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Phase I trial of a formulated IL-12 plasmid in combination with carboplatin and docetaxel chemotherapy in the treatment of platinum-sensitive recurrent ovarian cancer☆

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HIGHLIGHTS

- Feasibility of a novel treatment approach involving local IL-12 gene therapy and IV standard chemotherapy for ovarian cancer is described
- The combination treatment was safe and associated with anticancer efficacy and IL-12 biological activity
- Addition of local IL-12 gene therapy to standard chemotherapy offers a novel approach to the treatment of advanced cancers

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ABSTRACT

Objectives. The primary objective of this study was to evaluate the safety and tolerability of a formulated IL-12 plasmid administered intraperitoneally (IP) in conjunction with intravenous (IV) carboplatin/docetaxel in platinum-sensitive ovarian cancer patients.

Methods. Escalating doses of IL-12 plasmid (phIL-12) formulated with the lipopolymer PEG-PEI-Cholesterol (PPC) were administered IP every 10–11 days for a total of four treatments and the highest dose was expanded to eight treatments. Patients also received IV carboplatin (AUC 5) and docetaxel (75 mg/m^2) every 21 days. Patients were followed for safety, biological activity and antitumor activity after phIL-12/PPC treatment.

Results. All 13 patients enrolled in the study received both phIL-12/PPC and chemotherapy treatment. There were 49 plasmid-associated adverse events (AEs). The most common AEs were abdominal pain, transient hypotension, low grade fever, catheter site pain, chills, dysgeusia, infusion-related reaction, and nausea. These AEs appeared to be plasmid dose related. Grade 3 AEs included manageable abdominal pain and cytokine release syndrome. There were no dose limiting toxicities and the plasmid treatment did not augment the chemotherapy-associated AEs. The best overall antitumor response (17% CR, 33% PR, 42% SD and 8% PD) was typical of the patient population enrolled for the study. Translational studies showed rise in IFN-γ and TNF-α concentrations in a dose dependent manner.

Conclusions. The escalating doses and cycles of intraperitoneal phIL-12/PPC when combined with carboplatin/docetaxel chemotherapy in recurrent ovarian cancer patients were well tolerated and did not appear to exacerbate the side effects or attenuate the efficacy of the chemotherapy treatment.

Introduction

Advanced epithelial ovarian carcinoma is one of the most lethal gynecologic malignancies. Due to the lack of effective screening strategies and to nonspecific presenting symptoms, a majority of ovarian cancer patients present with advanced stage disease. Despite advances in surgical cytoreduction and in chemotherapy options, most ovarian cancer patients will eventually develop resistance to chemotherapy and ultimately succumb to their disease [1,2]. Given these realities, there has been significant interest in developing

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therapies that are novel in their mechanisms of action and can be combined with chemotherapy treatments to achieve better long-term clinical outcomes. Immunotherapy is an attractive novel approach for the treatment of ovarian cancer particularly since ovarian cancers are considered immunogenic tumors.

Interleukin-12 is a pluripotent cytokine with potent immunostimulatory and anti-angiogenic properties [2,3]. The precedence for a therapeutic role of IL-12 in ovarian cancer is based on epidemiologic and preclinical data [3–7]. The clinical investigation of IL-12 in ovarian cancer patients has been evaluated in limited number of studies. Intraperitoneal (IP) administration of rIL-12 in patients with peritoneal metastases of solid tumors including ovarian cancer elicited favorable immune responses but also produced serious hematologic and liver toxicities [8,9]. In renal cell carcinoma, melanoma, cutaneous T-cell lymphoma, and squamous cell carcinoma, rIL-12 treatment produced objective tumor responses and robust biological and immunological responses but also resulted in dose and schedule dependent serious hematologic and liver toxicities [10–14].

