Cancer Chemother Pharmacol (2006) 58: 759–764
DOI 10.1007/s00280-006-0235-4

ORIGINAL ARTICLE

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A Phase 2 trial of the liposomal DACH platinum L-NDDP in patients with therapy-refractory advanced colorectal cancer

Received: 16 November 2005 / Accepted: 7 March 2006 / Published online: 22 May 2006

Abstract *Purpose*: L-NDDP (Aroplatin^{TM}) is a liposomal formulation of *cis-bis*-neodecanoato-*trans-R,R*-1,2-diaminocyclohexane platinum (II), a structural analogue of oxaliplatin. In a Phase 1 trial, the maximum tolerated dose (MTD) of L-NDDP was 312.5 mg/m^2 with myelosuppression as dose limiting toxicity (DLT). We conducted a Phase 2 trial of L-NDDP in patients (pts) with advanced colorectal cancer (CRC) refractory to 5-fluorouracil/leucovorin or capecitabine and irinotecan to investigate the anti-tumor response of L-NDDP and to further characterize its toxicity profile in this population. *Methods*: L-NDDP was administered intravenously, once every 28 days. The starting dose was 300 mg/m^2, with possible intra-patient dose escalation in the absence of grade 2 or higher drug-related toxicity. Patients were treated until disease progression or unacceptable toxicity. Of 20 eligible patients all were evaluable for toxicity and 18 were evaluable for response. Hematologic toxicities included anemia (grades 1–4) in 20% of pts and leucopenia, neutropenia and thrombocytopenia (grade 1/2) in 5% of patients each. Common non-hematologic toxicities included nausea (75%), vomiting (60%), and fatigue (70%), reversible infusion reactions (chest/back pain or shortness of breath; 40%), transient transaminase elevations (35%) and hyperbilirubinemia (20%). Grade 3–4 toxicities included infusion reaction (20%), vomiting (15%), fatigue (15%), anemia (10%) and ALT/AST elevation (5/15%). Peripheral neuropathy (grade 1/2) was seen in 15% of pts. One of 18 pts had a confirmed PR (5.6%), three (16.7%) had stable disease (≥3 months) and 14 pts progressed. L-NDDP was well tolerated in this group of refractory patients and demonstrated evidence of anti-tumor activity. *Conclusion*: Further studies of L-NDDP, preferably in combination with other agents such as fluoropyrimidines, are warranted.

Keywords DACH platinum · L-NDDP · Advanced colorectal cancer

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Introduction

Colorectal carcinoma (CRC) accounts for approximately 15% of all new cancers in the United States, with more than 130,000 new cases diagnosed annually [13]. There has been a modest increase in the overall 5-year survival rate, from 41% in the 1950s to 54% in the 1980s. However, the prognosis of patients with advanced disease is still disappointing with more than 90% of those eventually dying within 5 years from diagnosis.

For almost four decades the treatment of advanced CRC was primarily based on 5-fluorouracil (5-FU) therapy. The objective responses were in the range of 15–20%, and the median survival in metastatic disease ranged between 10 and 12 months [1, 16]. Irinotecan (CPT-11), a topoisomerase I inhibitor, became available in the late 1990s for patients with 5-FU-resistant CRC and was subsequently also approved in combination with 5-FU and leucovorin (Saltz and Douillard regimens) for first-line therapy of metastatic CRC [4, 5, 22, 23]. A new generation of orally available fluoropyrimidines, such as capecitabine and UFT has been shown to be equivalent to bolus fluorouracil, thus adding some convenience and flexibility to colorectal cancer regimens [6, 25]. Oxaliplatin, a di-amino-cyclo-hexane (DACH) platinum, was the first platinum drug to show some in vitro activity in colorectal cancer cell lines. Oxaliplatin showed synergy with fluorouracil, both in vitro and in vivo [2, 7, 8]. Single-agent oxaliplatin demonstrated a response rate of 1.3% in therapy-refractory patients with

metastatic CRC [21]. Oxaliplatin was more active in combination with infusional 5-FU/leucovorin (FOLFOX), where objective responses were seen in 45% of chemotherapy-naïve patients with metastatic CRC [9]. This translated into a 4.5 months survival benefit associated with FOLFOX when compared to irinotecan plus 5-FU/leucovorin (IFL) [9]. Oxaliplatin therapy is associated with characteristic early-onset neurotoxicity including paresthesias, dysesthesias, cold hypersensitivity, pain in jaw or eyes, ptosis, visual or voice changes [26]. In those patients remaining on therapy for longer periods, this is often followed by cumulative sensory-motor neuropathy.

