Sunitinib Plus Paclitaxel in Patients with Advanced Esophageal Cancer

A Phase II Study from the Hoosier Oncology Group

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Abstract: The combination of sunitinb (37.5 mg orally daily) + paclitaxel (90 mg/m^2 intravenously on days 1, 8, 15 every 4 weeks) was examined in patients with advanced esophageal or *gastroesophageal* junction cancer, and progression-free survival (PFS) was compared to that of historical controls. The end points included response rate, overall survival, and toxicities. Twenty-eight patients were enrolled at six centers. Median age was 59.5 years. The 24-week PFS rate was 25% (90% confidence interval [CI], 12–42%). Three (11%) of 23 evaluable patients had a response (1 complete response and 2 partial response) (90% CI, 3−25%). Median overall survival was 228 days (90% CI, 140–283 days). Grade 3/4 toxicities included leukopenia/neutropenia (25%), anemia (18%), fatigue (11%), and hemorrhage (11%). There were four grade 5 toxicities including upper gastrointestinal hemorrhage (n = 2), gastrointestinal/esophageal fistula (n = 1), and unexplained death (n = 1). In our study, we found that sunitinib + paclitaxel in patients with advanced esophageal or *gastroesophageal* junction cancer had a 24-week PFS no better than the PFS of historical controls. The combination also had a high rate of serious toxicities and will not be pursued.

Key Words: Sunitinib, Paclitaxel, Esophageal, Gastroesophageal junction, Angiogenesis, Tyrosine kinase inhibitors.

(*J Thorac Oncol.* 2012;7: 760–763)

Despite advances in staging and treatment for patients with esophageal cancer, the relative 5-year survival rate for all stages remained at an estimated 19% between 1999 and 2005.[1] Response rates (RRs) to classic chemotherapeutic regimens range from 15 to 48% and are typically short in duration.[2,3] Angiogenesis is a critical factor in tumor growth and metastatic spread. In patients with esophageal cancer, 30 to 60% of them have overexpression of vascular endothelial growth factor (VEGF), which has been correlated with greater microvessel density, advanced disease, and poor prognosis.[4] Inhibition of angiogenesis with compounds like sunitinib maleate, a well-tolerated oral inhibitor of tyrosine kinase with activity against VEGF receptors (types 1–3), platelet-derived growth factor α and platelet-derived growth factor β, c-kit, and fetal liver tyrosine kinase receptor 3,[5] is a novel therapeutic approach that has demonstrated activity in a variety of malignancies. In preclinical studies, gastric and esophageal cancer cell lines overexpressed VEGF, proliferated in the presence of recombinant VEGF, and were inhibited in a dose-dependent manner by sunitinib.[6] Sunitinib has been studied for locally advanced esophageal cancer[7] and studies in patients with relapsed/refractory metastatic disease are ongoing. On the basis of this preclinical and clinical work, the known overexpression of VEGF in esophageal cancer, the hypothesized synergy between VEGF inhibition, and the antiangiogenic effects of taxane therapy,[4] we conducted this multi-institutional phase II study to evaluate the efficacy of sunitinib + paclitaxel in patients with advanced esophageal or *gastroesophageal* (GE) junction carcinoma.

PATIENTS AND METHODS

Patients enrolled on study included adults with histologically proven recurrent or metastatic esophageal or GE junction squamous cell or adenocarcinoma, who had received less than two chemotherapy regimens for locally advanced or metastatic disease, and had measurable and/or evaluable disease as per the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. All patients had an Eastern Cooperative Oncology Group performance status of 0 to 2. Key exclusion criteria included prior exposure to an epidermal growth factor receptor inhibitor or any other antiangiogenic agents.

Each treatment cycle was defined as 28 days and included paclitaxel 90 mg/m^2 intravenous infusion over 60 minutes on

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Disclosure: This work was supported by Pfizer.

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ISSN: 1556-0864/12/0704-0760

TABLE 1. Demographics (Intention to Treat n = 28)

Characteristics	Category/ Statistics	*n*/Value	%
Sex	Female	5	18
	Male	23	82
Race	Caucasian	27	96
	African American	1	4
Ethnicity	Non-Hispanic	27	96
	Not reported	1	4
Age	Median	59.5 yr	
	Range	40–84 yr	
ECOG PS	0	15	54
	1	11	39
	2	2	7
Tumor site	Esophagus	22	79
	Gastroesophageal junction	6	21
Histology	Adenocarcinoma	26	93
	Squamous cell carcinoma	2	7
Prior treatment	Yes	11 (9 with prior chemo)	39
	No	17	61

ECOG PS, Eastern Cooperative Oncology Group performance status.

