

Carboplatin-etoposide combination chemotherapy in metastatic castration-resistant prostate cancer: A retrospective study

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Abstract. The combination of cisplatin or carboplatin and etoposide is the standard treatment for certain poorly differentiated neuroendocrine cancers, such as small-cell lung cancer. The aim of this study was to assess the efficacy and tolerability of the carboplatin-etoposide regimen in metastatic castration-resistant prostate cancer (mCRPC). A total of 27 patients treated by carboplatin [area under the curve (AUC)=5] and etoposide (100 mg/m² intravenous infusion on days 1-3 or 75 mg orally/day for 10 days) for mCRPC were included for analysis. The median progression-free survival was 3.3 months [95% confidence interval (CI): 1.9-4.2] and the median overall survival (OS) was 8.1 months (95% CI: 4.06-12.36). The main grade 3-4 toxicities were haematological, namely anemia (33.3%), neutropenia (25.9%) and thrombocytopenia (22.2%), whereas the most common non-hematological toxicity was asthenia (22.2%). The efficacy, compliance and safety profile were generally similar between the oral and intravenous etoposide groups. Pretreated patients with mCRPC may benefit from the carboplatin-etoposide regimen in terms of OS. The toxicities were acceptable, without reported treatment-related mortality. Therefore, the oral etoposide regimen may be a viable alternative for improving the quality of life of the patients. However, this regimen requires further prospective investigation to confirm its efficacy.

Introduction

Prostate cancer is the second most frequently diagnosed type of cancer and the sixth leading cause of cancer-related mortality in men, accounting for 14% (903,500) of total new cancer cases and 6% (258,400) of total cancer deaths in men in 2008 (1). The treatment paradigm for metastatic castration-resistant prostate cancer (mCRPC) is changing rapidly and numerous treatments are available. In heavily pretreated patients, neuroendocrine transdifferentiation may be a mechanism of treatment escape (2-5). The combination of cisplatin or carboplatin and etoposide is the standard treatment for certain poorly differentiated neuroendocrine cancers, such as small-cell lung cancer (6). Of note, the combination of carboplatin and etoposide has provided encouraging results in mCRPC. In a phase II trial by Loriot *et al* (7) assessing the combination of carboplatin [area under the curve (AUC)=5 on day 1] and etoposide (80 mg/m²/day, intravenous infusion on days 1-3) following first-line treatment with docetaxel, the response rate was 23%, the median progression-free survival (PFS) was 2.1 months (range, 0.6-9.6 months) and the median overall survival (OS) was 19 months (range, 2.1-27.7 months). A phase II trial by Fléchon *et al* (8) investigating patients with anaplastic progressive mCRPC assessed carboplatin (AUC=4 on day 1) and etoposide (100 mg/m²/day as an intravenous infusion on days 1-3). The response rate was 8.9%, the PFS was 2.9 months [95% confidence interval (CI): 1.7-3.5] and the median OS was 9.6 months (95% CI: 8.7-12.7).

Prolonged fractionated oral administration of etoposide may provide a theoretical advantage in terms of toxicity over intravenous administration of a bolus dose. A phase I trial by Thiery-Vuillemin *et al* (9) evaluating the combination of carboplatin (AUC=5 on day 1) and oral etoposide (25 mg, 3 times daily) in 19 patients with varied solid tumors, 3 of whom had prostate cancer, reported an acceptable toxicity profile.

In the University Hospital of Besançon, administration of carboplatin-etoposide, orally or intravenously, has been used for heavily pretreated patients with mCRPC. This

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retrospective study aimed to assess the efficacy and tolerability of this regimen and compare the efficacy and tolerability of carboplatin plus oral etoposide vs. carboplatin plus intravenous etoposide.

Patients and methods

Study population. The Bonne Pratiques de Chimiothérapie (BPC[®]) software, which is a computer software for chemotherapy prescription from the medical office to the centralized pharmaceutical unit in charge of antineoplastic drug preparations, has been routinely used since 2001. The BPC[®] software prospectively registers the type of disease, the physician in charge, the date of treatment cycles, the type of regimen, the possible dose adjustments, the cause of interruption and the treatment delay. Through this database, all consecutive patients with metastatic prostate cancer treated by carboplatin (AUC=5) and etoposide (100 mg/m² intravenous infusion on days 1-3 every 3 weeks, or 75 mg orally administered daily for 10 days every 4 weeks) in the Federative Regional Cancer Institute of Franche-Comté were identified.

