Tailor-Made Medicine for Colorectal Cancer

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In chemotherapy for colorectal cancer, the therapeutic effects of anti-epidermal growth factor receptor (EGFR) drugs can be predicted based on the RAS genetic type, while adverse events of irinotecan are predictable based on gene polymorphism of UGT1A1, an enzyme that metabolizes irinotecan. Such personalized medication based on the characteristics of each case of colorectal cancer is referred to as "tailor-made medicine". This therapeutic approach is likely to improve the efficacy of treatment, decrease adverse events, improve safety, and reduce medical expenses.

Key words: tailor-made medicine, colorectal cancer, anti-EGFR monoclonal antibodies, RAS mutation, UGT1A1

Introduction

In conventional treatment, the same drug is used for the same disease in all patients. However, such treatment has patient-dependent outcomes, may cause adverse events, and may require a long period of time to evaluate the effects. Progression of interpretation of the etiology and course of disease at the molecular level has shown that patients with the same disease can have differences in genes and proteins, and such differences can affect therapeutic outcomes and adverse events. Medication appropriate for each patient is referred to as tailor-made medicine. In this review, we discuss tailor-made medicine for colorectal cancer.

RAS gene and anti-EGFR drugs

Proteins such as epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF) are often overexpressed in cancer cells, and proliferation of these cells can be inhibited by blocking individual growth factors. Colorectal cancer cells have overexpression of EGFR, a receptor for EGF, and undergo growth due to the interaction of EGF with EGFR. Several proteins are involved in signaling related to cancer cell proliferation via EGF. Among them, a protein called RAS has an anticancer effect when an antibody for EGFR (an anti-EGFR drug) is administered, provided that the RAS protein is normal (wild type). Anti-EGFR drugs are molecular-targeted drugs that are administered for metastatic colorectal cancer alone or concomitantly with a cytotoxic anticancer drug. Anti-EGFR drugs are thought to cause less serious side effects than cytotoxic anticancer drugs, but still have particular adverse events, including causing skin trouble.

A mutated RAS protein continues to send signals that induce cancer cell proliferation, even in the presence of an anti-EGFR drug, and this limits the anticancer efficacy of the drug. RAS has 3 major isoforms: KRAS, NRAS and HRAS. In clinical studies, such as the OPUS and CRYSTAL trials, anti-EGFR drugs have been found to be ineffective in patients with a mutated KRAS gene. In addition, the recent PRIME study suggested that anti-EGFR drugs are also ineffective in patients with mutated NRAS. The incidence of RAS gene mutation is determined by adding the rates of KRAS and
NRAS mutations. In colorectal cancer, the incidence of KRAS mutation is 35-40% in Europe/United States and Japan\textsuperscript{5,6}, while that of NRAS mutation is 10-15% in Europe/US\textsuperscript{3,5}, giving a total RAS mutation rate of about 50%. There are only a few detailed reports on NRAS in Japan and more information is needed.

It is important to examine the RAS gene before administration of an anti-EGFR drug in patients with colorectal cancer. This procedure is a key step in tailor-made medicine, and is facilitated by the recent development of a test kit for simple detection of a RAS mutation in 4 to 5 hours. This kit is covered by insurance and provides the appropriate environment for tailor-made medicine.

Findings from a typical case treated with tailor-made medicine are illustrated in Figure-1 to 3. The patient was a 60-year-old female who developed melena and was diagnosed with transverse colon cancer based on the results of colonoscopy and barium enema (Figure-1). Abdominal enhanced CT showed two liver metastases and para-aortic lymph node metastasis (Figure-2, 3). The tumor was diagnosed as RAS wild type based on the results of biopsy. Since the tumor was metastatic colorectal cancer (T3N2M1b, cStage IVB, UICC 7th edition\textsuperscript{7}), FOLFOX (5-fluorouracil, levofolinate, oxaliplatin) plus an anti-EGFR drug were administered for 6 courses after ileostomy. This treatment was effective for the primary lesion, liver metastases, and para-aortic lymph nodes (Figure-1 to 3), and carcinoembryonic antigen (CEA), a tumor marker, was significantly decreased (14.1 to 2.3 ng/ml). Radical surgery (R0 resection\textsuperscript{8}) was performed 5 months after the start of chemotherapy.

**Irinotecan and UGT1A1**

Irinotecan is a particularly effective drug among cytotoxic anticancer drugs for colorectal cancer. Irinotecan is used for metastatic colorectal cancer\textsuperscript{9} and is administered mainly with 5-fluorouracil and levofolinate as a key drug in chemotherapy for...
colorectal cancer. Irinotecan is transformed into SN-38, an active metabolite, in vivo by carboxylesterase, and SN-38 exerts anticancer action, but also causes adverse events. SN-38 is detoxified after glucoronate conjugation in the liver by UGT1A1 (Figure-4).

UGT1A1 is a highly polymorphic gene and the polymorphisms alter the expression level of UGT1A1 and change the enzyme activity. As a result, serious adverse events develop in some cases. In a retrospective study in Japanese subjects, the incidence of adverse events such as leucopenia and diarrhea was approximately 7 times higher in patients who were *28 homozygote or heterozygote [11]. In another study in Japanese subjects, grade 3 or 4 neutropenia developed at a high rate in patients who were *6 and *28 compound heterozygote [12]. Therefore, both *28 and *6 UGT1A1 are important for prediction of toxicity of irinotecan in Asian people. Genetic analysis of UGT1A1 is covered by insurance and the measurement can be completed in several days using a 2-ml serum sample. Genetic polymorphism of UGT1A1 should be examined before administration of irinotecan. If a polymorphism associated with adverse events is detected, administration of irinotecan should be suspended or the dose should be decreased. This provides another example of tailor-made medicine for colorectal cancer.

Discussion

In drug therapy for colorectal cancer, a molecular-targeted drug is used concomitantly with a cytotoxic anticancer drug. If efficacy of an anti-EGFR drug is not predicted in tailor-made medicine, alternative drugs should be administered. Similarly, if adverse events of irinotecan are likely, treatment should be switched to other drugs to decrease or avoid adverse events. Such tailor-made medicine is likely to be beneficial to the patient in increasing the efficacy of treatment, decreasing the time required, and reducing the costs.

Conclusion

In this review, tailor-made medicine for colorectal cancer has been described. The therapeutic efficacy of an anti-EGFR drug can be predicted based on the RAS gene type. In addition, a gene polymorphism in UGT1A1 allows prediction of the adverse events of irinotecan before use. These effects show the importance of genetic testing before administration of these drugs.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the content of this paper.

References


