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Comparison Between Biweekly and Weekly Cetuximab in Patients With Metastatic Colorectal Cancer: A Meta-analysis

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Abstract. *Background/Aim: Although weekly administration of cetuximab is the standard regimen in patients with metastatic colorectal cancer (mCRC), the efficacy and safety of a biweekly regimen is a pending issue. We conducted this meta-analysis to compare the efficacy and safety of a biweekly vs. a weekly regimen of cetuximab in the treatment of mCRC. Patients and Methods: We conducted a comprehensive electronic literature search up to January 2020 to identify studies directly comparing the efficacy and safety of biweekly cetuximab administration and conventional weekly administration in patients with mCRC. We then performed a meta-analysis using random-effects models to calculate risk ratios and mean differences with 95% confidence intervals. Results: Four studies with a total of 381 patients were included in this meta-analysis. The meta-analysis showed that biweekly administration conferred equivalent efficacy, including objective response rate, disease-control rate, progression-free survival, and overall survival, as well as safety, including skin toxicity, gastrointestinal toxicity, and hematologic toxicity, compared with weekly administration in patients with mCRC. Conclusion: Results from this meta-analysis support the administration of biweekly instead of weekly cetuximab, which is beneficial for both patients and health resources.*

Cetuximab, an IgG1 human/mouse chimera-type monoclonal antibody, binds to the extracellular domain of the epidermal growth factor receptor (EGFR), inhibiting ligand binding and downstream signaling (1). In preclinical models, cetuximab was found to promote apoptosis, angiogenesis, and metastasis, and inhibit tumor cell proliferation (2, 3). Furthermore, antitumor antibody-dependent cell-mediated cytotoxicity is also known to play a role in the mode of action of cetuximab (4).

The clinical efficacy of weekly cetuximab in patients with metastatic colorectal cancer (mCRC) has been demonstrated in randomized phase II and III clinical trials, either as monotherapy, or in combination with oxaliplatin- and irinotecan-based chemotherapy regimens in first- and subsequent-line treatment (5-10). Cetuximab is approved in several countries for clinical use in patients with mCRC. National Comprehensive Cancer Network (NCCN) Guidelines® version 2.2020 suggest that both weekly and biweekly (every 2 weeks) cetuximab are indicated in combination with oxaliplatin- and irinotecan-based therapy or monotherapy in *KRAS*/*NRAS*/*BRAF* wild-type patients. In contrast, only conventional weekly cetuximab has been approved in Japan for initial IV infusion of 400 mg/m^2 on day 1 infused over 120 min followed by weekly doses of 250 mg/m^2 infused over 60 min.

A pharmacokinetic study by Tabernero *et al.* (11) demonstrated no significant differences between weekly cetuximab of 250 mg/m^2 (following an initial dose of 400 mg/m^2) and biweekly cetuximab of 500 mg/m^2 in combination with irinotecan. Considering that many commonly used chemotherapy agents for mCRC are administrated on a biweekly basis, the synchronization of the administration of cetuximab administered on an every-2-weeks schedule commonly implemented for chemotherapy would be more convenient for the patient and most likely reduce the overall medical cost and effort of healthcare providers. However, the studies investigating the clinical efficacy and safety of biweekly cetuximab compared with standard weekly cetuximab are limited. Therefore, we conducted a meta-analysis regarding this issue to determine if the clinical data support the use of biweekly cetuximab.

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Key Words: Cetuximab, metastatic colorectal cancer, biweekly, weekly.

Patients and Methods

Search strategy. A comprehensive electronic literature search was conducted with the cutoff of January 2020 using MEDLINE (PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar. The search was limited to English language and human studies. Two independent investigators (A.M. and S.J.) performed the search using the keyword terms "cetuximab" AND "colorectal" AND ("biweekly" or "every 2 weeks"), and discrepancies were resolved by consensus. Reference lists of all relevant articles were hand-searched for additional studies that had been initially overlooked using this search strategy. The quality of the included studies was assessed using the Jadad score (12) and the Newcastle-Ottawa scale (NOS) (13) for randomized controlled trials (RCTs) and observational studies, respectively. Studies were considered to be of high quality if they had a Jadad score ≥3 or were ≥7 on NOS. Systematic review and meta-analysis were performed under the recommendations of preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2015 (14). No ethical approval or patient consent was required because all analyses were based on previously published data.

Inclusion and exclusion criteria. We defined the inclusion and exclusion criteria a priori. Published studies were included if they included mCRC patients and met the following criteria: they were RCTs or other direct comparative studies evaluating predefined outcomes in patients who were treated with biweekly cetuximab or weekly cetuximab. Case reports or reports with incomplete data were excluded.

Data extraction and outcome measures. Baseline information was extracted from the original studies, including first author, country, study design, recruitment period, sample size, concomitant chemotherapy regimen, age, gender, performance status, primary site, *EGFR* status, *RAS* status, treatment line, treatment cycles, dose of cetuximab, and follow-up period. Outcome measures used were objective response rate (ORR), disease-control rate (DCR), progression-free survival (PFS), and overall survival (OS), as well as adverse events (skin toxicity, gastrointestinal, and hematological).

