

**Keywords:** castration-resistant prostate cancer; docetaxel; gemcitabine; oxaliplatin

# Gemcitabine–oxaliplatin plus prednisolone is active in patients with castration-resistant prostate cancer for whom docetaxel-based chemotherapy failed

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**Background:** There has been no previous study on the activity of gemcitabine in combination with oxaliplatin (GemOx) for castration-resistant prostate cancer (CRPC).

**Methods:** The GemOx was preclinically tested for cytotoxic activity in human prostate cancer cell lines. Clinically, patients with CRPC who failed prior docetaxel were treated with gemcitabine 1000 mg m<sup>-2</sup> and oxaliplatin 100 mg m<sup>-2</sup> intravenously every 2 weeks and prednisolone 5 mg orally twice daily. The primary end point was the prostate-specific antigen (PSA) response rate.

**Results:** The GemOx displayed synergistic effects based on Chou and Talalay analysis. In the phase II study, 33 patients were accrued. The median dose of docetaxel exposure was 518 mg m<sup>-2</sup>. A total of 270 cycles were administered with a median of eight cycles per patient. A PSA response rate was 55% (95% CI, 38–72) and radiologic response rate was 82% (9 out of 11). With a median follow-up duration of 20.5 months, the median time to PSA progression was 5.8 months (95% CI, 4.4–7.2) and the median overall survival was 17.6 months (95% CI, 12.6–22.6). The most frequently observed grade 3 or 4 toxicities were neutropenia (13%) and thrombocytopenia (13%).

**Conclusions:** The GemOx is active and tolerable in patients with metastatic CRPC after docetaxel failure (NCT 01487720).

Standard of care in first-line symptomatic metastatic castration-resistant prostate cancer (mCRPC) is docetaxel-based chemotherapy. The SWOG 9916 and TAX327 studies revealed docetaxel with estramustine or prednisone could not only improve the quality of life and prostate-specific antigen (PSA) response, but also prolong the survival compared with mitoxantrone plus prednisone in mCRPC (Petrylak *et al*, 2004; Tannock *et al*, 2004). However, the

efficacy of the drug has not been long-lasting and nearly all patients have disease progression in a median of 6–8 months (Lee *et al*, 2010). When progression develops on or after docetaxel, standard of care includes cabazitaxel, abiraterone, enzalutamide, or Radium-223 (de Bono *et al*, 2010, 2011; Scher *et al*, 2012; Parker *et al*, 2013). However, when this trial was designed, few treatment regimens could be applied to these patients that gave

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a reasonable response and benefits after failure on a docetaxel-based regimen.

Gemcitabine is a nucleoside analogue with activity against a broad spectrum of solid tumours, such as pancreatic cancer, non-small cell lung cancer, bladder cancer, and ovary cancer (Hertel *et al*, 1990). In an *in vitro* model, gemcitabine exhibited a strong anti-proliferative and colony formation-inhibitory effect in prostate cancer cell lines (Cronauer *et al*, 1996). When gemcitabine alone was tried as first-line therapy for mCRPC, the PSA response rate was only 9%, but the disease control rate (DCR) was 32% with a median duration of 7.1 months (Morant *et al*, 2000). When gemcitabine was combined with prednisone and zoledronic acid in pretreated patients with mCRPC, the PSA response rate was 23% with a DCR of 57% (Di Lorenzo *et al*, 2007).

Oxaliplatin causes DNA damage at the same sites of adduct formation as cisplatin does but overcomes cisplatin resistance in a wide range of solid tumours *in vitro* and *in vivo* (Mathe *et al*, 1989; Tashiro *et al*, 1989). Droz *et al* (2003) performed a phase II study in 54 patients with mCRPC who were randomised to receive oxaliplatin either alone or in combination with 5-fluorouracil. More than 50% of the patients had received prior chemotherapy, including cisplatin. Despite heavy pretreatment, PSA declines were noted in 11% and 19% of patients in each arm. During the conduction of the current study, a pilot trial of oxaliplatin and capecitabine including 14 patients with mCRPC after progression to docetaxel was reported. The results were promising: the PSA response rate was 57%, with a median time to progression of 14.5 weeks with no unexpected toxicities (Gasent Blesa *et al*, 2011).