The Doubs Cancer Registry provided information on patient outcomes, patient and tumor characteristics and survival data. To complete the database, a retrospective search through the medical charts was conducted to collect information on the site of metastatic lesions, performance status (PS), lines of anti-cancer treatment, adverse events, treatment response and date of progression. The biological status was assessed after each cycle and tumor response was assessed at 3 and 6 months after treatment initiation. This database has been approved by the National Commission on Informatics and Liberties (no. 2012-412 of 22/11/2012). The protocol was approved by the Central Ethics Committee (Comité de Protection des Personnes Est-II).

Statistical analysis. The primary objective was the assessment of the efficacy of the carboplatin-etoposide regimen in terms of OS. The secondary endpoints were PFS, treatment response, compliance and safety of the carboplatin-etoposide regimen. In addition, carboplatin plus oral etoposide and carboplatin plus intravenous etoposide were compared in terms of PFS, OS, compliance (measured by dose intensity of oral etoposide and intravenous etoposide) and safety.

The PFS was determined from the date of initiation of carboplatin-etoposide treatment to disease progression or death from any cause. Progression was defined as the earliest indication of radiological progression according to the Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 (10), or biological progression, according to prostate-specific antigen (PSA) levels as determined by the criteria of the Prostate Cancer Clinical Trials Working Group (11). Patients who remained alive without disease progression were censored at the last follow-up. The OS was estimated from the time of the carboplatin-etoposide initiation to death from any cause. Patients who remained alive were censored at the last follow-up. The response rate was estimated according to RECIST 1.1.

PFS and OS were estimated using the Kaplan-Meier method and described as median and 95% CI. Survival curves were compared using the log-rank test. A univariate Cox regression analysis for OS were performed to estimate hazard ratio (HR) with its 95% CI. The factors investigated as potentially asso-

ciated with OS were analyzed using the Cox proportional hazard model and included age (>63 vs. <63 years), type of tumor (adenocarcinoma vs. mixed tumor with neuroendocrine component), PS (0/1 vs. 2/3), metastatic site (bone alone vs. bone ± visceral metastases), chemotherapy regimen (etoposide administered orally or intravenously). The median follow-up was estimated using the reverse Kaplan-Meier method.

Overall response rate (ORR) was defined as the sum of complete response and partial response. Dose intensity was defined as the amount of oral or intravenous etoposide administered during the entire treatment. Toxicity events were reported according to the National Cancer Institute's Common Toxicity Criteria v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). Continuous variables were described as median and qualitative variables were described as frequencies and percentages. A P-value of <0.05 was considered to be statistically significant. All the statistical analyses were performed using SAS[®] 9.3 software (SAS Institute Inc., Cary, NC, USA) and R-2.15.3 software (<http://www.r-project.org/>).

Results

Patient characteristics. Between 2006 and 2013 a total of 27 patients with mCRPC were treated at the Department of Oncology, University Hospital of Besançon (Besançon, France) with a carboplatine-etoposide regimen. Of the 27 patients, 17 (63%) received oral etoposide and 10 (37%) intravenous etoposide.

The baseline characteristics of the patients are presented in Table I. The mean age was 63.4 years (range, 49-75 years), and the median Gleason score was 8. The majority of the patients (85%) exhibited a good Eastern Cooperative Oncology Group (ECOG) PS at diagnosis (0-1). A total of 25 patients (92.6%) had bone metastases, 20 patients (74%) presented with visceral ± bone metastases and 7 patients presented with bone metastases without visceral metastases. The carboplatin-etoposide regimen was commonly administered as second- and further-line treatment (85% of the cases). The baseline characteristics of the patients were similar between the carboplatin plus oral etoposide and the carboplatine plus intravenous etoposide arms.

Therapeutic efficacy. The median follow-up was 41.5 months (95% CI: 10-50.5 months). A total of 21 patients (77.8%) had succumbed to the disease at the time of the data cut-off and 26 patients experienced disease progression.

The median PFS was 3.27 months (95% CI: 1.90-4.19) and the median OS was 8.06 months (95% CI: 4.06-12.36). No significant difference was found between the two groups (log-rank, P=0.84). One complete and 5 partial responses were observed, adding up to an ORR of 18.5%. Stable disease was reported in 4 patients (14.8%) (data not shown).

The median OS was 5.2 months (95% CI: 3.8-6.6) for the carboplatin plus oral etoposide group, compared to 6.1 months (95% CI: 2.0-10.3) in the carboplatin plus intravenous etoposide group. No significant difference was found between the two groups (log-rank, P=0.47). In the univariate Cox analysis, none of the variables were found to be associated with OS (Table II).

Table I. Patient characteristics.

