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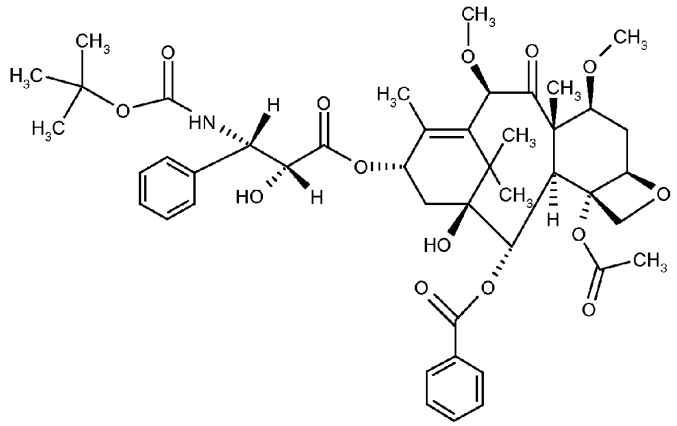
(54) **Title**: NOVEL ANTITUMORAL USE OF CABAZITAXEL



(I)

(57) **Abstract**: The invention relates to a compound of Formula (I): which may be in base form or in the form of a hydrate or a solvate, in combination with prednisone or prednisolone, for its use as a medicament in the treatment of prostate cancer, particularly metastatic prostate cancer, especially for patients who are not catered for by a taxane-based treatment.

NOVEL ANTITUMORAL USE OF CABAZITAXEL

The present invention relates to a novel antitumoral use of cabazitaxel in the treatment of prostate cancer, which may be metastatic, especially for patients who are not catered for by a taxane-based treatment. In particular, the present invention relates to the use of cabazitaxel in the treatment of patients with castration resistant metastatic prostate cancer, who have been previously treated with a docetaxel based regimen, an unmet medical need.

[Technical problem]

Prostate cancer affects a large proportion of the male population worldwide: 680 000 cases worldwide in 2002; it is predicted that there will be 900 000 new cases per year up to 2010 (*CA Cancer J. Clin.,* **2005**, *55*, 74-108). It is the most frequently occurring cancer in men after lung cancer.

Prostate cancer is generally treated at the start by depriving the androgenic hormones, i.e. by surgical excision of the testicles **The Current State of Hormonal Therapy for Prostate Cancer** CA **Cancer** J. Clin., May 2002; 52: 154-179, or by radiotherapy treatment **External beam radiation therapy for prostate cancer** CA **Cancer** J. Clin., Nov. 2000; 50: 349-375. Treatments with antiandrogens or hormone manipulations are associated with responses of short duration and without any improvement in the survival time.

The use of cytotoxic chemotherapy is not a routine treatment, whereas its role in alleviating the symptoms and reducing the levels of PSA (prostate-specific antigen) is established. No monotherapy has obtained a degree of response of greater than 30%; combinations with an effect on PSA levels were tested. No effect on the survival time was seen and, what is more, the toxicity of these treatments, particularly on elderly patients, is problematic since, in addition to their tumour, they are generally suffering from related health problems and have a limited reserve of bone marrow.

Until recently, the chemotherapies used were limited to cyclophosphamide, anthracyclines (doxorubicin or mitoxantrone) and estramustine, and the effects of these treatments are relatively mediocre. Palliative effects were observed in patients following the administration of corticoids alone or of mitoxantrone with either prednisone or hydrocortisone. Following Phase II trials, the combination of mitoxantrone with corticoids was recognized as the reference treatment for hormone-resistant prostate cancer. More recently, treatments with docetaxel in combination with estramustine or prednisone have made it possible to treat cancers that are resistant to hormone deprivation **Advances in Prostate Cancer Chemotherapy: A New Era Begins** CA **Cancer** J. Clin., Sep. 2005; 55: 300-318, the survival was improved by 2.4 months.

It is generally accepted that the responses in advanced prostate cancers are difficult to evaluate on account of the heterogeneity of the disease and the lack of consensus regarding the treatment response criteria. Many patients with metastatic prostate cancer have no measurable disease, but have symptoms dominated by bone metastases. Measurement of the PSA level has been found to be a means for evaluating novel candidates and also the measurement of the tumour when this is possible, the measurement of bone tumours, the quality of life and the measurement of the pain.