Gemcitabine plus oxaliplatin combination (GemOx) has been widely studied in pancreatic cancer and has been reported to be safe and effective in germ cell tumours even after intense prior treatments (Kollmannsberger *et al*, 2004; Louvet *et al*, 2005). Given the activity of single agents on mCRPC and the safety of the combination regimen in other solid cancers, further research on this combination is needed for patients with mCRPC (Santisteban *et al*, 2008). Therefore, we conducted a study to assess preclinical activity and synergism in a prostate cell line and to evaluate the clinical activity of GemOx in patients with mCRPC after failure of docetaxel-based regimens.

## MATERIALS AND METHODS

**Cell culture and cell viability assays.** The human prostate cancer cell lines LNCaP, PC3, and DU145 were obtained from American Type Culture Collection (Manassas, VA, USA). All lines were maintained in RPMI-1640 medium supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin. CellTiter 96 AQueous One Solution Cell Proliferation Assay (Promega, Madison, WI, USA) was used to determine cytotoxic effects after treatment with drugs. Cells were seeded at  $2-3 \times 10^3$  cells per well in 96-well plates and then treated with various concentrations of gemcitabine (Sigma-Aldrich, St. Louis, MO, USA) or oxaliplatin (Sanofi-Aventis Korea, Seoul, Korea) or with a combination of gemcitabine and oxaliplatin (fixed concentration ratio of 5:1) for 72 h. At the end of the treatment period, 20  $\mu$ l of 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium(MTS) reagent was added to each well, and then incubated for 2 h at 37 °C. Cell viability was measured via the absorbance at 490 nm on a spectrophotometer (VICTOR X3; Perkin Elmer, Seoul, Korea) with a PerkinElmer 2030 Workstation software. Each experimental condition was performed in triplicate and repeated at least twice. All values were normalised with respect to the viability of untreated cells.

**Evaluation of synergy.** The combined drug effects were evaluated via Chou and Talalay analysis (Chou, 2010). This method involves

the plotting of dose-effect curves for each drug and for multiply diluted, fixed-ratio combinations with the median-effect equation:  $\left(\frac{fa}{fu}\right) = \left(\frac{D}{Dm}\right)^m$ , where  $D$  is the dose of drug,  $fa$  is the fraction of cells affected by dose ( $D$ ), and  $fu$  is the fraction of unaffected cells (i.e.,  $fu = 1 - fa$ ).  $Dm$  is the median-effect dose (i.e., the dose at which 50% of cells are affected) and  $m$  is a coefficient signifying the shape of the dose-effect relationship, where  $m = 1$ ,  $> 1$ , and  $< 1$  indicate hyperbolic, sigmoidal, and flat sigmoidal dose-effect curves, respectively. In this equation, if the values for  $Dm$  and  $m$  are known, then the dose ( $D$ ) for any given degree of effect ( $fa$ ) can be determined. Based on this model, a combination index (CI) was calculated as:  $CI = \left[\frac{(D)_{drug1}}{(Da)_{drug1}}\right] + \left[\frac{(D)_{drug2}}{(Da)_{drug2}}\right]$ , where the denominator  $(Da)_{drug1}$  is the dose of drug 1 that affects a fraction ( $fa$ ) of cells when used alone and  $(Da)_{drug2}$  is the dose of drug 2 that affects the same fraction ( $fa$ ) of cells when used alone. The numerators,  $(D)_{drug1}$  and  $(D)_{drug2}$ , are the doses of drugs 1 and 2 that when used in combination also affect the same fraction ( $fa$ ) of the cells. If the sum of these two fractional terms is equal to 1, then additivity is indicated. If the CI value is  $< 1$ , then synergy is indicated, and if the CI value is  $> 1$ , then antagonism is indicated. The experimental data were analysed with the CompuSyn software (Combosyn Inc., Paramus, NJ, USA).

