Overview

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Title: Phase Ib/II Trial of Gemcitabine, Cisplatin, and Lenalidomide as First-Line Therapy in Patients With Metastatic Urothelial Carcinoma

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Disclosures

Neeraj Agarwal: Amgen, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Imclone, Medivation, Takeda, Novartis, Pfizer (RF); **Matthew D. Galsky:** Dendreon, Astellas, Jannsen, GlaxoSmithKline, BioMotiv,Dual Therapeutics (RF). The other authors indicated no financial relationships.

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Author Summary: Abstract and Brief Discussion

Background

Outcomes with current chemotherapy in metastatic urothelial carcinoma (MUC) remain poor. Lenalidomide, an antiangiogenic and immunomodulatory agent, enhances the effects of chemotherapy in preclinical studies. In this phase Ib/II study, we sought to determine a tolerable dose of lenalidomide in combination with gemcitabine and cisplatin (GCL) in patients with MUC and to explore the safety and activity of this regimen.

Methods

Patients with chemotherapy-naïve MUC received gemcitabine 1,000 mg/m^2 on days 1 and 8 and cisplatin 70 mg/m^2 on day 1 every 21 days. In phase Ib, there were four planned escalating dose levels of lenalidomide (10, 15, 20, and 25 mg) daily on days 1–14.

Results

Seven patients received GCL in phase Ib. The dose of lenalidomide was not escalated beyond 10 mg because of cytopenias requiring repeated dose delays and reductions. Two additional patients were enrolled in phase II, but the study was ultimately terminated due to poor tolerability and slow accrual. The most frequent grade $\geq$3 adverse events were cytopenias and diarrhea. Three of the nine patients experienced an objective response (one complete response, two partial responses).

Conclusion
Chronic administration of the GCL regimen was poorly tolerated because of additive and cumulative myelosuppression.

Discussion
Each year in the United States, more than 60,000 patients develop urothelial carcinoma (UC) and more than 12,000 die of the disease [1]. The combination of gemcitabine and cisplatin (GC) is a standard first-line therapy for metastatic UC (MUC) based on a randomized study demonstrating similar efficacy and less toxicity compared with a regimen of methotrexate, vinblastine, doxorubicin, and cisplatin [2]. Although the tolerability of chemotherapy for patients with MUC has improved, there have been no improvements in the efficacy of treatment for the past several decades, and novel approaches are clearly needed.

Lenalidomide, a potent thalidomide analog with antiangiogenic and immunomodulatory properties, has demonstrated antiproliferative and antiangiogenic effects in cell culture and xenograft models of UC and has been shown to enhance the antiproliferative properties of GC [3, 4]. Based on such findings, we initiated a phase Ib/II study exploring the combination of GC plus lenalidomide in chemo-naïve patients with MUC. Only one patient experienced a protocol-defined dose-limiting toxicity (grade 4 thrombocytopenia lasting $>$7 days) during phase Ib. However, a decision was made to expand the lenalidomide 10-mg dose-level cohort because of the need for frequent dose delays and dose reductions of gemcitabine, cisplatin, and lenalidomide, often occurring after cycle 1 (Fig. 1), to better characterize the safety and tolerability of the combination. There were no further dose-limiting toxicities, and phase II was opened at the lenalidomide 10-mg dose level. The trial was terminated after enrollment of an additional two patients because the regimen was deemed poorly tolerated for chronic administration because of the need for repeated dose delays and reductions coupled with slow accrual.

These findings highlight three critical points. First, conventional phase I designs aimed at defining recommended phase II dosing using only first-cycle toxicity data may not be optimal in the era of molecularly targeted therapies typically administered in a chronic fashion and often characterized by persistent and/or cumulative toxicities [5]. Second, despite promising preclinical data, there are practical challenges in combining targeted therapies with cytotoxic agents, sometimes related to off-target effects [6]. Third, poor accrual remains a critical barrier to progress in clinical drug development [7].

Trial Information

Disease	Bladder Cancer
Stage of disease / treatment	Metastatic / Advanced
Prior Therapy	None
Type of study - 1	Phase I
Type of study - 2	Phase II
Primary Endpoint	Recommended Phase II Dose
Primary Endpoint	Toxicity
Primary Endpoint	Tolerability
Investigator's Analysis	Poorly Tolerated/Not Feasible

Drug Information

Drug 1 **Generic/Working name**	Lenalidomide
Trade name	Revlimid
Company name	Celgene
Drug type	Biological
Drug class	Angiogenesis inhibitor, immunomodulator
Dose	Milligrams (mg) per flat dose
Route	Oral (po)
Schedule of Administration	Daily

