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ORIGINAL ARTICLE

Meta-analysis of incidence and risk of hypokalemia with cetuximab-based therapy for advanced cancer

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Abstract
Purpose To gain a better understanding of the incidence and risk of hypokalemia in patients who received cetuximab-based therapy.
Patients and methods Databases, including Pubmed, EMBASE, The Cochrane Library, annual meeting of American Society of Clinical Oncology (2000–2008), and Web of science were searched to identify relevant studies. Eligible studies were prospective phase II–III clinical trials of patients with cancer assigned cetuximab at the dose of 400 mg/m^2 IV on day 1 and 250 mg/m^2 weekly thereafter. The primary endpoint was incidence of hypokalemia.
Results Eleven clinical reports were identified which included a total of 2,254 patients who were available for analysis, with 1,324 patients assigned cetuximab-based treatment. The results showed high incidence of grade 3 and 4 hypokalemia [6.2% (95% CI 4.9–7.7)] and high incidence of all-grade hypokalemia [8.0% (95% CI 4.5–13.9)] associated with cetuximab-based therapy for advanced cancer. Compared with non-cetuximab therapy, cetuximab-based therapy has higher risk of grade 3 and 4 hypokalemia [1.81 (95% CI 1.12–2.93)].
Conclusion Cetuximab-based therapy is associated with a significant risk of hypokalemia. Early monitoring and effective management of hypokalemia is important for patients that received cetuximab-based therapy.

Keywords Cetuximab · Hypokalemia · Cancer

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Introduction

The epidermal growth factor receptor (EGFR) is a transmembrane receptor possessing tyrosine kinase activity which is stimulated by growth factors such as transforming growth factor-α (TGFα) and EGF [1–4]. This receptor is over-expressed by a variety of tumor cell lines, including 25–80% of colorectal carcinomas, [3, 4] and is associated with advanced cancer [4]. Furthermore, EGF is crucial for tumor cell proliferation, inhibition of apoptosis, and other processes important for cancer progression, including angiogenesis, invasion, and metastasis [1–4], making EGF a promising target for anticancer agents [1–5].

Cetuximab (ErbituxTM1) is a chimeric monoclonal antibody, highly selective for the epidermal growth factor receptor (EGFR). It induces a broad range of cellular responses in tumors expressing EGFR, enhancing sensitivity to radiotherapy and chemotherapeutic agents [1, 2, 4]. The clinical efficacy of cetuximab in colorectal cancer, head and neck cancer, non-small cell lung cancer, and pancreatic cancer is currently undergoing evaluation in several controlled trials and the results showed that cetuximab improves survival for advanced non-small cell lung cancer and colorectal cancer [6]. As a result, cetuximab was approved by the Food and Drug Administration (FDA) for use in metastatic colorectal in February 2004 [7, 8].

With the use of cetuximab, its substantial adverse events were observed in practice. Acneiform rash, diarrhea, fatigue, neutropenia, hypertension, nausea, infusion-related or hypersensitivity reactions, and hand-foot skin reaction were very common during the administration of cetuximab for advanced cancer. In addition, hypokalemia is a major adverse event that was often ignored in most of clinical trials. Some studies reported the occurrence of hypokalemia [9]. Hypokalemia is a common and important finding in

hospitalized patients because it may provoke cardiac arrhythmias and/or respiratory arrest [10]. And it is also a dangerous adverse effect occurring in outpatients, who are monitored much less closely than hospitalized patients. Therefore, it is important to evaluate the incidence and risk of hypokalemia with cetuximab-based therapy for advanced cancer. Because of the limited number of patients in trials, the overall incidence and risk of hypokalemia with cetuximab-based therapy is not known. To our knowledge, so far there has been no systematic review with a greater capacity to evaluate them. Therefore, we conducted this quantitative meta-analysis to evaluate the available evidence from the relevant trials.

Methods

Literature search

Trials were identified by systematically searching the electronic databases Pubmed, Embase, the Cochrane Library without language restriction. The search used the following key words, "cetuximab" or "Erbitux" limited by "humans". In addition, we manually searched all of the abstracts that contained "cetuximab" and "hypokalemia", presented at recent 2000–2008 American Society of Clinical Oncology (ASCO) annual meetings. If the data from meeting abstracts and published clinical trials were duplicated, only the updated and informative one can be preserved. Re-references of eligible studies and previous reviews were also scrutinized for any other relevant trials. Web of science was also searched to ensure that no studies were missed. The latest search was done in December 2008.

