pISSN 1598-2998, eISSN 2005-9256

Cancer Res Treat. 2016;48(3):1084-1091

http://dx.doi.org/10.4143/crt.2015.405

Original Article

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Cisplatin, Gemcitabine, and Lapatinib as Neoadjuvant Therapy for Muscle-Invasive Bladder Cancer

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Received October 22, 2015
Accepted November 9, 2015
Published Online December 2, 2015

Purpose

We sought to investigate the safety and efficacy of gemcitabine, cisplatin, and lapatinib (GCL) as neoadjuvant therapy in patients with muscle-invasive bladder cancer (MIBC) planned for radical cystectomy.

Materials and Methods

Four cycles of GCL were administered as neoadjuvant therapy for patients with MIBC. Although initially designed as a phase II efficacy study with a primary endpoint of pathologic complete response at the time of radical cystectomy, the dose selected for investigation proved excessively toxic. A total of six patients were enrolled.

Results

The initial four patients received gemcitabine 1,000 mg/m^2 intravenously on days 1 and 8 and cisplatin 70 mg/m^2 intravenously on day 1 of each 21-day treatment cycle. Lapatinib was administered as 1,000 mg orally daily starting one week prior to the initiation of cycle 1 of gemcitabine and cisplatin (GC) and continuing until the completion of cycle 4 of GC. These initial doses were poorly tolerated, and the final two enrolled patients received a reduced lapatinib dose of 750 mg orally daily. However, reduction of the lapatinib dose did not result in improved tolerance or drug-delivery, and the trial was terminated early due to excessive toxicity. Grade 3/4 toxicities included diarrhea (33%), nausea/vomiting (33%), and thrombocytopenia (33%).

Conclusion

The addition of lapatinib to GC as neoadjuvant therapy for MIBC was limited by excessive treatment-related toxicity. These findings highlight the importance of thorough dose-escalation investigation of combination therapies prior to evaluation in the neoadjuvant setting, as well as the limitations of determination of maximum tolerated dose for novel targeted combination regimens.

Key words
Urothelial carcinoma, Drug therapy, Molecular targeted therapy, Epidermal growth factor receptor, Cystectomy

Introduction

The definitive management of muscle-invasive bladder cancer (MIBC) has traditionally involved curative-intent radical cystectomy with bilateral pelvic lymph node dissection. [1] In 2003, in a phase III Intergroup study of MIBC patients, a significant improvement in overall survival (OS) was demonstrated with the addition of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy to radical cystectomy [2]. A subsequent meta-analysis of over 3,000 patients reported an absolute improvement in 5-year OS of 5% with the use of platinum-based combination neoadjuvant chemotherapy [3]. Therefore, the

currently accepted standard of care in surgically-fit patients with MIBC is the use of cisplatin-based neoadjuvant chemotherapy prior to radical cystectomy [4].

In the metastatic setting, similar OS and response rates with an improved toxicity profile have been demonstrated with the regimen of gemcitabine and cisplatin (GC) when compared with conventional-dose MVAC [5]. These findings have commonly been extrapolated to the perioperative setting and have resulted in the frequent use of GC as neoadjuvant chemotherapy. Indeed, a recent survey of U.S. medical oncologists at both academic and community centers found that 90% offer GC as neoadjuvant chemotherapy for MIBC [6].

Importantly, the survival benefit of neoadjuvant chemotherapy appears to be related to downstaging of the tumor to a complete pathologic response (pT0). For example, in the intergroup trial, neoadjuvant MVAC was associated with a significantly increased pT0 rate (38% vs. 15%), and patients who successfully attained a pT0 response achieved a more durable survival benefit (5-year survival rate of 85%) [2]. Therefore, novel methods for maximizing the pT0 rate with neoadjuvant therapy are highly desired.

