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Larotaxel with Cisplatin in the First-Line Treatment of Locally Advanced/Metastatic Urothelial Tract or Bladder Cancer: A Randomized, Active-Controlled, Phase III Trial (CILAB)

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Key Words
Cisplatin · Larotaxel · Survival · Taxoids · Urologic neoplasms · XRP9881

Abstract
Background: This open-label, randomized phase III trial evaluated larotaxel/cisplatin versus gemcitabine/cisplatin as first-line treatment for locally advanced (T4b) or metastatic urothelial tract or bladder cancer. ***Methods:*** Patients were randomized to larotaxel 50 mg/m^2 with cisplatin 75 mg/m^2 every 3 weeks (larotaxel/cisplatin) or gemcitabine 1,000 mg/m^2 on days 1, 8, and 15 with cisplatin 70 mg/m^2 on day 1 every 4 weeks (gemcitabine/cisplatin). The primary endpoint was overall survival (OS). ***Results:*** The trial was prematurely closed following the sponsor's decision to stop clinical development of larotaxel (n = 337 randomized). The larotaxel dose was reduced to 40 mg/m^2 and cisplatin to 60 mg/m^2 following a data monitoring committee safety review of the first 97 patients. At the time of analysis, the median OS was 13.7 months [95% confidence interval (CI) 11.2–17.1] with larotaxel/cisplatin and 14.3 months (95% CI 10.5 to not reached) with gemcitabine/cisplatin [hazard ratio (HR) 1.21; 95% CI 0.83–1.76; p = 0.33]. The median progression-free survival (PFS) was 5.6 months (95% CI 4.1–6.2) with larotaxel/cisplatin and 7.6 months (95% CI 6.6–9.1) with gemcitabine/cisplatin (HR 1.67; 95% CI 1.24–2.25). More myelosuppression was observed with gemcitabine/cisplatin. ***Conclusion:*** There was no difference in OS. Although the trial was closed prematurely, PFS appeared worse with larotaxel/cisplatin, suggesting that larotaxel/cisplatin does not improve outcomes versus cisplatin/gemcitabine.

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Introduction

Bladder cancer is the ninth most common cancer worldwide and affects three times more men than women [1]. At initial diagnosis, approximately 30% of patients present with locally invasive or metastatic disease. Standard first-line treatment for nonresectable locally invasive or metastatic bladder cancer is combination chemotherapy. The M-VAC (methotrexate/vinblastine/doxorubicin/cisplatin) regimen was associated with a survival advantage in the 1980s [2, 3]. More recently, gemcitabine/cisplatin demonstrated similar levels of activity in the metastatic setting, but with an improved safety profile versus M-VAC [4, 5]. Gemcitabine/cisplatin and M-VAC are currently the most common first-line chemotherapy regimens for locally invasive or metastatic bladder cancer [6–8]. However, overall survival (OS) remains poor (approximately 12–15 months) [9] and new therapies are required with improved efficacy and tolerability profiles.

The taxanes docetaxel and paclitaxel are among the most active and most widely used cytotoxic drugs. Phase II trials of patients with advanced bladder cancer treated with the combination of a taxane and cisplatin have reported response rates (RRs) of 52–70%, times to progression of 5–7 months, and OS of 8–14 months, with a safety profile consistent with that reported in patients with other solid tumors [10–14]. However, a phase III trial conducted by the Hellenic Cooperative Oncology Group found that docetaxel in combination with cisplatin was less effective than M-VAC (both regimens given with prophylactic granulocyte colony-stimulating factor) in terms of RR, progression-free survival (PFS), and OS [15].

Larotaxel (XRP9881) is a next-generation semisynthetic taxane that has a similar mode of action to docetaxel and paclitaxel, with evidence of several possible advantages including activity in taxane-resistant tumor cells and the ability to cross the blood-brain barrier [16, 17]. Preliminary clinical data in metastatic breast cancer and non-small cell lung cancer suggested activity and an acceptable safety profile [18, 19]. Furthermore, preclinical and early clinical data suggested synergy between larotaxel and cisplatin [19, 20].

The aim of this phase III study (CILAB: cisplatin + larotaxel in first-line treatment of locally advanced/metastatic urothelial tract or bladder cancer; clinicaltrials.gov identifier NCT00625664) was to evaluate larotaxel plus cisplatin compared with gemcitabine plus cisplatin in terms of OS as first-line treatment for advanced urothelial tract or bladder cancer.

