Int J Clin Exp Med 2017;10(8):12193-12198
www.ijcem.com /ISSN:1940-5901/IJCEM0047030

Original Article

The efficacy of molecular targeted agents in the treatment of gastroesophageal junction cancer: a systematic review and meta-analysis

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Received November 1, 2016; Accepted June 22, 2017; Epub August 15, 2017; Published August 30, 2017

Abstract: During the past decades, several prospective trials have been conducted to assess the efficacy of molecular targeted agents (MTAs) in the treatment of gastroesophageal junction (GEJ) carcinoma, but the results are controversial. We performed a systematic literature search to identify prospective randomized controlled trials (RCTs) investigating the efficacy of MTAs in the treatment of GEJ carcinoma patients. The endpoint was overall survival (OS) with secondary endpoints progression-free survival (PFS). Statistical analyses were conducted by using Comprehensive Meta Analysis software (Version 2.0). A total of 818 GEJ carcinoma patients from eight RCTs were included for analysis. The pooled results demonstrated that the use of MTAs significantly improved OS (HR 0.67, 95% CI: 0.50-0.92, *P*=0.013) and PFS (HR 0.79, 95% CI: 0.65-0.95, *P*=0.012) in EGJ carcinoma. Subgroup analyses favored greater benefit for OS (HR 0.48) and PFS (HR 0.61) in chemotherapy-refractory patients compared to chemotherapy-native patients (HR 0.94 and 0.91, respectively). No publication bias was detected by Begg's and Egger's tests for PFS (*P*=0.26 and *P*=0.05) and OS (*P*=0.80, and *P*=0.48). Our data indicates that the addition of MTAs to standard therapy in GEJ carcinoma patients significantly improves OS and PFS. Sub-group analysis indicates that improved efficacy is only observed in second-line setting, but not in the first-line setting. Further RCTs with larger samples are needed to confirm these findings.

Keywords: Meta-analysis, gastroesophageal junction cancer, systematic review, molecular targeted agents

Introduction

Although the incidence of gastric is declining, the incidence of gastroesophageal junction (GEJ) carcinoma is increasing [1] and the treatment of GEJ carcinoma remains a significant clinical challenge with median survival of less than 1 year [2, 3]. Chemotherapy remains the cornerstone of treatment for GEJ patients with locally advanced and metastatic disease, but it provides modest survival benefit for these patients. During recent decades, the molecular mechanism underling carcinogenesis and metastasis has been elucidated, which leads to identify novel drugs for the treatment of GEJ carcinoma [4-6]. These drugs target key molecules or signaling pathways which regulate cell growth and proliferation, angiogenesis, and invasion [6, 7]. The initial first line phase III trial with bevacizumab failed to show survival benefit in gastric or GEJ patients, but recently reported phase III trials with ramucirumab and apatinib had shown improved overall survival in these patients. However, both gastric and GEJ patients are included for analysis in these published trials, the role of molecular targeted agents (MTAs) in GEJ patients remains undetermined. Thus, we undertake this systematic review and meta-analysis to evaluate the overall effect of MTAs, in combination with chemotherapy or as monotherapy, in the treatment of metastatic GEJ patients, with respect to the outcomes of overall survival and progression-free survival.

