The Influence of OPRM1 A118G Polymorphism on the Dosage of Morphine in Patients with Advanced Liver Cancer

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ABSTRACT

This study was conducted to investigate the influence of μ-opioid receptor gene *(OPRM1) A118G* polymorphism on dosage of morphine in advanced liver cancer patients. Seventy patients with advanced liver cancer at Changyi People's Hospital, Shandong Province, China, were included from February 2019 to December 2020. The dosage of morphine in patients with *OPRM1 A118G* different genotypes was compared. Thirty patients (42.86%) were of *AA* genotype, 35 (50.00%) were *AG* genotype and 5 (7.14%) were *GG* genotype. There was a significant difference in morphine dosage within the first 24 hours in patients with *AA, AG* and *GG* genotypes (all p <0.001), and morphine dosage in patients with *GG* genotype was the highest. In conclusion, *OPRM1 A118G* genotype may affect the dosage of morphine in advanced liver cancer patients. More dosages of morphine are needed for pain control in patients with *G* allele.

Key Words: *μ-opioid receptor gene (OPRM1), Gene polymorphism, Liver cancer, Morphine.*

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Cancer pain is one of the common symptoms of patients with advanced cancer, which is a unique and chronic pain with complex mechanism. Opioid analgesic medication is one of the main treatment methods for cancer pain, which mainly plays an analgesic role through μ-opioid receptor gene (*OPRM1*) encoded μ-opioid receptor. Among opioid analgesic medication, morphine is a first-line opioid painkiller.[1]

OPRM1 is the most closely related to cancer pain. Among the *OPRM1* gene polymorphism, *A6V*, *N40D*, *R260H*, *R265H* and *S268P* are associated with cancer pain, among which *A118G* (*N40D*) is the most closely related one. The single nucleotide polymorphism of *OPRM1 A118G* has become a hot topic in the genetic pharmacology of opioids. *A118G* mutation refers to the nucleotides at the position 118 of *OPRM1* gene mutated from adenylate *(A)* to guanylate *(G)*. Therefore, asparagine at the position 40 of μ opioid receptor is replaced with aspartic acid. *OPRM1 A118G* can be divided into *AA* type, *AG* type and GG type, according to the mutation type.

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Researches discovered that, compared with cancer patient with *AA* genotype, *AG* genotype *OPRM1* cases needed a higher dose of morphine.[2] But it is reported that for cancer cases undergoing radical gastrectomy, *OPRM1 A118G* polymorphism did not produce a marked effect in postoperative opioid analgesics fentanyl dose.[3] Thus it can be seen that the influence of *OPRM1 A118G* on the demand of painkillers remains unclear. At present, there are few reports on the influence of *OPRM1 A118G* polymorphism on the dosage of morphine in patients with advanced liver cancer. The purpose of this study was to investigate the influence of *OPRM1 A118G* polymorphism on the dosage of morphine, a pain analgesic, in patients with advanced liver cancer.

A total of 70 patients with advanced liver cancer, who visited Changyi People's Hospital, Shandong Province, China, for pain relief from February 2019 to December 2020, were included. This observational study was approved by the Hospital Ethics Committee. The inclusion criteria were patients diagnosed with advanced liver cancer, age ≥18 years, Chinese origin, moderate or severe cancer pain, clinical stage III-IV, who met the indications of morphine treatment and used morphine for the first time; good treatment compliance; clear thinking; and able to make a correct judgment of their own pain. The exclusion criteria were non-Chinese origin, other moderate and severe pain due to non-cancerous cause; liver rupture; patients who did not cooperate with treatment; or dropped out of the research due to serious nausea, vomiting and other reasons.

Table I: Comparison of the two groups of related parameters.

Parameter	Patients with AA genotype (n=30)	Patients with AG genotype (n=35)	Patients with GG genotype (n=5)	p-value
VAS score before morphine treatment	4.74±0.39	4.83±0.44	4.76±1.20	0.792
VAS score at 24 hours after morphine treatment	1.76±0.14	1.71±0.15	1.78±0.45	0.431
Morphine dosage within the first 24 hours (mg)	29.05±2.38	45.30±4.21	81.01±16.66	<0.001

All patients were given routine hepatoprotective drugs and symptomatic treatment. Oral morphine sustained-release tablets were given that the initial dose was 20 mg/day, twice/day, the dose was adjusted according to the analgesic effect, and the maximum dose was 100 mg/day.

Before treatment, 5 mL peripheral venous blood was collected and placed in ethylenediamine tetraacetic acid anticoagulant tube. Leukocyte DNA was extracted and the DNA purity was detected. *OPRM1 A118G* polymorphism was detected with polymerase chain reaction-restriction fragment length polymorphism.

