Adverse effects of cabazitaxel at a dose of 20 mg/m² vs. 25 mg/m² in patients with castration resistant prostate cancer: retrospective analysis of case-series

José de Jesús Rivera-Cortez*, Perla Pérez-Pérez and Eduardo Cárdenas-Cárdenas

Department of Medical Oncology, Centro Médico Nacional 20 de Noviembre, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Mexico City, Mexico

Abstract

Introduction: In patients with castration-resistant prostate cancer (CRPC), the TROPIC study established cabazitaxel 25 mg/m² as the standard second-line chemotherapy. In order to reduce the adverse effects, the PROSELICA study evaluated whether the decrease in the dose of cabazitaxel at 20 mg/m² was not inferior fulfilling the objective. We propose this study to know the side effects of cabazitaxel in our population. Materials and methods: Patients > 18 years with CRPC, treated with cabazitaxel at a dose of 20 mg/m² and 25 mg/m², from 2014 to 2017, in a population of Centro Médico Nacional 20 de Noviembre, ISSSTE. Results: 41 patients were recruited. In both groups the most common toxicity was diarrhea in > 90% of the patients, however, grade 3-4 diarrhea in the 20 mg/m² cabazitaxel group was 24% compared to the 25 mg/m² group of 31.2%. A 12% of febrile neutropenia was observed in the control group compared to none patient at a dose of 20 mg/m². Conclusions: In our population, better tolerance of cabazitaxel at a dose of 20 mg/m² compared to 25 mg/m² is corroborated, we believe that the use of such dose should be a standard, as part of the tools available for the CRPC.

Key words: Cabazitaxel 20 mg/m². Castration-resistant. Prostate cancer. Second line. Adverse effects.

Introduction

Prostate cancer (PCa) is the most common neoplasm in men and a major cause of cancer-associated deaths¹. In Mexico, according to GLOBOCAN 2018 data, 25,049 new cases of PCa are estimated, which is equivalent to 13.1% of all neoplasms. The estimated number of deaths due to this cause is 6,915, which is equivalent to 8.3%².

Androgen deprivation therapy (ADT) is the initial standard treatment for patients with PCa³, either with bilateral orchietomy (surgical castration) or chemical castration; both procedures are equivalent in terms of efficacy⁴. However, the vast majority of patients will experience disease progression, with the condition then being regarded as castration-resistant prostate cancer (CRPC)⁵, defined as disease progression despite ADT, either biochemical progression, with a consecutive increase in prostate-specific antigen (PSA) of 50% over nadir in three determinations separated by a 1-week period each or PSA > 2 ng/mL, or radiological progression, with the appearance of new bone or visceral lesions; in addition, the patient must have serum testosterone levels < 50 ng/dL⁶.

Cytotoxic chemotherapy was relatively ineffective in these patients, until the development of taxanes ¹, as demonstrated by the TAX 327 trial, which established...
docetaxel 75 mg/m² every three weeks plus prednisone 5 mg twice daily as the standard treatment for patients with castration-resistant metastatic PCAs. An alternative schedule is docetaxel 50 mg/m² every two weeks, with benefit in time to treatment failure and overall survival (OS) in comparison with administration every three weeks, as well as a better toxicity profile.

After progression to up-front docetaxel, patients who maintain a good performance status will be candidates for new treatment lines. The phase III TROPIC trial positioned the combination of cabazitaxel 25 mg/m² plus prednisone 10 mg/day as second-line chemotherapy standard treatment after progression to up-front docetaxel. However, due to the significant toxicity observed in this study, the PROSELICA study recently assessed whether the decrease in the cabazitaxel dose to 20 mg/m² every three weeks was non-inferior to 25 mg/m² every three weeks. As a result, a median OS of 13.4 months was obtained for the of 20 mg/m² dose vs. 14.5 months with the 25 mg/m² dose, with non-inferiority being demonstrated.

**Material and methods**

The records of patients diagnosed with PCa treated at the Medical Oncology Department of the National Medical Center 20 de Noviembre during the 2014-2017 period were reviewed. The following information was obtained from subjects who met the inclusion criteria: age, performance status according to the Eastern Cooperative Oncology Group (ECOG) scale, Gleason score, prior lines of treatment, cabazitaxel initial dose and number of cycles received, dose adjustment, side effects (diarrhea, neutropenia, febrile neutropenia), as well as dose reduction and whether hospitalization was required, in addition to the reason for treatment discontinuation.

Regarding the study inclusion criteria, patients older than 18 years, with a histologically-confirmed diagnosis of PCa at clinical stage IV with castration resistance criteria were included. In addition, patients had to have shown progression to one or more lines of treatment and had to have received at least one cycle of treatment with cabazitaxel.

Treatment response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and toxicity was evaluated using the common terminology criteria for adverse effects (CTCAE), version 4.

Statistical analysis was carried out using the STATA® software, version 13.0, with the purpose to identify statistically significant relationships between variables and the occurrence of adverse effects associated with cabazitaxel treatment at a dose of 20 vs. 25 mg/m². Descriptive statistics, median and range were used for quantitative variables, as well as frequency and percentages for qualitative variables. For between-group comparisons, the chi-square test or Fisher’s exact test were used for qualitative variables, as well as Wilcoxon rank-sum test for quantitative variables.

