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A DOSE ESCALATION, SAFETY, AND TOLERABILITY STUDY OF MN-029 IN PATIENTS WITH ADVANCED SOLID TUMORS

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Abstract

Purpose—To assess the maximum-tolerated dose (MTD), dose-limiting toxicity (DLT), safety, and tolerability of MN-029, a novel vascular disrupting agent, in patients with advanced solid tumors.

Study Design—MN-029 was administered weekly for 3 consecutive weeks out of 4; 2 cycles were planned. Dose escalation proceeded by 100% per toxicity criteria. Intra-patient dose escalation was permitted.

Results—Twenty patients received a total of 151 infusions of MN-029. No DLTs or grade 4 toxicities occurred. The most common adverse events were nausea, vomiting, arthralgias, and headache. One patient developed acute substernal chest pain 4 days after his first dose of MN-029 and was removed from the study. An MTD was not determined. The recommended phase II dose was identified as 180 mg/m²/week. One patient with advanced pancreatic cancer attained a partial response lasting 10 weeks.

Conclusions—MN-029 was well tolerated in this schedule. Further development of this class of agents is warranted, especially in combination with other anti-cancer treatments.

Keywords

Phase I; vascular disrupting agent; angiogenesis; pathologic neovascularization

INTRODUCTION

Vascular disrupting agents (VDAs) may cause tumor necrosis by binding to the cytoskeletal tubulin of tumor-related endothelial cells [1–4]. In contrast to anti-angiogenic agents that prevent further development of the tumor neovascular network, VDAs selectively shutdown already existing tumor-related neovasculature, leading to extensive tumor cell necrosis. The specificity and therapeutic index of VDAs are based on distinctions of tumor-related neovasculature. Vascular disrupting agents work by acting at the colchicine binding site of

the β subunit of endothelial tubulin, resulting in depolymerization of microtubules and disorganization of actin and tubulin. Disruption of the endothelial cytoskeleton then results in detachment from the vessel wall, leading to a temporary reduction in blood flow [3]. Tumor necrosis then ensues quickly following drug exposure, concentrated most densely in the center of the lesion. This often leaves a viable rim of tumor cells at the periphery, possibly due to the lower interstitial pressure at the rim of the tumor, compared to the center of the tumor, and to the diffusion of nutrients from normal peripheral vessels [5]. Clinical trials of VDAs have demonstrated anecdotal disease activity in patients with adrenocortical carcinoma, sarcoma, and anaplastic thyroid cancer [3,6–10]. Toxicities encountered reflect the off-target vascular activity of these compounds and have included acute coronary syndrome, acute alterations in blood pressure, heart rate and ventricular conduction, and hot flashes [11].

MN-029, methyl 6-[(4-[(2S)-2-aminopropanoyl]amino)phenyl]thio]-1H-benzimidazol-2-ylcarbamate, is a novel tubulin-binding VDA. It is a prodrug that is converted *in vivo* via enzymatic hydrolysis of L-alanine to the active compound, MN-022. MN-029 and MN-022 have been shown to inhibit tubulin polymerization and to disrupt capillary tube formation in HUVECs at nanomolar concentrations. Tumor growth inhibition was demonstrated with MN-029 alone, as well as in combination, with cytotoxics, in nude mice xenograft models of NSCLC, colon cancer, and sarcoma, with maximal tumor necrosis at 18–24 hours post-treatment [12]. Nonclinical pharmacokinetic studies of MN-029 revealed that it is hepatically metabolized to MN-022 and that both renal and hepatobiliary elimination pathways are utilized.

