Clinical Cancer Research

Randomized Phase II Trial of Custirsen (OGX-011) in Combination with Docetaxel or Mitoxantrone as Second-line Therapy in Patients with Metastatic Castrate-Resistant Prostate Cancer Progressing after First-line Docetaxel: CUOG Trial P-06c

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Abstract

Purpose: Clusterin (CLU) is an antiapoptotic, stress-induced protein conferring treatment resistance when overexpressed. This study tested custirsen, a CLU inhibitor, in patients with metastatic castration-resistant prostate cancer (mCRPC) progressing during or within 6 months of initial docetaxel therapy.

Patients and Methods: Men were randomized to receive either docetaxel + prednisone + custirsen (DPC) or mitoxantrone + prednisone + custirsen (MPC).

Results: Forty-two patients received study treatment. Toxicity was similar in both arms. Twenty patients treated with DPC received a median of 8 cycles; overall survival (OS) was 15.8 months. Median time to pain progression (TTPP) was 10.0 months; 10 of 13 (77%) evaluable patients had pain responses. Three of 13 (23%) evaluable patients had objective partial responses. Prostate-specific antigen (PSA) declines of 90% or more, 50% or more, and 30% or more occurred in 4 (20%), 8 (40%), and 11 (55%) patients, respectively.

Twenty-two patients treated with MPC received a median of 6 cycles; OS was 11.5 months. The median TTPP was 5.2 months; 6 of 13 (46%) evaluable patients had pain responses. No objective responses were observed. PSA declines of 50% or more and 30% or more occurred in 6 (27%) and 7 (32%) patients, respectively.

Low serum CLU levels during treatment showed superior survival for patients based on modeling with proportional hazard regression with a time-dependent covariate and different landmarks.

Conclusions: Custirsen plus either docetaxel or mitoxantrone was feasible in patients with progressive mCRPC following first-line docetaxel therapy. Pain relief was higher than expected, with interesting correlations between serum CLU and survival. A phase III trial evaluating the pain palliation benefit of custirsen with taxane therapy is ongoing. *Clin Cancer Res; 17(17); 5765–73. ©2011 AACR.*

Introduction

Docetaxel is standard first-line chemotherapy for men with metastatic castration-resistant prostate cancer (mCRPC; 1, 2). With progression, survival is less than 1 year (3–6). Second-line treatment with mitoxantrone and retreatment with docetaxel are commonly used despite limited data on safety and efficacy. A pressing need exists for novel therapeutics that target the molecular basis of treatment resistance in mCRPC.

Experimental and clinical studies have associated elevated clusterin (CLU) levels with development of treatment resistance in prostate, lung, breast, ovarian, and other cancers (7–12). CLU is a stress induced, cytoprotective chaperone (8–13) upregulated to inhibit cell death that confers broad-spectrum resistance by inhibiting protein aggregation and proteotoxic stress, cytochrome C release, and Bax and caspase activation (13–18). CLU is an attractive candidate for inhibition at the mRNA level.

Custirsen, a second-generation antisense oligonucleotide (ASO), has high affinity for CLU RNA, with increased potency, and a prolonged tissue half-life compared with

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Translational Relevance

Many strategies used to induce the apoptosis of cancer cells also induce stress responses that activate survival pathways and promote emergence of a treatment resistant phenotype. Clusterin (CLU) is a stress-activated cytoprotective chaperone upregulated by a variety of anticancer therapies that confers treatment resistance when overexpressed. Preclinical studies have shown that targeted knockdown of CLU enhances the effects of cytotoxic drugs, including docetaxel, in docetaxel-refractory cells. This clinical trial provides evidence that combining custirsen with chemotherapy is feasible in patients with progressive metastatic castration-resistant prostate cancer following first-line docetaxel therapy and, as pain relief was higher than expected, provided some proof-of-principle of enhanced docetaxel activity. Moreover, it reaffirms that custirsen treatment significantly decreases levels of its target protein, CLU, and for the first time identifies correlations between serum CLU and survival that support further evaluation of serum CLU as a predictive biomarker. Two phase III trials evaluating custirsen plus docetaxel are currently ongoing.

first-generation ASOs. Custirsen potently suppresses CLU levels both *in vitro* and *in vivo* (19, 20). In preclinical CRPC prostate cancer models, treatment with custirsen increased tumor cell death and improved chemosensitivity to multiple drugs, including docetaxel and mitoxantrone (19, 21–25). A phase I study used a novel neoadjuvant designed to identify the optimal biologic dose for custirsen in prostate cancer tissue (26). CLU levels decreased in a dose-dependent manner, with 92% knockdown of CLU protein and mRNA at the 640-mg dose; the mean apoptotic indices increased 3-fold.