Epidermal growth factor receptors 1 and 2 (EGFR and HER-2) are frequently overexpressed in bladder urothelial carcinomas and have been associated with a poor prognosis. [7,8] Up to 70% of urothelial carcinomas overexpress EGFR and/or HER-2, and ligand-induced EGFR/HER-2 heterodimerization may trigger potent proliferative and survival signals [7,9]. Therefore, dual-inhibition of EGFR and HER-2 represents an attractive therapeutic strategy for management of urothelial carcinoma.

Lapatinib (Tykerb, GlaxoSmithKline, London, UK) is a small molecule tyrosine kinase inhibitor that targets both the EGFR and HER-2 receptors, thereby resulting in inhibition of downstream effector pathways, growth arrest, and cellular apoptosis [10,11]. A preclinical study of lapatinib in combination with GC in human bladder cancer cell lines demonstrated anti-tumor activity with synergistic effects [12]. The suggested dose range for lapatinib in phase II trials is 1,250-1,500 mg daily [13,14], and multiple prior clinical trials of lapatinib in combination with cytotoxic chemotherapy have been conducted with daily lapatinib doses of 1,250-1,500 mg [15,16]. In addition, a phase I trial in metastatic bladder cancer of gemcitabine, cisplatin, and lapatinib (GCL) at a dose range of 750-1,250 mg daily reported a maximum tolerated lapatinib dose of 1,250 mg daily [17].

Based on these background findings, we designed a prospective phase II trial to evaluate the safety and efficacy of neoadjuvant GCL in patients with MIBC undergoing radical cystectomy. The selected lapatinib dose was 1,000 mg daily, and the efficacy of GCL treatment was to be assessed by the rate of pT0 response at the time of radical cystectomy. However, due to excessive therapy-related toxicities at the selected treatment dose, the study was terminated prematurely. Here, we report the study results for eligible patients treated on the neoadjuvant GCL protocol and discuss the difficulties with determination of reliable maximum tolerated dose in the evaluation of novel targeted combination regimens.

Materials and Methods

1. Eligibility

Eligible patients were required to have pathologically-confirmed MIBC after an initial transurethral resection of the bladder tumor (TURBT) and no evidence of nodal or distant metastatic disease (clinical stage T2-T4, N0, M0). An archived tumor specimen from a prior TURBT was required to demonstrate overexpression of EGFR and/or HER-2 by standard immunohistochemistry (IHC) assay (> 1+ expression). Patients were required to have adequate bone marrow, cardiac, hepatic, and renal function, including an estimated creatinine clearance > 60 mL/min (determined by Cockcroft-Gault formula calculation) and a baseline left ventricular ejection fraction ≥ 50% (assessed by multigated acquisition scan or echocardiography). In addition, eligible patients were required to have an Eastern Cooperative Oncology Group performance status of 0-1 and must have been deemed a suitable candidate for radical cystectomy with curative intent. Because lapatinib is a substrate for CYP3A4, the concomitant use of medications that are inducers or inhibitors of CYP3A4 was prohibited.

2. Study design and treatment plan

This study was designed as a non-randomized, single-institution, open-label study to evaluate the safety and efficacy of four cycles of neoadjuvant GCL. Treatment consisted of gemcitabine 1,000 mg/m^2 intravenously on days 1 and 8 and cisplatin 70 mg/m^2 intravenously on day 1 of each 21-day treatment cycle. Carboplatin area under the curve 4.5 on day 1 of each treatment cycle could be substituted at the discretion of the treating physician for renal or other toxicity requiring discontinuation of cisplatin. Lapatinib 1,000 mg was administered orally and continuously once daily in the morning and in a fasting state starting on day –7 (1 week prior to cycle 1 day 1 of GC) and continuing until cycle 4 day 21. In cases of drug-related toxicity ≥ grade 3, a one-time dosage reduction of lapatinib to 750 mg once daily was permitted. In addition, a delay in lapatinib treatment

was permitted for up to 2 weeks to allow for resolution of drug-related toxicities. Prophylactic anti-emetics were administered at the discretion of the treating physician. The protocol-specified management of diarrheal toxicity included the initiation of anti-motility agents every 2-4 hours until resolution of symptoms for at least 12 hours. After completing four cycles of GCL therapy, patients proceeded to radical cystectomy with pelvic lymph node dissection and urinary diversion. This study was approved by the University of Pennsylvania's Institutional Review Board, and all patients signed informed consent.