Ricart et al. identified 180 mg/m² as the maximum tolerated dose (MTD) of single agent MN-029 administered intravenously every 3 weeks to 28 patients with advanced solid tumors [13]. Pharmacokinetic studies showed that MN-022 was acetylated to MN-021 and that plasma concentrations of all 3 compounds increased with dose. Three dose limiting toxicities were seen: 1 episode of transient coronary ischemia at 180 mg/m², presumably due to coronary vasospasm (without sequelae and with preservation of myocardial function), along with 1 occurrence of transient ischemic attack and 1 grade 3 elevation of transaminases in a patient with liver metastases, both at 225 mg/m². Common mild to moderate toxicities included nausea and vomiting, hypotension, fatigue, and diarrhea. Nine of 34 patients experienced stable disease, including 2 patients with carcinoid tumors who each completed over 20 cycles of treatment. Reductions in tumor blood flow were seen by DCE-MRI imaging at doses exceeding 80 mg/m² [13].

Here, we report a phase 1 study conducted to determine the safety and tolerability of MN-029 administered weekly in patients with refractory solid tumors.

PATIENTS AND METHODS

Patient selection

Eligible patients were at least 18 years of age, and had a histologically documented, advanced solid tumor that was refractory to standard therapy or for which no curative therapy was available. Other inclusion criteria included: Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; adequate bone marrow function (absolute neutrophil count $\geq 1,500$ cells/ μ l, platelet $\geq 100,000$ / μ l, hemoglobin ≥ 9.0 g/dL); adequate hepatic function (total bilirubin ≤ 1.5 mg/dL, or $\leq 1.5 \times$ the institutional upper limit of normal (IULN), whichever was higher, aspartate transaminase $\leq 3 \times$ IULN, and alanine aminotransferase $\leq 3 \times$ the IULN); adequate renal function (serum creatinine $\leq 1.5 \times$ IULN); and life expectancy greater than 12 weeks. If patients were experiencing pain, it had to be no greater than grade 1 per the National Cancer Institute (NCI) Common Terminology

Criteria for Adverse Events (CTCAE) version 3.0. Lastly, electrocardiograms (ECGs) could not demonstrate evidence of clinically significant ventricular arrhythmias or acute ischemic changes.

Exclusion criteria included the following: brain metastasis or primary brain tumors; ≤ 4 weeks since prior chemotherapy, radiation, or investigational therapy; having not recovered from the toxic effects of prior therapy to $\leq$ grade 1; major surgery within 4 weeks; peripheral neuropathy $\geq$ grade 2; small vessel pathology, such as occurring with diabetes mellitus or autoimmune disease; pregnant or lactating women; uncontrolled intercurrent illness, including history of myocardial infarction within the past 12 months, symptomatic heart failure, unstable angina pectoris, cardiac arrhythmia, uncontrolled hypertension, ongoing or active infection, or psychiatric/social situations that would limit compliance with study requirements; history of high dose chemotherapy with autologous stem cell rescue or bone marrow transplantation; history of cerebrovascular accident or transient ischemic attack within 6 months of treatment; history of coagulopathy or the current use of drugs affecting coagulation (e.g., aspirin, anticoagulant therapy, or non-steroidal anti-inflammatory drugs); history of HIV positivity; or history of severe allergic reactions to excipients.

All patients had to practice effective birth control. Before entering the study, each patient gave written informed consent indicating that they were aware of the investigational nature of the study, according to institutional and federal guidelines. The protocol was approved by the Institutional Review Boards at the 3 participating centers.

Study design

This was a multi-center phase 1, dose-escalating trial designed to determine the safety, tolerability, and maximum tolerated dose (MTD) of MN-029 in advanced solid tumors. MN-029 was administered at a rate of 2 milliliters per minute weekly for three consecutive weeks. A follow-up visit with safety assessments took place on day 21. Treatment was repeated every 28 days. The planned treatment schedule was 2 cycles, but subjects could receive further treatment pending the investigator's judgment. The starting dose of MN-029 was 4 mg/m². Adverse events were evaluated using the NCI CTCAE, version 3.0 guidelines.

