Table 1. Patient characteristics

Characteristic		Number of patients (N = 124)
Median age, years (range)		63 (23–79)
Gender	Male/female	74/50
Performance status	0–1/2	111/13
Pathology	Wel or mod/por	113/11
Peritoneal metastasis	Yes/no	26/98
Liver metastasis	Yes/no	69/55
Metastatic sites	1–2/> 3	99/25
First-line treatment	FOLFOX/FOLFOX+BV	107/17
Response to first-line FOLFOX	CR/PR/SD/PD	0/54/47/23
PFS of first-line FOLFOX	< 6 months/> 6 months	49/75
Cause of oxaliplatin discontinuation	Disease progression/other	65/59
Leukocyte count (/L)	$< 8\times10^9/\geq 8\times10^9$	110/14
ALP (IU/L)	< 400/≥ 400	70/54
LDH (IU/L)	< 400/≥ 400	98/26
CEA (ng/mL)	< 500/> 500	110/14

Abbreviations: ALP = alkaline phosphatase; CEA = carcinoembryonic antigen; CR = complete response; LDH = lactate dehydrogenase; mod = moderately differentiated adenocarcinoma; PD = progressive disease; PFS = progression-free survival; por = poorly differentiated adenocarcinoma; PR = partial response; SD = stable disease; wel = well-differentiated adenocarcinoma.

A multivariate prognostic model was constructed by incorporating all 5 prognostic factors, and patients were categorized into 3 risk groups: patients without any prognostic factors (low-risk, n = 55), patients with 1 prognostic factor (intermediate-risk, n = 32), and patients with 2 or more prognostic factors (high-risk, n = 37). Overall survival from initiation of second-line chemotherapy was 23.5 months (95% CI, 18.7–not reached), 14.6 months (95% CI, 8.4–19.9), and 5.5 months (95% CI, 4.2–8.9), respectively (Figure 1).

Significant survival differences among the 3 risk groups were observed ($p < .001$). PFS of second-line chemotherapy of each risk groups was 6.1 months (95% CI, 4.1–8.5), 3.4 months (95% CI, 2.3–5.4), and 2.6 months (95% CI, 1.6–2.9), respectively (Figure 2), and significant differences were observed between each groups ($p < .001$). If we limited the patients who did not receive anti-EGFR antibody (n = 91), a similar difference in overall survival was observed in these 3 risk groups (median 18.8 months vs 14.1months vs 5.0 months, $p < .001$).

Salvage chemotherapy after disease progression was performed in 95% (46 of 48 progressed patients) of good-risk patients, 67% (21 of 31 progressed patients) of intermediate-risk patients, and 41% (15 of 36 progressed patients) of high-risk patients; all between-group differences were statistically significant ($p < .001$).

DISCUSSION

In this study, we identified 5 independent prognostic factors in patients with MCRC undergoing irinotecan-based second-line chemotherapy after first-line FOLFOX. Additionally, we defined 3 risk groups using these 5 prognostic factors that significantly differed in survival rate and probability of receiving further salvage chemotherapy. To the best of our knowledge, this is the first report to evaluate pretreatment clinical prognostic factors in MCRC patients undergoing second-line therapy. These results may be useful when selecting the appropriate treatment line for cetuximab.

Cetuximab appears to improve the prognosis of MCRC patients when used in the third-line setting compared to best supportive care alone, and irinotecan plus cetuximab has been shown to result in a higher response rate in patients with irinotecan-refractory MCRC (over half of whom also had oxaliplatin-refractory disease) compared to cetuximab alone.[5,6] In contrast, the combination of irinotecan plus cetuximab did not improve overall survival in the second-line setting following first-line oxaliplatin-based chemotherapy.[7]

Based on these results, it may be optimal to use cetuximab in the third-line setting due to its toxicity profile and ability to restore irinotecan responsiveness even after irinotecan failure. However, considering the efficacy of cetuximab in MCRC, opportunities to administer cetuximab to MCRC patients, particularly those with wild-type *KRAS* disease, should not be missed.[9–12]

Our risk classification results suggest that cetuximab is not required during second-line treatment in low-risk patients due to their favorable prognosis (almost as long as first-line treatment [> 20 months]) and higher probability of receiving salvage chemotherapy (> 90%). In contrast, it might be optimal to use cetuximab in the second-line setting for high-risk patients with wild-type *KRAS* disease, to ensure that the opportunity to use cetuximab is not lost.

Determination of the optimal treatment for patients with intermediate-risk disease is more challenging and should therefore be conducted on an individual basis. For example, as PS2 had a significantly higher HR compared to other prognostic factors, cetuximab may be appropriate in second-line treatment of PS2 patients without prognostic factors. Risk classification may also

Table 2. Univariate survival analysis

Characteristic	Cut-off	n	HR	95% CI	*p* value
Age (years)	< 65	50	0.85	0.53–1.36	.51
	≥ 65	74	ref		
Gender	Male	74	0.61	0.38–0.98	.04
	Female	50	ref		
Performance status	0–1	111	ref		
	2	13	4.2	2.3–7.6	< .001
Pathology	Well to mod	115	ref		
	Por	9	3.4	1.7–6.9	.001
Peritoneal metastasis	Yes	26	3.1	1.87–5.1	< .001
	No	98	ref		
Liver metastasis	Yes	69	1.37	0.86–2.1	.18
	No	55	ref		
Metastatic site	1 or 2	99	ref		
	≥ 3	25	1.94	1.12–3.36	.017
Response to FOLFOX	Responder	54	ref		
	Nonresponder	70	1.92	1.18–3.2	.008
Cause of oxaliplatin discontinuation	Progression	65	2.18	1.36–3.49	.001
	Other	59	ref		
PFS of first-line FOLFOX (months)	< 6 months	49	2.95	1.81–4.81	< .001
	≥ 6 months	75	ref		
Leukocyte count (/L)	$< 8\times10^9$	110	ref		
	$> 8\times10^9$	14	3.7	1.97–6.9	< .001
ALP (IU/L)	< 400	70	ref		
	≥ 400	54	1.81	1.13–2.9	.013
LDH (IU/L)	< 400	98	ref		
	≥ 400	26	2.78	1.61–4.8	< .001
CEA (ng/mL)	< 500	110	ref		
	≥ 500	14	2.36	1.26–4.1	.007

Abbreviations: ALP = alkaline phosphatase; CEA = carcinoembryonic antigen; CI = confidence interval; CR = complete response; HR = hazard ratio; LDH = lactate dehydrogenase; mod = moderately differentiated adenocarcinoma; PD = progressive disease; PFS = progression-free survival; por = poorly differentiated adenocarcinoma; PR = partial response; ref = reference value; SD = stable disease; wel = well-differentiated adenocarcinoma.

Table 3. Multivariate survival analysis[1]

Factors	HR	*p* value	95% CI
Performance status 2	4.8	< .001	2.55–10.2
Pathologic por	3.50	.002	1.60–7.96
Peritoneal met	2.10	.009	1.20–3.68
LDH ≥ 400 (IU/L)	2.05	.019	1.13–3.74
PFS < 6 months	1.80	.040	1.08–3.01

[1]Adjusted by gender, liver metastasis, metastatic sites, response to FOLFOX, cause of oxaliplatin discontinuation, leukocyte count, ALP, and CEA.
Abbreviations: CI = confidence interval; HR = hazard ratio; LDH = lactate dehydrogenase; met = metastasis; PFS = progression-free survival; por = poorly differentiated adenocarcinoma.

be important for designing future clinical trials evaluating second-line treatment of MCRC and should be included as a stratifying factor considering the significantly different prognosis of each risk group.

This analysis had several methodologic limitations. First, it was a retrospective cohort design that evaluated the association between various prognostic factors and overall survival in patients who received several irinotecan-containing regimens (FOLFIRI, irinotecan, and S-1 plus irinotecan). However, the classification system used in this study has also proven to be similarly useful when patients are stratified by treatment regimen or bevacizumab use.

Second, the utility of salvage chemotherapy other than cetuximab or panitumumab is unknown, as no other treatment has been demonstrated to prolong the survival of patients with MCRC. However, the probability of receiving salvage chemotherapy in our study suggests the possibility that patients may have a chance to receive benefit from third-line chemotherapy, including anti-EGFR antibody therapy (in wild-type *KRAS* cases).