Statistical analysis. Pooled risk ratios (RR), representing the risks of an adverse event occurring with biweekly cetuximab compared with weekly cetuximab, were calculated using the DerSimonian–Laird random-effects model along with 95% confidence intervals (95%CIs) (15, 16). Considering the between-study heterogeneity, a "random-effects" meta-analytical technique was applied, resulting in a more conservative calculated RR than that obtained with a fixed-effects model. An RR of <1 favored the biweekly group, and the point estimate of the RR was considered statistically significant at $p<0.05$ if the 95%CI did not include the value 1. The mean difference (MD) was used as the effect measure for continuous variables, and continuous variables were pooled using the inverse variance method. Data analysis was performed using Review Manager (RevMan) v5.3 software (Cochrane Collaboration, Copenhagen, Denmark). Study heterogeneity was measured using the χ^2 and I2 statistics, with $p<0.05$ and $I^2\geq50\%$ indicating heterogeneity (17). Publication bias was estimated using visual inspection of a funnel plot, and asymmetry was assessed formally using the Begg's rank correlation test.

Results

Study selection and characteristics of included studies. The initial systematic literature search identified 292 citations. One hundred eighty-six and 80 studies were excluded because of duplication of titles and abstract screening, respectively. Twenty-two of 26 studies were excluded after full-text review. The remaining four studies (18-21) (published 2008-2016) were finally included in the meta-analysis. A PRISMA flow diagram of the detailed literature search and selection process is shown in Figure 1. The included studies consisted of one RCT (18), two prospective cohort studies (19, 21), and one retrospective observational study (20). The sample sizes of the four studies varied from 40 to 152. The number of studies in each treatment line of cetuximab were as follows: first, 2; third, 1; and second/fourth, 1. Cetuximab was administrated concomitantly with irinotecan in two studies, FOLFOX4 (5-fluorouracil, leucovorin, and oxaliplatin) in one study, and XELOX (capecitabine plus oxaliplatin) in one study. All four studies reported our predefined outcomes, but median PFS and OS in Mrabti *et al*. (20) was not available for meta-analysis because 95%CIs were not provided with the data. Of the 381 patients included in the meta-analysis, 195 (51.2%) were treated with biweekly cetuximab and 186 (48.8%) were treated weekly. Baseline characteristics of the included studies are shown in Table I.

Comparisons of treatment efficacy. The ORR in biweekly and weekly treatment groups from all four studies (18-21) were 43.1% (84/195) and 35.5% (66/186), respectively. The meta-analysis for ORR demonstrated no significant difference between the two groups, with a pooled RR of 0.93 (95%CI=0.74-1.18, $p=0.57$) (Figure 2A). Moderate between-study heterogeneity was observed ($\chi^2=6.65$, $I^2=55\%$, $p=0.08$). No significant publication bias was observed using the Begg's test ($p=1.000$). Sensitivity analysis by omitting one study in each turn to detect the source of heterogeneity showed that the study by Mrabti *et al*. (20) was the source, but the result of meta-analysis with omitting the data was consistent. The DCR in biweekly and weekly groups from all four studies (18-21) was 83.1% (162/195) and 72.6% (135/186), respectively. The meta-analysis showed a significantly better DCR in the biweekly group than in the weekly group, with an RR of 0.64 (95%CI=0.42-0.98, $p=0.04$), without significant between-study heterogeneity ($\chi^2=3.30$, $I^2=9\%$, $p=0.35$) (Figure 2B) and publication bias (Begg's test; $p=0.174$).

In the analyses of PFS and OS, data from three studies (18, 19, 21) were available. No significant differences were observed in PFS and OS between the biweekly and weekly groups [PFS: MD (95%CI)=0.03 (–1.02-1.08); $p=0.96$, OS: MD (95%CI)=1.10 (–6.70-8.91), $p=0.78$, respectively]. Although PFS analysis did not show significant between-

