論　文　要　旨

論　文　題　目

大腸癌肝転移の初回化学療法の治療効果判定におけるCT上の形態変化の有用性

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ABSTRACT

Background: It was reported that morphologic response to preoperative chemotherapy was an independent prognostic factor in patients who underwent hepatic resection of colorectal liver metastases (CLM). The aim of this study was to evaluate the predictive value of morphologic response to first-line chemotherapy in patients with CLM**.**

Methods: We assessed 41 patients with CLM who received fluorouracil-based chemotherapy with or without bevacizumab as first-line chemotherapy between April 2006 and June 2012. Three blinded radiologists evaluated computed tomography (CT) images and classified as optimal, incomplete or none response according to the morphologic criteria. Response to systemic chemotherapy was also evaluated according to RECIST. Predictive factors associated with Progression-free survival (PFS) were identified in multivariate analysis.

Results: Twenty three patients (56%) received chemotherapy with bevacizumab, while 18 patients (44%) received chemotherapy without bevacizumab. Optimal morphologic response was observed in 11 patients (48%) treated with bevacizumab and in 5 patients (28%) treated without bevacizumab (p=0.19). Eight patients (20%) underwent hepatic resection after chemotherapy. The median follow-up period was 31.3 months. The

median PFS was 13.3 months for patients with optical morphologic response and 8.7 months in those with incomplete/none morphologic response (p=0.0026). On multivariate analysis, PS and morphologic response were significant independent predictors of PFS.

Conclusion: Optimal morphologic response was significantly associated with PFS in patients with CLM who were treated with fluorouracil-based chemotherapy as first-line chemotherapy.

Introduction

In patients with metastatic colorectal cancer (mCRC), fluorouracil-based chemotherapy has been performed as first-line chemotherapy. FOLFOX, which is a chemotherapy regimen consisting of 5-FU/leucovorin (LV) plus oxaliplatin, prolonged progression-free survival (PFS) compared with 5-FU/LV [1]. 5-FU/LV plus irinotecan (FOLFIRI) also provided a significant clinical benefit [2]. Randomized study comparing FOLFOX with FOLFIRI demonstrated similar efficacy [3]. The combination of capecitebine plus oxaliplatin (XELOX) was found to be non-inferior to FOLFOX in terms of PFS in NO16966 trial [4]. Therefore, FOLFOX, FOLFIRI, and XELOX are considered to be the standard chemotherapy in patients with mCRC.

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, improved the outcome in patients with mCRC when used in combination with cytotoxic regimen. In randomized studies, the addition of bevacizumab to oxaliplatin-based chemotherapy (FOLFOX or XELOX) improved PFS [5], and the addition of bevacizumab to irinotecan-based chemotherapy improved not only PFS but also overall survival (OS) [6].

Recently, it was reported that the morphologic criteria observed on computed tomography (CT) significantly associated with pathologic response and OS in patients

with colorectal liver metastases (CLM) undergoing chemotherapy with bevacizumab [7]. Morphologic response to preoperative chemotherapy was also an independent prognostic factor in patients who underwent hepatic resection of CLM [8].

The aim of this study was to evaluate the predictive value of morphologic response to first-line chemotherapy with or without bevacizumab in patients with CLM.

Patients and methods

Between April 2006 and June 2012, we assessed patients with CLM who received fluorouracil-based chemotherapy with or without bevacizumab as first-line chemotherapy at 2 institutions. Patients seemed to be unsuitable for hepatic resection were eligible for this study.

Eligible patients also fulfilled the following criteria: (1) a histologically confirmed diagnosis of adenocarcinoma of the colorectum; (2) treatment with first-line therapy; (3) no extrahepatic disease except the primary tumor. Patients with a history of previous chemotherapy were excluded from this study.

All patients were considered to be unsuitable for upfront hepatic resection because they had at least one of the following reasons: more than four metastases, any liver metastasis with diameter >5 cm, synchronous metastases and technically difficult to

resect, for example, because the metastases involved intrahepatic vascular structures. Among these patients, 41 patients in whom both pre- and post-chemotherapy CT images were available were included in this study.

Chemotherapy regimens were selected individually. Treatments were repeated until disease progression, the occurrence of unacceptable toxicity, or the patient's refusal to continue therapy.

All patients underwent enhanced CT at the start of chemotherapy and then every 2-3 months. Enhanced CT scans were performed with multi-slice CT, using a triphasic liver protocol or single-phase technique. Three blinded radiologists evaluated CT images and classified as optimal, incomplete or none response according to the morphologic criteria [7]. Morphologic response was assessed at the first follow-up CT compared with baseline CT. Group1 metastasis had morphology of homogeneous and hypoattenuation with a thin, sharply defined tumor-normal liver interface. Group3 metastasis had morphology of heterogeneous attenuation with a thick, poorly defined tumor-normal liver interface. Group2 metastasis had morphology that did not qualify for either Group1 or 3.

