が調べられている．これらの遺伝子型についてはnull型の同型ホモ接合体（欠損型）が存在し，欠損型の人は該当する酵素をもたない．これらの酵素の存在の有無と転移性大腸癌に対するFOLFOX療法の治療効果に関しては，統計学的に関連性は見いだされていない[11,16]．

おわりに

近年の分子標的治療は，真に癌関連分子を標的にしており，その遺伝子発現の有無や伝達経路に関与する遺伝子の発現をみることで，その効果予測は可能と思われる．従来から行われてきた抗癌剤治療に関しては，いまだ的確な効果予測因子を見いだせていないものの，本稿で述べた大腸癌に対するFOLFOX療法のように，5-FUとオキサリプラチンのそれぞれの薬剤に関与する遺伝子の詳細な研究解析が進んだ結果，多くの情報が得られてきており，効果あるいは予後予測因子として実臨床で十分活用できると考えられる．今後，これら遺伝子に加えて新たな5-FUとオキサリプラチンに共通の治療効果予測分子マーカーの発見が期待される．

文　献

1) Kim SH, et al: Prognostic value of ERCC1, thymidylate synthase, and glutathione S-transferase pi for 5-FU/oxaliplatin chemotherapy in advanced colorectal cancer. Am J Clin Oncol 32: 38-43, 2009.
2) Ahn MJ, et al: Thymidylate synthase, thymidine phosphorylase, VEGF and p53 protein expression in primary colorectal cancer for predicting response to 5-fluorouracil-based chemotherapy. Cancer Res Treat 37: 216-222, 2005.
3) Shirota Y, et al: ERCC1 and thymidylate synthase mRNA levels predict survival for colorectal cancer patients receiving combination oxaliplatin and fluorouracil chemotherapy. J Clin Oncol 19: 4298-4304, 2001.
4) Uchida K, et al: Thymidylate synthase, dihydropyrimidine dehydrogenase, ERCC1, and thymidine phosphorylase gene expression in primary and metastatic gastrointestinal adenocarcinoma tissue in patients treated on a phase I trial of oxaliplatin and capecitabine. BMC Cancer 8: 386, 2008.
5) Morganti M, et al: Relationships between promoter polymorphisms in the thymidylate synthase gene and mRNA levels in colorectal cancers. Eur J Cancer 41: 2176-2183, 2005.
6) Pullarkat ST, et al: Thymidylate synthase gene polymorphism determines response and toxicity of 5-FU chemotherapy. Pharmacogenomics J 1: 65-70, 2001.
7) Jakobsen A, et al: Thymidylate synthase and methylenetetrahydrofolate reductase gene polymorphism in normal tissue as predictors of fluorouracil sensitivity. J Clin Oncol 23: 1365-1369, 2005.
8) Dotor E, et al: Tumor thymidylate synthase 1494del6 genotype as a prognostic factor in colorectal cancer patients receiving fluorouracil-based adjuvant treatment. J Clin Oncol 24: 1603-1611, 2006.
9) Marcuello E, et al: Single nucleotide polymorphism in the 5′ tandem repeat sequences of thymidylate synthase gene predicts for response to fluorouracil-based chemotherapy in advanced colorectal cancer patients. Int J Cancer 112: 733-737, 2004.
10) Stoehlmacher J, et al: A multivariate analysis of genomic polymorphisms: prediction of clinical outcome to 5-FU/oxaliplatin combination chemotherapy in refractory colorectal cancer. Br J Cancer 91: 344-354, 2004.
11) Ruzzo A, et al: Pharmacogenetic profiling in patients with advanced colorectal cancer treated with first-line FOLFOX-4 chemotherapy. J Clin Oncol 25: 1247-1254, 2007.
12) Zhang W, et al: Association of methylenetetrahydrofolate reductase gene polymorphisms and sex-specific survival in patients with metastatic colon cancer. J Clin Oncol 25: 3726-3731, 2007.
13) Curtin K, et al: MTHFR C677T and A1298C polymorphisms: diet, estrogen, and risk of colon cancer. Cancer Epidemiol Biomarkers Prev 13: 285-292, 2004.
14) Park DJ, et al: ERCC1 gene polymorphism as a predictor for clinical outcome in advanced colorectal cancer patients treated with platinum-based chemotherapy. Clin Adv Hematol Oncol 1: 162-166, 2003.
15) Park DJ, et al: A Xeroderma pigmentosum group D gene polymorphism predicts clinical outcome to

platinum-based chemotherapy in patients with advanced colorectal cancer. Cancer Res 61: 8654-8658, 2001.
16) Stoehlmacher J, et al: Association between glutathione S-transferase P1, T1, and M1 genetic polymorphism and survival of patients with metastatic colorectal cancer. J Natl Cancer Inst 94: 936-942, 2002.
17) Moscow JA, et al: Expression of anionic glutathione-S-transferase and P-glycoprotein genes in human tissues and tumors. Cancer Res 49: 1422-1428, 1989.

切除不能進行再発大腸癌に対するmFOLFOX6の治療効果とTS，DPD，TP，ERCC-1蛋白発現の検討

桑原　公亀[*1]　隈元　謙介[*1]　石橋敬一郎[*1]　岡田　典倫[*1]　石 畝　亨[*1]
大澤　智徳[*1]　芳賀　紀裕[*1]　三浦　一郎[*2]　石田　秀行[*1]

〔*Jpn J Cancer Chemother* 38(12): 2224-2227, November, 2011〕

The Relationship between the Efficacy of mFOLFOX6 Treatment and the Expression of TS, DPD, TP, and ERCC-1 in Unresectable Colorectal Cancer: Kouki Kuwabara[*1], Kensuke Kumamoto[*1], Keiichiro Ishibashi[*1], Norimichi Okada[*1], Toru Ishiguro[*1], Tomonori Ohsawa[*1], Norihiro Haga[*1], Ichiro Miura[*2] and Hideyuki Ishida[*1] ([*1]*Dept. of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University,* [*2]*Tokyo Central Pathology Laboratory*)

Summary

It has been reported that thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD), thymidine phosphorylase (TP), and excision repair cross-complementing-1 (ERCC-1) were useful markers to predict the efficacy of anti cancer agents including 5-fluorouracil (5-FU) and oxaliplatin for unresectable advanced colorectal cancer. In this study, we analyzed the relationship between the expression of these enzymes and the clinical significance in 49 Stage IV colorectal cancer patients who received mFOLFOX6 as a first-line treatment and evaluated the usefulness of these enzymes for predicting the efficacy of mFOLFOX6. There was no relationship between the expression of each enzyme and response rate. The progression-free survival of the patients with low TP expression was significantly longer than that of the patients with high TP expression ($p<0.01$). In the analysis of overall survival, the patients with low TP or low DPD expression were better than that with high TP expression or high DPD expression ($p=0.04$, $p=0.04$, respectively). Our results indicated that TP and DPD expression would be a useful marker to predict the efficacy of mFOLFOX6 in the patients with unresectable colorectal cancer. Key words: Colorectal cancer, Thymidylate synthase (TS), Dihydropyrimidine dehydrogenase (DPD), Thymidine phosphorylase (TP), Excision repair cross-complementing-1 (ERCC-1)

要旨　切除不能進行再発大腸癌におけるmFOLFOX6の治療効果予測因子として，5-fluorouracil (5-FU) や oxaliplatin の薬剤代謝関連酵素である thymidylate synthase (TS)，dihydropyrimidine dehydrogenase (DPD)，thymidine phosphorylase (TP)，excision repair cross-complementing-1 (ERCC-1) の有用性が報告されている。今回，治癒切除不能 Stage IV 大腸癌に一次治療として mFOLFOX6 を施行された 49 例を対象に，mFOLFOX6 療法の奏効率，無増悪生存期間，全生存期間と各酵素の発現レベルの関連について解析し，効果あるいは予後予測因子としての有用性を検討した。いずれの酵素も発現レベルと奏効率に関連は認められなかった。TP 低発現は高発現より無増悪生存期間 ($p<0.01$) および全生存期間 ($p=0.04$) が長く，DPD 低発現は高発現より全生存期間が長かった ($p=0.04$)。TS，ERCC-1 発現と予後に関連は認められなかった。今回の結果より，TP，DPD が進行大腸癌の mFOLFOX6 施行例の効果予測因子として有用であることが示唆された。

はじめに

近年の化学療法の進歩は，切除不能進行大腸癌患者の生存期間の延長に寄与している。しかし，すべての大腸癌患者が化学療法の恩恵を受けるわけではなく，実地臨床に有用な治療効果および予後予測因子の早期確立が望まれる。5-fluorouracil (5-FU) / Leucovorin と oxaliplatin の併用療法である FOLFOX 療法の効果予測因子として，5-FU や oxaliplatin の薬剤代謝関連酵素である thymidylate synthase (TS)，dihydropyrimidine dehydrogenase (DPD)，thymidine phosphorylase (TP)，excision repair cross-complementing-1 (ERCC-1) の有用性が報告されている[1,2]。5-FU の標的分子として知られている TS やピリミジン分解経路の律速酵素である DPD は，

[*1] 埼玉医科大学総合医療センター・消化管・一般外科
[*2] 東京セントラルパソロジーラボラトリー

連絡先: 〒350-8550 川越市鴨田 1981　埼玉医科大学総合医療センター・消化管・一般外科
桑原　公亀

表1 患者背景

性別	男性 30例，女性 19例
年齢	67（32～82）歳
標的病変の臓器数	1.5（1～3）個
標的臓器	肝: 37例，肺: 12例，リンパ節: 9例，腹膜: 17例，その他: 4例
mFOLFOX6投与回数	9（4～39）回
Oxaliplatinのrelative dose intensity	76.5（28.1～100）%
腫瘍縮小効果	CR: 1例，PR: 17例，SD: 16例，PD: 15例
観察期間	21.8（3.1～54.2）か月
二次治療	FOLFIRI: 25例，FOLFIRI＋bevacizumab: 10例，その他: 4例

5-FUの薬剤動態に大きく関与している。TPは5-FUのプロドラッグであるdoxifluridine（5′-DFUR）を5-FUに変換する酵素であり，多くの悪性腫瘍において高発現しており，TPの発現は独立した予後因子と考えられている。またERCC-1は，oxaliplatinのような抗癌剤により癌細胞がDNA損傷を受けた時にその修復にかかわる遺伝子であり，この遺伝子発現が高いほどoxaliplatinに対する耐性が強いと考えられている[3]。今回われわれは，治癒切除不能Stage Ⅳ大腸癌に一次治療でmFOLFOX6療法を施行した症例における原発巣のTS，DPD，TP，ERCC-1の蛋白発現を検索し，mFOLFOX6療法の効果や予後との関連を検討したので報告する。