**Patients.** Patients had pathologically proven prostate cancer and clinical or radiologic evidence of metastatic disease, with documented disease progression according to the Prostate Cancer Clinical Trials Working Group (PCWG) v2.0 criteria during or within 6 months of completion of docetaxel treatment (Scher *et al*, 2008). Eligible patients were at least 20 years of age, with an ECOG performance status of 0-2 and a PSA level of  $\geq 2.0$  ng ml<sup>-1</sup>. Patients who had previous cytotoxic chemotherapy other than docetaxel, such as estramustine, mitoxantrone, etoposide, cyclophosphamide, or cabazitaxel, were also allowed to enter the study. Other inclusion criteria included previous and ongoing castration; antiandrogen withdrawal followed by progression that had to have taken place at least 6 weeks before enrollment, and adequate haematological, hepatic, renal, and cardiac function. Exclusion criteria included active grade 2 or worse peripheral neuropathy, prior  $\beta$ -particle-emitting radioisotope therapy, other tumour type other than adenocarcinoma, central nervous system metastasis, and any other serious medical, psychological, or social condition that would preclude study treatment. All patients were informed of the investigational nature of this study and signed a written informed consent. The protocol was approved by institutional review board (2008-0603) and registered at ClinicalTrials.gov (NCT01487720).

**Chemotherapy.** The combination of gemcitabine and oxaliplatin (GemOx) regimen comprised a gemcitabine 1000 mg m<sup>-2</sup> intravenous infusion at a fixed dose rate (10 mg m<sup>-2</sup> per minute) and a 2-h intravenous infusion of oxaliplatin at a dose of 100 mg m<sup>-2</sup> on day 1. Treatment was repeated every 2 weeks. A maximum of 12 cycles of therapy were permitted unless patient refusal, unacceptable toxicity, or disease progression occurred.

**Pretreatment and on-treatment evaluation.** Pretreatment evaluations included a medical history, ECOG performance status, physical examination, laboratory screening, serum PSA concentration, CT, bone scan, and EKG. Pain and analgesic consumption were assessed at baseline. Pain was assessed with the McGill-Melzack Present Pain Intensity (PPI) scale (Melzack, 1975) and analgesic score was derived from consumption normalised to morphine equivalents (Tannock *et al*, 1996). Physical examinations and blood tests were repeated before each treatment cycle and at the end of treatment. Prostate-specific antigen, PPI and analgesic score were checked every cycle, and bone scan and CT results were

checked every 4 cycles (8 weeks). All adverse events were graded according to NCI CTCAE v 3.0 criteria.

**Statistical consideration.** This was an open label, single-centre, and phase II study. The primary end point was the frequency of PSA response defined by PCWG v.1.0 criteria (Bublely *et al*, 1999): PSA decline  $\geq 50\%$  confirmed with two consecutive measurements. In contrast to PCWG v.1.0, patients with a PSA level of 2–5 ng ml<sup>-1</sup> were considered as evaluable for PSA response. Accrual of 33 patients was needed to detect a 30% PSA response rate compared with a null hypothesis of  $\leq 10\%$ . A statistical level of significance of 0.05, a power of 80%, and a drop-out rate of 10% were assumed to test this hypothesis. Secondary end points included RECIST response, pain response (Melzack, 1975; Tannock *et al*, 1996), maximal and 12-week PSA decline, time to PSA progression, composite progression-free survival (PFS), and overall survival (OS). Composite progression was defined according to the PCWG v. 2.0 criteria as the occurrence of one or more of the following: PSA progression, progression of soft tissue disease per RECIST, bone scan progression (defined as the appearance of two or more lesions attributable to prostate cancer), skeletal event (defined as fracture or bone pain resulting in the need for radiotherapy or surgery), or symptomatic progression (defined as worsening of ECOG performance status and/or increased pain). Increase in pain was defined as the appearance of new pain or an increase in PPI score  $\geq 2$  on two consecutive assessments at least 2 weeks apart.

