Case reports

A case of metastatic colon cancer with RAS wild tumor progressed during the treatment with mFOLFOX6 plus panitumumab

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Abstract

We herein report a case of metastatic colon cancer RAS wild tumor progressed during the treatment with FOLFOX + panitumumab and then recognized as BRAF mutation and MSI-H. Seventy eight years-old male patient showed anastomotic recurrence of colon cancer after curative resection of Stage II ascending colon cancer six years before the appearance of the recurrence. Six months after R0 resection, surveillance CT was performed and diagnosed as recurrent tumor invaded to duodenum. For R0 resection, mFOLFOX6 plus panitumumab therapy was initiated to expect early tumor shrinkage because of RAS wild tumor. However, tumor progressed after 4 cycles. The second-line therapy was not able to started because the disease progression was extremely rapid. He died 4 months after initiation of therapy. BRAF mutation and MSI-H were recognized from his tumor by the additional analyses.

Keywords: RAS wild, BRAF mutation, microsatellite instability

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Introduction

In the subgroup analysis according to the gene mutation in PRIME study, overall survival (OS) in the patients with RAS wild type colon cancer treated with panitumumab plus FOLFOX4 was 25.8 months. Comparing with 20.2 months in the patients with FOFOX4, OS was significantly prolonged by additional panitumumab however the OS in the BRAF mutant patients was most unfavorable. Since all RAS mutation testing has recently become possible, inappropriate use of anti-EGFR antibodies has been possibly avoided in Japan. However the analyses of MSI and BRAF mutation were not covered in the medical insurance until recently. Therefore, the best regimen might not be selected to expect the best response.

Under such situation, we experienced a case of metastatic colon cancer with RAS wild gene progressed despite perfoming the mFOLFOX6 plus panitumumab therapy to expect early tumor shrinkage because of considering the difficulty of R0 resection. It was recognized as BRAF mutation and MSI-H after his death.

Case report

Seventy eight years-old male patient showed an anastomotic recurrence of colon cancer after curative resection of Stage II ascending colon cancer six years before the appearance of the recurrence. Six months after R0 resection, surveillance CT was performed and diagnosed as recurrent tumor invaded to duodenum (Fig. 1A). For R0 resection, mFOLFOX6 plus panitumumab therapy was initiated to expect early tumor shrinkage because his cancer defined as RAS wild tumor. The first evaluation of the chemotherapy effect was performed after 4 cycles (Fig. 1B). The tumor size was expanded to 50 mm large and the invasion to the duodenum progressed. The response was assessed as progressive disease (PD). Although the second-line therapy was scheduled, it was not able to initiate because his condition was judged as unfit for chemotherapy due to the rapid progression. And then he died 4 months after initiation of therapy. In order to elucidate why the anti-EGFR antibody had no effect in this case regardless of the RAS wild type, the presence or absence of BRAF mutation and MSI were analyzed.

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The mutation in V600E was observed concerning BRAF. The MSI was showed as MSI-H by the definition of the replication errors in BAT25 and BAT26.

**Discussion**

Because the anti-EGFR antibody can be expected to have early tumor shrinkage against RAS wild-type colorectal cancer, it is often used for the first-line treatment of mCRC in which R0 resection is considered to be difficult. In recent years, BRAF gene status and the sidedness of the primary site have been pointed out as predictive factors for the further tumor effects. Although mCRC with the BRAF mutant has not be indicated for treatment because it is not expected to be effective as first-line treatment in Western guidelines, the BRAF testing was not possible in Japan. The BRAF genetic test and...
MSI test have finally been able to perform under covering the medical insurance in December 2018.

Since our case had RAS wild-type tumor and he was expected for conversion surgery, we selected combination chemotherapy with panitumumab in expectation of early tumor shrinkage. However, the first evaluation for tumor effect was assessed as PD, and then he died only 4 months after the initiation of chemotherapy due to the rapid progression. After that the mutation in V600E was observed concerning BRAF and the MSI was defined as MSI-H.

The BRAF gene is downstream of the RAS gene and a serine / threonine kinase that transmits signals to MEK. Most cases of the mutations were defined in codon 600 mutations from valine to glutamate (V600E), and it was recognized in our case. This mutation is a rare mutation; observed in only a few percent of colorectal cancer, and it is recognized as a poor prognosis for the cases with this mutation. Since FOLFOXIRI + bevacizumab is considered to be the only useful regimen, the several clinical trials are ongoing using the BRAF inhibitor combined with the anti-EGFR antibody, he PI3K inhibitor or the MEK inhibitors 8).

Additionally, the MSI status in our case was MSI-H. The colorectal cancer with MSI-H has been noticed that it is difficult to obtain the effect of chemotherapy in general. Therefore, if we had this genetic informations before the chemotherapy was initiated, the surgery might have been strongly considered to achieve the R0 resection and the MSI status currently both covered by the insurance, such cases with BRAF mutant and MSI-H may be successfully and appropriately treated with drug therapy newly established.

Conflicts of interest:

All authors declare no conflict of interest related of this publication.

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