ECF chemotherapy for liver metastases due to castration-resistant prostate cancer

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Cite as: *Can Urol Assoc J* 2014;8(9-10):353-7. http://dx.doi.org/10.5489/cuaj.2029
Published online October 13, 2014.

Abstract

Introduction: Most men with metastatic castration-resistant prostate cancer (CRPC) have biochemical response to docetaxel, but the objective response rate is low. Liver metastases are uncommon with CRPC and associated with shorter survival. More active treatment might benefit these patients. Epirubicin, cisplatin and flurouracil (ECF) is a standard regimen for gastric cancer and response in CRPC liver metastases has been reported. We reviewed our experience with ECF in CRPC with the primary objective of determining its anti-tumour activity in patients with liver metastatic CRPC.

Methods: Men with CRPC treated with ECF were identified from electronic databases and data were extracted from medical records. Men with tumours showing neuroendocrine features were excluded.

Results: In total, we identified 14 CRPC patients treated with ECF were identified, of which 8 had liver metastases. The median age was 56 (range: 42-76) and all had multiple poor prognostic features. A median of 6 cycles of ECF were administered (range: 1-10) and toxicities were similar to previous reports. Of the 8 patients with liver metastases, 5 had partial remission.

Conclusions: ECF was highly active in this small selected group of younger men with liver metastases from CRPC and multiple poor prognostic features. Despite important limitations, this is the third report of high objective response rates with ECF in CRPC. Objective response rates are low with current monotherapies. A higher probability of ORR is preferred for critical organ disease, therefore the anti-tumour activity should encourage testing of ECF in comparison to the most active current therapies.

Introduction

Prostate cancer remains the third most common cause of cancer death in North American men.[1] Although most men with recurrent or metastatic prostate cancer experience remission with androgen deprivation therapy (ADT), cancer progression inevitably occurs despite ADT – a condition referred to as castration-resistant prostate cancer (CRPC).[2] In men with metastatic CRPC, docetaxel-based palliative chemotherapy has been an accepted standard, based on a mild adverse effect profile and improvements in overall survival, palliative response and quality of life response reported in 2 large clinical trials.[3,4] In most men, CRPC is manifest as lymph node and bone metastases, however, a minority have visceral metastases and may succumb to organ failure. With docetaxel, about 50% of men achieve a prostatic-specific antigen (PSA) response, but the tumour objective response rate is much lower.[5] The benefits of docetaxel monotherapy in such patients are uncertain and more active chemotherapy is needed. Combination chemotherapy with epirubicin, cisplatin and low-dose continuous infusion 5-fluorouracil (ECF) was first reported as highly active in advanced gastric cancer.[6] Chao and colleagues[7] reported response in 3 of 5 CRPC patients with liver metastases treated with ECF. ECF has been selectively used at our centre in men with biologically aggressive metastatic CRPC over the past 15 years.

The purpose of this retrospective study was to review this experience to better define the anti-tumour activity of ECF.

Methods

Patients with metastatic CRPC who received ECF at our institution were identified from electronic patient and oncology pharmacy databases. Patients treated for other cancer types, including small cell carcinoma of the prostate and prostate cancers with neuroendocrine features, were excluded. We gathered baseline demographic, tumour and prior treatment data, details of ECF treatment delivery, reasons for discontinuing treatment, and grades 3-5 treatment related adverse events (symptomatic and asymptomatic) using the Common Toxicity Criteria for Adverse Events (CTCAE, v. 3.0).[8] ECF was given as described by Findlay and colleagues:[6] epirubicin 50 mg/m^2 intravenous (IV) day 2, cisplatin 60 mg/m^2 IV day 1, and 5-fluorouracil 200 mg/m^2/day as a continuous IV infusion daily; with cycles repeated every 21 days. In some patients, carboplatin dosed to AUC (area under the

curve) 5 was substituted for cisplatin given that carboplatin has also been active in combination with epirubicin and 5-fluorouracil.[9] All patients received prednisone 5 mg by mouth twice a day, and continued on ADT. Complete clinical and toxicity reviews were conducted at the beginning of each cycle. Tumour imaging and the duration of treatment were at the investigators' discretion. Visceral response was defined in the involved organs using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria whenever possible.[10] PSA response was defined as per the Prostate Cancer Working Group 2 (PCWG2) criteria.[11] Pain response was not rigorously assessed, and was evaluated based on symptom changes and analgesic use noted by the investigators and compared to baseline. Disease progression and response duration were defined by PCWG2 PSA criteria, the appearance of new or enlargement of existing lesions, or clinical deterioration due to disease. Overall and progression-free survivals were plotted using the Kaplan-Meier method and calculated from the date ECF was started. All patients gave written informed consent for ECF treatment and this study was approved by Western University's Human Subjects Research Ethics Board.

