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A Phase II Trial of R115777, an Oral Farnesyl Transferase Inhibitor, in Patients with Advanced Urothelial Tract Transitional Cell Carcinoma

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BACKGROUND. R115777 is a potent farnesyl transferase inhibitor and has significant antitumor effects in vitro and in vivo.

METHODS. The objective of the current study was to determine the objective response proportion in patients with metastatic transitional cell carcinoma (TCC) of the urothelial tract who received treatment with R115777 at a dose of 300 mg orally given twice daily for 21 days followed by 7 days of rest for every 4-week cycle. Thirty-four patients with TCC were enrolled in this Phase II study. Patients were allowed to have received a maximum of one prior systemic chemotherapy regimen, not including chemoradiation or neoadjuvant chemotherapy. All patients were required to have an Eastern Cooperative Oncology Group performance status of 0–2 and adequate bone marrow, hepatic, and kidney function.

RESULTS. Twice daily administration of oral R115777 was tolerated well. R115777 was absorbed rapidly after oral administration. Grade 3–4 neutropenia (according to the National Cancer Institute Common Toxicity Criteria [version 2.0]) was observed in 5 patients (15%). Grade 3–4 nonhematologic toxicity was rare, consisting of rash and diarrhea in 1 patient each. Two patients (6%) without prior chemotherapy demonstrated partial responses. Thirteen patients (38%) achieved disease stabilization according to World Health Organization criteria that lasted a median of 4 months. No complete responses were observed.

CONCLUSIONS. The objective response rate of R115777 was not sufficient to warrant future investigation in TCC as a single agent. Preliminary evidence of the activity of R115777 in 2 chemotherapy-naïve patients may warrant further investigation in combination with first-line chemotherapy. ***Cancer*** **2005;103:2035–41.**

KEYWORDS: bladder neoplasms, transitional cell carcinoma, farnesyl transferase inhibitor, Ras proteins, Phase II clinical trials, chemotherapy, salvage therapy.

Although recent advances in chemotherapy for transitional cell carcinoma (TCC) of the urothelial tract have improved its therapeutic index, combination chemotherapy for TCC still is associated with significant morbidity. Consequently, the development of novel agents with more activity and less toxicity is necessary. Cisplatin-containing regimens (methotrexate, vinblastine, doxorubicin, and cisplatin; cisplatin, methotrexate, and vinblastine; and gemcitabine/cisplatin combinations) are the most commonly used first-line regimens for patients with advanced TCC and reportedly yield responses in 30–70% of patients.[1–3] However, durable complete remissions in patients with advanced disease are rare, and the median survival remains approximately 12 months. Once patients progress after first-line chemotherapy, there is no accepted standard therapy.

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Although second-line chemotherapy (using agents such as ifosfamide, paclitaxel, and docetaxel) frequently is undertaken in this setting, response rates are low, and the duration of response tends to be short.[4–6] In addition, cumulative toxicities often reduce quality of life and prevent further treatment.

Ras is a 21-kilodalton (kD) GTPase that is important in the transduction of cell growth and proliferation signals. It has been shown that constitutive activation of Ras by mutation is oncogenic. However, for Ras to be active, it must be tethered by a farnesyl moiety to the inner surface of the cell membrane. This farnesylation is performed by the enzyme farnesyl transferase (FT). It has been shown that the inhibition of FT activity not only inhibits Ras membrane association and activity but also reduces malignant cell growth and proliferation in vitro and in vivo.[7] Consequently, FT has been identified as a promising target for novel antitumor therapies. Although Ras activation has been identified as an important step in the oncogenesis of many malignancies and was discovered first in bladder carcinoma, to our knowledge the exact frequency of Ras mutations in bladder carcinoma is not known. Many series have demonstrated conflicting results, with Ras mutations observed in 1–80% of patients.[8–11] It is now generally accepted that activating Ras mutations are relatively rare events in bladder carcinoma, reportedly on the order of 10%.[12]

