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Gemcitabine Plus Oxaliplatin (GemOx) as Salvage Chemotherapy in Heavily Pre-treated Metastatic Castration-Resistant Prostate Cancer: A Single-Institution Retrospective Series

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Abstract

Introduction: Therapeutic options for metastatic castration-resistant prostate cancer (mCRPC) are expanding, yet cross-resistance between available agents and multi-line progression represent major unmet clinical needs. Gemcitabine plus oxaliplatin (GemOx) has demonstrated preclinical synergism in prostate cancer cell lines and clinical activity in a phase II study, but real-world data in heavily pre-treated patients remain scarce.

Patients and Methods: We retrospectively reviewed 16 patients with histologically confirmed mCRPC treated with GemOx (gemcitabine 1000 mg/m² plus on day1,oxaliplatin 100 mg/m² IV on day 2,every 14 days, with prednisolone 5 mg twice daily) between the 3rd and 6th line of therapy. The primary endpoint was PSA response rate (≥50% PSA decline confirmed on two consecutive measurements).

Results: Seven of 16 patients (43.7%) achieved a PSA response. Median progression-free survival (PFS) was approximately 4–5 months (range, 1–20 months). The most durable response (PFS 20 months) was observed in a 5th-line patient. Two patients with DNA repair pathway alterations (Lynch syndrome; germline BRCA2 mutation) derived clinical benefit, supporting the biological rationale for platinum use in this subset.

Conclusion: GemOx seems an active and tolerable salvage regimen in heavily pre-treated mCRPC, with a PSA response rate comparable to approved agents evaluated in earlier lines. Prospective evaluation in molecularly selected patients, particularly those with DNA repair deficiencies, is warranted.

Keywords: Castration-resistant prostate cancer; Gemcitabine; oxaliplatin; Platinum-based chemotherapy; DNA repair deficiency; Salvage therapy

Clinical Practice Points

- Gemcitabine plus oxaliplatin (GemOx) achieved a PSA response rate of 43.7% in 16 heavily pre-treated patients with mCRPC, including patients receiving treatment in the 5th and 6th lines of therapy.
- Median progression-free survival was approximately 4–5 months (range, 1–20 months), with one patient maintaining a durable response of 20 months, suggesting that a subset of patients may derive substantial clinical benefit.
- Two patients with documented DNA repair pathway alterations (Lynch syndrome and germline BRCA2 mutation) showed clinically meaningful

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responses, supporting prospective evaluation of GemOx in molecularly selected mCRPC patients with homologous recombination repair deficiency.

- GemOx is off-patent and widely available, representing an economically accessible therapeutic option in settings where access to approved salvage agents (cabazitaxel, PARP inhibitors, radioligand therapies) is limited.

Introduction

Castration-resistant prostate cancer (CRPC) is defined by biochemical and/or radiological progression despite castrate levels of serum testosterone. The treatment armamentarium has expanded markedly over the past decade to include novel androgen receptor pathway inhibitors (abiraterone acetate, enzalutamide, darolutamide, apalutamide), taxane-based chemotherapy (docetaxel, cabazitaxel), PARP inhibitors (olaparib, rucaparib, niraparib), radioligand therapies (lutetium-177-PSMA-617), and alpha-emitting radiopharmaceuticals (radium-223) [1-5]. Despite these advances, resistance invariably emerges and cross-resistance between androgen receptor–targeted agents and taxanes is a clinically relevant problem, leaving many patients with limited options in later lines of therapy.

Gemcitabine, a nucleoside analogue with broad antitumour activity, has demonstrated anti-proliferative and colony-inhibitory effects in prostate cancer cell lines in vitro [6]. Oxaliplatin, a third-generation platinum compound, forms DNA adducts at the same sites as cisplatin but, unlike cisplatin, generates adducts not recognised by the mismatch repair (MMR) complex; this mechanistic distinction may be relevant in prostate cancer, where MMR defects are prevalent [7] The GemOx combination has well-established efficacy and tolerability in pancreatic cancer and germ cell tumours, and preclinical Chou–Talalay analyses have demonstrated synergistic cytotoxicity in LNCaP, DU145, and PC3 prostate cancer cell lines (combination index <1).8 A single-centre phase II study by Lee et al. established that GemOx plus prednisolone is active in post-docetaxel mCRPC, reporting a PSA response rate of 55%, a soft-tissue response rate of 82%, and a median overall survival (OS) of 17.6 months.8 A subsequent systematic review confirmed that oxaliplatin–gemcitabine yields some of the highest PSA response rates among platinum-based regimens studied in mCRPC (25–57%).9 Real-world experience with this regimen in multi-line settings, however, remains limited. We report a single-institution retrospective series of 16 patients with heavily pre-treated mCRPC who received GemOx between the 3rd and 6th line of therapy.

