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Bone-targeted Novel Cytotoxic Polybisphosphonate Conjugate in Castration-resistant Prostate Cancer: A Multicenter Phase 1 Study

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Abstract. *Background: Osteodex (ODX) is a cytotoxic bone-targeting polybisphosphonate, intended for treatment of bone metastasis from castration-resistant prostate cancer (CRPC). The primary objective of this study was to describe the tolerability and toxicity of such treatment by defining its maximum tolerated dose (MTD) and dose-limiting toxicity (DLT). Patients and Methods: Twenty-eight patients with castration-resistant prostate cancer and confirmed bone metastasis were assigned to seven infusions of ODX every third week, divided in seven ascending dose cohorts. Results: No DLT's were observed and as pre-specified, the highest dose administered was defined as MTD. In total, 206 adverse events (AE) were recorded and 13,6% were classified as treatment-related, while none were serious or severe (SAE). No cumulative toxicity and no renal toxicity were recorded. Conclusion: ODX was well tolerated, with few and mild side-effects and with apparent treatment efficacy in the highest dose cohort. Further clinical development is currently in progress.*

It is well-accepted, that castration-resistant prostate cancer (CRPC) has a propensity to spread to the skeleton, preferably pelvis, ribs, long bones and vertebral bodies (1). The prognosis has been bleak with a short survival time. However, in the last decade several important breakthroughs have been made starting with the first-generation taxanes (docetaxel) followed by a second-generation development (cabazitaxel). In the last few years, novel endocrine therapies (abiraterone and enzalutamide), a radiopharmaceutical (radium-223) and the immunotherapeutic concept (sipuleucil-T) have emerged for treatment for CRPC (2). The above treatment options have all shown an overall survival benefit. However, their modes of action as well as, their treatment-related side-effects are very different. The disturbance of normal bone turnover caused by bone metastasis, with progressive break down of bone and metastatic growth, results in symptomatic skeletal events (SSEs), like skeletal-related pain, pathological fractures, spinal cord compression (3). SSEs result in decreased quality of life and high health care costs (4).

OsteoDex (ODX) is a novel bifunctional cytotoxic bone-targeting polybisphosphonate. The two principal functions are potent bone resorption inhibitory efficacy and high antitumor cell efficacy (*i.e.* ODX targets the two most important constituents of the vicious disease cycle (5): the bone resorbing cells and the tumor cells). Preclinical investigations of ODX demonstrated a potent anti-bone resorption efficacy and high antitumor efficacy that includes significant additional efficacy on soft tissue lesions, even though, ODX is primarily a bone-targeting agent (6-8). The present multicenter study investigates the toxicity and tolerability of ODX in 28 CRPC patients with bone metastasis. The patients were divided in seven ascending-dose cohorts with four patients in each cohort. Since ODX contains bisphosphonate moieties and is administered as an intravenous (IV) infusion, special attention was given to monitor potential kidney toxicity, being a risk organ when infusing bisphosphonates. This was a first-in-man study and therefore the initial dosing was cautious.

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Table I. *Adverse events overview.*

	Cohort (dose level [mg/kg])[1]							
	1 (0.1)	2 (0.3)	3 (0.6)	4 (0.9)	5 (1.2)	6 (1.5)	7 (3.0)	All
N of subj. (total)	4	4	4	4	4	4	4	28
N of subj. with AEs[3]	4	3	4	4	4	4	4	27
N of subj. with AEs related to ODX	2	1	4	1	-	-	1	9
N of subj. with severe AEs[2]	2	2	3	3	4	3	-	17
N of subj. with SAEs	2	2	2	3	3	3	-	15
N of AEs	22	23	46	34	34	20	27	206
N of AEs related to ODX	4	7	9	1	-	-	7	28
N of AEs leading to discontinuation of ODX	-	3	2	-	2	-	-	7
N of severe AEs[2]	5	3	4	10	9	6	-	37
N of SAEs	5	4	2	4	6	5		26
N of SAEs related to ODX	-	-	-	-	-	-	-	-

[1]The investigational product was administered every 3 weeks; [2]CTCAE grade ≥3; *i.e.* severe, disabling or fatal AEs; [3]Referred to as "exposed patients".

