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Original Research Article

Catechol-*O*-methyltransferase gene polymorphism affects amount of the morphine required within a certain period by gastrointestinal cancer patients with cancer pain

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Abstract: There are individual differences in the amount of administered opioid required in cancer patients, but genetic factors are not only related to their clinical state. Genetic polymorphisms in catechol-*O*-methyltransferase (COMT), a metabolic enzyme of catecholamines, are suggested to be responsible for differences in pain sensitivity. We examined the correlation between COMT gene polymorphism and administered opioid dose and the dosage increase during the administration period in gastrointestinal cancer patients treated at our hospital. Twenty-four patients with gastrointestinal cancer who underwent surgical resection at our hospital and had surgical specimens were included. Total DNA was extracted from the paraffin-embedded specimen and the gene polymorphism of COMT was measured by genotyping assay. The administered opioid dose and the period from the start of opioid administration to the maximum dose for each case were examined, and the increment per day was compared between each single nucleotide polymorphism (SNP). Among 24 cases, one case was A/A type (4.2%), 11 were A/G (45.8%), and 12 were G/G (50.0%). No significant difference was observed in the maximum dose between A/G or G/G (p = 0.76). The administered dose increment per day was larger in the case of A/G type than for G/G (p = 0.04). In this study, it was shown that the A/G type cases require more opioid in a certain period of time than G/G type cases. For these cases, it was considered that prompt adjustment of the optimum opioid dose administered was necessary according to the patient's pain complaints.
Keywords: COMT, opioids, cancer pain, gene polymorphism, gastrointestinal cancer, morphine.

INTRODUCTION

Cancer patients may often be in a condition involving pain regardless of the stage. Cancer pain can be seen in any stage of cancer, and it is necessary to listen and respond quickly to the complaint. In a response to the issue of severe pain, WHO published a cancer pain therapy method in 1996 [1], and this is still the strategy that forms the backbone of pain control in the current era.

Morphine has since long played a pivotal role in pain management. Not only morphine, but also other opioids with various characteristics have been developed and are used in clinical practice nowadays.

It is common in clinical practice to see that there are individual differences in the amount and effect of opioids used in similar disease states. Genetic factors are known to be related to these individual differences. Gene polymorphism, especially single nucleotide polymorphism (SNP), is one of the principal causes of such individual differences. SNP has been confirmed in various genes and is considered to be one of the causes of various processes such as cause of disease and drug metabolism. Regarding the effects of opioids, various studies have been done before explaining individual differences, including SNP of opioid receptors [2-4].

Catechol-*O*-methyltransferase (COMT) is an intracellular enzyme located in postsynaptic neurons and is involved in the inactivation of neurotransmitters of catecholamines [5, 6]. COMT has been suggested to be related to psychiatric diseases such as schizophrenia and depression [7-12]. In addition, previous reports showed that COMT activity is involved in pain sensitivity [13-15]. In this study, we examined the relationship between SNPs of the COMT gene and the opioid dose of gastrointestinal cancer patients and its increase during the administration period.

Experimental Section

Twenty-four Japanese patients with gastrointestinal cancer were administered opioid drugs against cancer pain accompanying recurrent or residual tumors. The types of disease are listed in Table 1. All patients had undergone surgical tumor removal.

Formalin-fixed paraffin-embedded (FFPE) preparations were made of the tumor specimens using the standard method. The block was cut into 10 μm sections, and the normal tissue adjacent to the tumor was obtained manually using a scalpel. Total DNA was extracted from the samples using the QIAamp® DNA FFPE Tissue Kit (QIAGEN K.K., Tokyo, JAPAN) based on the manufacturer's protocol. A SNP genotyping assay was performed using the StepOne® (Life Technologies Japan Ltd., Tokyo, JAPAN) real-time polymerase chain reaction system with TaqMan® genotyping assays (Life Technologies Japan Ltd.) for COMT gene SNPs (SNP ID: rs4680, Assay ID: C__25746809_50) based on the manufacturer's protocol. We investigated the opioid dose from the start of drug use to the time of death (synonymous with maximum administration dose). As the type of opioid drug administered was different in each case, all opioids were converted into oral morphine amounts and compared using a conversion table (Table 2) that is commonly used in clinical practice. The maximum dose of opioid in each case was compared and examined for each SNP. In addition, the period from the start of opioid administration to the maximum dose for each case was examined, and the increment per day was compared between all SNPs. The statistical analyses were performed using MedCalc® for Windows, version 17.6 (MedCalc software, Mariakerke, Belgium). The statistical significance of the differences in the maximum amount of opioid drug for each SNP and in the increased amount of opioid drug administered was calculated by the Mann–Whitney *U*-test. Statistical significance was set as $p \leq 0.05$.

