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ORIGINAL ARTICLE

Phase I study of weekly DN-101, a new formulation of calcitriol, in patients with cancer

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Abstract
Background DN-101 is a new, high-dose, oral formulation of calcitriol under investigation for the treatment of cancer. We sought to evaluate the tolerability and pharmacokinetics (PK) of weekly doses of DN-101 in patients with advanced cancer.

Methods Patients who completed a previously reported single dose escalation study of DN-101 [Beer et al. (2005) Clin Cancer Res 11:7794–7799] were eligible for this continuation weekly dosing study. Cohorts of 3–10 patients were treated at doses of 15, 30, 45, 60, and 75 μg calcitriol. Once 45 μg was established as the maximum tolerated dose (MTD), this cohort was expanded to include 18 patients. Dose limiting toxicity (DLT) was defined as ≥grade 2 hypercalcemia or ≥grade 3 persistent treatment-related toxicities.
Results Thirty-seven patients were recruited. DLT of transient reversible grade 2 hypercalcemia (serum calcium of 11.6–12.5 mg/dL) occurred in two of six patients treated with 60 μg of DN-101. No DLT was observed in the 18 patients who received DN-101 weekly at 45 μg. Overall, DN-101 was well tolerated. The most frequent adverse events were fatigue (27%), hypercalcemia (19%, including five grade 1, two grade 2, and no grade 3 or 4 events), and grade 1 nausea (16%). PK parameters following repeat dosing were comparable to those for the initial dose ($n = 4$).
Conclusion The MTD for weekly DN-101 was established as 45 μg. The DLTs observed were two episodes of rapidly reversible grade 2 hypercalcemia in two of the six patients treated at 60 μg weekly. Repeat doses of DN-101 at 45 μg weekly are well tolerated and this dose is suitable for studies of weekly DN-101 in cancer patients.

Keywords Calcitriol · Vitamin D · Pulse dosing · Phase I

OHSU and Dr. Beer have a significant financial interest in Novacea, Inc., a company that may have a commercial interest in the results of this research and technology. This potential conflict was reviewed and a management plan approved by the OHSU Conflict of Interest in Research Committee and the Integrity Program Oversight Council was implemented.

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Introduction

There is a strong pre-clinical rationale for developing vitamin D receptor ligands for the treatment of cancer.

Calcitriol, 1,25-dihydroxycholecalciferol (1,25-OH_2D_3) is the most potent natural ligand for vitamin D receptor. Its activity as a growth inhibitor in numerous in vitro and in vivo models of cancer is well established [1, 2]. Pro-apoptotic and anti-angiogenic activity has also been demonstrated (reviewed in Beer and Myrthue [3]).

In addition to single agent activity, calcitriol and its analogues enhance the activity of a number of antineoplastic treatments, including dexamethasone [4, 5], retinoids [6, 7], tamoxifen [8–10], radiation [11, 12], docetaxel [13], paclitaxel [14], platinum compounds [15, 16], mitoxantrone [17], doxorubicin [18], etoposide [19], and non-steroidal anti-inflammatory agents [20].

In in vivo pre-clinical models, antineoplastic effects of calcitriol require concentrations that are considerably higher than the physiologic range, typically at least nanomolar concentrations. Such concentrations are not achievable with daily dosing due to dose-limiting hypercalcemia and hypercalcuria [21–24]. Less frequent dosing circumvents this limitation and allows substantial dose escalation. Subcutaneous calcitriol administration every other day produced peak blood calcitriol concentrations (C_{max}) of approximately 0.7 nM [25]. Weekly administration of oral calcitriol (Rocaltrol, Roche Pharmaceuticals, Nutley, NJ, USA) allowed further dose escalation [26, 27]. In these trials, weekly administration of oral calcitriol was shown to be safe and peak concentrations of approximately 2 nM were achieved. Further dose escalation was limited not by toxicity, but by non-linear pharmacokinetics (PK) at higher doses [26, 28]. Similar but somewhat lower peak concentrations were reported when Rocaltrol was given on three consecutive days every 7 days with paclitaxel [29] with dexamethasone [30] or in combination with zoledronic acid [31].

These dose escalation trials of calcitriol demonstrated that using commercially available formulations, at higher doses, calcitriol levels do not increase linearly with increasing doses. Commercial formulations of calcitriol (dose range 0.25–0.5 μg capsules) were developed for low-dose replacement therapy and not for high-dose cancer treatment. Further development of calcitriol for cancer therapy was limited by the apparent absorption limitation along with significant inter-patient variability in blood levels and the need for patients to consume a very large number of capsules (typically 70–100). Dose escalation of the commercially available liquid formulation also showed similar PK limitations [28].