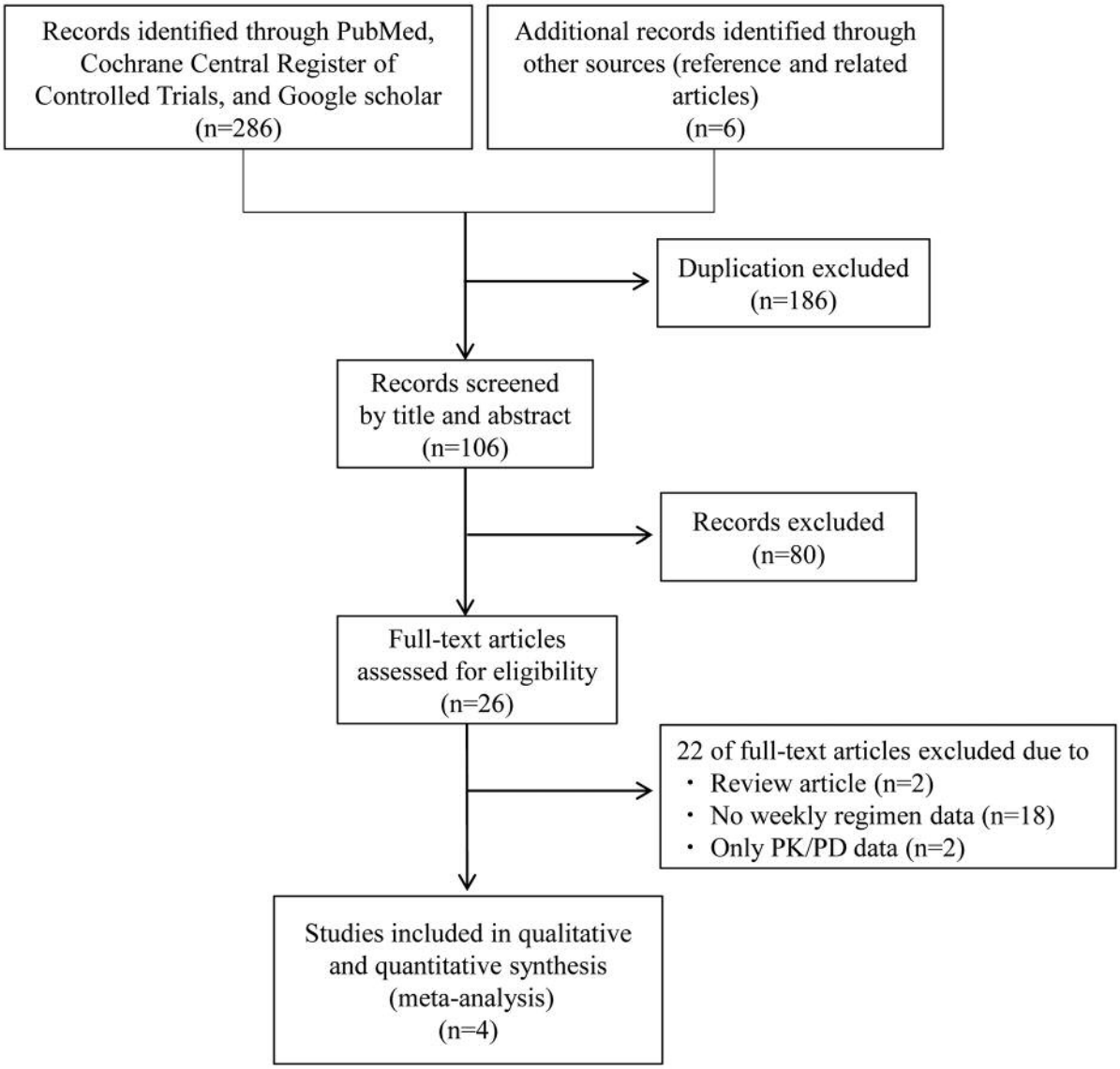

Figure 1. *Flow chart of selection of studies for inclusion in the meta-analysis.*

study heterogeneity, OS analysis showed moderate heterogeneity (PFS: χ^2=1.42, I^2=0%, p=0.49, OS: χ^2=6.11, I^2=67%, p=0.05, respectively) (Figure 3A and B).

Comparisons of adverse events. Meta-analyses of all four studies (18-21) regarding adverse events between the biweekly and weekly groups are shown in Table II. No significant differences in adverse events, including grade 3 or 4 skin toxicity, gastrointestinal toxicity, hematologic toxicity, and any grade of skin toxicity, were observed between the two groups. Meta-analysis of any grade of skin toxicity had moderate between-study heterogeneity, but others had no heterogeneity.

Discussion

The current meta-analysis aimed to compare the treatment efficacy and safety between biweekly cetuximab and conventional weekly cetuximab in patients with mCRC. The results demonstrated that both efficacy and safety of biweekly cetuximab were at least equivalent to weekly administration. It is noteworthy that DCR, among the predefined outcomes, was increased in the biweekly administration group.

The efficacy of monoclonal antibodies against EGFR was investigated initially in animal studies in the 1980s. In 2004, cetuximab was approved by both the US FDA and the EMA

for use in EGFR-expressing *(K)RAS*-unselected chemorefractory mCRC. In 2013, extended RAS testing was required by the FDA and EMA for predicting response to anti-EGFR agents, cetuximab, and panitumumab. To date, >480,000 patients with mCRC have received cetuximab-based therapy worldwide (>240,000 patients have received panitumumab) (22). Anti-EGFR agents, which bind to the extracellular domain of EGFR, block the ligand binding-induced receptor dimerization and subsequent tyrosine kinase activation (1). Cetuximab-induced inhibition of EGFR signaling results in downregulation of downstream targets, including phosphorylated mitogen-activated protein kinase (pMAPK) and pAkt. It is also associated with inhibition of Ki67 and increased p27 expression (23, 24). Cetuximab, in particular, is also able to induce natural killer cell-driven antibody-dependent cellular cytotoxicity against tumor cells (4). The standard weekly cetuximab regimen in patients with mCRC as monotherapy or in combination with oxaliplatin- and irinotecan-based chemotherapy has shown efficacy in first- and subsequent-line treatments (5-10). However, weekly cetuximab administration does not match with the administration of chemotherapy regimens with which cetuximab is commonly combined (*e.g.* FOLFIRI and FOLFOX are given on an every-2-weeks basis). The efficacy and safety of biweekly cetuximab administration have been pending issues.

The pharmacokinetic data demonstrated that cetuximab has a long terminal half-life (110 hours), allowing administration on a biweekly schedule. Indeed, active serum concentrations of cetuximab were maintained throughout the 2-week dosing period with such a regimen (25, 26). The feasibility of biweekly cetuximab administration was previously evaluated in a two-part phase I dose escalation study (11, 27). This study showed that cetuximab may be safely administrated as a monotherapy or in combination with FOLFIRI at doses of 400-700 mg/m^2 on a biweekly schedule. A cetuximab dose of 500 mg/m^2, not 400 mg/m^2, every 2 weeks exhibited predictable pharmacokinetics that were similar to those of the conventional weekly dose regimen of 250 mg/m^2 (following an initial dose of 400 mg/m^2). At steady state, the mean area under the plasma concentration-time curve (AUC) of the 500 mg/m^2 dose over a 2-week period was twice that of the 250 mg/m^2 dose over a 1-week period, indicating that exposure to cetuximab was similar with the two dosing regimens. A pharmacodynamics study investigating markers of EGFR signaling, such as pEGFR, pMAPK, Ki67, and p27 protein expression from skin biopsies demonstrated no major differences in the inhibition of EGFR signaling between weekly and biweekly regimens of cetuximab administration (11, 27).