Drug 2 **Generic/Working name**	Cisplatin
Drug type	Other
Drug class	Alkylating agent
Dose	Milligrams (mg) per square meter (m2)
Route	IV
Schedule of Administration	Every 21 days
Drug 3 **Generic/Working name**	Gemcitabine
Drug type	Other
Drug class	Antimetabolite
Dose	Milligrams (mg) per square meter (m2)
Route	Other
Schedule of Administration	Days 1 and 8, every 21 days

Dose Level	Dose of Drug: Lenalidomide	Dose of Drug: Cisplatin	Dose of Drug: Gemcitabine	Number Enrolled	Number Evaluable for Toxicity
1	10 mg	70	1,000	9	9

Patient Characteristics

Number of patients, male	6
Number of patients, female	3
Stage	IV
Age	Median (range): 69
Number of prior systemic therapies	Median (range): 0
Performance Status:	ECOG 0—0 1—8 2—1 3— Unknown—
Other	Not collected
Cancer Types or Histologic Subtypes	Urothelial Carcinoma 9

Primary Assessment Method

Experimental Arm: Total Patient Population

Number of patients screened:	10
Number of patients enrolled:	9
Number of patients evaluable for toxicity:	9
Number of patients evaluated for efficacy:	9
Evaluation method:	Other
Response assessment CR:	11%
Response assessment PR:	22%
Response assessment SD:	33%
Response assessment PD:	22%
Response assessment other:	11%

Dose Limiting Toxicity							
Dose Level	**Dose of Drug: Lenalidomide**	**Dose of Drug: Cisplatin**	**Dose of Drug: Gemcitabine**	**Number Enrolled**	**Number Evaluable for Toxicity**	**Number With a Dose Limiting Toxicity**	**Dose Limiting Toxicity Information**
1	10 mg	70	1,000	9	9		

Assessment, Analysis, and Discussion

Completion:	Study terminated before completion
Terminated reason:	Toxicity
Pharmacokinetics / Pharmacodynamics:	Not Collected
Investigator's Assessment:	Poorly Tolerated/Not Feasible

Discussion

There have been no improvements in survival outcomes in patients with metastatic urothelial carcinoma (MUC) since the advent of the MVAC regimen (methotrexate, vinblastine, doxorubicin, cisplatin) in the 1980s. Gemcitabine plus cisplatin (GC) has emerged as a treatment standard for MUC based on better tolerability compared with MVAC and similar efficacy [8]. Although MUC is a chemosensitive disease, response durations are generally short and most patients succumb to their disease. Novel approaches for the management MUC are critically needed [9].

Multiple lines of evidence support targeting angiogenesis in urothelial carcinoma. Higher levels of vascular endothelial growth factor (VEGF) in urine predict an increased risk of recurrence in patients with non-muscle-invasive urothelial carcinoma [10]. The level of VEGF gene expression has been associated with disease-specific survival in patients with locally advanced urothelial carcinoma [11]. Microvessel density, a histological measure of angiogenesis, predicts subsequent muscle invasion in non-muscle-invasive bladder cancer [12] and has been shown to correlate directly with tumor grade, stage, and poor prognosis in bladder cancer [13]. Inhibitors of angiogenesis have shown activity in preclinical models of urothelial carcinoma [14, 15] as well as in clinical trials [16, 17]. In a single-arm phase II study, 43 chemotherapy-naïve patients with metastatic or unresectable UC were treated with a combination of GC plus bevacizumab (GCB), a monoclonal antibody that binds circulating VEGF. Although, the study-defined goal of 50% improvement in progression-free survival was not met, treatment with GCB was associated with an intriguing median overall survival of 19.1 months (95% confidence interval: 12.4–22.7) [16]. These results have led to an ongoing U.S. intergroup phase III study comparing GC and GCB in chemotherapy-naïve patients with advanced UC (CALGB 90601; NCT00942331).

In addition to targeting angiogenesis, the immune system may also be exploited as a novel approach to the treatment of advanced UC. Combining cytotoxic chemotherapy and immunotherapies may result in additive or synergistic effects based on several lines of evidence. Chemotherapy, for example, has been demonstrated to sensitize tumor cells to cytotoxic T lymphocytes (CTLs) by making tumor cells more permeable to granzyme B [18]. In addition, platinum-based therapy has been shown to downregulate the inhibitory STAT6 and programmed death receptor-ligand 2 (PD-L2) pathway and sensitize tumor cells to T-cell-mediated cytotoxicity [19]. Gemcitabine has been shown to induce apoptosis of tumor cells, thereby increasing tumor antigen cross-presentation, leading to priming of tumor-specific $CD8^+$ T cells [20]. Gemcitabine has also been shown to have selective detrimental effects on protumorigenic immune cells, which may skew the immune system toward antitumor T-cell responses [21], and has been shown to function in synergy with immunotherapeutic modalities in transgenic mice [22].