R115777 (tipifarnib; Zarnestra™; Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium) is a competitive inhibitor of FT that has shown promising antineoplastic properties in preclinical studies.[7] Oral administration at a dose of 200–300 mg twice daily led to effective plasma levels of drug.[13] It was shown that the maximum tolerated dose of R115777 as a single agent was 300 mg twice daily for 21 consecutive days, followed by 7 days of rest for every 28-day cycle.[14] To test the hypothesis that FT inhibition will result in tumor regression in patients with metastatic or unresectable TCC, a Phase II trial of oral R115777 was undertaken. Initially, only "front-line" patients who had received no prior chemotherapy were eligible. However, due to slow patient accrual, the study population was broadened subsequently to include "second-line" patients who had received one prior systemic chemotherapy regimen. Pharmacokinetic evaluation of R115777 was conducted to ensure that the results of this study would not be confounded by concerns over lack of absorption, particularly in patients who may have intestinal urinary reconstructions.

MATERIALS AND METHODS

Eligibility

Patients with histologically proven, metastatic TCC of the urinary tract and an Eastern Cooperative Oncology Group performance status < 2 were eligible for this study. Patients with small foci of squamous differentiation or rare foci of adenocarcinoma in the setting of predominant TCC histology were eligible. This study was opened initially to patients without prior chemotherapy, although it was amended subsequently to include patients who had received a maximum of one prior systemic chemotherapy regimen (not including neoadjuvant chemotherapy or chemoradiation) to enhance accrual. All patients had to have last received any prior chemotherapy at least 4 weeks prior to enrollment. Prior radiation therapy was permissible provided it was completed > 4 weeks prior to study entry. Treatment with any other cancer therapy, including intravesical therapy, was prohibited during the study. All patients had bidimensionally measurable disease documented within 28 days prior to enrollment. Patients with measurable lesions in a prior radiation port that represented the only site of measurable disease had to have completed radiation > 2 months previously and were required to have biopsy-confirmed presence of active disease. All patients were age ≥ 18 years and were without known active central nervous system metastases. Required laboratory parameters included adequate bone marrow function (neutrophil count $> 1500/\mu L$ and platelet count $> 100{,}000/\mu L$), adequate hepatic function (aspartate transaminase < 2 times the upper limit of normal [ULN], bilirubin within normal limits), and adequate kidney function (serum creatinine < 2 times the ULN). All patients provided written informed consent in accordance with the precepts of the Helsinki Declaration and with all local, state, federal, and institutional review board guidelines.

Dosing and Administration

The current study was a nonrandomized, open-label study. Patients received 300 mg of R115777 orally twice daily for 21 consecutive days followed by 7 days of rest. This 28-day cycle was repeated at least twice. The R115777 doses were taken with food approximately 12 hours apart. The prophylactic use of myeloid colony-stimulating factors was prohibited.

Pretreatment and Follow-Up Studies

Patients were monitored routinely for adverse events. Complete blood counts were obtained at weekly intervals during the first 2 cycles and on Days 1 and 15 of subsequent cycles. Biochemistry was performed on

Day 1 of each cycle. Because several retinal signal-transduction proteins are farnesylated, ophthalmologic examinations were required at baseline and every 8 weeks throughout therapy. Disease assessments with computed tomography scans or magnetic resonance images were obtained at baseline and then every 2 months until disease progression, the initiation of new therapy, or death. Patients who were found to have progressive disease were discontinued from the study treatment. Patients who achieved a complete objective response were planned to continue on treatment. If the complete response was confirmed at least 28 days later, then 2 additional cycles of therapy were planned. Patients who achieved a partial response or stable disease continued treatment until disease progression or toxicity precluded further treatment.