Two monoclonal antibodies, bevacizumab, targeting the vascular endothelial growth factor, and cetuximab, targeting the epidermal growth factor, became available in 2004 for the treatment of metastatic CRC [3, 12].

L-NDDP (Aroplatin^{TM}) is a structural analogue of oxaliplatin, a *cis-bis*-neodecanoato-*trans-R,R*-1,2-diaminocyclohexane platinum (II) (NDDP) incorporated in multilamellar liposomes that are formed upon reconstitution with acidified saline solution. Liposomal components are DMPC (1,2-Dimyristoylphosphatidylcholine) and DMPG (1,2-Dimyristoylphosphatidylglycerol). Preclinical data shows that L-NDDP has a different biodistribution than first- or second-generation platinums, with accumulation of elemental platinum in organs such as the liver, spleen and lymph nodes, and a different toxicity profile [15, 17, 20].

L-NDDP has been shown to induce cytotoxicity in the human ovarian tumor cell line A2780 and in cisplatin-resistant A2780/PPD cells, indicating that L-NDDP does not share cross-resistance to cisplatin [10]. Similarly, L-NDDP was active in both cisplatin-sensitive human colon carcinoma LoVo cells and in cisplatin-resistant LoVo/PDD cells [11]. Recent unpublished pre-clinical data suggest, L-NDDP to have lower IC_{50} values than oxaliplatin, carboplatin or cisplatin in several cancer cell lines (Antigenics, Inc., unpublished data).

L-NDDP was first synthesized at MD Anderson Cancer Center in the 1980s. In a Phase 1 trial conducted at MD Anderson in 1987, patients with advanced malignancies received L-NDDP via the intravenous route. In this study, intra-patient dose escalation was used to determine a maximum tolerated dose (MTD) of 312.5 mg/m^2 with myelosupression as dose-limiting toxicity (DLT). Neurotoxicity was rare and nephrotoxicity not reported [18].

Most early-phase trials with L-NDDP conducted throughout the 1990s have focused on intraperitoneal and intrapleural routes of administration demonstrating clinical activity in these settings [19].

With the new role of oxaliplatin in the treatment of CRC, there is also a renewed interest in other DACH platinum agents. Objectives of this trial were to investigate anti-tumor response, optimal dosing, and safety of L-NDDP in a defined population of patients with advanced, therapy-refractory CRC.

Patients and methods

Patients

Male or female patients with locally recurrent and unresectable (AJCC Stage III), or metastatic (Stage IV) colorectal cancer, aged $\geq$18 years, with an ECOG performance score of 0–2, measurable disease according to RECIST criteria [24] and disease refractory to 5-FU/leucovorin or capecitabine, and irinotecan (either in combination or sequence) were eligible for enrollment. In addition, patients were required to have adequate organ functions as defined by: absolute neutrophil count (ANC) $\geq 1.5\times10^9$/l; platelet count $\geq 100\times10^9$/l, creatinine $\leq$1.5 mg/dl, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $<$100 IU, total bilirubin $<$2.0 mg/dl, and cardiac function of NYHA class I or II. No prior therapy with oxaliplatin was allowed.

Study conduct, objectives and L-NDDP treatment

The study was conducted according to ICH-Guidelines for Good Clinical Practice and the Declaration of Helsinki. The study was approved by the institutional review board (IRB) at the Arizona Cancer Center and all patients have provided informed consent. The study was sponsored by Antigenics Inc., New York, NY, USA.

The primary objective of this single-institution Phase 2 trial was to examine objective response to single-agent L-NDDP in patients with advanced CRC, who previously progressed on 5-fluorouracil/leucovorin or capecitabine and irinotecan therapies. The secondary objective was to investigate optimal dosing and further characterize the toxicity profile for L-NDDP monotherapy in this population.