TABLE 2. Selected Hematologic Toxicities Irrespective of Causality Attributed (n = 28)

	Grade 3		Grade 4		Grade 3/4	
Leukopenia/neutropenia	6	21%	1	4%	7	25%
Anemia	3	11%	2	7%	5	18%
Thrombocytopenia	1	4%	0	—	1	4%
Febrile neutropenia (fever without clinically or microbiologically documented infection) (ANC <1.0, fever ≥38.5°C)	1	4%	0	—	1	4%

ANC, absolute neutrophil count.

days 1, 8, and 15 and sunitinib maleate 37.5 mg orally daily.[8] Participants were scheduled to receive four cycles of the combination therapy. Treatment was discontinued upon disease progression or unacceptable toxicity. After four cycles, paclitaxel was discontinued and each patient was allowed to continue on sunitinib maleate for two more cycles provided he/she did not have disease progression, intolerable side effects, or adverse reactions.

Patients were evaluated at the beginning of each treatment cycle. Before odd-numbered cycles, a disease evaluation per RECIST criteria was performed. At the end of the study, patients, including those who discontinued protocol therapy early, were evaluated 30 days after the last dose. Patients were then serially followed up for duration of response and for survival. All toxicities were measured according to the National Cancer Institute Common Toxicity Criteria version 3.0.

The primary end point was the rate of nonprogressive disease at 6 months. Nonprogressive disease was defined as a complete response, partial response, or stable disease. A predetermined improvement from 25 to 50% in nonprogressive disease rate was deemed reasonable for the proposed regimen as two prior phase II trials of paclitaxel therapy alone demonstrated a median duration of response ranging from 119 to 172 days[9,10] and we anticipated prolonged duration of response with the addition of antiangiogenic therapy. With 26 subjects, the study had more than 80% power based on one-sided test with error rate controlled at 5%.

RESULTS

Twenty-eight patients were enrolled at six participating centers. Patient demographics and disease characteristics are summarized in Table 1. Over 80% of the participants were men, with a median age at enrollment of 59.5 years (age range of 40–84 years). All tumors were located in the esophagus (22/28 or GE junction [6/28]). Ninety-three percent of the tumors (n = 26) were adenocarcinoma and 7% (n = 2) were squamous cell carcinoma. Nine of 28 patients had received prior chemotherapy.

The median follow-up was 222 days, with a range of 15 to 629 days. Six patients (22%) completed less than one cycle of therapy. Seven patients (25%) finished all four cycles and went on to receive maintenance treatment (median length of maintenance treatment was 54 days). At the end of the study, 23 patients (82%) were evaluable. Five patients were not evaluable owing to no postbaseline assessment. Reasons for coming off study included death caused by progressive disease (n = 20 [71%]), death caused by other reasons (n = 2 [7%]), and refusal to follow-up (n = 1 [4%]). Among the 28 patients, 10 (36%) had dose modification and 16 (57%) had dose delay of sunitinib. Fifteen (54%) had dose modification of paclitaxel, and 14 (50%) had dose delay of paclitaxel.

Toxicity data for all patients are summarized in Tables 2 through 4. The most common toxicities reported included fatigue, anemia, and leukopenia/neutropenia. Grade 3 and grade 4 toxicities included leukopenia/neutropenia (25%), anemia (18%), fatigue (11%), and hemorrhage (11%). There were four grade 5 toxicities including two deaths caused by upper gastrointestinal hemorrhage and one caused by gastrointestinal/esophageal fistula (Table 4). Three of the four events were considered treatment-related deaths. Sunitinib-related toxicities including diarrhea, rash, hemorrhage, thrombosis, and hypertension were also observed.

The 24-week progression-free survival (PFS) rate was 25% (7/28) (90% CI, 12–42%) for the combined regimen. Of the 23 evaluable patients, 3 (11%) had a measurable response by RECIST criteria (90% CI, 3−25%). A complete response was observed in one patient and partial response observed in two patients. For the three patients who responded, the durations of response were 29, 56, and 72 days, respectively. For the 28 intention-to-treat patients, the 1-year overall survival (OS) rate was 20% (90% CI, 9−34%). Median OS was 228 days (90% CI, 140–283 days). The median PFS was 112 days (90% CI, 54–150).