Ⅰ. 対象と方法

1. 対　象

当科で2005年12月～2008年4月の間に，RECIST分類（ver 1.1）で評価可能な標的病変を有する治癒切除不能Stage Ⅳ大腸癌に対し，原発巣を切除後，一次治療としてmFOLFOX6療法を施行した症例のうち，原発巣のTP，DPDの蛋白発現量の定量あるいは免疫組織化学的染色でTS，ERCC-1発現を検討した49例を対象とした。

2. 各酵素発現の評価法

1）腫瘍組織中TP，DPD蛋白量の測定

標本摘出後，速やかに腫瘍組織（500 μg以上）を採取し，解析時まで－80℃で凍結保存した。凍結組織に10倍量の10 mM Tris-HCl bufferを添加してホモジェナイズし，上清のTP，DPD蛋白発現量をenzyme-linked immunosorbent assay（ELISA）法で測定した[4,5]。蛋白量で補正した値を最終測定値とした。最終測定値を30パーセンタイル，70パーセンタイル値で高発現，中等度発現，低発現に分けた。ELISA法によるTP，DPDの定量は中外製薬株式会社との間で共同研究契約を締結し，中外製薬研究所に依頼した。

2）TS，ERCC-1の免疫組織化学的染色

TS，ERCC-1の免疫組織化学的染色はABC法で行い，一次抗体として，TSはウサギポリクローナル抗体（Taiho Pharmaceutical，Saitama，Japan），ERCC-1はマウスモノクローナル抗体（Exalpha Biologicals，Inc，Shirley，MA，USA）を使用した。TS，ERCC-1の各々の発現については，染色強度（weak，moderate，strong）をKwon[6]らの方法で判定した。染色強度の判定は，治療成績の情報のない病理専門医が行った。

3. 検討項目

TP，DPD発現は，高発現/中等度発現と低発現の2群間で，またTS，ERCC-1はstrong（高発現）/moderate（中等度発現）とweak（低発現）の2群間で奏効率，無増悪生存期間，全生存期間の関係について比較検討した。

材料の保管・利用に関し，患者から文書による同意を得た。本研究は埼玉医科大学総合医療センター倫理委員会の承認の下に行われた。

4. 統計学的解析

連続変数はmedian（range）で記載した。2群間の比較にはχ^2検定を用いた。生存率はKaplan-Meier法に従って算出し，生存期間の比較にはlogrank testを用いた。$p<0.05$を有意差ありとした。

Ⅱ. 結　果

1. 背景因子

年齢は67（32～82）歳。男性30例，女性19例。標的病変を有する臓器数は1.5（1～3）個で，標的病変の内訳は肝37例，肺12例，リンパ節9例，腹膜17例，その他4例であった。mFOLFOX6療法の投与回数は9（4～39）回で，oxaliplatinのrelative dose intensityは，76.5（28.1～100）%であった。画像上の腫瘍縮小効果は，CR 1例，PR 17例，SD 16例，PD 15例であり，奏効率

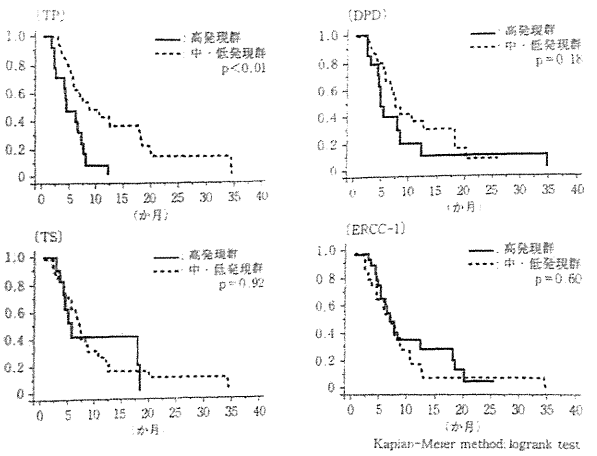

図 1 無増悪生存期間

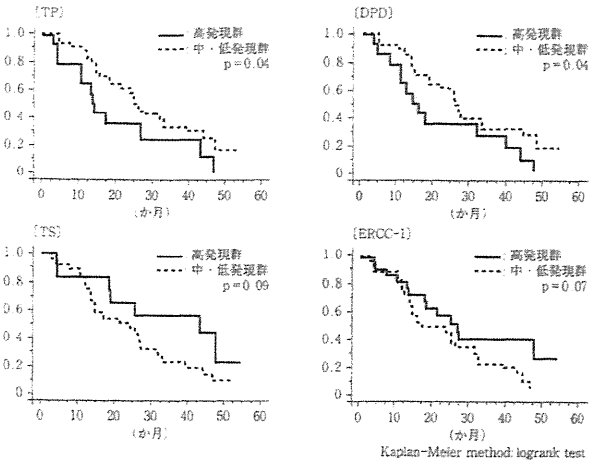

図 2 全生存期間

は37%であった。二次治療は39例（80%）に施行され，その内訳はFOLFIRI±bevacizumab 35例，その他4例であった。観察期間は21.8（3.1～54.2）か月であった（表1）。

2. TP，DPDの蛋白量

TPの蛋白発現量の中央値は88.1（35～2,538）U/mg proteinであり，DPDの蛋白発現量の中央値は31.7（8.6～187.2）ng/mg proteinであった。

3. TS，ERCC-1の免疫組織化学的染色

TSの染色強度は高発現12例，中等度発現16例，低発現21例に，ERCC-1の染色強度は高発現22例，中等度発現12例，低発現15例に分類された。

4. 奏効率

TP，DPD高発現群と中等度・低発現群との間に奏効率に差を認めなかった（p=0.73，p=0.45）。また，TS，ERCC-1のいずれの染色強度と奏効率についても高発現群と中等度・低発現群との間に有意差は認められなかった（p=0.33，p=0.25）。

5. 無増悪生存期間

TPの中等度・低発現群の無増悪生存期間は，高発現群より有意に延長していた（8.5 vs 4.3か月，p<0.01）。その他の酵素発現と無再発生存期間には関連は認められなかった（図1）。

6. 全生存期間

TPの中等度・低発現群の全生存期間は高発現群より有意に延長していた（25.5 vs 13.8か月，p=0.04）。また，DPDの中等度・低発現群の全生存期間も高発現群よりも有意に延長していた（25.5 vs 14.4か月，p=0.04）。TS（p=0.09）とERCC-1（p=0.07）については，高発現群のほうが中等度・低発現群より全生存期間が延長する傾向を認めた（図2）。

III. 考 察

これまでの諸家の報告によれば，TS，DPD，TPは，いずれも発現が低いほうが5-FU感受性が高く，ERCC-1も発現が低いほうがoxaliplatinの感受性が高いと考えられている。今回の検討では，5-FUとoxaliplatinを併用するmFOLFOX6療法の治療効果とこれら酵素群との関連を解析した。TPとDPD発現は，低い群が高い群よりも予後が有意に良好であった。この結果は，従来の見解と矛盾せず，治癒切除不能Stage IV大腸癌に対するmFOLFOX6療法の治療効果および予後予測因子として，TPやDPDの有用性を改めて示唆するものと考えられた。

5-FUの抗腫瘍効果には，RNAとDNAの合成阻害作用がある。後者は5-FUがfluorodeoxyuridine（FdUrd）からfluorodeoxyuridine monophosphate（FdUMP）に代謝され，還元型葉酸（Leucovorin）の代謝物である5,10-CH_2-THF（5,10-methylenete trahydroforate）とともに共有結合し，強固な三者結合体を形成し，deoxyuridine monophosphate（dUMP）からdeoxythymidine monophosphate（dTMP）への酵素変換作用を阻害することで，腫瘍中のdTMPおよびdTTPを枯渇させ，DNA合成阻害を引き起こす。この経路においてTPは，*in vitro*では5-FU→FdUrdの反応を触媒し，5-FU効果規定因子と考えられたが，生体内ではデオキシリボースーリン酸のレベルが低いため，逆にFdUrd→5-FU方向への反応を触媒している。また，原発巣のTPが高発現の切除不能・再発大腸癌に対する5-FUの効果は不良であることが報告されていることから，TPは5-FU感受性因子というよりは，腫瘍悪性度の指標としての位置付けが重要であると考えられている。TPには5-FUのプロドラッグである5'-DFURを5-FUに変換する酵素

作用もあり，capecitabine以外の5-FU系抗癌剤では効果に乏しいことが報告されている。

DPDは5-FUの分解の律速酵素であり，腫瘍との悪性度と相関しないが[7]，Terashimaら[8]は，DPD活性は5-FU感受性の重要な指標になると報告している。本検討では，無増悪生存期間では有意差はなかったが，全生存期間ではDPDが低・中等度発現であるほうが有意に延長していた。今回の症例ではFOLFIRIへの移行も高く，二次治療以降でも5-FUが長期間投与されていることが，DPDの発現程度が全生存期間のみに影響したと考えられる。

TSについては，TS低発現のほうが高発現より奏効しやすく，生存期間の延長が得られるとする報告が多いが[9,10]，その逆の報告も認められる[11]。今回の検討では，無増悪生存期間では差は認めなかったが，全生存期間では高発現のほうが長くなる傾向を認めた。またERCC-1は，cisplatinやoxaliplatinなどの白金系抗癌剤で引き起こされるDNA障害に関与し，それらの薬剤感受性を低下させることが知られている[3]。ERCC-1が高発現の場合，oxaliplatinの効果は期待できない可能性が考えられるが，今回の検討ではTSと同様に無増悪生存期間では差を認めなかったが，全生存期間ではERCC-1高発現のほうが長くなる傾向を認めた。この理由は不明であるが，mFOLFOX6では5-FU/Leucovorinの効果に対するTS発現と，oxaliplatinの効果に対するERCC-1の相互関係がmFOLFOX6の効果の解釈を複雑にしている可能性も示唆されており[12,13]，今後，検討の余地が残っているものと考えられる。