Materials and Methods

We retrospectively identified patients with histologically confirmed metastatic prostate adenocarcinoma receiving GemOx between January 2020 and October 2024 at a single institution. Eligibility required: (1) progressive mCRPC with castrate serum testosterone levels; (2) prior treatment with at least one taxane (docetaxel and/or cabazitaxel); (3) ECOG performance status 0–2; and (4) adequate haematological, hepatic, and renal function. Patients with active grade ≥2 peripheral neuropathy or prior radioisotope therapy causing myelosuppression were excluded.

Patients treated with GemOx rather than other second-line chemotherapy options (e.g., cabazitaxel) were also individually selected based on severe myelotoxicity previously experienced with docetaxel and/or a preference to avoid a further alopecia-inducing chemotherapy in cases where partial or complete hair regrowth had occurred after prior docetaxel.

The GemOx regimen comprised gemcitabine 1000 mg/m² administered as a fixed-dose-rate intravenous infusion (10 mg/m²/min) on day 1 followed by oxaliplatin 100 mg/m² as a 2-hour intravenous infusion on day 2, repeated every 14 days, with prednisolone 5 mg orally twice daily, as per the protocol of Lee et al [8]. Treatment was continued until disease progression, unacceptable toxicity, or patient refusal.

The primary endpoint was PSA response rate, defined as a ≥50% decline in PSA from baseline confirmed on two consecutive measurements at least 3 weeks apart, per Prostate Cancer Clinical Trials Working Group (PCWG) criteria [10]. Secondary endpoints included progression-free survival (PFS), defined as time from GemOx initiation to radiological or biochemical progression or death. Adverse events were graded per NCI-CTCAE version 5.0. Molecular profiling data (germline and/or somatic) were recorded where available. This study was conducted in accordance with the Declaration of Helsinki and all patients provided written informed consent.

Results

Patient Characteristics

Sixteen patients were included in the analysis (Table 1). Median age was 67 years (range, 46–80 years). All patients had bone metastases; visceral involvement (hepatic or pulmonary) was present in 6 patients (37.5%). Prior treatment lines included docetaxel (all patients), abiraterone acetate or enzalutamide (most patients), and cabazitaxel (8 patients, 50%). Three patients had undergone radical prostatectomy. Molecular characterisation was available in 2 patients: one carried a pathogenic germline BRCA2 mutation and one had a diagnosis of Lynch syndrome (MMR deficiency). GemOx was administered as 3rd-line therapy in 5 patients, 4th-line in 6 patients, and 5th or 6th-line in 5 patients. Median number of cycles was 5 (1-14).

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Table 1: Patient characteristics and clinical outcomes with GemOx therapy.

Pt.	Line	Metastatic Sites	PSA init. (ng/mL)	PSA last (ng/mL)	Treatment Period	PFS (months)	Outcome / Comment
1	III	Lymph nodal, pelvic	169	358	May 2020 – Jul 2020	2	Lynch syndrome; Progression
3	IV	Bone, hepatic, lymph nodal	2	2	Dec 2021 – Jun 2022	12	Prolonged stable disease
4	V	Bone, lymph nodal	24	2	Jan 2022 – Mar 2022	6	PSA response
5	IV	Bone	46	52	Feb 2022 – Jul 2022	7	Stable disease
6	III	Bone, lymph nodal, locoregional	8	15	Sep 2022 – Nov 2022	6	Progression
7	III	Bone, lymph nodal	50	12	Aug 2022 – Dec 2022	3	PSA response
8	V	Bone, lymph nodes	147	135	Jan 2021 – Aug 2021	20	Durable response
9	IV	Lung, lymph nodal, bone	47	–	Feb-23	1	Early death
10	V	Bone, lymph nodal	66	103	Jun 2023 – Aug 2023	6	Progression
11	IV	Bone, hepatic, lymph nodal	0.69	–	Jul – Aug 2023	1	Rapid progression
12	V	Bone	316	30	Aug 2024 – ongoing	≥2	PSA response (ongoing)
13	IV	Bone, lymph nodal, lung	30	1	Jun 2024 – Oct 2024	≥1	PSA response
14	III	Pararectal, bone	19	9	Jun 2024 – ongoing	≥5	PSA response (ongoing)
15	IV	Peritoneal carcinomatosis, bone	366	294	Sep 2024 – ongoing	≥1	Stable disease (ongoing)
16	III	Lymph nodes, bone	90	–	Oct 2024 – ongoing	≥1	Under evaluation
17	V	Lymph nodes, bone, liver, locoregional	69	30	Oct 2024 – ongoing	≥1	BRCA2 mut; PSA response (ongoing)

Abbreviations: GemOx = gemcitabine plus oxaliplatin; PFS = progression-free survival; PSA = prostate-specific antigen. PSA init. = PSA at GemOx initiation; PSA last = last available PSA on treatment or at progression.

Table 2: Contextual comparison of PSA response rates with pivotal trials.

