RESEARCH ARTICLE

Meta-analysis of Six Randomized Control Trials of Chemotherapy Plus Anti-HER Monoclonal Antibody for Advanced Gastric and Gastroesophageal Cancer

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Abstract

Background: A meta-analysis was performed to examine the benefit/risk ratio for the addition of anti-HER MoAbs to chemotherapy in patients with advanced gastric and gastroesophageal cancer from six randomized phase II/III trials. Materials and Methods: We searched relative trials from Pubmed, EMBASE, Cochrane library databases, China National Knowledge Infrastructure databases, Google Scholar and the NIH ClinicalTrials. Primary outcomes were overall response rate (ORR), progression-free survival (PFS), overall survival (OS). Secondary outcomes were toxicities. All analyses were performed using STATA 12.0. Results: This meta-analysis included six randomized controlled trials (RCTs) with 2,297 patients and we demonstrated that the anti-HER MoAbs arm did have a positive effect on ORR in the anti-HER MoAbs arm (OR 1.28, 95% CI 1.00-1.64, p=0.01). There was an increasing benefit regarding OS (HR 0.74, 95% CI 0.60-0.88, p<0.05) and PFS (HR 0.72, 95% CI 0.60-0.84, p<0.05) in the anti-HER2 subgroup, but a reduction of OS (HR 1.11, 95% CI 0.87-1.36, p<0.05) and PFS (HR 1.13, 95% CI 0.98 -1.28, P<0.05) in anti-EGFR subgroup. Some grade 3-4 toxicity had a significantly higher incidence in the anti-HER MoAbs arm. There was no significant publication bias for all endpoints. Conclusions: The addition of trstuzumab MoAb to chemotherapy for gastric and gastroesophageal cancer significantly improved outcome of OS and PFS endpoints, while other MoAbs led to no improvement in results. Some adverse events were increased in anti-HER MoAbs arm compared with the control.

Keywords: EGFR antibody - trastuzumab - gastric and gastroesophageal cancer - chemotherapy - meta-analysis

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Introduction

Gastric cancer was the second most common cause of death related to cancer worldwide, with especially high prevalence in Asia. In 2008, 988602 new cases were diagnosed and 737419 people died of this disease worldwide (Ferlay et al., 2010; Jemal et al., 2011). Research showed early-stage gastric and gastroesophageal cancer are curable with a 5-year overall survival rate of 93% by surgical treatment (Sasako, 2003). However, most of gastric cancer patients present with advanced disease when diagnosed and surgery is limited to operate. Chemotherapy is proved to be the most effective treatment. Studies showed that treatment with combination chemotherapy improves outcomes compared with single-drug chemotherapy or no chemotherapy in patients with advanced gastric cancer (Ajani, 2006; Wagner et al., 2006). Several clinical studies proved that Flurouracil-based neoadjuvant chemotherapy (NAC) can safely improve overall survival rate of patients with gastric and gastroesophageal cancer (Ychou et al., 2011; Nordlinger et al., 2013). S-1 is also proved to be an effective adjuvant treatment for East Asian patients who have undergone gastrectomy and S-1 based regimens are associated with acceptable response and toxicity in patients with colon cancer (Sakuramoto et al., 2007; Zhang et al., 2014). However, a meta-analysis indicated that neoadjuvant chemotherapy is not effective in 3-year disease-free survival and the adverse effects in gastrointestinal problems and leukopenia is relative high (Li et al., 2010). Therefore, new treatments showing acceptable toxicity and prolonging overall survival rate are urgently needed.

Recent years, more and more tumor biomarkers have been developed and the targeted therapy is showing great affection in advanced cancers. The human epidermal growth factor (EGF) receptor (HER) family is composed of EGFR/HER-1/ErbB1, HER-2/ErbB2, HER-3/ErbB3, and HER-4/ErbB4. HER family possesses protein tyrosine kinase (PTK) activity and mediates intracellular signaling events leading to cancer cell proliferation, survival, and resistance to therapy (Olayioye et al., 2000; Yarden et al., 2001). The EGFR pathway has been recognized as one

