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Systemic Chemotherapy with and without Anti-EGFR Antibody in the First-line Treatment of Metastatic Colorectal Cancer

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Abstract

To define whether or not the addition of anti-EGFR monoclonal antibodies to standard chemotherapy, compared with chemotherapy alone, can improve Overall Survival (OS) and Progression-Free Survival (PFS) in the patients with Metastatic Colorectal Cancer (mCRC), and evaluate the influence of KRAS mutant status on the efficacy of anti-EGFR antibodies in the first-line setting. Medline, Embase and the Cochrane controlled trials register were searched. Six trials were identified, covering a total of 4,988 subjects. A significant benefit of anti-EGFR based regimen as first-line treatment was found for OS (HR, 0.89, 95% CI: [0.80, 0.99]; P=0.04) and for PFS (HR, 0.85 [0.77, 0.94]; P=0.002) among the overall population. The PFS benefit are probably limited to KRAS wild-type patients (HR, 0.83 [0.69, 0.99] P=0.03). No significant benefit was found among KRAS-positive patients: The summary HRs was 1.13 [0.91, 1.39] (P=0.26) for PFS, 1.06 [0.94, 1.19] (P=0.34) for OS, respectively. In conclusion, our data demonstrated that the addition of anti-EFGR antibodies to chemotherapy for mCRC improved overall and progression-free survival for the overall population in the first-line setting. And the benefit from anti-EGFR antibodies as first-line treatment seems to be limited to patients with KRAS wild-type tumors with respect to PFS.

Keywords: Colorectal cancer; Anti-EGFR monoclonal body; First-line therapy

Introduction

Standard systemic chemotherapy has improved the outcome of patients with advanced colorectal rectal cancer (CRC) [1-3], but the disease is still incurable in the majority of patients. Recently, the development of anti-Epidermal Growth Factor Receptor (EGFR) antibody, cetuximab or panitumumab, have provided a new treatment option [4]. Several metastatic colorectal cancer (mCRC) trials have demonstrated the efficacy of anti-EGFR antibodies, as monotherapy [5,6] or combined with chemotherapy [7,8], after the failure of previous chemotherapy treatment. In the first-line setting, building on promising results from phase I/II trial [9], Several phase III studies examining the activity of cetuximab or panitumumab have provided encouraging results [10,11]. First-line treatment with anti-EGFR antibodies has produced a pronounced shift in the treatment framework for patients with mCRC. The substantial clinical benefits of first-line anti-EGFR antibodies treatment for patients with mCRC in the subsequent trials raise this question about whether first-line treatment with the combination of anti-EGFR antibodies and chemotherapy is more beneficial than systemic chemotherapy alone for the overall population or for the molecularly defined subpopulation. With variable results, we did this pooled-analysis to address those issues at least in part. In some trials [10-12], the definition of molecular characteristic of EFGR wild-type mutant has been documented to enable the selection of patients most likely to benefit from particular treatments. We also undertook a subgroup analysis to investigate whether tumor KRAS mutation status was predictive of a favorable outcome to anti-EFGR antibodies plus systemic chemotherapy.

Methods

Literature search strategy

Medline, Embase and the Cochrane controlled trials register were searched for randomized control trials (RCTs) using the medical subject headings of colorectal cancer combining with each of the following terms of phrases: anti-EGFR targeted therapy, anti-EGFR monoclonal antibody, cetuximab, panitumumab. Reference lists from studies selected for this review were also hand-searched.

Selection of studies

Studies were eligible for inclusion in the meta-analysis if they met all the following criteria: (1) they were published up to June 2011 and written in English. (2) They dealt only with patients with mCRC or Advanced Colorectal Cancer (ACC) in the first-line setting. (3) They provided data on PFS and OS regardless of immunohistochemical evidence of EGFR expression. (5) Intervention: anti-EGFR antibody plus the same chemotherapy regimen. (6) Control: systemic chemotherapy alone. Multiple reports of a single study were considered as one publication, and only the most recent and complete data were examined. All potentially relevant articles were reviewed by two independent investigators (L.D.W and Z.X.S.).