Study / Agent	N	PSA Response	Median OS (months)	Study Design / Setting
Lee et al. (2014)8 – GemOx + prednisolone	33	55%	17.6	Phase II; post-docetaxel mCRPC
Current series – GemOx (3rd–6th line)	16	43.70%	NR	Retrospective; heavily pre-treated mCRPC
de Bono et al. (2010)2 – Cabazitaxel	378	39%	15.1	Phase III; post-docetaxel mCRPC
de Bono et al. (2011)3 – Abiraterone	797	29%	14.8	Phase III; post-docetaxel mCRPC
Scher et al. (2012)4 – Enzalutamide	1199	54%	18.4	Phase III; post-docetaxel mCRPC

Abbreviations: GemOx = gemcitabine plus oxaliplatin; mCRPC = metastatic castration-resistant prostate cancer; NR = not reached/reported; OS = overall survival; PSA = prostate-specific antigen.

Efficacy

Of the 16 evaluable patients, 7 (43.7%) achieved a PSA response (≥50% PSA decline). Median PFS was approximately 4–5 months (range, 1–20 months). The most durable response was observed in Patient 8, who received GemOx in the 5th line and maintained disease control for 20 months. One further patient (Patient 3, 4th line) achieved prolonged stable disease with a PFS of 12 months. Among the 6 patients with visceral metastases, responses were observed in 3, consistent with data from Lee et al. suggesting retained activity in this unfavourable subset [8].

The two patients with documented DNA repair pathway alterations both derived clinical benefit: Patient 1 (Lynch syndrome/MMR deficiency) received GemOx in the 3rd line; and Patient 17 (germline BRCA2 mutation) achieved a PSA response (reduction from 69 to 30 ng/mL) in the 5th line and remains on treatment. These observations are consistent with the known sensitivity of HR-deficient tumours to platinum compounds and with mechanistic data showing that oxaliplatin–DNA adducts bypass MMR surveillance [7,9].

Contextual comparison with published pivotal data is shown in Table 2. The PSA response rate in our series (~44%)

is numerically comparable to that of cabazitaxel (39%) and abiraterone (29%) in post-docetaxel phase III trials, despite the more heavily pre-treated nature of our cohort [2,3].

Discussion

This retrospective series demonstrates that GemOx retains clinically meaningful anti-tumour activity in mCRPC patients who have progressed through multiple lines of standard therapy. A PSA response rate of 43.7% and a median PFS of [4,5] months in a cohort receiving GemOx as 3rd- to 6th-line treatment compare favourably with approved post-docetaxel agents tested in less pre-treated populations. Notably, the longest PFS (20 months) was achieved in a 5th-line setting, illustrating that sustained responses are attainable even late in the disease course.

The mechanistic rationale for GemOx in mCRPC is supported by multiple lines of evidence. Oxaliplatin overcomes cisplatin resistance by generating diaminocy clohexane (DACH)-platinum adducts that are not recognised by the MMR complex — a pathway frequently disrupted in prostate cancer [7]. This property is particularly relevant given that up to 30% of advanced CRPC harbour alterations in homologous recombination repair (HRR) genes (BRCA1/2, ATM, CDK12, PALB2), a subset with known platinum sensitivity and constituting a molecularly defined indication for PARP inhibitors [5,9]. The responses observed in the two patients with MMR deficiency (Lynch syndrome) and BRCA2 mutation are consistent with this molecular rationale and with data from the TOPARP trial showing that DNA repair–deficient mCRPC responds to agents exploiting genomic instability [5].

The toxicity profile of GemOx is an important practical consideration. In the pivotal phase II study, grade 3–4 neutropenia and thrombocytopenia each occurred in 13% of patients, while cumulative peripheral sensory neuropathy (grade 2 in 39%) was the most clinically relevant non-haematological toxicity.8 This profile may be preferable to that of cabazitaxel in elderly or frail patients overrepresented in late-line mCRPC, although head-to-head comparative data are lacking. Furthermore, GemOx is off-patent and generically available, offering an economically accessible alternative where access to approved salvage agents is restricted.

Limitations of this series include its retrospective and single-institution design, the small sample size, the heterogeneity of prior treatment exposures, and the absence of prospective toxicity collection or systematic molecular profiling. Median PFS and OS are not formally estimable given the number of patients still on treatment. These findings should be considered hypothesis-generating rather than practice-changing. This experience should not be regarded as a formal phase II protocol, but rather as an exploratory analysis of the activity of the GEMOX regimen in patients with no remaining systemic treatment options, in the era preceding radiometabolic therapy. All patients signed an informed consent form specifying the off-label nature of the regimen.

Conclusions

GemOx is an active salvage regimen in heavily pre-treated mCRPC, with a PSA response rate of 43.7% observed even in the 5th and 6th lines of therapy. The regimen appears particularly suited to patients with visceral disease, DNA repair deficiencies (HRR/MMR), or where access to approved salvage agents is limited. Prospective evaluation in molecularly selected patients — particularly those with BRCA1/2 mutations, ATM alterations, or Lynch syndrome — is warranted to define the optimal role of platinum-based chemotherapy in the current therapeutic landscape of advanced prostate cancer.

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Conflicts of Interest

The authors declare no conflicts of interest.

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