3. Study evaluations

Clinical and radiologic assessment, including detailed medical history, review of concomitant medications, physical examination, laboratory testing, evaluation of cardiac function, and disease imaging (computed tomography [CT] or magnetic resonance imaging of abdomen/pelvis, CT chest or chest X-ray) was performed at baseline and upon completion of chemotherapy. A complete blood count (CBC) and comprehensive metabolic profile were performed at baseline and on day 1 of each treatment cycle. A CBC was also repeated on days 8 and 15 of each treatment cycle. Toxicity was assessed before each treatment and monitored throughout the course of therapy. Adverse events (AEs) were graded using National Cancer Institute Common Toxicity Criteria (NCI-CTC) ver. 3. Radical cystectomy pathology was reviewed per institutional protocol, and a postchemotherapy pTpN stage was assigned using the 1997 American Joint Committee on Cancer (AJCC) staging classification system. Patients were evaluated in follow-up for ongoing toxicity, disease recurrence, and disease-specific survival, and OS. Post-treatment follow-up consisted of clinical and laboratory assessment every 3 months, as well as a chest X-ray and cross-sectional imaging of the abdomen and pelvis every 6 months.

4. Statistical analyses

This study was initially designed as a phase II efficacy study utilizing a Simon 2-stage optimal design with a primary end point of pT0 rate, defined as no evidence of residual disease based on pathological review of the surgical specimen. The study was designed to detect an improvement in the pT0 rate from the historical rate of 30% with gemcitabine/cisplatin neoadjuvant therapy to the alternative hypothesis of a 50% pT0 rate with 90% power and a type I error rate of 0.10. A target accrual of 46 patients was established, with 22 evaluable patients in the first stage of the study. If at least eight of these 22 patients demonstrated a pT0 response, then an additional 24 evaluable patients would be enrolled. Otherwise, the therapy would be declared ineffective, and the trial would stop. If at least 18 of the 46 total enrolled patients demonstrated a pT0 response, then GCL would be considered worthy of further investigation. The probability of early termination under the null hypothesis (pT0 rate of ≤ 30%) was 67%. Additional early stopping rules for excessive toxicity were included.

Secondary objectives were to determine the toxicities of the neoadjuvant regimen, estimate progression-free survival (PFS) and OS using the Kaplan-Meier method, and to perform exploratory correlative analyses testing the association between EGFR and HER-2 status and pT0 response at cystectomy. Analyses were based on an intent-to-treat design.

Results

1. Patient characteristics

Between December 2008 and July 2011, only six patients with MIBC were accrued and treated. Demographic and patient characteristics are shown in Table 1. Four men and two women were treated. The mean age of patients at the time of study enrollment was 61 years. The results of EGFR and HER-2 IHC assays are shown in Table 2. Five patients overexpressed EGFR, three patients overexpressed HER-2, and three patients overexpressed both EGFR and HER-2.

2. Treatment exposure and toxicities

Only three patients (50%) completed four full cycles of GC. Three patients were switched from cisplatin to carboplatin due to renal toxicity (n=2) or severe nausea/vomiting (n=1). The first four patients received the protocol-specified dose of lapatinib 1,000 mg daily. Only one patient completed four cycles of lapatinib at this full dose. Dose reduction or discontinuation was required in the other three patients at this dose level. Due to toxicity concerns, the final two patients received a reduced starting dose of lapatinib of 750 mg daily. One patient completed four full cycles of lapatinib 750 mg daily; however, the other patient at this dose level discontinued therapy due to toxicity. All six patients proceeded to surgical resection, and no excess surgical complications were noted.