DN-101 is a high-dose formulation of calcitriol developed specifically for cancer treatment. This concentrated formulation (15 or 45 μg per capsule) allows treatment with an acceptable number of capsules. We previously examined the tolerability and PK of DN-101 in a single-dose study and showed that C_{max} and area under the concentration curve (AUC) are linear over a broad range of doses [32]. Improved absorption allowed higher concentration of calcitriol to be achieved in patients than had been previously possible. Here we report on the safety, tolerability, and dose limiting toxicity (DLT) of DN-101 administered weekly, an extension of the previously reported single-dose study.

Methods

This study represents an extension of the previously reported study of the safety and PK of a single-dose of DN-101 [32]. All but one of the patients enrolled in the single-dose study also took part in the extension. The DLT was assessed separately in the single-dose study (previously reported) and in this multiple-dose study.

Patients

To be eligible for the weekly dosing study reported here, the patients had to have received DN-101 the single dose portion of this study (Part A). Eligible patients had advanced solid tumors that had failed at least one prior therapy. Patients with prostate cancer with a rising PSA after therapy with curative intent or failing hormonal therapy were also eligible.

For patients with tumors other than prostate cancer, the intent was to enroll patients for whom standard therapies were no longer available. Because the number of standard therapies varies considerably among tumor types, the number of prior therapies required beyond one was not specified. The more liberal entry criteria for prostate cancer patients reflected the more extensive prior experience with high-dose calcitriol in this disease.

Other inclusion criteria included: ECOG performance status $\leq$2, life expectancy $\geq$3 months, white blood cell count $\geq$3,000/mm^3, neutrophil count $\geq$1,500/mm^3, platelet count $\geq$100,000/mm^3, serum creatinine <1.5 mg/dL, albumin >3.0 gm/dL, serum calcium <upper limit of normal (ULN).

Patients were excluded for uncontrolled heart failure, a history of cancer-related hypercalcemia, known hypercalcemia, or vitamin D toxicity, known hypersensitivity to calcitriol, kidney stones within 5 years, or any significant active medical illness that would preclude protocol treatment in the opinion of the investigator. Additionally, patients were not eligible if they had investigational therapy within the past 30 days, calcitriol

within 3 months, or concurrent active treatment for cancer (except for androgen deprivation for prostate cancer). The following concomitant medications were excluded: calcium- or magnesium-containing antacids, bile-resin binders, calcium supplements, and ketoconazole or related compounds.

A negative urine pregnancy test was required of women of childbearing potential and both men and women agreed to use effective contraception. The study was approved by the Institutional Review Boards of the Oregon Health and Science University, and the Roswell Park Cancer Institute. Signed informed patient consent was obtained prior to any procedures.

Dose escalation

The starting dose of DN-101 was 15 μg. The planned dose escalation called for the following doses: 30, 60, 90, 105, 135, 165, 210, 270, and 345 μg, continuing to increase by up to 30% until the maximum tolerated dose (MTD) was reached. At least three patients were to be enrolled at each dose level and monitored for 7 days before the dose was increased to the next dose level.

Dose limiting toxicity was defined as grade 2 or higher hypercalcemia (>11.5 to 12.5 mg/dL), or grade 3 or higher toxicities that were deemed treatment related by the investigator and resulted in discontinuation of the study drug or were deemed persistent by the investigator. The MTD was defined as that dose at which no more than one patient experienced a DLT.

If one of three patients at any dose level experienced a DLT, the cohort receiving that dose was to be expanded to at least six patients to further examine the toxicity profile of that dose. If two or more patients at a dose level experienced a DLT within 7 days, further dose escalation was not pursued and either additional patients would be evaluated at the preceding dose plus 50%, or the MTD was defined as the preceding dose. Patients were not replaced if they encountered a DLT.

Treatment

Initially, the study examined DN-101 in the first week and offered patients treatment with commercially available Rocaltrol (Roche Pharmaceuticals). The protocol was then amended to allow for DN-101 to be used throughout. Thus, the first 12 patients started weekly treatment with Rocaltrol. Of these 12 patients, nine completed all repeat dosing using Rocaltrol and three switched to DN-101 after a protocol amendment. The remaining 25 patients received DN-101 exclusively. Treatment was administered weekly by mouth. The distribution of doses tested and formulation used is detailed in Table 2.

Patients were asked to drink 3–4 cups (24–32 ounces) of water or electrolyte-containing fluids above their usual intake starting 12 h before the dose; oral hydration was continued for 3 days after dosing. Treatment was discontinued for toxicities that met the definition of a DLT. Treatment was to be delayed if the product of serum calcium (in mg/dL) × serum phosphorus (in mg/dL) exceeded 70. Treatment duration was at the discretion of the individual investigator. Patients could also be withdrawn from this study if they withdrew consent or declined to continue in the study, or if there was evidence of disease progression or unacceptable toxicity despite dose modification.

