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Original article

A multinomial Phase II study of lonafarnib (SCH 66336) in patients with refractory urothelial cancer☆

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Abstract

Purpose: Protein farnesylation by farnesyltransferase (FTase) is required for membrane localization and effective signal transduction by G-proteins, including Ras. Lonafarnib inhibits FTase and has shown antitumor activity in both preclinical and clinical settings. As disturbances in Ras signaling pathways have been implicated in the pathogenesis of transitional cell carcinoma (TCC), the antitumor activity of lonafarnib was studied in a National Cancer Institute of Canada Clinical Trials Group Phase II trial in patients with previously treated TCC.

Patients and Methods: Patients had at least 1 prior chemotherapy regimen for advanced unresectable or metastatic TCC, or recurrence less than 1 year after adjuvant or neoadjuvant chemotherapy. Lonafarnib was given at a dose of 200 mg PO twice daily continuously, with cycles repeated every 4 weeks.

Results: Between December 1999 and December 2000, 19 eligible patients were enrolled at 8 National Cancer Institute of Canada Clinical Trials Group centers. Median time on treatment was 7.1 weeks (range, 0.6–23.9). Drug-related Grade 3 toxicities included fatigue, anorexia, nausea, confusion, dehydration, muscle weakness, depression, headache, and dyspnea. Five patients discontinued the study protocol due to toxicity. No responses were observed in 10 patients who were evaluable. Of 9 patients not evaluable for response, 5 had symptomatic progression, fulfilling multinomial criteria to stop the study after the first stage.

Conclusion: No single-agent activity of lonafarnib was observed in this study of patients with aggressive TCC failing prior chemotherapy.

Keywords: Bladder neoplasms; Drug therapy; Farnesyltransferase; Lonafarnib

1. Introduction

Cellular Ras proteins are bound to the internal surface of the cell membrane and subserve a critical role in growth factor signaling pathways linking cell surface receptors to nuclear transcription factors [1]. Specifically, activated Ras proteins trigger a cascade of phosphorylation events through the PI3 kinase/AKT and Raf/Mek/Erk kinase pathways, implicated in cell survival and cell proliferation, respectively [2]. Mutations in Ras proteins typically inhibit guanosine triphosphate hydrolysis, inducing a continuous mitogenic signal and a malignant phenotype, and these are associated with many human cancers [3,4]. Ras signaling may be pharmacologically targeted at the level of Ras protein expression, Ras protein processing, and downstream Ras effectors [5]. Ras proteins require posttrans-

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lational isoprenoid lipid modification by farnesyltransferase (FTase) for activity, and a number of drugs with preclinical activity as FTase inhibitors (FTI) have been identified and studied in cancer patients. The HMG-CoA reductase inhibitor lovastatin and the limonene derivative perillyl alcohol have been studied because of FTI activity but have shown little evidence of clinically significant antitumor activity [6–8]. A number of drugs investigated for FTI activity have shown preclinical evidence of antitumor activity including L-778123, FTI-277, FTI-2153, RPR-115135, and RPR-130401 [9–13]. Three drugs have shown activity as single agents in patients with leukemia, myelodysplastic syndromes, or refractory solid tumors, and are undergoing further clinical study either as single agents or in combination with cytotoxics: tipifarnib (R115777), lonafarnib (SCH 66336), and BMS-214662 [5].