Pharmacokinetics

A sparse sampling procedure was followed to characterize the pharmacokinetics of R115777.[15] During the first treatment cycle, on Days 1, 8, 15, and 22, a single venous blood sample was collected before the morning dose of R115777. A second venous blood sample was collected on treatment Day 15, at least 1 hour after the first sample. On Day 1 of the second treatment cycle, a venous blood sample was collected after the morning dose of R115777. All samples were collected in heparinized tubes, centrifuged (2500 revolutions per minute [rpm] at $\times$ 1000 *g* for 10 minutes), and separated plasma was stored at $-$ 20 °C. Plasma R115777 concentrations were measured by validated liquid chromatography using a tandem mass spectrometry method (with a lower limit of quantification of $<$ 2 ng/mL) at Johnson & Johnson Pharmaceutical Research and Development (Beerse, Belgium).[16]

A Bayesian estimation of pharmacokinetic parameters of R115777 was implemented in NONMEM software using the POSTHOC option. The results of a previous population pharmacokinetic analysis of R115777 using data from six Phase I trials were used to describe the time course of R115777 plasma concentration. The pharmacokinetic model is a three-compartment disposition model, with first-order elimination from a central compartment and sequential zero order-first order absorption process and lag time.[17] Summary statistics of the oral clearance, apparent volume of distribution, and absorption time were calculated from the individual Bayesian estimation of pharmacokinetic parameters.

Toxicity Assessment and Dose Reduction

At each visit, patients were assessed for toxicity according to the National Cancer Institute Common Toxicity Criteria (version 2.0). Dose reductions were required for Grade 3 or 4 hematologic toxicity, Grade 3 nonhematologic toxicity other than nausea and emesis, Grade 2 renal toxicity, and Grade 2 neurotoxicity. After interruption to allow for recovery to Grade 1 toxicity or better, the dosage of R115777 was reduced to 200 mg twice daily after a first occurrence or to 100 mg twice daily after recurrent toxicity. No more than two dose reductions were allowed. If recovery from Grade 3 nonhematologic toxicity, Grade 2 neurotoxicity or renal toxicity, or Grade 3 or 4 hematologic toxicity required $>$ 3 weeks of delay in treatment, then patients were removed from therapy. Cessation of R115777 therapy was mandated for patients with neurotoxicity $\geq$ Grade 3,or with any Grade 4 nonhematologic toxicity.

Endpoints

The primary endpoint of this prospective Phase II study was the objective response proportion. Response was evaluated according to World Health Organization criteria.[18] Secondary objectives were to determine the time to disease progression in these patients and to assess the safety of R115777 with this dosing regimen. The time to progression was defined as the number of days from the first day of treatment either to the first occurrence of disease progression (or death if progression had not occurred) or, if no progression occurred, then to the last follow-up date or to the initiation of subsequent therapy. Survival was measured as the number of days from the first day of treatment to death or the last follow-up date (censored) for patients who were still alive at the time of last follow-up.

Statistical Analysis

A sample size of 32 patients was sufficient to detect a response proportion $\geq$ 20% compared with the null hypothesis of 5% with a power of 90% and an $\alpha = 0.10$. A two-stage Simon minimax design was used to allow for early termination due to lack activity of R115777.[19] Eighteen patients were planned for in the first stage; if no responders were reported, then the study was to be terminated for lack of activity. Otherwise, the study was to continue to accrue an additional 14 patients. Because of poor accrual, the study was amended to include patients who previously had received chemotherapy. However, the sample size and statistical power were not changed because it was not clear that the response proportion of first-line and second-line patients would be different. Descriptive statistics were used to characterize the patient sample, response proportion, toxicity, and results of the pharmacokinetic studies. The Kaplan–Meier product-limit method was

