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BRIEF ARTICLE

Phosphatase and tensin homolog expression related to cetuximab effects in colorectal cancer patients: A meta-analysis

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Abstract

AIM: To investigate the correlation between expression of phosphatase and tensin homolog (PTEN) and cetuximab effects in colorectal cancer.

METHODS: We searched PubMed, EMBASE and ASCO to identify eligible studies. Finally, 8 randomized control studies were included in the meta-analysis. STATA 10.0 Software was used to investigate heterogeneity among individual studies and to summarize all the studies. Risk ratios (RRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) were used to assess the strength of the association.

RESULTS: Compared with 20 of 266 patients with loss of PTEN, 206 of 496 patients with intact PTEN protein expression had a better objective response rate to cetuximab-based therapy (RR, 4.75; 95% CI, 2.59-8.72; $P < 0.001$). PTEN positivity was associated with better progression-free survival (PFS) (HR, 0.675; 95% CI, 0.473-0.964; $P = 0.031$) but not with better overall survival (OS) (HR, 0.608; 95% CI, 0.411-0.899; $P = 0.013$). In patients with KRAS wild-type status, PTEN positivity did not predict a longer PFS or OS (PFS: HR, 0.707; 95% CI, 0.440-1.138; $P = 0.154$; OS: HR, 0.943; 95% CI, 0.646-1.377; $P = 0.761$).

CONCLUSION: Expression of PTEN is related to the effect of cetuximab in colorectal cancer patients and should be considered in treatment with cetuximab.

Key words: Phosphatase and tensin homolog; Cetuximab; Colorectal cancer; Prognosis; Meta-analysis

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INTRODUCTION

Colorectal cancer (CRC) is the fourth common malignancy and the second leading cause of cancer death in Western countries[1]. More than half of CRC patients will develop metastatic lesions (mCRC), which are often found in the liver[2]. Although novel pharmaceutical and surgical interventions have been introduced to treat mCRC, the 5-year survival rate for mCRC remains below 10%[3,4]. Recently cetuximab, a monoclnonal antibody that targets the epidermal growth factor receptor (EGFR) has

been proven to be efficacious in mCRC patients[3]. Cetuximab binds to EGFR *via* its ligand-binding domain to inhibit the activation of EGRF signaling. In clinical trials, cetuximab has been reported to achieve a response rate of 10% as a single agent and of 23%-25% in combination with chemotherapy[5,6]. The addition of cetuximab to chemotherapies enhances their antitumor activity[7]. The proposed mechanisms include: reducing tumor cell proliferation, angiogenesis, and DNA repair capacity; increasing apoptosis; and inducing cell cycle arrest at treatment-sensitive points[5]. These effects may enhance and restore tumor sensitivity to cytotoxic agents[8].

In CRC patients, EGFR is overexpressed in 75% of the tumors and its overexpression is associated with worse outcome[3,9]. EGFR was accordingly an obvious candidate for targeted therapy in this malignancy[5]. The tumor suppressor phosphatase and tensin homolog (PTEN) is an important negative regulator of cell-survival signaling[1]. To date, there is evidence to suggest that loss of expression of PTEN has negative association with the prognosis of CRC, especially mCRC. Loss of PTEN expression results in increased phosphatidylinositol phosphate-3 concentration, which induces subsequent protein kinase B hyperphosphorylation, thus protecting cancer cells from apoptotic stimuli[10-12]. In Addition, underexpression of PTEN confers resistance to cetuximab-induced apoptosis[10].

It is important to reveal the relation between the expression of PTEN and the prognosis of mCRC patients treated with cetuximab, as this will be helpful for adopting appropriate targeted therapy for patients[13]. At present, there are many studies which have reported the clinical outcomes of cetuximab in mCRC patients with loss of expression of PTEN. Hence, we carried out a meta-analysis to analyze the relation between the expression of PTEN and prognosis of CRC patients treated with cetuximab.