Patients and Methods

Design. An open-label, multiple ascending dose multicenter study, EudraCT NUMBER 2011-002850-30, The ClinicalTrials.gov identifier for the study is NCT01595087. The Swedish Medical Product Agency and the Ethics Committee at Norrlands Universitetssjukhus, Umeå, Sweden, approved this study.

Patients. Inclusion criteria: histologically- or cytologically-confirmed diagnosis of adenocarcinoma of the prostate with evidence of metastatic disease from bone scan and/or other imaging modality and with an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2. Evidence of prostate specific antigen (PSA) progression in two consecutive determinations at minimum of one week interval and with castrate level of serum testosterone (<1.7 nmol/l). Failing or not tolerating docetaxel therapy or for other reasons not suitable for such therapy. Laboratory requirements: Neutrophils $\geq 1.5\times10^9$/l, Hemoglobin ≥90 g/l, Platelets $\geq 100\times10^9$/l. Hepatic function: Total S-bilirubin ≤1.5-times the upper limit of normal (ULN) aspartate aminotransferase (ASAT) /alanine aminotransferase (ALAT) ≤2.5 times ULN. Renal function: S-Cr ≤1.5-times the upper limit of normal (ULN). Electrolytes: S-sodium, S-potassium, S-calcium (S-albumin corrected), S-phosphate, S-magnesium, all within normal ranges. No evidence (≤5 years) of prior malignancies, except successfully treated basal cell or squamous cell carcinoma of the skin.

Exclusion criteria: Concurrent use of other anticancer agents or treatments, with the following exception: a stable dosage of luteinizing hormone-releasing hormone (LHRH) agonist/antagonist, polyestradiol phosphate, bicalutamide, flutamide or cyproterone was allowed. Any treatment modalities involving chemotherapy, radiation or major surgery within 4 weeks prior to treatment in this study. Simultaneous participation in any other study involving investigational drugs or having participated in a study less than 4 weeks prior to start of study treatment. Any condition, including the presence of laboratory abnormalities, which confounds the ability to interpret data from the study or places the patient at unacceptable risk if he participates in the study. Known brain metastases, dental surgery (dental extraction), periodontal disease, local trauma including poorly fitting dentures within 6 months prior to the first dose of study drug. Treatment with bisphosphonates within 4 weeks prior to first dose of study medication. The procedures and study flow is illustrated in Table I. Eligible subjects were sequentially assigned to one of seven ascending dose levels, 0,1 mg/kg to 3 mg/kg, starting with the lowest dose (4 subjects /dose level). ODX was administered every third week as an infusion at no longer than 20 minutes after appropriate dilution. Before receiving each ODX dose, the patients were given one injection of Promiten® (300 mg) to prevent possible allergic reactions. Each patient, when receiving his first dose of ODX, was monitored in the hospital during 24 hours. Each subject was to receive at least 4 doses of ODX at 3-week intervals (maximum: 7 doses). The duration of the study for the individual subject was approximately 25 weeks from screening to the follow-up visit 3 weeks after the last dose. Every visit included physical examination, pain and analgesic assessment, concomitant medication, adverse event recording and blood tests (safety serum markers, bone metabolism markers, serum-PSA).

A data monitoring committee (DMC) consisting of a principal investigator, a sponsor's medical expert and a trial statistician were responsible for monitoring/reviewing all study related safety data and for providing recommendations as to whether dose escalations could proceed as planned. A dose escalation meeting was called when data were available for all patients in a cohort after their 6th visit. The recommendation to escalate the dose or not depended on the occurrence of DLTs, in particular changes in S-Cr values from baseline (visit 1) to the first 3-week period (visit 6 pre-dose).

