JBUON 2017; 22(4): 900-904
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

A meta-analysis of clinical trials over regimens with or without cetuximab for advanced gastric cancer patients

Lianhua Ji[1,2], Dongying Gu[1], Xinguang Tan[2], Hui Sun[2], Jinfei Chen[1]

[1]Department of Oncology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China; [2]Department of Oncology, Pukou Center Hospital, Nanjing, China

Summary

Purpose: *To evaluate the efficiency and toxicity of treatment with or without cetuximab in patients with advanced gastric cancer (AGC).*

Methods: *Randomized phase III clinical trials (RCTs) on chemotherapy with or without cetuximab for AGC were searched in PUBMED and CNKI. A total of 874 patients were analyzed for their overall survival (OS), disease control rate (DCR), and toxicity. Reported hazard ratio (HR) with 95% CI from each study were used as the primary outcome measure.*

Results: *Three RCTs were detected on chemotherapy with or without cetuximab regimens for AGC. Chemotherapy plus cetuximab was not significantly advantageous over chemotherapy alone for OS rate and DCR odds ratio (OR) (OS: OR=0.89, 95% CI=0.50-1.56; DCR:OR=1.11, 95% CI=0.78-1.59). However, haematological toxicity and neutropenia were lower in the experimental group (chemotherapy plus cetuximab) than in the control group (chemotherapy alone) (OR=0.65, 95% CI=0.50-0.84). No evidence of publication bias was found in this study.*

Conclusion: *Adding cetuximab to chemotherapy does not improve OS or DCR compared with chemotherapy alone. Cetuximab-containing combination chemotherapy can reduce the risk of neutropenia.*

Key words: *advanced gastric cancer, cetuximab, chemotherapy, meta-analysis*

Introduction

The morbidity and mortality of gastric cancer continues to decline in recent years [1]. However, gastric cancer is still the third common cancer in the world [2]. It is one of the leading causes of cancer-related death globally. There are several kinds of gastric cancer treatments such as surgery, radiotherapy and chemotherapy [3]. Resection of disease has been accepted as one of the most important and effective treatments. However, most patients are diagnosed as AGC, which bears poor prognosis with only 30-50% of 5-year survival [4]. Therefore, treatment of AGC remains challenging. In order to improve survival outcomes of patients with AGC, several studies were conducted to compare chemotherapy with or without cetuximab [5-10].

Cetuximab is a recombinant chimeric monoclonal antibody directed against the human epidermal growth factor receptor (EGFR). Increased levels of EGFR have been associated with poor prognosis in gastric cancer [11]. Overexpression of EGFR has been reported in AGC and gastric cancer seems to be a good candidate for chemotherapy combined with anti-EGFR drugs [12]. Based on the above research results, we can infer that both chemotherapy with or without cetuximab are effective treatment methods to improve the survival of patients with gastric cancer. But patients subjected to chemotherapy combined with cetuximab suffer of higher toxicity and higher treatment cost than when receiving chemotherapy alone.

Correspondence to: Jinfei Chen, PhD. Department of Oncology, Nanjing First Hospital, Nanjing Medical University, 68 Changle Road, Nanjing, 210006, China.
Tel: +86 25 87726242, Fax: +86 25 87726234, E-mail: jinfeichen@sohu.com; 252850185@qq.com
Received: 03/01/2017; Accepted: 24/01/2017

The efficiency of the two kinds of therapies is still unclear. To choose the best treatment plan for patients diagnosed with AGC, we performed a meta-analysis of all available published RCTs and evaluated the efficacy of the two treatment methods and the safety of cetuximab.

Methods

Literature search

All published studies were searched in PUBMED and CNKI up to January 2016. Reference articles and previous systematic evaluations were also looked for other relevant trials (Table 1). The following key words were included in the search strategy, which combined gastric, cancer, cetuximab, randomized, trials. The RCTs included in the meta-analysis should meet the following criteria: (i) patients were pathological diagnosed with AGC; (ii) studies comparing chemotherapy plus cetuximab to that without cetuximab: mono and combined chemotherapy with cetuximab vs mono and combined chemotherapy without cetuximab; (iii) RCTs, and review or prospective controlled research. A standardized form was used by two reviewers for independent evaluation in the research contained in this study. Comprehensive review was done for each article to eliminate repetitions.