MATERIALS AND METHODS

Eligibility criteria

The purpose of this research was to systematically review the published articles of cetuximab-based chemotherapy in CRC (both primary and metastatic). Studies which reported the patients' PTEN status and compared the prognosis, were included in the analysis. The primary outcomes of interest were overall survival (OS) and progression-free survival (PFS). Care was taken to include only primary data or data that superseded earlier work.

Identification of studies

The search for studies was performed using the electronic database PubMed with the keywords "colorectal cancer", "cetuximab" and "PTEN". We also referred to the electronic database ASCO and EMBASE. All studies matching the eligibility criteria were retrieved and their bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant studies were identified through hand-searching to identify the additional studies. Data from review articles, case reports, abstracts, and letters were not included. Pharmaceutical industries and authors were not contacted. Characteristics of the studies were extracted from published articles and summarized in a consistent manner to aid comparison[14].

Statistical analysis

The meta-analysis was conducted by using Stata software (version 10.0; StataCorp Lakeway, College Station, TX, United States). Before performing the analyses, data of each published study were carefully checked and verified for coherence with the original publications. The strength of the association between status of PTEN and response of cetuximab-based therapy was measured by the risk ratio (RR) with 95% confidence intervals (CIs). Individual trial level time-to-event data was summarized by the hazard ratio (HR) with 95% CIs. Pooled estimations of RR and HR were obtained by calculating a weighted average of RR and HR from each study.

Statistical heterogeneity between studies was evaluated with the χ^2 test with significance set at a P value of 0.05. The percentage of total variation across the studies, with higher values indicating a greater degree of heterogeneity, was measured by the I^2 statistic. If the P value was $\leqslant 0.05$, the assumption of homogeneity was deemed invalid, and the DerSimonian-Laird method[15] (random-effects model) was used after exploring the causes of the heterogeneity; otherwise, the Mantel-Haenszel method[16] (fixed-effects model) was used. In the absence of heterogeneity, the fixed-effects and random-effects models provided similar results. I^2 lay between 0% and 100%, and a value of 0% indicated no observed heterogeneity, while larger values indicated increasing heterogeneity[17].

Findings of the meta-analysis are depicted in classical Forest plots, with point estimates and 95% CIs for each trial and overall size of the squares proportional to the effect size[18]. It was statistically significant when the two-tailed P value < 0.05. Publication bias was adjusted using the trim-and-fill method, and assessed by visual inspection of funnel plots (Figure 1)[19].

RESULTS

Description of studies

After exclusion of duplicate and irrelevant studies (Figure 2), our search yielded 8 eligible published studies that were retrieved for more detailed evaluation and meta-analysis[3,5,9,10,20-23]. The main characteristics of these selected studies are summarized in Table 1, and the description of PTEN status listed in Table 2. Most of the patients received a cetuximab-based therapy as second-line or later therapy after chemotherapy failure. All 8 studies including a total of 698 patients, of whom 513 were allocated to cetuximab plus irinotecan and others to cetuximab only or with various regimens as shown in detail in Table 1. The outcome measures of the above studies were evaluated based on the Response Evaluation Criteria in Solid Tu-

Table 1 The main characteristics of the 8 selected studies

First Author	Year	Type of study	*n*	Chemotherapy regimen						
				Ctx only	Ctx plus iri	Ctx plus folfiri	Ctx plus folfox	Pan	Ctx plus oxa	Ctx plus oxa and cap
Sartore-Bianchi *et al*[3]	2009	Cohort study	110	14	74	0	0	22	0	0
Negri *et al*[5]	2009	Retrospective study	50	0	36	0	0	0	14	0
Laurent-Puig *et al*[9]	2009	Retrospective study	173	3	141	28	0	0	0	0
Loupakis *et al*[10]	2009	Retrospective cohort study	102	2	100	0	0	0	0	0
Perrone *et al*[21]	2009	Cohort study	32	0	32	0	0	0	0	0
Frattini *et al*[20]	2007	Cohort study	27	0	23	0	0	0	0	4
Razis *et al*[22]	2008	Retrospective study	72	1	13	27	18	-	-	-
Sartore-Bianchi *et al*[23]	2009	Cohort study	132	15	94	0	0	23	0	0

CTX: Cetuximab; Pan: Panitumumab; oxa: Oxaliplaten; cap: Capecitabine.