## RESULTS

**Synergism in human prostate cancer cell lines.** The 50% inhibitory concentrations (IC<sub>50</sub>) in single-drug experiments with 72 h exposure to gemcitabine and oxaliplatin were, respectively, 1.23 and 1.06  $\mu\text{M}$  for LNCaP cells,  $2.06 \times 10^6$  and 5.66  $\mu\text{M}$  for PC3 cells, and 9.92 and 9.06  $\mu\text{M}$  for DU145 cells (Table 1). The sensitivity to gemcitabine and oxaliplatin was higher in LNCaP cells than in DU145 cells. PC3 cells were relatively refractory to gemcitabine but sensitive to oxaliplatin. The CI values at concentrations corresponding to fraction affected (fa) of 0.5, 0.75, 0.9, and 0.95 are summarised in Table 2. Gemcitabine–oxaliplatin combinations displayed synergistic effects in three cell lines, with the synergism most pronounced in LNCaP cell lines. However, in the PC3 cells, the gemcitabine–oxaliplatin combination suggested partial antagonism for concentrations corresponding to an fa of 0.9.

**Patient demographics.** Between 23 December 2009 and 27 November 2012, 33 patients were enrolled in this study. The patient and disease characteristics are summarised in Table 3. Of the 33 patients, 33% had measurable disease and 42% had visceral metastases. The median dose of docetaxel received before the study was 518 mg m<sup>-2</sup> (interquartile range, 316–870), and only one patient (3%) received a cumulative dose of docetaxel  $< 225$  mg m<sup>-2</sup>. About 77% of patients had progressive disease during docetaxel treatment.

**Efficacy.** Post-chemotherapy 12-week and maximal PSA decline following treatment is shown in Figure 1. A PSA response was seen in 18 of 32 evaluable patients (55%; 95% confidence interval (CI), 38–72%). The PSA response was not available in one patient who had died of viral pneumonia after first cycle. Among 11 patients with measurable disease, 9 achieved partial response and 2 had stable disease with a response rate of 82%. Pain response was observed in 13 of 24 patients (54%) with baseline PPI  $\geq 2$ . With a median follow-up duration of 20.5 months with reverse Kaplan–Meier methods (Shuster, 1991) (95% CI, 14.5–26.7), the median time to PSA progression was 5.8 months (95% CI, 4.4–7.2;

Table 1. Effects of gemcitabine and oxaliplatin alone or in combination on prostate cancer cell lines

| Cell lines | IC <sub>50</sub> <sup>a</sup> |                               |                               |
|------------|-------------------------------|-------------------------------|-------------------------------|
|            | Gemcitabine ( $\mu\text{M}$ ) | Oxaliplatin ( $\mu\text{M}$ ) | GemOx (5:1) ( $\mu\text{M}$ ) |
| LNCaP      | 1.23                          | 1.06                          | 0.53                          |
| DU145      | 9.92                          | 9.06                          | 3.73                          |
| PC3        | $2.06 \times 10^5$            | 5.66                          | 7.22                          |

Abbreviations: GemOx = gemcitabine plus oxaliplatin combination; IC<sub>50</sub> = 50% inhibitory concentration.  
<sup>a</sup>IC<sub>50</sub> values were obtained from the CompuSyn software by determining the dose that caused a 50% reduction in the control values.