Based on these pharmacological backgrounds, several single-arm clinical trials have been conducted and reported the efficacy and safety of a biweekly cetuximab regimen

Table I. *Characteristics of the included studies.*

Author (year)	Country (institutions)	Study design	Study quality (NOS)	Recruitment period	Sample size	Concomitant Cx	Group (sample size)	Age (range)	Female (%)	Performance status (%)	Primary site (colon/rectum)	EGFR positive (%)	RAS wild (%)	Treatment line	Treatment cycles	Dose of cetuximab	Follow-up period (months)
Hazama (2016)	Japan (multiple)	PCS	7	2012-2013	40	Xelox	Biweekly (26)	65.5 (33-85)	10 (39)	0: 21 (80), 1: 5 (19)	14 (54)/ 12 (46)	26 (100)	26 (100)	1st	6.5 (5-13)	500 mg/m^2	NA
							Weekly (14)	71.5 (58-83)	5 (36)	0: 11 (79), 1: 3 (21)	11 (79)/ 3 (21)	14 (100)	14 (100)	1st	4.5 (3.5-7.8)	400 mg/m^2→ 250 mg/m^2	NA
Brodowicz (2013)	Austria (multiple)	RCT (phase II)	2*	2007-2009	152	FOLFOX4	Biweekly (77)	62 (30-75)	35 (45)	32 (42)**	55 (71)/ 22 (29)	48 (62)	77 (100)	1st	34 (2-152)***	500 mg/m^2	28.7
							Weekly (75)	56 (30-8-)	30 (40)	30 (40)**	40 (53)/ 35 (47)	43 (57)	75 (100)	1st	31 (1-142)***	400 mg/m^2→ 250 mg/m^2	31.3
Mrabti (2009)	Morocco	RCS	8	2004-2007	50	Irinotecan	Biweekly (18)	54 (33-80)	13 (72)	NA	12 (67)/ 6 (33)	(56)	NA	2-4th	7	500 mg/m^2	34.2
							Weekly (32)	53 (28-85)	12 (38)	NA	27 (84)/ 5(16)	(63)	NA	3rd	7	400 mg/m^2→ 250 mg/m^2	
Pfeiffer (2008)	Denmark	PCS	8	2005-2008	139	Irinotecan	Biweekly (74)	63 (23-78)	28 (38)	0,1: 68 (92), 2,3: 6 (8)	55 (74)/ 19 (26)	NA	NA	3rd	17 (2-52)***	500 mg/m^2	NA
							Weekly (65)	57 (29-77)	25 (38)	0,1: 53 (82), 2,3: 12 (18)	41 (63)/ 24 (37)	NA	NA	3rd	16 (1-51)***	400 mg/m^2→ 250 mg/m^2	NA

NOS: Newcastle-Ottawa scale; Cx: chemotherapy; PCS: prospective cohort study; RCT: randomized controlled trial; RCS: retrospective cohort study; NA: not applicable; *assessed using the Jadad score; **Karnofsky PS 100; ***Exposure time of cetuximab (weeks).