Toxicity information is summarized in Table 3. Grade 3-4 toxicities included: diarrhea (n=2), nausea/vomiting (n=2), and thrombocytopenia (n=2). Grade 2-3 renal toxicity was observed in two patients, requiring a switch from cisplatin to carboplatin. Two serious AEs were reported. The first was an inpatient hospitalization for fever that was considered unrelated to study treatment. The second was an inpatient

Table 1. Patient demographics and clinical characteristics

Patient No.	Age (yr)	Sex	ECOG PS	Comorbidity	Tobacco exposure[a]	Clinical stage[b]	Presence of hydronephrosis	Serum creatinine (mg/dL)	Hemoglobin (g/dL)
1	57	F	0	Hypertension, hyperlipidemia, osteoarthritis	Former (60 pack years)	T4 N0	Yes	0.86	9.9
2	65	M	0	Hypertension, transient ischemic attack, hyperlipidemia	Former (50 pack years)	T4 N0	Yes	0.97	13.7
3	48	M	0	Hypertension, hyperlipidemia	Current (30 pack years)	T3 N0	No	0.94	14.8
4	65	M	0	Hypertension	Former (20 pack years)	T3 N0	Yes	0.80	14.5
5	60	F	0	COPD, asthma, hypertension, hyperlipidemia, DVT	Former (30 pack years)	T2 N0	No	1.08	11.6
6	68	M	0	Hypertension, hyperlipidemia	Former	T3 N0	Yes	1.48	13.2

ECOG PS, Eastern Oncology Cooperative Group performance status; F, female; M, male; COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis. [a]Pack-years=number of packs/day×number of years tobacco exposure, [b]Based on American Joint Committee on Cancer (AJCC) staging classification (1997).

Table 2. Tumor receptor status

Receptor status	No. (%)
EGFR +/HER-2 –	2 (33)
EGFR +/HER-2 +	3 (50)
EGFR –/HER-2 –	1 (17)
EGFR –/HER-2 +	0

EGFR, epidermal growth factor receptors 1; HER-2, epidermal growth factor receptor 2.

hospitalization for diarrhea and dehydration that was deemed probably related to study treatment. There were no treatment related deaths. As the toxicity stopping rule was exceeded within the first six accrued patients, this study was reviewed with the study medical monitor and terminated early.

3. Clinical efficacy

Only one of six patients (17%) achieved the primary end point of this study of a pT0 response following neoadjuvant GCL (Table 4). One additional patient had organ-confined disease (pT2). Postcystectomy pathology demonstrated non-organ confined disease in four patients (67%) (pT3 or pT4), and three patients (50%) had pathologic lymph node involvement. Three patients developed disease progression at 5, 7, and 8 months following the initiation of therapy, respectively. Two of these patients died of disease. The remaining three patients, including the two patients with pT0 and pT2 surgical pathology, were alive with no evidence of disease at 14, 16, and 24 months after the initiation of therapy. Due to early termination of the study, follow-up for the estimation of PFS and OS was discontinued.

Discussion

To the best of our knowledge, this is the first clinical report on the use of lapatinib in combination with cisplatin-based chemotherapy as neoadjuvant therapy in MIBC. The addition of lapatinib to standard neoadjuvant GC was poorly tolerated, resulting in dose reduction or discontinuation of therapy in the majority of treated patients. The observed dose-limiting toxicities included those typically associated with lapatinib (diarrhea), as well as toxicities commonly associated with GC (nausea/vomiting, thrombocytopenia, and renal injury). Given the limited number of treated patients, conclusions concerning whether lapatinib resulted

Table 3. Treatment toxicities[a)]