Material and methods

Selection of studies

We conducted a computer-based literature search of Pubmed (data from Jan 2000 to

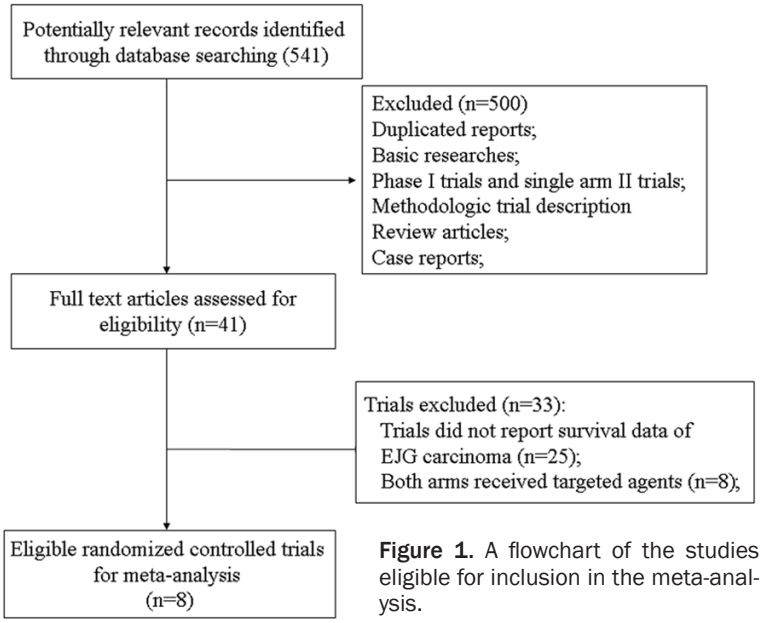

Figure 1. A flowchart of the studies eligible for inclusion in the meta-analysis.

October 2016), Embase (data from Jan 2000 to October 2016) and the Cochrane Library electronic databases(data from Jan 2000 to October 2016), by using the following key words: "bevacizumab", "aflibercept", "sorafenib", "sunitinib", "vandetanib", "axitinib", "pazopanib", "regorafenib", "apatinib", "ramucirumab", "trastuzumab", "cetuximab", "panitumumab", "erlotinib", "gefitinib", "lapatinib", "randomized" and "esophagogastric carcinoma". To identify unpublished trials, we also searched virtual meeting presentations from the American Society of Clinical Oncology (http://www.asco.org/ASCO) conferences. Each publication was reviewed and in cases of duplicate publication we used the most recent and updated report of that trial.

Data extraction and clinical end point

The systematic review and meta-analysis complied with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [8] and any discrepancy between the reviewers was resolved by consensus. We sought to identify randomized controlled trials comparing survival in gastroesophageal junction cancer with the use of MTAs and chemotherapy versus chemotherapy alone, or the use of MTAs as monotherapy with best supportive care. To be eligible for consideration, trials were needed to restrict enrolment to adenocarcinoma patients with primary site located in the gastroesophageal junction carcinoma. Prospective randomized controlled trails comparing therapies with or without MTAs; Trials reported overall survival (OS) or progression-free survival (PFS) data. The quality of reports of clinical trials was assessed and calculated using the 5-item Jadad scale including randomization, double-blinding, and withdrawals as previously described [9].

Data analysis

Statistical analysis of the overall hazard ratio (HR) for OS and PFS was calculated using Version 2 of the Comprehensive Meta Analysis program (Biostat, Englewood, NJ). A statistical test with a *p*-value less than 0.05 was considered significant. HR>1 reflected more deaths or progression in MTAs-containing regimens group, vice versa. Between-study heterogeneity was estimated using the χ^2-based Q statistic [10]. The I^2 statistic was also calculated to evaluate the extent of variability attributable to statistical heterogeneity between trials. If heterogeneity existed, data were analyzed using a random-effects model. In the absence of heterogeneity, a fixed-effects model was used. The presence of publication bias was evaluated by using the Begg and Egger tests [11]. All *p*-values were two-sided. All *CI*s had a two-sided probability coverage of 95%.

Results

Search results

A total of 541 studies were identified from the database search (**Figure 1**). Forty one articles were retrieved in full text and consequently 8 studies were identified [12-19]. The baseline characteristics of these studies were listed in **Table 1**. A total of 818 GEJ patients were available for the meta-analysis. All patients included in the trials were required to have an adequate renal, hepatic and hematologic function. The quality of each included study was roughly assessed according to Jadad scale. Three trials had Jadad score of 5, and five trials had Jadad scores of 3.