TABLE 1
Pretreatment Patient Characteristics

Characteristic	No. of patients (%)
Total no. of patients	34
Male:female ratio	21/13
Median age (yrs) (range)	64 (41–84)
White race	32
ECOG performance status at baseline	
0	16
1	15
2	3
Site of primary tumor	
Bladder	25
Renal pelvis	8
Ureter	1
Site of metastasis	
Visceral[a]	21 (62)
Liver	6
Lung	13
Other	9
Lymph node only	13 (39)
Bone	1 (3)
Previous chemotherapy	23 (68)

ECOG: Eastern Cooperative Oncology Group.
[a] Some patients who had visceral metastases had more than one site of metastases.

used to estimate the time to disease progression and overall survival.[20]

RESULTS

Patient Characteristics

Thirty-four patients with metastatic TCC of the urothelial tract were enrolled in this study. Patient characteristics are summarized in Table 1. For 25 patients, the bladder was the primary site of disease. The renal pelvis and ureters were the primary disease sites for eight patients and one patient, respectively. Twenty-one patients (62%) had visceral metastases. Twenty-three patients had received previous first-line chemotherapy for metastatic disease, and 11 patients had not.

The median number of cycles administered was 2 (range, 1–15 cycles). Nine patients did not undergo a postbaseline response evaluation due to early discontinuation of the drug. Reasons for early discontinuation included early death in three patients; withdrawal of consent in three patients; and withdrawal due to toxicity, switch to radiotherapy, and injury unrelated to drug in one patient each. Therefore, these patients were scored as nonresponders.

Antitumor Activity

Nine of 34 enrolled patients did not undergo postbaseline tumor evaluation due to early discontinuation of R115777, including 3 deaths prior to the first response evaluation. On an intent-to-treat basis, 2 of 34 enrolled patients achieved a partial response during treatment with R115777, leading to an overall response proportion of 6% (upper 95% confidence limit = 20%) (see Table 2). Both patients had not received prior chemotherapy. One responder with pelvic metastases experienced a partial response (after 6 cycles of therapy) that lasted 10 months. The second responder had extensive visceral involvement, including pulmonary, hepatic, abdominal, mediastinal, and pelvic metastases: This patient demonstrated a partial response of pulmonary metastases after 2 cycles and still was responding after 11 cycles of treatment. Thirteen patients (38%) achieved disease stabilization (according to World Health Organization criteria) that lasted a median of 4 months (range, 3–8 months). None of the 23 patients who had received prior chemotherapy demonstrated an objective response to R115777. The median time to disease progression using Kaplan–Meier estimates was 2.8 months (95% confidence interval [95% CI], 1.9–3.7 months), and the overall median survival for patients in this trial was 6.8 months (95% CI, 2.7–16.1 months).

TABLE 2
Response to R115777

No. of patients (%)				
Complete response	Partial response	No change	Progressive disease	Not evaluable
0 (0)	2 (6)	13 (39)	10 (29)	9 (26)

Toxicity

In general, treatment was tolerated well. Five patients required dose reductions, and 4 patients required treatment delays ≥ 1 week. Grade 3 or 4 drug-related adverse events are shown in Table 3. Five patients (15%) had Grade 3 or 4 neutropenia, including 2 patients with febrile neutropenia. One of those patients developed neutropenic fever and died 3 days after the last dose of R115777 without any evidence of hematologic recovery prior to death: No source of infection was identified. Three patients developed transient Grade 3 thrombocytopenia. Grade 3 nonhematologic toxicity was limited to diarrhea and rash (1 patient each).

Two patients developed Grade 2 peripheral neuropathy. In one patient, the neuropathy (sensory) resolved after temporary discontinuation of the study drug and did not reappear with resumption of therapy, which included eight additional cycles. The sec-

TABLE 3
Drug-Related Grade[a] 3 and 4 Toxicity Related to R115777

	No. of patients (%)	
Toxicity	**Grade 3**	**Grade 4**
Hematologic		
Neutropenia	3 (9)	—
Febrile neutropenia	1 (3)	1 (3)
Thrombocytopenia	3 (9)	—
Anemia	1 (3)	—
Nonhematologic		
Diarrhea	1 (3)	—
Rash	1 (3)	—