The primary objective of the current study was to evaluate the safety of treating patients with mCRPC who progressed after first-line docetaxel chemotherapy with custirsen and prednisone in combination with either docetaxel + prednisone + custirsen (DPC) or mitoxantrone + prednisone + custirsen (MPC). The DPC arm of the study was motivated by preclinical data that custirsen resensitizes docetaxel-refractory prostate cancer cells to docetaxel (25).

Patients and Methods

Study design

This was an open label, noncomparative, randomized study at 10 Canadian sites to evaluate the safety and efficacy of 2 second-line treatments for mCRPC. The primary endpoint was safety. Exploratory endpoints analyzed included measures of efficacy [pain response and time to pain progression (TTPP); prostate-specific antigen (PSA) response; measurable disease response; progression-free survival (PFS); and overall survival (OS)] and the relationship between serum CLU levels and survival.

Eligibility criteria

Patients had a histologic diagnosis of adenocarcinoma of the prostate, metastatic disease by imaging, and 2 or more cycles of first-line docetaxel-based chemotherapy, with disease progression documented within 6 months of discontinuing treatment. Patients had a Karnofsky performance status (PS) of 60% or more, had adequate organ function, and had recovered from prior therapy-related toxicity to grade 2 or less. Documentation and maintenance of a castrate serum testosterone level was required. Exclusion criteria included other active malignancies, congestive heart failure, and central nervous system metastases. No change in current bisphosphonate usage was permitted. All patients provided written informed consent, and the study was approved by local Research Ethics Boards.

Treatment plan

Custirsen, 640 mg, (supplied by OncoGenex Technologies Inc.) was administered i.v. 3 times during a 9-day loading-dose period followed by once-weekly administration. Premedication included ibuprofen or acetaminophen. Either docetaxel, 75 mg/m^2 i.v. for 60 minutes, or mitoxantrone, 12 mg/m^2 i.v. for 30 minutes, was administered on day 1 of each 21-day cycle. Patients were premedicated with corticosteroids and received 5 mg of prednisone orally twice daily unless they were intolerant of steroids. Study treatment was continued until completion of 9 cycles; disease or prostate-cancer pain progression; need for radiation therapy; deterioration of PS; unacceptable toxicity; or more than a 3-week delay in treatment. Patients did not discontinue study therapy for PSA progression. Patients were followed every 2 months for survival. Growth factor administration and blood transfusions were at the discretion of the investigator. Bone and CT scans were obtained at baseline, every 3 cycles, and with symptoms of disease progression. Responses were confirmed 3 or more weeks after the initial scan. Blood tests and pain assessment data were collected prior to the first loading dose, on day 1 of each cycle until progression, and at an end-of-treatment visit.

Dose modifications

Adverse events (AE) were graded according to the Common Terminology Criteria for Adverse Events v3.0. Dose modifications were made on day 1 of each cycle. Patients were removed from therapy for recurrence of toxicity despite 2 dose-reductions or grade 4 life-threatening AEs. Docetaxel or mitoxantrone was held until recovery for a neutrophil count less than 1.5×10^9 cells/L or platelet count less than 100×10^9/L. The dose of either drug was reduced at the next cycle for grade 3/4 hematologic toxicity lasting more than 7 days; febrile neutropenia or infection with neutropenia; and grade 4 thrombocytopenia or gross bleeding associated with a platelet count less than 50×10^9/L. Both drugs were held until recovery and subsequently dose-reduced or discontinued depending on the level of increase in aspartate aminotransferase (AST) and/or bilirubin. Docetaxel or mitoxantrone was held

and subsequently dose-modified for grade 4 non–life-threatening and any other grade 3 or prolonged grade 2 toxicity related to study treatment and considered to be clinically significant. Patients receiving mitoxantrone were removed from therapy for symptomatic congestive heart failure. Custirsen was dose-modified for hyponatremia.