We have recently described a DNA-based approach to IL-12 delivery that involves IP administration of IL-12 plasmid formulated with a lipopolymer PEG-PEI-Cholesterol (PPC) delivery system to achieve local concentrations of IL-12 at tumor site with minimal increases in systemic circulation [15]. The safety, biological activity and efficacy of this approach have been demonstrated in a mouse model of peritoneally disseminated ovarian tumors [16]. In platinum-resistant recurrent ovarian cancer patients, escalating doses of IP phIL-12/PPC were safe and did not result in hematological or liver toxicities [17] that are typically associated with rIL-12 administration (8-14).

In this report, we have examined the safety and tolerability of IP pIL-12/PPC treatment in combination with carboplatin/docetaxel therapy in women with platinum-sensitive ovarian cancer. The rationale for an IL-12 gene combination with a cytotoxic drug is supported by preclinical data from ovarian and other cancers [18–21].

Methods

This multicenter Phase I study was conducted with the approval of the Institutional Review Board and Institutional Biosafety Committees of participating sites. Patients were provided written informed consent prior to participating in the study. The major eligibility criteria included females (≥18 years age) with histologically confirmed disease, >6 month of platinum-free interval, measurable disease ≤ 5.0 cm, and performance status score of 0, 1, or 2 per Eastern Cooperative Oncology Group (ECOG). We limited the measurable disease to <5 cm because we were concerned about getting an IP port in safely and about a larger mass affecting distribution. Laboratory requirements included absolute neutrophil count ≥ 1500/mm^3, platelets ≥ 100,000/ml, serum creatinine ≤ 2 mg/dL, AST (SGOT)/ALT (SGPT) ≤ 5 × institutional upper limit of normal, and serum bilirubin ≤ 2 mg/dL. Major exclusion criteria included serious uncontrolled medical illness or disorder, abdominal surgery or active infection within four weeks of study entry, intraabdominal disease > 5.0 cm in diameter, prior whole-abdominal irradiation, suspected bowel obstruction or known extensive adhesive disease, recurrence solely outside of the abdominal cavity, autoimmune disorders, known human immunodeficiency virus infection, hepatitis B, hepatitis C, prior IP drug administration, a life expectancy <3 months, or prior immunotherapy for ovarian cancer. Screening evaluations were performed within 21 days prior to the drug administration.

The study was conducted in 2 stages. In stage 1, patients were grouped into three dose-escalating cohorts (12 mg/m^2, 18 mg/m^2, and 24 mg/m^2 DNA), each cohort receiving plasmid treatments every 10–11 days for a total of four treatments. Dose escalation proceeded in the standard 3 + 3 modified Fibonacci fashion. The highest tolerated dose from stage 1 was expanded to additional 4 patients (cohort 4) in stage 2 where each patient received plasmid treatment every 10–11 days for a total of up to 8 treatments. The plasmid infusion was achieved via an SC Port-A-Cath catheter (SIMS Deltec, Inc. St Paul, MN 55112) as described previously (17). In both stages patients also received standard clinical doses of intravenous (IV) carboplatin (AUC of 5) and docetaxel (75 mg/m^2) every 21 days for up to 6 cycles. Therefore, every other phIL-12/PPC treatment coincided with chemotherapy treatment. Oral corticosteroids were given to reduce hypersensitivity reactions from docetaxel treatment.

Clinical and laboratory safety evaluations (serum chemistry and hematology) were performed at screening, prior to each dose of study drug, 1 week following the last dose of study drug, and 5 ± 1 weeks following the last dose of study drug (or early termination). Adverse events (AEs) were graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0. Conventional CT with contrast was performed with cuts of ≤10 mm in contiguous slice thickness to assess the tumor responses. All measurable visceral lesions were evaluated by RECIST criteria using RECIST version 1. CA-125 levels were measured in serum samples collected at screening, and 1 week after each of the four treatments and thereafter. Blood and peritoneal fluid samples were collected before and 24 h after each treatment to quantify IL-12, IFN-γ and TNF-α levels using a commercially available enzyme linked immunosorbant assay [17].

