

Case Report

Two Cases of Long-Term Control of Metastatic Colorectal Cancer via FTD/TPI plus Bevacizumab in Elderly Patients

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Keywords

Colorectal cancer · Chemotherapy · FTD/TPI + bevacizumab · Elderly patient

Abstract

With advances in new cytotoxic drugs and molecular-targeted drugs, the prognosis of patients with metastatic colorectal cancer (mCRC) has improved. However, physicians often hesitate to administer intensive standard regimens to elderly patients with mCRC. Recently, first-line regimens that are effective in and well-tolerated by patients who are not eligible for intensive chemotherapy have been established. However, the therapeutic strategies to adopt after the failure of first-line treatment for patients who are not eligible for intensive chemotherapy remain unclear. We herein report two cases of long-term control of mCRC via FTD/TPI+bevacizumab (Bmab) as second- or third-line treatment in elderly patients without severe adverse events. In case 1, first-line treatment with Tegafur-Uracil, which is a prodrug of 5-FU, caused disease progression in a short period after the initiation of chemotherapy. In case 2, intensive first-line treatment caused severe adverse events, and treatment was discontinued. However, in both cases, disease control was obtained for a long time without severe adverse events by subsequent treatment with FTD/TPI+Bmab. The success in these present cases indicates that

FTD/TPI+Bmab as a second- or third-line treatment is a therapeutic option for elderly patients with mCRC who are not eligible for intensive chemotherapy, even after failure of treatment with 5-FU.

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Introduction

Owing to the advances in new cytotoxic drugs and molecular-targeted drugs, the prognosis of patients with metastatic colorectal cancer (mCRC) has improved. However, physicians often hesitate to administer intensive standard regimens to elderly patients with mCRC, as elderly patients are often frail and have a deteriorated internal organ function. Recently, first-line regimens that are effective in and well-tolerated by patients who are not eligible for intensive chemotherapy, such as Capecitabine+Bevacizumab (Bmab) and Tefafur-Uracil (UFT)/Leucovorin(LV)+Bmab, have been established [1, 2]. However, the therapeutic strategies to adopt after the failure of first-line treatment for patients who are not eligible for intensive chemotherapy remain unclear. We herein report two cases of long-term control of mCRC via FTD/TPI+Bmab as second- or third-line treatment in elderly patients.

Case Reports

Case 1

An 85-year-old man who had undergone ileocecal resection and lymph node dissection for stage IIIC cecal cancer was found to have intraabdominal nodules, with fluorodeoxyglucose-positron emission tomography showing an abnormal uptake, 2 years after surgery (Fig. 1a, b). The patient was diagnosed with peritoneal dissemination. Given his advanced age, he was deemed ineligible for intensive chemotherapy. He received Tegafur-Uracil/Leucovorin+Bmab therapy. However, only three months later, the patient was judged as having progressive disease due to the increase in his intraabdominal nodules (Fig. 2a) and the appearance of new pulmonary nodules (Fig. 2b). After the failure of first-line treatment, the patient received FTD/TPI+Bmab as second-line treatment, as his RAS status was mutant-type. FTD/TPI+Bmab treatment was continued for six months without severe adverse events until disease progression.

Case 2

An 84-year-old man who had undergone right hemi-colectomy and lymph node dissection for stage IIIB ascending colon cancer was diagnosed with multiple pulmonary metastases 4 years after surgery (Fig. 3a). Following nine cycles of mFOLFOX6+Bmab, a partial response was obtained (Fig. 3b). However, the treatment was discontinued due to severe gastrointestinal toxicity, and the patient needed hospitalization for one month. Although the general condition improved by hospitalization, CT showed an increase in pulmonary metastases (Fig. 3c). The patient received irinotecan+cetuximab as second-line treatment, as his RAS status was wild-type. However, second-line treatment resulted in a judgment of progressive disease after only two months, and the patient received FTD/TPI+Bmab as third-line treatment. Stable disease continued for more than one year with FTD/TPI+Bmab treatment without severe adverse events except for neutropenia, even though severe adverse events had occurred during the first-line treatment.