Patients and Methods

Previously untreated patients ≥18 years old with histologically/cytologically confirmed transitional cell carcinoma of the urothelial tract or bladder that was locally advanced (T4b) or metastatic (lymph node or visceral) were eligible. Additional inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, and no prior palliative chemotherapy. Exclusion criteria included disease localized only to the radiation fields without radiologically confirmed disease progression within the radiation fields after completion of prior radiotherapy; treatment with neoadjuvant chemotherapy if <6 months had passed between the end of therapy and relapse; prior radiotherapy within 6 weeks of enrolment; surgery within 3 weeks of randomization; pathologically node positive with no residual disease after surgery; inadequate bone marrow function (absolute neutrophil count $<1.5 \times 10^9$/l, platelet count $<75 \times 10^9$/l, or hemoglobin <9.0 g/dl) and liver function [alkaline phosphatase (AP) >5.0 × ULN or aspartate transaminase (AST)/alanine transaminase (ALT) >1.5 or 2.5 × ULN if AP is >2.5 or 1.5 × ULN, respectively; or total bilirubin >1.0× the ULN]; history or new evidence of brain metastases or leptomeningeal disease, and pregnancy or lactation.

Study Design

This was a prospective, multicenter, multinational, open-label, randomized (1:1) phase III study. The primary efficacy endpoint was OS (defined as the time between the date of randomization and the date of death due to any cause). In the absence of confirmation of death, survival time was censored at the last date the patient was known to have been alive or the study cutoff date, whichever occurred first. Secondary efficacy endpoints included PFS and overall RR.

This study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The study protocol and consent form were approved by the local ethics committee or institutional review board of each center. All patients provided written informed consent before enrolment.

Treatments and Assessments

Patients were randomized (1:1) to treatment with larotaxel 50 mg/m^2 in combination with cisplatin 75 mg/m^2 every 3 weeks (larotaxel/cisplatin arm) or to gemcitabine 1,000 mg/m^2 on days 1, 8, and 15 in combination with cisplatin 70 mg/m^2 on day 1 every 4 weeks (gemcitabine/cisplatin arm). Randomization was performed using balanced blocks via an interactive voice response system, with disease stage (locally advanced vs. metastatic), ECOG PS (0 or 1 vs. 2), and region as stratification factors. An ad hoc data monitoring committee (DMC) meeting was held on March 4, 2009, to review data from the first 97 patients treated because 4 deaths (1 sudden death, 1 cardiac arrest, 1 septic shock, and 1 convulsion) had been reported during the study treatment in 13 patients enrolled in India. At the time of the meeting, a total of 12 deaths had occurred during the study treatment among the 138 patients enrolled in 18 countries. The DMC observed more deaths during the treatment period in the larotaxel/cisplatin arm (n = 9) compared with the gemcitabine/cisplatin arm (n = 3) and recommended continuation of the study with two protocol modifications: exclusion of patients with ECOG PS 2 at study entry (deletion of the stratification factor)

Table 1. Demographics and baseline characteristics of all randomized patients (ITT population)

	Larotaxel + cisplatin (n = 166)	Gemcitabine + cisplatin (n = 171)
Median age, years	64.0	64.0
Range	42–82	35–85
Males, n	139 (84)	138 (81)
ECOG performance status[a], n		
0	71 (45)	70 (44)
1	81 (51)	83 (52)
2[b]	6 (4)	7 (4)
Primary site, n		
Bladder	124 (75)	131 (77)
Urothelial tract	42 (25)	40 (23)
Median time from first diagnosis to randomization, months	9.8	9.1
Range	0.1–190.5	0.4–196.5
Histologic type, n		
Transitional cell	162 (98)	170 (99)
Other[c]	4 (2)	1 (0.6)
Extent of disease at study entry[d], n		
Locally advanced	15 (9)	18 (11)
Metastatic	151 (91)	151 (89)
Organs involved[e], n		
Lymph nodes	117 (70)	130 (76)
Lungs	61 (37)	48 (28)
Bladder	43 (26)	48 (28)
Bone	30 (18)	47 (27)
Liver	30 (18)	35 (20)
Muscle/soft tissue	22 (13)	23 (13)
Number of organs involved[f]		
1	55 (33)	49 (29)
2	71 (43)	65 (38)
≥3	40 (24)	56 (33)
Patients with measurable disease, n	148 (89)	161 (94)
Prior chemotherapy[g], n		
Adjuvant	31 (19)	29 (17)
Neoadjuvant	8 (5)	7 (4)
Prior surgery, n	148 (89)	151 (88)
Prior radiotherapy, n	16 (10)	18 (11)

Figures in parentheses are percents.