Drug administration

MN-029 was supplied by MediciNova, Inc. in 10 and 20 mL, single-use, flint glass vials at a concentration of 5 mg/mL. Study drug doses less than 20 mL (i.e., < 100 mg) were diluted to a total volume of 20 mL with normal saline and administered IV as a 10-minute infusion. Doses with a volume greater than 20 mL were administered undiluted at an infusion rate of 2 mL/min.

Dose escalation

The first cohort consisted of at least 1 subject. Subsequent dose escalations followed an accelerated titration design with initial escalation of 100% in a cohort. Investigator teleconferences were held prior to each dose escalation and at the investigator's request as a means to monitor safety throughout the study. This escalation scheme continued until the occurrence of any $\geq$ grade 2 toxicity related to MN-029. At that point, cohorts were expanded to 3 subjects, and dose escalations were reduced to 50% of the current dose level. Once the first dose limiting toxicity (DLT) occurred, the cohort was expanded to at least 6 subjects. If only 1 of 6 subjects in the expanded cohort experienced a DLT, further dose escalation was reduced to 25% of the current dose level. If ≥ 2 of 6 subjects at a given dose level experienced a DLT, or if 2 subjects experienced a DLT prior to completing the cohort, dose escalation was halted, and the dose level below the DLT level was considered the

MTD. During the conduct of the trial, an intervening dose level could be evaluated to more fully characterize the MTD level.

Intra-subject dose escalation was permitted upon completion of the 2 protocol-mandated treatment cycles. Subjects were eligible to extend dosing at the highest dose level proven tolerable.

Dose limiting toxicities were judged to be at least possibly related to MN-029 during cycle 1 of treatment as follows: any $\geq$ grade 3 non-hematologic toxicity, other than fatigue, diarrhea, alopecia, nausea, or vomiting (however, nausea or vomiting occurring with maximal preventive pre-medication was considered a DLT); grade 4 pain that did not remit to $\leq$ grade 2 within 24 hours of treatment with opiate analgesics; hypersensitivity-related toxicity $\geq$ grade 3 with pre-medication; grade 4 thrombocytopenia, neutropenia, or anemia on the next scheduled dosing day; or any occurrence of febrile neutropenia.

Patients were removed from protocol treatment for disease progression, unacceptable adverse events, intercurrent illness that prevented further treatment, unscheduled treatment delays exceeding 24 hours, subject's withdrawal of consent, investigator's discretion, or greater than two dose reductions. Dose modifications and delays were specified in the protocol. Participants were followed for a minimum of 4 weeks following their termination from study visit.

Pretreatment and follow-up studies

History, physical examination, weight, assessment of ECOG performance status, CBC, PT/INR, PTT, total bilirubin, AST, ALT, creatinine, sodium, potassium, chloride, bicarbonate, albumin, calcium, and alkaline phosphatase were obtained from all patients at baseline and at the beginning of subsequent cycles. Additional pre-registration studies included measurement of height, serum pregnancy testing for women of childbearing age, an ECG, fecal occult blood testing, and a urinalysis. Tumor assessments were obtained by imaging at baseline and at the end of each of the first two cycles of treatment. For patients receiving extended treatment beyond cycle 2, disease evaluation by imaging was performed after the completion of every other cycle. Patients with measurable disease had their tumor response assessed using the Response Evaluation Criteria in Solid Tumors (RECIST). All patients with responding tumors were required to have response confirmed no sooner than 4 weeks after the first documented response.

Electrocardiograms were performed hourly times 4 through the first treatment of MN-029 (cycle 1, day 1) and then at 24 hours after dosing. They were performed subsequently at the investigator's discretion and at the termination visit.

All patients who completed at least 1 dose of MN-029 and underwent 1 post-treatment efficacy assessment were considered evaluable for efficacy. All patients who received at least 1 dose of study drug were evaluable for safety/toxicity.