Table 1. Trials comparing cetuximab containing and non-cetuximab containing chemotherapies, treatment schedules and quality of each trial

Study	*Regimen*	*Patients, n*	*DCR (%)*
Lordick et al.	Cetuximab + capecitabine and cisplatin	397	83.6
	Capecitabine and cisplatin 23 (65.7)	378	83.9
Zhang et al.	Cetuximab + S-1 and oxaliplatin	31	87.1
	S-1 and oxaliplatin	25	76
Meng et al.	Cetuximab + 5-Fu + irinotecan	24	79
	5 FU+irinotecan	19	57.9

Statistics

OS was used as the main outcome measurement. Secondary outcome measurements evaluated were DCR and toxicities. HR and 95% CI from given data, directly or indirectly, estimated the effect of related measures. Appropriate data were extracted for the estimation of the log HR and its variance as previously described [13,14]. Standard techniques for meta-analysis were used to calculate the pooled estimates [15]. The meta-analysis was performed via a fixed-effects model or a random-effects model. Heterogeneity was tested using the Cochrane Q statistic test and was quantified with the I^2 score [16]. Heterogeneity was considered statistically significant when $p<0.05$. Begg's and Egger's tests were used to evaluate the publication bias of the studies [15,17,18]. All tests were two-sided, and the analyses were conducted using the Stata 8.2 (Stata Corp LP, College Station, TX).

Results

There were 3 randomized phase III trials in this meta-analysis, including one European [19] and two Chinese [20,21]. These trials included 874 patients with AGC, of which 452 received chemotherapy containing cetuximab. We evaluated the treatment schedule and quality of each trial (Table 1).

Overall survival

The OS rate was reported in two trials [19,20], during which 452 patients received chemotherapy with cetuximab while 422 patients received chemotherapy alone. However, only one trial (EXPAND) [19] reported the HR of outcome. The other two trials [20,21] showed that the median OS of the experimental and control group was 14.0 and 12.2 months, without significant difference (p=0.698, I^2=0.0%; Figure 1).

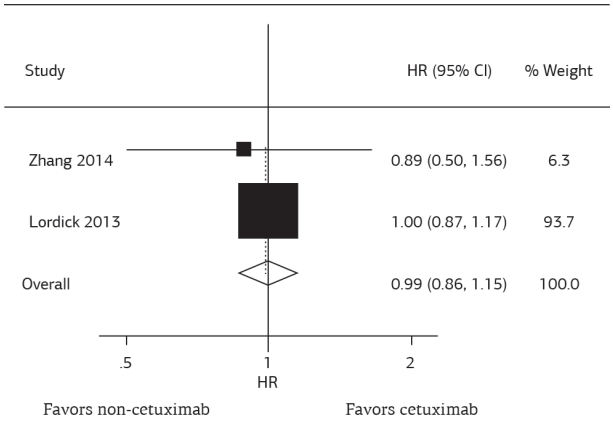

Figure 1. Overall survival of patients with advanced gastric cancer after chemotherapy containing cetuximab and chemotherapy alone. HR: hazard ratio.

Disease control rate

The DCR ranged between 79-87.1% in patients treated with chemotherapy with cetuximab and 57.9-83.9% in those with chemotherapy alone. Meta-analysis of the pooled data demonstrated that the DCR was not significantly different between the two therapies (OR=1.11, 95% CI=0.78 -1.59, p=0.548; Figure 2). Also, no significant heterogeneity was found in all trials (p=0.222, I^2=33.5%).

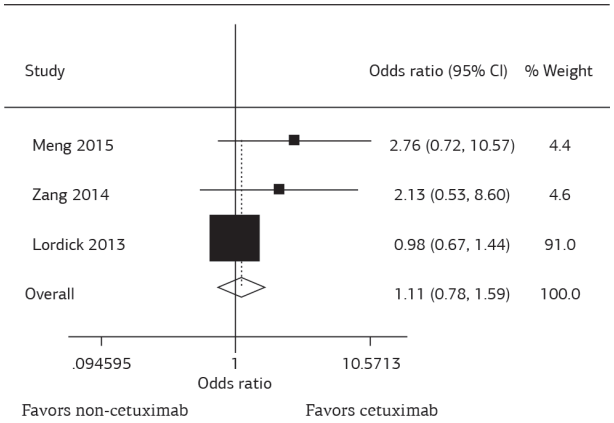

Figure 2. Disease control rate of patients with advanced gastric cancer after cetuximab containing and non-cetuximab-containing combination chemotherapy.

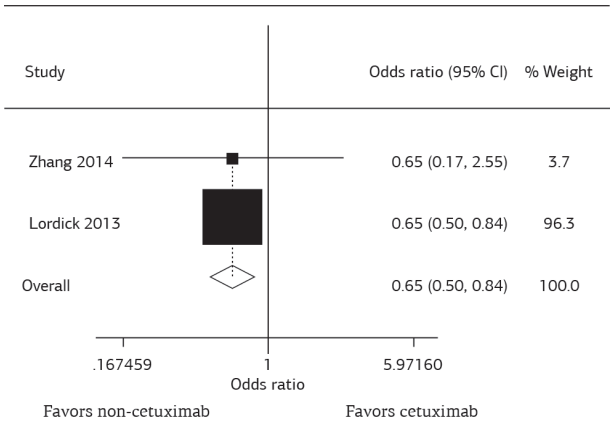

Figure 3. Neutropenia in patients with advanced gastric cancer after cetuximab-containing and non-cetuximab-containing chemotherapy.