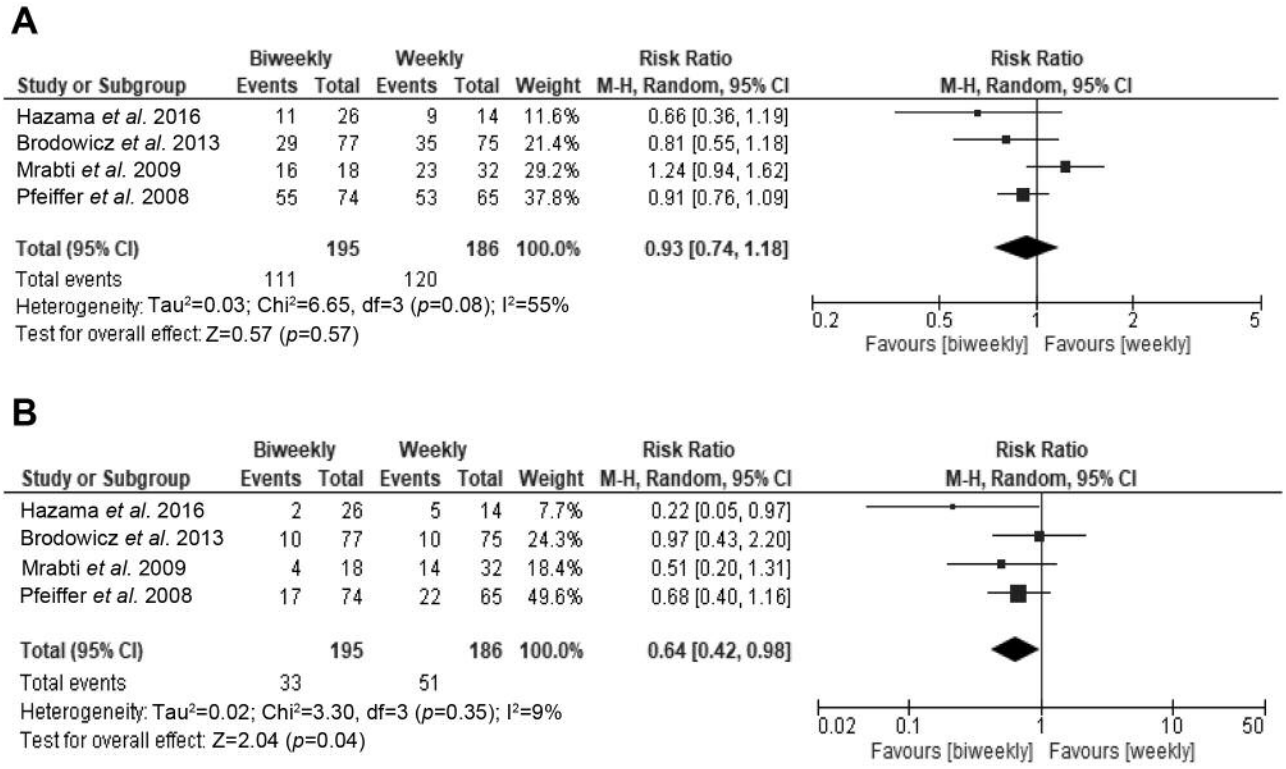

Figure 2. *Meta-analysis of objective response rate (A) and disease-control rate (B) between biweekly cetuximab and weekly cetuximab in patients with metastatic colorectal cancer.*

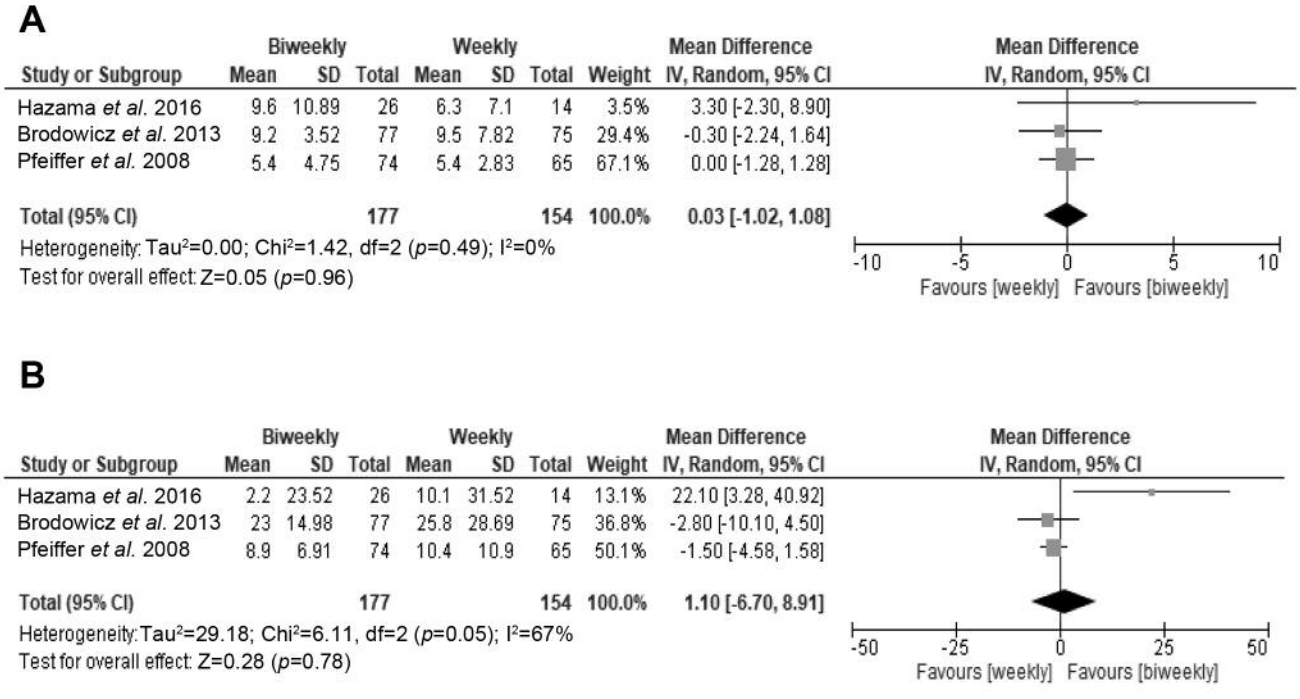

Figure 3. *Meta-analysis of progression-free survival (A) and overall survival (B) between biweekly cetuximab and weekly cetuximab in patients with metastatic colorectal cancer.*

Table II. *Comparison of adverse events between biweekly and weekly cetuximab.*

Outcome	No. of studies	Sample size (biweekly/weekly)	Risk Ratio	95%CI	*p*-Value	Heterogeneity		
						χ^2	I^2 (%)	*p*-Value
Skin toxicity (any grade)	3	229 (118/111)	0.91	0.67-1.24	0.56	5.51	64	0.06
Skin toxicity (grade 3 or 4)	4	381 (195/186)	0.73	0.25-2.14	0.56	5.23	43	0.16
Gastrointestinal toxicity (grade 3 or 4)	4	381 (195/186)	0.68	0.28-1.65	0.39	4.90	39	0.18
Hematologic toxicity (grade 3 or 4)	4	381 (195/186)	1.11	0.70-1.75	0.66	3.18	6	0.36

CI: Confidence interval.