Table 1. Baseline characteristics of eight trials in the meta-analysis

Author/year	Phase	Line of treatment	No. of patients for analysis	Tumor location	Treatment regimens	Primary endpoint	Jadad score
Hecht J.R. et al/2016	III	First-line	43	GE junction	Lapatinib+CAP+L-OHP	OS	5
					Placebo+CAP+L-OHP		
Wilke H. et al/2014	III	Second-line	137	GE junction	Ramucirumab+paclitaxel	OS	5
					Placebo+paclitaxel		
Fuchs C.S. et al/2013	III	Second-line	91	GE junction	Ramucirumab	OS	3
					Placebo		
Dutton S.J. et al/2014	III	Second-line	97	GE junction	Gefitinib	OS	5
					Placebo		
Waddell T. et al/2013	III	First-line	169	GE junction	Panitumumab+EPI+L-OHP+CAP	OS	3
					EPI+L-OHP+CAP		
Ohtsu A. et al/2011	III	First-line	103	GE junction	Bevacizumab+chemotherapy	OS	3
					Chemotherapy		
Rao S. et al/2010	II	First-line	72	GE junction	Matuzumab+EPI+DDP+CAP	ORR	3
					EPI+DDP+CAP		
Bang Y.J. et al/2010	III	First-line	106	GE junction	Trastuzumab+chemotherapy	OS	3
					Chemotherapy		

Abbreviation: L-OHP, oxaliplatin; EPI, epirubicin; DDP, cisplatin; CAP, capecitabine; OS, overall survival; ORR, objective response rate.

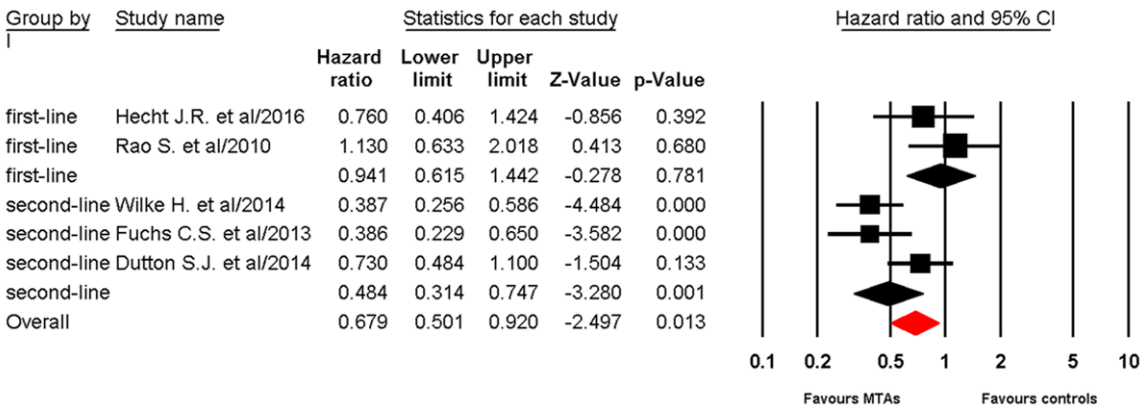

Figure 2. Random-effect of Model of Hazard Ratio (95% CI) of OS associated with therapies with or without MTAs.

Overall survival

Five trials reported OS data of EGJ carcinoma patients. The pooled results demonstrated that MTAs containing therapies significantly improved OS in comparison with non-MTAs containing therapies (HR 0.68, 95% CI: 0.50-0.92, *P*=0.013, **Figure 2**) using a random-effects model (I^2=69.2%, *P*=0.011). Subgroup analysis according to treatment-line (chemotherapy-refractory versus chemotherapy native) indicated that MTAs-containing regimens as second-line therapy significantly improved OS (HR 0.48, 95% CI: 0.31-0.75, *P*=0.001) in patients with EGJ carcinoma, while no significantly improved overall survival benefits was observed in the first-line setting (HR 0.94, 95% CI: 0.62-1.44, *P*=0.78, **Figure 2**).

Progression-free survival

Six trials reported PFS data. The pooled hazard ratio for PFS demonstrated that MTAs-containing regimens significantly improved PFS giving HR 0.79 (95% CI: 0.65-0.95, *P*=0.012, **Figure 3**), compared with non-MTAs containing regimens. There was no significant heterogeneity between trials (I^2=45.8%, *P*=0.10), and the pooled HR for PFS was performed by using fixed-effects model. Sub-group analysis accord-