Lonafarnib is an orally, bioavailable tricyclic nonpeptidyl nonsulfhydryl FTI with preclinical activity in human cancers expressing H-ras and K-ras [14]. Phase I trials have evaluated several dosing schedules. Adjei et al identified a recommended Phase II dose (RP2D) of 350 mg PO bid when lonafarnib was given for 7 consecutive days out of 21 [15]. Gastrointestinal toxicity (nausea, vomiting, and diarrhea) and fatigue were dose-limiting toxicities (DLT), and one partial response in a patient with nonsmall cell lung cancer was seen. Hurwitz et al identified a RP2D of 200 mg PO bid when given for 14 consecutive days out of 28, with nausea, diarrhea, and malaise as DLT [16]. In a continuous dosing study, Eskens et al reported DLT of Grade 4 vomiting, Grade 4 neutropenia and thrombocytopenia, and the combination of Grade 3 anorexia and diarrhea, with reversible Grade 3 plasma creatinine increase at a dose of 400 mg PO bid [17]. After dose reduction, at 300 mg bid, the DLT consisted of Grade 4 neutropenia, Grade 3 neurocortical toxicity, and a combination of Grade 3 fatigue with Grade 2 nausea and diarrhea. The recommended dose for Phase II studies was 200 mg bid. Awada et al identified a RP2D of 300 mg PO, with continuous once daily dosing with similar DLT [18]. No patients with urothelial cancer were studied in these trials.

Bladder cancer is the fifth most common cancer in North American men and caused over 13,000 deaths in the U.S. in 2003 [19]. Transitional cell cancer (TCC or urothelial cancer) is the most common histologic subtype. Metastatic TCC is a virulent but chemosensitive neoplasm. Although 50% of patients will have objective response to chemotherapy, such as gemcitabine plus cisplatin or methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC); nearly all succumb to progressive disease within 2 years of treatment [20]. Paclitaxel is the most active and commonly used single agent in TCC refractory to cisplatin-based chemotherapy; however, the most active paclitaxel-based combination reports a response rate of less than 50% and median survival of 7.5 months [21–23]. Ras mutations occur in 30% of epithelial cancers, usually K-ras. Only mutations in H-ras are important in TCC and have been detected in 30% to 45% of tumors [24,25]. Increased transcription of Ras genes has been observed in bladder cancer specimens relative to normal epithelium [26]. Activity of lonafarnib was observed in 1 of 2 bladder tumors using the human tumor cloning assay [27]. Thus, our rationale for this trial was a pragmatic one, based on limited preclinical data, the theoretical role of H-ras, and limited efficacy of standard therapies in this population, to evaluate the antitumor activity of lonafarnib in patients with urothelial cancer refractory to first-line cytotoxic treatment.

2. Patients and methods

2.1. Patients

Eligible patients were at least 18 years of age and had histologically or cytologically confirmed TCC, and documented evidence of locally advanced unresectable or metastatic disease not amenable to curative radiotherapy or surgery. Patients had a minimum of one prior chemotherapy regimen for advanced disease, or had progressed after receiving adjuvant or neoadjuvant chemotherapy within the previous 12 months. Patients were required to have disease measurable by the Response Evaluation Criteria in Solid Tumors criteria, an Eastern Cooperative Oncology Group performance Status ≤ 2, and adequate organ function as defined by: granulocyte count $\geq 1{,}500/mm^3$, platelet count $\geq 100{,}000/mm^3$, serum creatinine ≤ 1.5 upper normal limit (UNL) or creatinine clearance ≥ 50 ml/min, serum bilirubin ≤ 1.5 UNL, AST ≤ 2.5 UNL or ≤ 5 UNL if documented hepatic metastases, and serum calcium within 10% of normal range. Exclusion criteria included known brain or leptomeningeal disease, uncontrolled infection, concurrent treatment with other experimental drugs or anticancer therapy, serious illness or medical conditions, clinical evidence of congestive heart failure, myocardial infarction within 6 months, QTc prolongation more than 440 msec, and bone as the only site of measurable disease. The study was reviewed and approved by the Research Ethics Board of each participating institution, was conducted in accordance with the Helsinki Declaration, and all patients gave written informed consent.

2.2. Study design

This was a multicenter, open-label, single-arm 2-stage Phase II study, with a multinomial endpoint that considered rates of both objective response and progressive disease. Baseline investigations included physical and ophthalmological examination, complete blood count (CBC) and differential CBC, serum chemistries, urinalysis, electrocardiogram, chest x-ray, abdominal computerized tomography, and any additional imaging required to image the sites of tumor for baseline measurement. While on treatment, patients were reassessed every 4 weeks with toxicity assessment, repeat physical examination including clinical tumor