文　献

1) Metzger R, Danengerg K, Leichman CG, *et al*: High basal level gene expression of thymidine phosphorylase (platelet-derived endothelial cell growth factor) in colorectal tumors is associated with nonresponse to 5-fluorouacil. *Clin Cancer Res* **4**(10): 2371-2376, 1998.
2) 勝又健次，壽美哲生，和田建彦・他: 大腸癌のThymidine Phosphorylase, Thymidylate Synthase, Dehydropyrimidine Dehydrogenase発現と予後および術後補助療法との関連．癌と化学療法　**31**(9): 1357-1360, 2004.
3) Altaha R, Liang X, Yu JJ, *et al*: Excision repair cross complementing-group 1: gene expression and platinum resistance. *Int J Mol Med* **14**(6): 959-970, 2004.
4) Mori K, Hasegawa M, Nishida M, *et al*: Expression levels of thymidine phosphorylase and dihydropyrimidine dehydrogenase in various human tumor tissues. *Int J Oncol* **17**(1): 33-38, 2000.
5) Nishida M, Hino A, Mori K, *et al*: Preparation of anti-human thymidine phosphorylase monoclonal antibodies useful for detecting the enzyme levels in tumor tissues. *Biol Pharm Bull* **19**(11): 1407-1411, 1996.
6) Kwon HC, Roh MS, Oh SY, *et al*: Prognostic value of expression of ERCC1, thymidylate synthase, and glutathione *S*-transferase P1 for 5-fluorouracil/oxaliplatin chemotherapy in advanced gastric cancer. *Ann Oncol* **18**(3): 504-509, 2007.
7) Etienne MC, Chéradame S, Fischel JL, *et al*: Response to fluorouracil therapy in cancer patients: the role of tumoral dihydropyrimidine dehydrogenase activity. *J Clin Oncol* **13**(13): 1663-1670, 1995.
8) Terashima M, Fujiwara H, Takagane A, *et al*: Prediction of sensitivity to fluoropyrimidines by metabolic and target enzyme activities in gastric cancer. *Gastric Cancer* **6**(*Suppl* 1): 71-81, 2003.
9) Paradiso A, Simone G, Petroni S, *et al*: Thymidilate synthase and p53 primary tumour expression as predictive factors for advanced colorectal cancer patients. *Br J Cancer* **82**(3): 560-567, 2000.
10) Johnston PG, Fisher ER, Rockette HE, *et al*: The role of thymidylate synthase expression in prognosis and outcome of adjuvant chemotherapy in patients with rectal cancer. *J Clin Oncol* **12**(12): 2640-2647, 1994.
11) Soong R, Shah N, Salto-Tellez M, *et al*: Prognostic significance of thymidylate synthase, dihydropyrimidine dehydrogenase and thymidine phosphorylase protein expression in colorectal cancer patients treated with or without 5-fluorouracil-based chemotherapy. *Ann Oncol* **19**(5): 915-919, 2008.
12) 石橋敬一郎，岡田典倫，石畝　亨・他: 切除不能・再発大腸癌における一次治療mFOLFOX6療法の治療効果とTS/ERCC-1蛋白発現の検討．癌と化学療法　**37**(12): 2532-2535, 2010.
13) Kim SH, Kwon HC, Oh SY, *et al*: Prognostic value of ERCC1, thymidylate synthase, and glutathione S-transferase π for 5-FU/oxaliplatin chemotherapy in advanced colorectal cancer. *Am J Clin Oncol* **32**(1): 38-43, 2009.

本論文の要旨は第33回日本癌局所療法研究会において発表した。

切除不能大腸癌同時性肝転移におけるmFOLFOX6療法の効果

近谷 賢一 石橋敬一郎 田島 雄介 幡野 哲 天野 邦彦
石畝 亨 桑原 公亀 傍島 潤 大澤 智徳 岡田 典倫
隈元 謙介 芳賀 紀裕 岩間 毅夫 石田 秀行*

〔*Jpn J Cancer Chemother* 38(12): 2211-2213, *November*, 2011〕

Therapeutic Effect of mFOLFOX6 for Synchronous Unresectable Liver Metastases from Colorectal Cancer: Kenichi Chikatani, Keiichiro Ishibashi, Yusuke Tajima, Satoshi Hatano, Kunihiko Amano, Toru Ishiguro, Koki Kuwabara, Jun Sobajima, Tomonori Ohsawa, Norimichi Okada, Kensuke Kumamoto, Norihiro Haga, Takeo Iwama and Hideyuki Ishida (*Dept. of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University*)

Summary

The current chemotherapy for metastatic colon cancer has improved an overall survival. In this study, we retrospectively analyzed the efficacy of mFOLFOX6 in colorectal cancer patients with synchronous unresectable liver metastases and compared the prognosis between before and after the administration of mFOLFOX6. The subject was 28 patients of colorectal cancer with synchronous unresectable liver metastasis who received mFOLFOX6 as a first-line treatment from 2005 to 2010. The median frequency of mFOLFOX6 was 10 times (range, 2-24 times), relative dose intensity of oxaliplatin was 75.0% (range, 42.9-100), response rate was 32%, and median progression-free survival was 9.9 months. Surgical resection of colorectal liver metastases was performed to 4 patients (14.3%) as a conversion therapy. The overall survival of the patients with mFOLFOX6 was significantly better than that of 31 patients who received the chemotherapy via hepatic artery or the chemotherapy before the administration of oxaliplatin (31.8 months vs. 15.1 months, $p<0.01$). Our results suggested that mFOLFOX6 treatment for unresectable liver metastases of colorectal cancer was made not only the conversion therapy possible, but it has improved the prognosis when compared with previous treatment without oxaliplatin. **Key words:** Colorectal cancer, Liver metastasis, mFOLFOX6

要旨 切除不能進行再発大腸癌に対する近年の化学療法の進歩は著しく，生存期間の延長に大きく寄与している。今回われわれは，oxaliplatin導入以後の切除不能大腸癌同時性肝転移症例の治療成績を解析するとともに，oxaliplatin導入以前の治療成績と比較した。2005年12月～2010年3月の期間，切除不能大腸癌同時性肝転移にて，一次治療としてmFOLFOX6を施行した28例を対象とし，その治療成績をretrospectiveに検討した。mFOLFOX6投与回数の中央値は10(2～24)回，oxaliplatinのrelative dose intensityは75.0 (42.9～100)%であった。奏効率は32%，無増悪生存期間中央値は9.9か月であった。4例(14.3%)にconversion therapyとして肝転移切除を施行することができた。全生存期間は，oxaliplatin導入以前に肝動脈化学療法や全身化学療法を行った31例より有意に良好であった(中央値31.8 vs 15.1か月，$p<0.01$)。今回の結果から，切除不能大腸癌同時性肝転移に対するmFOLFOX6療法は，conversion therapyをも可能にし，oxaliplatin導入以前の治療法よりも生存期間の延長に大きく寄与していた。

はじめに

2005年にoxaliplatinが本邦に導入されたが，本邦での実地臨床における切除不能大腸癌に対する治療成績は必ずしも明らかになっていない。

今回，切除不能大腸癌同時性肝転移に対する一次治療として行ったmFOLFOX6の治療効果をretrospectiveに検討したので報告する。

I. 対象・方法

当科で2005年12月～2010年3月までの間に，肝転移巣のみに切除不能転移巣を認める切除不能大腸癌同時性肝転移に対し，一次治療mFOLFOX6を導入した28例(bevacizumabの併用は4例)を対象とした。mFOLFOX6

* 埼玉医科大学総合医療センター 消化管・一般外科

連絡先: 〒350-8550 川越市鴨田1981 埼玉医科大学総合医療センター 消化管・一般外科
近谷 賢一

表 1 肝転移症例患者背景

性別	男性/女性 21/7
年齢（歳）*	67（33～79）
mFOLFOX6 施行回数*	10（2～24）
Oxaliplatin の relative dose intensity（%）*	75.0（42.9～100）
原発巣切除（%）	23 例（82.1）
Bevacizumab 併用	4 例
二次治療	FOLFIRI 10 例
	FOLFIRI＋bevacizumab 4 例

*: median（range）

表 2 腫瘍縮小効果

CR	1（3.5%）	9（32.1%）	21（75%）
PR	8（28.6%）		
SD	12（42.9%）		
PD	7（25.0%）		

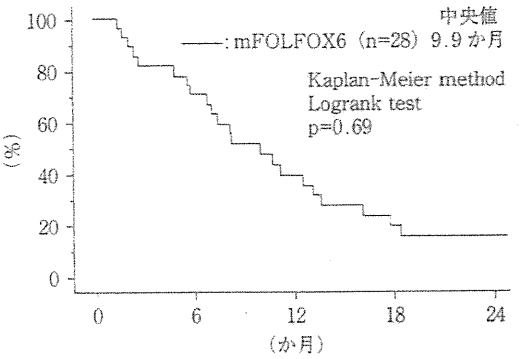

図 1 無増悪生存期間

施行回数，奏効率，無増悪生存期間について検討した。また治療後に肝転移巣が縮小し，切除可能となった症例の詳細についても検討した。さらに mFOLFOX6 導入以前に，肝動脈化学療法や全身化学療法などの治療を行った切除不能大腸癌同時性肝転移 31 例を対照に，全生存期間について比較した。

連続変数の記載は中央値（範囲）で記載した。生存率は Kaplan-Meier 法に従って算出し，生存期間の比較には logrank test を用いた。$p<0.05$ を有意差ありとした。

II. 結　果

1. 患者背景

年齢は 67(33～79)歳，男性 21 例，女性 7 例であった。mFOLFOX6 療法の投与回数は 10（2～24）回，oxaliplatin の relative dose intensity は 75.0（42.9～100）% であった。mFOLFOX6 施行前に原発巣を切除した症例は 23 例であった。二次治療は 14 例（50%）に施行され，内容は FOLFIRI 10 例，FOLFIRI＋bevacizumab 4 例であった（表 1）。

2. 奏効率・無増悪生存期間

腫瘍縮小効果は CR 1 例，PR 8 例，SD 12 例，PD 7 例であり，奏効率は 32.1%，病態制御率は 75% であった（表 2）。無増悪生存期間中央値は 9.9 か月であった（図 1）。

3. Conversion therapy 移行例

mFOLFOX6 療法導入前に原発巣を切除した 23 例のうち，mFOLFOX6 療法後に肝切除が可能となった症例は 2 例（8.7%）であった。1 例は，mFOLFOX6 を 10 回施行後に肝切除術を施行した。その後化学療法は行わず，肝切除より 23 か月後に肺転移を認めた。二次治療として FOLFIRI を導入するも，肺転移確認後 13 か月で原癌死した。もう 1 例は mFOLFOX6 を 14 回施行後に肝転移巣が縮小し，肝切除を施行した。術後 mFOLFOX6 を 6 回施行し経過観察となっていたが，肝切除 13 か月後に肝再発が認められた。mFOLFOX6 を 8 回施行し，画像上肝転移巣は消失。人工肛門閉鎖術時に瘢痕化した肝転移の一部を切除したところ，肝転移巣には癌細胞の遺残は認めなかった。さらにその 10 か月後に肝再発を認め，肝切除を施行。3 回目の肝切除から 14 か月の現在，無再発生存中である。原発巣を切除せずに mFOLFOX6 療法後に転移巣が切除可能となり，原発巣とともに切除が行われたのが 2 例であった。1 例は，mFOLFOX6＋bevacizumab を 12 回施行後に原発巣切除と瘢痕化した多発肝転移の一部を切除したところ，肝転移巣に癌細胞の遺残は認めなかった。術後化学療法は施行しなかったが，術後 26 か月経過した現在無再発生存中である。もう 1 例は mFOLFOX6 を 15 回施行後，原発巣切除と瘢痕化した多発肝転移の一部を切除したところ，肝転移巣に癌細胞の遺残は認めなかった。術後 mFOLFOX6 を 6 回施行し，術後 30 か月経過した現在無再発生存中である。