Discussion

FTD/TPI is an oral anticancer agent containing trifluridine (FTD) and thymidine phosphorylase inhibitor (TPI). FTD exerts anticancer effects by being incorporated into DNA, and TPI maintains the serum concentration of FTD by preventing its rapid degradation [3, 4]. FTD/TPI has been reported to exert antitumor effects against 5-FU-resistant tumors [5], as FTD and FdUrd, a derivative of 5-FU, are incorporated into DNA with different efficiencies [6]. Therefore, FTD/TPI is a drug that can be expected to be effective even after the failure of the treatment with 5-FU. Indeed, in case 1, FTD/TPI+Bmab treatment was effective even after the failure of treatment with Tegafur-Uracil, which is a prodrug of 5-FU.

In the phase III RECURSE trial, which included patients who had received at least two prior regimens of standard chemotherapies, the overall survival (OS) and the duration to worsening performance status were significantly better in patients with mCRC treated with FTD/TPI than in those treated with placebo (OS: 7.1 vs. 5.3 months; duration to worsening performance status: 5.7 versus 4.0 months) [7]. Furthermore, Bmab was found to improve outcomes when administered with FTD/TPI compared with FTD/TPI alone [8]. In addition, FTD/TPI is a drug that can be safely administered to elderly patients, because it was reported that there were no marked differences in terms of the incidence of adverse events between elderly patients and others [9]. In case 2, FTD/TPI+Bmab treatment has been continued for more than one year without severe adverse events, even though severe adverse events requiring hospitalization occurred during the first-line intensive standard treatment. Similarly, in case 1, FTD/TPI+Bmab treatment was continued without severe adverse events for six months until disease progression.

When managing elderly patients, physicians should plan treatment strategies after the failure of the first-line treatment, taking into account the age-specific characteristics.

In the REGOTAS trial, which included patients with mCRC treated with late-line chemotherapy, no significant differences in the OS were noted between patients treated with FTD/TPI or regorafenib [10]. However, in the subgroup analyses according to age, FTD/TPI was reportedly more effective in prolonging the OS than regorafenib in patients ≥ 65 years of age [10]. Thus, FTD/TPI is thought to be more suitable than regorafenib for elderly patients in terms of efficacy, although the associated adverse events are different.

Anti-EGFR antibodies are drugs that have excellent therapeutic outcomes and are used not only as front-line treatment but also for salvage-line treatment. As the objective response rate of anti-EGFR antibody monotherapy for patients with RAS wild-type mCRC was relatively high (approximately 20%) [11] in late-line treatment, it may be better to administer anti-EGFR antibody first, rather than FTD/TPI, for patients with RAS wild-type mCRC. However, the incidence of skin and subcutaneous tissue toxicities that diminish the quality of life, such as acne-like rash and paronychia, is very high (any grade: 86%–88%, Grade 3 or higher: 9.6%–12.4%) [11], leading to the discontinuation of the chemotherapy. Furthermore, the incidence of infusion reaction is not low [11]. Therefore, careful management is required for the use of anti-EGFR antibodies. In addition, it was recently reported that the efficacy of anti-EGFR antibody against right-sided colon cancer is poor [12].

Although irinotecan is a key drug for the treatment of mCRC, the incidence of grade 3 or higher diarrhea is relatively high (15.7%) [13]. Furthermore, the incidence of grade 3 or higher diarrhea is even higher (38.6%) in patients ≥ 65 years of age [14]. Therefore, irinotecan is a somewhat hard-to-use drug for elderly patients.

In conclusion, the success in these present cases indicates that FTD/TPI+Bmab as a second- or third-line treatment is a therapeutic option for elderly patients with mCRC who are not eligible for intensive chemotherapy, even after failure of treatment with 5-FU.