Results

Fourteen eligible men treated between November 1996 and December 2010 were identified (Table 1). Nine had ECF as first-line treatment and 5 had prior chemotherapy. At baseline prior to ECF chemotherapy, the median age was 56 (range: 42-76), the median baseline PSA was 184.6 µg/L (range: 0.1-782.3), and the median Eastern Cooperative Oncology Group performance status score was 2 (range: 1-3). The median number of metastatic sites was 2 (range: 1-3). Nine patients had visceral metastases (8 liver and 1 lung). Bone and lymph node metastases were also present in 10 and 6 patients, respectively. Cancer-related pain was present in 12 patients. Of the 5 patients who had chemotherapy prior to ECF, 4 had docetaxel/prednisone and 1 had 3 prior non-docetaxel regimens (estramustine/vinblastine, mitoxantrone, and oral cyclophosphamide). ADT consisted of luteinizing hormone-releasing hormone agonist therapy in all patients, except one treated with bilateral orchidectomy. No patients received hematopoietic growth factors during ECF.

Fourteen patients received a median 6 cycles of ECF (range: 1-10) (Table 2). Five patients were switched from cisplatin to carboplatin and 1 patient received carboplatin only. The median duration of ECF treatment was 18 weeks (range: 1-36). There were no toxicity-related deaths. Grade 3 and 4 neutropenia was seen in 1 patient, thrombocytopenia in 1 and anemia in 2; 1 patient had febrile neutropenia (Table 2). Grade 3 and 4 mucositis, stomatitis, and hand-foot syndrome each occurred in 1 patient.

For all 14 patients, PSA response at 12 weeks was seen in 9 of 11 evaluable patients (81.8%; 95% confidence interval [CI], 59.0 to 100.0%), and the median maximum PSA decline in these patients was 83% (range: 34-99). In addition, 7 of 12 evaluable patients with cancer pain at baseline clinically had improvement with ECF. The overall median progression-free survival was 4.4 months (range: 2.6-17.9) and the median overall survival was 10.4 months (range: 3.1-36.4).

All 9 patients with visceral metastases could be assessed for visceral organ response. Of these, 6 patients had partial remission, 1 stable disease, and 2 had disease progression for an overall objective response rate of 67% (95% CI, 34

Table 1. Patients' pre-treatment characteristics

Patient	Age (years)	ECOG score	Sites of metastases	Pain	Prior chemotherapy	Time from ADT (weeks)	Baseline PSA (µg/L)
1	42	3	Liver, bone, LN	Y	N	17	278.9
2	72	2	Liver, bone, adrenal	N	Y (EV, MP,CP)	143	20.6
3	56	1	Bone	Y	Y (DP)	34	24.3
4	52	3	Liver, bone	Y	N	9	441.9
5	55	1	Liver, RPLN	Y	N	87	320.4
6	76	1	Liver	N	N	68	421
7	66	2	Liver (diffuse), bone	Y	N	97	494
8	47	1	Bone	Y	Y (DP)	39	90.3
9	56	3	RPLN	Y	N	169	782.3
10	57	1	Liver, bone, RPLN	Y	N	38	17
11	70	2	Liver, bone, RPLN	Y	Y (DP)	757	480.2
12	50	1	Lung, bone	Y	N	46	<0.1
13	53	3	Peritoneal, omental, RPLN	Y	N	21	0.56
14	66	2	Bone	Y	Y (DP)	95	<0.1

ECOG: Eastern Cooperative Oncology Group performance status score; Y: yes; N: no; ADT: androgen deprivation therapy; PAS: prostatic-specific antigen; LN: lymph nodes; EV: estramustine, vinblastine, prednisone; MP: mitoxantrone, prednisone; CP: cyclophosphamide, prednisone; DP: doxetaxel, prednisone; RPLN: retroperitoneal lymph nodes.