Lenalidomide is a potent thalidomide analog with both antiangiogenic and immunomodulatory properties. In a preclinical model, lenalidomide demonstrated activity against UC cells attributable to direct tumor cell apoptosis and antiangiogenic activity [3]. In another study, the combination of lenalidomide with GC demonstrated at least additive antiproliferative effects on UC cells [4]. In phase I studies in patients with advanced solid tumors, lenalidomide has been shown to increase peripheral blood levels of interleukin 2 (IL-2), IL-15, granulocyte-macrophage colony-stimulating factor, and natural killer cells and to decrease peripheral blood regulatory T cells [23].

Based on these findings, we initiated a phase Ib/II study exploring the combination of GCL in chemo-naïve patients with MUC. Only one patient experienced a formal dose-limiting toxicity (grade 4 thrombocytopenia lasting $>$7 days) during phase

Ib. However, a decision was made among the investigators not to further dose-escalate lenalidomide due to the need for serial dose delays and dose reductions of gemcitabine, cisplatin, and lenalidomide, often occurring after cycle 1 (Tables 1 and 2, Fig. 1), and instead enroll additional patients at the lenalidomide 10-mg dose level to better characterize the safety and tolerability of the combination. There were no additional dose-limiting toxicities, and phase II was opened at the lenalidomide 10-mg dose level. However, the combination was subsequently deemed poorly tolerated for chronic administration, and the study was terminated for this reason, coupled with slow accrual.

The study opened to accrual at the Huntsman Cancer Institute at the University of Utah, Salt Lake City, Utah; the National Cancer Institute, Bethesda, Maryland;, and the Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, New York. Over the course of 19 months, 9 patients were enrolled, for an enrollment of approximately 0.5 patient per month. At this rate of enrollment, it was estimated that the study would take more than five additional years to accrue. The poor accrual was felt to be multifactorial related, at least in part, to the large proportion of patients with MUC that are "cisplatin ineligible" [24, 25].

These findings highlight three critical points. First, as has been highlighted by other investigators, conventional phase I designs aimed at defining recommended phase II dosing using only first-cycle toxicity data may not be optimal in the era of molecularly targeted therapies typically administered in a chronic fashion and often characterized by persistent and/or cumulative toxicities [5]. Second, despite often promising preclinical data, there are practical challenges in combining targeted therapies with cytoatoxic agents [6]. Third, poor accrual remains a critical barrier to progress in clinical drug development [7].

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Figures and Tables

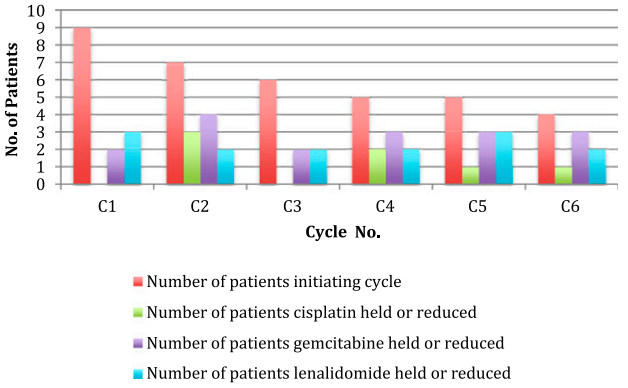

Figure 1. Dose delays and dose reductions.

Table 1. Toxicities of all grades across the study

	Grade, *n* (%)[a]			
Adverse events	**1**	**2**	**3**	**4**
Abdominal pain	1 (11)	1 (11)	1 (11)	
ALP increase	1 (11)		1 (11)	
Alopecia	3 (33)			
ALT increase			1 (11)	
Anemia		1 (11)	3 (33)	
Angular chelitis	1 (11)			
Anorexia	1 (11)	2 (22)		
Ascending cholangitis			1 (11)	
AST increase		1 (11)		
Blurred vision			1 (11)	
Bone pain, right midthigh and all pain	1 (11)			
C. difficile infection		1 (11)		
Cold	2 (22)			