Outcome measures

We considered the treatment effects (anti-EGFR treatment group vs. control) on OS and PFS between the groups for the overall population as the primary outcome, for the subpopulation defined by KRAS mutation status as secondary outcome. PFS was measured

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from the date of enrollment, randomization or treatment start until disease progression, relapse, or death. OS was measured from the date of enrollment, randomization or treatment start until death from any cause.

Quality assessment

Two reviewers (L.D.W and Z.X.S.) independently assessed the quality of selected studies using the following criteria: (1) generation of allocation concealment, (2) description of drop-outs, (3) masking of randomization, intervention, outcome assessment, and (4) intention-to-treat (ITT) analyses. Each criterion was rated as yes, no or unclear.

Statistical analysis

All survival data (PFS, OS), were pooled and reported as Hazard Ratio (HR) with genetic inverse variance method. For each included RCT, for the purpose of analysis, we calculated the log rank of HR, and its standard error to perform this meta-analysis. A value less than 1.0 means, the anti-EGFR effect is more favorable in patients with mCRC compared with chemotherapy alone, whereas a value greater than 1.0 means the opposite. We extracted survival data on the treatment effect for overall population, KRAS-mutant and wild-type subpopulation respectively. When not available from the trial reports, they were estimated with the methods proposed by Parmar et al. [13] and described elsewhere [14]. A random effects model was used for all the analyses, which incorporates the variability of results among trials and provided a more conservative estimate of an effect size by producing greater Confidence Intervals (CIs) [15].

We tested for heterogeneity of between-study and between-subgroup with the Cochrane χ^2 test (considered significant at the 0.10 level) and quantified its extent with the I^2 statistic. If significant heterogeneity existed, it would be appropriate to pool the data using random-effects model, but not fixed-effect model.

Begg's funnel plots [16] and Egger's test [17] were used to detect possible publication bias, and meta-regression analysis was employed to detect the source of heterogeneity in the survival analysis (considered significant at the 0.15 level). All meta-analyses were completed using Review Manager (version 5.1, The Cochrane Collaboration, Oxford, England) and Stata ver.10 software (College Station, TX, USA).

Author	N	Therapy Regimen	EGFR analysis*	Publication status
Cutsem et al. [10]	1,198	E: FOLFIRI + cetuximab C: FOLFIRI	Yes	Published
Borner et al. [18]	74	E: XELOX + cetuximab C: XELOX	No	Published
Bokemeyer et al. [12]	337	E: FOLFOX-4 + cetuximab C: FOLFOX-4	Yes	Published
Douillard et al. [11]	1,183	E: FOLFOX-4 + panitumumab C: FOLFOX-4	Yes	Published
Maughan et al. [21]	1,630	E: OX-based therapy + cetuximab C: OX-based therapy	Yes	Published
Tveit et al. [19]	566	E: FLOX + cetuximab C: FLOX	Yes	Abstract

FOLFIRI: Irinotecan, Leucovorin and Fluorouracil; XELOX: Oxaliplatin and Capecitabine; FOLFOX-4: Oxaliplatin, Leucovorin, and Fluorouracil; BSC: Best Supportive Care; OX: Oxaliplatin; FLOX: Oxaliplatin, Leucovorin, and Fluorouracil
*Whether this trial evaluated the efficacy of anti-EGFR antibody on the status of KRAS mutant.

Table 1: Characteristics of included studies.