Characteristics	All patients (n=27)	Oral etoposide (n=17)	Intravenous etoposide (n=10)	P-value
Age, years [mean (range)]	63.4 (49-75)	63.1 (57.1-72.9)	63.8 (49.9-75.4)	0.96
ECOG Performance status, n (%)				0.55
0-1	23 (85.2)	14 (82.4)	9 (90.0)	
>1	4 (14.8)	3 (17.6)	1 (10.0)	
Gleason score, n (%)				0.28
6-7	10 (37.0)	5 (50.0)	5 (29.4)	
8-10	17 (63.0)	5 (50.0)	12 (70.6)	
PSA, ng/ml [median (range)]	104 (0.23-2,471)	172 (0.23-2,471)	51 (1.15-504)	0.18
Previous hormone therapy regimens, n (%)				0.55
1	17 (63.0)	10 (58.8)	7 (70.0)	
2	10 (37.0)	7 (41.2)	3 (30.0)	
Previous chemotherapy, n (%)				0.07
0	4 (14.8)	2 (11.8)	2 (20.0)	
1	12 (44.5)	5 (29.4)	7 (70.0)	
2	6 (22.2)	5 (29.4)	1 (10.0)	
3	4 (14.8)	4 (23.5)	0 (0.0)	
4	1 (3.7)	1 (5.9)	0 (0.0)	
Metastatic sites, n (%)				0.21
Bone	25 (92.6)	16 (94.1)	9 (90.0)	
Lymph nodes	12 (44.4)	10 (58.8)	2 (20.0)	
Liver	4 (14.8)	2 (11.8)	2 (20.0)	
Lung	3 (11.1)	2 (11.8)	1 (10.0)	
Other viscera	7 (26.0)	3 (17.6)	3 (30.0)	

ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.

Compliance. Dose reduction was required in 78% (21/27) of the patients. Chemotherapy was interrupted in 3 cases (11%) due to toxicity. No treatment-related deaths were reported. The dose intensity was 77% for oral etoposide and 80% for intravenous etoposide (P=0.57).

Adverse effects. The adverse events are presented in Table III. Grade 3-4 adverse events were observed in 14 patients (52%). The most common grade 3-4 haematological toxicities were anemia, neutropenia and thrombocytopenia, in 9 (33.3%), 7 (25.9%) and 6 (22.2%) patients, respectively. The most common non-hematological grade 3-4 toxicity was asthenia in 6 (22.2%) patients.

The safety profile was generally similar between the oral etoposide and intravenous etoposide groups (Table II).

Discussion

This retrospective analysis assessed the efficacy and tolerability of the combination of carboplatin and etoposide in heavily pretreated mCRPC patients. In a phase II study by Loriot *et al* (7), 40 patients, following failure of standard

treatment with docetaxel, received a median of 3 cycles of a combination of carboplatin (AUC=5) on day 1 and intravenous etoposide (80 mg/m²/day) for 3 consecutive days. The median PFS and OS were 2.1 and 19 months, respectively. The majority of grade 3-4 toxicities were haematological (38% neutropenia and 25% anemia). No thrombocytopenia was observed.

In a phase II study by Fléchon *et al* (8), 55 patients received a median of 4 cycles of carboplatin (AUC=4) on day 1 and intravenous etoposide (100 mg/m²/day) for 3 consecutive days. The median PFS and OS were 2.9 and 9.6 months, respectively. The majority of grade 3-4 toxicities were haematological (65.5% neutropenia, 32.7% thrombocytopenia and 27.3% anemia). In our study, the median PFS was 3.3 months and the median OS 8.1 months. The majority of grade 3-4 toxicities were also haematological (33.3% anemia, 25.9% neutropenia and 22.2% thrombocytopenia). In the study of Loriot *et al* (7), only 10% of the patients had visceral disease and the patients were treated by carboplatin-etoposide after only one cycle of first-line docetaxel-based chemotherapy, which may explain the prolonged OS (19 months).

Poorly differentiated neuroendocrine prostate cancer (small-cell carcinoma, initially referred to as 'anaplastic') is

Table II. Cox univariate analysis for overall survival.

Variables	Median (95% CI)	Log-rank P-value	Univariate Cox analysis HR (95% CI)
Age, years		0.88	
<63	10.22 (3.63-14.59)		1
≥63	7.93 (3.70-14.98)		0.93 (0.39-2.21)
ECOG performance status		0.88	
0-1	7.80 (4.06-12.36)		1
>1	8.72 (3.63-14.98)		1.07 (0.41-2.81)
Gleason score		0.17	
6-7	3.88 (1.54-14.59)		1
8-10	8.72 (4.29-14.98)		0.53 (0.21-1.33)
PSA, ng/ml		0.31	
≤104	7.80 (2.0-NR)		1
>104	8.06 (4.00-12.36)		1.58 (0.64-3.89)
No. of previous hormone therapy regimens		0.73	
1	8.06 (3.70-12.36)		1
2	6.85 (3.14-NR)		0.85 (0.34-2.13)
No. of previous chemotherapies		0.52	
0-1	8.72 (3.14-42.36)		1
>1	7.80 (4.0-12.36)		1.33 (0.54-3.29)
Metastatic sites		0.94	
Bone ± visceral/lymph node	8.06 (4.0-12.36)		1
Bone only	8.47 (2.0-14.98)		1.18 (0.49-2.81)
Chemotherapy regimen		0.47	
Oral etoposide	5.2 (3.8-6.6)		1
Intravenous etoposide	6.1 (2.0-10.3)		0.70 (0.28-1.85)

CI, confidence interval; HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; NR, not reached.