Confusion			1 (11)	
Constipation	5 (55)	2 (22)		
Cough	4 (44)	1 (11)		
Creatinine increased	2 (22)	2 (22)		
Dehydration		1 (11)	1 (11)	
Diarrhea	3 (33)	3 (33)	2 (22)	
Dizziness		4 (44)		
Dry mouth	1 (11)			
Dyspnea	2 (22)			
Edema	2 (22)	2 (22)		
Erythematous rash	1 (11)			
Fatigue		4 (44)	1 (11)	
Febrile neutropenia			1 (11)	
Fever	1 (11)			
Flu-like symptoms	1 (11)			
Hand tremors	1 (11)			
Hearing loss	1 (11)	1 (11)		
Hematuria		3 (33)		
Hydrocephalus		1 (11)		
Hypercalcemia	1 (11)			
Hyperkalemia	1 (11)			
Hypernatremia	1 (11)			
Hypertension		1 (11)		
Hypoalbuminemia		2 (22)		
Hypocalcemia			1 (11)	
Hypokalemia	1 (11)		2 (22)	
Hypomagnesium			1 (11)	
Hyponatremia			1 (11)	
Hypoxia		1 (11)		
Leukopenia		2 (22)	1 (11)	2 (22)
Lightheadedness	1 (11)			
Loss of appetite	1 (11)			
Lower back pain	1 (11)			
Mouth sores		2 (22)		
Mucositis	1 (11)			
Nausea	2 (22)	6 (66)		
Neuropathy		6 (66)		
Neutropenia			3 (33)	4 (44)
Oral thrush	1 (11)			
Pain extremities	3 (33)	1 (11)		
Pancytopenia		1 (11)	1 (11)	
Phlebitis, left lower leg		1 (11)		
Pruritus	1 (11)			
Rhinorrhea	1 (11)			
Right-heel numbness	1 (11)			
Shortness of breath		1 (11)		
Sore throat	1 (11)			
Syncope	1(11)			

Tachycardia	1 (11)	1 (11)		
Taste alteration		2 (22)		
Thrombocytopenia	2 (22)	3 (33)	3 (33)	1 (11)
Thromboembolism		4 (44)		
Tinnitus	2(22)			
Urinary frequency	1(11)			
Urinary hesitancy	1(11)			
Urinary tract infection		3 (33)	1(11)	
Vomiting	7 (77)	1 (11)		
Watering eye left	1 (11)			
Weakness		1 (11)		

[a]There were no grade 5 toxicities.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; *C. difficile*, *Clostridium difficile*.

Table 2. Toxicities of all grades in cycle 1 only

	Grade, *n* (%)[a]			
Adverse events	**1**	**2**	**3**	**4**
Abdominal pain	1 (11)	1 (11)		
Alopecia		2 (22)		
ALT increase		1 (11)		
Anemia		1 (11)	2 (22)	
Angular chelitis	1 (11)			
Anorexia		1 (11)		
Ascending cholangitis			1 (11)	
AST increase	1 (11)			
Cold	1 (11)			
Confusion			1 (11)	
Constipation	2 (22)	4 (44)		
Cough			3 (33)	
Creatinine increase	1 (11)	2 (22)		
Dehydration	1 (11)			
Depression	1 (11)			
Diarrhea	3 (33)	1 (11)		
Dizziness	1 (11)	1 (11)		
Dyspnea	2 (22)			
Edema limbs	3 (33)	1 (11)		
Fatigue	3 (33)	3 (33)	2 (22)	
Fever	2 (22)			
Hearing loss	1 (11)			
Hematuria		1 (11)		
Hyperkalemia	1 (11)			
Hypocalcemia	1 (11)			
Hypokalemia			1 (11)	
Hyponatremia			1 (11)	
Hypoxia		1 (11)		

Leukopenia			1 (11)	2 (22)
Lightheadedness	1 (11)			
Loss of appetite	1 (11)			
Mucositis	1 (11)	1 (11)		
Nausea	2 (22)	4 (44)		
Neuropathy	1 (11)	1 (11)		
Neutropenia		2 (22)	1 (11)	3 (33)
Pain, extremities	1 (11)			
Pancytopenia		1 (11)		
Pruritus	1 (11)			
Sinus tachycardia		1 (11)		
Sore throat	1 (11)			
Taste alteration	2 (22)			
Thrombocytopenia	1 (11)	2 (22)	1 (11)	1(11)
Thromboembolism		2 (22)		
Urinary hesitancy	1 (11)			
Urinary tract infection		1 (11)		
Vomiting	5 (55)			

[a]There were no grade 5 toxicities. Only one patient experienced a protocol-defined dose-limiting toxicity (grade 4 thrombocytopenia lasting >7 days). Dose of lenalidomide was not escalated beyond the 10-mg daily dose-level cohort due to the need for frequent dose delays and dose reductions of gemcitabine, cisplatin, and lenalidomide, often occurring after cycle 1.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.