[a] n = 158 for larotaxel + cisplatin; n = 160 for gemcitabine + cisplatin.

[b] Enrolled before the DMC recommendation (March 4, 2009) to exclude patients with an ECOG PS of 2.

[c] Transitional cell and adenocarcinoma, signet-ring cell adenocarcinoma, urothelial carcinoma with squamous metaplasia, urothelial carcinoma, and papillary urothelial carcinoma.

[d] n = 169 for gemcitabine + cisplatin.

[e] Organs with an incidence >10%.

[f] n = 170 for gemcitabine + cisplatin.

[g] n = 38 for larotaxel + cisplatin; n = 34 for gemcitabine + cisplatin.

and a reduction of the doses in the experimental arm for all new and ongoing patients (larotaxel from 50 to 40 mg/m^2 and cisplatin from 75 to 60 mg/m^2 every 3 weeks).

Tumor assessments, involving abdominal, pelvic, and chest CT, or MRI scans, and other exams as clinically indicated, were performed at baseline and every 8 weeks. Assessment of responses was based on Response Evaluation Criteria in Solid Tumors (RECIST). Assessments were repeated to confirm a partial or complete response (at least 4 weeks after the initial documentation of the response) and at the end of the study treatment.

Patients were treated until RECIST-defined disease progression, unacceptable toxicity, or patient refusal of further study treatment. Safety was assessed by adverse-event (AE) reporting, physical examination, and laboratory analysis. AEs and laboratory data were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Statistical Analysis

Assuming the median OS in the control arm (gemcitabine/cisplatin) was 14 months, a total of 511 deaths was needed to detect with 90% power a 25% reduction in the hazard ratio (HR) (i.e. median survival time of 18.7 months) in the larotaxel/cisplatin arm relative to the control arm using a two-sided log-rank test at a significance level of 0.05. Based on an anticipated accrual period of 30 months followed by a 7-month follow-up after randomization of the last patient, approximately 900 patients (450 in each arm) were required to achieve the targeted number of events. The planned cut-off for efficacy endpoints was when 511 deaths had occurred. An interim futility analysis was planned after 200 PFS events had occurred, and the trial was to be stopped if the conditional power was <40% based on the original hypothesis (HR ≥1.05 in favor of the gemcitabine/cisplatin arm).

The intention-to-treat (ITT) population included all randomized patients and was the primary analysis population for OS and PFS. Tumor response was assessed in the evaluable patient population, which consisted of all randomized and treated patients with measurable disease at study entry, without major protocol deviations, and who could be evaluated for response. The safety population included all patients who received at least one dose of the study drug.

The primary analysis of OS and PFS was the comparison between treatment groups using a log-rank test stratified by extent of disease (locally advanced or metastatic) as declared at randomization. HRs and corresponding confidence intervals (CIs) were estimated using a Cox proportional hazards model stratified for the same factor. Kaplan-Meier estimates of survival were provided. The overall RR was summarized using descriptive statistics and 95% CIs.

Results

This trial was prematurely discontinued before the planned interim analysis after the sponsor's decision to stop clinical development of larotaxel. This decision was based on the lack of larotaxel efficacy versus comparators in previous randomized studies (one in pancreatic cancer and two in breast cancer) and the DMC recommen-

dation to reduce the dose of larotaxel and cisplatin in the current study, in part due to the incidence of toxicity (mainly infections). For these two reasons it was deemed unlikely that the trial would meet its primary efficacy endpoint of a 25% reduction in the HR for OS. Patients on treatment at the time of study discontinuation and deriving benefit could continue treatment. The cutoff date for analysis of the primary endpoint was February 11, 2010.

Patients

Between February 2008 and February 2010, three hundred thirty-seven patients were randomized; 137 were enrolled before the DMC recommendation/protocol amendment to reduce the larotaxel/cisplatin dose. Demographics and characteristics of the patients were balanced between the two treatment arms (table 1).