Optimal response was defined as a change in morphology from Group3 or 2 to Group1 after chemotherapy (Fig.1). Incomplete response was defined as a change in

morphology from Group3 to Group2. Morphologic response was defined as none response if the metastasis did not changed or increased in morphology. In discordant cases in response evaluation, the images were reviewed together by radiologists and a consensus resolution was reached. Response to systemic chemotherapy was also evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) [9]. The patients with complete response (CR) or partial response (PR) were categorized as responders and the remaining patients with either stable disease (SD) or progression disease were categorized as non-responders.

Statistical analysis

PFS was defined as the period from the date of treatment start to the date of disease progression or death from any cause. Patients undergoing hepatic resection were censored at the time of surgery. PFS was calculated with the Kaplan-Meier method, and the significant differences between survival curves were determined by the log-rank test. The chi-squared test and Fisher's exact test were used for frequency comparisons. To identify predictive factors for PFS, univariate and multivariate analysis were performed using by Cox proportional hazards model. All statistical analyses were performed with JMP version 10 (SAS Institute, Cary, NC, USA), and a two-sided *P*

values of <0.05 was considered to indicate statistical significance.

Results

Patients characteristics

The patients characteristics are shown in Table 1. The median age was 67 years (range, 52-80). Most patients (90%) had a good performance status (ECOG PS 0 to 1). Thirty two patients (78%) had synchronous liver metastases and 36 patients (88%) had multiple liver lesions. All patients received fluorouracil-based chemotherapy as first-line treatment, including FOLFOX (n=34; 83%), XELOX (n=4; 10%), S-1 plus oxaliplatin (n=1; 2%), FOLFIRI (n=1; 2%), and 5-FU/LV (n=1; 2%). Twenty three patients (56%) received chemotherapy plus bevacizumab, while 18 patients (44%) received chemotherapy alone.

Efficacy

Assessment of first-line chemotherapy response using RECIST showed that 3 patients (7%) were classified with CR, 18 patients (44%) were classified with PR, 19 patients (46%) were classified with SD, and 1 patient (2%) was classified with PD. The overall response rate and disease control rate were 51% and 98%, respectively.

The response rate was comparable between 48% in the chemotherapy plus bevacizumab and 56% in the chemotherapy alone (p=0.62).

According to morphologic response criteria, optimal morphologic response was observed in 16 patients (39%), 13 patients (32%) had incomplete response, and 12 patients (29%) had none response. Optimal morphologic response was observed 11 (48%) of 23 patients treated with chemotherapy plus bevacizumab and 5 (28%) of 18 patients treated with chemotherapy alone (p=0.19). Eight patients (20%) underwent hepatic resection after chemotherapy. The median follow-up period was 31.3 months. The median PFS by morphologic response was 13.3 months in patients with optimal response and 8.7 months in those with incomplete/none response (p=0.0026; Fig.2A), while the median PFS by RECIST was 11.1 months in responders and 7.1 months in those with non-responders (p=0.021; Fig.2B).

Predictors for PFS

Table 2 lists the results of univariate and multivariate analysis of the predictors of PFS. PS and morphologic response were significant independent predictors of favorable outcome (p=0.030 and 0.0086, respectively). RECIST was not a significant predictor (p=0.57). Therefore, morphologic response was superior to RECIST for

prediction of PFS.

Discussion

It is very important to identify a predictor of favorable outcome in patients treated with chemotherapy. RECIST criteria are the current standard in assessing tumor response of solid tumors to cytotoxic agents [9]. However, it was reported that tumor response according RECIST was not predictive of PFS or OS benefit for mCRC treated with chemotherapy with or without bevacizumab [10].

In our present study, we evaluated the predictive value of morphologic response to first-line chemotherapy with bevacizumab or without bevacizumab in patients seemed to be unsuitable for upfront hepatic resection from colorectal cancer. The median PFS was significantly longer in patients with optical morphologic response than those with incomplete/none morphologic response. On multivariate analysis, morphologic response was significant independent predictor of PFS and morphologic response was superior to RECIST for prediction of PFS. Therefore, our study indicated that morphologic response to chemotherapy with or without bevacizumab might be useful to predict PFS in patients with CLM.

