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Effects of Budesonide on Cabazitaxel Pharmacokinetics and Cabazitaxel-Induced Diarrhea: A Randomized, Open-Label Multicenter Phase II Study

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Abstract

Purpose: Forty-seven percent of patients in the pivotal trial of cabazitaxel reported diarrhea of any grade. Aiming to reduce the incidence of diarrhea, we studied the effects of budesonide on the grade of cabazitaxel-induced diarrhea during the first two treatment cycles.

Experimental Design: Between December 2011 and October 2015, 246 metastatic castration-resistant prostate cancer patients were randomized to receive standard-of-care cabazitaxel 25 mg/m^2 every 3 weeks plus prednisone 10 mg/day (group CABA) or same dose/schedule of cabazitaxel with concomitant budesonide 9 mg daily during the first two treatment cycles (group BUD). The occurrence of diarrhea was reported by physicians and by patients in a diary. χ^2 tests were used to compare incidence numbers. An intention-to-treat principle was used.

Results: In the phase II trial, 227 patients were evaluable. Grade 2–3 diarrhea occurred in 35 patients (15%) and grade 4 diarrhea was not reported. The incidence of grade 2–3 diarrhea was comparable in both treatment groups: 14 of 113 patients in group CABA (12%) versus 21 of 114 patients in group BUD (18%; $P = 0.21$). Seven patients were admitted to the hospital with diarrhea ($n = 5$ group CABA vs. $n = 2$ group BUD). PSA response was seen in 30% of patients and was not affected by budesonide coadministration ($P = 0.29$). Also, other toxicities were not affected by budesonide coadministration.

Conclusions: The incidence of cabazitaxel-induced diarrhea was notably lower than reported in the TROPIC trial and appears manageable in routine clinical practice. Budesonide coadministration did not reduce the incidence or severity of cabazitaxel-induced diarrhea. *Clin Cancer Res; 23(7); 1679–83. ©2016 AACR.*

Introduction

Several therapeutic options are available for the treatment of metastatic castration-resistant prostate cancer (mCRPC). Cabazitaxel is currently approved for treatment of mCRPC after progression on docetaxel treatment. In the registration trial of cabazitaxel, diarrhea was reported in 47% of patients (1). Six percent of patients had grade 3–4 diarrhea, requiring hospital admissions (1).

To avoid dose reductions of an effective regimen and to preserve patients' quality of life, we aimed to search for measures to reduce the incidence and severity of cabazitaxel-induced diarrhea. It has previously been shown that coadministration of budesonide is able to reduce the incidence of diarrhea in irinotecan as well as in 5-fluorouracil (5-FU)–treated patients (2, 3). Budesonide, a locally active corticosteroid, reduced diarrhea with $\geq$2 grades in 86% of irinotecan and in 57% of 5-FU–treated patients that suffered from grade 3–4 diarrhea and did not respond to loperamide treatment (2). In the second study, budesonide coadministration in patients treated with irinotecan resulted in shorter and fewer periods of diarrhea compared with placebo (3). Budesonide has a 90% first-pass effect and thus a low systemic availability, so little to none systemic toxicity can be

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

In the pivotal trial of cabazitaxel, cabazitaxel-induced diarrhea was dose limiting: 47% of patients reported any grade of diarrhea. In 6% of patients, even hospital admission was required due to this toxicity. Obviously, diarrhea reduced patients' quality of life and sometimes even the opportunity of treatment. In the current study, we investigated the hypothesis that the corticosteroid budesonide decreases the incidence and severity of cabazitaxel-induced diarrhea during the first two treatment cycles. Unfortunately, budesonide did not influence the incidence and severity of diarrhea. However interestingly, the incidence of diarrhea was lower in our trial compared with the previous phase III study, indicating that diarrhea is dose limiting for less patients than thought before. In addition, diarrhea is manageable in daily practice.

expected from budesonide coadministration. On the basis of these data, we hypothesized budesonide to be a safe and a potent drug to prevent cabazitaxel-induced diarrhea. As the coadministration of budesonide and cabazitaxel has never been tested, our study was conducted in two parts. First, we investigated the safety of budesonide on the pharmacokinetics of cabazitaxel in a limited-size crossover trial, to exclude a negative effect of budesonide on cabazitaxel exposure. Next, a sufficiently powered randomized phase II study was conducted to explore the effects of budesonide on cabazitaxel-induced diarrhea, the CABARESC study.