Statement of Ethics

Written ethical approval for the publication on the present case report was obtained from the patient.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

References

- Cunningham D, Lang I, Marcuello E, Lorusso V, Ocvirk J, Shin DB, et al.; AVEX study investigators. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2013 Oct;14(11):1077–85.
- Nishina T, Moriawaki T, Shimada M, Higashijima J, Sakai Y, Masuishi T, et al. Uracil-Tegafur and Oral Leucovorin Combined With Bevacizumab in Elderly Patients (Aged ≥ 75 Years) With Metastatic Colorectal Cancer: A Multicenter, Phase II Trial (Joint Study of Bevacizumab, Oral Leucovorin, and Uracil-Tegafur in Elderly Patients [J-BLUE] Study). *Clin Colorectal Cancer*. 2016 Sep;15(3):236–42.
- Tanaka N, Sakamoto K, Okabe H, Fujioka A, Yamamura K, Nakagawa F, et al. Repeated oral dosing of TAS-102 confers high trifluridine incorporation into DNA and sustained antitumor activity in mouse models. *Oncol Rep*. 2014 Dec;32(6):2319–26.
- Fukushima M, Suzuki N, Emura T, Yano S, Kazuno H, Tada Y, et al. Structure and activity of specific inhibitors of thymidine phosphorylase to potentiate the function of antitumor 2'-deoxyribonucleosides. *Biochem Pharmacol*. 2000 May;59(10):1227–36.
- Emura T, Suzuki N, Yamaguchi M, Ohshimo H, Fukushima M. A novel combination antimetabolite, TAS-102, exhibits antitumor activity in FU-resistant human cancer cells through a mechanism involving FTD incorporation in DNA. *Int J Oncol*. 2004 Sep;25(3):571–8.
- Sakamoto K, Yokogawa T, Ueno H, Oguchi K, Kazuno H, Ishida K, et al. Crucial roles of thymidine kinase 1 and deoxyUTPase in incorporating the antineoplastic nucleosides trifluridine and 2'-deoxy-5-fluorouridine into DNA. *Int J Oncol*. 2015;46(6):2327–34.
- Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al.; RECURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med*. 2015 May;372(20):1909–19.
- Kuboki Y, Nishina T, Shinozaki E, Yamazaki K, Shitara K, Okamoto W, et al. TAS-102 plus bevacizumab for patients with metastatic colorectal cancer refractory to standard therapies (C-TASK FORCE): an investigator-initiated, open-label, single-arm, multicentre, phase 1/2 study. *Lancet Oncol*. 2017 Sep;18(9):1172–81.
- Van Cutsem E, Benedetti FM, Mizuguchi H, Mayer RJ, Falcone A, Garcia-Carbonero R, et al. TAS-102 versus placebo (PBO) in patients (pts) ≥ 65 years (y) with metastatic colorectal cancer (mCRC): An age-based analysis of the recourse trial. *J Clin Oncol*. 2016;34(suppl 4s):abstract 638.
- Moriwaki T, Fukuoka S, Taniguchi H, Takashima A, Kumekawa Y, Kajiwarra T, et al. Propensity Score Analysis of Regorafenib Versus Trifluridine/Tipiracil in Patients with Metastatic Colorectal Cancer Refractory to Standard Chemotherapy (REGOTAS): A Japanese Society for Cancer of the Colon and Rectum Multicenter Observational Study. *Oncologist*. 2018 Jan;23(1):7–15.
- Price TJ, Peeters M, Kim TW, Li J, Cascinu S, Ruff P, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. *Lancet Oncol*. 2014 May;15(6):569–79.
- Arnold D, Lueza B, Douillard JY, Peeters M, Lenz HJ, Venook A, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. *Ann Oncol*. 2017 Aug;28(8):1713–29.