Efficacy analyses

Pain was assessed on an 11-point numeric rating worse pain scale (WPS; 27). Analgesics were coded according to the World Health Organization analgesic ladder, which classifies analgesics into 3 levels: level 1: mild (nonopioids); level 2: moderate (codeine-class opioids); and level 3: strong (morphine-class opioids) (28). Patients with a baseline WPS of 2 or more and/or receiving opioids were considered evaluable for pain response. Pain response was defined as 2-point or more reduction in the WPS from baseline without an increase in the analgesic level, or a reduction in the analgesic level from 3 to 2 or less or from 2 to 1 or less, without an increase in the WPS, both maintained for 3 or more weeks. TTPP for all patients was defined as the time from start of study treatment to a 2-point or more increase from the average of all previous WPS scores; an increase in analgesic level from 0 or 1 to 2 or 3, or from level 2 to 3, both maintained for 3 or more weeks; or requirement for radiation therapy.

PSA response was defined as a decrease in PSA values of 50% or more relative to baseline on 2 or more consecutive measurements 4 to 6 weeks apart. Disease progression was defined as 1 or more of the following: measurable progression by Response Evaluation Criteria in Solid Tumors (RECIST), pain progression, and deterioration of PS, the latter two due to prostate cancer progression. OS was defined as the time from the start of study treatment to the date of death. OS time was censored at the date of the last follow-up for subjects who were still alive. PFS was defined as the time from the start of study treatment to the first documentation of disease progression or the date of death. Patients who failed to return for assessments or received new anticancer therapy were censored at the time of the last disease assessment.

Serum clusterin analysis

Serum CLU samples were collected at baseline and on day 1 of each cycle. Samples were analyzed at Mayo Clinical Trial Services utilizing the BioVendor Clusterin ELISA kit, a solid-phase ELISA in microplate format designed for the quantitative measurement of human CLU in serum, plasma, and cerebrospinal fluid.

Statistical considerations

The planned sample size was 20 patients per arm. With 20 patients, an AE with 10% probability of occurrence is highly likely to be observed at least once with 88% probability. Patients were centrally randomized to eliminate subjectivity in arm selection. The primary analysis set included patients who initiated both custirsen and chemotherapy. The primary endpoint was safety, reported as the percentage of patients experiencing any serious or grade 3 or more AE. Feasibility, reported as the median number of treatment cycles administered within treatment arms, was also of interest. Assessments for PSA response and TTPP were preplanned.

To evaluate the effect of custirsen on CLU, minimum CLU levels during treatment were compared with baseline levels using a 2-sided paired t test. In addition, exploratory analyses to assess the relationship between survival and serum CLU levels were done using a proportional hazard regression procedure. A CLU response was defined as 3 successive CLU levels during therapy less than or equal to median baseline CLU for the population. Patients with less than 3 CLU levels during therapy were defined as non-responders. The starting survival model included the baseline CLU level (as above or below the baseline median), the chemotherapy arm, a time-dependent variable indicating the start of response, and all interactions (3-way or below). The model reported is the most parsimonious hierarchical step-down model using a 0.1 criterion for exclusion of terms. Only patients with baseline and assessments through the day 50 landmark (∼cycle 3 day 1) were included in the analyses to reduce the bias related to censoring due to early deaths (29). Other patient selection criteria, including no landmark and a day 30 landmark (∼cycle 2 day 1), were evaluated to assess robustness of the conclusions.

To assess the consistency of the results, in addition to the hazard regression analysis, Kaplan–Meier estimates for 3 classifications of patients were plotted based on median baseline CLU ($\leq$ median vs. > median); median minimum CLU ($\leq$ median vs. > median) for the population during treatment; and a threshold minimum CLU level of 45 μg/mL or less ($\leq$ 45 vs. >45 μg/mL) during treatment. Although several threshold minimum CLU levels were evaluated, 45 μg/mL was chosen as a value between the median baseline CLU level of 54 μg/mL and the median minimum CLU level of the population during treatment of 34 μg/mL. Survival by the above described classifications was compared using a median estimate and log-rank test.

Results

Patient characteristics and demographics at study entry

Between July 2006 and April 2007, 45 patients were randomized (21 to the DPC arm and 24 to the MPC arm). Three patients (1 in the DPC arm and 2 in the MPC arm) did not initiate both components of the study (custirsen and chemotherapy) and, therefore, were not included in the primary analysis set. Baseline characteristics of the 20 remaining patients in the DPC arm and 22 in the MPC arm are presented in Table 1. For the entire population, the median age was 66 (range, 48–81) years and median PSA was 130 (range, 5–3570) ng/mL. Forty-three percent were on opioids for pain. The median time from the end of first-line therapy to study treatment was 4.2 (range, 0.6–11) months.