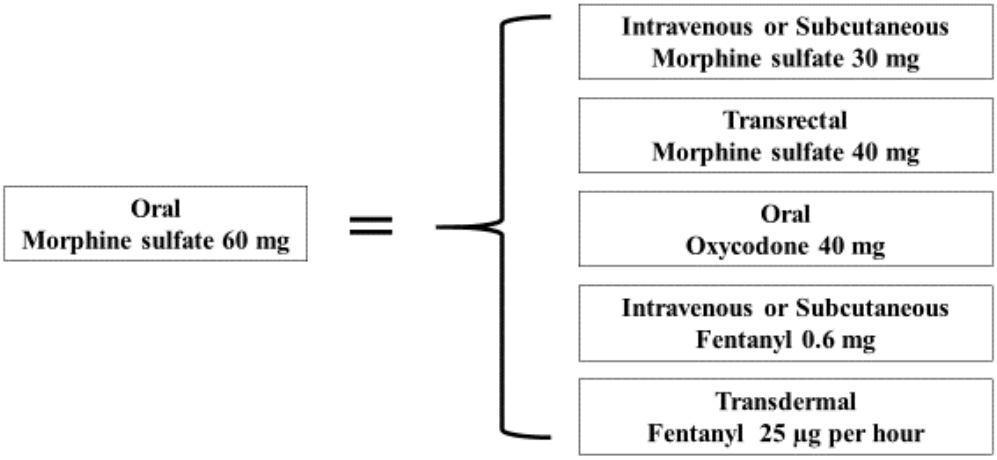
RESULTS

COMT gene polymorphisms in these patients were classified into three groups: A/A, A/G, and G/G. In this study, one of the 24 patients (4.2%) was of type A/A, 11 (45.8%) were A/G type, and 12 (50.0%) were G/G type (Table 3). When comparing A/A and A/G SNP, no correlation was found between the maximum administrated dose and each SNP ($p = 0.76$) (Figure 1). The increment per day (the value obtained by dividing the final total dose by the period from the start of administration) was significantly larger in the case of A/G type than in the G/G type ($p = 0.04$) (Figure 2).

Table 1. Number of patients with pain due to various types of cancer included in this study.

Disease	Number of patients (%)
Gastric cancer	14 (58.3%)
Colorectal cancer	5 (20.8%)
Esophageal cancer	2 (8.3%)
Intestinal bowel cancer	1 (4.2%)
Bile duct cancer	1 (4.2%)
Pancreatic cancer	1 (4.2%)
Total	24 (100%)

Table 2. Conversion table used to convert drug dosage to equivalent dose of oral morphine.



Table−3. Frequency of occurrence of the different types of COMT gene polymorphism.

COMT Genotype	Number of patients (%)
A / A	1 (4.2)
A / G	11 (45.8)
G / G	12 (50.0)
Total	24 (100)

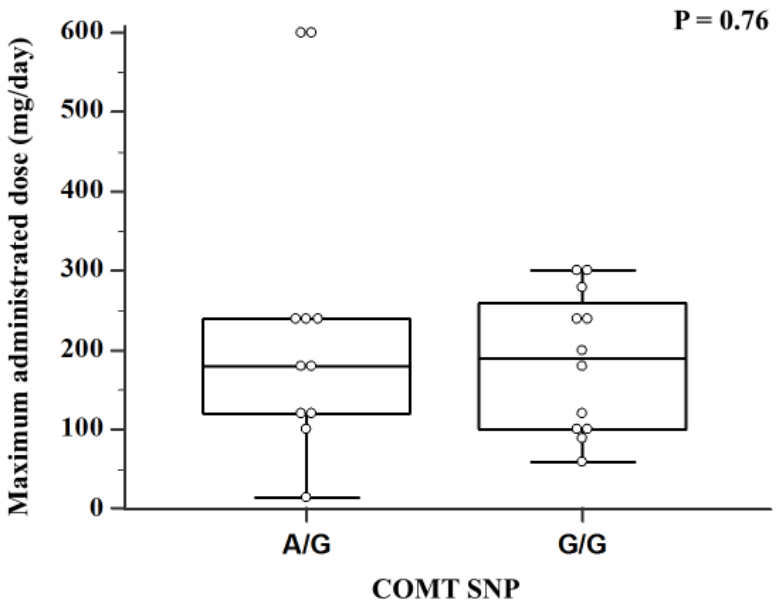


Fig-1: Maximum administered dose of opioid for different COMT gene polymorphisms. No correlation was found between the maximum administrated dose and each SNP.