Third, *KRAS* status was not evaluated in all patients, since most of the patients initiated treatment before the introduction of cetuximab. As cetuximab should only be used in patients with wild-type *KRAS* disease, *KRAS* status should be evaluated in all patients prior to selection of third-line

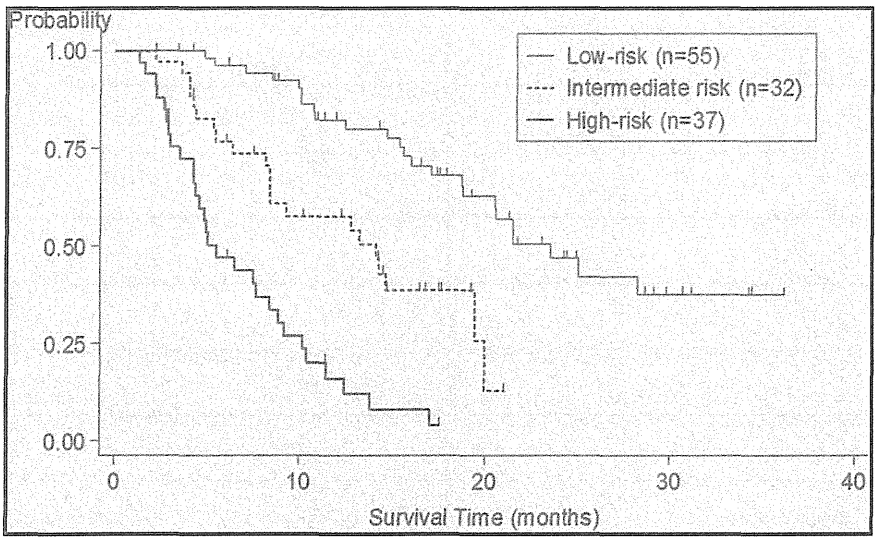

Figure 1. Overall survival according to risk group. Median overall survival from initiation of second-line chemotherapy was 23.5 months (95% CI, 18.7–not reached) in the low-risk group, 14.6 months (95% CI, 8.4–19.9) in the intermediate-risk group, and 5.5 months (95% CI, 4.2–8.9) in the high-risk group.

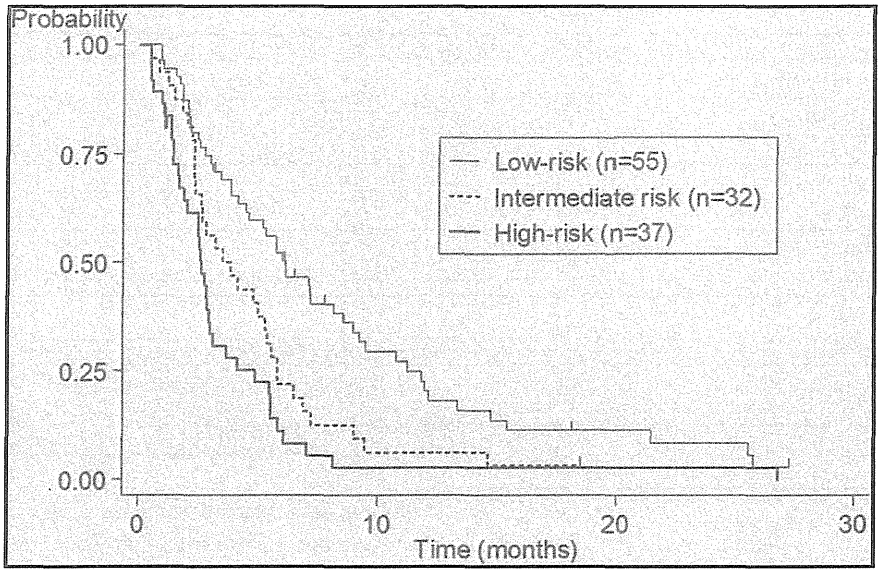

Figure 2. Progression free survival according to risk group. Median progression free survival from initiation of second-line chemotherapy was 6.1 months (95% CI, 4.1–8.5) in the low-risk group, 3.4 months (95% CI, 2.3–5.4) in the intermediate-risk group, and 2.6 months (95% CI, 1.6–2.9) in the high-risk group.

chemotherapy. Finally, the moderate sample size of this study necessitates confirmation of these results in a large cohort study, similar to the EPIC study.

In summary, several prognostic factors for survival after second-line therapy for MCRC and probability of receiving salvage chemotherapy were identified in this study. This risk classification system might be useful for determining which patients should receive cetuximab in the second-line setting rather than the third-line setting.

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Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

—Note—

進行・再発大腸がん患者の mFOLFOX6 及び FOLFIRI 療法における悪心・嘔吐発現状況に関する後ろ向き調査

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Induced Nausea and Vomiting Induced by mFOLFOX6 and FOLFIRI with Advanced Colorectal Cancer: A Retrospective Survey

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Controlling of chemotherapy-induced nausea and vomiting (CINV) is very important for the continuation of chemotherapy, especially for outpatients. CINV can significantly affect a patient's quality of life, leading to poor compliance with further chemotherapy treatment. In this retrospective study, we investigated the incidence of CINV induced by mFOLFOX6 and FOLFIRI in 59 outpatients (32 males and 27 females) with advanced colorectal cancer to evaluate CINV severity using the Common Terminology Criteria for Adverse Events v.3.0. The incidence of nausea in the female group receiving FOLFIRI (grade 1: 66.7% and grade 2: 20.0%) was significantly higher than that in the male group (grade 1: 23.1% and grade 2: 7.7%, $p=0.0066$). The incidence of nausea in the younger (<63 years old) group receiving FOLFIRI (grade 1: 57.1% and grade 2: 28.6%) was significantly higher than that in the older (≧63 years old) group (grade 1: 35.7%, $p=0.0031$). Multivariable logistic regression analysis indicated that patients who were female or younger had a significantly higher incidence of nausea or vomiting than patients who were male or older, respectively, when treated with FOLFIRI. This suggests that gender (female) and age (younger) are factors predicting poor antiemetic control in outpatients receiving FOLFIRI, but not those treated with mFOLFOX6. Information on such predictive factors should be useful to promote the effectiveness of cancer chemotherapy.

Key words——antiemesis; chemotherapy-induced nausea and vomiting (CINV); FOLFIRI; mFOLFOX6; age; gender

緒　　言

がん化学療法の副作用の中で患者にとって最もつらい症状の1つである悪心・嘔吐に対する支持療法では，5-hydroxytryptamine-3 受容体拮抗剤 (5-HT_3) と dexamethasone (Dexa)，及び高度催吐性薬剤に対しては aprepitant を併用することが American Society of Clinical Oncology (ASCO) や National Comprehensive Cancer Network (NCCN) のガイドラインで推奨され，その発現リスク別の支持療法も示されている.[1,2] また最近，日本においても制吐薬適正使用ガイドライン[3]が出版されたが，かならずしもガイドラインに沿った支持療法が化学療法時に用いられているわけではないとの報告もあり，ガイドラインに基づいた制吐支持療法の実施が求められている.[4]

一方，外来で行われるがん化学療法は年々増加している．その背景には，副作用の少ない化学療法レジメンの開発や，支持療法剤の進歩により，外来でも安全に管理することが可能となった[5]こと，それにより患者の生活スタイルが維持されるようになったこと，さらには外来化学療法加算の創設が挙げられる．これらの利点を最大限に活かすためには，抗がん剤の投与時のみならず在宅時に発現する副作用

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についても，その発現状況を正確に把握するとともに，適切な支持療法の実施に努めることが重要である．また，悪心・嘔吐の発現リスクが高まる患者個別の因子として，女性あるいは若年者が高度催吐リスクに分類されているcisplatinで報告[6,7]されているが，中等度催吐リスクに分類されている薬剤については，同様な関連性を示す報告はない．

そこで今回，中等度催吐リスクに分類されている薬剤について悪心・嘔吐の発現リスクを把握し，適正な制吐支持療法を実施する目的で，特に進行・再発大腸がん患者において広く実施されているmFOLFOX6療法及びFOLFIRI療法に着目した．これらのレジメンはともに進行・再発大腸がんの一次治療及び二次治療で用いられ，同等の効果であると報告[8]されているが，副作用の特徴は異なっている．悪心・嘔吐の発現頻度は報告[8]されているが，患者個別の因子に関する報告はない．今回，これらのレジメンを実施した患者を対象に，診療記録を用いた後ろ向き調査にて検討を行ったところ，若干の知見を得たので報告する．

方　　法

1. 対象患者　愛知県がんセンター中央病院において，2009年6月25日から2010年5月25日までに外来化学療法室にて制吐支持療法として5-HT_3及びDexaの前投薬を含むmFOLFOX6療法又はFOLFIRI療法を施行された進行・再発大腸がん患者を対象とした．ただし，抗がん剤投与が初回の患者，オピオイドを併用していた患者は対象より除外した．本研究の実施に当たり，愛知県がんセンター倫理審査委員会の承認を得た（受付番号3-26）．