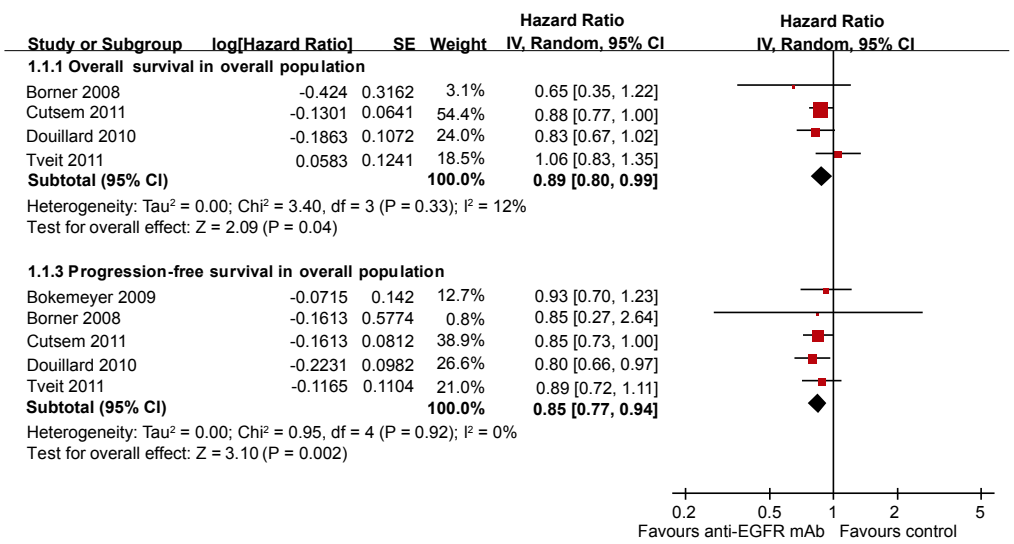

Figure 1: Meta-analysis of the treatment effects (anti-EGFR antibody vs control) on overall survival (top) and progression-free survival (below) with anti-EGFR antibody for the overall population, HR, hazard ratio; CI, 95% confidence interval. Random, random-effects model.

Statistical significance was defined as a P value of less than 0.05 for all tests except those for heterogeneity and regression.

Results

A comprehensive search of Medline, Embase, and the Cochrane controlled trials register and the Science Citation Index yielded 659 articles, of which 6 studies met the predetermined inclusion criteria. The six trials enrolled a total of 4,988 patients. Their characteristics are described in Table 1. Four included RCTs reported final analyses. None was double-blinded. All studies reported intention-to-treat (ITT) analyses and description of drop-outs except for the two [18,19]. We did not find any graphical or statistical evidence of publication bias for all outcomes.

As shown in Figure 1, a significant benefit of anti-EGFR based treatment as first-line treatment was found for overall survival (OS) (HR, 0.89, 95% CI: [0.80, 0.99]; P=0.04) and for progression-free survival (PFS) (HR, 0.85 [0.77, 0.94]; P=0.002) respectively, among the overall population.

As shown in Figure 2, top, the random-effects summary relative HR comparing the treatment effect on PFS between the addition of anti-EGFR antibodies to chemotherapy and systemic chemotherapy alone was 0.83 [0.69, 0.99] (P=0.03), indicating that benefits from anti-EGFR regimens are probably limited to KRAS wild-type patients. However, the survival benefit for the addition of anti-EGFR antibodies to chemotherapy was not detected in Figure 3 (HR, 0.92 [0.78, 1.08], p=0.30). As shown in Figure 2 & 3, pooling 4 analyses of randomized trials of anti-EGFR antibodies plus chemotherapy versus systemic chemotherapy alone, no significant benefit was found for overall or progression-free survival from anti-EGFR based treatment among KRAS-positive patients: The summary HRs were 1.13 [0.91, 1.39] (P=0.26) for PFS, 1.06 [0.94, 1.19] (P=0.34) for OS, respectively.

