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A Phase I Trial of Oblimersen Sodium in Combination With Cisplatin and 5-Fluorouracil in Patients with Advanced Esophageal, Gastroesophageal Junction and Gastric Carcinoma

Rachel Raab, MD[1], **Joseph A. Sparano, MD**[1], **Allyson J. Ocean, MD**[2], **Paul Christos, MPH, MS**[2], **Mark Ramirez, MD**[1], **Vincent Vinciguerra, MD**[3], and **Andreas Kaubisch, MD**[1]

[1]New York Cancer Consortium (www.newyorkcancerconsortium.org), including the Montefiore-Einstein Cancer Center, Bronx, NY

[2]New York Presbyterian-Cornell Medical Center, New York, NY

[3]North Shore University Hospital, Manhasset, NY

Abstract

Purpose—To determine the maximum tolerated dose of oblimersen, an antisense oligonucleotide directed to the Bcl-2 mRNA, in combination with cisplatin and 5-flourouracil in patients with advanced gastric and esophageal carcinoma.

Methods—Patients were treated with escalating doses of oblimersen administered by continuous intravenous infusion (CIVI) days 1 to7, CIVI 5-fluorouracil (5-FU) days 4 to 7, and cisplatin on day 4 every three weeks.

Results—Fifteen patients received a total of 49 courses of oblimersen at doses of 3, 5, or 7 mg/kg/d given as a seven day CIVI in combination with 4 or 5 day CIVI of 5-FU (1000 or 750 mg/m2/d) plus intravenous cisplatin (100 or 75 mg/m2 over 2 hours). The recommended phase II dose of oblimersen was 5 mg/kg/day in combination with 5-FU (750 mg/m2/day for 4 days) and cisplatin (75 mg/m2). The most common grade 3 to 4 adverse events that occurred in at least 10% of patients at all dose levels included neutropenia (33%), hypokalemia (27%), infection (20%), and mucositis, fatigue, dizziness, thrombosis, and dehydration (in 13% for each category).

Conclusion—The combination of oblimersen with 5-FU and cisplatin chemotherapy is feasible in patients with advanced upper gastrointestinal cancer, with antitumor activity observed in gastric carcinoma.

INTRODUCTION

Adenocarcinoma of the upper gastrointestinal tract, including the distal esophagus, gastroesophageal junction, and stomach was diagnosed in approximately 37,000 individuals in the United States in 2007, and was associated with about 25,000 deaths.[1] Most patients present with advanced disease associated with a poor prognosis, with a five year survival rate of about 5 to 15%.[2] Because of the limited activity of single agent chemotherapy, combination regimens are commonly used, which generally include 5-flourouracil (5-FU) and cisplatin; response occurs in about 20%, and median survival is approximately 7 to 10 months.[3] New strategies are needed to enhance the activity of cytotoxic therapy.

Corresponding author: Joseph A. Sparano, MD, New York Cancer Consortium Coordinating Center, Montefiore Medical Center-Weiler Division, Department of Oncology, 2 South - Room 47-48, 1825 Eastchester Road, Bronx, NY 10461, Phone 718-904-2555, Fax 718-904-2892.

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One of major mechanisms of action of cytotoxic therapy is induction of apoptosis, or programmed cell death.[4] Bcl-2 is an endogenous protein that inhibits apoptosis by interacting with Bax and other proapoptotic proteins, which in turn prevents mitochondrial release of cytochrome that triggers the apoptotic cascade. Overexpression of Bcl-2 has been associated with resistance to cytotoxic chemotherapy in hematologic malignancies and solid tumors, including gastrointestinal cancer.[5] Kim et al evaluated an 18-mer phosphorothiated oligonucleotide antisense to Bcl-2 in the MKN-45 gastric carcinoma cell line in a mouse xenograft model alone or in combination with cytotoxic agents.[6] Bcl-2 was down-regulated to 60% of its initial value after treatment with 1.0 muM of the anti-Bcl-2 antisense molecule compared with the controls of random and mismatched oligonucleotides, and enhanced the sensitivity of the xenograft to doxorubicin, cisplatin, and paclitaxel by 3–4-fold in vitro. In addition, the antitumor effect of cisplatin and paclitaxel were significantly enhanced in the xenograft model.

