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Docetaxel plus cetuximab as second-line treatment for docetaxel-refractory oesophagogastric cancer: the AGITG ATTAX2 trial

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Background: Cetuximab can reverse chemotherapy resistance in colorectal cancer. This study evaluated the efficacy and safety of the combination of docetaxel and cetuximab as a second-line treatment in docetaxel-refractory oesophagogastric cancer.

Methods: Patients received docetaxel 30 mg m^{-2} on days 1 and 8, every 3 weeks and cetuximab 400 mg m^{-2} on day 1, then 250 mg m^{-2} weekly. Biomarker mutation analysis was performed.

Results: A total of 38 patients were enrolled. Response rates were PR 6% (95% CI 2–19%), s.d. 43% (95% CI 28–59%). Main grade 3/4 toxicities were febrile neutropenia, anorexia, nausea, diarrhoea, stomatitis, and acneiform rash. Median progression-free and overall survival were 2.1 and 5.4 months, respectively. A landmark analysis showed a trend to improved survival times with increased grade of acneiform rash. No *KRAS*, *BRAF* or *PIK3CA* mutations were observed.

Conclusion: Cetuximab and docetaxel achieve modest responses rates, but maintain comparable survival times to other salvage regimens with low rates of toxicity.

We have shown that weekly docetaxel-based regimens have encouraging activity in oesophagogastric cancer, and less haematologic toxicity than 3-weekly regimens (Tebbutt *et al*, 2010). Synergy between taxanes and HER-targeted therapies has been observed in tumour types such as breast cancer (Slamon *et al*, 2001), suggesting that the combination of docetaxel and cetuximab may be of interest. This combination has been administered safely in non-small cell lung cancer patients (Kim *et al*, 2009). Also, cetuximab has been shown to reverse chemotherapy resistance in irinotecan-refractory colorectal cancer (Cunningham *et al*, 2004). This ability to potentiate previously ineffective treatments may offer an important salvage treatment for patients with an otherwise very poor prognosis.

Given this background, this study tested the combination of weekly docetaxel with cetuximab in docetaxel-refractory patients with oesophagogastric cancer.

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MATERIALS AND METHODS

Eligibility. The AGITG ATTAX2 study was approved by the Research Ethics Committee of each participating institution. All patients provided written informed consent.

The ATTAX2 study was available for patients who had participated in the ATTAX study, receiving prior weekly docetaxel (Tebbutt *et al*, 2010) and who progressed either during or within 6 months of docetaxel-based chemotherapy according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0.

Recruitment was initially restricted to patients whose tumours had detectable EGFR as assessed by immunohistochemistry and was amended in December 2005 to include any EGFR status.

Study design and treatment. The ATTAX2 study was a non-randomised, phase II, open-label, multicentre study of a weekly docetaxel schedule with cetuximab.

Patients received: docetaxel (Taxotere; Sanofi-Aventis, Paris, France) 30 mg m^{-2} (or at the last dose given on the ATTAX study, if the dose had been reduced due to toxicity) on days 1 and 8 every 3 weeks; and cetuximab (Erbitux; Merck KGaA, Darmstadt, Germany) 400 mg m^{-2} on day 1, then 250 mg m^{-2} weekly.

Treatment continued in the absence of disease progression or request by the patient or physician.

Evaluation and outcomes. Patients were assessed clinically at baseline, before every treatment cycle, and radiographically every 6 weeks.

Quality of life was assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, Version 3.0 (1 February 2003), together with the oesophageal-specific module (OES 18) or the gastric module (STO 22), depending on the site of disease.

Statistical analysis. The primary clinical endpoint of the study was response rate, as assessed by RECIST version 1.0. Secondary endpoints were overall survival (OS), progression-free survival (PFS), treatment-related toxicity, disease-associated symptoms, and quality of life.

The study used a Simon's two-stage design. The first stage required two or more confirmed responses in the first 17 patients. The second stage involved complete accrual to 35 patients.

Treatment was expected to achieve a response rate of 20%. The lowest limit of therapeutic effect considered to be of interest was a response rate of 6%. Based on these limits, and 80% power and a 95% confidence level, five or more responses in the total cohort were required to determine that a regimen was active.

***KRAS*, *BRAF* and *PIK3CA* analysis.** Mutational status of *KRAS*, *BRAF* and *PIK3CA* was determined using high-resolution melt analysis as described in the Supplementary Information (Krypuy *et al*, 2006; Do and Dobrovic, 2012). Correlation of results to response rate, PFS, and OS was performed using a Cox regression model.

RESULTS

Patient characteristics. Between April 2005 and February 2007, 38 patients were registered from nine institutions in Australia. One patient was ineligible because they had no measurable disease, and two patients had only 8 days of treatment and no subsequent valid RECIST tumour assessments. Baseline characteristics are described in Supplementary Table 1.

Treatment. The median number of cycles delivered per patient was 2, with a range of 1–15. Dose intensities compared with the starting dosages were: docetaxel, 99%; and cetuximab, 99%. Treatment delays of more than 1 week occurred for five patients (13%).