Table 2. Combination index (CI) values of gemcitabine plus oxaliplatin (5:1) at concentrations corresponding to a fraction affected (fa) of 0.5 and above in prostate cancer cell lines

| Cell lines | CI     |         |        |         |
|------------|--------|---------|--------|---------|
|            | fa 0.5 | fa 0.75 | fa 0.9 | fa 0.95 |
| LNCaP      | 0.44   | 0.12    | 0.12   | 0.14    |
| DU145      | 0.38   | 0.21    | 0.18   | 0.20    |
| PC3        | 0.21   | 0.57    | 1.52   | 2.97    |

Figure 2) and median composite PFS was 5.4 months (95% CI, 3.5–7.3). At the time of this analysis (30 July 2013), 17 patients had died and the median OS was 17.6 months (95% CI, 12.6–22.6; Figure 2) with a 1-year survival rate of 65%.

**Treatment exposure.** A total of 270 cycles were administered with a median number of cycles of 8 (range, 1–12). The median total cumulative doses of oxaliplatin and gemcitabine were 825 mg m<sup>-2</sup> (range, 100–1200) and 8250 mg m<sup>-2</sup>, respectively. The relative dose intensity of GemOx was 77.8% (range, 54.4–99.4). Dose reductions were reported for 6 patients (18%) and treatment delays occurred in 25 patients (76%). The primary reason for treatment discontinuation was disease progression ( $n = 13$ , 49%), followed by toxicity ( $n = 8$ , 24%). Other reasons included concomitant infection ( $n = 2$ , pulmonary mycobacterial infection), aggravation of chronic obstructive pulmonary disease ( $n = 1$ ), and refusal ( $n = 2$ ). Seven patients (21%) completed the planned twelve cycles of chemotherapy.

**Adverse events.** The frequencies of haematological and non-haematological adverse events are shown in Table 4. Events of haematologic grade 3–4 toxicity included neutropenia (13%), thrombocytopenia (13%), leukopenia (10%), febrile neutropenia (urinary tract infection associated with neutropenia, 3%), and anaemia (3%). The majority of non-haematologic toxicities were grade 2 or less and peripheral sensory neuropathy was the most common (39%) non-haematologic grade 2 toxicity, followed by asthenia (23%) and stomatitis (23%). Three patients died within 30 days of the last protocol treatment. After the seventh cycle of GemOx therapy, grade 5 upper gastrointestinal bleeding occurred in a 67-year-old patient who had disseminated lung and liver metastases that were markedly improved with protocol therapy. This event was managed at the local hospital and the exact cause of bleeding was not reported. Grade 5 viral (parainfluenza virus and rhinovirus) pneumonia occurred 4 weeks after completion of the

Table 3. Patient and disease characteristics (n = 33)

| Variable   | n (%)                 |
|--|-----------------------|
| Age (years), median (range)                      | 67 (52–88)            |
| ≥65 years  | 67%                   |
| <b>Karnofsky performance status</b>              |                       |
| 90–100   | 9 (27%)               |
| 80–70  | 19 (58%)              |
| 60   | 5 (15%)               |
| PSA (ng ml <sup>-1</sup> ), median (range)       | 33.4 (2.4–1060.0)     |
| PSA DT (mo), median (range)                      | 1.5 (0.1–7.0)         |
| Measurable disease                               | 11 (33%)              |
| <b>Disease sites</b>                             |                       |
| Bone   | 32 (97%)              |
| LN   | 15 (45%)              |
| Lung   | 7 (21%)               |
| Liver  | 7 (21%)               |
| <b>Gleason score</b>                             |                       |
| 8–10   | 27 (82%)              |
| 7  | 2 (6%)                |
| NA   | 4 (12%)               |
| Presence of pain                                 | 24 (73%)              |
| Anaemia (Hb < 13.5 g dl <sup>-1</sup> )          | 31 (94%)              |
| LDH > ULN  | 12 (40%) <sup>a</sup> |
| <b>Prior docetaxel dose (mg m<sup>-2</sup>)</b>  |                       |
| Median (range)                                   | 518 (120–1500)        |
| <b>Number of patients progressed<sup>b</sup></b> |                       |
| During last docetaxel treatment                  | 24 (77%)              |
| <3 mo since last docetaxel dose                  | 26 (84%)              |
| ≥3 mo since last docetaxel dose                  | 5 (16%)               |
| <b>Radiation</b>                                 |                       |
| Curative   | 6 (18%)               |
| Palliative                                       | 12 (36%)              |
| <b>Prior exposure to chemotherapy</b>            |                       |
| Estramustine                                     | 11 (33%)              |
| Etoposide  | 2 (6%)                |
| Cyclophosphamide                                 | 2 (6%)                |
| Mitoxantrone                                     | 4 (12%)               |
| Docetaxel rechallenge                            | 5 (15%)               |
| Cabazitaxel                                      | 2 (6%)                |
| <b>Pattern of progression</b>                    |                       |
| PSA progression                                  | 32 (97%)              |
| Bone scan progression                            | 14 (42%)              |
| RECIST progression                               | 11 (33%)              |
| Symptomatic progression                          | 14 (42%)              |

