A Phase II Study of Capecitabine, Oxaliplatin, and Bevacizumab in the Treatment of Metastatic Esophagogastric Adenocarcinomas

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AUTHOR SUMMARY

ABSTRACT

Background. Esophageal and gastric cancers often present at an advanced stage. Systemic chemotherapy is the mainstay of treatment, but survival with current regimens remains poor. We evaluated the safety, tolerability, and efficacy of the combination capecitabine, oxaliplatin, and bevacizumab in the treatment of metastatic esophagogastric adenocarcinomas.

Methods. Thirty-seven patients with metastatic or unresectable gastric/gastroesophageal junction tumors were enrolled and treated with capecitabine 850 mg/m² BID on days 1–14, and oxaliplatin 130 mg/m² with bevacizumab 15 mg/kg on day 1 of a 21-day cycle. The primary endpoint was progression-free survival (PFS). Secondary endpoints included response rate (RR) and overall survival (OS). Neuropilin-1 (NRP1) and -2 (NRP2) mRNA expression was evaluated in archived tumor.

Results. Thirty-five patients were evaluable for efficacy. Median PFS was 7.2 months; median OS was 10.8 months. RR was estimated at

Figure 1. Percentage of tumor change from baseline per subject. Each bar represents one subject.

Figure 2. Kaplan-Meier progression-free survival plot for patients with metastatic esophagogastric adenocarcinomas according to NRP2 mRNA expression. The relative amount of NRP2 mRNA was normalized to GAPDH mRNA and expressed as $\Delta CT = [CT(NRP2) - CT(GAPDH)]$. Patients were divided based on the median ΔCT NRP2 value. Tick marks indicate patients free of recurrence at their last follow-up.

51.4%. The regimen was tolerable with expected drug class-related toxicities. NRP2 mRNA levels significantly correlated with PFS ($p = 0.042$) and showed a trend toward significance with OS ($p = 0.051$). Nonsignificant trends for NRP1 were noted for higher expression levels and worse outcome.

Conclusions. Bevacizumab can be given safely with chemotherapy in patients with metastatic esophagogastric adenocarcinomas. The combination of capecitabine, oxaliplatin, plus bevacizumab has activity comparable to other bevacizumab-containing regimens in metastatic gastroesophageal cancer. *The Oncologist* 2013;18:271–272

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DISCUSSION

For metastatic/unresectable esophagogastric adenocarcinomas, there are many different chemotherapy options, but a true standard has yet to emerge. Based on clinical use of bevacizumab in a variety of other solid tumors and promising preliminary reports in metastatic gastric cancer, we evaluated the addition of bevacizumab to capecitabine and oxaliplatin in the first-line treatment of metastatic esophagogastric adenocarcinomas.

Overall, this regimen was generally well tolerated. Toxicity was assessed via NCI Common Toxicity Criteria version 3.0. Expected chemotherapy-related toxicities were common, including fatigue, hand-foot syndrome, anorexia, and peripheral neuropathy. These toxicities were readily manageable with standard dose adjustments and supportive care. Grade 3–5 events included grade 3 hypertension ($n = 2$), grade 3 hemorrhage ($n = 1$), grade 3 venous thrombosis ($n = 4$), grade 3 dural-cutaneous fistula ($n = 1$), grade 4 perforation/fistula ($n = 1$) and grade 5 perforation/fistula.

Thirty-five of the 37 treated patients were evaluable for efficacy. With a median follow-up of 328 days, median PFS was 7.2 months (95% C.I.: 5.4–8.5) and median time to progression was 7.2 months (95% C.I.: 6.5–8.5). Median OS for this population was 10.8 months (95% C.I.: 8.7–14.5). RR was estimated at 51.4% (95% CI: 35.5–67.1%), including one complete

response and 17 partial responses. An additional 12 patients had stable disease ranging from 3–15 months duration.

We evaluated the correlation of Neuropilin-1 and -2 (NRP1 and NRP2), transmembrane glycoproteins that interact with several members of the VEGF family, by real-time quantitative RT-PCR in tumors from 33 patients. NRP2 mRNA levels demonstrated a significant inverse correlation with PFS ($p = 0.042$, Cox model with continuous NRP2) and showed a trend toward statistical significance with OS ($p = 0.051$; significance defined as $p = 0.05$). Patients with NRP2 expression greater than the median had shorter PFS and OS compared with patients having NRP2 expression less than the median. While NRP1 mRNA levels were not significantly associated with PFS or OS, non-significant inverse trends were noted for higher expression levels and worse outcome ($p = 0.08$ and $p = 0.18$, respectively).

In conclusion, the combination of capecitabine, oxaliplatin and bevacizumab appears to have moderate clinical activity. NRP2, and to a lesser degree NRP1, were inversely correlated with clinical outcome. Further study is needed to better define the role of these co-receptors in gastric cancer biology and as potential markers of sensitivity and resistance to anti-VEGF therapy.

DISCLOSURES

Author disclosures available online.