The sequence of the forward primer of *OPRM1* exon was *5'-GGTCAACTTGTCCCACTTAGATCGC-3',* and the sequence of reverse primer of *OPRM1* exon was *5'-AATCACATACATGACCAGGAAGTTT-3'.* The PCR reaction conditions were that 94℃ 3 min, 94℃ 30 s, 62℃ 1 min, 72℃ 1 min, 30 cycles, 72℃ 10 min, product purification and sequencing.[4] The genotype was determined according to the base at the position 118 of *OPRM1* exon 1. *AA* type was wild type, *GG* type was homozygous variant, and *AG* type was variant hybrid type.

Before morphine treatment and 24 hours after morphine treatment, visual analogue scale (VAS) was measured by a specially-assigned person. VAS score method was to draw a 10 cm horizontal line on the paper. One end is marked with 0, indicating no pain; the other end with 10, indicating severe pain; and the middle numbers indicate different degrees of pain. The patients marked points representing the intensity of their pain. The distance between the painless point (0) and the patients' mark was measured with a ruler to determine the score. The dosage of morphine in the first 24 hours was observed.

Data were analysed by SPSS version 25.0 software. The measurement data in accordance with normal distribution were expressed by mean ± SD. One-way ANOVA was used to compare quantitative data among multiple groups, and LSD-t test was used for pairwise comparison. The counting data were represented by n (%) and Chi-square test was used for significance. The sample population representatives were tested by Hardy-Weinberg genetic balance rule. The $p < 0.05$ was considered as the threshold of significance.

Among the 70 patients, 48 were males (68.57%) and 22 were females (31.43%). They were 50-82 years of age with an average age of 68.21 ±7.97 years. The disease duration was 2-4 years, with an average of 3.16 ± 0.39 years. Forty--four patients were Child-Pugh Grade A (62.86%), and 26 were Child-Pugh Grade B (37.14%). Fifteen patients had hilar hepatic tumor (21.43%), 35 single tumor (50.00%), and 20 multiple tumor (28.57%).

All patients were tested for *OPRM1* genotyping. The results showed that 30 patients (42.86%) were *AA* type, 35 (50.00%) were *AG* type and 5 (7.14%) were *GG* type. The frequency of allele *A* was 67.86% (95/140) and the frequency of allele *G* was 32.14% (45/ 140). The distribution frequency of genotype was in accordance with Hardy-Weinberg balance (X^2=0.640, p=0.726), which indicated that the patients included had good group representativeness.

There was no significant difference in VAS score between *AA, AG* and *GG* genotypic patients before morphine treatment and 24 hours after morphine treatment (p=0.792 and 0.431, respectively, Table I).

There was a significant difference in morphine dosage within the first 24 hours in patients with *AA*, *AG* and *GG* genotypes (all $p < 0.001$, Table I). The morphine dosage in patients with *GG* genotype was higher than that in patients with *AA* genotype or *AG* genotype within the first 24 hours (both $p < 0.001$, Table I). The morphine dosage in patients with *AG* genotype was higher than that in patients with *AA* genotype within the first 24 hours ($p < 0.001$, Table I).

The results of this study showed that the dosage of morphine was higher in patients with advanced liver cancer carrying *G* allele, and higher dosages of morphine were needed in patients with *GG* genotype of *OPRM1 A118G* polymorphism to achieve pain control. The results of this study were basically consistent with those of Klepstad *et al.*[5] The *OPRM1 (A118G)* gene mutation can cause the change of μ-opioid receptor protein, affect the activation of morphine active metabolite morphine-6-glucuronic acid (M6G), and lead to individual differences in analgesic efficacy of morphine.[6]

There were some limitations in this study. Firstly, the concentration of morphine and its metabolites in plasma were not measured, and the pharmacokinetics of morphine was not studied. Secondly, the sample size included in this study was small and only Chinese patients were included. The results may be biased. It is necessary to increase the sample size in further study to investigate the exact mechanism of the influence of *OPRM1 A118G* polymorphism on the dosage of morphine in patients with liver cancer.

OPRM1 A118G genotype may affect the dosage of morphine in patients with advanced liver cancer. More dosages of morphine are needed for pain control in patients with *G*

allele, and patients with *AA* genotype need less morphine for pain control. *OPRM1 A118G* gene polymorphism may be used as a basis for guiding the dosage of morphine.

ETHICAL APPROVAL:
This study was conducted after obtaining approval from the Research Ethical Committee of Changyi People's Hospital, China.

PATIENTS' CONSENT:
Informed consents were obtained from all patients.

CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
HC: Conception of idea, data collection, manuscript writing.
XC: Conception of idea, and initial draft.
SY: Needful correction and advice, statistics finalisation.

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