The demographic data and incidence of treatment-related AEs are presented as percent values of the total subjects enrolled in the study. All other data is presented as average value plus standard deviations where indicated.

Results

A total of 13 patients were enrolled in the study: 3 patients each in Cohorts 1 through 3 (dose escalation) and 4 patients in Cohort 4 (cycle escalation). A total of 7 patients were enrolled in the highest dose cohort (24 mg/m^2). Three of those patients received 4 weekly treatments and four patients received 6–8 weekly treatments at the same dose. The demographic and baseline characteristics of patients enrolled in the study are summarized in Table 1. The median platinum-free interval for all cohorts was 11 months with a range of 7.8 months to 48.7 months. The majority of patients (76.9%) had Stage III (including Stage IIIC) cancer upon the initial diagnosis, while all 3 patients in Cohort 3 initially had Stage IV disease. All patients in Cohorts 1 through 3 received 4 doses of phIL-12/PPC as planned. Two patients in Cohort 4 did not complete all 8 treatments, dosing was discontinued in both patients after 6 treatments due to port malfunction or disease progression.

All 13 patients reported at least 1 treatment-emergent AE (TEAE), with a total of 406 TEAEs reported. The incidence of TEAE reported in at least 20% of patients overall are listed in Table 2. A total of 139 TEAEs were reported as phIL-12/PPC related. The definitely related AEs were abdominal pain (10 patients); hypotension (3 patients); low-grade fever (2 patients), catheter site pain, chills, dysgeusia, infusion-related reaction, and nausea (1 patient each). A majority of the definitely related TEAEs were reported by patients receiving the highest plasmid dose of 24 mg/m^2.

Only 3 Grade 3 TEAEs were considered to be probably or definitely related to study drug. These included abdominal pain (2 events reported in 1 patient in Cohort 2 and considered to be definitely related to study drug) and cytokine release syndrome and hypotension (both reported in 1 patient in Cohort 4 and considered to be probably and definitely related to study drug, respectively). The cytokine release syndrome AE was characterized in the affected patient by chills, rigor and drop in blood pressure from pre-treatment level of 120/75 (HR 75 bpm) to lowest blood pressure recorded of 80/40 (HR 94 bpm) within 24 h after the treatment. The patient responded to IV fluids and an anti-pyretic and subsequently received 4 subsequent doses of phIL-12/PPC. The patient experienced a similar AE on the day of the 6th dose and she responded to the measures employed with her prior AE.

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Table 1
Demographic & baseline characteristics.

Category	Cohort 1 12 mg/m^2 4 doses (N = 3)	Cohort 2 18 mg/m^2 4 doses (N = 3)	Cohort 3 24 mg/m^2 4 doses (N = 3)	Cohort 4 12 mg/m^2 8 doses (N = 4)	Total
Age (years)					
n	3	3	3	4	13
Mean (SD)	56.0 (6.56)	56.0 (7.55)	60.0 (10.44)	69.3 (5.62)	61.0 (8.84)
Min, Max	50, 63	49, 64	48, 67	62, 75	48, 75
Race, n (%)					
White	3(100)	3(100)	3(100)	4(100)	13(100)
Weight (kg)					
n	3	3	3	4	13
Mean (SD)	72.9 (19.3)	67.3 (1.4)	85.3 (6.4)	66.0 (13.4)	72.3 (13.3)
Min, Max	61.4, 95.3	66.2, 68.9	78.9, 90.3	51.7, 83.9	51.7, 95.3
Body Surface Area (m^2)					
n	3	3	3	4	13
Mean (SD)	1.77 (0.29)	1.75 (0.01)	1.82 (0.12)	1.68 (0.19)	1.75 (0.17)
Min, Max	1.60, 2.10	1.75, 1.76	1.68, 1.90	1.48, 1.92	1.48, 2.10
Stage at Initial Diagnosis, n (%)					
Stage III	0	0	0	1 (25.0)	1 (7.7)
Stage IIIC	3 (100)	3 (100)	0	3 (75.0)	9 (69.2)
Stage IV	0	0	3 (100)	0	3 (23.1)
Prior Chemotherapy Regimens, n					
Taxol-Carboplatin	2	3	0	2	7
Taxotere-Carboplatin	1	0	0	2	3
Docetaxel-Carboplatin	0	0	1	0	1
Docetaxel-Carboplatin-Bevacizumab	0	0	1	0	1
Paclitaxel-Carboplatin	0	0	1	0	1
Taxol	0	1	0	0	1
Platinum-Free Interval, (months)					
n	3	2	3	4	12
Mean (SD)	30.5 (20.8)	19.0 (14.3)	9.1 (0.9)	12.8 (3.7)	17.3 (13.2)
Median	35	–	9.3	13.3	11
Min, Max	7.8, 48.7	8.9, 29.1	8.0, 9.8	7.9, 16.7	7.8, 48.7

