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Lapatinib versus lapatinib plus capecitabine as second-line treatment in human epidermal growth factor receptor 2-amplified metastatic gastro-oesophageal cancer: A randomised phase II trial of the Arbeitsgemeinschaft Internistische Onkologie

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Abstract ***Introduction:*** Human epidermal growth factor receptor 2 (HER2) amplification is present in a subgroup of gastroo-esophageal cancers (GCs). HER2 inhibition with trastuzumab has shown to improve outcomes in advanced disease. Lapatinib ditosylate (LAP), a dual anti-epidermal growth factor receptor (EGFR) and anti-HER2 tyrosine kinase inhibitor with preclinical activity against GC, has been approved in HER2-positive breast cancer. We aimed to study the activity of LAP in HER2-amplified GC.

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Materials and methods: Patients (pts) with HER2-positive (gene amplification or increased copy numbers based on predefined criteria) advanced GC were randomly allocated 1:1 to receive LAP 1250 mg per day 1–21 plus capecitabine (CAP) 2000 mg/m^2 on days 1–14 of a 21-day cycle or LAP 1500 mg monotherapy day 1–21 after having failed on a platinum-based first-line therapy. HER2 status was assessed centrally. The primary end-point was the objective response rate (ORR) as assessed by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). We aimed to include 38 pts per arm to show an interesting response rate of $\geqslant$20% in either of the two arms.

Results: 37 pts were enrolled (18 to LAP + CAP, 19 to LAP). Pts had received a median of three prior treatment lines. 12 pts in the LAP + CAP group (67%) and 12 pts in the LAP group (63%) had received prior trastuzumab. Only two pts (11.1%; 95% confidence interval (CI): 1.37–34.7), both in the LAP + CAP arm, achieved an objective response. The study was closed prematurely for futility. Median time to progression was 42 (95% CI: 38–61) days in the LAP group and 83 (95% CI: 42–86) days in the LAP + CAP group. Other secondary efficacy end-points (progression-free and overall survival) were comparable in the two treatment groups. Rates of diarrhoea were higher with LAP + CAP (61%; 95% CI: 35–83) compared to 26% (95% CI 9–51) with LAP mono, whereas other adverse events were mostly similar between the groups (18 [100%] versus 17 [90%]).

Discussion: Lapatinib showed insufficient activity in HER2-amplified pretreated advanced GC. The safety profile of LAP or LAP + CAP was as expected with some more toxicity in the combination arm. (ClinicalTrials.gov Identifier, NCT01145404).

1. Introduction

Gastro-oesophageal cancer (GC) is one of the leading causes of cancer-related death worldwide [10]. For patients with advanced disease, outcomes are poor with a median survival of 8–12 months with first-line chemotherapy [14]. Despite recent advances in the molecular characterisation of GC, there is still a lack of effective targeted therapies. The human epidermal growth factor receptor 2 (HER2) is overexpressed in approximately 20% of GC patients. In HER2-positive advanced GC, the international phase III 'Trastuzumab for Gastric Cancer' (ToGA) study showed a significant improvement in overall survival with the addition of trastuzumab to cisplatin and a fluoropyrimidine [1]. Consequently, recent practice guidelines recommend trastuzumab in combination with chemotherapy represents as the standard of care for first-line treatment of HER2-positive advanced GC [15,21]. Unfortunately, when primary or secondary resistance occurs survival is short with a median of only 3–4 months [11]. Post-progression chemotherapy with single agents is effective in advanced GC and has now become a proven treatment option, although the benefit compared to active symptom control is moderate with an improvement in median survival of only 1.5 months [4,5,11]. Recently, the results of the RAINBOW trial have demonstrated that the combination of the vascular endothelial growth factor (VEGF) receptor-2 antibody ramucirumab in combination with paclitaxel can prolong survival by 2.2 months compared with paclitaxel alone and represents a new effective treatment option in second-line therapy of advanced gastric cancer [23].

Lapatinib (LAP) is an orally available small molecule that inhibits the tyrosine kinases of HER2 and epidermal growth factor receptor (EGFR). In preclinical studies, lapatinib has shown to selectively inhibit HER2-amplified human GC cells and was synergistic with trastuzumab *in vitro* and *in vivo* [22]. Lapatinib was not cross-resistant with trastuzumab in breast cancer cells [12]. The rationale for combining lapatinib and capecitabine in patients with fluoropyrimidine-refractory tumours was the assumption that lapatinib may restall sensitivity to fluoropyrimidines. However, results of the randomised Phase III TRIO-013/Logic trial could not demonstrate a significant improvement in overall survival with the addition of LAP to capecitabine (CAP) plus oxaliplatin (CapeOx) as first-line treatment of advanced HER2-positive GE cancer [8]. Subsequently, the recently published Asian TyTAN trial also failed to show a significant survival benefit for the combination of LAP and paclitaxel to weekly paclitaxel alone in the second line treatment of HER2-amplified GC [17]. Recent evidence has shown that inhibition of EGFR with monoclonal antibodies has not improved outcomes in advanced GC [13,20].

This phase II randomised study was designed to explore the activity and safety of LAP either given alone or in combination with CAP in advanced HER2-positive GC previously treated with a platinum-based first-line therapy.

2. Methods

This multicentre, open-label, randomised, controlled phase II study was conducted at 11 active institutions