Abbreviations: DT = doubling time; LDH = lactate dehydrogenase; LN = lymph node; mo = months; PSA = prostate-specific antigen; ULN = upper limit of normal.  
<sup>a</sup>Available in 30 patients.  
<sup>b</sup>Available in 31 patients.

last cycle of protocol therapy in a 62-year-old patient. The third and final patient to die also suffered from grade 5 viral pneumonia with grade 4 neutropenia that occurred on day 7 after the first cycle of protocol therapy. In all cases, the direct causal relationship with the protocol therapy was difficult to determine.

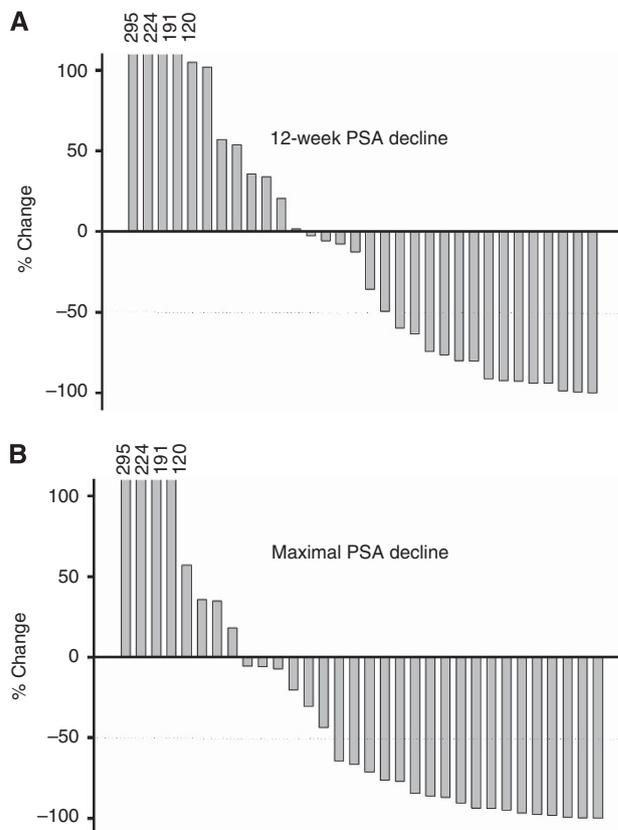


Figure 1. Post-chemotherapy 12-week (A) and maximal PSA decline (B) following gemcitabine plus oxaliplatin combination chemotherapy.

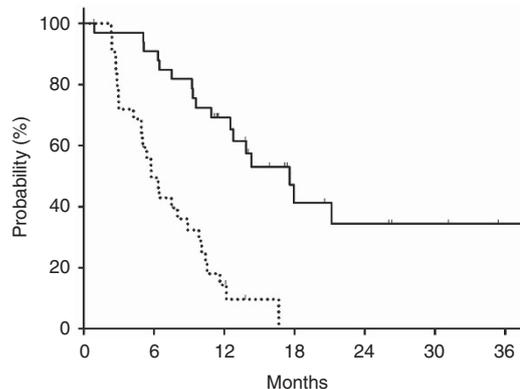


Figure 2. Time to PSA progression (dotted line) and overall survival (solid line) in patients with mCRPC treated with GemOx combination chemotherapy after failure of docetaxel.