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of the key proliferative pathways which was deregulated during tumorigenesis. EGFR over-expressed in 30% and up to 90% of gastric and oesophageal cancers (Yonemura et al., 1989; Hirono et al., 1995). There are two classes of anti-EGFR agents: the monoclonal antibodies and small-molecule tyrosine kinase inhibitors (Huang et al., 2004; Tabernero, 2007). Panitumumab is a fully human immunoglobulin G2 monoclonal antibody directed against EGFR, which showed survival benefits in OS and PFS in gastric cancer and advanced colorectal cancer (Douillard et al., 2010a; Waddell et al., 2013). Cetuximab is a chimeric monoclonal antibody that binds to the EGFR and blocks the EGFR signaling cascade, producing significant clinical benefit with acceptable toxicity in patients with advanced/metastatic non-small cell lung cancer (NSCLC) (Mendelsohn et al., 2003; Ibrahim et al., 2011), while results showed no significant benefit of OS (HR 1.00; 95% CI 0.87-1.1; p=0.95) and PFS (HR 1.09; 95% CI 0.92-1.29; p=0.32)in the intention-to-treat population with advanced gastric cancer (Lordick et al., 2013). Matuzumab is a humanized anti-EGFR monoclonal antibody (anti-EGFR MoAb). Clinical trial demonstrated that the combination of matuzumab with epirubicin, cisplatin and capecitabine (ECX) chemotherapy does not add any significant activity to this regimen with respect to ORR, PFS and OS in patients with advanced oesophago-gastric cancer (Rao et al., 2010). Trastuzumab is a monoclonal antibody that targets human epidermal growth factor HER2. HER2 gene is over-expressed in 20–25% of invasive breast cancers and is associated with poor disease-free survival. The addition of 1 year of adjuvant trastuzumab significantly improved disease-free and overall survival among women with HER2-positive breast cancer (Slamon et al., 1987; Goldhirsch et al., 2013). HER2 is also reported to be associated with tumor tumorigenesis in gastric cancer (Bang et al., 2010; Sawaki et al., 2012; Shen et al., 2013). There are no trials studying HER3 and HER4 antibody in gastric and gastroesophageal cancer. The role about ORR, OS and PFS of the anti-HER MoAbs in the therapy of gastric and gastroesophageal cancer has not yet been clarified, also, the adverse events (AEs) associated with these agents is different and uncertain (Lenz, 2006; Perez et al., 2008). Actually, the efficacy and safety of anti-HER MoAbs therapy is disputed in gastric and gastroesophageal cancer. We collected the RCTs containing anti-HER MoAbs-based chemotherapy arm and chemotherapy arm. The aim of this meta-analysis was to provide an overall appraisal of the benefit/risk ratio associated with the addition of anti-HER MoAbs to chemotherapy treatment for gastric and gastroesophageal cancers.

Materials and Methods

Search Strategy

We conducted the study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2010). Two authors (Luo and Han) used a broad search strategy independently with key words "gastric/stomach/gastroesophageal/esophagogastric/gastroenterological", "cancer/carcinoma/tumor/neoplasm/adenocarcimoma," and "C-255/Panitumumab/Matuzumab/Nimotuzumab/trstuzumab/Zalutumumab/cetuximab/Erbitux/anti-HER MoAb /anti-epidermal growth factor receptor antibody" in Pubmed (data from 1966to March 2014), EMBASE (data from 1980 to March 2014), Cochrane library databases (up to March 2014) and China National Knowledge Infrastructure databases for relevant trials. An additional search through Google Scholar and the clinical trial registration website (http://www.ClinicalTrials.gov) is conducted to obtain information on the registered RCTs. Each study was reviewed by two authors (Luo and Han) and discrepancies were resolved by the third author (Jiang) to ensure that only the qualified RCTs were included in this meta-analysis.

Selection Criteria

Publications were eligible if they met the following criteria: (1) studies aimed to compare efficacy or safety between anti-HER MoAbs-based chemotherapy and chemotherapy as first-line therapy for patients with advanced gastric and gastroesophageal carcinoma; (2) available data for calculating the efficacy or safety were provided; (3) phage II and III randomized controlled trials. The exclusion criteria were: (1) studies with insufficiently published data for efficacy and safety; (2) phage I clinical trials; (3) retrospective trials, reviews, case reports and comments.