2. 調査方法　全対象症例の診療録（医師記録，看護記録，薬剤管理指導記録）及び処方・注射オーダリング情報より，年齢，性別，Performance Status (PS)，合併症，及び悪心・嘔吐の発現を調査した．悪心・嘔吐に関しては，Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v. 3.0) に基づき，前回の化学療法後から今回の来院時までの発現についてGrade評価された記録を抽出した．なお，調査期間中に調査日を6回設け，調査日直近に実施された化学療法について調査し，前回までの調査で対象とした患者は除外した．調査日の設定については，事前に対象患者の情報を得ることなく設定した．

3. 患者個別因子の検討　悪心・嘔吐の発現頻度と性別及び年齢との関連性の検討を，mFOLFOX6療法を施行した患者及びFOLFIRI療法を施行した患者とに分けて行った．2群比較にて発現頻度と性別及び年齢の関連性を検討した後，各因子の交絡による影響を除いた結果を得るため，ロジスティック解析を行った．なお，年齢の2群比較については，全体の中央値であった63歳を基準とし，63歳未満群及び63歳以上群の2群に分けて比較した．

4. 統計学的解析　Grade評価を含めた悪心・嘔吐の発現頻度の比較には，2群比較ではMann-Whitney *U*-testを用い，$p<0.05$の場合を有意とした．ロジスティック解析についてはエクセル統計2008（株式会社社会情報サービス）を用いて行い，$p<0.05$の場合を有意とした．

結　　果

1. 患者背景　患者背景をTable 1に示す．mFOLFOX6療法が施行された患者群とFOLFIRI療法が施行された患者群との間で患者背景に差は認められず，また特記すべき合併症もなかった．mFOLFOX6療法及びFOLFIRI療法のレジメンについて，Table 2に示した．

2. 悪心・嘔吐発現状況　mFOLFOX6療法が施行された患者群では，悪心の発現頻度はGrade 1が45.2%（14/31），Grade 2が3.2%（1/31）であり，嘔吐の発現頻度はGrade 1が12.9%（4/31），Grade 2が3.2%（1/31）であった．FOLFIRI療法が施行された患者群では，悪心の発現頻度はGrade 1が46.4%（13/28），Grade 2が14.3%（4/28）であり，嘔吐の発現頻度はGrade 1が14.3%（4/28），Grade 2が3.6%（1/28）であった．両群の間に違いは認められなかった［Mann-Whitney *U* test, $p=0.1972$（悪心），$p=0.8613$（嘔吐）］．

制吐支持療法については，5-HT_3及びDexaの前投薬について薬剤又は投与量の違いが認められた．前投薬の5-HT_3は1例でazasetron 10 mg，それ以外ではgranisetron 3 mg，同じく前投薬のDexaは5例で16 mg，1例で12 mg，それ以外では8 mgであった．また，化学療法後にDexaが12例で投与されていた．

mFOLFOX6療法が施行された患者群では，化学

Table 1. Characteristics of Patients

	All	mFOLFOX6	FOLFIRI
Number of patients	59	31	28
Gender			
Male/Female	32/27	19/12	13/15
Age			
Median	63	64	63
Range	40–82	46–82	40–74
Performance status			
0/1/2	10/48/1	5/25/1	5/23/0
Number of prior chemotherapy			
1/2/3/4/5	11/23/14/5/6	8/9/9/2/3	3/14/5/3/3
Number of cycle			
Median	5	4	6
Range	2–33	2–11	2–33
Relative dose intensity			
Average	93.1	95.2	90.7
Range	60–100	65–100	60–100

Table 2. Chemotherapy Regimens

		Number of patients	
		Male	Female
mFOLFOX6	L-OHP 85 mg/m^2, levofolinate 200 mg/m^2, 5-FU 400 mg/m^2, 5-FU 2400 mg/m^2, every 2 weeks	4	2
mFOLFOX6+BV	L-OHP 85 mg/m^2, levofolinate 200 mg/m^2, 5-FU 400 mg/m^2, 5-FU 2400 mg/m^2, BV 5 or 10 mg/kg, every 2 weeks	15	10
FOLFIRI	CPT-11 150 mg/m^2, levofolinate 200 mg/m^2, 5-FU 400 mg/m^2, 5-FU 2400 mg/m^2, every 2 weeks	2	1
FOLFIRI+BV	CPT-11 150 mg/m^2, levofolinate 200 mg/m^2, 5-FU 400 mg/m^2, 5-FU 2400 mg/m^2, BV 5 or 10 mg/kg, every 2 weeks	11	14

BV: bevacizumab, CPT-11: irinotecan, L-OHP: oxaliplatin.

療法後の Dexa 投与ありの場合，Grade 1 が 60.0% (3/5)であり，化学療法後の Dexa 投与なしの場合，Grade 1 が 42.3% (11/26)，Grade 2 が 3.8% (1/26) であった．FOLFIRI 療法が施行された患者群では，化学療法後の Dexa 投与ありの場合，Grade 1 が 14.3% (2/7)，Grade 2 が 14.3% (2/7) であり，化学療法後の Dexa 投与なしの場合，Grade 1 が 52.4% (11/21)，Grade 2 が 9.5% (2/21)であった．いずれにおいても化学療法後の Dexa 投与有無による有意な差は認められなかった [Mann-Whitney U test, $p>0.9999$ (mFOLFOX6), $p=0.7498$ (FOLFIRI)]．同様に嘔吐でも化学療法後の Dexa 投与有無による発現頻度の違いは認められなかった．

3. 悪心・嘔吐の発現頻度に及ぼす性別の影響　mFOLFOX6 療法では男性と女性で有意な差は認められなかった (Table 3)．FOLFIRI 療法では悪心の発現頻度について女性が，男性と比較して有意に高率であった (Table 3)．

4. 悪心・嘔吐の発現頻度に及ぼす年齢の影響　mFOLFOX6 療法では 63 歳未満群と 63 歳以上群で有意な差は認められなかった (Table 3)．FOLFIRI 療法では悪心・嘔吐の発現頻度について 63 歳未満群が 63 歳以上群と比較して有意に高率であった (Table 3)．

5. レジメン別悪心・嘔吐の発現に関連する因子の多変量解析　各レジメンにおける悪心・嘔吐の発現頻度と性別及び年齢との関連性についてロジスティック回帰分析を行い，性別と年齢の交絡を調整した結果を得た (Table 4)．FOLFIRI 療法において，悪心については性別のオッズ比は 17.69 であ

り，女性での発現頻度が有意に高かった．嘔吐については性別のオッズ比は10.49であり，女性での発現頻度が高い傾向にあったが有意差は認められなかった．年齢ではオッズ比が0.85であり，若年者で発現頻度が有意に高かった．mFOLFOX6療法では性別，年齢による悪心・嘔吐発現頻度の有意差は認められなかった．

考　　察

今回，外来化学療法における制吐支持療法を用いたmFOLFOX6療法及びFOLFIRI療法における悪心の発現リスク因子について小規模ながら見い出すことができた．

Table 3. Effects of Gender and Age on Nausea (a) and Vomiting (b) Induced by mFOLFOX6 or FOLFIRI

(a) Nausea

		mFOLFOX6				FOLFIRI			
		G0	G1	G2	*p* value	G0	G1	G2	*p* value
Gender	Male	9	9	1	0.4885	9	3	1	*0.0066
	Female	7	5	0		2	10	3	
Age	<63	5	10	0	0.1685	2	8	4	*0.0031
	≧63	11	4	1		9	5	0	

(b) Vomiting

		mFOLFOX6				FOLFIRI			
		G0	G1	G2	*p* value	G0	G1	G2	*p* value
Gender	Male	16	2	1	>0.9999	12	1	0	0.1887
	Female	10	2	0		11	3	1	
Age	<63	12	3	0	0.6427	9	4	1	*0.0157
	≧63	14	1	1		14	0	0	

G0, G1, G2: Grade 0, Grade 1, Grade 2 (Common Terminology Criteria for Adverse Events version 3.0). Mann-Whitney *U*-test. *$p<0.05$.