Although not statistically significant, optimal morphologic response was higher in the

patients treated with chemotherapy plus bevacizumab than in the patients treated chemotherapy alone. A previous study indicated that bevacizumab was strongly associated with an optimal morphologic response in the multivariate analysis [8]. Boonsirkamchai et al. [11] concluded that RECIST were insufficient to assess response for chemotherapy with bevacizumab in CLM and the combined use of RECIST and morphologic response criteria was necessary for optimal evaluation. To assess morphologic response is not difficult to determine except for the small lesions (usually <1 to 1.5 cm) [8], morphologic response criteria can be useful tool to assess tumor response in patients with CLM in clinical practice.

Several tumor response evaluation criteria were developed to assess the response with the introduction of molecular-targeted agents. With anti-EGFR therapy, early tumor shrinkage (ETS) was important predictor of favorable outcome in patients with mCRC who received cetuximab with chemotherapy [12, 13]. In the case of patients with hepatocellular carcinoma (HCC) treated with sorafenib, modified RECIST (mRECIST), which taking tumor vascularity into account and was designed specifically for HCC, was indicated to be more beneficial for the assessment of the treatment efficacy than RECIST criteria [14, 15]. Furthermore, new CT response criteria evaluating not only tumor size but also tumor density were proposed to assess the response to imatinib for

patients with gastrointestinal stromal tumor and the criteria showed significantly better correlation with time to progression than RECIST [16].

Our study had several important limitations. It was a retrospective study of a small number of patients. Selection bias may have potentially our results. Our findings should thus be confirmed in prospective clinical trials.

In conclusion, optimal morphologic response was significantly associated with PFS in patients with CLM who were treated with fluorouracil-based chemotherapy as first-line chemotherapy. Chemotherapy with bevacizumab tends to have a higher optimal morphologic response than chemotherapy without bevacizumab. The results from this study indicated optimal morphologic criteria to be superior to RECIST for prediction of PFS.

Disclosure

The authors have no conflicts of interest to declare.

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Table 1. Baseline characteristics

	No. of Patients	%
Age, years		
Median	67	
Range	52-80	
Gender		
Male	29	71
Female	12	29
PS		
0	24	59
1	13	32
2	3	7
3	1	2
Primary tumor		
Colon	29	71
Rectum	12	29
Number of metastases		
Solitary	5	12
Multiple	36	88
Occurrence of metastases		
Synchronous	32	78
Metachronous	9	22
Size of metastases, mm		
Median	39	
Range	10-134	
Fluorouracil-based chemotherapy regimen		
Chemotherapy with bevacizumab	23	56
Chemotherapy without bevacizumab	18	44

Table 2. Univariate and Multivariate Analysis of Progression-Free survival

		Univariate analysis			Multivariate analysis		
Factors for criteria	N	HR	95%CI	*P*	HR	95%CI	*P*
Age							
<65	18						
≥65	23	2.29	1.07-5.19	0.033	1.56	0.68-3.83	0.30
PS							
0-1	37						
≥2	4	3.90	1.10-11.0	0.037	4.41	1.18-13.8	0.030
Occurrence of metastases							
Metachronous	9						
Synchronous	32	1.26	0.54-3.44	0.61			
Number of metastases							
Solitary	5						
Multiple	36	2.37	0.49-42.4	0.34			
Size of metastases							
<5cm	26						
≥5cm	15	1.15	0.53-2.37	0.72			
Bevacizumab							
Yes	23						
No	18	1.39	0.66-2.87	0.38			
RECIST							
Responder	21						
Non-responder	20	2.40	1.13-5.31	0.023	1.30	0.53-3.32	0.57
Morphologic response							
Optimal	16						
Incomplete/none	25	3.83	1.60-10.69	0.0021	3.56	1.36-10.86	0.0086

Fig. 1. Optimal morphologic response after treatment. (a) baseline CT. (b) the first follow-up CT.