This study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki (2008 version), the principles of Good Clinical Practice (CPMP/ICH/135/95), the EU Directive 2001/20/EC and the relevant laws and regulations in Sweden. Written informed consent was obtained from all subjects

Table II. *Severe adverse events – MedDRA system organ classes (FAS). AEs are sorted by incidence. Percentages are given in brackets.*

	Cohort (dose level [mg/kg])							
MedDRA System organ class (SOC)	1 (0.1)	2 (0.3)	3 (0.6)	4 (0.9)	5 (1.2)	6 (1.5)	7 (3.0)	All
N of subj. (total)	4	4	4	4	4	4	4	28
N of subj. affected	2	2	3	3	4	3	-	17
General disorders and adm. site conditions			1 (25.0)	3 (30.0)	2 (22.2)	2 (33.3)		8 (21.6)
Musculoskeletal and connective tissue disorders	3 (60.0)	1 (33.3)	1 (25.0)	2 (20.0)	1 (11.1)			8 (21.6)
Renal and urinary disorders		1 (33.3)		1 (10.0)	2 (22.2)	1 (16.7)		5 (13.5)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			2 (50.0)	1 (10.0)	1 (11.1)			4 (10.8)
Gastrointestinal disorders	1 (20.0)	1 (33.3)		1 (10.0)				3 (8.1)
Infections and infestations	1 (20.0)				1 (11.1)	1 (16.7)		3 (8.1)
Cardiac disorders					1 (11.1)	1 (16.7)		2 (5.4)
Hepatobiliary disorders					1 (11.1)			1 (2.7)
Investigations						1 (16.7)		1 (2.7)
Nervous system disorders				1 (10.0)				1 (2.7)
Surgical and medical procedures				1 (10.0)				1 (2.7)
Total	5 (100)	3 (100)	4 (100)	10 (100)	9 (100)	6 (100)	-	37 (100)

Adm: Administrations.

prior to entry into the study. The investigator explained to each subject both orally and in writing (subject information sheet), the nature, significance, risks and implications of the trial.

Evaluation of the subjects' quality of life (QoL) was one of the secondary objectives of this study. QoL was assessed using the FACT-P questionnaire (Swedish version) at each visit prior to infusion of ODX (at visit 1 also 24 hours post infusion) and at follow-up (three weeks post last infusion). FACT-P data were analyzed according to the scoring and interpretation instructions provided by the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system (www.facit.org).

Statistical methods. A comprehensive statistical analysis plan (SAP) was finalized before database lock. Quantitative data were summarized by descriptive statistics. For qualitative data, frequency tables were prepared. All data were presented by cohort and in total, as appropriate. Missing data were not replaced. No adjustment for or investigation of center effects was planned. The primary analysis population was the full analysis set (FAS), *i.e.*, the population of all subjects who received at least one dose of the investigational product in this study. FAS was also the population used for the analysis of safety parameters (safety population) and secondary variables.

Results

Summary, adverse events. Twenty-eight patients were recruited in three centers in Sweden between January 31, 2012 and June 5, 2013. In total, 206 adverse events (AE) (*i.e.* any untoward medical occurrence that may present during treatment) were recorded, 28 of which (13,6%) were classified as treatment-related events. However, none were serious or severe events (SAE) , *i.e.* result in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, result in persistent or significant disability/incapacity or is an important medical event. Transient arthralgia and musculoskeletal pain were the typical treatment related complaints, usually moderate however resulting in one withdrawal. No cumulative toxicity was recorded (Table I, see AE overview).

All subjects experienced at least one AE except for one subject in cohort 2 (0.3 mg/kg); 9 of 28 subjects experienced at least one AE judged as related to treatment with ODX, seventeen subjects experienced at least one severe AE (Grade 3 or higher) and fifteen subjects experienced at least one serious AE. The lowest number of AEs was observed in cohort six (20 AEs) and the highest number in cohort three (46 AEs). The majority of AEs were of mild or moderate severity and their outcome was "recovery", either complete or with sequelae. Twenty-six of 206 AEs (12.6%) were classified as serious (SAE, Table II). There were five AEs in four subjects with the outcome death and none of these AEs was related to treatment with ODX (Table III).