Statistical design

The primary objective of this trial was to assess the L-NDDP efficacy as measured by overall response probability. It was assumed that L-NDDP would not be of further interest if the true confirmed response probability was 5% or less, but of considerable interest if it was 20% or more. A two-stage design was used. Initially, 20 subjects were to be accrued. If at least one confirmed response was observed among first 20 subjects, an additional 20 were to be accrued. Five or more confirmed responses out of the total 40 subjects was considered evidence that the treatment regimen is of further interest

Study treatment

NDDP (Fig. 1) is incorporated into multilamellar liposomes that are formed upon reconstitution with acidified saline solution. NDDP and the liposomal components DMPC and DMPG were delivered to the hospital pharmacy as lyophilized powder in a single vial accompanied by a second vial of the acidified saline solution and were stored at 4°C. Reconstitution was performed under

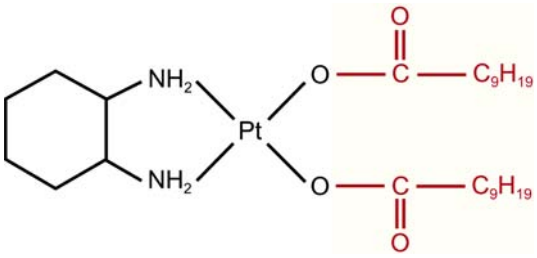

Fig. 1 Chemical structure of NDDP (*cis-bis*-neodecanoato-*trans-R,R*-1,2-diaminocyclohexane platinum) prior to liposomal encapsulation

shaking at room temperature for 2 h. L-NDDP was given intravenously within 2–8 h after reconstitution and with a starting infusion rate of 4 mg/min, which was repeated in 4-week intervals. All patients commenced treatment at a starting dose of 300 mg/m^2, with potential intra-patient dose escalation to 375 and 470 mg/m^2 or de-escalation to 250 or 200 mg/m^2 depending on toxicity. Toxicity was assessed using the NCI Common Toxicity Criteria (CTC) v2. Dose adjustments were performed according the following criteria: dose escalation in case of grade 0 or 1 toxicity, maintenance of dose in case of grade 2 toxicity, and dose de-escalation in case of grade 3 or 4 toxicity. All patients were followed for clinical response according to the RECIST criteria [24] in 3-month intervals from the initiation of therapy. Criteria for discontinuation were either disease progression (PD), intolerance to the drug or non-compliance with the study requirements. Antiemetic prophylaxis was allowed at the discretion of the treating physician.

Results

Twenty patients with advanced CRC were enrolled in the study and were treated with L-NDDP. There were 13 males and 7 females with a median age of 58 years (range 45–70). Fifteen patients were Caucasians, four were Hispanic and one was Native American. All 20 patients had initiated at least 1 course of therapy and were evaluable for toxicity, and 18 patients have had at least 1 follow-up visit for tumor response and were evaluable for clinical response. The median duration on study treatment for all patients was 2 months (range 1–7). All patients had Stage IV colorectal cancer and had previously failed 5-FU/LV or capecitabine and irinotecan. The median number of prior chemotherapeutic agents for advanced disease was 2 (range 1–4). Patient characteristics at baseline are summarized in Table 1.

Median cumulative dose of administered L-NDDP in 20 patients was 637.5 mg/m^2 (range 36–2,175 mg/m^2). One patient did not complete the first dose of L-NDDP due to an infusion-related reaction. The median number of treatment cycles administered was two. Patients without a grade 2 or higher adverse event after the first course of L-NDDP were dose escalated to 375 mg/m^2 on the subsequent course. Nine patients had a dose escalation to the 375 mg/m^2 dose level. Patients with a grade 3 or higher adverse event were dose de-escalated to the next lower dose level. Only three patients required dose de-escalation, two of which were previously escalated to 375 mg/m^2.

Table 1 Baseline patient characteristics

	$N=20$	%
Median age	58 (range 45–70)	
Gender		
Male	13	65
Female	7	35
ECOG score		
0	16	80
1	4	20
Race		
Caucasian	15	75
Hispanic	4	20
Native American	1	5

The most relevant toxicities associated with L-NDDP are displayed in Tables 4 and 5 as treatment-emergent adverse events (AEs). There was no substantial myelosupression, without grade 3 or 4 neutropenia or thrombocytopenia. Neutropenia, leucopenia or thrombocytopenia were seen in only one patient each and were grade 1 or 2 (see Tables 2, 3). Four patients (20%) experienced anemia, grade 2 in 10 % and grade 4 in another 10% of patients. Nausea occurred in 15 patients (75%) with only one grade 3 event. Vomiting occurred in 12 patients; 3 had grade 3 events. ALT elevation was observed in five patients, of whom three cases were grade 3 or 4 events. AST elevation was also observed in two of the five patients who experienced ALT rise and in one case was a grade 3 event. Transaminase elevations were reversible, and have not required treatment delay or discontinuation.