Patients and Methods

Pharmacokinetic study

In a randomized crossover pharmacokinetic study, we investigated the effects of budesonide on the exposure of cabazitaxel (see The Dutch Trial Registry; www.trialregister.nl, number: NTR2840).

Metastatic CRPC patients with documented disease progression during or after docetaxel therapy were eligible for study participation. Disease progression was defined as at least two consecutive rises in PSA (taken $\geq$1 week apart) or progression according to RECIST (version 1.1; ref. 4). Patients had to be $\geq$18 years of age. A World Health Organization performance status of $\leq$1 and adequate renal, hepatic, and hematopoietic functions were required for study inclusion. Patients had to be able to take oral drugs. The use of strong CYP3A inhibitors or inducers was prohibited. Patients with an ostomy, ulcerative colitis, Crohn disease, or celiac disease were excluded from participation. Chemotherapy or radiotherapy <4 weeks before start with cabazitaxel was prohibited.

Patients were randomized to receive standard-of-care cabazitaxel 25 mg/m^2 every 3 weeks plus prednisone 10 mg without budesonide in course 1 and with daily 9 mg budesonide (3 capsules of 3 mg) in course 2. In group B, budesonide was only added to the first cycle of cabazitaxel in the opposite order. After the completion of all study-related procedures, that is, after the second cycle of cabazitaxel, all patients continued their treatment with cabazitaxel according to standard of care without concomitant budesonide. Patients as well as their treating physicians documented diarrhea and other (serious) adverse events in a diary or patient record, respectively.

Pharmacokinetic sampling and analysis. Cabazitaxel pharmacokinetic sampling was performed prior to infusion, 30 minutes after start, and 5 minutes before stop of the infusion. Postinfusion, samples were drawn at 5, 15, 30 minutes, 1, 2, 4, 6, 11, and 23 hours. Samples were collected in the presence of lithium heparin and processed to plasma, which were thereafter added into polypropylene tubes and stored at $\leq$70°C until the time of analysis. Analyses were done using a validated LC/MS–MS method as described by de Bruijn and colleagues (5). AUCs from 0 to 24 hours (AUC 0–24 h) were estimated doing a noncompartmental analysis using Phoenix version 6.1 (Pharsight).

Statistics for pharmacokinetic analyses. Patients were considered evaluable for analysis when two cabazitaxel courses had been administered and when all pharmacokinetic samples had been obtained. A difference in pharmacokinetics was defined as a difference in cabazitaxel AUC of >20%. On the basis of a power analysis assuming an interindividual variability in cabazitaxel pharmacokinetics of 20% and a power of 80%, with a two-sided $P \leq 0.05$, a sample size of 18 patients was calculated. A Student t test was used for statistical testing.

Randomized phase II trial

The randomized open-label phase II multicenter study was registered in the European Clinical Trials Database (number 2011-003346-40) and in the Dutch Trial Registry (number NTR2991). Inclusion and exclusion criteria are as mentioned in the pharmacokinetics study. However, chemotherapy or radiotherapy <4 weeks before start with cabazitaxel was permitted.

For the stratification of patients, the following factors were used: age ($\geq$65 vs. <65 years), center of enrolment, and previous radiotherapy on back, abdomen, or pelvis (yes vs. no).

Treatment. Patients were digitally randomized to receive either standard-of-care cabazitaxel 25 mg/m^2 every 3 weeks plus prednisone 10 mg/day (group CABA) or cabazitaxel plus prednisone 10 mg/day with concomitant budesonide 9 mg daily for 44 consecutive days (group BUD). Budesonide was added for the first two courses, as diarrhea was expected to occur in the first two treatment cycles (1). Prednisone had to be started at least one week before the first cycle of cabazitaxel. Patients started budesonide 2 days before their first cabazitaxel administration and took budesonide one hour before breakfast. Cabazitaxel was continued for a maximum of 10 cycles for the evaluation of toxicity, but could be continued beyond 10 cycles if it was in the interest of the patient, unless progression or unacceptable toxicity occurred. Standard premedication was given (1). In case of severe toxicity, one dose reduction of 20% (to 20 mg/m^2) was allowed. Delay between two cabazitaxel cycles was allowed for as long as necessary to recover from toxicity. In case of delay of the second cabazitaxel cycle, budesonide was continued unless contraindicated.