Table 1. Response rate

n **= 35 evaluable points**	**Number**	**% (95 % confidence interval)**
Confirmed complete response	0	0 (0–10)
Confirmed partial response[a]	2	6 (2–19)
Stable disease[b]	15	43 (28–59)
Progressive disease	18	51 (36–67)

[a]Median duration of partial response: 5.2 months [b]Median duration of stable disease: 2.1 months

Efficacy. The interim response analysis met the criterion for the study to continue. Of the 38 final patients recruited, 35 patients were assessable for response, none had a complete response, 2 had a partial response, and 15 had stable disease (Table 1). Tumour progression had occurred within 9 and 13 days of docetaxel in the patients with response, indicating that both cases were refractory to docetaxel. A waterfall plot of unconfirmed responses showed additional evidence of minor degrees of tumour regression (Figure 1).

At the median follow-up time of 18.9 months, all patients had died. Median PFS was 2.1 months (Figure 2A), and median OS was 5.4 months (Figure 2B).

Toxicity. Toxicity is summarised in Supplementary Table 2. One patient had grade 4 febrile neutropenia. The most significant common adverse events were grade 3 or 4 fatigue, grade 3 anorexia, grade 3 diarrhoea, grade 3 nausea, grade 3 acneiform rash, and grade 3 stomatitis.

A landmark analysis showed a trend to improved survival times with increased grade of acneiform rash (grade 0 *vs* grade 1: HR 0.73 (95% CI 0.32–1.66), $P = 0.45$; grade 0 *vs* grade 2/3: HR 0.58 (95% CI 0.22–1.50), $P = 0.26$) (Figure 3).

Disease-associated symptoms and quality of life. Improvement in a specific disease-associated symptom or aspect of quality of life was defined as an increase of 10 points or more for that questionnaire item for more than 3 weeks. Improvement in global health and quality of life was seen in 27% of patients, nausea and vomiting in 18%, fatigue in 33%, and pain in 40%, respectively. The most striking improvement was in dysphagia in patients with oesophageal disease, among whom 50% improved, compared with 27% of patients with gastric disease.

***KRAS*, *BRAF*, and *PIK3CA* analysis.** Of the 38 patients that participated in the study, 37 consented to tissue banking. Of 31 samples received, 3 further samples were unsuitable for testing. Of the 28 samples from which DNA was extracted, genotyping was not possible for almost half of these samples due to sample size, tumour purity, DNA quality and so on. Of the genotyped samples, 100% were wild type for *KRAS* exon 2 (18 out of 18 patients), *BRAF* exon 15 (17 out of 17 patients), and *PI3KCA* exon 20 (18 out of 18 patients). Of the ATTAX2 responders, one was wild type for *KRAS* exon 2, *BRAF* exon 15, and *PI3KCA* exon 20, and it was not possible to genotype the other responder for the reasons already stated. Therefore, no correlation between ATTAX2 response and *KRAS, BRAF,* or *PI3KCA* status could be determined.

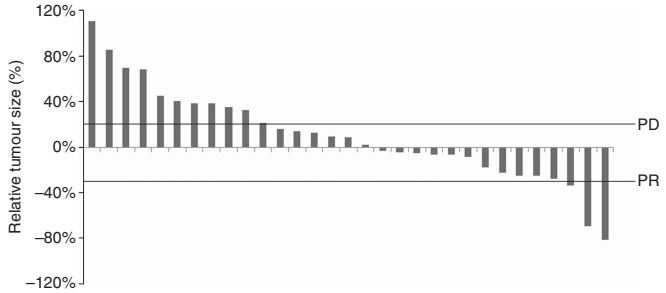

Figure 1. Waterfall plot showing tumour size at best unconfirmed response relative to tumour size at baseline ($n = 31$).