Max = maximum value; Min = minimum value; SD = standard deviation; One patient in 18 mg/m^2 cohort failed the inclusion criteria of >6 month platinum-free interval and therefore disregarded in the calculation for median platinum-free interval.

In the treatment group where patients received higher than 4 treatments the number of AEs considered probably or definitely related to phIL-12/PPC treatment were 30 for the cycle 1–4 treatment phase and 29 for the cycle 5–8 treatment phase. There were no clinically significant or drug-related trends noted in laboratory test results. There were no deaths resulting from an AE and no patients discontinued from the study because of an AE. In addition, there were no TEAEs reported that were judged to be DLTs.

Table 2
Incidence of adverse events reported by at least 20% of patients after phIL-12/PPC and carboplatin/docetaxel treatment.

Adverse events	Cohort 1 12 mg/m^2 4 doses (N = 3)	Cohort 2 18 mg/m^2 4 doses (N = 3)	Cohort 3 24 mg/m^2 4 doses (N = 3)	Cohort 4 24 mg/m^2 6–8 doses (N = 4)	Total
Alopecia	3 (100)	2 (66.7)	3 (100)	3 (75.0)	11 (84.6)
Pyrexia	2 (66.7)	2 (66.7)	3 (100)	4 (100)	11 (84.6)
Abdominal pain	3 (100)	3 (100)	1 (33.3)	3 (75.0)	10 (76.9)
Nausea	3 (100)	1 (33.3)	2 (66.7)	4 (100)	10 (76.9)
Dysgeusia	3 (100)	2 (66.7)	0	3 (75.0)	8 (61.5)
Fatigue	3 (100)	3 (100)	0	2 (50)	8 (61.5)
Insomnia	1 (33.3)	3 (100)	0	3 (75)	7 (53.8)
Vomiting	2 (66.7)	0	2 (66.7)	3 (75.0)	7 (53.8)
Constipation	0	3 (100)	1 (33.3)	2 (50)	6 (46.2)
Hyperhidrosis	3 (100)	1 (33.3)	0	2 (50)	6 (46.2)
Anaemia	1 (33.3)	0	3 (100)	1 (25.0)	5 (38.5)
Chills	1 (33.3)	0	0	4 (100)	5 (38.5)
Diarrhoea	1 (33.3)	0	2 (66.7)	2 (50)	5 (38.5)
Dyspepsia	1 (33.3)	1 (33.3)	1 (33.3)	2 (50)	5 (38.5)
Anxiety	1 (33.3)	1 (33.3)	1 (33.3)	1 (25.0)	4 (30.8)
Decreased appetite	2 (66.7)	1 (33.3)	0	1 (25.0)	4 (30.8)
Hypotension	1 (33.3)	0	0	3 (75.0)	4 (30.8)
Neutropenia	0	0	3 (100)	1 (25.0)	4 (30.8)
Urinary tract infection	1 (33.3)	1 (33.3)	0	2 (50)	4 (30.8)
Blood creatinine increased	1 (33.3)	1 (33.3)	0	1 (25.0)	3 (23.1)
Dehydration	1 (33.3)	0	0	2 (50)	3 (23.1)
Cellulitis	2 (66.7)	0	0	1 (25.0)	3 (23.1)
Infusion site erythema	0	0	0	3 (75.0)	3 (23.1)