Selection criteria

Citations selected from this initial search were subsequently screened for eligibility using the following criteria: (1) participating patients with cancer at baseline; (2) phase II–III clinical prospective trial; (3) cetuximab at the dose of 400 mg/m^2 IV on day 1 and 250 mg/m^2 weekly thereafter; (4) data available for the events or incidences of hypokalemia. Reports were excluded using the following criteria: (1) phase I clinical trial for variations in dosage and time; (2) retrospective trial; (3) any review, comment, and case report.

Data extraction

Two reviewers abstracted data independently and reached consensus on all items. The following data were abstracted directly from the included trials: first author, publication year, study design, tumor type, phase of trial, line of treatment, intervention, number of patients, number of patients eligible for hypokalemia evaluation, median age, sex ratio, dose of cetuximab administered, and events or incidences of hypokalemia. All RCTs included were evaluated for the quality according to Jadad's score [11].

Clinical endpoint

The primary endpoint was the incidence of all-grade hypokalemia. Grade of hypokalemia was defined according to Common Terminology Criteria for Adverse Events v3.0 (CTCAE) [12] as follows: grade 1/2, local laboratory value ~3.0 mmol/L; grade 3, 3.0–2.5 mmol/L; grade 4, <2.5 mmol/L. We included the incidence of all-grade hypokalemia and of grades 3 and 4 in this pooled analysis.

Statistical analysis

All data analyses were performed using version 2 of the Comprehensive Meta Analysis programme (Biostat, Englewood, NJ, USA). The events or incidences of hypokalemia both all-grade and high grade (grade 3 and 4) were summarized from the data of all eligible trials. For each eligible trial, the proportion and 95% confidence interval (CI) of patients with hypokalemia were calculated.

Both the fixed-effect model and the random-effects were considered for pooled analysis. The standard Q test was applied to investigate the statistical heterogeneity between trials and a I^2 value larger than 50% were defined as heterogeneity. If any heterogeneity existed, the following techniques were employed to explain it: (a) subgroup analysis; (b) sensitivity analysis performed by excluding the trials which potentially biased the results, and (c) the random effect model was used after efforts were made to explore the cause of the heterogeneity.

Results

Of the 725 reports screened, 11 clinical reports (5 abstracts and 6 fulltexts) were identified in which the events or incidences of hypokalemia resulting from cetuximab-based therapy were reported (Fig. 1) [9, 13–22].

Of these 11 reports, three are randomized controlled trials (RCTs), eight are single-armed trial; three are phase III trials, and eight are phase II trials; one trial reported ceutximab-based therapy as second line treatment, and ten as first line treatment. Underlying advanced cancer included head and neck cancer, colorectal cancer, non-small cell lung cancer, gastric cancer, ovarian cancer, and esophageal cancer. A total of 2,254 patients were available for analysis, with 1,324 patients assigned cetuximab-based treatment. The average Jadad's score of three RCTs are 3.67. Baseline

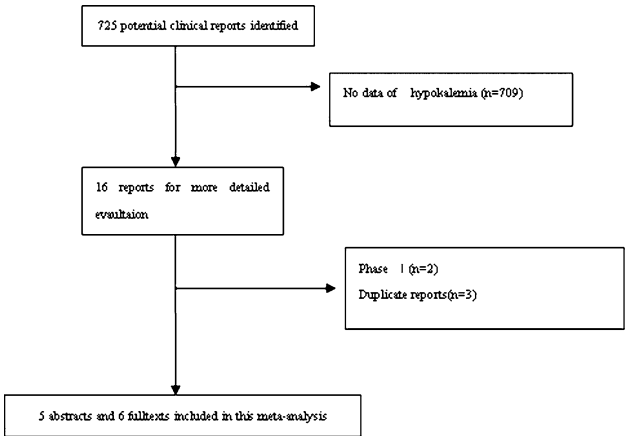

Fig. 1 Outline of the search- flow diagram

characteristics of these patients from the 11 trials are listed in Table 1.

Data for the events or incidences of grade 3 and 4 hypokalemia were available for pooled analysis from a total of 1,306 patients eligible in 11 clinical trials, who had various advanced cancer and were assigned ceutximab-based therapy (Fig. 2). The highest incidence of grade 3 and 4 hypokalemia was 16.7% [19], and the lowest incidence of grade 3 and 4 hypokalemia was 0.0% [18]. The pooled incidence of grade 3 and 4 hypokalemia was 6.2% (95% CI 4.9–7.7, heterogeneity $I^2 = 49.81\%$).There was no heterogeneity among studies, so we reported the incidence of grade 3 and 4 hypokalemia based on fixed effect model.

