Lapatinib in combination with capecitabine plus oxaliplatin (CapeOx) in HER2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma (AC): The TRIO-013/LOGiC Trial

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Background

- HER2 amplification is common in upper GI tract adenocarcinomas including gastric, gastro-esophageal and esophageal cancer.
- Inhibition of HER2 signaling improves clinical outcomes.
- Trastuzumab (Herceptin), a monoclonal antibody against HER2 was recently approved for the use of advanced gastric or gastro-esophageal cancer in combination with chemotherapy based on promising phase III clinical results (Bang, YJ et al, Lancet, 2010).
- Lapatinib ditosylate is a dual anti-EGFR and anti-HER2 tyrosine kinase inhibitor.
- Lapatanib is currently approved for HER2 positive breast cancer and has shown both preclinical efficacy and modest clinical efficacy in small singe agent exploratory studies of HER2+ upper GI tract adenocarcinomas.
- The authors performed a phase III, randomized, double blind trial evaluating the efficacy and safety of lapatinib in combination with capecitabine and oxaliplatin as the first-line treatment of advanced or metastatic HER2+ upper GI tract adenocarcinomas.

Materials and Methods

- All patients had pathologically confirmed adenocarcinoma.
- All subjects had overexpression or amplification of HER2 (IHC2+ and FISH amplified, or IHC 3+, or FISH, CISH, or SISH amplified).
- Subjects were randomized 1:1 to capecitabine and oxaliplatin every 3 weeks (oxaliplatin 130mg/m2 day 1; capecitabine 850mg/m2/BID days 1 — 14), and daily lapatinib (1250mg) or placebo.
- The primary efficacy population comprised all subjects whose tumors were confirmed to be FISH amplified by a central laboratory.
- The primary endpoint was overall survival (OS) of the primary efficacy population.
Secondary endpoints included progression free survival (PFS), overall response rate (ORR) and safety, quality of life (QOL) and molecular/pharmacogenetic analysis.

Materials and Methods

A total of 545 patients from 186 centers in 22 countries were randomized from 2008-2012, and 487 patients had HER2+ centrally confirmed.

The pretreatment characteristics were well balanced between the 2 arms with a median age of 60 years and 40% of patients enrolled were from Asia.

The primary endpoint of this study was not reached with a hazard ratio (HR) for OS of 0.91 (95% CI 0.73, 1.12, p=0.35) with a median survival of 12.2 vs. 10.5 months in the lapatinib vs. control arm.

A pre-specified subgroup analyses showed significant improvements with the addition of lapatinib in Asian patients with an increase in median survival of 10.9 to 16.5 months (HR= 0.68), and those under 60 years with a median survival increase of 9 to 12.9 months (HR=0.69).

The HR for uncensored PFS was 0.86 (95% CI 0.71 - 1.04, p=0.10), with median PFS of 6.0 vs. 5.4 months.

The analysis of PFS censored by the time of subsequent anticancer therapy as per protocol showed a HR of 0.82 (95% CI 0.68, 1.00, p=0.04).

The ORR was 53% in the lapatinib arm and 40% in the control arm.

Toxicity profiles were similar between the two arms except for increased overall diarrhea, and skin toxicity and grade 3+ diarrhea (12 vs. 3%) in the lapatinib arm.

Author's Conclusions

Although well tolerated, the addition of lapatinib to capecitabine and oxaliplatin did not improve overall survival in patients with HER2+ advanced or metastatic upper GI tract malignancies.

Subgroup analysis did reveal that Asian patients and those younger than 60 years might benefit from the addition of lapatinib.

Further clinical and molecular analysis from this trial will help to better define which patients may stand to benefit the most from lapatinib.

Clinical Implications

HER2 is commonly expressed in many gastric, gastro-esophageal and esophageal adenocarcinomas and is a potentially important therapeutic target.

The use of the monoclonal antibody trastuzumab against HER2 has shown clinical efficacy in these patients.

The authors present a randomized trial evaluating the utility of lapatinib in addition to standard chemotherapy for the treatment of HER2+ gastric, gastro-esophageal and esophageal malignancies.

Unfortunately, the trial failed to meet its primary endpoint and there was no OS benefit.

However, there was a significant survival benefit in both Asian and young patients.

Future research needs to explore how to best predict which patients will respond to lapatinib and how best to combine lapatinib with chemotherapy.
● The ongoing molecular analysis of this trial will hopefully provide more of these answers.
● As we learn more about HER2 targeted cancers in upper GI malignancies these therapies can eventually be introduced in the adjuvant or neoadjuvant setting.