- 13 Sobrero AF, Maurel J, Fehrenbacher L, Scheithauer W, Abubakr YA, Lutz MP, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol*. 2008 May;26(14):2311–9.
- 14 Rothenberg ML, Cox JV, DeVore RF, Hainsworth JD, Pazdur R, Rivkin SE, et al. A multicenter, phase II trial of weekly irinotecan (CPT-11) in patients with previously treated colorectal carcinoma. *Cancer*. 1999 Feb;85(4):786–95.

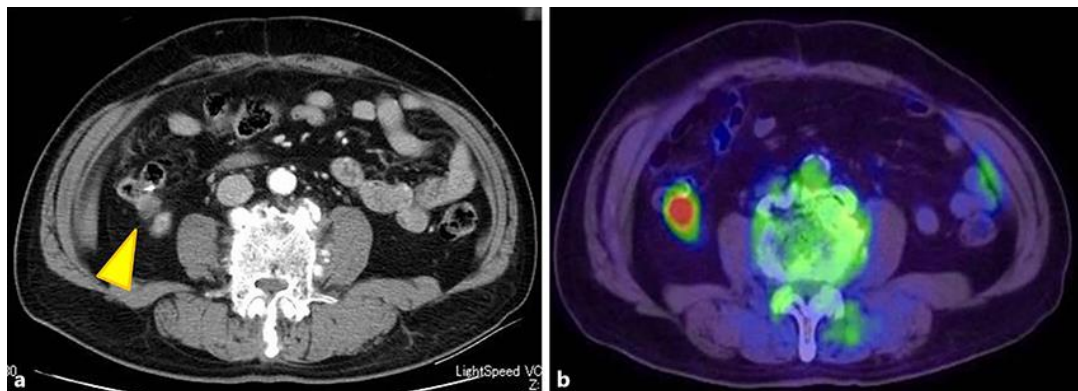


Fig. 1. (a) Computed tomography showed small intraabdominal nodules. (b) Fluorodeoxyglucose-positron emission tomography showed an abnormal uptake in the intraabdominal nodules.

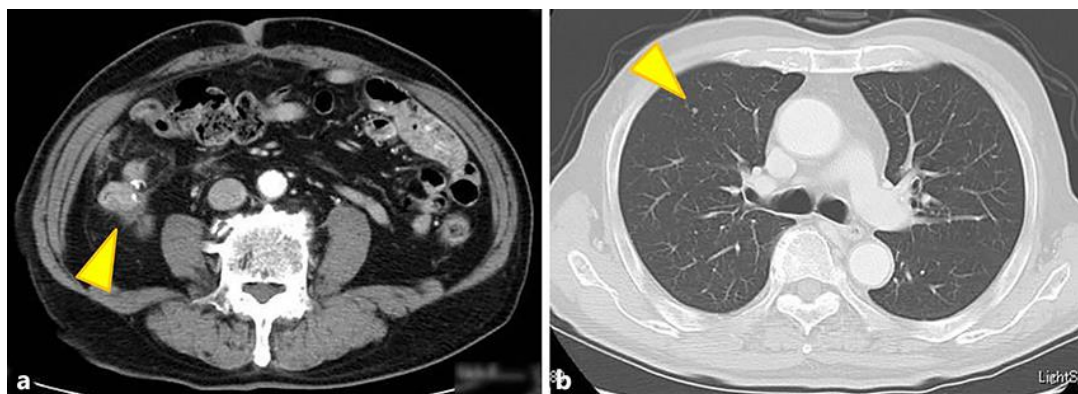


Fig. 2. Three months after the initiation of first-line treatment, computed tomography showed an increase in the intraabdominal nodules (a) and the appearance of new pulmonary nodules (b).



Fig. 3. (a) Computed tomography showed multiple pulmonary nodules. (b) Following nine cycles of mFOLFOX6+Bmab, computed tomography showed a decrease in the pulmonary nodules. (c) However, 10 months after the initiation of first-line treatment, computed tomography showed the regrowth of the pulmonary nodules.