(500 mg/m^2) in patients with mCRC as monotherapy or in combination with oxaliplatin- and irinotecan-based chemotherapy, such as OPTIMIX-ACROSS, NORDIC-7.5, and CELINE studies (28-30). Recently, the combination of a triple-drug chemotherapy regimen (FOLFOXIRI) with biweekly cetuximab as a first-line treatment of mCRC showed promising activity along with safety concerns in a single-arm phase II trial (31) and a randomized trial (32).

However, studies examining a direct comparison of efficacy and safety between biweekly cetuximab and conventional weekly cetuximab are limited. Among the included studies in our meta-analysis, the largest randomized phase II study by the Central European Cooperative Oncology Group (CECOG) (18) compared the efficacy and safety of FOLFOX4 plus biweekly cetuximab with weekly cetuximab in the first-line treatment of patients with *KRAS* wild-type mCRC. Of the 152 randomized eligible patients, 75 were treated weekly and 77 biweekly; ORRs (53% *vs*. 62%), PFS (median: 9.5 *vs*. 9.2 months), OS (median: 25.8 *vs*. 23.0 months), and DCR (both 87%) were comparable. Frequencies of grade 3/4 adverse events in the two groups were similar. Notably, the higher single dose of cetuximab in the biweekly regimen did not lead to any increased incidence of allergic reactions or infusion-related reactions. It is noteworthy that this trial was not statistically powered to establish non-inferiority of the biweekly regimen; therefore, we conducted a meta-analysis with an integration of related studies to make a current conclusion. The given results from this meta-analysis strongly support the findings of the randomized phase II study (18). The reason for the preferable DCR in the biweekly regimen is unknown. This result may suggest the better application of this regimen in the salvage setting considering the deteriorated patients' status and the therapeutic goal.

Cetuximab is unlikely to interact with other anti-cancer agents, although its rather long half-life and subsequent retention in the body has resulted in investigations of potential interactions between weekly cetuximab and irinotecan (25, 33). Czejka *et al*. (34) investigated the pharmacokinetics of irinotecan and the metabolite in combination with biweekly cetuximab in patients with mCRC and demonstrated that no significant pharmacokinetic interaction was observed between irinotecan and biweekly cetuximab.

This study has several limitations that must be taken into account. Only one randomized study was included in this meta-analysis, and the sample size of all included studies was relatively small. Therefore, there may have been considerable selection bias. All included studies were conducted before the general application of extended *RAS* testing, which may mislead the given results regarding current clinical settings.

In conclusion, biweekly administration of cetuximab with equivalent efficacy and safety to conventional weekly cetuximab would be beneficial for both patients and health resources.

Conflicts of Interest

The Authors have no conflicts of interest in relation to this study.

Authors' Contributions

Study concept and design: Matsuda A and Yamada T; Acquisition of data: Jamjittrong S, Kamonvarapitak T, and Sekiguchi K; Analysis and interpretation of data: Jamjittrong S, Shinji S, R Ohta, and Sonoda H; Drafting of the manuscript: Matsuda A and Jamjittrong S; Study supervision: Miyashita M, Suzuki H and Yoshida H.

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References

1 Li S, Schmitz KR, Jeffrey PD, Wiltzius JJ, Kussie P and Ferguson KM: Structural basis for inhibition of the epidermal growth factor receptor by cetuximab. Cancer Cell *7(4)*: 301-311, 2005. PMID: 15837620. DOI: 10.1016/j.ccr.2005.03.003

2 Huang SM, Bock JM and Harari PM: Epidermal growth factor receptor blockade with c225 modulates proliferation, apoptosis, and radiosensitivity in squamous cell carcinomas of the head and neck. Cancer Res *59(8)*: 1935-1940, 1999. PMID: 10213503.

3 Perrotte P, Matsumoto T, Inoue K, Kuniyasu H, Eve BY, Hicklin DJ, Radinsky R and Dinney CP: Anti-epidermal growth factor receptor antibody c225 inhibits angiogenesis in human transitional cell carcinoma growing orthotopically in nude mice. Clin Cancer Res *5(2)*: 257-265, 1999. PMID: 10037173.

4 Li X, Lu Y, Liang K, Pan T, Mendelsohn J and Fan Z: Requirement of hypoxia-inducible factor-1alpha down-regulation in mediating the antitumor activity of the anti-epidermal growth factor receptor monoclonal antibody cetuximab. Mol Cancer Ther *7(5)*: 1207-1217, 2008. PMID: 18483308. DOI: 10.1158/1535-7163.MCT-07-2187

5 Bokemeyer C, Bondarenko I, Hartmann JT, de Braud F, Schuch G, Zubel A, Celik I, Schlichting M and Koralewski P: Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: The OPUS study. Ann Oncol *22(7)*: 1535-1546, 2011. PMID: 21228335. DOI: 10.1093/annonc/mdq632

6 Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, Donea S, Ludwig H, Schuch G, Stroh C, Loos AH, Zubel A and Koralewski P: Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol *27(5)*: 663-671, 2009. PMID: 19114683. DOI: 10.1200/JCO.2008.20.8397