Table 1. Demographics at study baseline

	Docetaxel/ prednisone/custirsen ($n = 20$)	Mitoxantrone/ prednisone/custirsen ($n = 22$)	Total population ($N = 42$)
Median age, y, range	68 (48–80)	61 (49–81)	66 (48–81)
Median PSA, ng/mL, range	154 (5–3570)	116 (20–2776)	130 (5–3570)
PSA ≥20 ng/mL (%)	90	100	95
Median hemoglobin, g/dL, range	12.3 (9.0–13.7)	12.6 (8.5–14.3)	12.3 (8.5–14.3)
Median LDH, U/L, range	231 (157–596)	291 (142–1088)	270 (142–1088)
Karnofsky score (% of patients)	70%–80%: (35) 90%–100%: (65)	70%–80%: (41) 90%–100%: (59)	70%–80%: (38) 90%–100%: (62)
Receiving bisphosphonates (%)	40	36	38
Radiotherapy since progression (%)	50	45	48
Worst pain score ≥2 at study entry (%)	40	55	48
On opioids at study entry (%)	45	41	43
Sites of disease (% of patients)			
Bone	100	96	98
Node	65	50	57
Visceral	20	27	24
Measurable disease (% of patients)	65	50	57
Median time (mo) from end of first-line docetaxel therapy to study treatment (range)	4.9 (0.9–7)	3.9 (0.6–11)	4.2 (0.6–11)

Abbreviation: LDH, lactic dehydrogenase.

First-line docetaxel therapy prior to study entry

Patients had received a median of 10 (range, 2–22) of docetaxel. Twenty-two of 42 patients (52%) progressed while on first-line therapy. More patients on the MPC arm progressed while on first-line therapy (64%) than patients on the DPC arm (40%). The median time from the end of first-line therapy to progression for the remaining patients was 3.0 (1.1–6.4) months. Three patients received 1 to 2 "chemotherapy holidays" during first-line therapy. Thirty of 35 patients (86%) with available PSA data had 30% or more declines in PSA. Disease progression following first-line therapy was based on radiographic evidence in half the patients. Table 2 summarizes first-line therapy.

Protocol therapy received

A median of 8 (range, 1–9) cycles of DPC and 6 (range, 1–9) of MPC were administered. Treatment with DPC was discontinued early in 10 patients: 6 for disease progression,

Table 2. First-line docetaxel therapy received prior to study entry

	Docetaxel/prednisone/ custirsen ($n = 20$)	Mitoxantrone/prednisone/ custirsen ($n = 22$)	Total population ($N = 42$)
Median number of treatment cycles administered (range)	10 cycles (2–22)	10 cycles (2–22)	10 cycles (2–22)
≥30% decline in PSA at any time (%)[a]	88	84	86
Patients relapsing while receiving first-line therapy (%)	40	64	52
Median time from end of first-line therapy to disease progression for patients progressing after first-line therapy, mo (range)	2.5 (1.1–5.1)	4.3 (1.8–6.4)	3.0 (1.1–6.4)
Basis of progression (%):[b]			
Bone scan	20	27	24
CT scan	20	27	24
PSA only	60	45	52

[a]PSA data available on 35 of 42 patients.
[b]Patients could have progressed by more than one method.

Table 3. Number (%) of patients with more than 5% grade 3/4 adverse events in either arm

	Docetaxel/ prednisone/ custirsen *N* = 20	Mitoxantrone/ prednisone/ custirsen *N* = 22
Lymphopenia	6 (30%)	7 (32%)
Fatigue	7 (35%)	5 (23%)
Asthenia	3 (15%)	4 (18%)
Neutropenia	2 (10%)	4 (18%)
Leukopenia	1 (5%)	4 (18%)
Dyspnoea	1 (5%)	4 (18%)
Anemia		3 (14%)
Bone pain	1 (5%)	3 (14%)
Hyponatremia		3 (14%)
Insomnia		3 (14%)
Syncope	2 (10%)	
Chest pain		2 (9%)
Headache		2 (9%)
Infections	2[a] (9%)	1[b] (5%)
Febrile neutropenia		2 (9%)
Nausea		2 (9%)

[a]Urinary tract infection and injection site infection.
[b]Pneumonia and septicemia.