None of the patients received bisphosphonates while they were in the study.

Monitoring

A serum chemistry profile was monitored every 2 weeks. A urinalysis and a 24 h urine collection for creatinine clearance, quantitative protein, and calcium were obtained if a clinically significant elevation in serum creatinine or BUN were observed. A brief physical examination, adverse events assessment, ECOG performance status, and hematology profile were assessed every 30 days. As efficacy was not an objective of this study, disease measurements were not pre-specified; however, serum PSA was assessed every 30 days in all patients with prostate cancer.

Pharmacokinetics

Samples

Patients who received DN-101 at 30 or 45 μg were asked to participate in the assessment of DN-101 PK after at least 8 weeks of the study drug treatment. The goal of this effort was to perform an exploratory within-patient dose-adjusted comparison of the PK to those measured around the first dose. Blood levels were obtained in the outpatient setting before dosing and, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 (Day 2), 48 (Day 3), and 72 h (Day 4) after dosing. These were then compared to the week 1 PK parameters obtained for the same patients.

Analytical methods

Calcitriol plasma concentrations were determined by a commercial radioimmunoassay (DiaSorin, S.P.A.

Saluggia, Italy). For samples that contained calcitriol concentrations greater than the upper limit of detection of the method, the samples were diluted to a target concentration within the calibration curve and reassayed.

Pharmacokinetic analyses

Standard model-independent methods were used to determine descriptive PK parameters based on the plasma concentration-time data of each patient. Values of zero were assigned to plasma samples with adjusted concentrations (baseline subtraction) below zero. WinNonlin Professional 3.3 (Pharsight Corp., Mountain View, CA, USA) was used to complete PK analyses. Microsoft Excel (Redmond, WA, USA) was used to produce mean and standard deviation (SD) plasma concentrations. Maximum concentration (C_{max}), and time of C_{max} (T_{max}) were determined by visual examination of the data. T_{max} was reported as median and range and $T_{1/2}$ was expressed as the harmonic mean and pseudo SD based on the jackknife variance technique [33]. All other group results are reported as arithmetic mean and SD. The linear trapezoidal method was used to calculate the AUC. Paired, dose-adjusted comparisons were made between key PK parameters on therapy and in the first week.

Results

Patients

Of 38 patients who participated in the single-dose study between March 2002 and September 2003, 37 elected to participate in the repeat dosing study. One patient discontinued the study drug treatment due to disease progression after receiving the first dose of DN-101 (Part A) and did not enter the repeat dose portion of the study. Patient characteristics are summarized in Table 1. The majority of patients had prostate cancer. The median age was 71 (range 44–91) and the median ECOG performance status was zero.

Table 1 Patient characteristics

	Part B
Number	37
Age	
Median	71
Range	44–91
ECOG PS	
0	22 (59%)
1	14 (38%)
2	1 (3%)
Gender	
Male	34 (92%)
Female	3 (8%)
Tumor type	
Adenocarcinoma of the prostate	27 (73%)
Adenocarcinoma of the colon	7 (19%)
Adenocarcinoma of the rectum	1 (3%)
Gastric adenocarcinoma	1 (3%)
Squamous cell carcinoma of the head and neck	1 (3%)
Prior therapy	
Surgery	27 (73%)
Radiation	18 (49%)
Chemotherapy	13 (35%)
Hormonal therapy	18 (49%)
Immunotherapy	2 (5%)
Other (includes experimental trial, herbal medicine, calcitriol, steroid)	5 (13%)

Treatment

The number of patients treated at each dose level is summarized in Table 2. Doses between 15 and 75 μg were evaluated. The dose escalation proceeded as planned for the 15 and 30 μg groups. Two DLTs (both self-limited grade 2 hypercalcemia) were observed at the 60 μg dose after 2 months of therapy. As four of the patients at the 60 μg dose level were treated with Rocaltrol, a total of ten patients were entered at this dose level in order to study at least six patients receiving DN-101. Three patients were enrolled to the 75 μg dose level. Their dose was reduced to 45 μg as soon as the DLTs were noted in the 60 μg group.

Eighteen patients were then studied at the 45 μg dose. This number reflects an expansion of this group to gather more robust safety data for this dose and also included a number of patients who were offered participation in the repeat dosing after participating in the single-dose study at a broader range of doses.