7 Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I and Van Cutsem E: Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med *351(4)*: 337-345, 2004. PMID: 15269313. DOI: 10.1056/NEJMoa033025

8 Ocvirk J, Brodowicz T, Wrba F, Ciuleanu TE, Kurteva G, Beslija S, Koza I, Papai Z, Messinger D, Yilmaz U, Faluhelyi Z, Yalcin S, Papamichael D, Wenczl M, Mrsic-Krmpotic Z, Shacham-Shmueli E, Vrbanec D, Esser R, Scheithauer W and Zielinski CC: Cetuximab plus FOLFOX6 or FOLFIRI in metastatic colorectal cancer: CECOG trial. World J Gastroenterol *16(25)*: 3133-3143, 2010. PMID: 20593498. DOI: 10.3748/wjg.v16.i25.3133

9 Van Cutsem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pinter T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J and Rougier P: Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med *360(14)*: 1408-1417, 2009. PMID: 19339720. DOI: 10.1056/NEJMoa0805019

10 Van Cutsem E, Kohne CH, Lang I, Folprecht G, Nowacki MP, Cascinu S, Shchepotin I, Maurel J, Cunningham D, Tejpar S, Schlichting M, Zubel A, Celik I, Rougier P and Ciardiello F: Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: Updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol *29(15)*: 2011-2019, 2011. PMID: 21502544. DOI: 10.1200/JCO.2010.33.5091

11 Tabernero J, Cervantes A, Martinelli E, Vega-Villegas E, Rojo F, Casado AP, Ciardiello F, Zubel A and Baselga J: Optimal dose of cetuximab (c) given every 2 weeks (q2w): A phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of weekly (q1w) and q2w schedules in patients (pts) with metastatic colorectal cancer (mCRC). J Clin Oncol *24(18 suppl)*: 142s, 2006. DOI: 10.1200/jco.2006.24.18_suppl.3085

12 Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ and McQuay HJ: Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials *17(1)*: 1-12, 1996. PMID: 8721797. DOI: 10.1016/0197-2456(95)00134-4

13 Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M and Tugwell P: The newcastle-ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa (ON): Ottawa Hospital Research Institute; 2009.

14 Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA and Group P-P: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev *4:* 1, 2015. PMID: 4320440. DOI: 10.1186/2046-4053-4-1

15 DerSimonian R and Laird N: Meta-analysis in clinical trials. Control Clin Trials *7(3)*: 177-188, 1986. PMID: 3802833. DOI: 10.1016/0197-2456(86)90046-2

16 Li X, Mao W, Guo D and Xu H: Clinicopathological significance and diagnostic value of dlec1 hypermethylation in lung cancer: A meta-analysis. J Nippon Med Sch *86(2)*: 62-69, 2019. PMID: 31130567. DOI: 10.1272/jnms.JNMS.2019_86-201

17 Higgins JP, Thompson SG, Deeks JJ and Altman DG: Measuring inconsistency in meta-analyses. BMJ *327(7414)*: 557-560, 2003. PMID: 192859. DOI: 10.1136/bmj.327.7414.557

18 Brodowicz T, Ciuleanu TE, Radosavljevic D, Shacham-Shmueli E, Vrbanec D, Plate S, Mrsic-Krmpotic Z, Dank M, Purkalne G, Messinger D and Zielinski CC: FOLFOX4 plus cetuximab administered weekly or every second week in the first-line treatment of patients with KRAS wild-type metastatic colorectal cancer: A randomized phase II CECOG study. Ann Oncol *24(7)*: 1769-1777, 2013. PMID: 23559149. DOI: 10.1093/annonc/mdt116

19 Hazama S, Maeda H, Iwamoto S, Kim HM, Takemoto H, Kobayashi K, Sakamoto J, Nagata N, Oba K and Mishima H: A phase II study of xelox and cetuximab as first-line therapy in patients with KRAS wild type metastatic colorectal cancer (FLEET2 study). Clin Colorectal Cancer *15(4)*: 329-336, 2016. PMID: 27507128. DOI: 10.1016/j.clcc.2016.07.003

20 Mrabti H, De la Fouchardiere C, Desseigne F, Dussart S, Negrier S and Errihani H: Irinotecan associated with cetuximab given every 2 weeks versus cetuximab weekly in metastatic colorectal cancer. J Cancer Res Ther *5(4)*: 272-276, 2009. PMID: 20160361. DOI: 10.4103/0973-1482.59907

21 Pfeiffer P, Nielsen D, Bjerregaard J, Qvortrup C, Yilmaz M and Jensen B: Biweekly cetuximab and irinotecan as third-line therapy in patients with advanced colorectal cancer after failure to irinotecan, oxaliplatin and 5-fluorouracil. Ann Oncol *19(6)*: 1141-1145, 2008. PMID: 18281264. DOI: 10.1093/annonc/mdn020

22 Garcia-Foncillas J, Sunakawa Y, Aderka D, Wainberg Z, Ronga P, Witzler P and Stintzing S: Distinguishing features of cetuximab and panitumumab in colorectal cancer and other solid tumors. Front Oncol *9:* 849, 2019. PMID: 31616627. DOI: 10.3389/fonc.2019.00849

23 Albanell J, Codony-Servat J, Rojo F, Del Campo JM, Sauleda S, Anido J, Raspall G, Giralt J, Rosello J, Nicholson RI, Mendelsohn J and Baselga J: Activated extracellular signal-regulated kinases: Association with epidermal growth factor receptor/transforming growth factor alpha expression in head and neck squamous carcinoma and inhibition by anti-epidermal growth factor receptor treatments. Cancer Res *61(17)*: 6500-6510, 2001. PMID: 11522647.