Oblimersen sodium (G3139; Genasense, Genta Incorporated, Berkeley Heights, NJ) is a phosphorothionate antisense oligonucleotide that blocks the production of Bcl-2 protein by hybridizing to the first 6 codons of the Bcl-2 open reading frame mRNA, which leads to cleavage by endogenous RNAse H. In a phase I study of oblimersen in 35 patients with advanced cancer, the majority with prostate or renal cancer, treatment with oblimersen was well tolerated. The main adverse events were fatigue, anorexia, elevated transaminases, elevated creatinine, diarrhea, and anemia/thrombocytopenia. Oblimersen has been shown to enhance the effects of cytotoxic therapy in preclinical systems *in vitro* and *in vivo*, including cisplatin and 5-FU. [6–11] In combination with cytotoxic chemotherapy, oblimersen is well tolerated and without severe adverse events. Docetaxel, an agent active in the treatment of esophageal and gastric cancer, has also been shown to have activity when used in combination with oblimersen. A phase II trial of oblimersen and docetaxel in individuals with hormone refractory prostate cancer, demonstrated that the combination was active and without severe adverse events. A phase I trial oblimersen and docetaxel in patients with advanced breast cancer and other solid tumors demonstrated that the combination was active and well tolerated. Based upon the evidence supporting Bcl-2 as a therapeutic target, and the preclinical data supporting the combination of oblimersen with cisplatin and 5-FU in preclinical systems, we performed a pilot phase I trial to determine the recommended phase II dose of oblimersen that could be safely combined with 5-FU and cisplatin in patients with upper gastrointestinal cancer.

METHODS

Eligibility Criteria

Eligibility criteria included histologically or cytologically confirmed locally advanced, recurrent, or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus, or adenocarcinoma of the gastroesophageal junction, or stomach that was not amenable to potentially curative surgery or irradiation, and who had measurable or evaluable disease. Patients were allowed to have received up to one prior chemotherapy regimen, radiation, or chemotherapy plus irradiation. Other criteria included age at least 18 years, an Eastern Cooperative Oncology Group performance status 0, 1 or 2, life expectancy of at least 12 weeks, and adequate organ function, including bone marrow (absolute neutrophil count ≥ 1,500/ml, platelets ≥ 100,000), hepatic (total bilirubin within institutional limits, AST/ALT ≤ 2.5 × institutional upper limit of normal) and renal function (serum creatinine ≤ 1.5 mg/dl or creatinine clearance ≥ 60 ml/min/1.73 m2 for patients with creatinine levels above institutional normal). Exclusion criteria included patients who had chemotherapy or radiotherapy within 21 days of registration (6 weeks for nitrosoureas or mitomycin C, 2 weeks whether prior treatment was a weekly regimen), patients who had not recovered from grade 2 or worse adverse events due to prior chemotherapy, and patients who had

photodynamic therapy within 4 weeks of registration. Other exclusion criteria included active brain metastases, HIV infection, uncontrolled illnesses such as active infection, unstable angina, congestive heart failure, cardiac arrthymias, psychiatric illness that would limit compliance, history of prior oblimersen exposure or allergic reactions attributed to compounds with similar chemical or biologic composition as anti-sense oligonucleotides, cisplatin, 5-FU. The local institutional review board at each center approved the protocol, and all patients provided written informed consent. The trial was reviewed, approved, and sponsored by the National Cancer Institute Cancer Therapy Evaluation Program (Clinical Trials.Gov Identifier NCT00064259).

Treatment

Patients received oblimersen as a continuous intravenous infusion (CIVI) on days 1 to 7 at 1 of 3 dose levels (3, 5, or 7 mg/kg/d) in combination with CIVI 5-FU (1000 mg/m2/d or 750 mg/m2/d) on days 4 to 7 and cisplatin (100 mg/m2 or 75 mg/m2) on day 4. Courses of treatment were repeated every 21 days. Oblimersen was supplied by Genta Incorporated as a sterile solution in a 300-mg glass vial. Oblimersen was further diluted with sterile normal saline (0.9% sodium chloride injection, USP) to a final concentration between 1.5 mg/ml and 30 mg/ml. The final solution was infused continuously for 7 days (168 hours). Before to infusion, 5-FU was diluted into 240 ml in 0.9% sodium chloride and administered as a CIVI via Computerized Ambulatory Drug pump at a rate of 2 mL/hr for 5 days. Cisplatin was diluted in 0.9% sodium chloride injection to a volume of 250 to 500 ml depending on total calculated dose. Cisplatin was administered on day 4 of each 21-day cycle over 120 minutes. Patients received pre-hydration with at least 1 liter of normal saline sufficient to allow the patient to make at least 100 mL/hr of urine prior to receiving cisplatin. Patients received post-hydration with 1 liter of normal saline (containing any of 25 g mannitol, potassium chloride, or magnesium sulfate at the physician's discretion) over 4 hours. All patients received an antiemetic of the serotonin antagonist class and dexamethasone 20 mg by intravenous infusion prior to cisplatin administration. Granulocyte-colony stimulating factors were allowed during the second or subsequent cycles if the first cycle was complicated by grade 4 neutropenia. Erythroid stimulating agents were permitted for management of grade 3 (6.5–8 g/dL) or grade 4 hemoglobin (<6.5 g/dL) as well as for symptomatic grade 2 hemoglobin (8.5–10 g/dL).