Statistical methods

SAS® Version 8.2 was used to perform all statistical analyses. The primary outcome measure of this study was assessment of safety and toxicity of MN-029 and determination of the MTD in this population. Secondary objectives included assessment of anti-tumor activity per RECIST criteria. Data were summarized using descriptive statistics for continuous variables and using frequency and percentages for discrete variables. Data generated from the first 2 treatment cycles for all patients was pooled and analyzed separately from data generated from extended treatment. Efficacy was summarized by simple descriptive

summary statistics delineating complete and partial responses as well as stable and progressive disease, and the duration of stable disease.

RESULTS

Patient characteristics

Twenty patients enrolled between June 2005 and May 2006. Pretreatment characteristics are outlined in Table 1. One hundred fifty-one infusions of MN-029 were administered. Seventeen patients (85%) completed the first cycle of therapy, and 11 patients (55%) completed both cycle 1 and cycle 2. Four patients (20%) completed 4 cycles of MN-029, 3 completed 6, and 1 patient completed 8 cycles. The dose escalation schema, including intra-patient dose escalation, is listed in Table 2.

Dose limiting toxicities, maximum tolerated dose, and recommended phase II dose

No DLTs were observed in any patient during the first cycle of treatment. The dose of MN-029 was started at 4 mg/m² and then escalated by 100% in 5 cohorts. Dose escalation by 100% was halted since DLTs had been observed in another ongoing phase I study of single agent MN-029 at 225 mg/m² (transient ischemic attack and grade 3 elevation of transaminases in a patient with liver metastases) [13]. As such, the dose of MN-029 was escalated in our study to a maximum of 180 mg/m² for the final cohort, and this dose was identified as the recommended phase II dose (RP2D). An MTD, based upon toxicities encountered in this study, was not identified. Four patients with stable or responding disease were allowed to undergo intra-patient dose escalation to a maximum dose of 64 mg/m².

Dose escalation, toxicity, and safety

All 20 patients were evaluable for safety and toxicity. MN-029 was tolerated well overall. There were no deaths on study or within 30 days of follow-up. No grade 4 toxicities occurred. No patient had their MN-029 dose reduced due to toxicity. Table 3 lists the grade 2 and grade 3 toxicities that were observed, regardless of attribution.

All patients experienced at least 1 adverse event related to treatment, but the vast majority of these were grade 1. The most common adverse events related to study drug were nausea, vomiting, arthralgia, and headache. Venous thromboembolic events were not seen. There was no evidence of cumulative toxicity. Two patients had their treatment interrupted and came off study due to an adverse event. A 59 year old male experienced transient chest pain 4 days after receiving his first dose of MN-029 at 4 mg/m², and was discontinued from protocol treatment. This patient had a history of a myocardial infarction and unstable angina, although neither occurred within 12 months of enrollment. His ECG 24 hours following treatment (and prior to his chest pain) demonstrated stable first degree atrioventricular block (PR interval of 200 ms) without any acute ischemic changes. In addition, a 57 year old female experienced a 1 week treatment delay at C2D15 of treatment at 32 mg/m² due to hypomagnesemia. Her treatment resumed following supplementation, and she ultimately came off study due to cellulitis and chronic headache. Four additional patients experienced transient treatment delays due to grade 1 or 2 toxicities (grade 1 flank pain, hypokalemia, fever, cough, dyspnea, right-sided chest pain, and grade 2 hematuria in a patient with renal cell carcinoma and grade 2 sinus infection). These patients subsequently resumed treatment and ultimately discontinued protocol therapy due to progressive disease. Three patients experienced four grade 3 toxicities that were not considered DLTs: nausea and vomiting (the patient had not received maximal anti-emetics), hypokalemia (not related to study drug), and an increased level of alkaline phosphatase (not related to study drug). One patient with pancreatic cancer was hospitalized with cholangitis the day after signing her informed consent for enrollment but prior to her first dose of MN-029. She subsequently received 4

cycles of therapy after resolving this infection. There were no other serious adverse events throughout this protocol.