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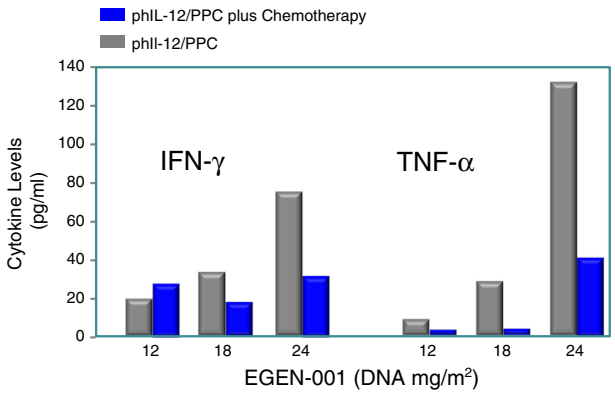

Fig. 1. IFN-γ and TNF-α levels in peritoneal fluid of ovarian cancer patients 24 h after phIL-12/PPC treatment administered alone (gray bars) or in conjunction with carboplatin and docetaxel chemotherapy (blue bars). The quantifiable limit of detection of IFN-α and IFN-γ assays was 2.2 pg/ml and 15.6 pg/ml, respectively.

Twelve patients were evaluable for response. Best overall response was 17% complete response, 33% partial response, 42% stable disease and 8% progressive disease. Ten out of twelve patients (83%) lived >12 months and 2 patients lived longer than 5 years. To this date, one of the two living patients has no evidence of disease. The median progression-free survival and overall survival for all treatment groups was 8.8 months and 16.6 month, respectively. In 11 out of 12 evaluable patients (92%), the CA-125 levels reduced from pre-treatment levels; in 7 of 12 evaluable patients (58%), the reduction was >50%.

Levels of IL-12 in all plasma samples and in all but 4 IP fluid samples were below the limit of detection. Low levels of TNF-α, but not of IFN-γ, were detected in some blood samples also (data not shown). In several instances, peritoneal fluid could not be collected due to inadequate aspiration of samples or to abdominal tenderness associated with aspiration attempts. This resulted in high variability in the cytokine data. The levels of IFN-γ were above the limit of detection in 20 IP fluid samples and the levels of TNF-α were above the limit of detection in 64 IP fluid samples and 94 blood samples. The average values of IFN-γ and TNF-α in peritoneal fluid samples with detectable cytokine concentrations 1 day after plasmid treatment are expressed in Fig. 1. Samples collected 7 days after plasmid treatment did not show quantifiable levels of the measured cytokines. The increases in cytokine concentrations appeared to be related to the plasmid dose (Fig. 1). The IFN-γ levels in peritoneal fluid samples of patients treated at 12, 18 and 24 mg/m^2 dose of phIL-12/PPC alone were increased over pre-treatment controls by 26.9%, 109.6% and 376.5%, respectively. In instances where chemotherapy coincided with phIL-12/PPC treatment the post-treatment increases in IFN-γ levels were reduced relative to samples where chemotherapy was not given with phIL-12/PPC (Fig. 1). The TNF-α levels in peritoneal fluid samples of patients treated at 12, 18 and 24 mg/m^2 dose of phIL-12/PPC were increased over pre-treatment controls by 64%, 1177.3%, and 2431.1%, respectively. Again, in the presence of chemotherapy treatment the TNF-α levels were reduced.