Objectives and endpoints. The primary objective of this trial was to study the effects of budesonide cotreatment on the grade of cabazitaxel-induced diarrhea during the first two treatment cycles. Primary endpoint was the difference in the incidence of grade 2–4 diarrhea in the budesonide cotreated arm compared with the arm without budesonide. Secondary objectives were to study the effects of budesonide on other cabazitaxel-induced adverse events and the effects of cabazitaxel and budesonide on PSA response.

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PSA response was defined as a >50% reduction in PSA after start of treatment with cabazitaxel. PSA at baseline was considered the last measured PSA value before start of cabazitaxel treatment.

Data acquisition. Patients kept a diary on their stools, comedication, and adverse events during the first two cabazitaxel cycles. Loperamide use in case of diarrhea was accepted according to regular protocol. G-CSF (prophylactic) was prescribed at physicians' discretion. Prior to each treatment cycle, PSA was measured, and adverse events were monitored. Common Terminology Criteria for Adverse Events versions 2–4 were used.

Statistical analyses for the phase II trial. The incidence of grade 2–4 diarrhea in the CABA group was estimated to be 25%. A reduction of 15% in the BUD group was considered clinically relevant, and a two-sided significance level of $\alpha = 0.05$ and a power of 80% were defined. Power calculation showed that 113 evaluable patients per treatment arm were required. After the first 57 evaluable patients in each arm were included, an interim analysis was performed. If the percentage of patients with grade 3–4 diarrhea in the BUD group would have exceeded the incidence observed in the CABA group by 15%, the study would have been terminated for reasons of futility.

The results of the primary endpoint of the phase II study were based on the information reported by physicians on the adverse event forms. Analyses were done according an "intention-to-treat" principle, that is, analyzed according to the treatment arm patients were assigned to at randomization. However, patients that were initially randomized but are considered nonevaluable afterwards, based on information that should have been available before randomization, were excluded from all analyses. The incidence and severity of adverse events were compared between both treatment arms using a χ^2 test.

Both the pharmacokinetics study and the randomized phase II study were approved by the ethics committee of the Erasmus University Medical Center (Rotterdam, the Netherlands) as well as approved by the local committees of the participating hospitals and performed according to the values of the Declaration of Helsinki. Written informed consent was obtained from all patients. Protocol violations were individually investigated and refereed regarding their potential effects on the primary endpoint.

Results

Effects of budesonide on cabazitaxel pharmacokinetics

Between May and August 2011, 21 patients were included in the pharmacokinetic study. Two patients were excluded after enrolment due to a decline in clinical performance status. One patient received only one course of cabazitaxel. The other 18 patients were evaluable for pharmacokinetic analyses. The median age at study entry was 67 years (range, 46–75). No statistically significant difference in mean dose-corrected AUC (0–24 hours) was found between the courses with concomitant budesonide (4.6 ng*h/mL; SD, 1.2) and without concomitant budesonide (4.2 ng*h/mL; SD, 1.1; $P = 0.21$; see Table 1). Therefore, budesonide coadministration was considered to be safe for investigation in the phase II study.

Patient and treatment characteristics in the phase II trial

Between December 2011 and October 2015, 246 patients were included in 22 different hospitals in the Netherlands (see Supplementary Table S1). All patients were randomized to one of both treatment arms. Patient characteristics are shown in Table 2. Nineteen patients were considered not evaluable (11 from group CABA and 8 from group BUD, see Supplementary Table S2). For the primary endpoint, 227 patients were considered eligible (CABA $n = 113$, BUD $n = 114$).

The median number of cabazitaxel cycles was six in both treatment arms. Reasons for discontinuing the study are shown in Supplementary Table S3. In 3 patients, diarrhea was one of the reasons for study discontinuation. Three patients in group BUD received no budesonide, 12 patients (11%) only in one cycle, and 96 patients (84%) received two cycles of cabazitaxel with concomitant budesonide. Three patients received >3 cycles with concomitant budesonide. For 25 patients (12%), a dose reduction was made in cycle 2. In one of these 25 patients (from group BUD), diarrhea was the reason for dose modification.

