Adding erlotinib to bevacizumab/chemoradiotherapy regimen for pancreatic cancer safe, tolerable

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The addition of high doses of erlotinib to the treatment regimen of bevacizumab and capecitabine with radiotherapy seems to benefit patients with locally advanced pancreatic cancer, according to results of a phase I study presented at the American Association for Cancer Research's Pancreatic Cancer: Progress and Challenges conference, held here June 18-21.

"The combination of erlotinib, bevacizumab, capecitabine and radiation was safe, well tolerated and showed promising activity in patients with unresectable, locally advanced pancreatic cancer," said Christopher H. Crane, M.D., professor, program director and section chief, gastrointestinal section, department of radiation oncology, The University of Texas MD Anderson Cancer Center in Houston.

A total of 17 patients with CT-staged, biopsy-proven, nonmetastatic, unresectable, locally advanced pancreatic cancer were enrolled in the phase I clinical trial from March 2008 to October 2010. A combination treatment regimen of bevacizumab, capecitabine and radiotherapy has been previously shown to be safe. The objective of this study was to determine the safety, tolerability and maximum tolerated dose of a combination of erlotinib, bevacizumab and capecitabine given with concurrent radiation.

Two patients were enrolled at dose levels (DLs) one to four, and nine patients at DL five. Following drug escalation, the patients were reassessed for potential surgical resection of their tumors.

"Of five patients who underwent margin-negative resections, four had tumors that were originally deemed unresectable; four were treated at DLs four or five; three patients had excellent pathological responses at pancreatectomy and are alive at 13, 21 and 22 months respectively with no local or distant failures," the researchers wrote in the study.

"We were pleasantly surprised by the long median survival duration (23.6 months from diagnosis) and high degree of pathologic response among the five patients that were able to have surgery," Crane said. "Importantly, there was also a very low toxicity rate. All of the events reported were known effects of the drugs or radiation."

A total of three patients at DL five developed a grade 3 acute toxicity (two with diarrhea and one with rash). Grade 4 or 5 toxicities were not seen. DL four was selected as the recommended dose.

"This is the third single-arm study using erlotinib concurrently with radiotherapy that has resulted in encouraging median survival duration," Crane said. "Based on our results, we suggest further studies are warranted using this combination in patients with locally advanced pancreatic cancer."

More information:

Abstract

Phase I Trial of Radiotherapy with Concurrent Bevacizumab, Erlotinib and Capecitabine for Locally Advanced Pancreatic Cancer (LAPC). Heath D. Skinner, Christopher H. Crane, Sunil Krishnan, Milind M. Javle, Robert A. Wolff, Jason B. Fleming, Marilyn V. Clemons, Mark F. Munsell, Marc E. Delclos, Prajnan Das. University of Texas M. D. Anderson Cancer Center, Houston, TX.

Background: The addition of bevacizumab to chemoradiotherapy (CRT) for LAPC has been shown to be safe. The objective of this study was to determine the safety, tolerability and maximum

tolerated dose (MTD) of the addition of erlotinib to this treatment regimen.

Methods: Seventeen patients with CT-staged biopsy-proven non-metastatic unresectable LAPC were enrolled between March 2008 and October 2010. Prior chemotherapy was permitted. All patients received 50.4 Gy (GTV only) in 28 fractions with concurrent capecitabine, bevacizumab and erlotinib. Dose was escalated using a continual reassessment method. Two patients each were enrolled at dose levels (DLs) 1-4 and 9 patients at DL 5. Bevacizumab was escalated from 5mg/Kg every two weeks (DLs 1-4) to 10mg/Kg (DL 5); erlotinib from 100 mg/day (DLs 1-2) to 150 mg/day (DLs 3-5); and capecitabine from 400mg/m2 twice daily on days of radiation (DL 1) to 600mg/m2 (DLs 2-3) to 825 mg/m2 (DLs 4-5). Reassessment for potential resection was performed 6-8 weeks later.

Results: With a median follow-up of 10 months (range 3-23), no grade 3 toxicities were observed in DLs 1-4. Three (33%) patients at DL 5 developed a grade 3 acute toxicity (2 diarrheas and 1 rash). No grade 4 or 5 toxicities were seen. DL 4, with a posterior probability of 0.122 of dose limiting toxicity, was selected as the MTD. Median survival was 19.4 months and time to distant progression was 9.8 months. Patients treated at DLs 4 and 5 had a median survival of 24 months. Of 5 patients who underwent margin-negative resections, 4 were originally deemed unresectable and 1 was borderline; 4 were treated at DLs 4 or 5 (36% of patients treated at these dose levels); 3 patients had excellent pathological responses (complete response, 5% viable tumor, and 20% viable tumor) at pancreatectomy and are alive at 13, 21 and 22 months respectively with no local or distant failures.

Conclusions: The combination of erlotinib, bevacizumab and capecitabine with radiotherapy for LAPC is safe and tolerable. Both the promising survival and the high rate of resectability at the higher dose levels suggest that this strategy of dual inhibition of growth factor receptor pathways during CRT warrants continued evaluation.

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