[a] Grade was determined according the the National Cancer Institute Common Toxicity Criteria (version 2.0).

ond patient with Grade 2 neuropathy (motor and sensory) improved to Grade 1 at the next follow-up visit. That patient went on to receive other chemotherapy. Five patients were removed from the study for adverse events, 4 of which were attributed to R115777. Ophthalmologic examination both at baseline and at the end of treatment or follow-up revealed that 1 patient had a subclinical hemorrhage in 1 eye that was not attributed to R115777. No other ophthalmologic abnormalities were observed.

Pharmacokinetics

Pharmacokinetic analysis of R115777 was performed on the basis of 96 plasma samples obtained from 28 patients. The time course of R115777 plasma concentration at the steady state is shown in Figure 1 after oral administration of 300 mg of R115777 twice daily. A descriptive summary of the R115777 pharmacokinetic parameters and their variability is shown in Table 4. Between-patient and within-patient variability in the pharmacokinetics of R115777 was high. At steady state, the mean plasma concentration of R115777, defined as the mean area under the concentration time curve $>$ 24 hours divided by 24 hours, was 675 nM (range, 223–1518 nM).

DISCUSSION

The development of less toxic therapies for TCC represents a critical, unmet need. The majority of patients with TCC tend to be older and have additional comorbidities that amplify the toxicities of cytotoxic chemotherapy. Often, these patients cannot tolerate cytotoxic second-line therapy due to cumulative chemotherapy toxicity, preexisting medical problems, or both. It has been shown that mutations in the Ras signal-transduction pathway are important in the growth and progression of a variety of cancers. Al-

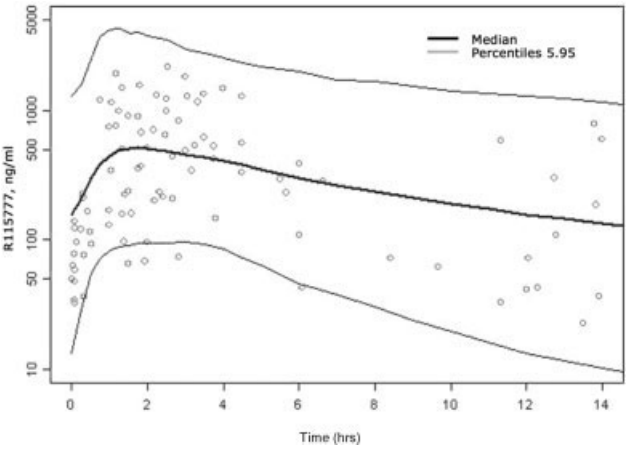

FIGURE 1. The circles in this figure represent observed plasma concentrations, and the lines represent the median and the 95% prediction intervals. This graph indicates that the plasma concentrations obtained fell into the expected prediction interval; consequently, it is feasible to use the population pharmacokinetic (PK) model to determine the Bayesian estimation of the individual PK parameters.

though the exact frequency of Ras mutations in bladder carcinoma is unclear, the inhibition of constitutive Ras pathway over-activity by FT inhibition has been effective in preclinical models. Consequently, the current study was undertaken in patients with advanced TCC.

In the current study, we investigated the activity of R115777, an oral FT inhibitor (FTI), in both treatment-naïve and pretreated patients with TCC. Because no responses were observed for R115777 in the 23 pretreated patients, and second-line chemotherapy with ifosfamide and taxanes yielded 15–20% response proportions,[21] using R115777 as second-line therapy was not promising.