Table 1. Pharmacokinetic effect of budesonide on cabazitaxel exposure

	Courses without budesonide	Courses with budesonide	*P*
AUC mean (SD)	4.16 (1.11)	4.6 (1.24)	0.21
AUC median (range)	4.48 (2.46–6.2)	4.43 (2.15–6.93)	

NOTE: All units are ng*h/mL.

Table 2. Patient characteristics

	Group CABA	Group BUD	Total
Total	113 (100%)	114 (100%)	227 (100%)
Median age at baseline	69	68	68
Range	49–85	51–83	49–85
Age ≥65 years	84 (74%)	84 (74%)	168 (74%)
Age <65 years	29 (26%)	30 (26%)	59 (26%)
WHO performance status (0–5)			
WHO 0	49 (43%)	43 (38%)	92 (41%)
WHO 1	64 (57%)	69 (61%)	133 (59%)
Not reported	—	2 (2%)	2 (1%)
Average number of stools baseline			
≤1	67 (59%)	55 (48%)	122 (54%)
1–2	21 (19%)	34 (30%)	55 (24%)
2–3	7 (6%)	6 (5%)	13 (6%)
3–4	3 (3%)	3 (3%)	6 (3%)
>4	1 (1%)	2 (2%)	3 (1%)
Unknown	14 (12%)	14 (12%)	28 (12%)
Type of castration			
Surgical	12 (11%)	19 (17%)	31 (14%)
Chemical	101 (98%)	95 (83%)	196 (86%)
Number of prior chemotherapeutic regimens			
1	102 (90%)	105 (92%)	207 (91%)
2	11 (10%)	7 (6%)	18 (8%)
3	—	1 (1%)	1 (0%)
4	—	1 (1%)	1 (0%)
Median	1	1	1
Range	1–2	1–4	1–4
Prior therapy with abiraterone			
No	82 (73%)	74 (65%)	156 (69%)
Yes	31 (27%)	40 (35%)	71 (31%)
Prior therapy with orteronel (TAK 700)			
No	106 (94%)	106 (93%)	212 (93%)
Yes	7 (6%)	8 (7%)	15 (7%)
Chemotherapy within the last 4 weeks before randomization			
No	78 (69%)	81 (71%)	159 (70%)
Yes	3 (3%)	3 (3%)	6 (3%)
Missing	32 (28%)	30 (26%)	62 (27%)
Prior irradiation back, abdomen, and/or pelvis			
No	53 (47%)	55 (48%)	108 (48%)
Yes	60 (53%)	59 (52%)	119 (52%)

Abbreviation: WHO, World Health Organization.

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Table 3. Effects of budesonide on diarrhea

	Group CABA	Group BUD	Total	*P*
Total	113 (100%)	114 (100%)	227 (100%)	—
Grade 2–3 diarrhea	14 (12%)	21 (18%)	35 (15%)	0.21
Grade 3 diarrhea	5 (4%)	4 (4%)	9 (4%)	0.72
Hospitalization with diarrhea	5 (4%)	2 (2%)	7 (3%)	0.25

Effects of budesonide on the incidence and severity of diarrhea

In group CABA, 14 of 113 patients (12%) had grade 2–3 diarrhea in one of the first two cycles of cabazitaxel treatment as reported by physicians (see Table 3). In group BUD, 21 of 114 patients (18%) had grade 2–3 diarrhea in either one or both ($n = 2$) of the first two cycles of cabazitaxel treatment ($P = 0.21$). Seven patients (3%; CABA $n = 5$, BUD $n = 2$) were hospitalized for diarrhea during cabazitaxel treatment. Grade 3 diarrhea occurred in 4% of patients. The incidence of grade 3 diarrhea was not different between group CABA ($n = 5$) and group BUD ($n = 4$; $P = 0.72$). Interestingly, no grade 4 diarrhea was observed. Data from patients' diaries is shown in Supplementary Table S4.

Effects of cabazitaxel and/or budesonide on PSA response

PSA decrease of at least 50% was seen in 30% of all patients (38/113 patients in group CABA vs. 31/114 in group BUD). Concomitant use of budesonide had no effect on PSA response ($P = 0.29$).

