Cetuximab plus FOLFOX for Patients with Metastatic Colorectal Cancer with Poor Performance Status and/or Severe Tumor-Related Complications

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Key Words

Colorectal cancer · Poor performance status · FOLFOX · Cetuximab

Abstract

Introduction: Cetuximab-based chemotherapy showed a statistically significantly higher response rate compared with chemotherapy such as FOLFOX. Therefore, FOLFOX plus cetuximab is suspected to be the best regimen to alleviate tumor-related symptoms with a high response rate.

Case Report: Here we present the results of 8 consecutive patients with metastatic colorectal cancer with poor performance status and/or severe complications who were treated with first-line FOLFOX with cetuximab. Six of 8 patients achieved an apparent clinical benefit, including radiological response and symptoms improvement. Two patients with *BRAF* mutation could achieve neither clinical benefit nor radiological response.

Conclusion: Although an optimal line of therapy with cetuximab is unclear yet with bevacizumab in mind, we propose that patients who need a tumor response to alleviate their symptoms due to advanced disease might be candidates for first-line cetuximab-based therapy as shown in our cases. Additionally, patients with *BRAF* mutant tumors might be important candidates for novel targeted therapy in the future to improve their poor prognosis.

Introduction

Cetuximab, a recombinant, human–mouse chimeric monoclonal IgG1 antibody that specifically targets the epidermal growth factor receptor (EGFR) has been shown to significantly improve the prognosis of metastatic colorectal cancer (MCRC) compared with best supportive care alone in the third-line setting [1].

Recently, cetuximab was approved as a treatment for MCRC in Japan. Although an optimal line of therapy with cetuximab is unclear yet with bevacizumab in mind [2], a cetuximab-based regimen showed a statistically significantly higher response rate compared with chemotherapy alone [3, 4], in contrast with bevacizumab, which did not show an improvement in objective response rate when given in combination with first-line oxaliplatin with fluoropyrimidine [5]. Therefore, we propose that patients who need a tumor response to alleviate their symptoms due to advanced disease might be candidates for first-line cetuximab-based therapy. To support this strategy, here we present the results of 8 consecutive patients with MCRC with poor performance status and/or severe complications who were treated with first-line FOLFOX with cetuximab.

Case Report

Between October 2009 and April 2010, 8 patients received FOLFOX plus cetuximab as first-line chemotherapy for MCRC (table 1). Eastern Cooperative Oncology Group (ECOG) performance status was 1 in 1 patient, 2 in 6 patients, and 3 in 1 patient. Six patients had symptomatic peritoneal disseminations with ascites. One patient had a complication of icterus due to severe liver metastases. One patient had rectal cancer with anorectal pain due to bone invasion. The primary tumor was present in 6 patients. *KRAS* status was evaluated using cycleave method and was wild type in all patients. All patients were treated with the approved dosage and schedule of cetuximab: initially 400 mg/m² followed by weekly infusions of 250 mg/m². The dose of FOLFOX was adjusted individually based on performance status or organ dysfunction. The median number of cetuximab administrations was 12 (range 3–25). Six of 8 patients achieved an apparent clinical benefit, as shown in fig. 1, fig. 2 and table 1. In contrast, 2 patients could achieve neither clinical benefit nor radiological response; these 2 patients were found to have the *BRAF* V600 mutation. Grade 3 skin toxicity was observed in 1 patient. Although no treatment-related deaths were observed, 1 patient with icterus experienced infection without neutropenia. The median survival of all patients was 5.2 months (range 2.5–14+ months).

Discussion

Although cetuximab was studied initially in pretreated patients, in contrast with bevacizumab [5], the CRYSTAL trial showed a survival benefit of first-line cetuximab, especially in patients with *KRAS* wild-type tumors [3]. In another study that used cetuximab with an oxaliplatin-based regimen, the combination showed a higher response rate compared with chemotherapy alone [4]. Disappointingly, combination chemotherapy of bevacizumab and cetuximab or panitumumab failed to show an improvement in efficacy [6, 7]. According to these results, the most recent NCCN guideline for the treatment of colon cancer recommended several first-line regimens: bevacizumab or cetuximab/panitumumab (*KRAS* wild type only) combined with irinotecan or oxaliplatin with fluoropyrimidines [2]. Since cetuximab or panitumumab is also effective even in patients with previous chemotherapy [1, 8], an optimal line of therapy with cetuximab or panitumumab is unclear yet with bevacizumab in mind [2]. As noted previously, since a cetuximab-based regimen showed a statistically significantly higher response rate compared with chemotherapy alone [3, 4], we supposed that patients who need a tumor response to alleviate their symptoms might be candidates for first-line

cetuximab-based therapy, although the results of an ongoing phase III study comparing bevacizumab and cetuximab as first-line chemotherapy are eagerly awaited.