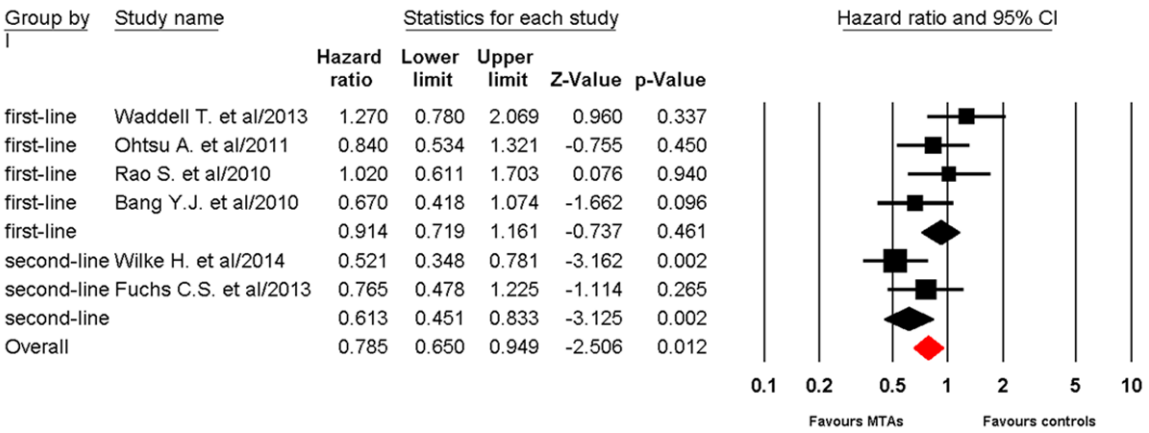

Figure 3. Fixed-effects Model of Hazard Ratio (95% CI) of PFS associated with therapies with or without MTAs.

ing to treatment line favored greater benefit for PFS in second-line settings (HR 0.61, 95% CI: 0.45-0.83, *P*=0.002) compared to first-line settings (HR 0.91, 95% CI: 0.72-1.16, *P*=0.46).

Publication bias

No significant asymmetry was observed in funnel plots (data not shown). In addition, Begg's and Egger's linear regression tests revealed an absence of publication bias (OS: *P*=0.80, and *P*=0.48; PFS:*P*=0.26 and *P*=0.05; respectively).

Discussion

During the past decade, considerable attention has been paid to EGJ carcinoma due to the marked increase in its incidence globally [20]. Despite the improvement in systematic chemotherapy, the clinical outcome of EGJ carcinoma remains poor with a median survival of 8-12 months with first-line chemotherapy [3]. Over the past years, novel targeted agents have been investigated, with or without chemotherapy, in first or subsequent lines, but the results are controversial. To our best knowledge, our study is the first meta-analysis to specially assess the efficacy of MTAs in the treatment of EGJ carcinoma. A total of 818 patients with EGJ carcinoma from eight RCTs are included for analysis. The pooled results demonstrate that the use of MTAs significantly improves OS (HR 0.67, 95% CI: 0.50-0.92, *P*=0.013) and PFS (HR 0.79, 95% CI: 0.65-0.95, *P*=0.012) in EGJ carcinoma. Pre-defined subgroup analyses demonstrates that the most consistent and statistically certain benefit is found when MTAs are used in second-line settings and beyond, and also as monotherapy. This benefit has obvious implications for clinical practice.

Unfortunately, no studies thus far have identified a predictive biomarker to assist patient selection for benefit from MTAs. In the AVAGAST first-line study with bevacizumab [21], high serum VEGF-A and low tissue neuropilin-1 were both shown to be prognostic biomarkers, but not necessarily predictive ones. Other studies had explored other biomarkers (such as VEGFC, VEGFR3, tissue VEGFR2) but these had not been significantly associated with outcome [22, 23].

There are limitations in our study that should be acknowledged. The most significant limitation is the reliance on data in the public domain (including conference presentations), leading to the risk of publication bias. However, the funnel plot does not show significant asymmetry, supporting a low likelihood of publication bias. An individual patient data meta-analysis would increase the ability to detect real differences by subgroups. Second, different targeted agents are included for analysis, which would increase the clinical heterogeneity among included trials, although we pool subgroup analysis according to tumor location. Furthermore, our study could not answer which targeted agent would be the best choice.

In summary, our meta-analysis has identified that the addition of MTAs to standard therapy improves outcomes in EGJ patients and that this benefit appears to be most certain with modern AAs (such as ramucirumab, regorafenib

and apatinib) when used as monotherapy in the chemo-refractory setting.

Acknowledgements

Application Foundation Project of Science & Technology Agency of Sichuan Province (13JC080).

Disclosure of conflict of interest

None.

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