Table 2. Chemotherapy treatment details

Patient	Regimen	Number of cycles (ECF/ECbF)	Duration (weeks)	Reason for discontinuation	Grade 3/4 TRAEs
1	ECF/ECbF	4 (3/1)	12	PD (symptomatic)	-
2	ECF/ECbF	6 (1/5)	18	PD	Grade 3 Neutropenia
3	ECF/ECbF	10 (8/2)	36	PD (PSA)	Grade 3 Neutropenia Grade 3 Anemia
4	ECF	4	15	PD (Symptoms)	Grade 3 Neutropenia
5	ECF	6	18	Adequate response	Grade 3 Neutropenia
6	ECF	8	27	Adequate response	Grade 3 Neutropenia, Grade 3 mucositis
7	ECF	8	26	Adequate response	Grade 3 Neutropenia
8	ECF	6	23	Asthenia	Grade 3 platelets/anemia Grade 3 neutropenia
9	ECF	1	1	Deterioration in PSA	Grade 3 neutropenia
10	ECF/ECbF	10 (8/2)	29	Adequate response	Febrile Neutropenia
11	ECarbF	4	18	Toxicity	Grade 4 Neutropenia
12	ECF	6	20	Adequate response	Grade 3 Neutropenia
13	ECF/ECbF	2 (1/1)	6	Patient request	Grade 3 Neutropenia
14	ECF	4	13	PD (Symptomatic)	Grade 3 Somatitis

ECF: epirubicin, cisplatin, fluorouracil; ECbF: epirubicin, carboplatin, fluorouracil; TRAEs: treatment-related adverse effects; PD: progressive disease; PSA: prostatic-specific antigen.

to 88%) (Table 3, Fig. 1a, Fig. 1b). The median response duration was 44 weeks (range: 18-77). Five of 8 patients with liver metastases had partial remission (62%). For the patients with liver metastases, the median progression-free survival was 6.0 months (range: 2.6-17.9) and the median overall survival was 7.0 months (range: 3.7-31.8).

Discussion

Non-skeletal visceral metastases occur in less than 25% of men with CRPC.[3] Although a frequent occurrence in most common solid tumours in adults, clinically significant liver metastases are very uncommon in CRPC. Consequently even expert genitourinary medical oncologists may have had little experience treating such patients. At our centre, we identified only 8 patients over 15 years with a severity of hepatic involvement warranting combination chemotherapy. However, this may be changing due to the introduction of novel survival-prolonging treatments. A recent report identified visceral metastases before death in 32% of men overall, and in 49% who had a computed tomography scan within 3 months of death (including 20% liver metastases).[12] It may be reflexive to offer standard palliative monotherapies, including docetaxel or newer agents, such as abiraterone or enzalutamide to patient with liver metastases. However, the overall benefits of these treatments were identified in populations with a vast majority of men having more indolent skeletal and nodal disease. Liver metastases may also lead quickly to death from organ failure, so treatment providing prompt and reliable tumour shrinkage may be desirable. In randomized trials, docetaxel/prednisone has been associated with objective response rates of only 12% to 35.5%.[3,13]

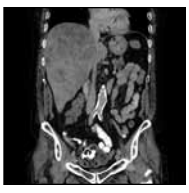

Fig. 1a. Patient 6: Abdominal computed tomography scan demonstrating liver metastases at baseline.

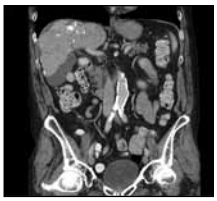

Fig. 1b. Patient 6: Abdominal computed tomography scan demonstrating objective response after six cycles of epirubicin, cisplatin, fluorouracil (ECF).

We report a population of men treated with ECF chemotherapy who had symptomatic metastatic CRPC and a poor prognosis. ECF treatment appeared feasible and safe as first- and second-line treatment in this population, and the nature and severity of adverse effects observed were similar to prior reports. Considering the characteristics of our population, a higher rate of biochemical and visceral metastatic objective response rate was observed than might be expected with docetaxel. There are 3 previous reports of ECF or ECarbF in CRPC. Chao and colleagues[7] initially reported the use of ECF in 21 patients with metastatic CRPC, and reported a response rate of 43% including objective response in 3 of 5 patients with liver metastases. Birtle and colleagues[9] reported on 80 patients with CRPC treated with ECarbF, and although no patients had visceral metastases, objective response was observed in 6 of 7 patients. Combining these data with our report provides an objective response rate of 62% (95% CI, 32-85%) for patients with liver metas-