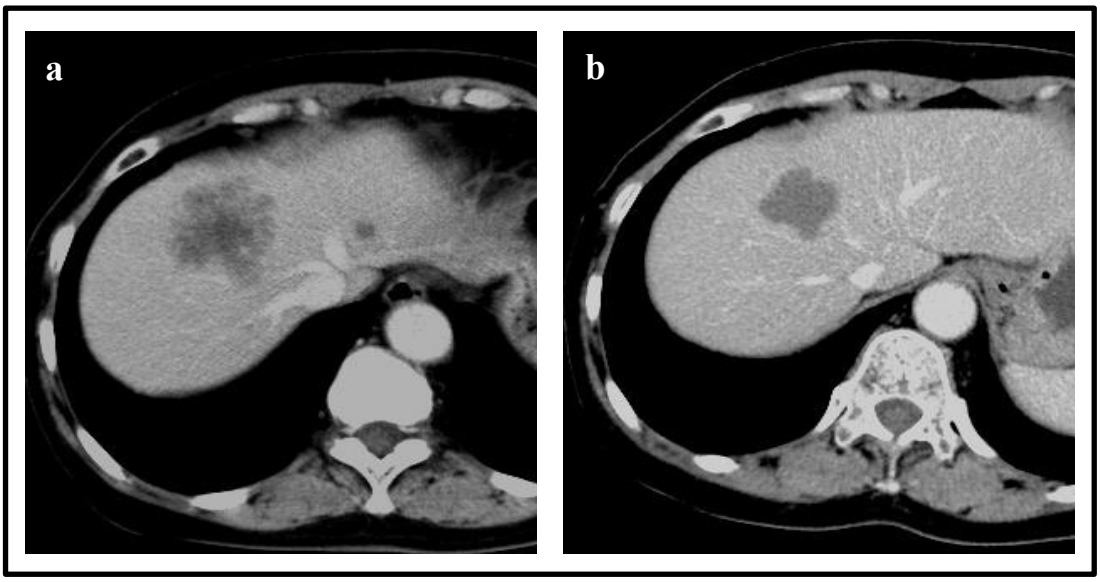

Fig. 2A. Progression-free survival by morphologic response criteria

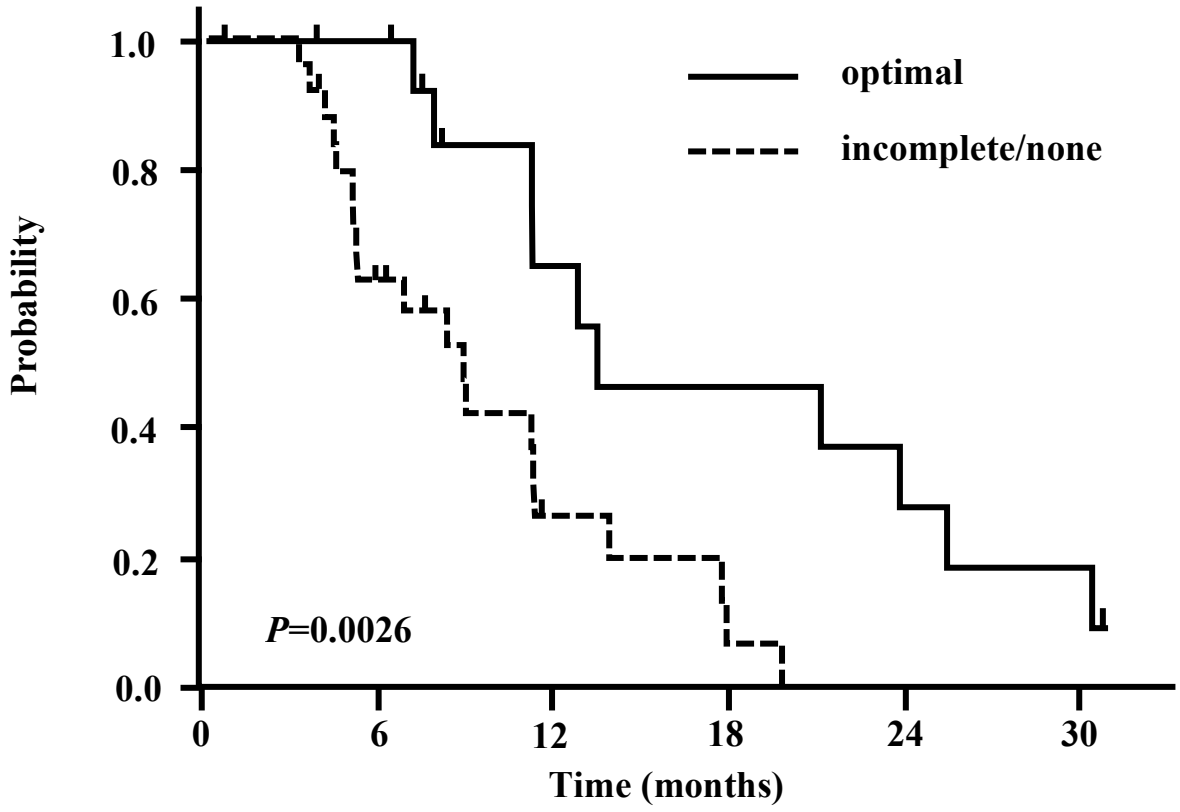

Fig. 2B. Progression-free survival by RECIST