4. mFOLFOX6 導入以前の症例との全生存期間の比較

mFOLFOX6 を施行した 28 例と mFOLFOX6 療法導入以前の切除不能同時性肝転移に対し，何らかの治療を

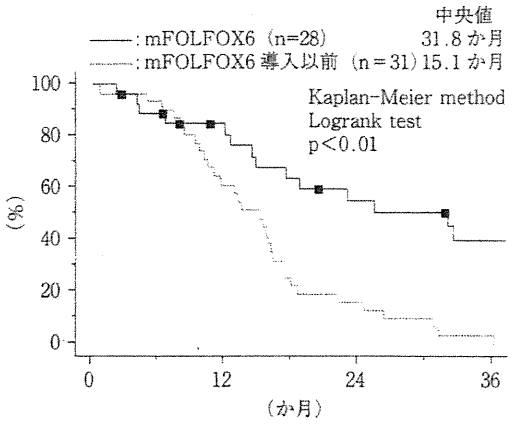

図2　全生存期間の比較

行った31例〔肝動脈化学療法22例，5-fluorouracil（5-FU）/Leucovorin（LV）4例，tegafur uracil（UFT）+LV 4例，tegafur，gimeracil and oteracil potassium（S-1）1例〕の全生存期間中央値は，各々31.8か月，15.1か月で，前者のほうが有意に良好であった（p<0.01），（図2）。

III．考　察

今回の検討から，従来行われてきた肝動脈化学療法や5-FUを主体とした全身化学療法と比較し，mFOLFOX6は著しい予後改善効果が得られることが確認できた。また従来の治療法では，conversion therapyに移行した症例がなかったのに対し，mFOLFOX6導入後には14.3%の症例がconversion therapyに移行できたことも注目すべきと思われる。oxaliplatinやirinotecan baseの化学療法後の大腸癌肝転移に対するconversion therapyは，4.5～23%[1-5]と報告されている。当科では，高齢者においても可能なかぎりmFOLFOX6療法を導入しており[6]，そのような背景を考慮した実地臨床においても臨床試験に遜色ない成績を得られることが確認できた。

今回の検討では，分子標的薬が本邦に導入されてからまだ日が浅いため，分子標的薬の生存期間や肝転移のR0切除率（conversion）への上乗せ効果を検討することはできなかった。N016966試験では，FOLFOX4またはXELOX療法にbevacizumabを併用することで0.7%[3]，CRYSTAL試験ではKRAS野生型の患者に対して，FOLFIRI療法にcetuximabを併用することで7.4%の肝転移R0切除率の上乗せ効果が認められている[4]。分子標的薬の上乗せ効果を検討する試験ではないが，CELIM試験ではFOLFIRI，FOLFOX6療法にcetuximabを併用することで，肝切除率が各々38%，30%と良好な成績であった[7]。今後，FOLFOX，XELOX，FOLFIRIといった基軸レジメンと分子標的薬の併用が，実地臨床においてもどの程度切除不能同時性肝転移をconversion therapyに導くことができるか確認することが必要である。

文　献

1) Tournigand C, André T, Achille E, *et al*: FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* **22**(2): 229-237, 2004.
2) Masi G, Loupakis F, Pollina L, *et al*: Long-term outcome of initially unresectable metastatic colorectal cancer patients treated with 5- fluorouracil/leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) followed by radical surgery of metastases. *Ann Surg* **249**(3): 420-425, 2009.
3) Saltz LB, Clarke S, Díaz-Rubio E, *et al*: Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* **26**(12): 2013-2019, 2008.
4) Van Cutsem E, Bokemeyer C, Heeger S, *et al*: Outcome acooding to metastatic site in patients with *KRAS* wild type tumors: Analysis from the CRYSTAL and OPUS studies. *J Clin Oncol* **29**(*Suppl* 4): abstr 472, 2011.
5) Tournigand C, Cervantes A, Figer A, *et al*: OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer—a GERCOR study. *J Clin Oncol* **24**(3): 394-400, 2006.
6) 石田秀行，石橋敬一郎，山口研成：高齢者大腸癌化学療法時の注意点と対策．外科　**72**(3): 267-271, 2010.
7) Folprecht G, Gruenberger T, Bechstein WO, *et al*: Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol* **11**(1): 38-47, 2010.

本論文の要旨は第33回日本癌局所療法研究会において発表した。

Int J Clin Oncol
DOI 10.1007/s10147-011-0298-z

ORIGINAL ARTICLE

Discrepancy between the NCI-CTCAE and DEB-NTC scales in the evaluation of oxaliplatin-related neurotoxicity in patients with metastatic colorectal cancer

Naohiko Inoue · Hideyuki Ishida · Motohiko Sano · Tohru Kishino · Norimichi Okada · Kensuke Kumamoto · Keiichiro Ishibashi

Received: 25 February 2011 / Accepted: 15 July 2011

Abstract
Background Several oxaliplatin-specific scales have been proposed in clinical practice to evaluate oxaliplatin-related neurotoxicity. We investigated whether there might be a discrepancy between the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) and the Neurotoxicity Criteria of Debiopharm (DEB-NTC), the commonly used oxaliplatin-specific scales, in the evaluation of peripheral neurotoxicity.
Patients and methods The subjects were 42 patients with metastatic colorectal cancer who received more than 6 cycles of first-line therapy with modified FOLFOX6 and more than 6 cycles of second-line therapy with FOLFIRI. The median number and cumulative dose of oxaliplatin administrations were 10.5 (range 6–22) and 889.4 mg/m^2 (range 484.5–1875.0 mg/m^2), respectively. The peripheral neurotoxicity was evaluated during mFOLFOX6 therapy and after its discontinuation using NCI-CTCAE ver. 3.0 and DEB-NTC. Data were collected prospectively and analyzed retrospectively.
Results The concordance rate of the peripheral neurotoxicity grade determined by these criteria was low: 48.8% during mFOLFOX6 and 47.3% after discontinuation of therapy. The cumulative dose of oxaliplatin-related peripheral neurotoxicity in 50% of the patients was lower when evaluated by DEB-NTC for both grades 1 ($P = 0.09$) and 2 ($P < 0.001$). The cumulative rate of improvement from grade 2 to 1 ($P < 0.001$) and from grade 2 to 0 ($P < 0.05$) after discontinuation of mFOLFOX6 therapy was higher when NCI-CTCAE was used for the evaluation.
Conclusion We found a discrepancy between the NCI-CTCAE and DEB-NTC scales in the evaluation of oxaliplatin-related neurotoxicity and suggest that the concomitant use of NCI-CTCAE and DEB-NTC would be useful to maintain oxaliplatin-based chemotherapy at higher quality.

Keywords Colorectal cancer · Oxaliplatin · Peripheral neurotoxicity · NCI-CTCAE · DEB-NTC

Introduction

Oxaliplatin-based chemotherapy has improved the outcomes of metastatic colorectal cancer patients [1, 2], and its efficacy as adjuvant chemotherapy for colon cancer has recently been reported [3, 4]. One of the important problems associated with oxaliplatin-based chemotherapy is its peripheral neurotoxicity, occurring mainly in the distal extremities, larynx, and the perilabial areas. This peripheral neurotoxicity includes acute toxicity, occurring during or within several hours of administration of oxaliplatin, and cumulative (chronic) toxicity, occurring with repeated administrations of oxaliplatin [2, 5–11]. The former is transient and is likely to be induced by cold stimulation; it is reported to occur in about 85–95% of the patients treated with the drug [2, 8–11]. The latter is one of the important reasons for discontinuation of oxaliplatin therapy, along with disease progression and hypersensitivity reaction [12, 13]. Cumulative (chronic) toxicity persists for a

N. Inoue · M. Sano · T. Kishino
Department of Pharmacy Services, Saitama Medical Center, Saitama Medical University, 1981 Kamoda, Kawagoe, Saitama 350-8550, Japan

H. Ishida (✉) · N. Okada · K. Kumamoto · K. Ishibashi
Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, 1981 Kamoda, Kawagoe, Saitama 350-8550, Japan
e-mail: 05hishi@saitama-med.ac.jp

Published online: 11 August 2011

prolonged period, even after discontinuation of oxaliplatin therapy. Although various methods to reduce oxaliplatin-related neurotoxicity have been proposed in recent years, no definitive method other than discontinuation of oxaliplatin has been established to date [5, 10, 14–19].

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) [20] scale has generally been used for the evaluation of adverse events related to anticancer drug treatment. The scale has also been commonly used for evaluation of the peripheral neurotoxicity associated with anticancer drugs. In addition, some other oxaliplatin-specific scales have also been proposed for evaluation of oxaliplatin neurotoxicity. However, to the best of our knowledge, there has been no report of a close comparison of the results of evaluation by NCI-CTCAE and such oxaliplatin-specific scales. One of the commonly used oxaliplatin-specific scales is the Neurotoxicity Criteria of Debiopharm (DEB-NTC) [21–23]. Peripheral neurotoxicity is classified into 5 grades (including death) in the NCI-CTCAE, but into 3 grades in the DEB-NTC. While grade 3 neurotoxicity is defined as peripheral neuropathy accompanied by functional impairment that interferes with daily living in both the NCI-CTCAE and DEB-NTC scales, the definitions of grade 1 and grade 2 neurotoxicities differ between the two scales. NCI-CTCAE places major emphasis on the severity of a range of objective neuropathies which exert no influence on daily living, whereas DEB-NTC places importance on the duration of the peripheral neurotoxicity (Table 1). The present study was aimed at evaluating the neurotoxicity of oxaliplatin using the two scales in patients receiving FOLFOX therapy for the treatment of colorectal cancer, determining the discrepancy between these scales, and examining the clinical significance of the two sets of evaluation criteria.