Table 2 Description of phosphatase and tensin homolog status

No.	Title of the study	Method
1	Analysis of PTEN, BRAF and EGFR status in determining benefit from cetuximab therapy in wild-type KRAS metastatic colon cancer	IHC
2	PI3KCA/PTEN deregulation contributes to impaired responses to cetuximab in metastatic colorectal cancer patients	FISH
3	PTEN expression and KRAS mutations on primary tumors and metastases in the prediction of benefit from cetuximab plus irinotecan for patients with metastatic colorectal cancer	IHC
4	PTEN status in advanced colorectal cancer treated with cetuximab	FISH
5	PIK3CA mutations in colorectal cancer are associated with clinical resistance to EGFR-targeted monoclonal antibodies	IHC
6	PTEN loss of expression predicts cetuximab efficacy in metastatic colorectal cancer patients	IHC
7	Potential value of PTEN in predicting cetuximab response in colorectal cancer: An exploratory study	FISH
8	Multi-determinants analysis of molecular alterations for predicting clinical benefit to EGFR-targeted monoclonal antibodies in colorectal cancer	IHC

PTEN: Phosphatase and tensin homolog; BRAF: V-raf murine sarcoma viral oncogene homolog; EGFR: Epidermal growth factor receptor; IHC: Immunohistochemistry; FISH: Fluorescence *in situ* hybridization.

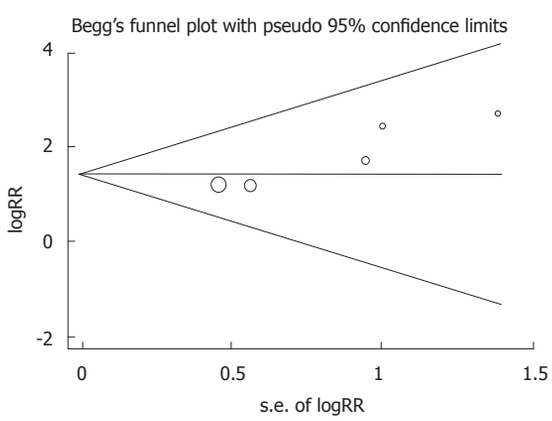


Figure 1 Begg's funnel plot of publication bias.