Clinical laboratory evaluation. ODX has multiple bisphosphonate moieties and is administered as an IV infusion and therefore kidney function was carefully recorded throughout the study (serum creatinine, S-Cr). The changes in individual S-Cr levels observed over time were generally moderate. The criteria for an S-Cr related DLT (*i.e.* the dose that yields toxicity that prevents increasing the dose), was S-Cr value ≥1.5 at visit 6, or >50% change of the baseline value, were met in none of the subjects (Table IV).

Table III. *Deaths full analysis set (FAS)*

Co-hort	Subj. no.	Preferred term	System organ class	Relationship to ODX
1	103	Bronchopneumonia	Infections and infestations	Not related
5	206	Acute hepatic failure	Hepatobiliary disorders	Not related
		Renal failure acute	Renal and urinary disorders	Not related
	306	Pneumonia	Infections and infestations	Not related
6	210	Sepsis	Infections and infestations	Not related

Table IV. *S-Cr concentrations and shifts between visit six and baseline (FAS).*

Parameter	Visit 6	Baseline (visit 1)		
		Below normal range N (%)	Within normal range N (%)	Above normal range N (%)
Creatinine	Above	0 (0.0)	3 (75.0)	1 (25.0)
	Below	1 (100.0)	0 (0.0)	0 (0.0)
	Normal	1 (4.5)	21 (95.5)	0 (0.0)

*Grey shaded cells=no shift.

Other biochemistry parameters. Shifts below or above the normal ranges were rare for all parameters and visits, including phosphate, calcium, glucose and hematology parameters. None was judged to be related to ODX treatment. Regarding the vital signs, physical examinations and electrocardiograms (ECG), corresponding shifts from normal to abnormal were comparatively rare for all examinations (abdominal, cardiac, neurological, *etc*.) or visits and without obvious trend or pattern.

Safety conclusions. No DLTs were observed in this study. Thus, as pre-specified in the study protocol, the maximum dose administered in this study, *i.e*., 3.0 mg/kg was defined as the MTD. There were no serious or severe treatment-related AEs reported. The safety data collected in this study were as to be expected for patients with advanced cancer. ODX was found to be safe and well tolerated.

Evaluation of efficacy. Evaluation of the subjects' PSA responses was one of the secondary objectives of this study. No apparent responses were recorded. All individual PSA concentrations determined at screening and during the study were above the normal range. In a number of subjects however, the PSA concentration remained largely constant during the course of the study. Evaluation of response markers related to bone metabolism, serum total alkaline phosphatase (S-ALP) serum type1 pro-collagen (S-PINP) and urinary collagen type 1 telopeptide (U-NTx) was one of the secondary objectives of this study. S-ALP was within the normal range in 11 out of evaluable 27 subjects. In some of subjects, the alkaline phosphatase (ALP) concentration shifted above the normal range during the course of the study. There were no ALP values below the normal range. At screening, U-NTx was within the normal range in 12 of 20 subjects with data. In some of these subjects, the U-NTx concentration shifted outside the normal range during the course of the study. In cohort seven (3 mg/kg) two out of four patients showed declining U-NTx values with ~33% and >80%, respectively. Cohort seven was added after an amendment to be able to evaluate a higher dose than cohort six (1.5 mg/kg), *i.e*. a doubling of the dose. S-P1NP was evaluated only in this cohort and two out of four patients showed a decline of ≥50%.

The functional assessment of cancer therapy-prostate (FACT-P). Within and between dose groups, individual FACT-P total scores showed, as expected, a considerable variability. Overall, FACT scores appeared to stabilize and improve over time.

Discussion

Relatively large proportions of prostate cancer patients develop CRPC, and the survival time varies between 12-36 months. Although the last decade has resulted in a handful of new approved drugs, *i.e*. drugs that improve the overall survival time for CRPC patients (10-14), there is an unmet need for new drugs with a positive impact on survival and quality of life. Quality of life is intimately related with side-

effects of the drugs that are used for treating the CRPC patient. The balance between advantage and adverse events (AE) is delicate in these often fragile patients. The taxanes (docetaxel, carbazitaxel) are associated with potentially debilitating and life threatening AEs, *e.g.* neutropenia, neutropenic fever (however rare but life threatening), diarrhea, sensory neuropathy and fatigue (15). The novel hormonal agents have more favorable toxicity profiles, usually AE grade 1 and 2, *e.g.* hypokalemia, hypertension, diarrhea, hot flashes and fatigue (16, 17).