Toxicity	Grade 1[b)]	Grade 2	Grade 3	Grade 4
Diarrhea	1	-	2	-
Nausea/Vomiting	3	-	2	-
Fatigue	1	4	-	-
ANC	1	2	-	-
Rash	3	1	-	-
Thrombocytopenia	-	2	1	1
Mucositis	1	-	-	-
Renal	1	1	1	-

ANC, absolute neutrophil count. [a)]Worst grade per individual patient report, [b)]Grade assigned per National Cancer Institute Common Toxicity Criteria, ver. 3.

in increased GC toxicities or vice versa cannot be clearly stated. In addition, due to the small sample size we cannot make conclusions regarding the observed pT0 rate of 17% compared to historical controls. Furthermore, while all enrolled patients had clinical N0 disease, it is noteworthy that pathologic node involvement was demonstrated in three patients following surgery. In all cases, repeat imaging performed in the immediate preoperative period showed no clinical evidence of regional nodal metastases. In addition, the clinical understaging of MIBC is a commonly observed phenomenon. Therefore, while it is likely that these findings represent subclinical nodal metastases discovered upon lymph node dissection, we cannot exclude the possibility of disease progression through the GCL neoadjuvant regimen.

The suggested dose range for lapatinib in phase II trials is 1,250-1,500 mg daily [13,14], and multiple clinical trials of lapatinib in combination with chemotherapy have been conducted with daily lapatinib doses of 1,250-1,500 mg [15,16]. In addition, lapatinib at daily doses of 750 mg, 1,000 mg, and 1,250 mg was studied in combination with standard-dose GC chemotherapy on a 28-day cycle length in a phase I study of advanced/metastatic bladder cancer patients [17]. This dose-finding study yielded a maximum tolerated lapatinib dose of 1,250 mg daily [17]. Although we selected a conservative lapatinib starting dose of 1,000 mg daily for the neoadjuvant GCL regimen, toxicities nonetheless proved to be treatment-limiting. Indeed, even with a lower starting dose of lapatinib 750 mg daily, one of two patients discontinued therapy due to excessive toxicity.

The reason for the discrepant toxicity findings between the reported phase I GCL study in metastatic disease and the current neoadjuvant GCL study is unclear. However, the limited number of treated patients and/or differences in the treatment schedule (21-day vs. 28-day cycle length) may have contributed to the observed differences. In addition, as the trials were conducted in different geographic locations (Europe vs. United States), regional or site-specific differences may have accounted for the observed differences. It is not likely that underlying patient comorbidities significantly influenced the tolerance of this neoadjuvant regimen, as all enrolled subjects demonstrated good functional status, adequate organ function, and baseline comorbidities common to the general bladder cancer population (tobacco exposure, hypertension, and hyperlipidemia).

These results again demonstrate the limitations of determining the maximum tolerated dose in novel targeted combination regimens due to the development of cumulative toxicities after multiple cycles of therapy, as has been previously described [18,19]. In particular, the late toxicities (occurring after cycle 1) of molecularly-targeted agents may not be adequately reflected in the conventionally-defined recommended phase II dose [18,20]. These current findings amount to a negative phase I study, and clearly demonstrate the critical importance of more complete GCL dose-escalation data before further study of this regimen in the neoadjuvant setting.

Urothelial cancer is regarded as a chemosensitive disease, and neoadjuvant chemotherapy for MIBC historically yields pT0 rates of 25%-35% [2,21], and a pT0 response has been associated with a durable survival benefit. However, there is an increasing general belief that further alterations in conventional cytotoxic chemotherapy will not dramatically improve important clinical outcomes in urothelial cancer. Based on a recently increased understanding of the molecular biology of urothelial cancer, the addition of targeted agents to cisplatin-based neoadjuvant chemotherapy is therefore a logical next step in an effort to improve pT0 rates and survival outcomes in MIBC. However, given the potential for poor drug tolerance and the conceivable resultant risk of patients receiving inadequate standard treatment, a thorough evaluation of the maximum tolerated combination therapy dose in the advanced disease setting is prudent prior to study in the curative-intent setting.