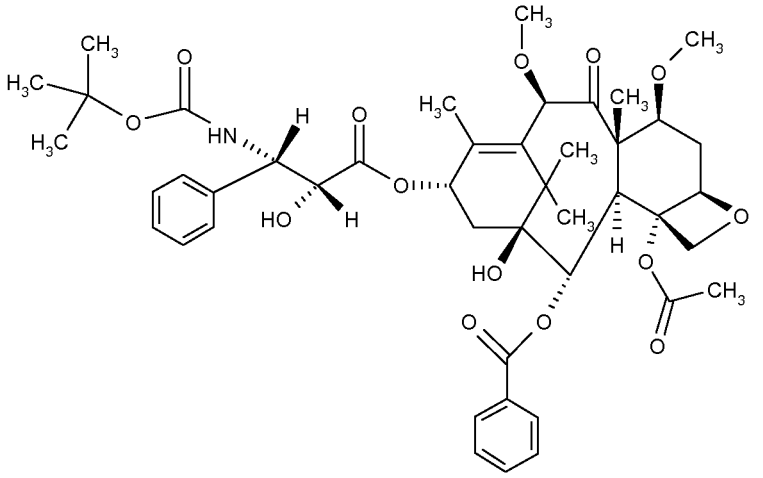
Furthermore, cancer may become resistant to the agents used, in particular to taxanes, which limits the possible treatment options. Several taxane resistance mechanisms have been described (expression of P-glycoprotein P-gp, *mdr-1* gene, modified metabolism of taxane, mutation of the tubulin gene, etc.): see *Drug Resistance Updates* **2001**, *4*(1), 3-8; J. Clin. Onc. **1999**, *17*(3), 1061-1070.

The technical problem that the invention intends to solve is that of providing a novel therapeutic option for treating prostate cancer, especially for patients who are not catered for by a taxane-based treatment, such as patients with castration resistant metastatic prostate cancer who have been previously treated with docetaxel (sold under the brand name Taxotere®) based regimen, an unmet medical need.

Four clinical trials on cabazitaxel are known since April 2006. Three monotherapy tests have made it possible to determine the maximum tolerated dose and the toxicities at the limit doses: these tests were performed on breast, sarcoma and prostate tumours. Doses of 10-30 mg/m^2 every three hours were used. A phase II trial was performed on patients with a breast cancer, who had previously received taxanes and anthracyclines as adjuvant (i.e. after a surgery) or as a first-line treatment. The response levels were 14.6% as adjuvant and 9.5% as second-line treatment.

[Brief description of the invention]

The invention relates to a novel antitumoral pharmaceutical therapeutic use comprising cabazitaxel of formula



The invention also relates to methods of treating patients with prostate cancer comprising administering an effective amount of the antitumoral agent cabazitaxel to said patient.

This antitumoral agent may be in the form of anhydrous base, a hydrate or a solvate, intended for treating prostate cancer, in particular for treating patients who are not catered for by a taxane-based treatment, such as patients who have been previously treated with a docetaxel-based regimen. This compound is preferably administered to a patient with advanced metastatic disease. In particular, the compound is administered to a patient with castration resistant prostate cancer. Cabazitaxel is preferably administered in combination with a corticoid chosen especially from prednisone and prednisolone. This corticoid is preferably administered at a daily dose of 10 mg orally.

In some aspects of the invention, cabazitaxel is administered in combination with prednisone for its use as a medicament in the treatment of patients with hormone-refractory prostate cancer who have been previously treated with docetaxel based regimen.

In some aspects of the invention, cabazitaxel is administered at a dose (defined for each administration) of between 20 and 25 mg/m^2. Cabazitaxel may be in the form of an acetone solvate. More particularly, the acetone solvate of cabazitaxel contains between 5% and 8% and preferably between 5% and 7% by weight of acetone.

In some aspects of the invention, cabazitaxel may be administered by intravenous infusion at a dose of between 15 and 25 mg/m^2, this administration cycle of the antitumour agent being repeated at an interval of 3 weeks between each cabazitaxel administration, which interval may be prolonged by 1 to 2 weeks depending on the tolerance to the preceding cabazitaxel administration.

In some embodiments, the effective amount of cabazitaxel produces at least one therapeutic effect selected from the group consisting of increase in overall survival, partial response, reduction in tumor size, reduction in metastasis, complete remission, partial remission, stable disease, or complete response.

The present invention also relates to a pharmaceutical composition that treats patients with prostate cancer comprising a clinically proven safe and effective amount of cabazitaxel.

Further embodiments of the invention comprise methods or using, treating, promoting, and providing cabazitaxel.

The present invention also relates to packages and articles of manufacture.

[Brief Description of the Drawings]

Figure 1 displays the Kaplan-Meier curves of the overall survival in a cabazitaxel study.

Figure 2 displays the Kaplan-Meier curves of progression-free survival in a cabazitaxel study.

Figure 3 shows an intention-to-treat analysis of overall survival in subgroups of patients defined by baseline characteristics. Hazard ratios <1 favor the cabazitaxel group, while those >1 favor the mitoxantrone group. CI denotes confidence intervals.

Figure 4 graphically depicts the proportion of patients with changes in ECOG performance status from baseline during treatment (safety population).

Figure 5 graphically depicts the proportion of patients with changes from baseline in the Present Pain Intensity score during treatment (ITT).

Figure 6 graphically presents the mean area under the curve for PPI and analgesic scores by treatment cycle.

Figure 7 graphically presents the mean AUC analgesic score.

[Description of the invention]

Definitions

- Effective amount, as used herein, means an amount of a pharmaceutical compound, such as cabazitaxel, that produces an effect on the cancer to be treated.

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