Data Extraction and Outcomes

Data retrieved from the publications included: author's name, year of publication, gender, age, disease stage, treatment, number of patients, median age, OS, PFS, ORR and adverse outcomes of interest. Adverse events were defined as per versions two or three of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) criteria (Colevas et al., 2004). All data were extracted independently by two investigators (Luo and Han), and any discrepancy between the reviewers was resolved by consensus. The data collection was in accordance with the Quality of Reporting of Meta-Analyses statement and we used the Jadad Scale to assess the quality of RCTs. Score ≥3 means high quality and score ≥1, <3 means medium quality (Jadad et al., 1996).

Statistical Analysis

The primary outcome for analysis was OS and PFS using HR with 95% CI and HR>1 reflects more deaths or progression in the anti-HER MoAbs arm (Parmar et al., 1998). For ORR and toxicities, the odds ratio (OR) with 95% CI was used and a benefit outcome in the anti-HER MoAbs arm for response or an unfavorable outcome for toxicities when OR>1. We performed a fixed-effect model when heterogeneity is not significant in trials, otherwise, random-effect model was used and meta-regression is performed to explain some heterogeneity. Heterogeneity was assessed by I^2 inconsistency test and $\chi 2$-based Cochran's Q statistic test in which.I^2 >50% or p<0.05 indicated significant heterogeneity. Publication bias was detected by Begg's test and Egger's test (Begg et al., 1994; Egger et al., 1997). All reported p values were two-sided and p<0.05 was considered significant. This article follows

Table 1. Characteristics of Six Trials Included in the Meta-analysis

Study	Year	Treatment	NO.	Media age (years)	Male (%)	Race (%)			Anti-EGFR-based therapy/control ECOG performance status (%)		Primary site (%)			Disease status (%)		Histological type (%)			Study quality
						White	Asian	Other	0-1	2	Stomach	GOJ	Other	Locally advanced	Metastatic	Intestinal	Diffuse	Mixed	Unknown	
Florian et al	2013	Capecitabine + cisplatin + cetuximab vs Capecitabine + cisplatin	455/449	60/59	75/74	52/55	38/37	9/8	100/100	0/0	83/83	16/16	2/1	4/3	96/97	36/33	17/21	5/6	42/40	2
Akira et al	2012	Trastuzumab + capecitabine + cisplatin vs capecitabine + cisplatin	51/50	63/63.5	78.4/80	0/0	100/100	0/0	100/100	0/0	96/88	4/13	0/0	0/2	100/98	73/84	10/8	8/18	0/0	2
Tom et al	2013	mEOC+panitumumab vs EOC (EOC=epirubicin, oxaliplatin and capecitabine)	278/275	63/62	83/82	NR	NR	NR	94/95	6/5	28/32	34/27	38/40	12/9	88/91	NR	NR	NR	NR	3
Rao et al	2010	ECX+matuzumab vs ECX (ECX=epirubicin, cisplatin and capecitabine)	35 / 36	59/64	69/75	NR	NR	NR	100/100	0/0	40/44	60/56	0/0	0/0	100/100	NR	NR	NR	NR	4
Shen et al	2013	chemotherapy + trastuzumab vs chemotherapy (chemotherapy =capecitabine Or 5-FU + cisplatin)	36/48	58.7/58.2	77.8/81.3	0/0	100/100	0/0	81/81	19/19	81/79	19/21	0/0	6/4	94/96	79/60	8/10	11/27	3/2	1
Bang et al	2010	Trastuzumab + chemotherapy (capecitabine + cisplatin or fluorouracil + cisplatin) vs chemotherapy	294/ 290	59.4/58.5	77/75	39/36	51/54	10/9	90/91	10/9	80/83	20/17	0/0	3/3	97/97	77/74	9/9	14/17	0/0	2

ECOG, Eastern Cooperative Oncology Group. GOJ, Gastro-oesophageal junction

Figure 1. Flow Chart of Trial Selection Process in the Meta-analysis

Figure 2.Summary Statistics and Corresponding Forest Plot for the Hazard Ratio (HR) with 95% CI (Confidence Interval) of Overall Survival. The comparison is between anti-HER MoAbs-based chemotherapy versus chemotherapy

the QUORUM and the Cochrane Collaboration guidelines (http://www.cochrane.de) for reporting meta-analysis. All analyses were performed using the STATA 12.0 package (StataCorp, College Station, TX, USA).