FOLFIRI療法誘発性の悪心・嘔吐においては女性あるいは若年者で発現リスクが高まる傾向が見い出され，ASCOガイドラインや制吐剤適正使用ガイドラインに記載されている内容を支持するものであった．一方，mFOLFOX6誘発性悪心・嘔吐の発現リスク因子については，若年者で発現リスクが高まる傾向はあったが有意差は認められず，性別についてはFOLFIRIと同様な傾向は認められなかった．

mFOLFOX6療法とFOLFIRI療法の選択において，いずれも進行・再発大腸がんの一次及び二次治療として国際的ガイドラインで推奨されているが，本研究ではmFOLFOX6が一次治療に選択されている症例がほとんどであり，患者背景による選択の違いはなかった．また，先行化学療法での悪心・嘔吐の発現状況については，今回は後ろ向き調査であったため評価していないが，本研究では無作為に特定の日に治療を受けた患者を抽出して調査を行っているため結果に大きく影響することはないと考えられる．

制吐支持療法については5-HT_3及びDexaの前投薬を含む患者を対象としたが，5-HT_3及びDexaの前投薬について薬剤又は投与量の違いが認められ，また5-HT_3及びDexaの前投薬以外の制吐剤が併用されている症例もあった．前投薬の5-HT_3は1例でazasetron 10 mg，それ以外ではgranisetron 3 mgであったが，これらの薬剤の制吐効果は同等であると報告されている．[9] 前投薬のDexaが8 mgより多かった6例のうち5例，化学療法後にDexaが処方されていた12例のうち7例で悪心が発現していたが，年齢，性別，及びレジメンに偏りはなかった．このうち遅発性の悪心・嘔吐発現に影響すると考え

Table 4. Multivariable Logistic Regression Analysis

	Relative factor	Odds ratio	(95% Confidence Interval)	*p* value
1. mFOLFOX6				
Nausea	Gender (Male *vs.* Female)	0.64	(0.13–3.10)	0.58
	Age	0.91	(0.81–1.01)	0.09
Vomiting	Gender (Male *vs.* Female)	1.08	(0.15–7.76)	0.94
	Age	0.96	(0.85–1.08)	0.52
2. FOLFIRI				
Nausea	Gender (Male *vs.* Female)	17.69	(2.20–142.1)	0.007
	Age	0.91	(0.82–1.01)	0.09
Vomiting	Gender (Male *vs.* Female)	10.49	(0.39–284.7)	0.16
	Age	0.85	(0.74–0.99)	0.04

られる化学療法後のDexa投与有無による悪心・嘔吐の発現頻度を比較したところ，違いは認められなかった．さらに5-HT_3及びDexa以外の制吐剤について，59例中16例で処方がされていたが，服用状況については確認できなかった．16例の処方内容としては，メトクロプラミドやラモセトロンの内服，ドンペリドン坐薬，及び予測性嘔吐を抑制するといわれているベンゾジアゼピン系薬剤等であった．処方されていた患者のうち13例が悪心・嘔吐発現例であり，そのうち9例が女性，10例が63歳未満であった．よって，これらの制吐剤がリスクを軽減することによるリスク因子に対する影響があったとは考え難く，今回見い出されたリスク因子の結果には影響を及ぼしていないと考えられる．

mFOLFOX6とFOLFIRIは5-FUとlevofolinateの併用療法に，oxaliplatin（L-OHP）又はirinotecan（CPT-11）を組み合わせたレジメンである．L-OHPとCPT-11はASCOのガイドラインにて中等度催吐性薬剤に分類されており，これまでに報告された悪心・嘔吐発現頻度は同等である．[10-12] CPT-11の薬理作用として，アセチルコリンエステラーゼを阻害することが知られているが，嘔吐中枢にはセロトニン受容体だけではなく，アセチルコリン受容体も存在している．CPT-11により引き起こされる悪心・嘔吐では，抗がん剤による嘔吐中枢の直接刺激だけでなく，アセチルコリンによる刺激も関与している可能性が考えられ，この作用機序の違いが悪心のリスク因子の違いに影響を及ぼしているのかもしれない．また，これまでに女性あるいは若年者で悪心・嘔吐の発現リスクが高まる傾向にあると報告されているのは，高度催吐リスクに分類されているcisplatinである[6,7]が，同じプラチナ系抗がん剤であるL-OHPでは同様のリスク因子が見い出されなかった．このように，同じ催吐性のある抗がん剤でも，悪心・嘔吐発現因子が異なる可能性が示唆されたため，今後はこの点にも配慮した副作用調査を行ったうえで，それぞれの催吐リスクに応じた対策が必要であると考えられた．

今回の調査で悪心の発現頻度が高かったFOLFIRI投与中の女性あるいは若年者に対しては，制吐支持療法を強化して悪心発現の予防に努めることが重要であると思われる．ASCOのガイドラインでは，中等度催吐性抗がん剤投与時における制吐支持療法として，5-HT_3及びDexaの前投薬と，投与後のステロイド剤内服を推奨しており，[2] CPT-11により誘発される悪心に対して，ステロイド剤の3日間投与が有効であることも報告されている．[13] また，制吐剤適正使用ガイドラインでは，中等度催吐性抗がん剤使用時のオプションとして，carboplatin, ifosfamide, methotrexate，並びにCPT-11など使用時にはaprepitantの併用も推奨されているため，今後さらに詳細な検討をしていきたい．

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CASE REPORT

A case of heavily pretreated rectal cancer with disseminated intravascular coagulation that improved following reintroduction of FOLFOX plus bevacizumab

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Abstract Disseminated intravascular coagulation (DIC) is a complication that may be experienced by patients with solid tumors. The prognosis of solid tumors with DIC is much poorer than those without DIC. Although treatment of the underlying disease is critical for improvement of DIC, the efficacy and safety of chemotherapy in patients with DIC associated with colorectal cancer are not clear. A 50-year-old man with advanced rectal cancer and multiple liver metastases experienced DIC during third-line treatment with cetuximab plus irinotecan, following 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX) plus bevacizumab and 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) plus bevacizumab. Combination chemotherapy consisting of FOLFOX plus bevacizumab was reintroduced. Although platelet and fresh-frozen plasma transfusions were required daily before chemotherapy, the patient's laboratory values improved after two cycles of chemotherapy, without severe toxicity. The patient was discharged, and FOLFOX plus bevacizumab has been continued on an outpatient basis without sign of recurrence of DIC as of December 2010 (4 months after initiation of chemotherapy). This case suggests that reintroduction of combination chemotherapy with FOLFOX plus bevacizumab is effective and feasible in patients with colorectal cancer with DIC and that chemotherapy may be a treatment option for such patients.

Keywords Colorectal cancer · Disseminated intravascular coagulation · FOLFOX · Reintroduction · Bevacizumab

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Introduction

Disseminated intravascular coagulation (DIC) is a fatal thrombohemorrhagic disorder involving the generation of intravascular fibrin and the consumption of coagulation factors and platelets. The resultant clinical condition is characterized by intravascular coagulation and hemorrhage. Underlying diseases causing DIC primarily include hematological malignancies, infection, sepsis, and trauma. Patients with solid tumors may also experience DIC during their clinical course; a frequency of 6.8% has been reported among 1,117 patients with various solid tumors [1]. The prognosis of patients with solid tumors complicated by DIC is much poorer than those without DIC. The frequency and prognosis of DIC in colorectal cancer is unknown, with only a few cases reported in the literature [2]. Although treatment for the underlying disease is critical for improvement of DIC, the efficacy and safety of chemotherapy in patients with DIC associated with colorectal cancer are not clear, because these patients are ineligible for clinical trials. Herein we report a case of heavily treated metastatic rectal cancer with DIC that responded to reintroduction of combination chemotherapy with modified FOLFOX6 (mFOLFOX6; 5-fluorouracil, leucovorin, oxaliplatin) plus bevacizumab.