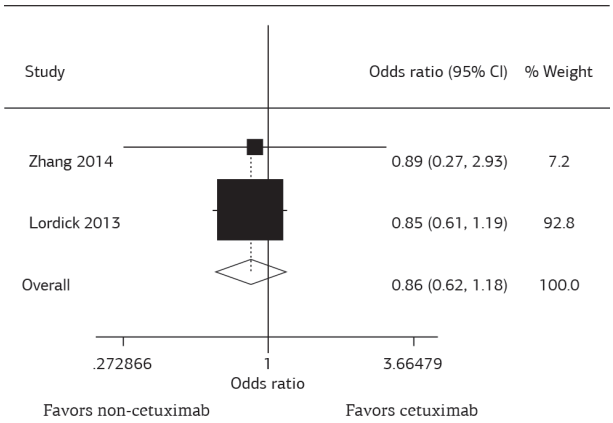

Figure 4. Thrombocytopenia in patients with advanced gastric cancer after cetuximab-containing and non-cetuximab-containing chemotherapy.

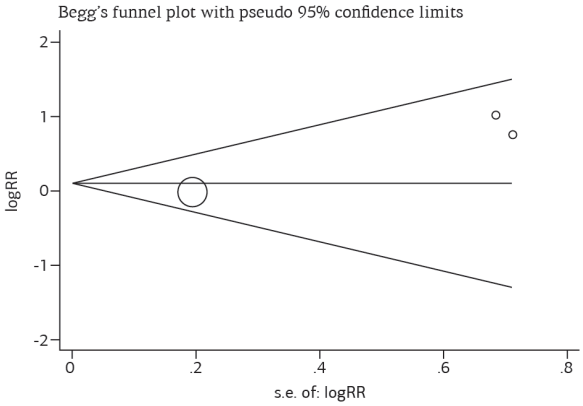

Figure 5. Begg's funnel plot and Egger's linear regression test showing the potential publication bias in DCR of advanced gastric cancer. RR: Risk ratio.

Toxicity

Toxicity was analyzed in all trials. Neutropenia was lower in patients after chemothetapy with cetuximab than those after chemotherapy alone (OR=0.65, 95% CI=0.50-0.84, p=0.001; Figure 3). Other toxicities such as thrombocytopenia was similar in patients after chemotherapy with cetuximab and chemotherapy without cetuximab (OR=0.86, 95% CI=0.62-1.18, p=0.3444; Figure 4). No significant differences in toxicity was found except for diarrhea.

Publication bias

Publication bias was studied by plotting Begg's funnel graph of OR. From the shape of the funnel figure, no publication bias was found (Figure 5) concerning the three endpoints (OS rate, DCR, and toxicity).

Discussion

In this meta-analysis, we estimated the relative efficacy and safety of chemotherapy with or without cetuximab for treating AGC. It was found that chemotherapy with cetuximab did not prolong the OS and DCR rates of patients with AGC. However, the toxicity between the two groups showed more neutropenia in the control group.

The present systematic review poses the question whether chemotherapy with cetuximab is better than chemotherapy alone for AGC patients. EGFR is expressed in gastric cancer and is associated with poor prognosis. Cetuximab is an anti-EGFR monoclonal antibody and adding cetuximab to first-line chemotherapy can improve the clinical outcome of patients with wild-type KRAS metastatic colorectal cancer [22,23], advanced non-small-cell lung cancer [24], and recurrent or metastatic squamous-cell carcinoma of the head and neck [25]. There are several phase II studies [5-10] of cetuximab plus various first-line chemotherapy regimens with response rates of 41–65%. There were also several phase III RCTs [19-21] aiming to assess the efficacy and safety of cetuximab in first-line chemotherapy in patients with unresectable advanced or metastatic gastric

adenocarcinoma . The findings of a European RCT [19] showed that adding cetuximab to capecitabine and cisplatin did not improve PFS compared with chemotherapy alone . However, Meng et al. [21] performed a randomized phase III trial of cetuximab combined with 5-FU and irinotecan for patients with HER2 positive AGC, and reported that the response rate and DCR of patients in the chemotherapy plus cetuximab group was higher than those in the chemotherapy alone group.

Factors such as limited number of trials, the different standards, methods or evaluation criteria used could lead to inconsistent results. To comprehensively evaluate the advantages and disadvantages of chemotherapy combined with cetuximab or not for patients with AGC, we conducted a meta-analysis of published data of related researches.