Eight patients experienced an infusion-related reaction (40%), which included one or more of the following: back, flank or abdominal pain, shortness of breath,

Table 2 Patients with selected treatment-emergent adverse events ($N=20$)

	Grade 1/2 *N* (%)	Grade 3/4 *N* (%)
Leukopenia	1 (5)	–
Neutropenia	1 (5)	–
Thrombocytopenia	1 (5)	–
Anemia	2 (10)	2 (10)
Alanine aminotransferase elevation	2 (10)	3 (15)
Aspartate aminotransferase elevation	1(5)	1 (5)
Hyperbilirubinemia	4 (20)	–
Fatigue	11 (55)	3 (15)
Infusion-related reaction (shortness of breath, throat tightness, chest pressure/pain, back/abdomen/flank pain)	4 (20)	4 (20)
Nausea	14 (70)	1 (5)
Vomiting	9 (45)	3 (15)

The worst event per patient is listed

Table 3 Frequent treatment-emergent adverse events, occurring in ≥20% of patients ($N=20$)

Adverse event	No. of patients[a]	%
Nausea	15	75
Anorexia	14	70
Fatigue	14	70
Vomiting	12	60
Constipation	10	50
Asthenia	8	40
Back Pain	8	40
Infusion related reaction	4	40
Pyrexia	7	35
Diarrhea	6	30
Dehydration	6	30
Alanine aminotransferase elevation	5	25
Dizziness	5	25
Headache	5	25
Insomnia	5	25
Pain	5	25
Lower abdominal pain	4	20
Anemia	4	20
Cough	4	20
Depression	4	20
Hiccups	4	20
Hyperbilirubinaemia	4	20
Peripheral edema	4	20
Tachycardia	4	20
Weight decreased	4	20

[a] Only the most severe event per patient is listed

throat tightness, chest tightness/pressure, or pain. These adverse events were graded 1–3 in severity and resolved in all cases on the same day, usually within 30–60 min. All patients except one who withdrew consent were able to continue with infusion, after receiving anti-histamines and hydrocortisone prophylaxis and/or after reduction of the L-NDDP infusion rate from 4 to 2 mg/min.

Peripheral neuropathy was mild and infrequent occurring only in 3 patients (15%) and after high cumulative doses of L-NDDP (1050, 2025, 2175 mg/m^2). Three patients experienced grade 1 neuropathy and one patient had grade 2 neuropathy. This patient remained on study protocol for more than 7 months and received the highest cumulative dose of L-NDDP of 2175 mg/m^2 before developing grade 2 sensory-motor neuropathy that eventually lead to treatment discontinuation. Neuropathy improved to grade 1, after 6 months from treatment discontinuation. Characteristics of neuropathy are summarized in Table 4. No ototoxicity was observed. There were two serious adverse events considered to be related to L-NDDP, one event of grade 3 infusion-related chest pain and 1 event of grade 4 anemia.

Table 4 Characteristics of neuropathy ($N=3$)

Description of neuropathy	Highest severity	Onset
Bilateral foot, sensory and tactile peripheral neuropathy	Grade 2	Course 6
Right hand peripheral neuropathy	Grade 1	Course 3
Neuropathy, distal unspecified	Grade 1	Course 3

Of 18 patients evaluable for response, one patient demonstrated a confirmed partial response (PR; see Fig. 2) and 3 patients had stable disease (SD) for at least 3 months. The PR was documented after six courses of L-NDDP therapy and was maintained after additional 6 months of follow-up. Fourteen patients had disease progression. Table 5 summarizes the response assessments.

After completing the first stage the study met the criterium for moving into the second stage. However, at the time of second stage initiation it became clear that oxaliplatin in combination with fluoropyrimidine is becoming preferred chemotherapy approach and that aroplatin