Case presentation

A 50-year-old man with advanced rectal cancer and multiple liver metastases was referred to our institution in February 2009. He noticed hematochezia for 1 month, and colonoscopy showed a rectal tumor that encircled half the bowel circumference and bled easily. A biopsy specimen of the rectal tumor showed poorly differentiated

adenocarcinoma without *KRAS* mutation, as evaluated by the Cycleave PCR method. Computed tomography (CT) revealed multiple metastases in the bilateral lobes of the liver and a thickness in the rectal wall that reflected the primary tumor (Fig. 1a). Because the multiple liver metastases were apparently unresectable, first-line chemotherapy with FOLFOX plus bevacizumab was initiated (bevacizumab 5 mg/kg, oxaliplatin 85 mg/m^2, L-leucovorin 200 mg/m^2, infusional 5-FU 2,400 mg/m^2, bolus 5-FU 400 mg/m^2; biweekly). Although stable disease was initially maintained, tumor progression was observed after 6 months of chemotherapy (Fig. 1b). Second-line chemotherapy with FOLFIRI (5-fluorouracil, leucovorin, irinotecan) plus bevacizumab also resulted in stable disease for approximately 11 months, but the tumor eventually progressed. Therefore, combination chemotherapy with irinotecan and cetuximab was started in July 2010. However, the patient complained of worsened fatigue and yellow-colored urine after two cycles of irinotecan plus cetuximab. He also experienced a small degree of hematochezia similar to that present at initial diagnosis. Physical examination showed icteric conjunctiva, although purpura was not apparent in his skin. Laboratory data included markedly reduced platelet counts (1.8×10^4/μl) and increased total bilirubin (4.5 mg/dl), aspartate transaminase (AST, 91 IU/l), alanine transaminase (ALT, 50 IU/l), and alkaline phosphatase (ALP, 1,427 IU/l). Coagulation tests also showed abnormal values as follows: prothrombin time/international normalized ratio (PT-INR), 2.09, fibrin degradation products (FDP), >80 μg/ml, D-dimer, 135.2 μg/ml, and fibrinogen (FIB), 31.4 mg/dl. A diagnosis of DIC was made according to the diagnostic criteria of the International Society of Thrombosis and Hemostasis [3]. CT on admission showed enlarged multiple liver metastases (Fig. 1c). These clinical features suggested DIC caused by progressed metastatic rectal cancer. Continuous intravenous nafamostat mesilate (0.5 mg/kg/h) and transfusion of platelets and fresh-frozen plasma were initiated. Dexamethasone (6.6 mg/day) was also started for fatigue. Although all effective agents for colorectal cancer had been already used for his cancer, the patient strongly desired to receive further chemotherapy. After written informed consent was obtained from the patient and his family, combination chemotherapy consisting of FOLFOX plus bevacizumab was reintroduced. Bevacizumab 5 mg/kg infused over 30 min was administered biweekly. FOLFOX with a reduced dose of oxaliplatin (50 mg/m^2) and infusional 5-FU (2,000 mg/m^2) was administered biweekly; bolus 5-FU was excluded because of liver dysfunction and icterus. Although platelet and fresh-frozen plasma transfusions were required daily during the first two cycles of chemotherapy, platelet counts, PT-INR, FIB, and D-dimer values improved to 6.1×10^4/μl, 1.06, 297 mg/dl, and 35.6 mg/l, respectively, thereafter (Fig. 2). No significant toxicities other than grade 1 anorexia and diarrhea were observed. CT after six cycles of chemotherapy showed that multiple liver metastases were slightly reduced in size (Fig. 1d). After four cycles of chemotherapy, the patient

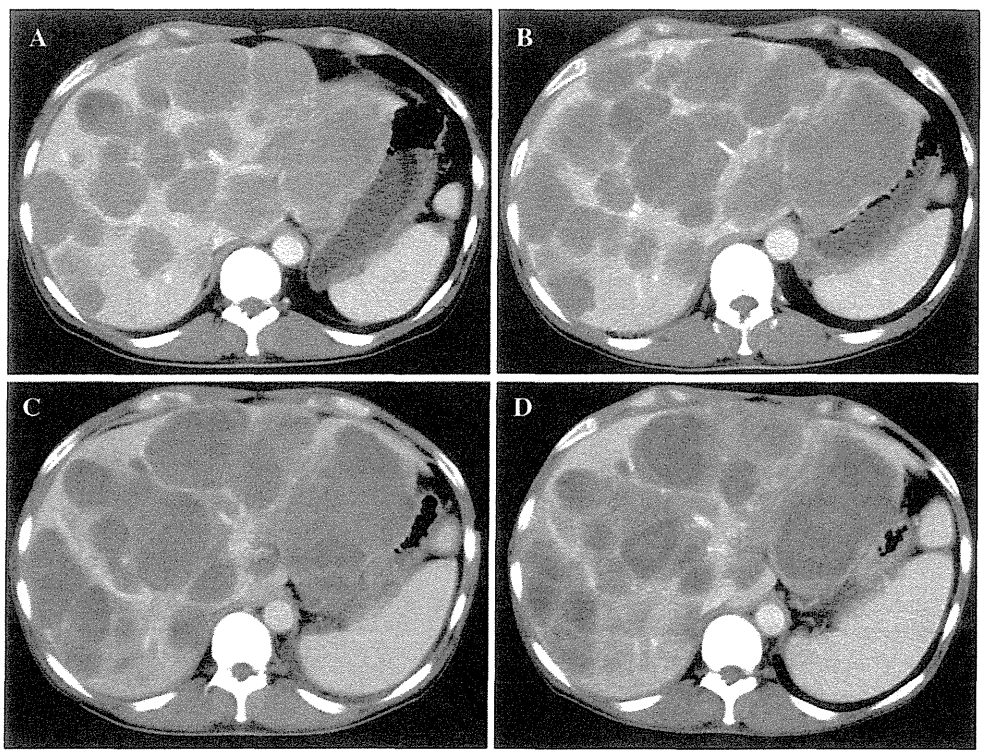

Fig. 1 **a** Computed tomography (CT) scan before introduction of 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX) plus bevacizumab shows multiple metastases in the bilateral lobes of the liver. **b** CT scan after 11 cycles of FOLFOX plus bevacizumab shows the multiple liver metastases were slightly enlarged. **c** CT scan before reintroduction of FOLFOX plus bevacizumab shows the multiple metastases in the bilateral lobes of the liver. **d** CT scan after 6 cycles of treatment shows the multiple liver metastases were slightly reduced in size

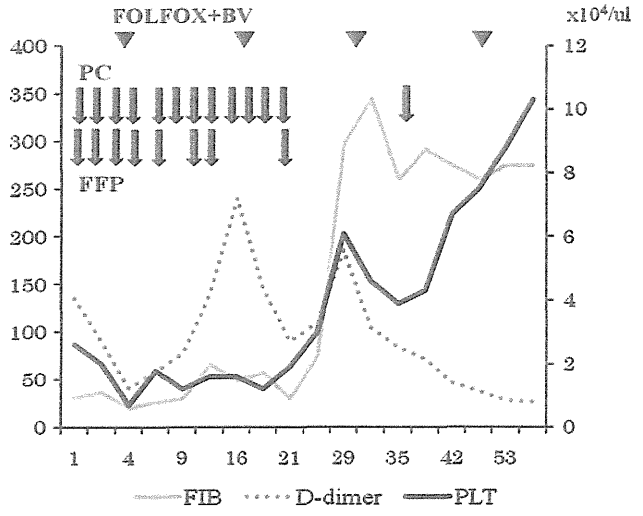

Fig. 2 Clinical course after chemotherapy. After two cycles of chemotherapy, coagulation test results improved; after four cycles of chemotherapy, the patient was discharged. *FIB*, fibrin degradation products; *PLT*, platelet counts; *PC*, platelet transfusion; *FFP*, fresh-frozen plasma transfusion; *FOLFOX*, 5-fluorouracil, leucovorin, oxaliplatin; *BV*, bevacizumab

was discharged, and the same treatment has been continued on an outpatient basis without sign of recurrence of DIC as of December 2010, which was 4 months after initiation of chemotherapy.

Discussion

To the best of our knowledge, this is the first case report of heavily pretreated rectal cancer with DIC that improved following reintroduction of chemotherapy with FOLFOX plus bevacizumab. Although anti-DIC therapy such as nafamostat mesilate may be another reason for improvement of DIC in this patient, the reduction of size of multiple liver metastases by reintroduction of FOLFOX plus bevacizumab suggested that chemotherapy mainly contributed to the improvement of DIC.