Criteria for Dose Escalation

Patients were treated in cohorts of 3 to 6 patients per dose level using standard criteria for dose escalation (escalate dose of 0 of 3 or 1 of 6 with dose limiting toxicity [DLT], treat 3 patients at same dose level if 1 of 3 have DLT). Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria (version 2.0). DLT was defined as grade 3 to 4 hematologic toxicity lasting more than 1 week after 5-FU/cisplatin, grade 3 to 4 nausea or vomiting occurring later than 11 days after cisplatin, grade 3–4 diarrhea occurring later than 10 days after 5-FU, and grade 3 to 4 mucositis at the beginning of the next cycle.

Tumor Response

Patients were evaluated for response by radiological examination (computerized tomography or magnetic resonance imaging) and/or physical examination every 2 cycles (every 6 weeks) for the first 12 weeks on protocol. Subsequent tumor measurements were done every 3 cycles (every 9 weeks). Response and progression were evaluated using the criteria proposed by the Response Evaluation Criteria in Solid Tumors Committee.[12]

Statistical Considerations

Objective response was calculated and a 95% confidence interval (CI) was estimated via binomial proportions. Progression-free survival and overall survival were analyzed using the Kaplan-Meier method and 95% CI (95% CI) were constructed using Greenwood's formula. All analyses were performed in SAS version 9.1 (SAS Institute, Inc., Cary, NC) and Stata version 8.0 (Stata Corporation, College Station, TX).

RESULTS

Patient Characteristics

A total of 17 patients were enrolled from 3 institutions between October 2003 and October 2005, of whom 15 were treated. One patient declined treatment after initial consent and registration, and a second patient developed rapidly progressive disease after consent and registration and became ineligible to begin therapy. The characteristics for the remaining 15 patients are shown in Table 1. The median age was 55 years (range: 36–65 years), median Eastern Cooperative Oncology Group performance status was 1 (range: 0–2), and 11 patients (73%) had received at least one prior chemotherapy regimen. Ten patients had gastric, 3 had esophageal cancer, and 2 had gastro-esophageal junction cancer.

Results of Dose Escalation

The results of dose escalation are shown in Table 2. A total of 49 courses of therapy were administered across 3 oblimersen dose levels. The median number of courses given was 2 (range: 1–12). At the first oblimersen dose level including 3 mg/kg/d of oblimersen plus 1000 mg/m2/d of 5-FU for 5 days and 100 mg/m2 of cisplatin, 1 of 4 patients had a DLT in cycle 1 (grade 3 mucositis). Although accrual could have continued at the same dose level, the protocol was amended to reduce the dose of 5-FU (to 750/mg/m2 for 4 days) and cisplatin (to 75 mg/m2) in order to make the regimen more tolerable over repeated cycles of therapy. At the second dose level that employed the same dose level of oblimersen (3 mg/kg/d) plus a reduced dose of 5-FU and cisplatin, none of 4 patients had a DLT during cycle 1. At the third dose level, which included an escalated dose of oblimersen (5 mg/kg/d), none of 3 patients had a DLT during cycle 1 (dose level 3a). The dose was subsequently escalated to 7 mg/kg/d of oblimersen with a DLT event observed in the first patient, and the protocol was modified to continue additional accrual at dose level 3; 3 additional patients were accrued (dose level 3b in Table 2). The study was then closed to accrual due to uncertainty regarding the future development of oblimersen.