Two partial responses were observed in the 11 first-line patients (18% relative risk in that subgroup). Although this was an unplanned subset analysis, the level of activity within this subgroup is of interest and suggests that combining R115777 with conventional first-line combination chemotherapy agents may be warranted. A Phase I trial has been reported testing gemcitabine plus cisplatin in combination with R115777 in patients with advanced malignancies and has demonstrated acceptable toxicity.[22]

The pharmacokinetics of orally administered R115777 in the current trial confirmed that the mean plasma levels of R115777 were within the mean inhibitory concentration range necessary for in vitro activity.[13] Consequently, it is unlikely that pharmacokinetic variability influenced the efficacy results more than other fundamental biologic factors.

One possible explanation for the failure of

TABLE 4
Pharmacokinetic Parameters of R115777 in Patients with Bladder Carcinoma

Pharmacokinetic Parameters	Geometric mean (95% CI)	Between-patient variability (%) (95% CI)	Within-patient variability (%) (95% CI)
Oral clearance (L/hr)	87.2 (74.4–100)	31.5 (22.0–38.7)	33.5 (26.1–39.5)
Apparent volume of distribution (L)	584 (491–677)	35.2 (26.1–42.4)	33.2 (21.1–41.9)
Absorption time (hrs)	3.1 (2.5–3.8)	30.2 (11.4–41.1)	82.3 (35.4–110.6)

95% CI: 95% confidence interval.

R115777 to show significant activity in TCC is the high prevalence of poor-risk patients in this study. Visceral metastases are associated with worse responses to chemotherapy and inferior overall survival.[23] Sixty-two percent of the patients treated in the current study had visceral metastases. This inclusion of more patients with a poor prognosis may have had an impact on the response rate, although the small numbers of patients involved in this study preclude any definitive conclusions.

Another potential explanation for the lack of response to R115777 is that the target of R115777, FT, is not important in human TCC pathogenesis. It is clear that malignant cells can bypass FT inhibition through geranylgeranylation of critical proteins, including Ras.[24] The importance of alternative pathways to prenylate Ras and other critical cell cycle-regulatory proteins (such as the Rho family of GTPases) is not clear in TCC.[25] In addition, whether inhibition of farnesylation of other proteins is necessary for the demonstration of the antineoplastic effects of R115777 and other FTIs is unknown. The importance of the Ras pathway itself as a therapeutic target in bladder carcinoma remains unclear.

In addition, the presence of Ras mutations was not evaluated as part of this study. It is possible that the intended downstream target of FTI, Ras alteration, was not present with great frequency in the patient population that was treated in the current study. The dependence of TCC on Ras alterations for continued growth and proliferation is unknown, and prior studies have failed to demonstrate a consistent correlation between Ras mutations, alterations in other components in the Ras pathway, and clinical efficacy of R115777.[13] Multiple studies in multiple solid tumor types have failed to show substantial activity for the FTIs as single agents, raising questions about the importance of FT inhibition in the treatment of advanced solid tumors.[16,26–30]

Phase I and II trials with R115777 have indicated an acceptable toxicity profile, which was confirmed by the current trial.[13,28–30] The overall toxicity profile in this patient population should not preclude combining R115777 with chemotherapy. Preclinical data suggest that FT inhibition has additive in vitro cytotoxicity with gemcitabine and synergistic in vitro cytotoxicity with cisplatin.[31] R115777 in combination with full-dose gemcitabine and cisplatin was tolerated well, as noted previously.[22] However, to our knowledge, chemotherapy in combination with R115777 in other solid tumors has not yet shown substantial improvement compared with chemotherapy alone.[32] Significant activity of single-agent R11577 has been seen in elderly patients with acute myeloid leukemia, and further research in that disease continues.[27,33]

Although novel biologic therapies are among the most promising new treatments currently in development for patients with advanced cancer, the presence of redundant pathways and the emergence of resistance have complicated treatment with these agents. In the future, combinations of agents that affect different pathways may prove to be the most effective in addressing the protean resistance pathways of advanced cancer. The incorporation of R115777 into combination chemotherapy for patients with bladder carcinoma, such as gemcitabine plus cisplatin, may be an avenue for future investigation.

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