In general, the prognosis of solid tumors complicated by DIC is dismally poor. A literature search of the Medline database (January 1966 to November 2010) using the keywords "DIC" and "colorectal cancer" revealed that only one previous report of patients with DIC associated with colorectal cancer who underwent chemotherapy has been published [2]. Nonaka et al. reported a case of rectal cancer with DIC that responded to combination chemotherapy with FOLFOX and summarized 21 cases of colorectal cancer with DIC in Japan, which were indexed in Japana Centra Revuo Medicina (http://search.jamas.or.jp/). These cases were commonly associated with a pathological diagnosis of poorly differentiated or signet ring-like cell adenocarcinoma, as well as bone marrow involvement. The present patient also had poorly differentiated adenocarcinoma, although no bone marrow involvement was detected. Among these 21 cases, 10 patients received chemotherapy but the other 11 patients did not. The median survival was 90 days (range, 68–210 days) in patients who received chemotherapy and 30 days (range, 13–51 days) in patients who did not [2]. However, all cases were chemonaïve at diagnosis of DIC, and no report evaluated the efficacy of chemotherapy for pretreated colorectal cancer with DIC, as in the present case. FOLFOX reintroduction is reported to be effective and associated with better survival in metastatic colorectal cancer [4, 5]. Reintroduction of oxaliplatin was feasible and resulted in a response or disease stabilization in 73% of patients who were previously treated with oxaliplatin for metastatic colorectal cancer [4]. Notably, one response occurred in a patient who had experienced progression during the first course of FOLFOX, similar to that which occurred in the present case. In addition, similar objective response rates to reintroduction of platinum-based chemotherapy have been reported in patients with platinum-resistant ovarian cancer [6]. Although further investigation is required to explain this curious response to reintroduction of FOLFOX plus bevacizumab even after disease progression during FOLFOX plus bevacizumab, we speculate that a relatively longer FOLFOX-free interval in the present patient may have contributed to this phenomenon. Additionally, there could be other reason for this response; existence of distinct clones of cells that respond differentially. Naing et al. [8] reported 4 cases in which patients' cancers responded when they were rechallenged with chemotherapies, despite the fact that their tumors had previously become refractory to those agents (after initial response). They suggested if a tumor responds but then becomes resistant to one or more treatments, it is conceivable that retreatment will be successful if changing therapies allows a clone of cells to re-emerge.

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, is reported to be associated with thromboembolism and bleeding [7]. However, we elected to use bevacizumab in this patient with life-threatening disease because of the anticipated synergistic antitumor effect with FOLFOX. No bevacizumab-related toxicities were observed in this patient; however, caution must be exercised when administering this agent.

In conclusion, the present case suggests that reintroduction of combination chemotherapy with FOLFOX plus bevacizumab is effective and feasible in patients with colorectal cancer with DIC, and that chemotherapy may be a treatment option for such patients.

Conflict of interest No author has any conflict of interest.

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ORIGINAL ARTICLE

Retrospective analysis of cetuximab monotherapy for patients with irinotecan-intolerant metastatic colorectal cancer

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Abstract
Background The efficacy and safety of cetuximab for irinotecan-intolerant patients has not yet been evaluated in detail.
Methods We retrospectively analyzed the efficacy and safety of cetuximab monotherapy for patients with metastatic colorectal cancer (MCRC) that was intolerant to irinotecan.
Results Among 105 patients who received cetuximab-containing chemotherapy until March 2010, 22 patients were treated with cetuximab monotherapy due to irinotecan intolerance. Cetuximab was given at the approved dosage to all patients. The performance status was 2 or 3 in 17 patients (77%). All but 1 patient had wild-type *KRAS* tumors. The causes of irinotecan intolerance were icterus ($n = 9$; 41%; median serum total bilirubin, 6.3 mg/dl), symptomatic peritoneal metastasis or obstruction ($n = 8$; 36%), and thrombocytopenia ($n = 1$; 5%). Four patients (18%) refused irinotecan due to previous irinotecan-associated toxicity. Two patients achieved a partial response with an apparent drop of serum bilirubin, for a response rate of 9.1%. The median progression-free survival and overall survival were 1.6 and 3.5 months, respectively. No grade 3 or 4 adverse events or treatment-related deaths were experienced.
Conclusion Cetuximab monotherapy for irinotecan-intolerant MCRC is feasible. However, the overall efficacy was modest in the present cohort, despite the fact that most of the patients had wild-type *KRAS* tumors; further effective therapies should be evaluated to improve the prognosis of this patient population.

Keywords Colorectal cancer · Cetuximab · Irinotecan intolerance

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Introduction

Cetuximab, a monoclonal antibody directed against epidermal growth factor receptor (EGFR), has been shown to significantly improve the prognosis of patients with metastatic colorectal cancer (MCRC) compared to best supportive care alone in the third-line setting (CO-17 study) [1]. Additionally, cetuximab plus irinotecan resulted in a higher response rate and longer progression-free survival (PFS) compared to cetuximab monotherapy, even in patients with irinotecan-refractory MCRC (BOND-1 study) [2]. Based on the results of these two trials, cetuximab plus irinotecan is considered to be a standard regimen for patients with irinotecan-refractory MCRC if tolerable, and cetuximab monotherapy is recommended for patients with irinotecan intolerance [3]. However, these two studies excluded patients with organ dysfunction, such as icterus, as well as those with a poor performance status (PS). Therefore, the true efficacy and safety of cetuximab monotherapy for patients with irinotecan-intolerant MCRC remains unclear. The prognosis of patients with MCRC with organ dysfunction and/or poor PS is extremely poor [4, 5]. For example, the median survival of patients with MCRC with icterus has been reported to be <1 month

when treated with either cytotoxic chemotherapy or supportive care alone [4]. In addition, cytotoxic chemotherapy is generally not indicated for patients with a poor PS; these patients tend to have a poor prognosis despite treatment [5].

Since monoclonal antibodies are considered to be metabolized by the reticuloendothelial system without undergoing hepatic or renal metabolism [6–8] and to be associated with low toxicity even in patients with a poor PS [9], we hypothesized that cetuximab would provide a treatment benefit even in patients with irinotecan intolerance due to organ dysfunction or poor PS. To address this issue, we conducted a retrospective analysis to evaluate the efficacy and safety of cetuximab monotherapy for patients with irinotecan-intolerant MCRC.

Patients and methods

Patients

Patients with histopathologically proven metastatic colorectal adenocarcinoma who received cetuximab monotherapy due to irinotecan intolerance were included. Irinotecan intolerance was determined by each physician and confirmed by medical records. No additional eligibility criteria, such as Eastern Cooperative Oncology Group PS or organ function, were used. The *KRAS* status (codon 12 and 13) of primary or metastatic tumors using surgical or biopsied specimens was evaluated using the Cycleave PCR method [10]. Although patients with *KRAS* mutations were generally excluded from receiving cetuximab, a few patients received cetuximab before the implications of *KRAS* mutation status on cetuximab efficacy were known. We treated 105 patients with cetuximab-containing chemotherapy between August 2008 and March 2010. Among them, 22 patients were treated with cetuximab monotherapy due to irinotecan intolerance, and were analyzed in this study. Written informed consent was obtained from each patient prior to chemotherapy.

Treatment plan

Cetuximab was given intravenously at an initial dose of 400 mg/m^2, followed by a weekly maintenance infusion of 250 mg/m^2 (the approved dosage). Patients received premedication with an antihistamine (e.g., diphenhydramine hydrochloride 50 mg IV) and dexamethasone 4 mg to minimize the risk of infusion-related reactions associated with cetuximab. Infusion-related toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 3.0). In general, grade 3–4 hypersensitivity necessitated cetuximab discontinuation; infusion was slowed to 50% of the prior infusion rate for grade 1–2 allergic/hypersensitivity reactions. Cetuximab was withheld for grade 3 skin toxicity until resolution to ≤grade 2. Other dose adjustments were made on an individual patient basis. Treatment was discontinued upon tumor progression, severe toxicity, or at the patient's request.

Evaluation of treatment

Medical history, physical examination, safety evaluation, and laboratory tests were performed prior to starting treatment and weekly thereafter. Toxicity was evaluated by CTCAE ver. 3.0. Responses were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) every 6–8 weeks or earlier if there were indications of treatment failure due to toxicity. PFS was measured from the initial date of cetuximab administration to the time when progression or death without evidence of progression occurred. Median survival time was estimated from the initial date of cetuximab administration to the date of death or last follow-up using Kaplan–Meier methodology.

Results

Patient characteristics

The characteristics of patients in this study are shown in Table 1. Their PS was generally poor, with 17 patients (77.3%) having a PS of 2 or 3. Twenty patients (90.9%) had previously received oxaliplatin-containing chemotherapy, 17 patients (77.3%) received irinotecan, and 15 patients (68.2%) received bevacizumab. Sixteen patients (72.7%) had peritoneal metastasis. All patients except for one had wild-type *KRAS* tumors. The causes of irinotecan intolerance were as follows: icterus in 9 patients (40.9%), with a median serum total bilirubin level of 6.3 mg/dl (range 2.3–13 mg/dl); symptomatic peritoneal metastasis or obstruction in 8 patients (36.4%); and thrombocytopenia in 1 patient (4.5%); in addition, 4 patients (18.2%) refused to receive irinotecan due to previous gastrointestinal toxicity associated with irinotecan treatment.