At the time of this analysis, 82% of all patients in the trial had discontinued treatment, 30% of whom stopped owing to disease progression and 28% because of an AE (table 2). The median number of treatment cycles administered was 5 in the larotaxel/cisplatin arm and 4 in the gemcitabine/cisplatin arm, corresponding to median treatment exposures of 15 and 16 weeks, respectively (table 3). The relative dose intensity was lower in the gemcitabine/cisplatin arm owing to gemcitabine dose omissions on day 1 (2 patients), day 8 (57 patients), and day 15 (107 patients).

Analysis of Survival and Response

The analysis of OS (primary endpoint) was based on a total of 107 deaths (56 in the larotaxel/cisplatin arm and 51 in the gemcitabine/cisplatin arm). There was no significant difference in OS between the two arms. The median OS was 13.7 months (95% CI 11.2–17.1) in the larotaxel/cisplatin arm and 14.3 months (95% CI 10.5 to not reached) in the gemcitabine/cisplatin arm (fig. 1a). The HR for larotaxel/cisplatin versus gemcitabine/cisplatin was 1.21 (95% CI 0.83–1.76; p = 0.33).

The analysis of PFS was based on a total of 184 events (101 in the larotaxel/cisplatin arm and 83 in the gemcitabine/cisplatin arm). PFS appeared better in the gemcitabine/cisplatin arm, with a median PFS of 7.6 months (95% CI 6.6–9.1) versus 5.6 months (95% CI 4.1–6.2) in the larotaxel/cisplatin arm (fig. 1b; HR 1.67; 95% CI 1.24–2.25). Similar results for OS and PFS were observed for the 137 patients randomized before the protocol amendment.

Tumor response was evaluable in 193 patients (57%) (90 in the larotaxel/cisplatin arm and 103 in the gemcitabine/cisplatin arm). The tumor RR was 31% (95% CI 22–41) in the larotaxel/cisplatin arm and 43% (95% CI 33–52) in the gemcitabine/cisplatin arm (table 4).

Table 2. Disposition of patients (ITT population)

Patients, n	Larotaxel + cisplatin (n = 166)	Gemcitabine + cisplatin (n = 171)
Patients off treatment	139 (84)	139 (81)
AEs	45 (27)	50 (29)
Disease progression	56 (34)	46 (27)
Poor compliance	1 (0.6)	2 (1)
Lost to follow-up	0 (0.0)	0 (0.0)
Other[a]	37 (22)	41 (24)
Ongoing treatment	23 (14)	27 (16)
Randomized and not treated	4 (2)	5 (3)

Figures in parentheses are percents.

[a] The main reason was patient and/or investigator decision: 31 patients in the larotaxel + cisplatin arm and 32 patients in the gemcitabine + cisplatin arm.

Table 3. Study drug exposure in the safety population

Drug	Cycles administered, n	Duration of exposure, weeks	Relative dose intensity, %
Larotaxel	5.0 (1.0–18.0)	15.3 (3.0–55.0)	97.5 (1.8–126.8)
Gemcitabine	4.0 (1.0–18.0)	16.4 (4.0–76.7)	75.9 (31.5–105.6)
Cisplatin			
+ larotaxel	5.0 (1.0–17.0)	15.0 (3.0–53.0)	96.5 (52.4–129.3)
+ gemcitabine	4.0 (1.0–18.0)	16.2 (4.0–76.7)	96.8 (49.5–107.5)

Data are presented as medians (range).

Safety

The rates of AEs were comparable in the two arms (98% for larotaxel/cisplatin and 99% for gemcitabine/cisplatin). A higher proportion of patients in the gemcitabine/cisplatin arm reported AEs grade ≥3 (77 vs. 57% for larotaxel/cisplatin). Similar proportions of patients in both groups reported serious AEs (40 and 39% of patients in the larotaxel/cisplatin and gemcitabine/cisplatin arms, respectively). Table 5 details the AEs in both treatment groups. The most frequent nonhematologic AE in both arms was fatigue; diarrhea was more frequent with larotaxel/cisplatin than with gemcitabine/cisplatin. More grade 3/4 hematologic abnormalities (neutropenia, thrombocytopenia, and anemia) were reported in