Table 1 Criteria of neurotoxicity according to the NCI-CTCAE ver. 3.0 and DEB-NTC scales

Grade	NCI-CTCAE	DEB-NTC
1	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling), but not interfering with function	Within 7 days
2	Sensory alteration or paresthesia (including tingling) interfering with function, but not interfering with ADL	More than 7 days
3	Sensory alteration or paresthesia interfering with ADL	Functional impairment interfering with ADL
4	Disability	–
5	Death	

ADL activities of daily living

Patients and methods

Patients

Severe neurotoxicity by oxaliplatin is generally associated with the cumulative dose of oxaliplatin. We therefore analyzed 42 patients with metastatic colorectal cancer who received more than 6 cycles of first-line therapy with modified FOLFOX6 (mFOLFOX6) [24] and more than 6 cycles of second-line therapy with FOLFIRI [18] after failure of mFOLFOX6 at our institute between October 2006 and June 2009 (Table 2). The male:female ratio was 23:19, and the median age of the patients was 63 years (range 32–79 years). Performance status (PS) determined according to the method of the Eastern Cooperative Oncology Group (ECOG) was PS 0 in 36 patients and PS 1 in 6 patients. The median number of oxaliplatin administrations was 10.5 (range 6–22), and the median total dose of oxaliplatin was 889.4 mg/m^2 (range 484.5–1875.0 mg/m^2). The primary site was the colon in 22 patients and the rectum in 20 patients. The target lesions were located in the liver in 22 patients, lung in 18 patients, peritoneum in 11 patients, lymph nodes in 11 patients, and adrenal gland in 1 patient. The objective tumor response was rated as complete response in one patient, partial response in 14 patients, stable disease in

Table 2 Patient characteristics

Male:female	23:19
Age (years)[a]	63 (32–79)
Number of oxaliplatin administrations[a]	10.5 (6–22)
Total dose of oxaliplatin (mg/m^2)[a]	889.4 (484.5–1875.0)
ECOG performance status (0:1)	36:6
Primary site	
Colon	22
Rectum	20
Target lesions[b]	
Liver	22
Lung	18
Peritoneum	11
Lymph node	11
Adrenal gland	1
Calcium/magnesium therapy	
Randomized controlled trial	17
Clinical practice	4
Reason for the discontinuation of mFOLFOX6	
Disease progression	20
Hypersensitivity reaction	12
Peripheral neurotoxicity	10

[a] Median (range)

[b] The subjects include overlapping cases

23 patients, and progressive disease in 4 patients. The reason for the discontinuation of mFOLFOX6 therapy was disease progression in 20 patients, hypersensitivity reactions in 12 patients, and peripheral neurotoxicity in 10 patients. Calcium/magnesium therapy was given before and after oxaliplatin therapy in a total of 21 (50%) patients. Of these, 17 patients received calcium/magnesium therapy in the clinical trial [25], and 4 received it in clinical practice.

mFOLFOX6 therapy

Oxaliplatin 85 mg/m^2 and levofolinate calcium 200 mg/m^2 were given concomitantly by drip infusion over 2 h, followed by rapid intravenous infusion of 5-fluorouracil (FU) at 400 mg/m^2. Thereafter, 5-fluorouracil was given at 2400 mg/m^2 as a continuous drip infusion over 46 h. The above procedure represented one cycle of treatment, and the treatment cycles were repeated every 2 weeks. The drugs were administered into the central vein via a subcutaneous indwelling port. Patients were hospitalized for the initial treatment, whereas the subsequent cycles were given in an outpatient chemotherapy clinic. Treatment was discontinued when evidence of disease progression (progressive disease, PD) was noted according to the Response Evaluation Criteria in Solid Tumors ver. 1.0 (RECIST) [26], or when there were intolerable adverse events. When an adverse event(s) of grade 3 or greater severity according to NCI-CTCAE ver. 3.0 occurred, the mFOLFOX6 therapy was suspended until the severity of the reaction improved to grade 2 or lower severity, and when mFOLFOX6 therapy was resumed, the dose of oxaliplatin was reduced to 70–80% of the initial dose level. 5-FU/LV therapy not combined oxaliplatin therapy was not adopted in any of the patients of this series. When calcium/magnesium was given to the patients, calcium gluconate hydrate 10 mL and 0.5 M magnesium sulfate 10 mL were dissolved together in 5% dextrose solution 100 mL, and given by intravenous drip infusion before and after the administration of oxaliplatin. FOLFIRI therapy was begun after a drug-free period of 4 weeks following the end of mFOLFOX6 therapy. FOLFIRI therapy was given a median 12 times (range 6–33).

Evaluation of neurotoxicity

On every visit of the patients to the clinic for chemotherapy, the patient's history was obtained by a nurse, pharmacist or physician in-charge at the outpatient chemotherapy clinic to determine the severity and duration of neurotoxicity according to both the NCI-CTCAE ver. 3.0 and DEB-NTC scales. The data were recorded prospectively in the medical charts, and later analyzed retrospectively.

Statistical analysis

The statistical software StatFlex ver. 6.0 (Artec, Osaka, Japan) was used for the statistical analysis. The κ statistic [27] was obtained to determine the rates of concordance of the neurotoxicity grades determined by the two sets of criteria. More specifically, the concordance was rated as follows: poor, $\kappa \leq 0.0$; slight, $0.0 < \kappa \leq 0.2$; fair, $0.2 < \kappa \leq 0.4$; moderate, $0.4 < \kappa \leq 0.6$; substantial, $0.6 < \kappa \leq 0.8$; almost perfect, $0.8 < \kappa \leq 1.0$. Curves of cumulative incidence and cumulative improvement of peripheral neurotoxicity were drawn by the Kaplan–Meier method, and the log-rank test was used for comparison of the curves. The results were regarded as statistically significant at $P < 0.05$.

Results

The median duration of mFOLFOX6 therapy was 181 days (range 91–422 days). Grade 0–2 peripheral neurotoxicity was recorded a total of 472 times during this period. The rate of concordance of grade 0–2 peripheral neurotoxicity as evaluated by the two sets of criteria was 48.8%, with $\kappa = 0.26$ (95% confidence interval 0.21–0.32) (Table 3). The median observation period after discontinuation of oxaliplatin, i.e., the median duration of FOLFIRI therapy, was 244 days (range 84–728 days). During this period, evaluation of neurotoxicity was carried out a total of 573 times. The rate of concordance of grade 0 to grade 2 peripheral neurotoxicity as evaluated by the two sets of criteria was again low, at 47.3%, with $\kappa = 0.18$ (95% confidence interval 0.13–0.22) (Table 4).

Figure 1a, b shows the cumulative incidence rates of grades 1 and 2 peripheral neurotoxicity during mFOLFOX6 therapy. According to both NCI-CTCAE ver. 3.0 and DEB-NTC, neurotoxicity of grade 1 or greater severity occurred in 41 of the 42 patients. There was a tendency for grade 1 neurotoxicity to be detected at a lower total dose of oxaliplatin when the evaluation was based on DEB-NTC

Table 3 Concordance rate of the peripheral neurotoxicity grade evaluated by NCI-CTCAE and DEB-NTC scales during mFOLFOX6 therapy

	DEB-NTC			
	Grade	0	1	2
NCI-CTCAE	0	103	73	24
	1	15	71	124
	2	3	8	61

Concordance rate 48.8%, κ 0.26 (95% confidence interval 0.21–0.32), $P < 0.001$

Table 4 Concordance rate of the peripheral neurotoxicity grade evaluated by NCI-CTCAE and DEB-NTC scales during FOLFIRI therapy

	DEB-NTC			
	Grade	0	1	2
NCI-CTCAE	0	23	24	49
	1	1	57	204
	2	0	10	178

Concordance rate 47.3%, κ 0.18 (95% confidence interval 0.21–0.32), $P < 0.001$

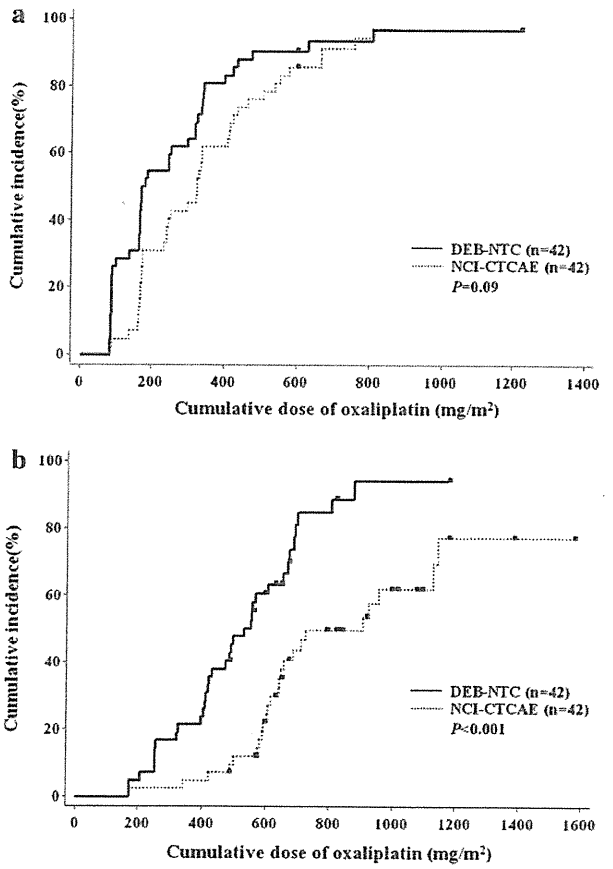

Fig. 1 **a** Cumulative incidence of grade 1, **b** cumulative incidence of grade 2 during mFOLFOX6 therapy

than when it was based on NCI-CTCAE ver. 3.0 ($P = 0.09$) (Fig. 1a). The total dose of oxaliplatin at which the incidence of grade 2 neurotoxicity reached 50% was 480 mg/m^2 when the evaluation was based on DEB-NTC and 627 mg/m^2 when the evaluation was based on NCI-CTCAE ver. 3.0; the total dose of oxaliplatin until the occurrence of grade 2 neurotoxicity was significantly lower when the evaluation was based on DEB-NTC ($P < 0.001$) (Fig. 1b). The cumulative dose between the occurrence of grade 1 neurotoxicity and increase in its severity to grade 2 was about 300 mg/m^2 according to evaluation by both DEB-NTC and NCI-CTCAE ver. 3.0. Grade 3 neurotoxicity (according to both NCI-CTCAE and DEB-NTC) occurred in 7 patients (16.7%).

Figure 2a–d shows the cumulative improvement of peripheral neurotoxicity during FOLFIRI therapy. Grade 3 peripheral neurotoxicity was found in 7 patients according to NCI-CTCAE ver. 3.0, and improved to grade 2 in 6 of these patients during the observation period. There was no difference in the improvement curves between the two sets of criteria ($P = 0.35$) (Fig. 2a). When the evaluation was based on NCI-CTCAE ver 3.0, improvement from grade 2 to grade 1 was found in 50% of the patients by 200 days after discontinuation of oxaliplatin, whereas when it was based on DEB-NTC, the rate of improvement within the observation period remained at 5% ($P < 0.001$) (Fig. 2b). In regard to the improvement from grade 2 to grade 0, the cumulative improvement reached a plateau at 40% during the observation period when the evaluation was based on NCI-CTCAE ver. 3.0, whereas when the evaluation was based on DEB-NTC, the cumulative improvement was determined to be only 5% ($P < 0.05$) (Fig. 2c). There was no significant difference in the curve of cumulative improvement from grade 1 to grade 0 between the two sets of criteria ($P = 0.19$) (Fig. 2d). However, a cumulative improvement of 45% was obtained during the observation period when the evaluation was based on NCI-CTCAE ver. 3.0, whereas the corresponding rate obtained was only 20% when the evaluation was based on the DEB-NTC scale.