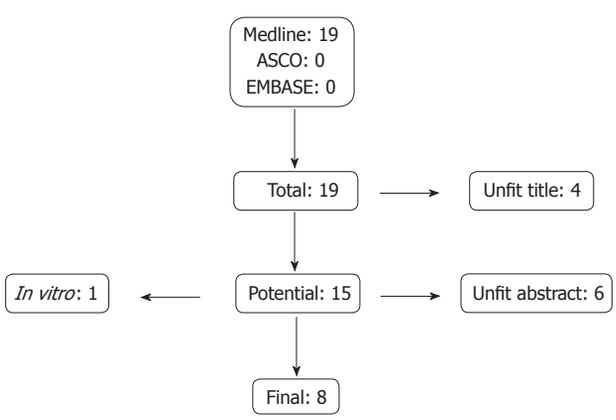
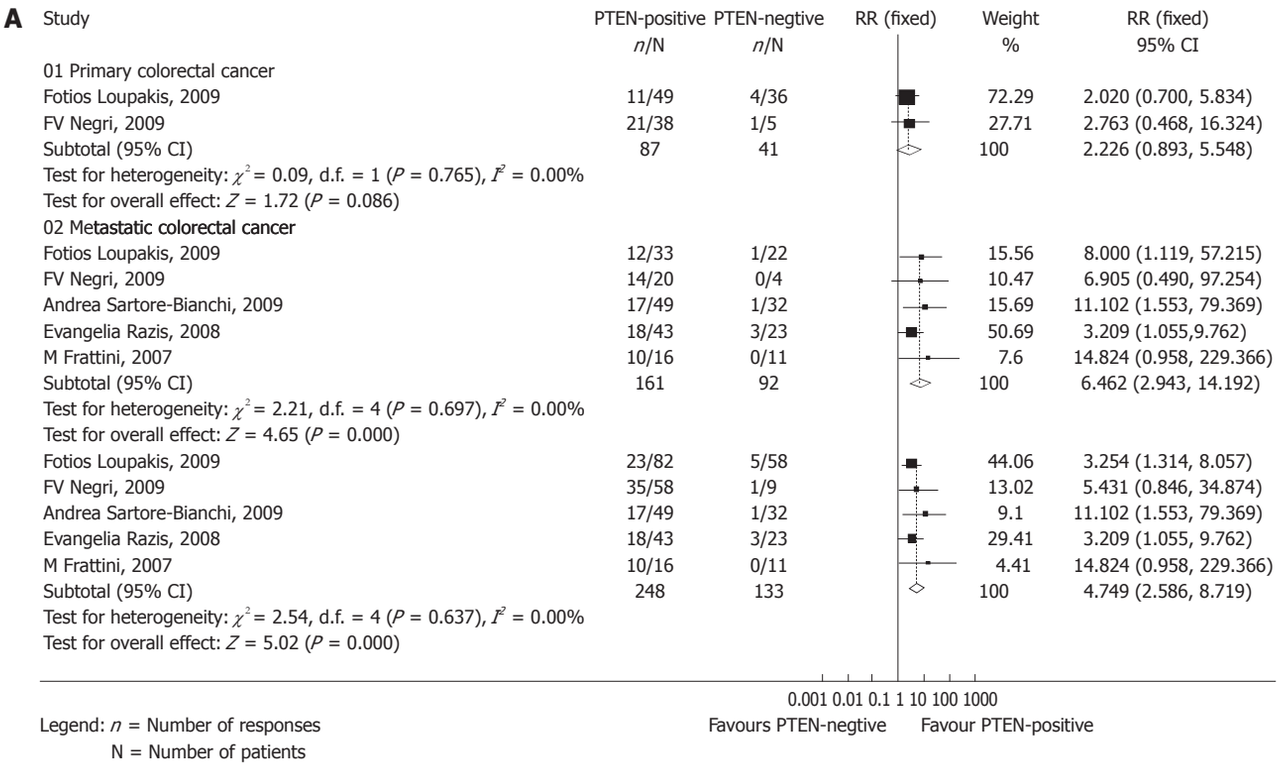


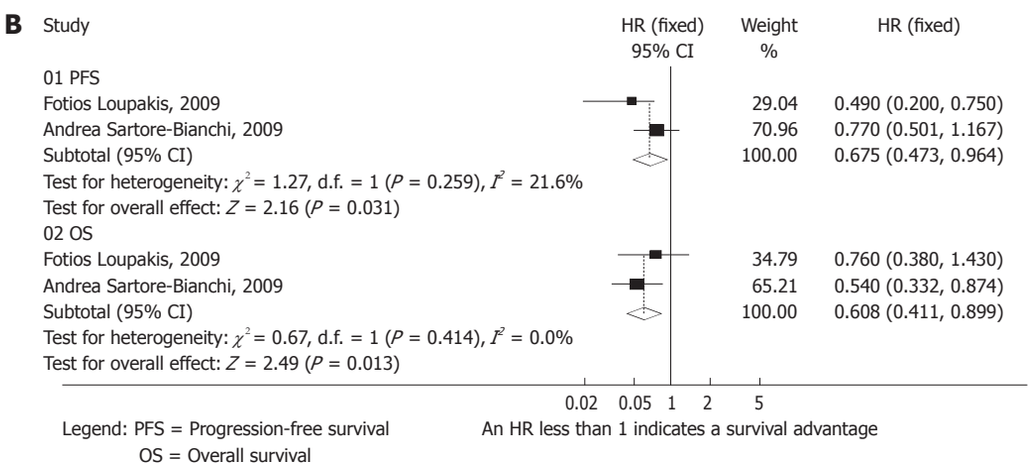
Figure 2 Selection of the studies.