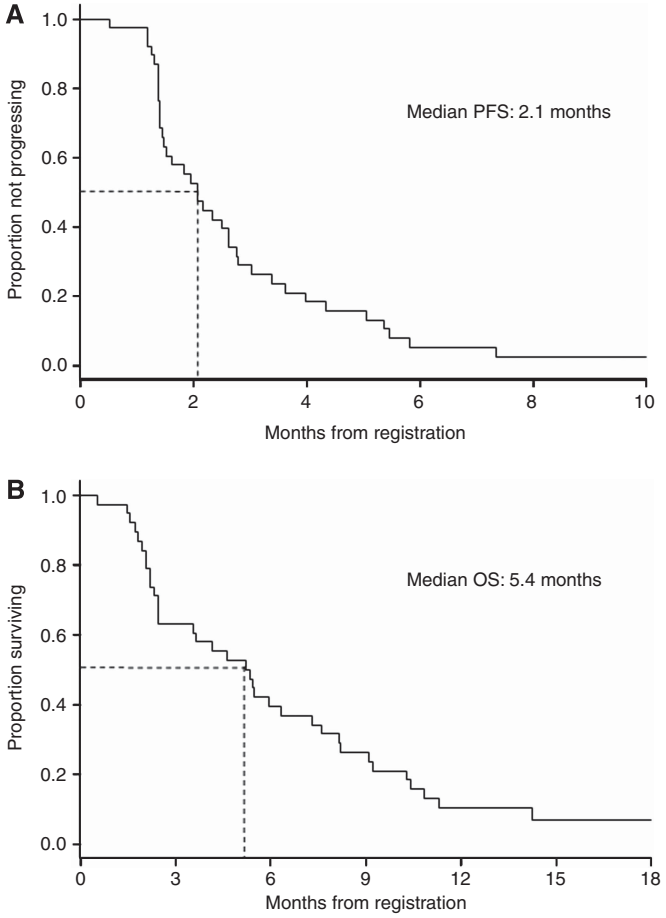

Figure 2. Kaplan–Meier curves of progression-free survival (**A**) and overall survival (**B**) for advanced oesophagogastric cancer patients treated with weekly docetaxel plus cetuximab ($n = 38$).

DISCUSSION

There is no consensus therapy for second-line treatment of advanced oesophagogastric cancer. Randomised studies support use of an irinotecan- or taxane-based regimen, with a recent phase III study of 193 patients demonstrating improved OS (median 5.1 months chemotherapy *vs* 3.8 months BSC, HR 0.63) (Kang *et al*, 2012).

The ATTAX2 study has shown that the combination of weekly docetaxel with cetuximab is a feasible treatment combination regimen for docetaxel-refractory advanced oesophagogastric cancer, with manageable rates of grade 3/4 toxicities. The observed response rate, median PFS and OS times are modest, but it is important to bear in mind that the patient population enrolled has a relatively poor prognosis. In this context, the combination of docetaxel and cetuximab appeared to demonstrate a level of activity, as there was tumour regression on waterfall plots and the patient population achieved an OS time comparable to other second-line studies. It is notable that responses occurred despite progression soon after docetaxel, suggesting that the activity is related to the EGFR inhibitor either alone or in combination.

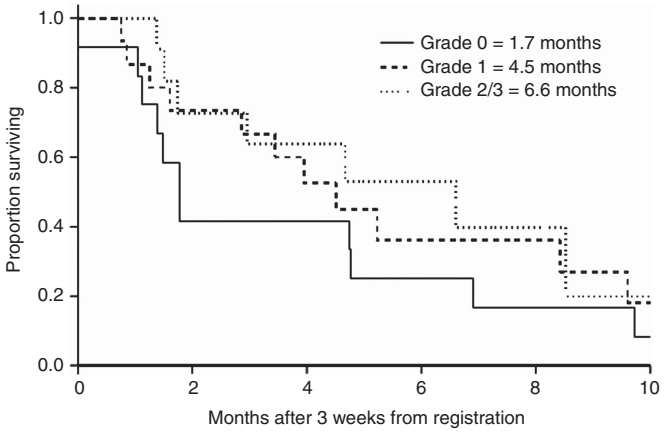

Figure 3. Kaplan–Meier curves of progression-free survival for patients with grade 0, grade 1 and grade 2/3 acneiform rash ($n = 38$).

The role of EGFR inhibitors in oesophagogastric cancer is however somewhat uncertain, as two recent phase III studies have failed to show any evidence of improved outcomes in the first-line setting (Carter, 2012; Waddell *et al*, 2012). In addition, a randomised study of gefitinib in the second-line setting of oesophageal cancer showed improved PFS to a modest extent, but did not affect OS (Ferry *et al*, 2012). Furthermore, a recently published phase II study showed minimal activity for cetuximab monotherapy in second line (RR 3%, PFS 1.6 months, OS 3.1 months) (Chan *et al*, 2011).

Many studies using a range of EGFR inhibitors have noted a correlation between better clinical outcomes and the development of rash (Susman, 2004; Bonner *et al*, 2010; Gatzemeier *et al*, 2011; Saridaki *et al*, 2011; Fleming *et al*, 2012). Although, it did not achieve statistical significance, our data is also in keeping with these observations with a similar trend to superior outcomes using a landmark analysis, suggesting that rash may also be a pharmacodynamic marker of benefit with EGFR inhibitors in oesophagogastric cancer.

We undertook an exploratory analysis of biomarkers as potential predictors of clinical benefit in this study. However, in keeping with other studies (refer to COSMIC), the rate of *KRAS*, *BRAF*, and *PI3KCA* mutations in this disease was very low, which precludes any definitive conclusions being drawn.

In conclusion, this study has demonstrated some activity for the combination of cetuximab and docetaxel in docetaxel-refractory oesophagogastric cancer. The degree of benefit is modest, but is in keeping with other studies in the second-line setting in this disease.

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Trial registration: The trial was registered with the ANZCTR as trial number ACTRN12606000181505.

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Supplementary Information accompanies the paper on British Journal of Cancer website (http://www.nature.com/bjc)