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A phase II study of farnesyl transferase inhibitor R115777 in pancreatic cancer: A Southwest oncology group (SWOG 9924) study

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Summary

Ninety per cent of pancreatic adenocarcinomas (PC) contain mutations of the K-Ras proto-oncogene resulting in constitutively activated Ras protein. A critical step in Ras activation is farnesylation of Ras protein. Farnesyl transferase inhibitors are compounds that inhibit farnesylation. We report the results of a phase II trial of R115777, an oral farnesyl transferase inhibitor, in patients with surgically incurable locally advanced or metastatic PC. Between 6/1/2000 and 11/20/2001, 58 cases were accrued, 53 of whom were eligible and analyzable. Patients were required to have a performance status (PS) 0 to 1, be able to take oral medications, and to have adequate renal, hepatic, and hematologic functions. Fifty-five percent were male. Median age was 64.7 years (38.9 to 80.6), and patients had no previous systemic therapy for advanced PC. Treatment consisted of R115777 300 mg po bid given for 3 out of every 4 weeks. Toxicities were as follows: Grade 3 in 19/53 (36%), grade 4 in 53 (173%), and grade 5 in 53 (8%). Most frequent toxicities were: anemia 35/53 (66%), fatigue and malaise 33/53 (62%), nausea 31/53 (58%). Grade 5 toxicities included: thromboembolism 1, infection 2, other 1. Median survival was 2.6 months (mo) (95% CI 2.1–3.6), 6-mo survival is 19% (95% CI, 8–29%), median time to treatment failure was 1.4 mo (95% GI 1.1–1.6). R115777 is ineffective as monotherapy in advanced pancreatic cancer.

Adenocarcinoma of the pancreas is an important cause of cancer death in the United States. This disease occurred in 30,000 patients in 2002 and it is at least 95% lethal [1]. The only curative therapy for this disease is surgical resection. However, only 15% of all cases are resectable and at most 15% of those cases will be long terms survivors [2, 3].

Since the large majority of pancreatic cancer cases have either locally advanced or disseminated metastatic carcinoma, the treatment of this disease with cytotoxic chemotherapy has been of great interest, although the results have been poor. The chemotherapeutic standard of care for pancreatic cancer, Gemcitabine, produced a partial response in only 5% of cases, although some clinical benefit (decreased pain, improvement in performance status) was seen in over 20% of patients [4]. Because of the poor results with standard therapies, the study of new treatments is an important endeavor in adenocarcinoma of the pancreas. This communication reports a clinical trial utilizing R115777 in pancreatic cancer. R115777 is a selective inhibitor of farnesyltransferase. Farnesyltransferase is an enzyme responsible for adding a 15-carbon farnesyl lipid to the carboxy-terminal cysteine of a number of cell-signaling proteins, including RAS [5]. *K-Ras* mutations occur in greater than 90% of pancreatic cancers [6] making it appropriate to study R115777 in pancreatic cancer. The results of the Southwest Oncology Group Phase II Trial (9924) are reported in this communication.

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Table 1. Patient characteristics

	R115777 ($n = 53$)	
Age		
Median	64.7	(38.9–80.6)
Sex		
Males	29	55%
Females	24	45%
Race		
White	45	85%
Black	7	13%
Asian	1	2%

Patient population

Patients had to have a cytologically or pathologically verified diagnosis of pancreatic adenocarcinoma. All patients had locally advanced or distant metastatic disease and were not surgically curable.

Patients could not have received prior chemotherapy, hormonal therapy, immunotherapy, radiation, or chemoradiotherapy as neoadjuvant or adjuvant treatment or as treatment for advanced pancreatic cancer. Palliative radiation to metastatic sites was allowed. Patients may have had prior surgery for pancreas cancer provided they were at least two weeks beyond surgery, and had recovered from all effects of surgery.

Patients had to have a Zubrod performance status of 0–1 and adequate renal, hepatic, and hematologic function. Patients were required to be able to swallow and/or receive enteral medications via a gastrostomy feeding tube. Intractable nausea or vomiting was not permitted. Patients could not be using a proton pump inhibitor. Patient characteristics are described in Table 1.

This Phase II study was designed with six-month survival as the primary endpoint. A true 50% six-month survival probability was considered sufficient to warrant further consideration of this agent. The targeted accrual goal was fifty eligible patients.

Treatment plan

The plan of treatment required administration of 300 mg of R115777 orally twice a day for 21 out of 28 days [5]. Dose modifications of R115777 were required for significant toxicity. Toxicity: toxicity was evaluated using the NCI Common Toxicity Criteria version 2.0.