**Salvage therapy.** After disease progression, 25 patients (76%) received subsequent therapy: cabazitaxel was administered in 17 and abiraterone was administered in 8. Metronomic oral cyclophosphamide therapy was given in 8 patients. Other treatments included docetaxel retreatment (*n* = 2), estramustine (*n* = 2), and enzalutamide (*n* = 2).

**DISCUSSION**

Our study showed synergistic activity between gemcitabine and oxaliplatin in a range of human prostate cancer cell lines. Based on encouraging preclinical results, a phase II study of a gemcitabine

Table 4. Adverse events possibly related to treatment (n = 31) by grade

| Adverse events                         | No. of patients (%) |                  |                |         |
|--|---------------------|------------------|----------------|---------|
|  | Grade 1             | Grade 2          | Grade 3        | Grade 4 |
| Anaemia                                | 13 (42)             | 8 (26)           | 1 (3)          | 0       |
| Leukopenia                             | 2 (6)               | 5 (16)           | 2 (6)          | 1 (3)   |
| Neutropenia                            | 7 (23)              | 2 (6)            | 3 (10)         | 1 (3)   |
| Thrombocytopenia                       | 8 (26)              | 2 (6)            | 3 (10)         | 1 (3)   |
| Neutropenic infection <sup>a</sup>     | 0                   | 0                | 1 (3)          | 0       |
| Non-neutropenic infection <sup>b</sup> | 0                   | 1 (3), pneumonia | 1 (3), colitis | 0       |
| Transaminitis                          | 2 (6)               | 1 (3)            | 0              | 0       |
| Asthenia                               | 10 (32)             | 7 (23)           | 0              | 0       |
| Anorexia                               | 10 (32)             | 6 (19)           | 0              | 0       |
| Nausea                                 | 4 (13)              | 2 (6)            | 0              | 0       |
| Vomiting                               | 2 (6)               | 0                | 0              | 0       |
| Stomatitis                             | 4 (13)              | 7 (23)           | 0              | 0       |
| Diarrhoea                              | 2 (6)               | 1 (3)            | 2 (6)          | 0       |
| Sensory neuropathy                     | 15 (48)             | 12 (39)          | 0              | 0       |
| Motor neuropathy                       | 5 (16)              | 5 (16)           | 0              | 0       |
| Allergy                                | 1 (3)               | 1 (3)            |                |         |
| Rash                                   | 1 (3)               | 1 (3)            |                |         |

<sup>a</sup>Neutropenic infection grade 5, viral pneumonia at first cycle day 7.

<sup>b</sup>Non-neutropenic infection grade 5, viral pneumonia after seventh cycle of chemotherapy.

and oxaliplatin combination was conducted. This regimen showed promising efficacy, especially in terms of PSA response (55%) and soft tissue response (82%), which were accompanied by a pain response (54%) with an acceptable toxicity profile in patients with mCRPC with prior docetaxel failure.

The PSA and soft tissue responses achieved with GemOx compare favourably with the results of newly approved agents, such as cabazitaxel (39% and 14%, respectively), abiraterone (29% and 14%, respectively), and enzalutamide (54% and 29%, respectively) and far better than those of mitoxantrone-prednisone (18% and 4%, respectively), which was the *de facto* standard worldwide when this trial was designed and the only agent reimbursed by public health insurance systems in Asian countries, including Korea, even after the approval of newer agents (de Bono *et al*, 2010, 2011; Scher *et al*, 2012). The composite PFS of 5.4 months of GemOx was better than the 2.8-month PFS of cabazitaxel, which had adopted the same definition of composite progression and comparable with the 5.6-month radiographic PFS of abiraterone (de Bono *et al*, 2010, 2011). Notably, the response rate was not inferior in patients with visceral metastases; in fact, the response rates seemed to be higher in patients with visceral metastases. As widely known, visceral metastases, such as liver or lung metastases, are, unlike bone or lymph-node metastases, not common and are regarded as late events in the course of disease progression and reported to be associated with anaplastic mCRPC with or without neuroendocrine differentiation (Aparicio *et al*, 2013). Platinum-based chemotherapy is the main therapeutic agent for neuroendocrine carcinoma, and this might be the reason why a higher response was achieved in patients with visceral metastases (Loriot *et al*, 2009; Aparicio *et al*, 2013).