Adverse Events

Adverse events occurring in all patients treated at all dose levels is summarized in Table 3. The most common grade 3 to 4 adverse events that occurred in at least 10% of patients at all dose levels included neutropenia (33%), hypokalemia (27%), infection (20%), mucositis (20%), fatigue (13%), dizziness (13%), venous thrombosis (13%), and dehydration (13%). One patient died within 30 days of protocol therapy that was possibly associated with treatment. This patient experienced fatigue, dizziness and dysphagia after cycle of therapy including 5 mg/kg/d of oblimersen; the dysphagia was felt to be secondary to gastroesophageal junction tumor obstruction. A stent was placed, and he received a second cycle of therapy that was associated with progressive fatigue, hypokalemia, and a decline in performance status; he subsequently died at home, without further available clinical details, and the exact cause of his demise was uncertain. It was felt, however, that his death was unrelated to protocol therapy and was secondary to his underlying malignancy.

Antitumor Activity—Three patients had an objective response (20%, 95% CI 0%, 31%). One patient with metastatic gastric carcinoma with pulmonary metastases, treated at dose level 1, had a complete remission that is maintained for at least 51 months. A second patient with gastric carcinoma, treated at dose level 2, has a partial response, but was subsequently lost to followup. One patient with squamous cell carcinoma of the esophagus, treated at dose level 3a, had a partial response that lasted 10 months. The median progression-free survival time for all 15 patients was 2.5 months (95% CI = 1.3 months, upper limit not estimated) and the median overall survival time was 7.5 months (95% CI = 3.7 months, 9.8 months).

DISCUSSION

Cytotoxic chemotherapy has been shown to improve survival and be cost effective when compared with best supportive care in patients with advanced gastric carcinoma.[13–15] A systematic analysis of randomized trials has also shown that combination chemotherapy regimens containing 5-FU was associated with improved survival compared with single agents (hazard ratio [HR] for death 0.83; 95% CI = 0.74 –0.93).[3] Survival was also improved by adding anthracyclines to 5-FU/cisplatin-containing regimens (HR = 0.77; 95% CI, 0.62 – 0.95) or by adding cisplatin to 5-FU/anthracycline-containing regimens (HR = 0.83; 95% CI, 0.76 – 0.91). In addition, a recent trial indicated that addition of docetaxel to 5-FU/cisplatin improved response, clinical benefit, and overall survival, but was associated with significantly more toxicity.[16, 17] Substituting oxaliplatin for cisplatin, and capecitabine for 5-FU respectively, do not diminish efficacy and results in a somewhat favorable toxicity profile. [18] Nevertheless, median survival for patients with advanced gastric cancer remains less than 1 year, and outcomes for patients with adenocarcinoma of the esophagus and gastroesophageal junction receiving similar therapy are likewise poor.

We sought to enhance the activity of cytotoxic therapy for these conditions by combining a Bcl-2 directed therapy with standard cytotoxic therapy. Bcl-2 overexpression is associated with poor prognosis and poor response to therapy in a number of cancer types, including gastric cancer.[19] Of interest, 6 antiapoptotic members of the Bcl-2 family have been identified and include Bcl-2, Bcl-w, Bcl-x, Mcl-1, Bfl-1, and Bcl-B. Bcl-B expression was examined in normal human tissues well as several types of human malignancy. The expression of Bcl-2 was associated with poor prognosis in prostate cancer, higher tumor grade in breast cancer, and microsatellite instability in colorectal cancers but in gastric cancer Bcl-B expression correlated with a better outcome and more differentiated histology. Oblimersen-induced down- regulation of Bcl-2 enhances the apoptotic effects of cytotoxic therapy in preclinical models, although other evidence suggests some of these effects may be mediated by mechanisms other than silencing intracellular Bcl-2.[20] Based on these considerations, we performed a phase I study to determine the maximum tolerated dose of oblimersen that could be used in combination with cisplatin and 5-FU in patients with advanced upper gastrointestinal cancer. As noted in other clinical trials combining chemotherapy with oblimersen,[21–27] we found that the combination was associated with a toxicity profile comparable to that expected for cisplatin/5-FU alone in this patient population. We determined the recommended phase II dose of oblimersen to be 5 mg/kg/d as a 7 day continuous IV infusion in combination with cisplatin 75 mg/m2 and 5-FU 750 mg/m2/d for 4 days. At these doses, no patients experienced dose- limiting toxicities during the first cycle of therapy. The cumulative dose administered over 7 days (35 mg/kg) is identical to the cumulative dose used in other trials when 7/mg/kd/d was given over 5 days. The predominant non-hematologic toxicities were mucositis, nausea, and fatigue and the predominant hematologic toxicities were neutropenia, anemia, and thrombocytopenia. Objective responses were observed in 2 of 10 patients with gastric carcinoma, one of which appears to be particularly durable; however, the sample size was insufficient to accurately determine the efficacy of the combination.