Dual-inhibition of EGFR and HER-2 with lapatinib monotherapy has been studied in the setting of metastatic urothelial cancer (mUC) with modest results. In a phase II study of lapatinib monotherapy as second-line treatment for mUC patients, lapatinib therapy did not meet the primary endpoint of an objective response rate of > 10% [9]. However, an OS benefit was noted for patients whose tumors overexpressed EGFR and/or HER-2 (≥ 2+ expression by IHC) [9]. In a histology-independent randomized discontinuation study of lapatinib monotherapy in HER-2 amplified tumors, including nine patients with advanced bladder cancer, the objective response rate was 3%, and 28% of patients achieved stable disease (including three bladder cancer patients) [22]. This study was terminated early due to the low response rate

Table 4. Pathologic outcomes at radical cystectomy

Variable	No. (%)	Clinical stage[a)]	Pathologic stage[a)]
Surgical pathology[a)]			
Organ confined disease	2 (33)	-	-
pT0	1 (17)	-	-
pTis-pT1	0	-	-
pT2	1 (17)	-	-
Non-organ confined disease	4 (67)	-	-
pT3-4	4 (67)	-	-
pN+	3 (50)	-	-
Individual patient pathologic outcomes			
Patient 1	-	T4 N0	T4 N2
Patient 2	-	T4 N0	T4 N2
Patient 3	-	T3 N0	T2a N0
Patient 4	-	T3 N0	T3b N2
Patient 5	-	T2 N0	T3b N0
Patient 6	-	T3 N0	T0 N0

[a)]Based on American Joint Committee on Cancer (AJCC) staging classification (1997).

and poor accrual. More recently, a phase II/III study of more than 200 patients with HER-1 or HER-2–positive mUC evaluated maintenance lapatinib following first-line chemotherapy. Maintenance lapatinib failed to improve PFS in this molecularly-defined population [23].

Several other therapies targeting EGFR and/or HER-2 have similarly been evaluated in the treatment of urothelial cancer. In a phase II study of 20 unselected patients with MIBC, neoadjuvant therapy with the EGFR inhibitor erlotinib was well-tolerated and yielded a pT0 rate of 25% [24]. A multicenter phase II study evaluated trastuzumab, the humanized monoclonal antibody targeting HER-2, in combination with paclitaxel, carboplatin, and gemcitabine in the treatment of patients with HER-2 overexpressing advanced urothelial cancers [25]. An overall response rate of 70% was demonstrated among 44 evaluable patients using this combination regimen [25]. Finally, recruitment for a phase II study of the EGFR and HER-2 inhibitor, afatinib, in patients with advanced urothelial cancers refractory to platinum-based chemotherapy is currently underway (NCT 02122172). Therefore, while results with lapatinib have thus far been discouraging, the targeting of EGFR and/or HER-2 remains an area of active investigation in the treatment of urothelial malignancy.

Conclusion

In this preliminary experience, the addition of the selected dose of lapatinib to standard GC neoadjuvant chemotherapy was not successful due to excessive toxicity. The clinical efficacy of the neoadjuvant GCL regimen cannot be determined due to the small patient sample size. The results of future and ongoing studies are needed to determine whether dual-inhibition of EGFR and HER-2 in combination with cisplatin-based chemotherapy is a safe and effective therapeutic strategy in MIBC. In addition, as oncology drug development continues its shift towards molecularly-targeted therapies, numerous clinical trials combining targeted therapies with conventional cytotoxic chemotherapy will undoubtedly be conducted. With this growing enthusiasm and mounting pressure for rapid drug development, the current findings illustrate the importance of careful step-wise drug development with thorough dose-finding for novel targeted therapies.

Conflicts of Interest

This trial was funded in part by a grant from GlaxoSmithKline.

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