Data for the events or incidences of all-grade hypokalemia were available for pooled analysis from a total of 1,306 patients eligible in 11 clinical trials who had various advanced cancers and were assigned ceutximab-based therapy (Fig. 2). The highest incidence of all-grade hypokalemia was 24.0% [21], and the lowest incidence of grade all grade hypokalemia was 2.9% [14]. The pooled incidence of all grade hypokalemia was 8.0% (95% CI 4.5–13.9, heterogeneity $I^2 = 84.78\%$). We analyzed the heterogeneity by subgroup analysis (according to tumor type, trial phase, trial design, treatment line) and sensitivity analysis; however, the heterogeneity still exists. The incidence of all-grade hypokalemia was reported based on random effect model (Fig. 3).

Three eligible RCTs that compared cetuximab-based therapy versus non-cetuximab-based therapy for advanced cancer have the data of grade 3 and 4 hypokalemia which included 915 patients in cetuximab group and 902 patients in non-cetuximab group (Fig. 4). Patients in cetuximab group (49/915) demonstrated a statistically significant risk of grade 3 and 4 hypokalemia compared with those in non-cetuximab group (28/902) (OR 1.81, 95% CI 1.12–2.93, Heterogeneity $I^2 = 0\%$).There is no heterogeneity among studies. The odd ratios of grade 3 and 4 hypokalemia were reported based on fixed effect model.

Table 1 Characteristics of eligible trials and patients

Study	Tumor	Phase	Trial design	Treatment line	Intervention	Usage of Pla	Patients	Median age	Sex (M/F)	Jadad's score
[9]	Head and neck cancer	III	RCT	First	Cet + Cis	Every 4 weeks	57	60.6	41/16	5
					Cis		60	58.3	50/10	
[13]	Head and neck cancer	II	Single arm trial	First	Cet + Cis + Rad	Every 3 weeks	22	57	NR	\
[14]	Colorectal cancer	II	Single arm trial	First	Cet + Cap + Iri	\	70	61.5	43/27	\
[15]	Colorectal cancer	II	Single arm trial	First	Cet + Iri + Leu	\	48	65	31/17	\
[16]	Head and neck cancer	II	Single arm trial	First	Cet + Car +Pac + Rad	Weekly for 5 weeks	29	55	18/11	\
[17]	Non-small cell lung cancer	II	Single arm trial	First	Cet + Car + Doc	Every 3 weeks for up to 6 cycles	80	63	42/38	\
[18]	Ovarian cancer	II	Single arm trial	First	Cet + Cab + Pac	Every 3 weeks for 6 cycles	40	54	NR	\
[19]	Gastric cancer	II	Single arm trial	First	Cet + Cis + Doc	Every 3 weeks for up to 6 cycles	48	64	34/14	\
[20]	Esophagogastric cancer	II	Single arm trial	First	Cet + Cab + Pac + Rad	Weekly for 6 cycles	60	60	50/10	\
[21]	Colorectal cancer	III	RCT	Second	Cet + Iri	\	648	61	405/243	3
					Iri		650	62	411/239	
[22]	Head and neck cancer	III	RCT	First	Cet + Cis/Cab + FU	Every 3 weeks	222	56	197/25	3
					Pla + FU		220	57	202/18	

Pla platinum, *Cet* cetuximab, *Iri* irinotecan, *Car* carboplatin, *Pac* paclitaxel, *Rad* radiation, *BSC* best support care, *Doc* docetaxel, *Cap* capecitabine, *Cis* cisplatin