Results

Eligible Studies

We identified 152 potentially relevant trials from our initial search strategies, and excluded 91 trials after a preliminary review of the title. The remaining 62 studies were assessed in abstracts and 45 trials were excluded. Then the remaining 17 trials were evaluated in full-text and 6 RCTs met the inclusion criteria for this meta-analysis (Figure 1), which included 2297 patients with gastric and gastroesophageal cancer. Table 1 summarized the baseline characteristics of the participants and the design of the included studies.

Overall survival

The heterogeneity in all trials regarding OS was significant in fixed model when pooling the HRs. So, a random model was used to pool HR and result in a significant improvement in anti-HER MoAbs group (HR 0.94, 95% CI 0.74-1.14, $p<0.05$), but with a significant heterogeneity ($I^2=63.8\%$, $p=0.017$). At the same time, we used cox regression analysis and find that the different monoclonal antibodies contribute greatly to the heterogeneity. After we divided the trials into two groups, a significant 26% improvement of OS was found in the anti-HER (Trastuzumab) subgroup (HR 0.74, 95% CI 0.60-0.88, $p<0.05$), but a significant 11% reduction of OS in anti-EGFR subgroup (matuzumab, cetuximab, panitumumab) subgroup (HR 1.11, 95% CI 0.87-1.36, $p<0.05$) in random model. The heterogeneity was not significant in each subgroup in both fix and random model (Figure 2).

Progression-Free Survival

There is significant heterogeneity between these studies in fixed model when pooling the HRs. We pooled the HRs in random model and find significant improvement in PFS (HR 0.94, 95% CI 0.72-1.16, $p<0.05$; $I^2=73.3\%$, $P=0.002$). Then we analysis heterogeneity by cox regression analysis and the results turned out to be homogeneous when subgrouped by MoAbs. A significant 28% improvement of PFS was found in the anti-HER2 subgroup (HR 0.72, 95% CI 0.60-0.84, $P<0.05$; $I^2=0.0\%$, $p=0.897$), but a significant 13% reduction of PFS in anti-EGFR subgroup (HR 1.13, 95% CI 0.98 -1.28, $P<0.05$; $I^2=0.0\%$, $p=0.739$, Figure 3).

Overall Response Rate

Data on overall response rate was available in five of the trials. The pooled OR for ORR showed significant benefit in anti-HER MoAb arm (OR 1.21, 95% CI 1.01-1.44, $p=0.036$), but significant heterogeneity exist among the studies even in random model. ($I^2=67.2\%$; $P=0.016$). Actually, the Rao study provided a pretty

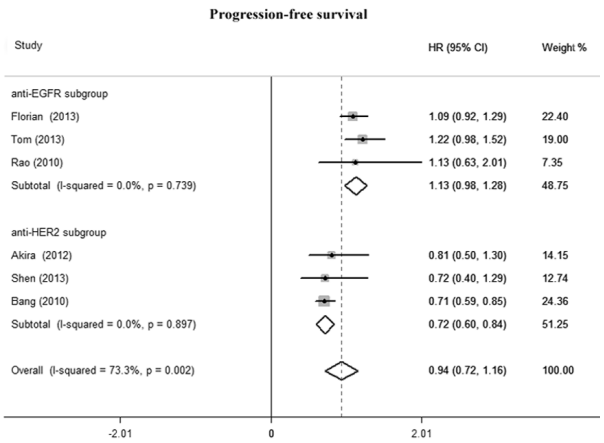

Figure 3. Summary Statistics and Corresponding Forest Plot for the Hazard Ratio (HR) with 95% CI (Confidence Interval) of Progression-free Survival. The comparison is between anti-HER MoAbs-based chemotherapy versus chemotherapy.

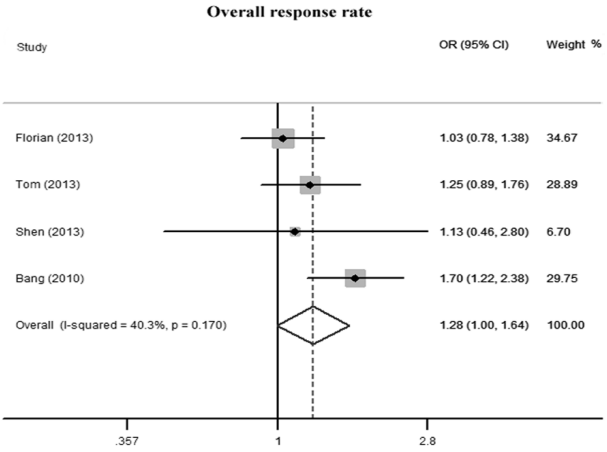

Figure 4. Summary Statistics and Corresponding Forest Plot for the Hazard Ratio (HR) with 95% CI (Confidence Interval) of Overall Response Rate. The comparison is between anti-HER MoAbs-based chemotherapy versus chemotherapy.