The primary objective of this study was to determine the MTD of ODX. Special focus was on changes in S-Cr levels indicating kidney toxicity. There are several risk factors for CRPC patients predisposing for renal deterioration, *e.g.* previous bisphosphonate use, use of NSAID (non-steroidal anti-inflammatory drugs) and advanced cancer disease (18-20). Androgen deprivation therapy (ADT), leads to metabolic changes including dyslipidemia and hyperglycemia and together with castrate levels of testosterone, the metabolic changes have secondary negative effects on kidney function, which ultimately might result in acute renal failure (21). This underscores the importance of focusing specially, at the kidney function when investigating newly developed and therefore potentially kidney toxic drug candidates for CRPC treatment.

ODX did not induce any apparent renal toxicity at any of the investigated dose levels (0.1-3 mg/kg). The criterion for an S-Cr related DLT *i.e.*, S-Cr value at visit 6 of ≥1.5 UNL, or change >50% of the baseline value, was not met in any of the subjects. The favorable toxicity profile of ODX found, is likely related to its construction *i.e.* with a carbohydrate backbone (dextran). It is well known that conjugation with dextran of potentially toxic compounds decreases toxicity *in vivo* and increases the therapeutic window (22-24).

In this study, 13.6% of the recorded AE's were related to the ODX treatment. The most common complaint was arthralgia and myalgia and can be classified as acute phase reactions. Except in one case, where the patient preferred to withdraw from the study, the symptoms resolved and could be handled with NSAID or paracetamol. Acute-phase reactions are well known to occur with IV-administered bisphosphonates (25). However, less common musculoskeletal AEs also occur with oral administration. The safety results consistently indicate that ODX is safe and well tolerated with repeated administrations every third week and no cumulative toxicity was seen over the study period.

Efficacy markers related to bone metabolism (S-ALP, P1NP and U-NTx) and PSA were included in the study to obtain a first indication of treatment efficacy. P1NP was only analyzed in cohort seven. Cohort seven has the double dose compared to cohort six and its inclusion was the result of an amendment to the study protocol. In this study, ALP did not seem sensitive enough as a treatment response marker. Although NTX showed considerable variations in the lower dose levels, a significant decrease in two out of four patients was recorded in the highest dose cohort, *i.e.* cohort seven. Due to this, S-P1NP was added as a bone-related marker for the four patients included in this cohort. P1NP is a precursor molecule in the synthesis of bone collagen. Recent studies have demonstrated its high sensitivity and specificity as a marker for bone metastases. Owing to the primarily blastic nature of the bone lesions from prostate cancer, P1NP seems to be suitable therapy response marker (26, 27). In cohort seven, two out of four patients showed a ≥50% decrease in their serum P1NP levels over the study period, judged as a result of the ODX treatment.

Serum PSA did not seem to be affected by ODX in this study. Even though some patients showed stabilization/drop in PSA, the data showed considerable variability. In general, there are several significant cautions to consider regarding interpretation of changes of PSA values over time, especially when evaluating new targeted cytotoxic therapies (28, 29). The MTD dose (3 mg/kg) determined in this study, will be further investigated in a pending randomized double-blind dose-finding multicenter phase 2 study. In the preclinical toxicity study (rats), the renal toxicity threshold dose was at 14 mg/kg, *i.e.* ~4.6-times higher. Additionally, preclinical *in vivo* studies demonstrate clear antitumor efficacy at ~2.5 mg/kg doses. In conclusion, ODX was found safe, with few and mild side effects at treatment with repeated administrations. Neither drug-related SEAs nor cumulative toxicity was noted. Apparent treatment efficacy was observed in the highest dose cohort. The results from this trial has formed the basis for an ongoing clinical phase 2 study.

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