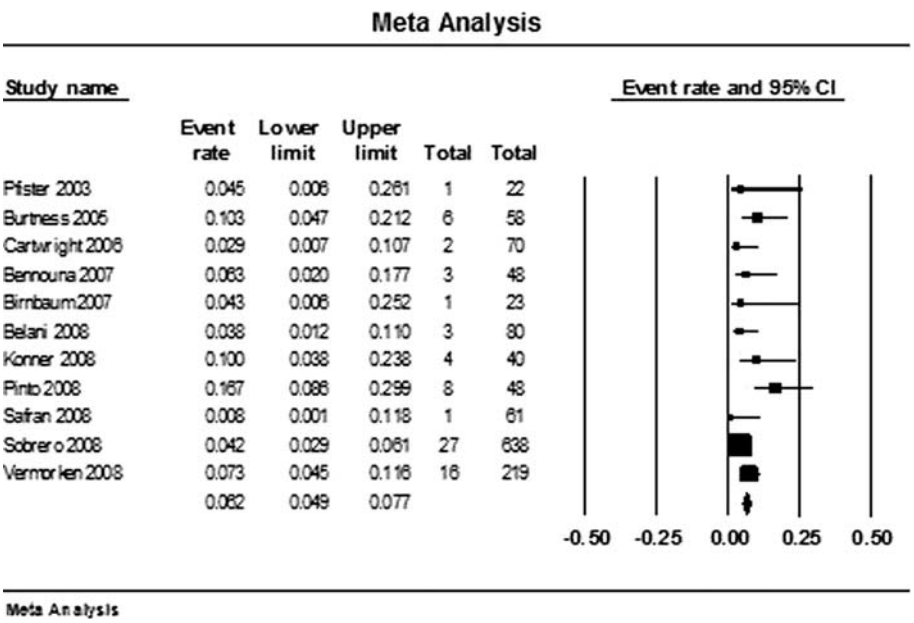

Fig. 2 Forest plot for meta-analysis of incidence of grade 3 and 4 hypokalemia for cetuximab-based treatment based on fixed effect model

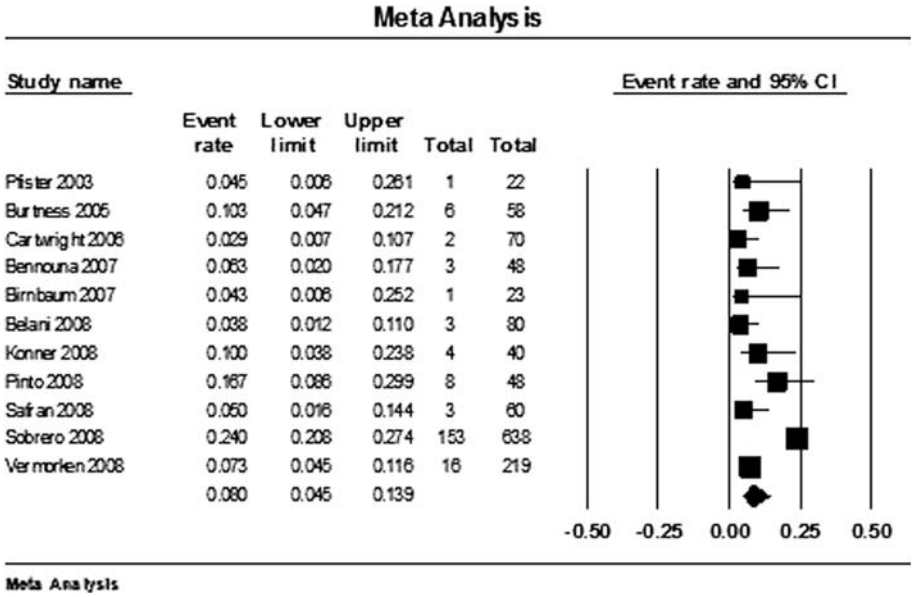

Fig. 3 Forest plot for meta-analysis of incidence of all-grade hypokalemia for cetuximab-based treatment based on random effect model

Discussion

Hypokalemia is a common and important finding in hospitalized patients because it may provoke cardiac arrhythmias and/or respiratory arrest [10]. Because the etiologies of hypokalemia are numerous, and the symptoms of hypokalemia weakness of skeletal, cardiae, and smooth muscles (cardiac arrhythmias, rhabdomyolysis, constipation and ileus), some patients could easily have been attributed to the underlying tumor or to previous chemotherapy regimens [23]. The diagnosis of cetuximab-induced hypokalemia may be overlooked [24]. Only systematic review of medication history allows recognition and prompt treatment. Here the results of this meta-analysis showed the high incidence of grade 3 and 4 hypokalemia [6.2% (95% CI 4.9–7.7)] and the high incidence of all-grade hypokalemia [8.0% (95% CI 4.5–13.9)] associated with cetuximab-based therapy for advanced cancer. Compared with non-cetuximab therapy, cetuximab-based therapy has a higher risk of grade 3 and 4 hypokalemia [1.81 (95% CI 1.12–2.93)]. So serum hypokalemia levels should be monitored well when cetuximab-based therapy was performed for advanced cancer.