Table 2. Grade 3 to 4 Adverse Events of Interest

Adverse event	OR	95% CI	*p* value
Diarrhoea	1.95	1.42-2.68	<0.01
Hypocalcaemia	1.41	1.04-1.92	0.02
Neutropenia	0.66	0.55-0.79	<0.01
Thrombocytopaenia	0.88	0.58-1.35	0.55
Vomiting	0.92	0.67-1.25	0.58
Fatigue	1.45	0.97-2.16	0.07
Febrile neutropenia	0.79	0.51-1.21	0.28
Nausea	0.94	0.66-1.33	0.71
Hand-foot syndrome	1.65	1.06-2.57	0.03
Mucositis	3.9	1.87-7.69	<0.01
Pulmonary embolism	1.79	1.12-2.88	0.02
Renal impairment	1.02	0.25-4.11	0.98
Pyrexia	11.4	0.63-205.9	0.1
Dehydration	1.57	0.60-4.1	0.36
Anorexia	1.14	0.67-1.92	0.64
Rash	30.4	7.40-125	<0.01

CI, confidence interval

lower OR (OR 0.33, 95% CI 0.12–0.87) and this may lead to the heterogeneity among the trials. When excluded the Rao study, the trials turned out to be homogeneous with a much favorable results (OR 1.28, 95% CI 1.10-1.64, p=0.01; I^2= 40.3%, p=0.170, Figure 4), Indicating that anti-HER MoAbs-based chemotherapy result in a significant improvement of overall response.

Grade 3 to 4 Toxicities

As the adverse events (AEs) were generally reported differently, we were unable to carry out a pooled analysis of all AEs. We summarized the Grade 3-4 AEs that at least reported in three trials and the toxic effects were showed in Table 2. Some of grade 3-4 adverse events like diarrhoea, hypocalcaemia, mucositis and rash were increasing after the addition of anti-HER MoAbs to chemotherapy. Only neutropenia was decreased in the treatment arm and AEs like thrombocytopaenia, vomiting, nausea, renal impairment and so on showed no statistically significant difference between the two arms.

Publication Bias

The Begg's test and Egger's test were performed to assess the publication bias. Publication bias was defined as P<0.05. No evidence for publication bias was shown in OS (Begg's p=0.707, Egger's p=0.806), PFS (Begg's p=0.707, Egger's p=0.869), and ORR (Begg's p=0.462, Egger's p=0.376).

Discussion

The benefit of systematic chemotherapy for advanced or recurrent gastric cancer has been known for a long time. Previous trials already demonstrated that ECF (epirubicin, cisplatin, and 5-FU) and DCF (docetaxel, cisplatin, and 5-FU) are superior to best supportive care in terms of survival and preservation of quality of life. (Ajani et al., 2002; Pozzo et al., 2004) While a meta-analysis showed adverse evidence for irinotecan combined chemotherapy therapy on the aspect of OS and AEs in patients with advanced or recurrent gastric cancer (Zeng et al., 2014). To improve the positive impact on the overall tolerability of therapy and potentially survival, targeted therapies represent its special advantage as a promising method. Whole brain radiotherapy concomitant with targeted therapy improved PFS and OS compared with radiotherapy group in brain metastasis patients (Cai et al., 2013). Over the past decade, the EGFR has been primary focus for biologically targeted therapies, with the most active treatments being monoclonal antibodies. Cetuximab is an FDA approved MoAb agent for use in advance or metastatic disease and exhibit efficacy in NSCLC and metastatic colorectal cancer (mCRC) (Butts et al., 2007; Rosell et al., 2008; Van Cutsem et al., 2009). However, No significant increase of OS was observed for panitumumab-FOLFOX4 versus FOLFOX4 in mCRC (median OS, 23.9 v 19.7 months, respectively; HR, 0.83; 95% CI, 0.67 to 1.02; P=.072) (Douillard et al., 2010b). Our meta-analysis was conducted for the main purpose of assessing the possible benefit in terms of OS, PFS and ORR by adding anti-HER MoAbs to chemotherapy. Overall, we noted that the anti-HER MoAbs arm do have an effect on OS (HR 0.94, 95% CI 0.74-1.14, p<0.05), but it may not be credible because of significant heterogeneity in the trials. Then,