Results

This study closed on June 1, 2001, having reached full accrual. Fifty-eight patients were registered, four of who were ineligible. One additional patient never received any treatment and is not analyzable for any endpoint. Fifty-three eligible patients were evaluated for toxicity. There were four treatment-related deaths. One patient was presumed to have died from aspiration after being hospitalized with Grade 4 vomiting and abdominal cramping and another patient died of Grade 4 diffuse intravascular coagulation after experiencing treatment-related sepsis and pneumonia. One patient died from a pulmonary embolism during treatment. One patient who experienced somnolence and asphasia was removed from treatment, and died in hospice care. This death was ruled possibly related to treatment though progressive disease could not be ruled out.

Nine other patients experienced Grade 4 toxicities: One patient experienced renal failure and leukopenia on cycle five; two had bilirubin increase, one of whom also had Grade 4 neutropenia and leukopenia; one had hypercalcemia, one had Grade 4.

Fatigue/malaise/lethargy and anorexia; two had neutropenia, one of whom also had Grade 4 hypokalemia; and two had anemia, one of whom also had Grade 4muscle weakness.

Statistical considerations

This study was designed to detect a difference between the null hypothesis of 30% six-month survival and the alternative hypothesis 50% six-month survival. The estimated six-month survival rate is 19% (95% confidence interval 8 to 29%), with a median of 2.6 months (Figure 1). The estimated median time to treatment failure is 1.4 months. (Figure 2) Out of the 52 eligible patients with measurable disease that were assessed for response, there were no confirmed complete or partial responses (95% confidence interval 0 to 7%). One patient had an unconfirmed partial response for an overall response rate of 2%. These data strongly suggest that R115777 is not an active agent in pancreatic cancer.

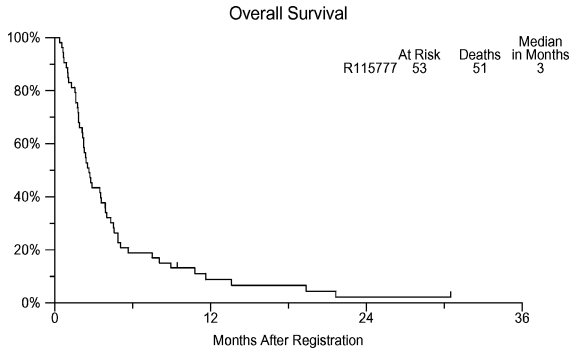

Figure 1. Estimated six-month survival rate.

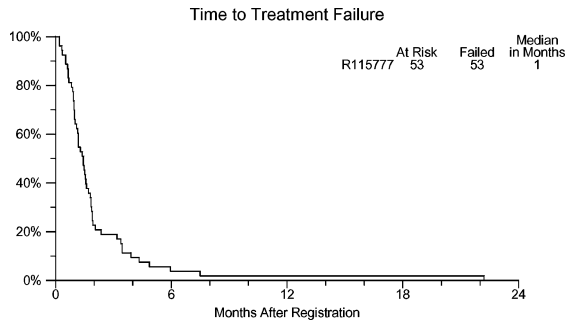

Figure 2. Estimated median time to treatment failure.

Discussion

The results of this study failed to show any benefit for R115777 treatment in adenocarcinoma of the pancreas. Median time to progression and median survival seen in 53 eligible patients receiving R115777 were inferior to the results seen with the standard of care chemotherapeutic agent, Gemcitabine [4]. Since R115777 is presumably a targeted therapy aimed at the enzyme farnesyltransferase which is important in RAS protein activation, it would be important to know if inhibition of farnesyltransferase was achieved with the dose of R115777 administered in this clinical trial. Although we have no way of knowing whether tumor farnesyltransferase was inhibited, there is evidence that the dose and schedule of R115777 used in our clinical trial could effectively inhibit the farnesyltransferase in peripheral blood monocytes. Cohen et al. [7] performed a Phase II trial of R115777 in pancreatic cancer patients using the identical dose and schedule of R115777 used in our clinical trial and also found no clinical benefit for R115777. They also measured farnesyltransferase inhibition in peripheral blood monocytes in 10 cases and found approximately 50% inhibition four hours after drug administration demonstrating that the dose and schedule (300 mg twice a day) of R115777 is biologically active.

In attempting to explain the negative results of R11577, one could argue that the dose was too low to be beneficial; however, doses equivalent to 300 mg BID were found to produce anti-tumor activity in preclinical models [5] and the toxicity we saw ($\geq$grade III in 32/53 cases), strongly suggests that a higher dose could not be given. Finally, is it possible that R115777 may not be active as a single agent but may be effective in combination with cytotoxic chemotherapy in pancreatic cancer? This is unlikely since one large Phase III study of Gemcitabine with or without R115777 reported by Van Cutsem et al. [8], demonstrated that Gemcitabine plus R115777 had no advantages over Gemcitabine alone. In summary, the results of Southwest Oncology Group Phase II trial 9924, show that R115777 in this dose and schedule is inactive inpancreatic cancer. Whether farnesyltransferase inhibition by other drugs may be effective is unknown, but it is likely that this approach to therapy of adenocarcinoma of the pancreas is unlikely to be fruitful.

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