Discussion

The present study revealed a discrepancy between the NCI-CTCAE ver. 3.0 and DEB-NTC scales in the evaluation of peripheral neurotoxicity associated with oxaliplatin-based chemotherapy for metastatic colorectal cancer. Specifically, it appears that grade 1 or grade 2 peripheral neurotoxicity after the start of mFOLFOX6 therapy can be detected earlier when the evaluation was based on DEB-NTC than when it was based on NCI-CTCAE ver. 3.0. With respect to evaluation of improvement in the peripheral neurotoxicity after discontinuation of oxaliplatin, grade 1 or grade 2 neurotoxicity persisted for longer when the evaluation was based on the DEB-NTC scale. In particular, it is noteworthy that scarcely any improvement of neuropathy was found during the observation period after discontinuation of oxaliplatin (84–728 days, median 240 days) in patients with grade 2 symptoms, i.e., those who had peripheral neuropathy persisting for at least 14 days. There was no close relationship between the grade of paresthesia and the duration of peripheral neurotoxicity.

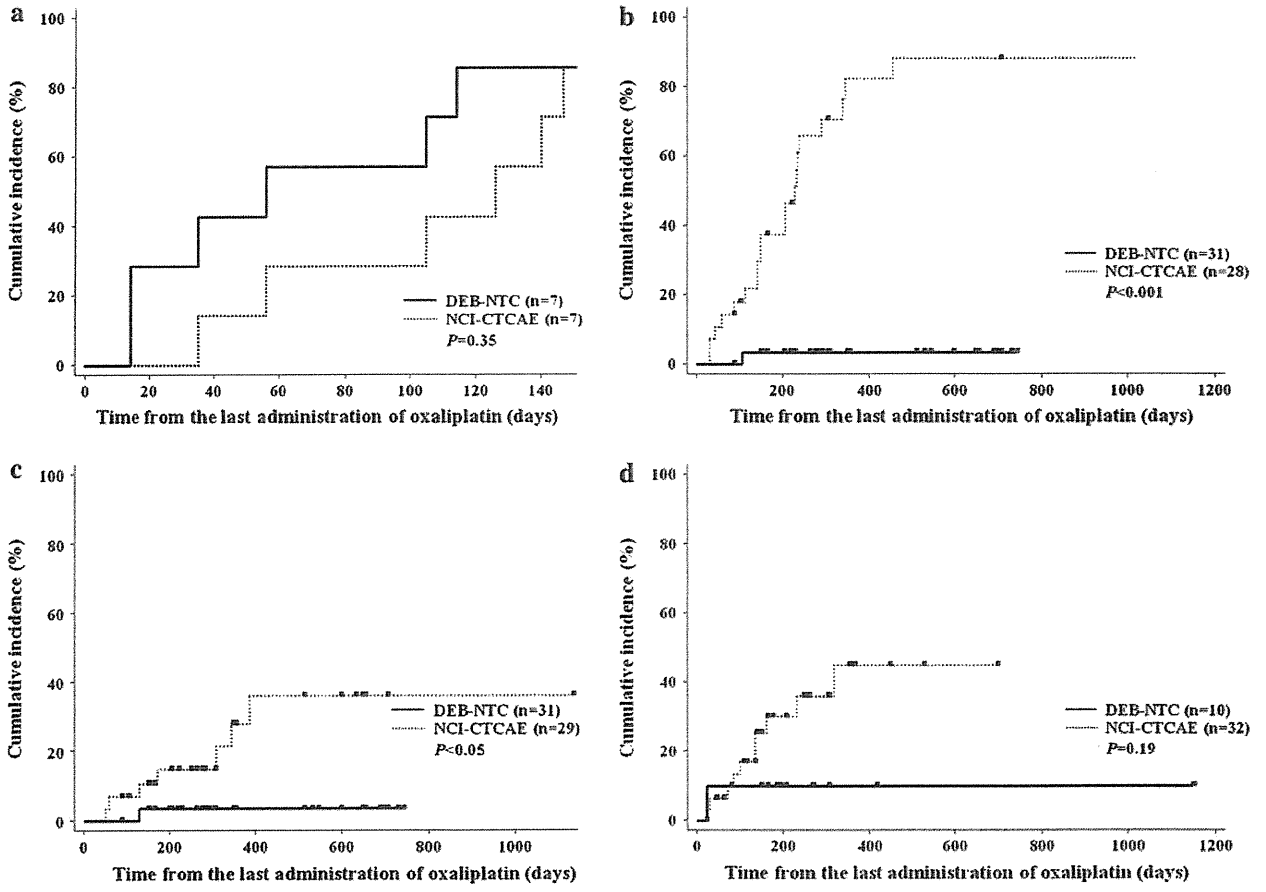

Fig. 2 **a** Cumulative improvement from grade 3 to grade 2, **b** cumulative improvement from grade 2 to grade 1, **c** cumulative improvement from grade 2 to grade 0, **d** cumulative improvement from grade 1 to grade 0 during FOLFIRI therapy

Therefore, we speculated that this discrepancy between the evaluations by NCI-CTCAE ver. 3.0 and DEB-NTC arose from the criteria used for toxicity up to grade 2, because the former criteria place stress on the grade of paresthesia, whereas the latter attach more importance to the duration of peripheral neurotoxicity.

How to apply these findings to practical oxaliplatin-based chemotherapy is an important issue. A key point in oxaliplatin-based chemotherapy is to prevent the appearance of grade 3 peripheral neuropathy. In patients with paraesthesias associated with pain or functional impairment persisting until the next cycle, oxaliplatin should be permanently discontinued [28]. Therefore, it is crucial to predict the development of grade 3 neuropathy as early as possible. The present study revealed that peripheral neuropathy persisting for at least 14 days, i.e., grade 2 neuropathy, was detected earlier, at an oxaliplatin dose 150 mg/m^2 lower, when the evaluation was based on DEB-NTC than when it was based on NCI-CTCAE ver. 3.0. Therefore, it is important to ask the patient carefully about the duration of neuropathy. When DEB-NTC is used for the evaluation of neuropathy in daily clinical practice, continuation of treatment should be considered as long as there is no interference with the patient's daily activities. However, there may be criticism that if a physician decides to discontinue or restart the chemotherapy according to the DEB-NTC scale, the total dose of oxaliplatin, which may affect the survival period, would be lower than that with the use of the NCI-CTCAE scale. We cannot address this issue exactly, but it deserves further investigation in future clinical trials or accumulated cases in clinical practice.

The usefulness of FOLFOX4 [2] and FLOX [4] as adjuvant chemotherapy for colon cancer has been reported. However, a follow-up study of the MOSAIC trial [3] showed that peripheral neuropathy was persistent in 15.4% of the surviving patients who were followed up for at least 4 years after adjuvant chemotherapy with FOLFOX4. In the MOSAIC study, peripheral neuropathy was evaluated by NCI-CTCAE ver. 1.0. It would be interesting to speculate on what results might have been obtained if the evaluation had been based on DEB-NTC, since even more delayed improvement of neuropathy tends to be obtained

when the evaluation is based on DEB-NTC than when it is based on NCI-CTCAE. If clinical trials aimed at reducing peripheral neuropathy in patients receiving oxaliplatin-based chemotherapy in the adjuvant setting are planned in the future, the use of DEB-NTC together with NCI-CTCAE is recommended for the evaluation of neuropathy. Although it would be ideal for specific scales to be designed for the evaluation of acute and chronic peripheral neuropathy, no such scales are available at present.

Some oxaliplatin-specific scales other than DEB-NTC have been proposed. In the NSABP C-07 study, Stephanie et al. [4] evaluated pain during oxaliplatin therapy by means of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Oxaliplatin-Specific Neurotoxicity Scale (NTX-12) and NCI-Sanofi grade. A questionnaire evaluation of the quality of life (QOL) of patients was also carried out in the N04C7 study [29]. In addition, de Gramont et al. [2] evaluated peripheral neurotoxicity as a factor affecting the patient's QOL using QOL scores. A patient-oriented survey technique based on the Patient Neurotoxicity Questionnaire (PNQ): oxaliplatin has also been reported. From this point of view, evaluation of the duration of peripheral neuropathy, a subjective variable that can only be described by the patients themselves, by DEB-NTC might be able to contribute to QOL improvement of the patients given oxaliplatin-based chemotherapy.

When evaluating the grade of peripheral neurotoxicity in patients examined in previous clinical trials or treated in clinical practice, attention should be paid to which set of criteria was used: NCI-CTCAE ver. 3.0 or other oxaliplatin-specific scales. At present, NCI-CTCAE is used commonly in many medical institutions for the evaluation of adverse events during anticancer drug treatment. When the grade was different between these scales, we preferred the evaluation using the NCI-CTCAE scale because NCI-CTCAE is believed to be a global standard. However, it would appear that the addition of DEB-NTC to NCI-CTCAE for the evaluation of adverse events in patients receiving oxaliplatin may contribute to the formulation of better treatment plans from the aspects of reduction, discontinuation, or even resumption of oxaliplatin therapy in the future.

In order to maintain comparability among the results of different trials, neurotoxicity should be always graded according to the NCI-CTCAE scale, and use of any oxaliplatin-specific scales should be regarded as supplemental. However, all physician-based assessment tools used to grade subjective toxicity phenomena, such as neurotoxicity, have shown dramatic disagreements between physician-reported and patient-reported severity of symptoms [30].

In the future, patient-based assessment of neurotoxicity could provide more reliable and more accurate information about the incidence and severity of oxaliplatin-induced neurotoxicity.

Conflict of interest No author has any conflict of interest.