Nine of the 20 enrollees were not able to complete the mandated 2 cycles of therapy. Of the 6 patients enrolled in the 180 mg/m² cohort, 5 were unable to complete 2 cycles of MN-029: 2 due to withdrawal of consent, 2 due to investigator's discretion, and 1 due to progressive disease. The 4 additional patients in the remaining cohorts who were not able to complete 2 cycles of treatment were removed due to progressive disease (N=3) and due to the adverse event of transient chest pain (N=1). Of the 11 patients who did complete 2 cycles of MN-029, 9 discontinued treatment due to progressive disease, 1 due to an adverse event (cellulitis and chronic headache), and 1 due to investigator's discretion.

Use of VDAs has been associated with cardiac toxicities [3,11]. As stated above, 1 patient with a history of coronary disease was removed from treatment after developing transient chest pain 4 days following his first dose of MN-029. Also, 2 patients experienced grade 1 elevations of their systolic and diastolic blood pressure during cycle 1 treatment with MN-029 at 180 mg/m² (peak pressures of 212/120 and 197/117). These elevations were asymptomatic and transient, normalizing within 2 hours post-treatment. Neither of these patients experienced an anti-tumor response to treatment. No clinically significant ECG changes were detected during treatment.

Efficacy

Fifteen patients were eligible for efficacy analyses based upon RECIST measurements; 5 did not undergo a post-treatment disease evaluation. One patient with pancreatic cancer and pulmonary metastases treated at the 32 mg/m² level attained a partial response lasting 74 days. Stable disease was observed in 7 patients (47%), with a median duration of 83 days. Progressive disease was seen in 7 patients (47%).

DISCUSSION

We determined a RP2D for MN-029 of 180 mg/m² when dosed every week for 3 consecutive weeks out of 4. This schedule proved well-tolerated, as no patient experienced a DLT or grade 4 toxicity; only 4 grade 3 toxicities were noted, none of which led to dose reductions or delays. We did not define an MTD by the occurrence of DLTs. Rather, our RP2D was determined by the finding in the contemporaneous single agent study by Ricart, et al., in which 180 mg/m² was identified as the DLT-defined MTD when MN-029 was administered only once every 3 weeks [13]. Our participants received a dose intensity of MN-029 triple that of the every 3 week schedule described by Ricart, et al., but did not experience greater or different toxicities. This finding suggests that toxicities associated with MN-029 were noncumulative [13].

The tolerability of MN-029 in our population appeared commensurate with that of other VDAs [6–10,13]. Commonly encountered toxicities included mild nausea, vomiting, arthralgias, and headache. In addition, 1 patient with a prior history of myocardial infarction experienced transient chest pain 4 days following his first dose of MN-029, and 2 patients experienced asymptomatic, transient elevations of their blood pressure during cycle 1 of treatment. Phase I investigation of two other VDAs, combretastatin A4 phosphate and ZD6126, was associated with the relatively infrequent, but persistent, findings of myocardial ischemia and asymptomatic decreases in left ventricular ejection fraction [6–10]. Gould et al. induced acute hemodynamic changes (elevations in blood pressure and heart rate), left ventricular myocardial fiber necrosis, and increases in serum troponin in rats following exposure to ZD6126; these effects were prevented by pre-administration of nifedipine and atenolol [14]. These authors concluded that myocardial ischemia occurs in rats secondary to

ZD6126-induced hemodynamic changes of hypertension and tachycardia, yielding an imbalance between myocardial oxygen delivery and demand that leads to inadequate myocardial perfusion [14]. Hypertension is not as frequently encountered in phase I trials of VDAs as it is with VEGF antagonists and tyrosine kinase inhibitors, where its incidence can approach 60% and where it has been noted as a potential biomarker of drug activity [15,16]. Clearly, the clinical development of both VDAs and VEGF antagonists requires thorough delineation of their vascular effects, both on- and off-target, as well as meticulous patient monitoring and the exclusion of patients with pre-existing cardiovascular disease [11].