Effects of budesonide on other cabazitaxel-induced adverse events

Budesonide had no statistically significant effect on the incidence and severity of neutropenia, leukopenia, thrombocytopenia, nausea, vomiting, alopecia, and motor and sensory neuropathy during the first two cycles (see Table 4). No correlation was seen between the occurrence of neutropenia and grade 2–4 diarrhea ($P = 0.32$).

Discussion

In this phase II trial, the incidence of diarrhea was found to be markedly lower than expected. Grade 3 diarrhea was reported in only 4% of patients and grade 4 was not reported at all, whereas 6% grade 3–4 diarrhea was reported in the TROPIC trial (1). As the physician-reported grades of diarrhea were complemented with data from the patient diaries in our study, the reported incidence of diarrhea is not likely to be an underestimation. Moreover, in the Italian and UK early access program and in the Spanish expanded access program, similar grades were reported (6–9). These data add to the accumulating evidence that real-world toxicity of cabazitaxel is less than that experienced in the TROPIC trial (1). Compared with our study, the TROPIC trial included a relatively large proportion of patients with more advanced disease, for example, patients with ECOG performance score ≥ 2 or with more than 2 lines of chemotherapy before inclusion, which may have caused them to be more prone to developing diarrhea. Furthermore, it has also been suggested that the large diversity of participating hospitals in the TROPIC trial may have contributed to the higher incidence of (severe) diarrhea (9).

The primary endpoint, that is, diarrhea $\geq$grade 2, was not affected by adding prophylactic budesonide to the first two cabazitaxel cycles. As this study was not designed to investigate the mechanism of diarrhea, we are only able to speculate on it. Chemotherapy-induced diarrhea is thought to be predominantly secretory with an exudative component and to be due to drug toxicity on rapidly dividing cells of the intestinal epithelium (10–12). The most plausible reason would be that cabazitaxel-induced diarrhea results from intestinal cytostatic effects rather than from inflammation. In that case, the mechanism that is targeted by budesonide is simply not present.

Loperamide use was accepted according to local protocol, and adequate use might have caused an underestimation of high-grade cabazitaxel-induced diarrhea. However, one might question the clinical relevance of this underestimation, as in daily clinical practice and presumably in the TROPIC trial, loperamide is used equally frequent, as it gets prescribed at physicians' discretion.

It is unlikely that the anticancer effect of cabazitaxel is altered by the coadministration of budesonide. In this study, the proportion of patients that had a PSA response was not statistically different between both arms. Moreover, in the trial preceding the CABARESC study, we have also shown that budesonide does not influence the pharmacokinetics of cabazitaxel. Although we cannot directly analyses (overall) survival, there is no reason to assume that there is a difference between both arms.

In conclusion, in this phase II study, the incidence of cabazitaxel-induced diarrhea is notably lower than anticipated, diarrhea is not dose limiting at the approved dose of 25 mg/m^2, and this side effect appears to be easily manageable in routine clinical practice. The addition of budesonide to cabazitaxel therapy however had no statistically significant or clinically relevant influence on the pharmacokinetics of cabazitaxel nor the incidence and severity of diarrhea.

Table 4. Effects of budesonide on adverse events

	Group CABA	Group BUD	Total	*P*
Total	113 (100%)	114 (100%)	227 (100%)	—
Neutropenia	55 (49%)	57 (50%)	112 (49%)	0.84
Leukopenia	47 (42%)	49 (43%)	96 (42%)	0.83
Thrombocytopenia	4 (4%)	4 (4%)	8 (4%)	0.99
Neuropathy, motor	5 (4%)	6 (5%)	11 (5%)	0.77
Neuropathy, sensory	29 (26%)	36 (32%)	65 (29%)	0.32
Alopecia	10 (9%)	13 (11%)	23 (10%)	0.52
Nausea	36 (32%)	36 (32%)	72 (32%)	0.96
Vomiting	20 (18%)	17 (15%)	37 (16%)	0.57

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Disclosure of Potential Conflicts of Interest

R.J. van Soest is a consultant/advisory board member for Janssen and Sanofi. R. de Wit is a consultant/advisory board member for Sanofi. R.H.J. Mathijssen reports receiving commercial research grants from Astellas and Sanofi. No potential conflicts of interest were disclosed by the other authors.

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