Toxicity

Repeated weekly treatment with DN-101 was generally well tolerated. No deaths occurred. DLTs were seen in two patients receiving the 60 μg dose. In both cases, these patients experienced rapidly reversible self-limited grade 2 hypercalcemia. Resolution to grade 0 was documented after 3 days in one patient and 6 days in the other. As both patients remained asymptomatic, no treatment for hypercalcemia was prescribed. The most frequent adverse events are reported in Table 3. For the 18 patients treated at the MTD of 45 μg DN-101, 67% of the patients continued treatment for >6 weeks, reaching a median cumulative dose of 518 μg calcitriol. None of the 18 patients at the MTD required dose modification. In the absence of

Table 2 Dose levels and study drug for weekly dosing

Initial weekly dose level (μg)	Number of patients (*n*)	Number treated with rocaltrol only	Number treated with rocaltrol, then DN-101	Number treated with DN-101 only
15	3	3		
30	3	2	1	
60	10	4	2	4
75	3			3
45	18			18
Total	37	9	3	25

Table 3 Grade 2 or greater adverse events related to weekly DN-101 reported in more than one patient

Adverse event	Severity grade			
	2	3	4	Total ($n = 37$)
Hypercholesterolemia	1 (2.7%)	1 (2.7%)	1 (2.7%)	3 (8.1%)
Hypercalcemia	2 (5.4%)			7 (5.4%)
Hypophosphatemia	2 (5.4%)			2 (5.4%)

Table 4 Comparison of PK parameters of DN-101 following single and repeat oral administration of DN-101

	Dose (μg)		AUC (pg h/mL)		Dose-normalized AUC (pg h/mL/μg)		AUC ratio	$T_{1/2}$ (h)		$T_{1/2}$ ratio
Patient	Single	Weekly	Single	Weekly	Single	Weekly		Single	Weekly	
1	30	30	12037.0	9826.5	401.2	327.6	0.81	14.2	6.8	0.48
2	90	45	23963.7	15271.1	266.3	339.4	1.27	6.9	9.8	1.42
3	105	45	33100.8	19601.6	315.2	435.6	1.38	14.0	17.8	1.27
4	135	45	34863.8	12213.7	258.3	271.4	1.05	17.7	9.7	0.55
						Mean	1.13		Mean	0.93

clinically significant renal toxicity, urinary calcium excretion was not examined; however, in part A of the study we reported that DN-101 significantly increased urinary calcium excretion.

Pharmacokinetics

Four patients participated in a PK study after at least 8 weeks of dosing. All four patients received repeat dosing with DN-101. Each of these patient's PK parameters were compared to their first week PK after adjustment for dose. Although this data set is very limited due to the small number of participant patients and should be viewed as only exploratory, the dose-normalized $AUC_{(0-inf)}$ and $T_{1/2}$ were comparable between single and repeat doses and there was no indication of accumulation or drug-induced metabolism (Table 4).

Discussion

DN-101 was very well tolerated on a weekly schedule. DLT of grade 2 hypercalcemia was found at the 60 μg dose level. An evaluation of a substantial number of patients treated at 45 μg demonstrated an excellent safety profile at this proposed phase II dose.

Exploratory comparison of PK after at least 8 weeks of treatment to first-dose PK showed no evidence of drug accumulation or alteration in AUC or the elimination of half-life with repeat dosing. This analysis was limited by its small sample size and was not powered to exclude even moderate differences.

Based on these results, a dose of 45 μg is recommended as a safe dose for phase II studies, although several caveats should be considered by the designers of future studies. First, grade 2 hypercalcemia was seen not earlier than 2 months. Much higher doses were safely administered as a single dose [32]. Thus, higher doses may be possible when DN-101 is administered less frequently than once per week or for limited time periods and future studies of such schedules should consider a dose escalation component. Further dose escalation of the weekly schedule may also be feasible when DN-101 is administered in combination with agents that reduce hypercalcemia. Bisphosphonates would be one obvious example, but steroids [34] and

taxanes [35] have also been shown to reduce hypercalcemia associated with calcitriol in preclinical systems. Finally, the protocol was quite conservative about definitions of DLT by defining it as grade 2 hypercalcemia. The patients who experienced these DLTs were asymptomatic and the hypercalcemia was self-limited. Thus, this definition of dose-limiting toxicity was more conservative than commonly used definitions in most phase 1 studies. Indeed, in the setting of cancer therapy, grade 2 hypercalcemia may not be clinically important. If DLT was set at grade 3 hypercalcemia, further dose escalation of DN-101 on a weekly schedule may be possible.

This study establishes a safe dose for repeat weekly dosing of DN-101. DN-101 is being examined as a single agent and in combination with several cytotoxic agents in several cancer clinical trials in a range of tumor types.

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