Oesophageal

Trastuzumab with trimodality treatment for oesophageal adenocarcinoma with HER2 overexpression (NRG Oncology/RTOG 1010): a multicentre, randomised, phase III trial

Howard P Safran, Kathryn Winter, David H Ilson, Dennis Wigle, Thomas DiPetrillo, Michael G Haddock, Theodore S Hong, Lawrence P Leichman, Lakshmi Rajdev, Murray Resnick, Lisa A Kachnic, Samantha Seaward, Harvey Mamon, Dayssy Alexandra Diaz Pardo, Carryn M Anderson, Xinglei Shen, Anand K Sharma, Alan W Katz, Jonathan Salo, Kara L Leonard, Jennifer Moughan, Christopher H Crane

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BACKGROUND

Trastuzumab is a monoclonal antibody against HER2 (also known as ERBB2). The primary objective of the NRG Oncology/RTOG-1010 trial was to establish whether trastuzumab improves disease-free survival when combined with trimodality treatment (paclitaxel plus carboplatin and radiotherapy, followed by surgery) for patients with untreated HER2-overexpressing oesophageal adenocarcinoma.

METHODS

NRG Oncology/RTOG-1010 was an open label, randomised, phase III trial for which patients were accrued from 111 NRG-affiliated institutions in the USA. Eligible patients were adults (aged ≥18 years) with newly diagnosed pathologically confirmed oesophageal adenocarcinoma, American Joint Committee on Cancer 7th edition T1N1-2 or T2-3N0-2 stage disease, and a Zubrod performance status of 0.0-2.0. Patients were stratified by adenopathy (no vs yes [coeliac absent] vs yes [coeliac present ≤2.0 cm]) and randomly assigned (1:1) to receive weekly intravenous paclitaxel (50 mg/m2 intravenously over 1.0 h) and carboplatin (area under the curve 2, intravenously over 30-60 min) for six weeks with radiotherapy 50·4 Gy in 28 fractions (chemoradiotherapy) followed by surgery, with or without intravenous trastuzumab (4.0 mg/kg in week one, 2.0 mg/kg per week for five weeks during chemoradiotherapy, 6.0 mg/kg once presurgery, and 6.0 mg/kg every three weeks for 13 treatments starting 21-56 days after surgery). The primary endpoint, disease-free survival, was defined as the time from randomisation to death or first of locoregional disease persistence or recurrence, distant metastases, or second primary malignancy. Analyses were done by modified intention to treat. This study is registered with Clinicaltrials.gov, NCT01196390; it is now closed and in follow-up.

FINDINGS

606 patients were entered for HER2 assessment from 30 Dec 2010 to 10 Nov 2015, and 203 eligible patients who were HER2-positive were enrolled and randomly assigned to chemoradiotherapy plus trastuzumab (n=102) or chemoradiotherapy alone (n=101). Median duration of follow-up was 2·8 years (IQR 1·4-5·7). Median disease-free survival was 19·6 months (95% CI 13·5-26·2) with chemoradiotherapy plus trastuzumab compared with 14·2 months (10·5-23·0) for chemoradiotherapy alone (hazard ratio 0·99 [95% CI 0·71-1·39], log-rank p=0·97). Grade 3 treatment-related adverse events occurred in 41 (43%) of 95 patients in the chemoradiotherapy plus trastuzumab group versus 52 (54%) of 96 in the chemoradiotherapy group and grade 4.0 events occurred in 20 (21%) versus 21 (22%). The most common grade 3.0 or worse treatment-related adverse events for both groups were haematological (53 [56%] of 95 patients in the chemoradiotherapy plus trastuzumab group vs 55 [57%] of 96 patients in the chemotherapy group) or gastrointestinal disorders (28 [29%] vs 20 [21 %]). 34 (36%) of 95 patients in the chemoradiotherapy plus trastuzumab group and 27 (28%) of 96 patients in the chemoradiotherapy only group had treatment-related serious adverse

events. There were eight treatment-related deaths: five (5.0%) of 95 patients in the chemoradiotherapy plus trastuzumab group (bronchopleural fistula, oesophageal anastomotic leak, lung infection, sudden death, and death not otherwise specified), and three (3.0%) of 96 in the chemoradiotherapy group (two multiorgan failure and one sepsis).

INTERPRETATION

The addition of trastuzumab to neoadjuvant chemoradiotherapy for HER2-overexpressing oesophageal cancer was not effective. Trastuzumab did not lead to increased toxicities, suggesting that future studies combining it with or using other agents targeting HER2 in oesophageal cancer are warranted.