References

1. Goldberg RM, Sargent DJ, Morton RF et al (2004) A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combination in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 22:23–30
2. de Gramont A, Figer A, Seymour M et al (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18:2938–2947
3. André T, Boni C, Navarro M et al (2009) Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAC trial. J Clin Oncol 27:3109–3116
4. Stephanie RL, Jacek AK, Reena SC et al (2007) Neurotoxicity from oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: NSABP C-07. J Clin Oncol 25:2205–2211
5. Grothey A (2003) Oxaliplatin-safety profile: neurotoxicity. Semin Oncol 30:5–13
6. Cavaletti G, Tredici G, Petruccioli MG et al (2001) Effects of different schedules of oxaliplatin treatment on the peripheral nervous system of the rat. Eur J Cancer 37:2457–2463
7. Krishnan AV, Goldstein D, Friedlander M et al (2005) Oxaliplatin-induced neurotoxicity and the development of neuropathy. Muscle Nerve 32:51–60
8. Grothey A (2005) Clinical management of oxaliplatin-associated neurotoxicity. Clin Colorectal Cancer 5(Suppl 1):S38–S46
9. Meyerhardt JA, Mayer RJ (2005) Systemic therapy for colorectal cancer. N Engl J Med 352:476–487
10. Gamelin E, Gamelin L, Bossi L et al (2002) Clinical aspects and molecular basis of oxaliplatin neurotoxicity: current management and development of preventive measures. Semin Oncol 29(5 Suppl 15):21–33
11. Choi J, Kong K, Mozaffar T et al (2006) Delayed oxaliplatin associated neurotoxicity following adjuvant chemotherapy for stage III colon cancer. Anti-cancer Drugs 17:103–105
12. Imada H, Kwakami K, Hiraoka T et al (2007) Drug information brochure for patients undergoing FOLFOX4 chemotherapy based on survey of adverse reaction. Peripheral neurotoxicity. J Cancer Chemother 34(9):1425–1430
13. Shouji D, Matsusaka S, Watanabe C et al (2008) Relative dose intensity of FOLFOX4 regimen. Jperipheral neurotoxicity. J Cancer Chemother 35(11):1895–1900
14. Gamelin L, Boisdron-Celle M, Delva R et al (2004) Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: a retrospective study of 161 patients receiving oxaliplatin combined with 5-fluorouracil and leucovorin for advanced colorectal cancer. Clin Cancer Res 10:4055–4061
15. Cascinu S, Catalano V, Cordella L et al (2002) Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: a randomized, double-blind, placebo-controlled trial. J Clin Oncol 20(16):3478–3483
16. Wilson RH, Lehky T, Thomas RR et al (2002) Acute oxaliplatin-induced peripheral nerve hyperexcitability. J Clin Oncol 20: 1767–1774
17. Tournigand C, Cervantes A, Figer A et al (2006) OPTMOX1: A randomized study of FOFOX4 or FOLFOX7 with oxaliplatin in a

stop-and-go fashion in advanced colorectal cancer—a GERCOR study. J Clin Oncol 24:394–400
18. Tournigand C, André T, Achille E et al (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 22:229–237
19. Maindrault-Grobel F, Tournigand C, André T et al (2004) Oxaliplatin reintroduction in patients previously treated with leucovorin, fluorouracil, and oxaliplatin for metastatic colorectal cancer. Ann Oncol 15:1210–1214
20. National Cancer Institute. National Cancer Institute Common Toxicity Criteria version 3.0. http://ctep.cancer.gov/
21. Boku N, Ohtsu A, Hyodo I et al (2007) Phase II study of oxaliplatin in Japanese patients with metastatic colorectal cancer refractory to fluoropyrimidines. Jpn J Clin Oncol 37:440–445
22. Christian L et al (2002) Prevention of oxaliplatin-induced peripheral sensory neuropathy by carbamazepine in patients with advanced colorectal cancer. Clin Colorectal Cancer 2:54–58
23. Lévi F, Perpoint B, Garufi C et al (1993) Oxaliplatin activity against metastatic colorectal cancer. A phase II study of 5-day continuous venous infusion at circadian rhythm modulated rate. Eur J Cancer 29:1280–1284
24. Allegra CJ, Yothers G, O'Connell MJ et al (2011) Phase III trial assessing bevacizumab in sages II and III carcinoma of the colon: results of NSABP protocol C-08. J Clin Oncol 29:1–4
25. Ishibashi K et al (2010) Effect of calcium and magnesium on neurotoxicity and blood platinum concentration in patients receiving mFOLFOX6 therapy: a prospective randomized study. Int J Clin Oncol 15:82–87
26. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205–216
27. Landis LR, Koch GG (1977) The measurement of observer agreement for categorical data. Biometrics 33:159–174
28. Caussanel JP, Lévi F, Brienza S et al (1990) Phase I trial of 5-day continuous venous infusion of oxaliplatin at circadian rhythm modulated rate compared with constant rate. J Natl Cancer Inst 82:1046–1050
29. Nikcevich DA, Grothey A, Sloan JA et al (2008) Effect of intravenous calcium and magnesium (IV CaMg) on oxaliplatin-induced sensory neurotoxicity (sNT) in adjuvant colon cancer: results of the phase III placebo-controlled, double-blind NCCTG trial N04C7. Proc Am Soc Clin Oncol 26 (abstr 4009)
30. Stephens RJ, Hopwood P, Girling DJ et al (1997) Randomized trials with quality of life endpoints: are doctors' ratings of patients' physical symptoms interchangeable with patients' self-ratings? Qual Life Res 6:225–236

Gastric Cancer
DOI 10.1007/s10120-011-0101-x

ORIGINAL ARTICLE

Combination chemotherapy with S-1 plus cisplatin for gastric cancer that recurs after adjuvant chemotherapy with S-1: multi-institutional retrospective analysis

Kohei Shitara · Satoshi Morita · Kazumasa Fujitani · Shigenori Kadowaki · Nobuhiro Takiguchi · Naoki Hirabayashi · Masazumi Takahashi · Masakazu Takagi · Yukihiko Tokunaga · Ryoji Fukushima · Yasuhiro Munakata · Kazuhiro Nishikawa · Akinori Takagane · Takaho Tanaka · Yoshiaki Sekishita · Junichi Sakamoto · Akira Tsuburaya

Received: 19 July 2011 / Accepted: 11 September 2011

Abstract
Background It is unclear whether S-1 plus cisplatin is effective for patients with recurrent gastric cancer after adjuvant S-1 chemotherapy.
Methods We retrospectively evaluated the efficacy of S-1 plus cisplatin in patients whose gastric cancer recurred after adjuvant S-1 chemotherapy.
Results In the 52 patients evaluated, the median duration of adjuvant S-1 chemotherapy was 8.1 months, and the median recurrence-free interval (RFI) since the last administration of adjuvant S-1 was 6.4 months. Among the 36 patients with measurable lesions, 7 achieved a complete or partial response, and 13 were evaluated as having stable

K. Shitara (✉)
Department of Clinical Oncology,
Aichi Cancer Center Hospital, 1-1 Kanokoden,
Chikusa-ku, Nagoya, Aichi 464-8681, Japan
e-mail: Kouheis0824@yahoo.co.jp

S. Morita
Department of Biostatistics and Epidemiology,
Yokohama City University Medical Center,
Yokohama, Japan

K. Fujitani
Department of Surgical Oncology,
National Osaka Medical Center, Suita, Japan

S. Kadowaki
Department of Gastroenterology,
Saitama Cancer Center Hospital, Saitama, Japan

N. Takiguchi
Department of Gastroenterological Surgery,
Chiba Cancer Center Hospital, Chiba, Japan

N. Hirabayashi
Department of Surgery, Hiroshima City Asa Hospital,
Hiroshima, Japan

M. Takahashi
Department of Gastroenterological Surgery,
Yokohama Municipal Citizens Hospital, Yokohama, Japan

M. Takagi
Department of Surgery, Shizuoka General Hospital,
Shizuoka, Japan

Y. Tokunaga
Department of Surgery, Osaka North Japan Post Hospital,
Osaka, Japan

R. Fukushima
Department of Surgery, Teikyo University School of Medicine,
Tokyo, Japan

Y. Munakata
Department of Surgery, Nagano Municipal Hospital,
Nagano, Japan

K. Nishikawa
Department of Surgery, Osaka General Medical Center,
Osaka, Japan

A. Takagane
Department of Surgery, Hakodate Goryoukaku Hospital,
Hakodate, Japan

T. Tanaka
Department of Surgery, Social Insurance Tagawa Hospital,
Tagawa, Japan

Y. Sekishita
Department of Surgery, Obihiro Kosei Hospital, Obihiro, Japan

J. Sakamoto
Young Leaders' Program in Medical Administration,
Nagoya University Graduate School of Medicine, Nagoya, Japan

A. Tsuburaya
Department of Gastrointestinal Surgery, Kanagawa Cancer
Center, Yokohama, Japan

Published online: 13 October 2011

disease, for an overall response rate of 19.4% and a disease control rate of 55.6%. For all patients, the median progression-free survival (PFS) was 4.8 months, and the median overall survival (OS) was 12.2 months. Compared with patients with an RFI of <6 months ($n = 25$), patients with an RFI of ≥6 months ($n = 27$) had a significantly higher response rate (5.0 vs. 37.5%, respectively), longer PFS (2.3 vs. 6.2 months, respectively), and longer overall survival (7.3 vs. 16.6 months, respectively). According to a multivariate Cox model including performance status (PS) and reason for discontinuation of adjuvant S-1, an RFI of 6 months was still significantly associated with PFS and OS.
Conclusions S-1 plus cisplatin is effective for patients with gastric cancer that recurs after adjuvant S-1 chemotherapy, especially for those with an RFI of ≥6 months.

Keywords Adjuvant chemotherapy · Gastric cancer · Recurrence · S-1

Introduction

Gastric cancer is the fourth most common malignancy in the world (988,602 cases in 2008, 7.8% of total malignancy cases) and the second leading cause of cancer death (737,419 deaths, 9.7% of total) [1]. The prognosis of patients with advanced or recurrent gastric cancer remains poor; chemotherapy confers only a minimal survival advantage, with a median survival of approximately 1 year. The most commonly used regimens are combination chemotherapy consisting of a fluoropyrimidine [5-fluorouracil (5-FU) or oral fluoropyrimidine] plus a platinum agent with or without docetaxel or anthracyclines [2–6].

S-1 is an oral anticancer drug composed of the 5-FU prodrug tegafur and two 5-FU modulators; it has achieved high response rates in patients with gastric cancer in phase II studies [7, 8]. In the Japan Clinical Oncology Group (JCOG) 9912 trial, which compared S-1, cisplatin plus irinotecan, and 5-FU, S-1 demonstrated non-inferiority compared to 5-FU [9]. In another phase III trial that compared S-1 alone to S-1 plus cisplatin (SPIRITS trial), S-1 plus cisplatin showed a significantly higher response rate (54 vs. 31%), longer progression-free survival (PFS; 6.0 vs. 4.0 months), and longer overall survival (OS; 13 vs. 11 months) [4]. Also, in a large, non-Japanese, phase III trial (the First-Line Advanced Gastric Cancer Study; FLAGS trial), S-1 plus cisplatin was associated with fewer toxic effects and demonstrated non-inferiority compared with 5-FU plus cisplatin by exploratory analysis [6]. Therefore, S-1 plus cisplatin is now considered to be one of the standard regimens for metastatic or recurrent gastric cancer.