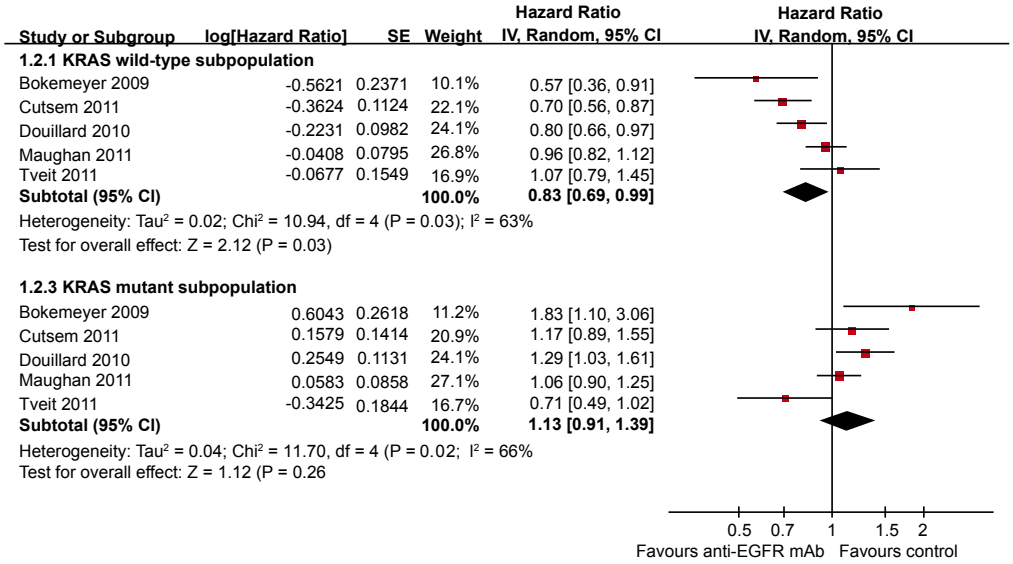

Figure 2: Meta-analysis of the treatment effects (anti-EGFR antibody vs control) on progression-free survival for the subpopulation defined by KRAS mutant status, HR, hazard ratio; CI, 95% confidence interval. Random, random-effects model.

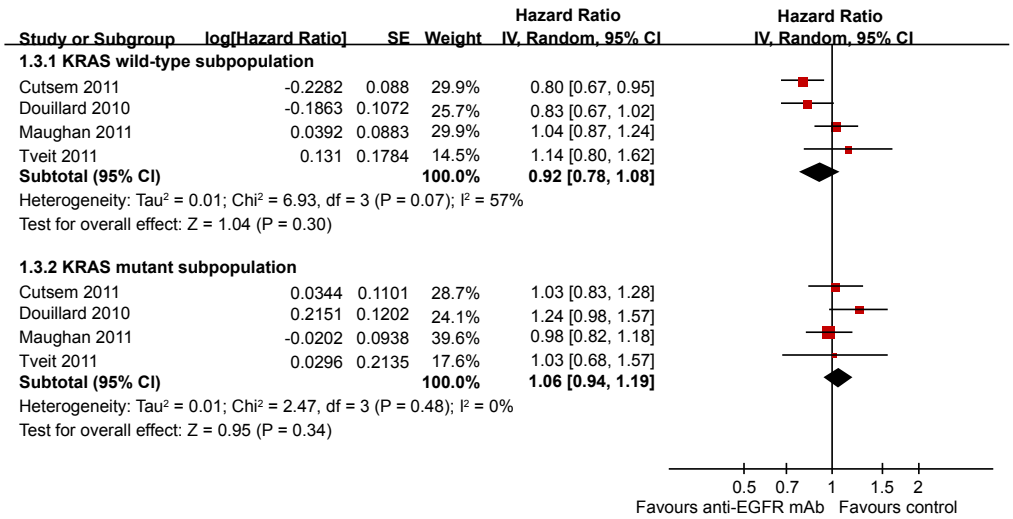

Figure 3: Meta-analysis of the treatment effects (anti-EGFR antibody vs control) on overall survival for the subpopulation defined by KRAS mutant status, HR, hazard ratio; CI, 95% confidence interval. Random, random-effects model.

Patients/covariates	Progression-free survival			Overall surival		
		SE	P-value		SE	P-value
Overall population						
Anti-EGFR antibody	0.0753	0.1146	0.558	0.0871	0.1400	0.597
Concomitant chemotherapy	0.0087	0.1039	0.939	0.0282	0.1558	0.873
Study type (Phase II/III)	-0.0044	0.5796	0.994	0.3125	0.3539	0.470
KRAS wild-type subpopulation						
Anti-EGFR antibody	0.0585	0.2072	0.796	0.1348	0.1980	0.566
Concomitant chemotherapy	0.1950	0.1678	0.329	0.1811	0.1537	0.360
KRAS mutation subpopulation						
Anti-EGFR antibody	-0.1298	0.4689	0.800	-0.2361	0.1380	0.229
Concomitant chemotherapy	0.0242	0.4832	0.963	0.0532	0.1796	0.795

Anti-EGFR antibody: Cetuximab vs. Panitumumab; Concomitant chemotherapy: Platinum vs. Non-platinum based chemotherapy

Table 2: Results of meta-regression analysis for heterogeneity among PFS and OS analyses.