mor criteria, PFS and OS. Patients with stable disease or progression of disease were defined as non-responders. Results are presented for the comparisons with the available data.

Analysis of status of the PTEN homolog and objective response

Five articles documented the response rate of cetuximab-based therapy (Figure 3A). There were 266 patients with loss of PTEN and 496 patients with normal expression of PTEN. In total, compared with 20 of 266 patients with loss of PTEN, 206 of 496 patients with intact protein expression had an objective response rate to cetuximab-based therapy (RR, 4.75; 95% CI, 2.59-8.72; $P < 0.001$). There was no heterogeneity between trials ($P = 0.637$, $I^2 = 0.0\%$). We also analyzed the response to cetuximab-based therapy in metastatic and primary colorectal tumors. Cetuximab-based therapy achieved significantly higher RR among patients with PTEN expression for metastatic tumors (RR, 6.46; 95% CI, 2.94-14.19; $P < 0.001$). In contrast, among 128 assessable primary tumors, 32 of 87 PTEN-positive and 5 of 41 PTEN-negative patients were





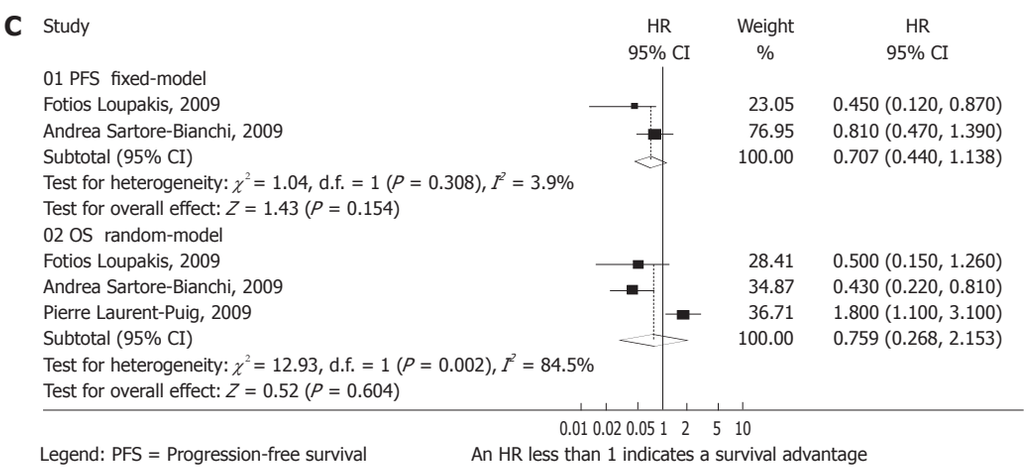


Figure 3 Analysis of status of the phosphatase and tensin homolog homolog. A: Analysis of status of the phosphatase and tensin homolog (PTEN) homolog and objective response; B: Analysis of status of the PTEN homolog and survival; C: Combined analysis of the PTEN homolog and Kirsten rat sarcoma 2 viral oncogene homolog (KRAS) status and survival. RR: Risk ratio; CI: Confidence interval; HR: Hazard ratio; OS: Overall survival; PFS: Progression-free survival.

responders, and there was no significant difference observed (RR, 2.226; 95% CI, 0.893-5.548; $P = 0.086$). There was no evidence for heterogeneity between the studies ($P = 0.697$, $I^2 = 0.0\%$; $P = 0.765$, $I^2 = 0.0\%$; respectively).

