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Clinical Trial Report

Phase II Trial of Erlotinib and Docetaxel in Advanced and Refractory Hepatocellular and Biliary Cancers: Hoosier Oncology Group GI06-101

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Abstract

Background Patients with advanced hepatocellular (HCC) and biliary tract carcinomas (BTC) have poor prognosis. While the EGFR pathway is overactive in HCC and BTC, single agent anti-EGFR therapies confer modest activity. Preclinical data showed synergistic antiproliferative and proapoptotic effects between anti-EGFR therapies and taxanes. We conducted a phase I study of erlotinib and docetaxel in solid tumors, and noted good tolerability and sustained complete (5 years +) and partial responses in patients with HCC and BTC. This trial evaluated the efficacy of erlotinib with docetaxel in refractory hepatobiliary cancers.

Methods Eligible patients were allowed to have two prior systemic therapies. Docetaxel 30 mg/m^2 i.v. was administered on days 1, 8, 15, and erlotinib 150 mg was dosed orally on days 2–7, 9–14, 16–28 of each 28-day cycle. The primary endpoint was 16 weeks progression-free survival (PFS), and secondary endpoints included response, stable disease, and overall survival. Tumor samples were analyzed for KRAS gene mutations and E-cadherin expression by immunohistochemistry (IHC). Patients with BTC and HCC were accrued and assessed in separate strata for the efficacy endpoints, but for the two-stage initial design of the study, combined PFS was considered. A Simon optimal two-stage design tested the hypothesis that the 16-week PFS is ≤ 15% (clinically inactive) versus the alternative of ≥ 30% (warranting further study).

Results Twenty-five patients, 14 with HCC and 11 with BTC, were enrolled. Common toxicities were rash (76%), diarrhea (56%), and fatigue (52%), mostly grade 1 or 2. No objective responses were seen. Seven BTC (64%) and 6 HCC patients (46%) had stable disease as best response, with a median duration of 16.1 weeks (95% CI 3.7–56.3) for BTC, and 17.6 weeks (95% CI 8.1–49.8) for HCC. The 16-week PFS was 64% for BTC (95% CI 29.7–84.5), and 38% for HCC (95% CI 14.1–62.8). Median overall survival was 5.7 and 6.7 months for BTC and HCC patients, respectively. BTC patients with grade ≥ 2 rash had higher median PFS (6.2 vs 2.2 months) and OS (14.2 vs 4.2 months). HCC patients with negative/low E-cadherin expression had higher median PFS (6.7 vs 2.1 months) and OS (14.5 vs 4 months).

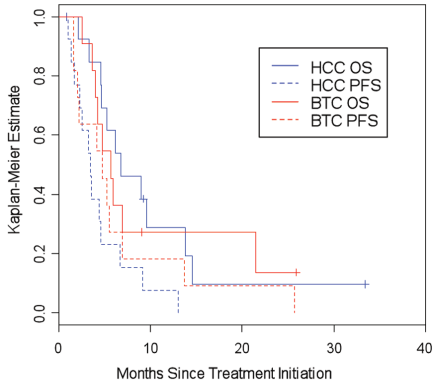
Conclusion Erlotinib with docetaxel met the 16-week PFS ≥ 30% endpoint, but overall survival was comparable to that seen with single-agent erlotinib. With the limitation of small numbers of patients, grade ≥ 2 rash (in BTC), and negative/low E-cadherin expression (HCC) were associated with higher PFS and OS.

Discussion Refractory biliary tract and hepatocellular cancers are difficult to treat, and no chemotherapy or biologically targeted therapies have impacted survival. Based on preclinical synergism and prior phase I data, we conducted a multi-institutional study sequentially combining the EGFR-targeted agent erlotinib with docetaxel.

Results from this study show that the primary endpoint, 16-week PFS of ≥ 30%, was met for the combined group of BTC and HCC patients (as originally planned in the study design), as well as in each disease category: 63.6% for BTC and 38.5% for HCC patients. Nevertheless, no patients attained an objective response and the median survival of 5.7 months for BTC, and 6.7 months for HCC patients (while heavily pretreated), is comparable to that seen with single-agent EGFR-targeted therapies. Safety analysis shows that this regimen was generally well tolerated, and most adverse events were grade 1 or 2. Few patients had reversible grade 3 transaminase elevation (8%), and severe anorexia, fatigue, and rash were uncommon. As expected, patients with grade ≥ 2 rash experienced higher PFS and OS, but this was noted only among the BTC group, likely because too few HCC patients had grade ≥ 2 rash.

KRAS is an important predictive marker for anti-EGFR therapies for lung and colorectal cancers, but for HCC or the heterogeneous group of BTC (with 10–50% KRAS mutations) no significant correlations have been established. We were not able to identify a correlation between KRAS and benefit from erlotinib-based therapy, as all but one HCC patient had KRAS wild type gene status. Preclinical data in multiple tumor types showed that E-cadherin, a signature marker for an "epithelial" tumor phenotype when overexpressed, predicts EGFR pathway activation and determines sensitivity to EGFR-targeted agents. E-cadherin is often seen as a poor prognostic marker when downregulated, as noted during cancer progression. Not all studies demonstrate beneficial effects from E-cadherin overexpression, possibly due to histological expression variability or tumor type specificity for this biomarker. Six BTC and 8 HCC patients had evaluable tumor samples for E-cadherin analysis. While the numbers were small and conclusions should be viewed with caution, negative/low E-cadherin expression was associated with improved PFS and OS for hepatobiliary cancers (most significant in HCC) in this refractory patient population where we expected lower expression levels.

In conclusion, the combination of erlotinib with docetaxel provided a 16-week PFS of ≥ 30% but showed no appreciable differences in overall survival from historical data with single-agent erlotinib. While EGFR represents an important target in this group of malignancies, it is clear that hepatobiliary cancers are heterogeneous, thus a meaningful improvement in survival most likely will require careful treatment selection based on patient tumor's molecular and genetic profiling.



Full Clinical Trial Report, including disclosures, may be found online at: http://clinicaltrialreports.theoncologist.com/reports/t11-253ctr-chiorean

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