Table III. Treatment-related toxicity.

Adverse events	All patients (n=27)	Oral etoposide (n=17)	Intravenous etoposide (n=10)	P-value
Anemia, n (%)	9 (33.3)	5 (29.4)	4 (40.0)	0.45
Thrombocytopenia, n (%)	6 (22.2)	3 (17.6)	3 (30.0)	0.46
Neutropenia, n (%)	7 (25.9)	3 (17.6)	3 (30.0)	0.46
Febrile neutropenia, n (%)	1 (3.7)	0	1 (10.0)	0.15
Asthenia, n (%)	6 (22.2)	2 (11.8)	4 (40.0)	0.09

a frequently under-recognized late manifestation of prostate cancer. Recognizing this subtype, which is considered to be a mCRPC, may be challenging. On the basis of autopsy series and other studies, neuroendocrine prostate cancer may represent ~25% of late-stage prostate cancers (12). The diagnosis of neuroendocrine cancer is associated with clinical features not considered characteristic of prostate cancer, such as visceral involvement, lytic bone metastases and low or

undetectable PSA levels; this subtype is also associated with a castration-resistant profile. Lorient *et al* (7) included patients who had mCPRC and in whom standard treatment with first-line docetaxel had failed. In the Fléchon *et al* (8) study, the patients had mCRPC with anaplastic characteristics, as defined by ≥1 of the following criteria at trial entry: Visceral metastases (lung, liver, or lymph node involvement, excluding bone metastases) or elevated neuroendocrine marker serum

levels (neuron-specific enolase and/or chromogranin A). In 2013, Aparicio *et al* (13) defined neuroendocrine prostate cancer as having 1 of 7 clinically assessable conditions, i.e., histological evidence of small-cell prostate carcinoma (pure or mixed), presence of visceral metastases alone, predominance of lytic bone metastases, bulky disease, inappropriately low PSA levels, neuroendocrine markers and a short interval to transition to an androgen-independent state. Therefore, a standardized definition of neuroendocrine prostate cancer is required.

Thiery-Vuillemin *et al* (9) demonstrated that the association of carboplatin (AUC=5 on day 1) and oral etoposide (25 mg, 3 times daily) in 19 patients with varied solid tumors, 3 of whom had prostate cancer, reported an acceptable toxicity profile. In our study, efficacy, compliance and safety was generally similar between the oral etoposide and intravenous etoposide groups. The number of medical visits was less significant in the oral etoposide group, which, in this palliative setting, may significantly improve the quality of life.

Other regimens appear to show similar results to ours, including metronomic 40 mg vinorelbine, with a median PFS of 4 months (33.0%; 95% CI: 15.6-55.3) (14). With eribulin, the median PFS was 1.9 months (95% CI: 0.03-9.9) and the median OS 20.8 months (95% CI: 2.2-32.4) (15). The combination of carboplatin-etoposide appears to be superior to other regimens, such as trabectedin (median PFS 1.5 months; 95% CI: 0.9-1.8) (16). With metronomic oral cyclophosphamide, the median PFS was 5 months (95% CI: 3-8) and the median OS 19 months (95% CI: 8-28) (17).

OS and PFS have significantly improved with the novel agents, particularly enzalutamide. In the AFFIRM study, enzalutamide significantly improved OS compared with placebo (HR=0.63; 95% CI: 0.53-0.75) (18), which suggests that conventional chemotherapies have their indications increasingly restricted, excluding docetaxel. Moreover, targeted therapy, such as cabozantinib, a novel experimental inhibitor of MET and vascular endothelial growth factor receptor 2, may be particularly effective in heavily pretreated patients with mCRPC. Cabozantinib achieved regression in 72% of patients with soft tissue lesions and an improvement in the bone scan in 68% of evaluable patients in a prospective study cohort including 171 mCRPC patients. These results prompted the initiation of two phase III trials on cabozantinib (19).

In conclusion, in certain histological types, including neuroendocrine carcinoma, aggressiveness and lack of targeted therapies may be an indication for etoposide and carboplatin combination treatment, with close follow-up for potential complications. However, further investigations are required to determine the potential efficacy of this regimen.

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