Treatment results

Median administration of cetuximab was 8 cycles (range 1–24). Among the 22 patients, there were 0 complete responses; 2 partial responses, with apparent drops in serum total bilirubin [from 8.9 to 1.1 mg/dl (Fig. 1) and from 2.4 to 0.8 mg/dl]; and 4 patients experienced stable

disease. Four patients had progressive disease, and 14 patients were not evaluable for radiological response due to symptomatic deterioration prior to radiological response evaluation ($n = 12$) and treatment withdrawal due to toxicity prior to response evaluation ($n = 2$). The overall response rate was 9.1% and the disease control rate was 27.3%. The median PFS was 1.6 months (Fig. 2). After a median follow-up of 4.7 months, 16 patients died of tumor progression while the other 6 patients remain alive. The median overall survival was 3.5 months (Fig. 2).

Table 1 Baseline characteristics of the patients

Gender	
Male/female	10/12
Age	
Median (range)	65 (41–83)
ECOG performance status	
0–1/2/3	5/10/7
Prior CTx for advance	
Oxaliplatin base	20
Irinotecan base	17
Bevacizumab	15
Prior CTx line	
1/more	4/18
Disease sites	
Liver	19
Peritoneum	16
Lung	10
Lymph node	12
Number of disease sites	
1–2/more	7/15
KRAS status	
Wild/mutant	21/1

ECOG Eastern Cooperative Oncology Group, *CTx* chemotherapy

Adverse events

Adverse event data related to cetuximab treatment are summarized in Table 2. Skin toxicity was the most common adverse event, with an incidence of 86.4%. Fever was observed in 7 patients (31.8%), and an infusion reaction occurred in 1 patient (4.5%). Fatigue and anorexia were observed at a high frequency, but these events may possibly have occurred due to disease progression. Chemotherapy was discontinued in 2 patients (9.1%) due to toxicity: grade 2 infusion reaction in 1 patient and patient refusal due to skin toxicity in 1 patient. There were no treatment-related deaths, and no patient experienced grade 3 or 4 adverse events during treatment.

Discussion

In this report, we retrospectively evaluated the efficacy and safety of cetuximab monotherapy in irinotecan-intolerant MCRC due to severe complications, such as icterus and gastrointestinal obstruction. The present results suggest

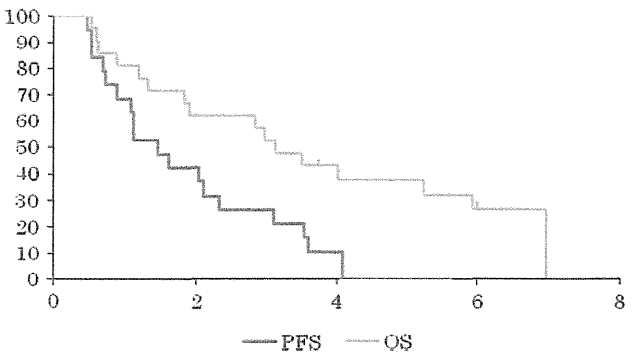

Fig. 2 Kaplan–Meier curves for progression-free survival (PFS) and overall survival. Median PFS was 1.6 months, and median overall survival was 3.5 months

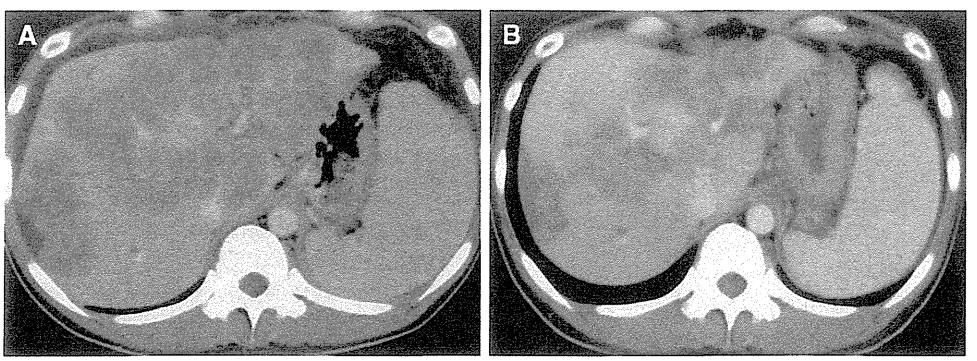

Fig. 1 A 40-year-old female with multiple liver metastases refractory to FOLFOX plus bevacizumab and irinotecan. **a** CT scan acquired prior to cetuximab monotherapy. She had icterus accompanied by serum total bilirubin of 8.9 mg/ml. **b** CT scan acquired after 2 months of chemotherapy. Apparent reductions in the size of multiple liver metastases were observed, and her total bilirubin decreased to 1.1 mg/dl

Table 2 Adverse events

Adverse events	G1–2 (%)	G3–4 (%)
Any	21 (95.5)	0 (0)
Leucopenia	1 (4.5)	0 (0)
Neutropenia	0 (0)	0 (0)
Febrile neutropenia	0 (0)	0 (0)
Anemia	2 (9.1)	0 (0)
Thrombocytopenia	1 (4.5)	0 (0)
Acneform rash	19 (86.4)	0 (0)
Fatigue	19 (86.4)	0 (0)
Anorexia	11 (50)	0 (0)
Fever	7 (31.8)	0 (0)
Nausea	5 (22.7)	0 (0)
Diarrhea	2 (9.1)	0 (0)
Infusion reaction	1 (4.5)	0 (0)

Grades were determined according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3.0

that cetuximab monotherapy is safe even in this patient population, and 2 patients achieved apparent tumor shrinkage with improvement of icterus.

In the BOND-1 study [2], cetuximab plus irinotecan showed a superior response rate and PFS compared to cetuximab monotherapy, even in patients with irinotecan-refractory MCRC. However, irinotecan is not suitable for many patients, including those with poor PS, liver dysfunction, and/or gastrointestinal obstruction. Irinotecan is primarily metabolized to 7-ethyl-10-hydroxy camptothecin (SN-38) in the liver [11]. SN-38 is primarily eliminated via conjugation by hepatic uridine-diphosphoglucuronosyl transferase, and is then excreted into the bile and stool. Therefore, irinotecan is toxic to patients with icterus or gastrointestinal obstruction, due to delayed excretion of SN-38. In the CO-17 study, cetuximab monotherapy was shown to significantly improve the prognosis of MCRC compared to supportive care alone [1]. However, both the CO-17 and BOND-1 studies excluded patients with organ dysfunction or PS3, and the proportion of patients with PS2 was low (23.4%); thus the true efficacy and feasibility of cetuximab monotherapy for patients with irinotecan-intolerant MCRC was previously unclear.

In the present study, there were no treatment-related deaths, and no patients experienced grade 3 or 4 adverse events during treatment, although grade 2 skin toxicity was observed in most patients and grade 2 infusion reaction occurred in 1 patient. The frequency and severity of toxicities did not differ from those of past pivotal studies [1, 2]. Since cetuximab is metabolized by the reticuloendothelial system without undergoing hepatic or renal metabolism, we planned to use cetuximab without dose reduction, even in patients with icterus or gastrointestinal obstruction.

Although 2 patients achieved an apparent response in this study, the overall response rate of 9.1% with median survival of 3.5 months was considered as modest and far from satisfactory despite the fact that most patients had wild-type *KRAS* tumors. In contrast, gefitinib showed impressive results for EGFR-positive non-small cell lung cancer patients with a poor PS, with an objective response rate of 66% and median survival of 17.8 months [12]. Recently, several biomarkers and clinical factors other than *KRAS* have been reported as predictive markers of the efficacy of anti-EGFR antibodies such as cetuximab or panitumumab [13]. However, further investigation to identify MCRC patients most likely to benefit from anti-EGFR antibody treatment appears to be necessary.

In conclusion, although the small sample size and retrospective design were major limitations of this study, the present results suggest that cetuximab monotherapy is feasible for irinotecan-intolerant MCRC with modest efficacy. Additional effective therapies should be evaluated to improve the prognosis of this patient population.

Conflict of interest No author has any conflict of interest.