Since this was an observational, analytical, longitudinal, retrospective cohort study that was risk-free for participants, obtaining patient informed consent was not necessary. Each participant’s data were obtained from electronic medical records, without interventions regarding diagnosis being included, and thus there was no risk of any kind for the patients, and confidentiality of their personal data was protected. In addition, the study was evaluated and approved by the National Medical Center 20 de Noviembre Research and Ethics Committee.

**Results**

A total of 41 patients who received cabazitaxel as part of CRPC treatment at the Medical Oncology Department of the National Medical Center 20 de Noviembre from July 1, 2013 to October 1, 2017, were recruited; regarding the cabazitaxel dose, 16 patients initially received the 25 mg/m² dose and 25 received the 20 mg/m² dose.

| Characteristic | 20 mg/m² dose patients (n = 25) | 25 mg/m² dose patients (n = 16) | p   |
|---------------|---------------------------------|---------------------------------|-----|
| Age (years)   | 67 (52-84)                      | 67.5 (47-79)                    | 0.728* |
| ECOG (%)      | 22 (88) 3 (12)                  | 16 (100) 0 (0)                  | 0.268† |
| Gleason (%)   | 1 (4) 7 15 (60)                | 2 (12.5) 11 (68.7)             | 0.499† |
| Prior lines of treatment (%) | 11 (44) 3 (12)                  | 8 (50) 7 (43.7)                | 0.636† |
|               | ≥ 1                              | ≥ 2                             | ≥ 3                          |

*p-value for Wilcoxon rank-sum test result.
†p-value for Chi-square test result.
Median age was 67 years for both groups. As for performance status, ECOG score was 1 in 100% of patients with the 25 mg/m² dose, and in 88% of those with the 20 mg/m² dose; of note, 12% of patients in the cabazitaxel 20 mg/m² group had ECOG 2.

The reported Gleason score was ≥ 8 in more than 60% of patients. Regarding previous treatment, 40% had received docetaxel as immediate prior line, whereas the remaining percentage had between 2 and 3 prior lines of treatment (abiraterone or chemotherapy). Table 1 summarizes patient characteristics by treatment group.

### Adverse effects

The adverse effects analyzed in this group of patients were those that have considerably limited cabazitaxel generalized use: neutropenia, febrile neutropenia and diarrhea, which are summarized in Table 2.

When the adverse effects occurring with both doses were analyzed, the most common toxicity was diarrhea (in > 90% of patients); however, it was grade 3-4 in 24% of patients in the cabazitaxel 20 mg/m² group, in comparison with 31.25% in the 25 mg/m² group. Neutropenia occurred in 24% of subjects with the 20 mg/m² dose, with grade 3-4 being observed only in 4% of patients, while in those receiving the 25 mg/m² dose, neutropenia occurred in 18.8%, and it was grade 3-4 in 12.5%; there were no febrile neutropenia events with 20 mg, and they occurred at a rate of 12.5% with 25 mg.

Median number of received cycles was 7 with 20 mg and 6 with 25 mg; dose reduction was necessary in 43.7% of the patients who received 25 mg/m², while in two patients who started at a dose of 20 mg/m² it was increased to 25 mg/m² in the course of their treatment (p = 0.017). Table 3 describes the most important adverse events by treatment group.

### Discussion

Cabazitaxel is an additional option for the treatment of patients with CRPC, but its generalized use is limited by known adverse effects and secondary deaths, as it was reported in the registration trial. The availability of options with a better toxicity profile, such as abiraterone or enzalutamide, has restricted the use of this drug. It is necessary taking into account that CPRC treatment optimal sequencing has not yet been established, although retrospective analyses indicate that the chemotherapy-oral therapy-chemotherapy sequence is ideal; therefore, it is important bearing in mind all treatment options in order to obtain the best survival in a patient with CRPC.
The PROSELICA trial revealed that the cabazitaxel 20 mg/m² dose is equivalent in efficacy to the 25 mg/m² dose, with a better tolerance profile⁵. In the FIRSTANA trial, when docetaxel was compared with cabazitaxel, it was concluded that toxicity can be lower with cabazitaxel at a 20 mg/m² dose in comparison with docetaxel, which is a widely-used drug in PCa⁹.

At the National Medical Center 20 de Noviembre, cabazitaxel was started at a dose of 25 mg/m² according to the TROPIC trial⁸, and subsequently it was administered at 20 mg/m² based on information provided by the PROSELICA trial⁹, which is why our study population was treated with 25 and 20 mg/m².

The purpose of our study was to compare the tolerance profile in a population affiliated to the ISSSTE, since it is known from the aforementioned study that adverse effects are lower. Some patients had been heavily treated with up to three previous lines of chemotherapy or oral therapy, which may also contribute to a higher incidence of diarrhea and neutropenia.

All patients who received the 25 mg/m² dose were prophylactically administered filgrastim or pegfilgrastim at each cycle. Those treated with the 20 mg/m² dose were not given prophylaxis with colony stimulating factor, except for four patients, given that the chemotherapy regimen used was cabazitaxel plus carboplatin, and prophylaxis administration was decided in those cases whose clinical presentation suggested neuroendocrine differentiation. In turn, this factor might have been an important cause for the increased incidence of neutropenia and diarrhea in patients receiving the cabazitaxel 20 mg/m² dose.

Conclusions

With the data obtained in this study, the superior tolerance of cabazitaxel at a dose of 20 mg/m² in comparison with 25 mg/m² is corroborated in a Mexican population, which is why we consider that the use of said dose should be standard, as part of the armamentarium for the treatment of CRPC.

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