In addition, the ACTS-GC trial has demonstrated that S-1 is also effective as adjuvant chemotherapy for Japanese patients who have undergone curative gastrectomy for locally advanced gastric cancer [10]. However, approximately 30% of patients still develop recurrence after curative resection followed by adjuvant S-1 [10]. As few patients who received adjuvant chemotherapy were included in the phase III trials described above [4, 7, 9], it is unclear whether patients who develop recurrence after adjuvant S-1 could achieve efficacy with S-1 plus cisplatin similar to that achieved in patients without adjuvant chemotherapy. To address this issue, we conducted the following multi-institutional retrospective analysis.

Patients and methods

Patients

This retrospective study was designed to evaluate the efficacy of first-line chemotherapy with S-1 plus cisplatin for recurrence in patients with gastric cancer who had undergone curative gastrectomy followed by adjuvant S-1 chemotherapy. Patients with histopathologically proven recurrent gastric adenocarcinoma after gastrectomy and lymph node dissection with no residual tumor were eligible for analysis. Additional eligibility criteria were: (1) previous adjuvant S-1 chemotherapy at a planned standard dose and schedule (80 mg/m^2 for 28 consecutive days followed by a 14-day rest; 42-day cycles to be repeated for 1 year); (2) Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2; (3) adequate bone marrow, hepatic, and renal function to be treated with S-1 plus cisplatin; (4) evaluable lesions according to Response Evaluation Criteria in Solid Tumors (RECIST ver. 1.1); and (5) treated with a standard regimen of S-1 plus cisplatin (S-1 80 mg/m^2 for 21 consecutive days followed by a 14-day rest; cisplatin 60 mg/m^2 intravenous infusion on day 8; 35-day cycles to be repeated) [4]. Written informed consent for treatment was obtained from each patient prior to treatment initiation. The Institutional Review Board of each participating center approved the study.

Evaluation of treatment and statistical analysis

The tumor response was assessed objectively according to RECIST ver. 1.1, and the best overall response was recorded as the antitumor effect for that patient. The disease control rate (DCR) represented the percentage of patients with a complete response (CR), partial response (PR), or stable disease (SD). PFS was measured from the date of initiation of S-1 plus cisplatin to the date of progressive disease or death from any cause. Time to treatment failure

(TTF) was measured from the date of initiation of S-1 plus cisplatin to the date of last administration of S-1. OS was estimated from the date of initiation of S-1 plus cisplatin to the date of death or last follow-up visit, using the Kaplan–Meier method. The interval from the last administration of adjuvant S-1 to recurrence was defined as the recurrence-free interval (RFI).

The Cox proportional hazards model was used to estimate the impact of the RFI on TTF, PFS, and OS, with adjustment for other factors that were shown to be significant with a univariate log-rank test. *P* values for testing differences between proportions and response rates were calculated with χ^2 tests for homogeneity or for trend, or with Fisher's exact test. Results were considered to be statistically significant when the *P* value was <0.05. All reported *P* values are two-sided. In particular, we compared the response rate, DCR, time to progression (TTP), PFS, and OS between patients with RFIs of ≥6 and <6 months, because several clinical trials in the first-line setting set this interval of ≥6 months as an inclusion criterion [5, 9, 11].

Results

Patient characteristics

A total of 406 patients with recurrent gastric cancer after adjuvant S-1 chemotherapy had received chemotherapy at 18 institutions until October 2010. Among them, 57 patients (14.0%) had received S-1 plus cisplatin as first-line chemotherapy for recurrence. After the exclusion of 5 patients (1 patient with a non-evaluable lesion and 4 patients with insufficient data), 52 patients were included in the final

Table 1 Patient characteristics

Characteristic	All ($n = 52$)	RFI <6 months ($n = 25$)	RFI ≥6 months ($n = 27$)	*P* value
Age, years				
Median (range)	61 (32–77)	59 (32–77)	62 (32–77)	
Gender, *n* (%)				
Male	30 (58)	15 (60)	15 (56)	0.75
Female	22 (42)	10 (40)	12 (44)	
ECOG PS at recurrence, *n* (%)				
0	32 (62)	11 (44)	21 (78)	*0.012*
1	20 (38)	14 (56)	6 (22)	
Histological type[a], *n* (%)				
wel or mod	27 (52)	10 (40)	17 (63)	0.1
por or sig	24 (46)	15 (60)	9 (33)	
Other	1 (2)	–	1 (4)	
Pathological stage[a], *n* (%)				
Stage I or II	8 (15)	4 (16)	4 (15)	0.57
Stage IIIA	17 (33)	6 (24)	11 (41)	
Stage IIIB	15 (29)	8 (32)	7 (26)	
Stage IV	12 (23)	7 (28)	5 (19)	
Site of recurrence, *n* (%)				
Peritoneum	21 (40)	7 (28)	14 (52)	0.08
Lymph node	25 (48)	13 (52)	12 (44)	0.59
Liver	14 (27)	10 (40)	4 (15)	*0.041*
Lung	4 (8)	3 (12)	1 (4)	0.262
Bone	6 (12)	1 (4)	5 (19)	0.102
Local	2 (4)	1 (4)	1 (4)	0.96
Number of recurrence sites, *n* (%)				
1	38 (73)	18 (72)	20 (74)	0.87
2 or more	14 (27)	7 (28)	7 (26)	

P values shown in italics indicate significant differences

RFI Recurrence-free interval, *PS* performance status, *ECOG* Eastern Cooperative Oncology Group, *wel* well-differentiated adenocarcinoma, *mod* moderately differentiated adenocarcinoma, *por* poorly differentiated adenocarcinoma, *sig* signet-ring-cell-like carcinoma

[a] According to the Japanese classification

analysis (Table 1). The median duration of adjuvant S-1 chemotherapy was 8.1 months (range 0.7–37.4 months), and the median RFI since the last administration of adjuvant S-1 was 6.4 months (range 0–81.3 months). Thirty of the 52 patients (57.7%) completed the planned duration of adjuvant S-1 therapy. In contrast, 14 patients discontinued S-1 due to disease recurrence, and 8 patients stopped therapy due to toxicity or patient refusal. Other than PS and liver metastasis, characteristics did not differ significantly between patients with an RFI of ≥6 months ($n = 27$) and those with an RFI of <6 months ($n = 25$) (Table 1).

Treatment results and efficacy

The median TTF was 4.1 months (95% confidence interval [CI] 2.5–5.1 months), with a median duration of follow-up of 32 months. Forty-four patients discontinued S-1 plus cisplatin due to disease progression ($n = 40$, 90.9%) or toxicity ($n = 4$, 9.1%). Of the 36 patients with measurable lesions, 7 achieved a CR ($n = 3$) or a PR ($n = 4$), and 13 were evaluated as having SD, for an overall response rate of 19.4% (95% CI 7.0–37.0%) and a DCR of 55.6% (95% CI 38.1–72.1%). The median PFS was 4.8 months (95% CI 3.9–6.2 months), and the median OS of all patients was 12.2 months (95% CI 10.2–16.6 months) (Fig. 1). Of the 44 patients who had discontinued S-1 plus cisplatin, 31 (70.4%) received second-line or third-line chemotherapy, including taxanes ($n = 25$) or irinotecan ($n = 17$).

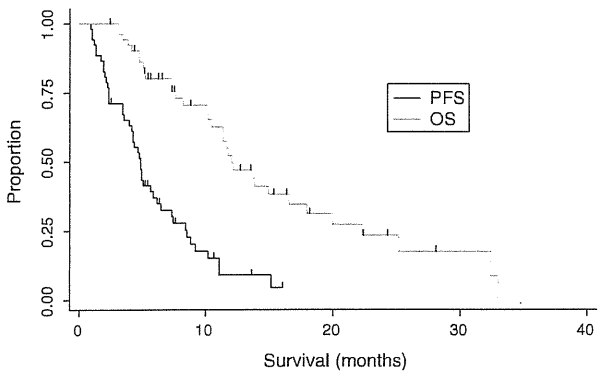

Fig. 1 Progression-free survival (*PFS*) and overall survival (*OS*) in all patients. The median PFS was 4.8 months (95% confidence interval [CI] 3.9–6.2 months), and the median OS was 12.2 months (95% CI 10.2–16.6 months). *PFS* progression-free survival, *OS* overall survival

Significance of the RFI

The response rate was significantly better in patients with an RFI of ≥6 months (37.5%; 95% CI 14–61%) than that in patients with an RFI of <6 months (5.0%; 95% CI 0–15%, $P = 0.014$, Table 2). In addition, compared with patients with an RFI of <6 months, patients with an RFI of ≥6 months had a significantly longer TTF (2.5 vs. 5.1 months, respectively, $P = 0.025$), longer PFS (2.3 vs. 6.2 months, respectively, $P < 0.001$, Fig. 2), and longer OS (7.3 vs. 16.6 months, respectively, $P = 0.003$, Fig. 2). According to a multivariate Cox model including PS and reason for discontinuation of adjuvant S-1, an RFI of 6 months was still significantly associated with PFS (hazard ratio [HR] 0.35, 95% CI 0.16–0.77, $P = 0.009$) and OS (HR 0.21, 95% CI 0.08–0.54, $P = 0.001$), although the association with TTF was not significant (HR 0.55, 95% CI 0.27–1.12, $P = 0.1$). When we divided the patients into two groups based on an RFI of 12 months, no significant difference between the groups was found in response rate, TTP, PFS, or OS.

Discussion

In the ACTS-GC study, adjuvant S-1 chemotherapy significantly improved the survival of patients who had undergone curative gastrectomy for locally advanced gastric cancer [10]. On the other hand, several small studies have suggested that patients with recurrence after adjuvant S-1 were refractory to S-1-containing regimens or had a worse prognosis compared with that of patients without adjuvant chemotherapy [12–14]. Although these reports never precluded the use of adjuvant S-1 chemotherapy, they raised the issue of how to treat recurrent disease after adjuvant S-1.

In the present retrospective study, we evaluated the efficacy of S-1 plus cisplatin in patients whose gastric cancer recurred after adjuvant chemotherapy with S-1. The response rate of 19.4% and PFS of 4.8 months were

Table 2 Objective response rates in patients with measurable lesions

	n	CR	PR	SD	PD	NE	ORR (%)	95% CI (%)
All	36	3	4	13	14	2	18.8	7–32
RFI <6 months	20	0	1	6	13	0	5.0	0–15
RFI ≥6 months	16	3	3	7	1	2	37.5	14–61

CR Complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *ORR* objective response rate, *CI* confidence interval