3 for toxicity (fatigue, bronchiolitis, and weakness), and 1 for withdrawal of consent. Treatment with MPC was discontinued early in 14 patients: 10 for disease progression, 3 for toxicity (dyspnea, weakness, and increased AST) and 1 at the investigator's discretion.

Toxicity

The most common toxicities felt to be related to either custirsen or docetaxel included fatigue (64%), chills (50%), nausea (50%), pyrexia (40%), anorexia (38%), diarrhea (36%), and vomiting (31%). More than 90% of the AEs were grades 1 and 2. In general, toxicities were similar between the arms. Thirty percent of patients on the DPC arm and 27% on the MPC arm had a documented serious AE. Sixty percent of patients on the DPC arm and 73% on the MPC arm had a grade 3 or higher AE. Grade 3/4 AEs are listed in Table 3. The most common grade 3/4 AEs on either arm were fatigue and lymphopenia, the latter of which was seen in 31% of all patients. Grade 3/4 neutropenia was low, occurring in 10% and 18% of patients treated with DPC and MPC, respectively. There was no grade 3/4 neuropathy. Two patients on the MPC arm had neutropenic fever, 1 patient died from pneumonia with septicemia, and 1 further patient died of heart failure following cycle 8.

Survival and disease progression

All patients were followed until death or a minimum of 39 months. No patient was lost to follow-up. Median OS from the start of study therapy was 15.8 months (95% CI, 9.9–23.3) for DPC, with 4 patients alive at 39 to 44 months, and 11.5 months (95% CI, 6.1–15.2) for MPC, with one alive at 43 months. The 2-year survival rate was 25% (95% CI, 9.1–44.9) for DPC and 14% (95% CI, 3.4–30.9) for MPC. Median PFS was 7.2 months (95% CI, 4.4–9.3) for DPC and 3.4 months (95% CI, 1.6–5.2) for MPC. Kaplan–Meier estimates for median OS from the start of first-line therapy was 30.2 months (95% CI, 19.9–36.4) for patients receiving DPC and 23.5 months (95% CI, 13.8–32.0) for those receiving MPC.

Eight patients on the DPC arm and 14 on the MPC arm progressed while receiving first-line therapy. The median survival of this group, irrespective of arm, was 9.9 months. For the remaining patients who progressed after discontinuing first-line therapy (median of 3.0 months), the OS was 17.9 months (21.4 and 12.8 months for the DCP and the MCP arms, respectively).

PSA response

A PSA response, defined as a confirmed decrease in PSA of 50% or more relative to baseline, was documented in 8 of 20 (40%) patients on the DPC arm and 4 of 22 (18%) on the MPC arm.

As illustrated in the waterfall plot in Fig. 1, of the 20 patients treated with DPC, 4 (20%), 8 (40%), and 11 (55%) had a PSA best percent change of 90% or more, >50% or more, and >30% or more, respectively. Of the 22 patients treated with MPC, 6 (27%) and 7 (32%) had a PSA best percent change of 50% or more and 30% or more, respectively.

Measurable disease response

Patient evaluability for response was defined as having measurable disease and at least one follow-up assessment. In the DPC arm, a confirmed partial response occurred in 3 (15%) of 13 evaluable patients for 4.6, 6.7, and 34.7

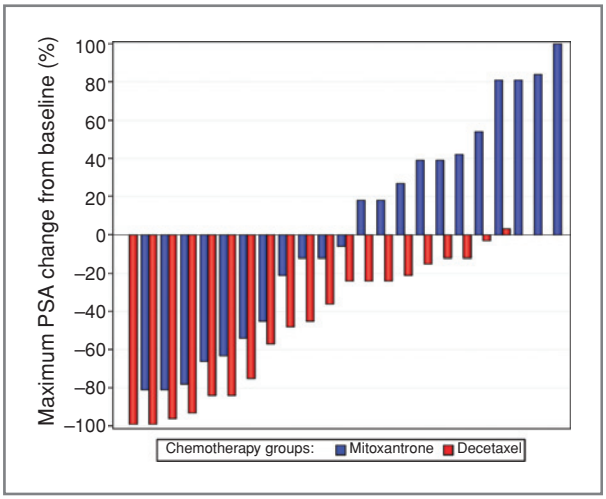

Figure 1. Best percent PSA change from baseline at or after 12 weeks. Calculated from lowest PSA value at any time after baseline while on treatment by individual patients. One patient in the mitoxantrone group had more than 200% increase in PSA. The value was truncated at 100%.

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