Analysis of status of the phosphatase and tensin homolog and survival

Only two trials involving 170 patients were included in this comparison, because none of the other eligibility criteria had sufficient follow-up data listed (Figure 3B). The HR summarizes survival for PTEN-positive compared with PTEN-negative patients after cetuximab-based therapy, with an HR of less than 1 indicating a survival advantage for expression of PTEN in colorectal tumors. As for PFS, PTEN positivity was associated with better survival (HR, 0.675; 95% CI, 0.473-0.964; $P = 0.031$). The analysis for OS confirmed that loss of PTEN was significantly associated with poor clinical outcome (HR, 0.608; 95% CI, 0.411-0.899; $P = 0.013$). There was no significant inter-trial heterogeneity for the end points of PFS ($P = 0.259$, $I^2 = 21.6\%$) or OS ($P = 0.414$, $I^2 = 0.0\%$).

Combined analysis of the PTEN homolog and KRAS status and survival

The studies selected for this analysis are listed in Figure 3C. The HR summarizes survival for PTEN-positive/wtKRAS *vs* PTEN-negative/wtKRAS, with an HR of less than 1 indicating a survival advantage for PTEN-positive/wtKRAS. Overall, among patients with KRAS wild-type status, PTEN positivity did not predict a longer PFS or OS (PFS: HR, 0.707; 95% CI, 0.440-1.138; $P = 0.154$; OS: HR, 0.943; 95% CI, 0.646-1.377; $P = 0.761$). Heterogeneity was not found among trials for the analysis of PFS ($P = 0.308$, $I^2 = 3.9\%$). However, there was marked inter-group heterogeneity for the combined analysis of OS making it difficult to obtain a clear conclusion ($P = 0.002$, $I^2 = 84.5\%$). To adjust for this bias, the trim-and-fill method was implemented. The adjusted estimates for OS were obtained by using the random-effects model (HR, 0.759; 95% CI, 0.268-2.153; $P = 0.604$). In the results from the data, there was no difference between the fixed-effects and the random-effects model, indicating the reliability of this meta-analysis, so we can reach a real conclusion.

DISCUSSION

Nowadays, there is a trend towards individualized treatment in tumor therapy. The optimized application of cetuximab has paved a way for individualized treatment of CRC[24]. In recent years, cetuximab has been widely used in the patients with mCRC, and most of the patients have better prognosis than those treated with combined chemotherapy alone. However, personalized cancer medication is based on the genetics of individual colorectal tumors[24]. Hence, the effects of molecular alterations, especially the activating mutations in the KRAS protein, and the corresponding therapeutic effect of cetuximab have been widely discussed[25-27]. KRAS mutation testing is used in the setting of EGFR-targeted therapy for metastatic disease worldwide[28]. Nevertheless, an intact KRAS is necessary but not sufficient to obtain benefit from EGFR inhibition[29-32]. Alterations in other downstream effectors of EGFR, such as BRAF and PIK3CA/PTEN have been found to give rise to cetuximab resistance[1,33]. Therefore, there is a deep need to reveal possible interactions between targeted agents, so that we can better select patients likely to respond to cetuximab-based treatment[28,29,34].

In this study, we focused on the association between the alteration of PTEN protein expression and the therapeutic effects of cetuximab in CRC patients. In addition, patients treated with panitumumab were also listed in the study search, because the two EGFR inhibitors, cetuximab (the chimeric IgG1 monoclonal antibody) and panitumumab (the humanized IgG2 monoclonal antibody), are currently approved in medication for CRC[34,35]. Both of the molecules bind to the EGFR, leading to inhibition of its downstream signaling and providing some clinical benefit.

PTEN is a tumor suppressor protein, which works as a negative regulator of PI3K/PTEN/Akt, which is a cell-survival signaling pathway[36]. Loss of PTEN expression was associated with the aggressive capacity of CRC, and that understanding the biologic mechanisms responsible for regulation of PTEN expression may allow better translational treatment of CRC patients. Furthermore, CRC patients with loss of PTEN expression show resistance to cetuximab[1].