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CLINICAL INVESTIGATION **Esophagus**

PHASE II STUDY OF CHEMORADIOTHERAPY WITH 5-FLUOROURACIL AND CISPLATIN FOR STAGE II–III ESOPHAGEAL SQUAMOUS CELL CARCINOMA: JCOG TRIAL (JCOG 9906)

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Purpose: In this Phase II study, we evaluated the efficacy and toxicity of chemoradiotherapy (CRT) with cisplatin (CDDP) and 5-fluorouracil (5-FU) for Stage II–III esophageal squamous cell carcinoma (ESCC).
Patients and Methods: Patients with clinical Stage II–III (T1N1M0 or T2–3N0–1M0) thoracic ESCC were enrolled between April 2000 and March 2002. Chemotherapy comprised two courses of protracted infusion of 5-FU (400 mg/m^2/day) on Days 1–5 and 8–12, and 2-h infusion of CDDP (40 mg/m^2) on Days 1 and 8; this regimen was repeated every 5 weeks. Concurrent radiotherapy involved 60-Gy irradiation (30 fractions) for 8 weeks with a 2-week break. Responders received two courses of 5-FU (800 mg/m^2/day) on Days 1–5 and CDDP (80 mg/m^2) on Day 1. Final analysis was conducted in March 2007. Survival and late toxicities were monitored for 5 years.
Results: The characteristics of the 76 patients enrolled were as follows: median age, 61 years; male/female, 68/8; performance status 0/1, 59/17 patients; Stage IIA/IIB/III, 26/12/38 patients. Of the 74 eligible patients, 46 (62.2%) achieved complete response. Median survival time was 29 months, with 3- and 5-year survival rates of 44.7% and 36.8%, respectively. Acute toxicities included Grade 3/4 esophagitis (17%), nausea (17%), hyponatremia (16%), and infection without neutropenia (12%). Late toxicities comprised Grade 3/4 esophagitis (13%), pericardial (16%) and pleural (9%) effusion, and radiation pneumonitis (4%), causing 4 deaths.
Conclusions: CRT is effective for Stage II–III ESCC with manageable acute toxicities and can provide a nonsurgical treatment option. However, further improvement is required for reduction in late toxicity. © **2011 Elsevier Inc.**

Esophageal squamous cell carcinoma, Chemoradiotherapy, Long-term toxicity, Salvage surgery.

INTRODUCTION

Esophageal cancer, a highly virulent malignancy, was responsible for 11,182 deaths in Japan in 2005, accounting for 3.4% of the country's total cancer deaths (1), with 35–40% of the patients diagnosed with Stage II–III disease. When this study was planned, the standard treatment for Stage II–III esophageal squamous cell carcinoma (ESCC) in Japan was esophagectomy with three-field lymph node dissection, followed by postoperative chemotherapy; the 5-year survival rate is reported to be 36.8–61% (2–4), with a high morbidity rate.

Chemoradiotherapy (CRT) has proved effective against resectable/unresectable ESCC. The Radiation Therapy Oncology Group (RTOG) trial 85-01 demonstrated the superiority of CRT with cisplatin (CDDP), 5-fluorouracil (5-FU), and concurrent irradiation (50.4 Gy) over radiotherapy alone (64 Gy) in patients with T1–3N0–1M0 esophageal cancer (5), in which the final outcome showed a 5-year survival rate of 26% in the CRT arm compared with 0% in the

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Conflict of interest: none.

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radiation-alone arm (6). Therefore, CRT is recognized as the standard noninvasive treatment for patients with localized esophageal cancer who opt for nonsurgical treatment.

CRT was introduced in Japan in the early 1990s as a treatment for potentially unresectable locally advanced ESCC. In a Phase II trial, 18 of 54 (33%) patients with clinical T4 and/or M1 lymph node ESCC, who received CDDP/5-FU with concurrent 60-Gy irradiation, achieved complete response (CR) with a 3-year survival rate of 23% (7). Since then, CRT has been clinically indicated for patients with resectable ESCC who refuse surgical resection. In a retrospective analysis, 55 patients with T1–3NanyM0 ESCC, who received CRT with CDDP, 5-FU, and concurrent 60-Gy irradiation, showed a CR of 70% and a 5-year survival rate of 46%, suggesting comparable outcomes with surgery (8). However, the results were retrospective. Thus, we conducted a Phase II study to evaluate the efficacy and toxicity, particularly the long-term outcome, of CRT for Stage II–III ESCC.

PATIENTS AND METHODS

Eligibility

The eligibility criteria were as follows: pathologically confirmed thoracic ESCC; clinical Stage II–III excluding T4 (T1N1M0 or T2–3N1–0M0: International Union Against Cancer [UICC] 1997); Eastern Cooperative Oncology Group (ECOG) performance status (PS), 0 or 1; and age, 20–70 years. Patients who had previously undergone therapy for esophageal cancer or chemotherapy/radiotherapy for other malignancies and who previously had had other active malignancies were excluded. All the patients had to meet the following laboratory criteria within 14 days before registration: leukocytes $\geq$3,000/mm^3; platelet count $\geq$100,000/mm^3; hemoglobin level $\geq$10 g/dL; aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $\leq$2 $\times$ the upper normal limit at the institution; total bilirubin $\leq$1.5 mg/dL; serum creatinine $\leq$1.2 mg/dL; creatinine clearance $\geq$50 mL/min; PaO_2 $\geq$70 mm Hg; and no major electrocardiogram abnormalities. Written informed consent was obtained from all the patients. The study protocol was approved by the JCOG Clinical Trial Review Committee and institutional review boards of the participating institutions.

Chemotherapy

Chemotherapy comprised two courses of protracted infusion of 5-FU (400 mg/m^2/day) on Days 1–5 and 8–12, and 2-h infusion of CDDP (40 mg/m^2) with adequate hydration and antiemetic coverage on Days 1 and 8; this regimen was repeated every 5 weeks. Responders additionally received two courses of 5-FU (800 mg/m^2/day) on Days 1–5 and CDDP (80 mg/m^2) on Day 1 (Fig. 1), repeated every 4 weeks. No further treatment was administered to patients with CR until disease progression. Additional chemotherapy courses were optional for patients with visible disease.

Administration of both chemotherapy agents was discontinued until toxicity improved to $\leq$Grade 2. The doses were reduced by 25% in the subsequent course after at least

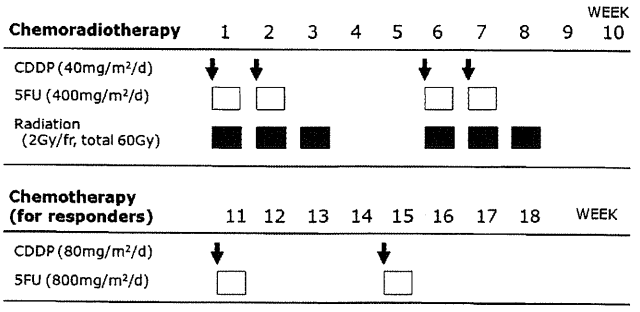

Fig. 1. Protocol scheme.

one of the following toxicities was observed: leukocytes <1,000/mm^3; platelet count <30,000/mm^3; total bilirubin >2.0 mg/dL; serum creatinine $\geq$2.0 mg/dL; Grade 3/4 stomatitis; or Grade 3/4 esophagitis. Total parenteral nutrition was provided as necessary. Treatment was terminated when disease progression was observed, patients refused to continue, or recovery from toxicity delayed the initiation of the second course by >3 weeks from the planned schedule.

Radiotherapy

Radiotherapy was delivered using megavoltage ($\geq$6 MV) x-rays; a total dose of 60 Gy was administered in 30 fractions. A 2-week break was provided after 30-Gy irradiation, and radiotherapy was resumed on Day 36 with the second chemotherapy course. The clinical target volume (CTV) for 60-Gy irradiation included the primary tumor plus a 5-cm craniocaudal margin, and the metastatic lymph nodes plus a 1-cm margin. Planning target volume was defined as CTV plus 5- to 20-mm margins for uncertainty. Elective nodal irradiation (40 Gy) of mediastinal and perigastric lymph nodes for all cases, cervical lymph nodes for an upper thoracic primary tumor, and celiac lymph nodes for a lower thoracic primary tumor was also performed. Three-dimensional computed tomography (CT) or X-ray simulation was performed, allowing two-dimensional anterior–posterior opposed fields and bilateral oblique boost. Heterogeneity-uncorrected doses were used.

Assessments

Esophagoscopy and CT were carried out after each course to assess the response. Primary tumor response was evaluated by endoscopy using the modified criteria of the Japanese Society for Esophageal Diseases (9). Complete response of lymph node metastasis was defined as the disappearance of all visible lymph node metastases on the CT or size reduction to $\leq$1 cm for $\geq$3 months after the completion of treatment. Overall CR was declared by an attending physician when CR at both a primary tumor and a lymph node was obtained without the appearance of a new lesion. Complete response was confirmed by reassessment at $\geq$4 weeks after the first assessment. Complete response cases were centrally reviewed, and CR was confirmed by extramural review of the CT scan and images of endoscopy.