TABLE 3. Selected Nonhematologic Toxicities Irrespective of Causality Attributed (n = 28)

	Grade 3		Grade 4		Grade 3/4		Grade 5	
Hemorrhage/bleeding	1	4%	2	7%	3	11%	2	7%
Thrombosis/thrombus/embolism	0	—	2	7%	2	7%	0	—
Fistula, GI/esophagus	1	4%	0	—	1	4%	1	4%
Rash/dermatologic complaints	0	—	1	4%	1	4%	0	—
Dyspnea	0	—	1	4%	1	4%	0	—
Neuropathy: motor	1	4%	0	—	1	4%	0	—
Allergic reaction/hypersensitivity (including drug fever)	2	7%	0	—	2	7%	0	—
Pulmonary (effusion, pneumonitis NOS)	2	7%	1	4%	3	11%	0	—
Fatigue (asthenia, lethargy, and malaise)	3	11%	0	—	3	11%	0	—
Diarrhea	2	7%	0	—	2	7%	0	—
Dysphagia	2	7%	0	—	2	7%	0	—
Hyponatremia	2	7%	0	—	2	7%	0	—
Hyperglycemia	2	7%	0	—	2	7%	0	—
Death NOS	0	—	0	0%	0	—	1	4%

GI, gastrointestinal; NOS, not otherwise specified.

DISCUSSION

The results of this multi-institutional phase II trial are, to our knowledge, the first reported study of sunitinib in advanced esophageal/GE junction cancer. This combination did not meet our predetermined goal of improved nonprogressive disease from 25 to 50% at 24 weeks. The majority of the patients completed less than two cycles and toxicities were significant with at least three treatment-related deaths.

Paclitaxel alone as first-line therapy for metastatic disease has demonstrated an RR ranging from 15 to 32% in two prior phase II studies of patients with advanced esophageal cancer.[9,10] This is inferior to RRs reported with use of regimens such as epirubicin + cisplatin + fluorouracil and epirubicin + oxaliplatin + capecitabine or paclitaxel containing combination regimens that have yielded higher RRs (40–54%) at the expense of higher toxicity rates, including docetaxel + cisplatin + 5-fluorouracil,[11] and oxaliplatin + paclitaxel.[12] Our study failed to show similar RRs with a reported overall RR of only 11% and a 24-week PFS rate estimated at 25% with increased toxicities.

VEGF inhibitors have been studied in patients with advanced esophageal cancer. In a phase II study combining irinotecan, cisplatin and bevacizumab,[13] a 65% overall RR was noted with a median time to progression of 8.3 months and a median survival of 12.3 months. A second study looking at docetaxel + cisplatin + 5-FU + bevacizumab demonstrated an improvement in PFS at 6 months from a historic control of 43% for docetaxel + cisplatin + fluorouracil alone to 79% with the addition of bevacizumab.[14] Grade 3 or 4 toxicities in both of these studies were fewer than appreciated in our study. Another study evaluating bevacizumab + cisplatin and capecitabine in advanced gastric cancer reported fewer serious toxicities than observed in our study, and although this study showed significant improvements in the overall RR and PFS, it failed to meet its primary end point of improved OS (10.1 versus 12.1 months [$p = 0.1$]).[15]

Sunitinib has been evaluated in esophageal cancer in the adjuvant setting, looking at neoadjuvant irinotecan + cisplatin combined with radiation followed by esophagectomy followed by adjuvant sunitinib therapy. In this phase II study, 70 patients were enrolled; following esophagectomy only 20 patients were fit enough to receive sunitinib therapy. Median OS in this locally advanced population was 26 months with a 2-year OS of around 50%. Specific toxicity data are not yet available.[7] Currently, there is an ongoing phase II study comparing sunitinib single agent to placebo therapy in relapsed or refractory esophageal or GE junction carcinoma (ClincalTrials.gov ID #NCT00702884). The sunitinib-specific toxicities observed in our study were similar to those previously reported; however, the increased incidence of grade 3/4/5 hemorrhage was concerning with this combination and was not previously reported in therapy with taxanes alone, combination regimens containing taxanes, or with other VEGF inhibitors. In conclusion, our study of the combination of sunitinib + paclitaxel in advanced esophageal and GE junction cancer was negative as it did not meet our primary end point of 50% PFS at 24 weeks, and with a high rate of serious toxicities, including four grade-5 events, this combination will not be pursued further.

TABLE 4. Grade 5 Toxicity and Treatment-Related Death Evaluable Population (n = 23)

	N	%	Cycle	Consequence	Attribution
Hemorrhage, GI/upper GI NOS	1	4	Maintenance	Death	Possible
Fistula, GI/esophagus	1	4	1	Death	Unrelated
Death NOS	1	4	2	Death	Probably
Hemorrhage, GI/stomach	1	4	2	Death	Possible

GI, gastrointestinal.

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