Table 3. Treatment efficacy

Patient	PSA response	Maximum PSA decline (%)	Pain improvement	Visceral response	PFS (months)	Survival (months)
1	PD	-	NE	PD	-	3.7
2	Y	59	N/A	PD	3.6	5.1
3	Y	98	Y	-	5.6	19.1
4	Y	47	N	SD	2.6	7.4
5	Y	85	Y	PR*	17.9	31.8
6	Y	99	N/A	PR	12.7	15.2
7	Y	89	Y	PR*	6	12.7
8	Y	34	N	-	3.9	35.3
9	NE	-	NE	-	-	3.1
10	Y	83	Y	PR	4.1	9.7
11	Y	47	Y	PR	7.6	7.8
12	N/A	-	Y	PR (lung)	13.8	36.4
13	N/A	-	Y	-	-	3.5
14	N/A	55	N	-	3	4.6

PSA: prostatic-specific antigen; PFS: progression-free survival; PD: progressive disease; NE: not evaluable; Y: yes; N/A: not applicable; N: no; SD: stable disease; PR: partial response; PR*: unequivocal radiological response on hepatic ultrasound compared to baseline computed tomography.

tases. McGovern and colleagues[14] reported on the use of ECarb plus IV bolus 5-fluorouracil in CRPC patients treated following prior progression despite docetaxel. The objective response rate was not reported and the PSA response rate was only 16%. Carboplatin may be as effective as cisplatin in ECF; however, these data suggest that infusional administration of 5-fluorouracil appears important. Use of capecitabine instead of infusional 5-fluorouracil (ECX) has been at least as effective as ECF in esophagogastric cancer.[15]

Oh and colleagues[16] reviewed the use of platinum-based chemotherapy in CRPC and identified objective response rates ranging from 45% to 65% with combinations of estramustine, carboplatin, and either paclitaxel or docetaxel in 6 phase II trials. In a subsequent report studying docetaxel plus carboplatin, the objective response rate was 25% in chemonaive patients who also received with estramustine, and 8% in patients progressing despite docetaxel.[17] Fléchon and colleagues[18] studied etoposide and carboplatin in a phase II trial enrolling men with visceral metastase and/or elevated neuroendocrine markers. Of the 56 patients, 37% had liver metastases and the objective response rate in patients with visceral metastases was 8.9%. Over the past 5 years at least 5 new agents have been approved for CRPC treatment. Cabazitaxel, abiraterone acetate and enzalutamide have been studied in large randomized trials of CRPC patients progressing despite prior docetaxel; all these trials included patients with visceral metastases.[19-21] The objective response rate with abiraterone in patients with visceral disease was 11%.[22] The overall objective response rate was 14.4% and 29% with cabazitaxel and enzalutamide, respectively.[19,20] Kelley and colleagues[13]compared docetaxel/prednisone with and without bevacizumab in a large randomized trial in chemotherapy-naïve CRPC patients. Although negative for its primary endpoint of overall survival, the objective response rate was higher with docetaxel plus bevacizumab (49.4% vs. 35.5%, $p = 0.0013$). Similarly, Tannock and colleagues[23] compared docetaxel/prednisone with and without aflibercept, and the objective response rate was higher with docetaxel plus aflibercept (38.4% vs. 28.1%, $p = 0.0043$).

Our report is limited by its retrospective nature, small sample size and changes in practice over its duration. We could not accurately assess palliative and quality of life effects, and it is unclear whether survival was improved. However, this is the third report showing consistently high objective response rates with ECF in men with CRPC.

Conclusion

Liver metastases are associated with more aggressive biology and it is clear that objective response rates are relatively low with available monotherapies, so more effective treatment for these patients is needed. The anti-tumour activity of ECF in this population encourages further prospective testing of ECF in men with visceral metastatic CRPC perhaps in comparison to enzalutamide or docetaxel plus bevacizumab or aflibercept.

Acknowledgements: The authors' appreciate the assistance of Ms. L. Riehl and Dr. D. Ballingall in the care of these patients.

Competing interests: Dr. Gupta, Dr. Potvin, Dr. Ernst and and Frances Whiston all declare no competing financial or personal interests. Dr. Winquist is currently participated in a clinical trial with Celgene, Eisai, Eli Lilly, Glaxo, Smith Kline and Janssen.

This paper has been peer-reviewed.

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