However, this study has a number of limitations. First, there were only 3 RCTs meeting the inclusion criteria, thus reducing the reliability of the analysis. Second, in these 3 included articles, the chemotherapy options to combine with cetuximab were different from each other. In these 3 articles cetuximab was combined with capecitabine and cisplatin, S-1 and oxaliplatin, 5-FU and irinotecan, which may be potentially heterogeneous. Finally, one RCT included Asian patients and the sample size was small, showing the need for more high-quality and large-sample RCTs to confirm the results of this meta-analysis.

Conflict of interests

The authors declare no confict of interests.

References

1. Kelley JR, Duggan JM. Gastric cancer epidemiology and risk factors. J Clin Epidemiol 2003;56:1-9.
2. Shin A, Kim J, Park S. Gastric cancer epidemiology in Korea. J Gastr Cancer 2011;11:135-140.
3. Orditura M, Galizia G, Sforza V et al. Treatment of gastric cancer. World J Gastroenterol 2014;20:1635-1649.
4. Persiani R, D'Ugo D, Rausei S et al. Prognostic indicators in locally advanced gastric cancer (LAGC) treated with preoperative chemotherapy and D2-gastrectomy. J Surg Oncol 2005;89:227-236; discussion 237-238.
5. Pinto C, Di Fabio F, Barone C et al. Phase II study of cetuximab in combination with cisplatin and docetaxel in patients with untreated advanced gastric or gastro-oesophageal junction adenocarcinoma (DOCETUX study). Br J Cancer 2009;101:1261-1268.
6. Richards D, Kocs DM, Spira AI et al. Results of docetaxel plus oxaliplatin (DOCOX) +/- cetuximab in patients with metastatic gastric and/or gastroesophageal junction adenocarcinoma: results of a randomised Phase 2 study. Eur J Cancer 2013;49:2823-2831.
7. Han SW, Oh DY, Im SA et al. Phase II study and biomarker analysis of cetuximab combined with modified FOLFOX6 in advanced gastric cancer. Br J Cancer 2009;100:298-304.
8. Lordick F, Luber B, Lorenzen S et al. Cetuximab plus oxaliplatin/leucovorin/5-fluorouracil in first-line metastatic gastric cancer: a phase II study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Br J Cancer 2010;102:500-505.
9. Kim C, Lee JL, Ryu MH et al. A prospective phase II study of cetuximab in combination with XELOX (capecitabine and oxaliplatin) in patients with metastatic and/or recurrent advanced gastric cancer. Investig New Drugs 2011;29:366-373.
10. Han SW, Oh DY, Im SA et al. Epidermal growth factor receptor intron 1 CA dinucleotide repeat polymorphism and survival of advanced gastric cancer patients treated with cetuximab plus modified FOLFOX6. Cancer Sci 2010;101:793-799.
11. Kopp R, Ruge M, Rothbauer E et al. Impact of epidermal growth factor (EGF) radioreceptor analysis on long-term survival of gastric cancer patients. Anticancer Res 2002;22:1161-1167.
12. Garcia I, Vizoso F, Martin A et al. Clinical significance of the epidermal growth factor receptor and HER2 receptor in resectable gastric cancer. Ann Surg Oncol 2003;10:234-241.
13. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Statist Med 1998;17:2815-2834.
14. Williamson PR, Smith CT, Hutton JL, Marson AG. Aggregate data meta-analysis with time-to-event outcomes. Statist Med 2002;21:3337-3351.
15. Chen J, Daggett H, De Waard M, Heinemann SH, Hoshi T. Nitric oxide augments voltage-gated P/Q-type Ca(2+) channels constituting a putative positive feedback loop. Free Radical Biol Med 2002;32:638-649.
16. Higgins JR, Thomson SG, Deeks JJ et al. Measuring inconsistency in metaanalyses. BMJ 2003;327:557-560.
17. Handoll HH. Systematic reviews on rehabilitation interventions. Arch Phys Med Rehabil 2006;87:875.
18. Thakkinstian A, McElduff P, D'Este C, Duffy D, Attia J. A method for meta-analysis of molecular association studies. Statist Med 2005;24:1291-1306.
19. Lordick F, Kang YK, Chung HC et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol 2013;14:490-499.

20. Zhang ZD, Kong Y, Yang W et al. Clinical evaluation of cetuximab combined with an S-1 and oxaliplatin regimen for Chinese patients with advanced gastric cancer. World J Surg Oncol 2014;12:115.
21. Meng W. Clinical evaluation of cetuximab combined with 5-FU and irinotecan for the patients with advanced gastric cancer .Chin J Integr Trad West Med Dig 2015;23:731-735.
22. Bokemeyer C, Bondarenko I, Hartmann JT et al. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. Ann Oncol 2011;22:1535-1546.
23. Van Cutsem E, Kohne CH, Lang I et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol 2011;29:2011-2019.
24. Pirker R, Pereira JR, Szczesna A et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 2009;373:1525-1531.
25. Vermorken JB, Mesia R, Rivera F et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116-1127.