nosebleeds or bleeding gums after brushing your teeth (da Costa et al., 2020). Or you may have lots of tiny red spots or bruises on your arms or legs (known as petechiae).

Loss of appetite and weight loss

You might not feel like eating and may lose weight. It is important to eat as much as you can. Eating several small meals and snacks throughout the day can be easier to manage. You can talk to a dietitian if you are concerned about your appetite or weight loss.

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