Discussion

We have previously demonstrated that IP administration of phIL-12/PPC as a single agent in platinum-resistant terminal ovarian cancer patients is safe. The primary objective of this study was to determine the safety of IP phIL-12/PPC in combination with IV carboplatin and docetaxel in platinum-sensitive ovarian cancer patients. The secondary objectives were to determine the preliminary efficacy of the combination treatment and biological activity of phIL-12/PPC. The results show that escalated doses of IP phIL-12/PPC (12, 18, 24 mg/m^2 DNA dose) administered once every week for 4 weeks in conjunction with carboplatin (AUC 5) and docetaxel (75 mg/m^2) were safe and well tolerated. Increasing the number of phIL12/PPC cycles from 4 to 8 treatments was also safe and well tolerated. The addition of phIL-12/PPC to carboplatin/docetaxel regimens did not exacerbate chemotherapy-related toxicity. The combination treatment was associated with IL-12 biological activity and antitumor activity. The commonly observed toxicities attributed to plasmid treatment were characterized by abdominal pain, low-grade fever, chills, and catheter site pain. None of the AEs were judged to be dose limiting toxicities.

Overall, the spectrum of phIL-12/PPC-related toxicities was similar to that observed in the monotherapy trial of phIL-12/PPC in ovarian cancer patients (17). The molecular basis of Grade 3 cytokine syndrome in one of the patients at the highest dose cohort could not be confirmed since 24 h post-treatment blood samples did not show elevated TNF-α or IFN-γ levels and the parallel peritoneal fluid samples could not be collected due to patient discomfort of the abdomen. The cytokine surge associated with monoclonal antibody treatment is observed within few hours after treatment [22]. The maximum tolerated dose was not observed although a majority of the drug-related AEs were reported at highest dose of 24 mg/m^2. AEs that were common with recombinant IL-12 treatment were low grade fever, chills, and abdominal pain. Serious systemic toxicities that have been reported with recombinant IL-12 treatment, including elevation in liver transaminases, anemia, neutropenia, thrombocytopenia, glycemia and hypoalbuminemia, were not observed associated with phIL-12/PPC treatment.

Increasing the number of phIL-12/PPC cycles from 4 to 8 treatments did not increase the number of AEs or cause new type of AE. These results demonstrate that the number of phIL-12/PPC treatment can be safely increased from 4 weekly treatments (17), to higher numbers. Maintenance treatments with anticancer agents are believed to have potential benefits [23]. The phIL-12/PPC offers a unique advantage over conventional cytotoxic therapies due to its safety for chronic treatment.

The addition of phIL-12/PPC treatment does not appear to attenuate the efficacy of chemotherapy treatment. An objective response rate of 50% (CR & PR) and disease stabilization rate of 42% together with a progression-free survival of 8.8 months and overall survival of 16.6 months is consistent with other reports in patient population of less than 12 month of median platinum-free interval. The contribution of IL-12 plasmid to the efficacy response is difficult to ascertain from a single arm design. A randomized trial of the phIL-12/PPC in combination with a standard chemotherapy regimen in platinum-resistant ovarian cancer patients is being considered for future.

Dose-dependent increases in IFN-γ and TNF-α concentrations demonstrate that phIL-12/PPC treatment elicits IL-12 biological activity. Combination with carboplatin/docetaxel attenuated the increase in TNF-α and IFN-γ response to phIL-12/PPC treatment. This attenuation could be due to the use of dexamethasone (16 mg/day) to prevent hypersensitivity to docetaxel. Administration of corticosteroids has been shown to inhibit cytokine production and impairs cellular immunity [24].

In summary, this study demonstrates the feasibility of IP delivery of an IL-12 gene plasmid and IV delivery of standard cytotoxic agents in ovarian cancer. Long-term treatment with an immune modulating agent in conjunction with cytotoxic agents is a promising approach to combatting difficult to treat cancers. Human clinical trials of phIL-12/PPC in combination with other cytotoxic agents for the treatment of peritoneal metastases of ovarian and other gynecologic and gastric malignancies are currently in progress.

Conflict of Interest

Drs. Ronald Alvarez, Joseph Kelly and Christina Chu received a research grant from EGEN, INC. for this research. Drs. Khursheed Anwer, Jason Fewell and Danny Lewis are EGEN employees.

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