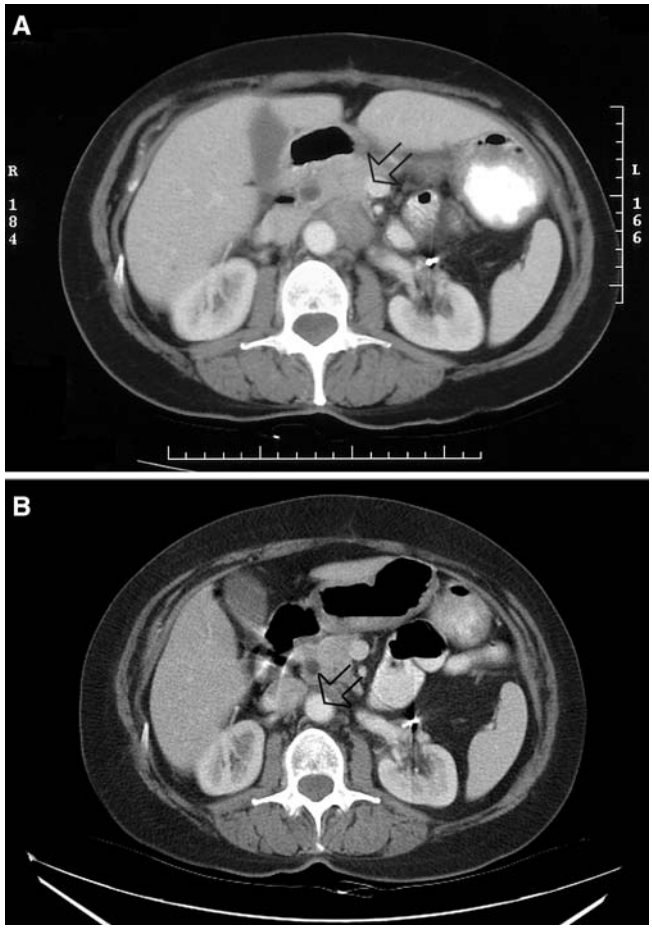

Fig. 2 Computerized tomography (*CT*) scan images from a patient with Stage IV colorectal cancer demonstrating a partial response (*PR*) after six cycles of L-NDDP therapy. **a** Baseline abdominal CT scan showing a left-sided para-aortic metastatic mass. **b** Significant reduction in tumor volume after six cycles of L-NDDP monotherapy (*arrow*), demonstrating a PR according to the RECIST criteria

Table 5 Response asessment ($N=18$)

	N	%
PR	1	5.6
SD	3	16.7
PD	14	77.8

also is likely to be more efficacious in combination with a fluoropyrimidine. Thus, we concluded that initially planned second stage of this study is not feasible anymore and would not necessarily provide additional relevant information. In addition, the sponsor has initiated preclinical studies employing modified L-NDDP formulation, with a goal of further improving tolerability (Antigenics, Inc., unpublished data).

Discussion

This Phase 2 study explored anti-tumor activity and tolerability of intravenous liposomal NDDP (Aroplatin^{TM}) in refractory patients with advanced CRC. This formulation of L-NDDP was well tolerated and 45% (9/20) of patients were able to receive an escalated dose of 375 mg/m^2 during the course of their treatment. Despite the fact that most of the patients had received 2 or 3 prior agents for advanced CRC, myelosupression was less common and less severe than expected based on the Phase 1 study report [18]. We did observe a difference in severity of myelosupression when our study data is compared to the prior phase 1 study. We believe this could be explained by the less heavily pretreated patient population that participated in our trial. The lack of grade 3/4 neutropenia and thrombocytopenia may be of interest in terms of combining L-NDDP with other potentially myelosuppressive drugs. Nausea, vomiting and diarrhea were common but mostly mild and easy to manage. Another common drug-related toxicity was reversible transaminase elevation. It is unclear whether this was related to the active compound or a transient effect of the liposomal formulation on the liver. Forty percent of patients experienced infusion-related reactions manifesting as shortness of breath and back or chest pain of grade 1–3 severity, which were medically controllable. In only one case was treatment discontinued. In our experience, temporary reduction of the infusion rate of L-NDDP from 4 to 2 mg/min and/or prophylaxis with antihistamine and dexamethasone allowed most of patients to continue treatment without interruption and further symptomatic reactions. The infusion reaction is likely attributable to the liposomal component of this L-NDDP formulation, as this was previously reported for other liposomal drugs such as Amphotericin B [14].

There were three patients who experienced drug-related grade 1 or 2 peripheral neuropathy, with an onset between the third and sixth course of therapy. In all cases, it occurred in patients who received high cumulative doses of L-NDDP (>3 cycles of therapy).

The modest response rate seen in this trial (5.6%; 95% CI of 1%, 26%) is comparable to the previously reported response rate of single-agent oxaliplatin (RR 1.3%) in a similar population of pre-treated patients with metastatic CRC [21]. This activity warrants further clinical evaluation of potential synergy between L-NDDP and other agents such as fluoropyrimidines (5-fluorouracil, capecitabine or tegafur).

Conclusions

The investigated formulation of L-NDDP, a liposomal DACH platinum, was generally well tolerated in this population of patients with advanced CRC refractory to 5-FU/leucovorin or capecitabine, and irinotecan. Given its unique tissue distribution, the observed anti-tumor activity and toxicity profile, further clinical investigation of L-NDDP, in combination with fluoropyrimidines and biologics is warranted.

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