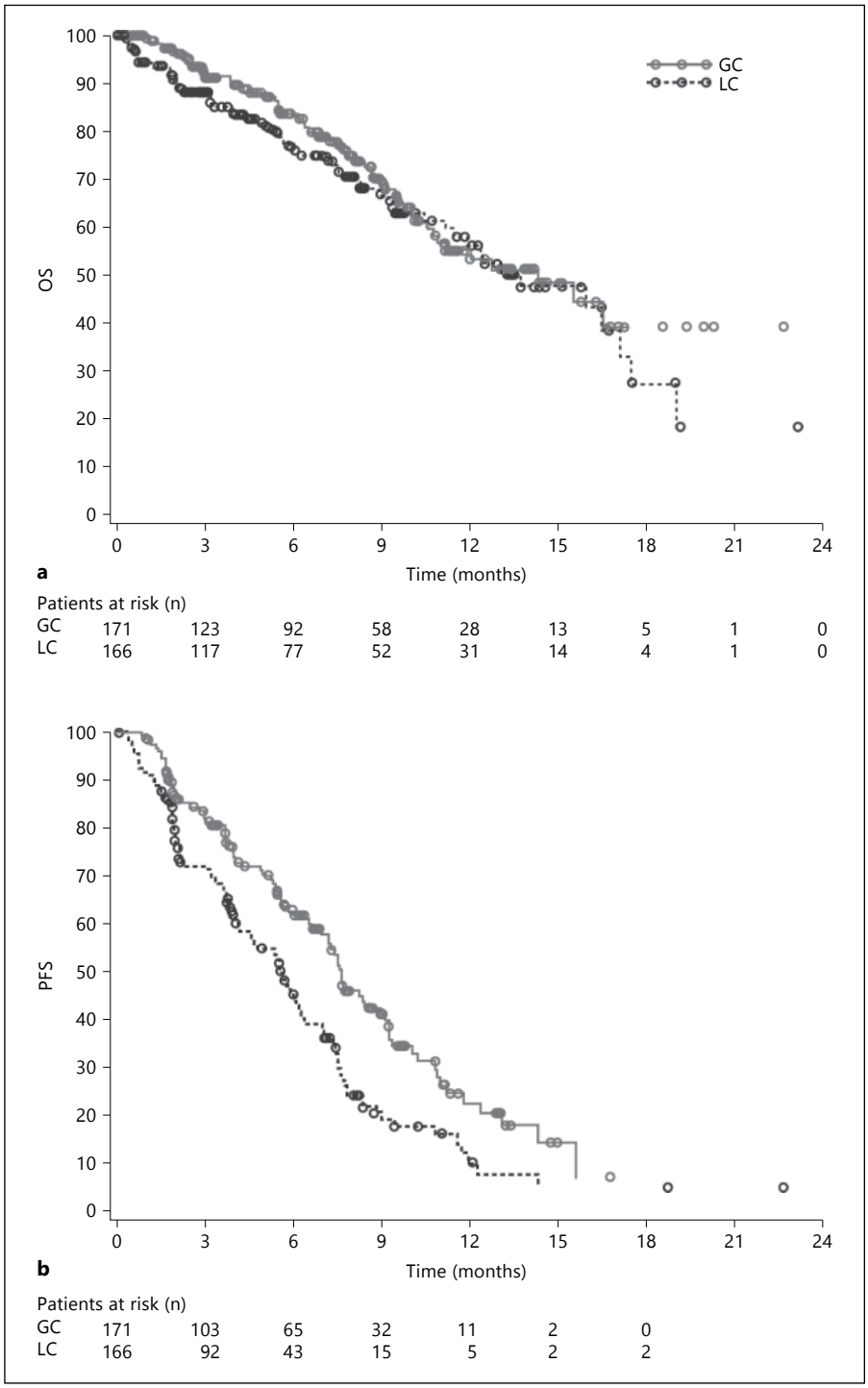

Fig. 1. Kaplan-Meier curves of OS (**a**) and PFS (**b**). GC = Gemcitabine/cisplatin; LC = larotaxel/cisplatin.

the gemcitabine/cisplatin arm. This was observed both before and after the dose reduction in the larotaxel/cisplatin arm (table 6). A total of 6 patients (3.7%) (3/68 and 3/94 pre- and postamendment, respectively) in the larotaxel/cisplatin arm and 10 (6.0%) patients (5/66 and 5/100 pre- and postamendment, respectively) in the gemcitabine/cisplatin arm experienced neutropenic complications (febrile neutropenia or neutropenic infection, any grade). There was more sensory neuropathy (all grades) in the larotaxel/cisplatin arm (23%) com-

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