We used meta-regression analysis to further evaluate the effect of concomitant chemotherapy and the specific type of anti-EGFR antibodies, with the results shown in Table 2, which demonstrates that neither was a significant source of heterogeneity for the treatment effect of anti-EGFR antibodies.

Because one of the included trials was phase II study, including samples that were substantially smaller than most of the other studies, we also completed influence analyses by recalculating pooled HRs for the sample on multiple occasions with 1 of the studies removed at each iteration in the overall population. For all studies, these analyses yielded HRs ranging from 0.86 [0.77, 0.95] to 0.91 [0.77, 1.08] for OS analysis and from 0.84 [0.76, 0.94] to 0.88 [0.78, 0.98] for PFS analysis in the overall population.

Discussion

Prior to our analysis, none of the randomized, controlled studies had demonstrated that the addition of anti-EFGR antibodies (cetuximab or panitumumab) to chemotherapy would significantly improve survival compared with conventional chemotherapy for the overall population of unselected patients in the first-line setting, and only one of them indicated PFS benefit. Pooling these survival data enabled us to increase the power of the survival analysis and confirmed a significant and consistent relative overall and progression-free survival benefit with the addition of anti-EGFR antibodies to chemotherapy for patients with mCRC relative to systemic chemotherapy alone as first-line treatment for the overall assessable population.

Influence analysis showed no substantial difference in pooled HRs when any single study was excluded. This was important because the only one phase II study were substantially smaller than most of the other studies.

It has been hypothesized that genetic aberrations of the KRAS genes encoding downstream effectors of EGFR-mediated signaling could be associated with resistance to anti-EGFR antibodies treatment, and preclude any beneficial effects of antibody therapy. In subsequent retrospective studies, the efficacy of both cetuximab and panitumumab has been documented to related with the KRAS mutation status [20]. More recently, several analyses of randomized controlled trials (RCTs) of anti-EGFR monoclonal antibodies have assessed the ability of KRAS mutations to predict clinical outcomes in the first-line setting. We pooled the survival data of the published evidence on the ability of KRAS mutation status to predict outcome to treatment with cetuximab or panitumumab in patients with mCRC. In line with earlier findings, our data indicates that the benefits conferred by anti-EGFR targeted treatment were largely limited to patients with KRAS wild-type tumors with respect to PFS in the first-line setting. And we did not detect any benefit of anti-EGFR antibodies for overall and progression-free survival in patients with KRAS mutant tumors. Unexpected, the survival benefit of anti-EGFR antibodies did not emerge in this pooled-analysis. The imbalance administration of anti-EGFR antibodies in the post-study phase could explain the absence of survival benefit at least in part.

In the meta-regression of all interesting variables (the type of anti-EGFR antibody (cetuximab vs. panitumuma) and concomitant chemotherapy (platinum vs. non-platinum based chemotherapy, study type (phase II vs. phase III) on the HRs, none of the individual study characteristics was significantly related to the predicted OR. Given the small number of studies included in the meta-regression, however, this interpretation must be tentative.

Several other limitations should be considered when interpreting our findings: Firstly, we had no access to primary data and only used abstracted data, while an individual patient data based meta-analysis would have provided a more robust estimate of the efficacy of the addition of anti-EGFR antibody to chemotherapy in the first-line setting [21]. Secondly, the effect of heterogeneity usually needs to be taken into account in meta-analysis. Last, relatively little information on the methods and analyses of this unpublished study [19] made detailed quality assessments challenging.

Conclusion

Our data demonstrated that the addition of anti-EFGR antibodies to chemotherapy for mCRC improved overall and progression-free survival for the overall population of unselected patients in the first-line setting. And the benefit from anti-EGFR antibodies as first-line treatment seems to be limited to patients with KRAS wild-type tumors with respect to PFS.

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