24 Baselga J: The EGFR as a target for anticancer therapy—focus on cetuximab. Eur J Cancer *37(Suppl 4):* S16-22, 2001. PMID: 11597400. DOI: 10.1016/s0959-8049(01)00233-7

25 Delbaldo C, Pierga JY, Dieras V, Faivre S, Laurence V, Vedovato JC, Bonnay M, Mueser M, Nolting A, Kovar A and Raymond E: Pharmacokinetic profile of cetuximab (erbitux) alone and in combination with irinotecan in patients with advanced EGFR-positive adenocarcinoma. Eur J Cancer *41(12)*: 1739-1745, 2005. PMID: 16051481. DOI: 10.1016/j.ejca.2005.04.029

26 Ettlinger DE, Mitterhauser M, Wadsak W, Ostermann E, Farkouh A, Schueller J and Czejka M: In vivo disposition of irinotecan (CPT-11) and its metabolites in combination with the monoclonal antibody cetuximab. Anticancer Res *26(2B)*: 1337-1341, 2006. PMID: 16619542.

27 Tabernero J, Ciardiello F, Rivera F, Rodriguez-Braun E, Ramos FJ, Martinelli E, Vega-Villegas ME, Rosello S, Liebscher S, Kisker O, Macarulla T, Baselga J and Cervantes A: Cetuximab administered once every second week to patients with metastatic colorectal cancer: A two-part pharmacokinetic/pharmacodynamic phase I dose-escalation study. Ann Oncol *21(7)*: 1537-1545, 2010. PMID: 19940007. DOI: 10.1093/annonc/mdp549

28 Fernandez-Plana J, Pericay C, Quintero G, Alonso V, Salud A, Mendez M, Salgado M, Saigi E, Cirera L and Group AS: Biweekly cetuximab in combination with FOLFOX-4 in the first-line treatment of wild-type KRAS metastatic colorectal cancer: Final results of a phase II, open-label, clinical trial (OPTIMIX-ACROSS study). BMC Cancer *14:* 865, 2014. PMID: 25417182. DOI: 10.1186/1471-2407-14-865

29 Kotake M, Aoyama T, Munemoto Y, Doden K, Kataoka M, Kobayashi K, Nishimura G, Fujita H, Nakamura K, Takehara A, Tanaka C, Sakamoto J, Nagata N, Oba K and Kondo K: Multicenter phase II study of infusional 5-fluorouracil (5-FU), leucovorin, and oxaliplatin, plus biweekly cetuximab as first-line treatment in patients with metastatic colorectal cancer (CELINE trial). Oncol Lett *13(2)*: 747-753, 2017. PMID: 28356954. DOI: 10.3892/ol.2016.5505

30 Pfeiffer P, Sorbye H, Qvortrup C, Karlberg M, Kersten C, Vistisen K, Lindh B, Bjerregaard JK and Glimelius B: Maintenance therapy with cetuximab every second week in the first-line treatment of metastatic colorectal cancer: The NORDIC-7.5 study by the nordic colorectal cancer biomodulation group. Clin Colorectal Cancer *14(3)*: 170-176, 2015. PMID: 25956187. DOI: 10.1016/j.clcc.2015.03.002

31 Saridaki Z, Androulakis N, Vardakis N, Vamvakas L, Kabouraki E, Kalbakis K, Hatzidaki D, Voutsina A, Mavroudis D, Georgoulias V and Souglakos J: A triplet combination with irinotecan (CPT-11), oxaliplatin (LOHP), continuous infusion 5-fluorouracil and leucovorin (FOLFOXIRI) plus cetuximab as first-line treatment in KRAS wt, metastatic colorectal cancer: A pilot phase II trial. Br J Cancer *107(12)*: 1932-1937, 2012. PMID: 23169296. DOI: 10.1038/bjc.2012.509

32 Cremolini C, Antoniotti C, Lonardi S, Aprile G, Bergamo F, Masi G, Grande R, Tonini G, Mescoli C, Cardellino GG, Coltelli L, Salvatore L, Corsi DC, Lupi C, Gemma D, Ronzoni M, Dell'Aquila E, Marmorino F, Di Fabio F, Mancini ML, Marcucci L, Fontanini G, Zagonel V, Boni L and Falcone A: Activity and safety of cetuximab plus modified FOLFOXIRI followed by maintenance with cetuximab or bevacizumab for ras and braf wild-type metastatic colorectal cancer: A randomized phase 2 clinical trial. JAMA Oncol *4(4)*: 529-536, 2018. PMID: 29450468. DOI: 10.1001/jamaoncol.2017.5314

33 Reynolds NA and Wagstaff AJ: Cetuximab: In the treatment of metastatic colorectal cancer. Drugs *64(1)*: 109-118; discussion 119-121, 2004. PMID: 14723561. DOI: 10.2165/00003495-200464010-00007

34 Czejka M, Gruenberger B, Kiss A, Farkouh A and Schueller J: Pharmacokinetics of irinotecan in combination with biweekly cetuximab in patients with advanced colorectal cancer. Anticancer Res *30(6)*: 2355-2360, 2010. PMID: 20651393.

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