we grouping the studies into two subgroups according to the MoAbs after regression analysis and surprised to find that there is a increasing benefit of OS in anti-HER2 subgroup (HR 0.74, 95% CI 0.60-0.88, $p<0.05$), but a significant 11% reduction of OS in anti-EGFR subgroup (HR 1.11, 95% CI 0.87-1.36, $p<0.05$). The reasons for this difference could be that trstuzumab is a MoAb specially targeting HER2 and all patients in anti-HER2 subgroup are diagnosed HER2 positive. The decreasing OS in anti-EGFR subgroup may due to the limited clinical trials in gastric and gastroesophageal cancer and in fact some trials in other cancers draw the similar conclusions (Douillard et al., 2010b; Crosby et al., 2013). The PFS was significantly improved in the anti-HER2 subgroup (HR 0.72, 95% CI 0.60-0.84, $P<0.05$; $I^2=0.0\%$, $p=0.897$), but was significantly reduced in anti-EGFR subgroup (HR 1.13, 95% CI 0.98 -1.28, $P<0.05$). It indicated that trstuzumab could prolong the life span of HER2 positive patients with gastric and gastroesophageal cancer. The result of ORR was different compared with OS and PFS. Addition of anti-HER MoAbs to chemotherapy increased the ORR in patients with gastric and gastroesophageal cancer. When we omitted the study with much lower odds ratio by Rao et al, the ORR was improved by 26% in anti-HER MoAb arm (OR 1.28, 95% CI 1.10-1.64, $p=0.010$). The reasons for low OR (OR 0.33, 95% CI 0.12–0.87) of Rao study is unclear and the limited patients number may contribute to it. Subgroup analysis of OS stratified by sex, ethnic origin, histological subclassification, ECOG performance status and extent of disease was reported only in three trials. We performed the analysis and found that all subgroup results were nearly consistent with the overall results (data not shown).

Some grade 3-4 adverse events were significantly more frequent in patients who received anti-HER MoAbs therapy. As expected, the risk of rash events increased significantly by 30 times. Rash is known to be associated with anti-EGFR therapy in patients receiving cetuximab therapy in many studies (Segaert et al., 2005; Lacouture et al., 2007; Hoag et al., 2009). Other AEs like diarrhoea, hypocalcaemia and mucositis also present a significantly higher incidence. It is similar with another meta-analysis reporting that the use of anti-EGFR MoAbs was associated with a significantly increased risk of toxicity compared with the controls (OR 1.4, 95%CI: 1.04–1.81, $p=0.024$) (Li et al., 2013). In our study, AEs like thrombocytopaenia, vomiting, nausea, renal impairment, fatigue, pyrexia , anorexia and dehydration have no difference between two arms.

Our meta-analysis has some limitations. First, as the individual data and original data were not available, the meta-analysis used pooled data were from published papers. Second, there are several anti-HER MoAbs in this meta-analysis, so different treatment strategy and duration contributed to increase the clinical heterogeneity of the meta-analysis, which made the interpretation of the meta-analysis more problematic. Third, data on quality of life were rarely available and none studies talked about economic costs, which led us not able to draw relative conclusion.

In conclusion, this meta-analysis indicated that the additional use of anti-HER MoAbs to chemotherapy result in significant benefit of ORR endpoint in patients with gastric and gastroesophageal cancer. There is significant benefit of OS and PFS by addition of trstuzumab, while the results were converse in anti-EGFR subgroup. In addition, anti-HER MoAbs-based chemotherapy significantly increased the risk of diarrhoea, hypocalcaemia, mucositis and rash comparing with chemotherapy. We recommended that trstuzumab can be used for HER2 positive gastric and gastroesophageal cancer, but, more high-quality randomized controlled trials of other anti-HER MoAbs are needed to provide more useful information. Meanwhile, the role of treatment dosage should be investigated more detail to improve patient safety profile in future trials.

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