Our results indicated that 1 patient with pancreatic cancer with pulmonary metastases treated at the 32 mg/m² level achieved a partial response lasting 74 days. Anti-tumor responses in single agent studies of VDAs have been uncommon, which is not surprising given the persistent viable rim of tumor seen following treatment in both animal models and humans [5]. Combining VDAs with conventional chemotherapeutics or radiation therapy has yielded enhanced preclinical anti-tumor activity [12,17–19]. Combretastatin and AVE8062, a water-soluble analog of combretastatin, are moving forward in phase II clinical trials in anaplastic thyroid cancer and non-small cell lung cancer in combination with cytotoxic chemotherapeutics.

In summary, we identified 180 mg/m² as the RP2D for the weekly times 3 out of 4 week schedule for the novel VDA, MN-029. Infrequent vascular toxicity occurred with MN-029, as they have with other VDAs. Vascular disrupting agents yield rapid shutdown of tumor neovasculature in preclinical models and have shown diminished tumor perfusion in early clinical trials [6,8,9,13]. Further laboratory and clinical development of this class of agents is warranted, and should lead to widening of their therapeutic ratio from the development of second generation agents that have enhanced specificity for tumor-related neovasculature [3–5]. Further, the development of non-invasive biomarkers of drug efficacy should be validated and standardized. Early results incorporating vascular-based imaging, serial assessment of circulating endothelial cells, and baseline measurement of angiogenic cytokines offer promising signals that these pharmacodynamic markers may aid in directing drug development [4,20–22]. Lastly, the sequence and dosing of combination regimens of VDAs with chemotherapeutics, radiation therapy, and with other targeted biologic anti-cancer agents, warrants thorough evaluation.

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Table 1

Patient demographics

	N
Number of patients	20
Median age (range)	59.5 (29–77)
Sex	
Male	13
Female	7
Performance status	
0	12
1	8
Primary tumor type	
Colorectal	6
Renal	4
Breast	3
Pancreas	3
Unknown primary (adenocarcinoma)	1
Salivary gland (parotid)	1
Ovarian	1
Cholangiocarcinoma	1
Prior systemic therapy*	
0	1
1	1
2	4
3	2
4	10
≥5	2
Prior radiotherapy	
Yes	12
No	8

* Includes conventional cytotoxic chemotherapy, targeted agents, hormonal agents, immunotherapy, and biologics.

Table 2

Dose escalation schema

Dose level	MN-029 (mg/m ²)	N	Number courses	Intra-patient dose escalation
1	4	2	3	1 patient escalated to 32 mg/m ² ; the other escalated to 64 mg/m ²
2	8	2	13	No
3	16	1	8	1 patient escalated to 64 mg/m ²
4	32	3	8	1 patient escalated to 64 mg/m ²
5	64	2	4	No
6	128	4	5	No
7	180	6	7	No

Table 3

Grade 2 and 3 toxicities, regardless of attribution

Description	Dose Level 1	Dose Level 2	Dose Level 3	Dose Level 4	Dose Level 5	Dose Level 6	Dose Level 7
Nausea/vomiting		1		1		1*	1
Pain		1	1			1	1
Increased alk phos		1				1	1*
Increased LFTs						1	1
Rash/dry skin		1				1	
Hyperbilirubinemia						1	
Proteinuria			1				
Hematuria				1			
Hypokalemia				1*			
Hypophosphatemia		1			1		
Sinus infection				1			
Cellulitis					1		
Cough		1					
Post-nasal discharge		1					
Headache		1					
Urinary retention			1				
RUE altered sensation							1
Leukopenia							1

* Grade 3 toxicities (all other toxicities are Grade 2)

Abbreviations: alk phos (alkaline phosphatase); LFTs (liver function tests); RUE (right upper extremity)