In our selected studies, patients with normal PTEN expression had higher RR in all CRC with cetuximab-based therapy (especially in mCRC). Also we revealed that patients with PTEN normal expression with cetuximab treatment have better prognosis than those without cetuximab treatment and statistical analysis (OS and PFS) also presents significant differences ($P < 0.05$). In these studies we concluded that PTEN be proposed as an independent predictive factor[1] of cetuximab efficacy. We suggested that PTEN could help to predict prognosis and efficacy of cetuximab. Diagnostic evaluation of PTEN expression might provide additional guidelines for the treatment strategies for CRC patients and valuable prognostic information.

On the other hand, we did a combined analysis of PTEN and KRAS status on OS and PFS. Unfortunately, among patients with wild-type KRAS, PTEN positivity did not predict longer PFS and OS. Only one report showed the interaction between KRAS mutations with or without expression of PTEN in CRC. Thus, we could not perform a meta-analysis. The conclusion obtained in the report was that the PFS and OS of PTEN-positive patients with KRAS mutations were not significantly longer than in all other patients who presented with KRAS mutations and were PTEN-negative[10]. Survival analyses by Loupakis *et al*[10] demonstrated that BRAF mutations (HR, 3.75; $P = 0.015$) but not PIK3CA mutations (HR, 1.20; $P = 0.672$), were significantly associated with decreased OS, whereas neither of these alterations was significantly

associated with PFS. Further clinical data are necessary to identify a certain genes-alteration signature to predict the therapeutic effects of cetuximab-based therapy.

There are some limitations in this meta-analysis. First, the numbers of published studies were not adequate for a comprehensive analysis. Second, only 3 trials reported data of PFS and OS, and a lack of the original data in some studies limited our evaluation of survival, which may cause serious confounding bias. Third, although significant heterogeneity in some end-point variables were at least partly overcome by random-effects analysis, there was still heterogeneity between the relevant studies for inclusion, which may have affected the final results.

In conclusion, our meta-analysis showed an important role of PTEN status in determining the application of cetuximab-based targeted therapy. More clinical trials are warranted in this field to obtain more accurate results. Further improvement in the tailoring of EGFR targeted therapies needs more studies on molecular dissection of the EGFR-initiated oncogenic signaling cascade.

COMMENTS

Background

Cetuximab as a monoclnonal antibody (mAb) that has been used in colorectal cancer (CRC) patients. However, the responses vary in different individuals. Phosphatase and tensin homolog (PTEN) is an important negative regulator and its downregulation has been found in many CRC patients. The relationship between PTEN expression and the effects of cetuximab in CRC patients is still uncertain. The aim of this meta-analysis was to obtain a correlation.

Research frontiers

Cetuximab is a mAb that targets the epidermal growth factor receptor (EGFR). It binds to EGFR *via* its ligand-binding domain to inhibit the activation of EGRF signaling. Cetuximab has been reported to achieve a response rate of 10% as a single agent and of 23%-25% in combination chemotherapy. PTEN is an important negative regulator of cell-survival signaling and underexpression of PTEN confers resistance to cetuximab-induced apoptosis.

Innovations and breakthroughs

Many studies have reported the clinical outcomes of cetuximab in CRC patients with loss expression of PTEN. An exact conclusion has not been achieved mainly because of the limitation of sample size. This is the first study to report the relation between the expression of PTEN and prognosis of CRC patients treated with cetuximab.

Applications

This study may be helpful for adopting appropriate target therapy of cetuximab in patients with CRC.

Terminology

PTEN is the tumor suppressor phosphatase and tensin homolog that plays as an important negative regulator of cell-survival signaling.

Peer review

This is an interesting manuscript presenting a systematic analysis of the impact of PTEN expression on CRC response to cetuximab. It has clear limitations due to the quality of published papers. However, its findings are interesting.

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