The association of cetuximab-based therapy with hypokalemia might be related to a direct nephrotoxicity of cetuximab. We cannot exclude the possible effects of nephrotoxic drugs such as platinum on potassium disorder; however, two randomized controlled trails [9, 22] which use

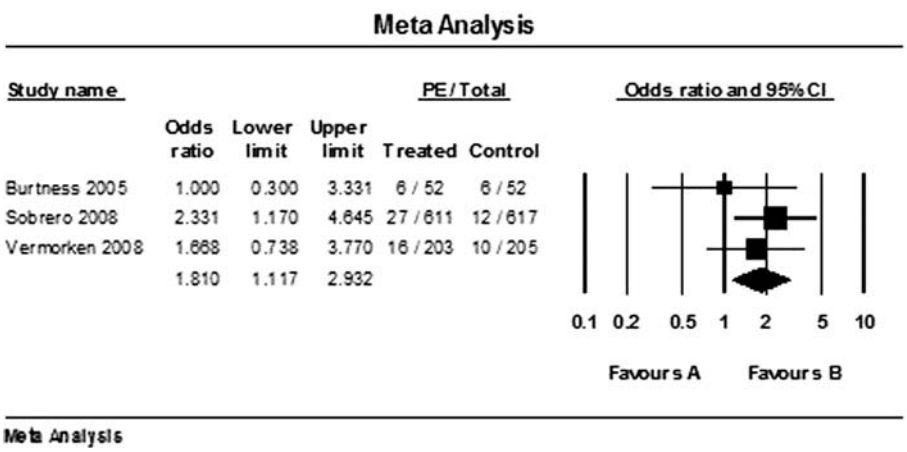

Fig. 4 Odds ratio of grade 3 and 4 hypokalemia of cetuximab-based therapy versus non-cetuximab-based therapy from three RCTs

the same dosage of cisplatin in both arms suggest that cetuximab-based therapy is associated with a higher risk of hypokalemia in spite of the administration of nephrotoxic drugs than non-cetuximab therapy. The exact mechanism of cetuximab's nephrotoxicity is still unknown, but it seems to be due to a tubular necrosis, predominantly in the distal convoluted tubule and the collecting ducts, which may result in salt wasting and stimulation of the renin-angiotensinaldosterone system, with consequent hypokalemic metabolic alkalosis [24]. Recent research found that the protein TRPM6 was a member of the transient receptor potential family of cation channels which has shown to mediate active transport preincubation with cetuximab abolished the stimulatory effect of EGF on TRPM6 activity [25]. Groenestege et al. [26] found that pro-EGF and TRPM6 are both predominantly expressed in distal convoluted tubule which is the main site of active renal Mg^{2+} reabsorption. They indicated that TRPM6 has a critical link between EGFR inhibition and hypomagnesemia, but the physiological relevance of this path way remains to be elucidated. However, magnesium deficiency contributes to K^+ wasting for it impairs Na–K-ATPase which would decellular uptake of K^+ [27]. Therefore, we believe that hypomagnesemia is a potential contributor to cetuximab-associated hypokalemia.

The treatment of hypokalemia consists of minimizing further potassium loss and providing potassium replacement. Potassium chloride or acetate is used for replacement depending on alkalosis or acidosis. Other modalities can be employed depending on the specific underlying pathologic condition [28]. A replacement strategy should be carried out gradually, rather than rapidly unless the patient is clinically unstable.

Several limitations of our analysis are worth consideration: first, as with every meta-analysis, results are affected by the quality of individual trials. These trials have different patient populations, concurrent chemotherapies, follow-up durations, and lengths of treatment. Various disease-related and treatment-related factors contributing to hypokalemia in the patients enrolled in the clinical trials. It is hardly for us to analyse the effects of these factors; however, two randomized controlled trails [9, 22] which use the same dosage of cisplatin in both arms suggest that cetuximab-based therapy is associated with a higher risk of hypokalemia in spite of the administration of nephrotoxic drugs than non-cetuximab therapy. Second, treatments were involved in a few trials based on the different tumor types; Third, not all articles has the available data of grade 4 hypokalemia. Fourth, the significant heterogeneity of the data exists in the incidences of all-grade hypokalemia. Finally, we cannot analyze all the confounding factors in the patient populations because of lacking of detailed information from the original trials we included.

In conclusion, our data have shown that cetuximab-based therapy is associated with a significant risk of hypokalemia. Early monitoring and effective management of hypokalemia is important for patients who receive cetuximab-based therapy.

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