The high rate of pain response (54%) indicates the palliative role of this combination, which would be based on a favourable anti-tumour response and high tolerability. Although, comparison between trials is difficult and might be misleading, the pain response achieved with GemOx looked better than those observed

for mitoxantrone-prednisone (8–29%) or cabazitaxel (9%), and comparable to those achieved with abiraterone (44%) (Tannock *et al*, 1996; de Bono *et al*, 2010).

The safety of this regimen seems to be acceptable. The level of haematologic toxicities observed in the current study compares favourably with that observed in the mitoxantrone-prednisone study and seems to be better than that of cabazitaxel (Tannock *et al*, 1996; de Bono *et al*, 2010). Although survival benefits have been proven with cabazitaxel, the toxicity is not negligible in elderly and frail patients, and the majority of patients need granulocyte colony-stimulating factor, with or without antibiotic prophylaxis. Although older and frailer patients were included in the current study and GemOx was given as a second-line therapy after docetaxel failure, the incidence and severity of adverse events in this study was similar to those of the E6201 study, which used GemOx as the first-line therapy against advanced pancreatic cancer (Poplin *et al*, 2009). However, as expected the incidence of cumulative peripheral sensory neuropathy (grade 2 in 39%), especially in patients who had already have docetaxel-associated or other neuropathy, was significant and 15% of patients refused further treatment due to neuropathy. In addition, there were three treatment-related mortality cases; one gastrointestinal bleeding and two viral pneumonias, one of which was accompanied by grade IV neutropenia. Although their direct causal relationship with study medication was difficult to derive as viral pneumonia was prevalent at that time, it alarms us that cytotoxic agents that have favourable toxicity profile in general population could lead to life-threatening outcome in this kind of frail populations.

For about a half century, platinum drugs have formed a cornerstone of the chemotherapy regimen for various malignancies. Its role in patients with mCRPC has also been studied (Choy *et al*, 2008). Conventional cisplatin or carboplatin has shown only modest activity on mCRPC when used in monotherapy or in combination with taxanes (Oh *et al*, 2007; Nakabayashi *et al*, 2008; Ross *et al*, 2008; Buonerba *et al*, 2011). Next-generation platinum agents, such as oxaliplatin and satraplatin, have better activity because diamminocyclohexane or asymmetrical amine and cyclohexamine platinum adducts from oxaliplatin and satraplatin, respectively, are not recognised by the mismatch repair (MMR) complex that recognises and repairs DNA damage inflicted by conventional platinum (Fink *et al*, 1996). The MMR defects, which have been regarded as one mechanism of cisplatin or carboplatin resistance, are prevalent in prostate cancer (Chen *et al*, 2001). Although the results of the SPARC phase III study have not shown an increase in OS with the use of satraplatin in the second-line setting, they did show a clinically and statistically significant benefit in time to progression, PSA response, pain response, and quality of life (Sternberg *et al*, 2009). The current study also showed the significant activity of oxaliplatin when combined with gemcitabine in mCRPC after failure of docetaxel. Further exploration of the use of platinum in mCRPC is warranted and could provide interesting insights, and platinum might be a viable treatment option in the future.

In conclusion, the GemOx combination chemotherapy is very active in patients with mCRPC after docetaxel failure. The PSA, soft tissue, and pain responses observed with this combination are promising and this regimen deserves further investigation.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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