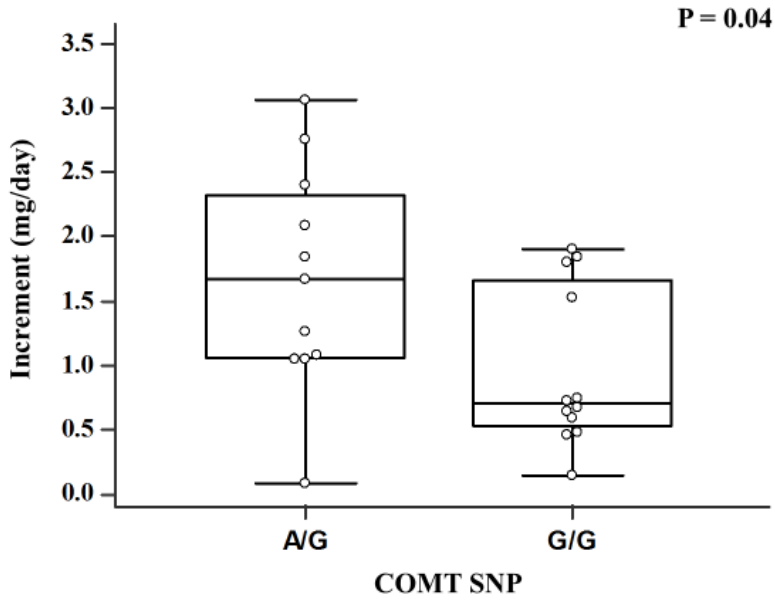


Fig- 2: Increment per day of opioid administration for different COMT gene polymorphisms. The increment per day was significantly larger in the case of A/G type than in the G/G type.

DISCUSSION

Cancer pain is largely dependent on the patient's subjective sensitivity, and it is treated in clinical practice by the method of accumulating dosages according to patient's request. Moreover, various factors such as disease condition, constitution, mental factors, and environment are known to be involved in pain control. Therefore, investigating more objective predicting factors of opioid effect is an important strategy for maintaining good pain control of patients. Research to identify the individual factors is important for realizing tailor-made medical care according to the patient's constitution.

Gastrointestinal cancer is often refractory to treatment generally, and the prognosis is poor in the case of advanced or recurrent tumors. The spread of the tumor also tends to be fast in cases such as advanced gastric, pancreatic, and biliary tract cancer, in which the survival time is often about 1–2 years even with various treatments. It is also known that gastrointestinal cancer has various advancing modalities such as metastasis of other organs, bone metastasis, and peritoneal dissemination. It often shows various symptoms including pain along with the spread of the tumor. Since cancer pain is a subjective complaint of a patient, it is necessary to quickly pick up an appeal of a patient and respond promptly.

We here examined the SNPs of the COMT gene and the dosage of opioid in patients with cancer pain. COMT is an enzyme involved in the metabolism of neurotransmitter catecholamines, and previous studies have shown that its activity changes with sensitivity to pain [16-18].

In this study, it was shown that the opioid requirement for a certain period of time for COMT A/G type cases was high compared with G/G type. This result indicates that A/G type patients required a large amount of opioid for their pain control. Among these cases, various types of gastrointestinal cancer were mixed and their prognosis was different; therefore, the increment of opioid was standardized based on the period of the opioid dosing and compared. For these cases, it was considered necessary to adjust the optimal opioid dose more promptly according to the patient's complaint of pain.

It is difficult to ascribe the effects of opioids to a single factor, but the possibility that gene polymorphism plays a part in it seems to be meaningful. In the future, it is expected that more individualized medical care will be realized by analyzing genetic factors including gene polymorphism of COMT.

CONCLUSION

This study demonstrates that COMT gene polymorphism is related to the increased use of opioids in gastrointestinal cancer patients. Depending on the polymorphism of the COMT gene, it seems that it is necessary to increase opioids promptly in reaction to complaints of pain of cancer patients.

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