Although we had initially planned to accrue an additional 12 patients at the recommended phase II dose, accrual to the study was discontinued because of uncertainty regarding future development of oblimersen when it was found that oblimersen failed to achieve statistically significant improvement in survival for patients with metastatic melanoma in a large randomized phase III trial. [28] The study included 771 patients with metastatic melanoma who were randomly assigned to receive dacarbazine alone (1,000 mg/m2) or the same dose of dacarbazine preceded by a 5-day CIVI of oblimersen sodium (7 mg/kg/d) every 3 weeks for up to 8 cycles. Oblimersen was associated with improved overall response (13.5% vs. 7.5%; P = 0.007) and progression-free survival (median: 2.6 vs. 1.6 months; P < 0.001), however, the survival endpoint was not met (median: 9.0 vs. 7.8 months; P = 0.077). An important finding in this study was that patients with normal baseline serum lactate dehydrogenase (LDH) received maximum benefit (including an overall survival benefit) from the addition of Genasense to dacarbazine. Moreover, treatment effect was highly correlated with the ratio of LDH to the upper limit of the normal reference range across all efficacy endpoints, that is the smaller the ratio of LDH to the upper limit of the normal reference range, the larger the treatment effect. Accordingly, additional evaluation of this combination (the AGENDA trial) is ongoing in chemotherapy-naïve patients with metastatic melanoma and low baseline LDH.[29] Further study in patients with cancer of the esophagus, gastroesophageal junction, and stomach should be considered in light of the findings observed in this study. Additional evaluation of this combination will depend on whether oblimersen is shown to produce clinical benefit in other disease.

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Table 1

Patient Characteristics

Total Patients	15
Gender	
Male	9
Female	6
Mean age (range)	55 years (36–65)
Performance Status (N=13)	
0	1
1	10
2	2
Tumor type	
Gastric	10
Esophageal	3
Gastroesophageal junction	2
Prior Chemotherapy	11
Prior surgery	12
Prior radiation therapy	3

Table 2

Dose Levels and Dose Limiting Toxicities

Dose level	Oblimersen (mg/kg/d)	Cisplatin (mg/m2)	5-Fluorouracil (mg/m2/d)	No. Patients	No. Cycles	No. Cycle 1 DLT
1	3	100	1000 × 5 d	4	14	1
2	3	75	750 × 4 d	4	14	0
3a	5	75	750 × 4 d	3	16	0
4	7	75	750 × 4 d	1	2	1
3b	5	75	750 × 4 d	3	7	0

Table 3

Adverse Events Observed in All Patients Treated at All Dose Levels (N=15 patients)

Adverse event	Grade 2	Grade 3	Grade 4
Hematologic			
Neutropenia	3 (20%)	3 (20%)	2 (13%)
Anemia	8 (53%)	1 (7%)	0
Thrombocytopenia	2 (13%)	1 (7%)	0
Infection		2 (13%)	1 (7%)
Gastrointestinal			
Mucositis	4 (27%)	3 (20%)	0
Nausea	4 (27%)	1 (7%)	0
Vomiting	2 (13%)	0	1 (7%)
Dysphagia	0	1 (7%)	0
Diarrhea	2 (13%)	0	0
Transaminase elevation	0	1 (7%)	0
Alkaline phosphatase	2 (13%)	1 7%)	0
Renal			
Creatinine	0	1 (7%)	0
Ureteral obstruction	0	0	1 (7%)
Constitutional			
Weight loss	2 (13%)	0	0
Anorexia	1 (7%)	0	0
Fatigue	3 (20%)	2 (13%)	0
Dizziness	1 (7%)	2 (13%)	0
Vascular/thrombosis	0	2 (13%)	0
Metabolic			
Hyperglycemia	1 (7%)	0	0
Hypokalemia	0	3 (20%)	1 (7%)
Hyponatremia	0	1 (7%)	0
Hypomagnesaemia	1 (7%)	0	0
Dehydration	1 (7%)	2 (13%)	0
Neurologic			
Sensory neuropathy	0	1 (7%)	0
Motor neuropathy	0	1 (7%)	0
Fluid retention			
Pleural effusion	0	1 (7%)	0
Ascites	0	1 (7%)	0
Peripheral edema	2 (13%)	0	0