For patients with poor general status or severe complications, fluoropyrimidine monotherapy with or without bevacizumab is recommended according to NCCN guidelines [2] and generally selected in clinical practice. However, we suspect that FOLFOX plus cetuximab might become an attractive regimen for these patients according to our results. Although FOLFOX and FOLFIRI (irinotecan with fluoropyrimidine) is considered to be similarly effective as first-line chemotherapy for MCRC, FOLFOX may be preferable in patients with severe abdominal symptoms or liver dysfunction as shown in our cases since toxicity of irinotecan is frequent in these complicated cases.

Our results are provocative for the following reasons: first, the regimen of cetuximab plus FOLFOX might be feasible, as it had activity in patients with MCRC with poor performance status or severe symptoms. In consideration of the risk-benefit balance, further investigations will be needed to clarify the distinct indication for either the intensive chemotherapy such as FOLFOX plus cetuximab or weak chemotherapy like fluoropyrimidine monotherapy for these patients. Second, *BRAF* might be an important negative marker for response to chemotherapy or a strong negative prognostic factor, as already reported [9–12]. Although the evaluation of *BRAF* status prior to treatment with an EGFR antibody is still controversial [2], patients with *BRAF* mutant tumors might be important candidates for novel targeted therapy in the future to improve their poor prognosis.

Table 1. Disease characteristics and outcomes of each patient

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age, gender	35, F	60, F	40, M	48, F	68, M	48, F	71, M	74, M
ECOG PS	3	2	2	1	2	2	2	2
Metastatic sites	Liver, ovary, peritoneum, ascites	Liver, pleural effusion	Peritoneum, lymph node, ascites		Liver, peritoneum, ascites	Liver, ovary, peritoneum, ascites	Liver, peritoneum, ascites	Liver, peritoneum, ascites
Complication	Abdominal distension	Icterus (T-bil 5.9 mg/dl)	Abdominal pain	Rectal pain	Ileus	Abdominal distension	Ileus	Abdominal distension
<i>KRAS</i> status*	Wild	Wild	Wild	Wild	Wild	Wild	Wild	Wild
<i>BRAF</i> status**	Wild	Wild	Wild	Wild	Mutant	Wild	Wild	Mutant
Cetuximab administration (times)	19	7	25	8	4	12	6	3
Clinical improvement	Yes PS 1, followed by colectomy	Yes PS1, T-bil 1.3 mg/dl	Yes PS1, ascites disappeared	Yes Improved pain, surgery (R0)	No –	Yes PS 1, ascites disappeared, surgery	Yes PS1, improved intestinal obstruction	No –
Skin toxicity (grade)	2	2	2	2	1	1	1	0
Survival (months)	14.3+	4.2	10.4	10.3+	2.5	10	5.2	3.5

F = Female; M = male; ECOG PS = Eastern Cooperative Oncology Group performance status; T-bil = total bilirubin.

* *KRAS* codon 12, 13, 61; ** *BRAF* V600.

Fig. 1. **a, b** CT scans of case 1 before treatment. Multiple liver metastases, massive ascites and ovarian metastases are seen. **c, d** CT scans of case 1 after 4 cycles of FOLFOX plus cetuximab. The multiple liver metastases and ovarian metastases were reduced in size, and the ascites had almost disappeared. This patient underwent resection of the primary tumor and closure of the colostomy.

Fig. 2. **a, b** CT scans of case 3 before treatment. Massive ascites and peritoneum dissemination are seen. This case was complicated with abdominal pain and the patient was unable to eat. **c, d** CT scans of case 3 after 4 cycles of FOLFOX plus cetuximab. The ascites had almost disappeared. The performance status was improved from 2 to 1 with sufficient oral intake.

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