Original Article

Human Mu-Opioid Receptor Gene A118G Polymorphism Predicts the Efficacy of Tramadol/Acetaminophen Combination Tablets (Ultracet) in Oxaliplatin-Induced Painful Neuropathy

Yu-Chang Liu, MD[1,2] and Wei-Shu Wang, MD, PhD[1,3]

BACKGROUND: The A118G polymorphism of the mu-opioid receptor gene (*OPRM1*), resulting in the substitution of an amino acid, has been found to be associated with functional effects and response to opioid treatment. The purpose of this study was to assess whether this polymorphism contributes to the variability in response to tramadol/acetaminophen combination tablets (Ultracet) for treating oxaliplatin-induced painful neuropathy. **METHODS:** A total of 96 patients with adenocarcinoma of the colon or rectum (n = 84), or stomach (n = 12) who had developed oxaliplatin-induced painful neuropathy were enrolled. Ultracet was administered at 1 tablet every 6 hours, and pain was assessed and scored using a visual analog scale (VAS). The *OPRM1* A118G polymorphism was examined with a polymerase chain reaction-direct sequencing method. **RESULTS:** The allelic frequency of variant (118G) allele was 39.6%, and the prevalence of *OPRM1*-118 AA, AG, and GG genotypes was 31.3% (n = 30), 58.3% (n = 56), and 10.4% (n = 10), respectively. For all patients, the mean pre-treatment and post-treatment VAS scores were 3.1 and 2.1, respectively ($P < .001$). Patients with AA genotype had a better analgesic effect than those with G allele variants (AG or GG genotypes). Pre-treatment and post-treatment VAS scores for patients with G allele variants were 3.1 and 2.6, respectively; however, for patients with AA genotype, pre-treatment and post-treatment VAS scores were 3.0 and 0.9, respectively ($P < .001$). The requirement for rescue analgesia was also higher for patients with G allele variants ($P = .01$). **CONCLUSIONS:** These data suggest that Ultracet is effective in the management of oxaliplatin-induced painful neuropathy. A118G polymorphism of *OPRM1*, by altered function of the mu-opioid receptor and consequential analgesic effect on opioid agents, could be a key determinant for decreased response to Ultracet. ***Cancer* 2011;000:000–000.** © *2011 American Cancer Society.*

KEYWORDS: *OPRM1*, polymorphism, oxaliplatin, painful neuropathy, Ultracet.

INTRODUCTION

Chemotherapy-induced peripheral neuropathy is common in patients treated with several classes of chemotherapeutic agents including taxanes, vinca alkaloids, and platinum-based compounds. Oxaliplatin, a platinum-based compound, is effective in the treatment of metastatic colorectal and gastric carcinomas; however, chemotherapy-induced peripheral neuropathy is frequently encountered.[1] Oxaliplatin-induced neuropathy includes an acute, transient peripheral nerve hyperexcitability, which can result in painful neuropathy, and a chronic, dose-related, sensory neuropathy with symptoms similar to those caused by cisplatin.[2] Development of chemotherapy-induced peripheral neuropathy results in severe disturbance of neurologic functions, and can have a significant impact on oxaliplatin treatment.

The treatment of chemotherapy-induced painful neuropathy remains largely ineffective. Although different strategies have been attempted, no pharmacological agent has yet been shown to be very helpful. Nonsteroidal anti-

Corresponding author: Wei-Shu Wang, MD, PhD, National Yang-Ming University School of Medicine, Taipei, Taiwan, Republic of China; Fax: (011) 886 3 9351 838; 11313@ymuh.ym.edu.tw

[1]National Yang-Ming University School of Medicine, Taipei, Taiwan, Republic of China; [2]Department of Radiation Oncology, National Yang-Ming University Hospital, Yilan, Taiwan, Republic of China; [3]Department of Medicine, National Yang-Ming University Hospital, Yilan, Taiwan, Republic of China

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inflammatory drugs (NSAIDs) have a modest effect in relieving neuropathy symptoms,[3] but it remains unclear whether inflammation is an important component of chemotherapy-induced painful neuropathy. Tricyclic antidepressants, including nortriptyline and amitriptyline,[4,5] and anticonvulsants, including carbamazepine and oxcarbazepine,[6,7] have been suggested as therapeutic options for neuropathic pain; however, there are few data to support their use in chemotherapy-induced painful neuropathy. Therefore, identification of alternative treatment strategies would be helpful for patients afflicted with chemotherapy-induced painful neuropathy.

Tramadol is a centrally acting analgesic that binds mu-opioid receptors and inhibits reuptake of norepinephrine and serotonin at synapses. Acetaminophen is a centrally acting analgesic that appears to relieve pain through both spinal and supraspinal levels. The combination of tramadol and acetaminophen may relieve pain through multiple pathways; this combination, in a fixed ratio of approximately 1:8, has been found to have a synergistic effect in animal models.[8] In a randomized placebo-controlled trial, tramadol/acetaminophen 37.5 mg/325 mg combination tablets (Ultracet) were effective in relieving fibromyalgia pain.[9] In addition, Ultracet is effective in the treatment of chronic low back pain,[10] osteoarthritis pain in subjects receiving a COX-2 inhibitor,[11] and breakthrough pain in cancer patients.[12] However, there remains a subgroup of patients who do not respond to Ultracet; therefore, identification of factors predictive of sensitivity to drugs for relieving pain is of extreme interest.

Genetic polymorphisms involved in the mu-opioid receptor have been associated with an altered pain threshold and susceptibility to opioid drugs. The most common coding region single nucleotide polymorphism in the *OPRM1* gene is the A118G (A to G substitution) polymorphism.[13] This polymorphism results in the substitution of the amino acid asparagine with aspartate at position 40, and has been found to be associated with possible functional effects that may affect morphine efficacy.[14] For patients with pain caused by malignant diseases, the A118G polymorphism in *OPRM1* significantly increases morphine requirements.[15] Individuals homozygous for the wild-type 118A allele required less intravenous patient-controlled analgesia consumption after total abdominal hysterectomy.[16] For patients undergoing painful cosmetic surgery, less than optimal or diminished analgesic effects of fentanyl were shown in individuals with 118G allele variants.[17] The mu-opioid receptor is also the primary site of action for several endogenous opioid peptides,[18] and altered *OPRM1* genotype has been associated with vulnerability for developing opiate addiction. One study has shown an increased affinity and potency of beta-endorphin on the homozygous G allelic receptor, resulting in increased vulnerability for developing addiction.[19]

On the basis of these earlier findings, we propose that Ultracet may be effective in relieving chemotherapy-induced painful neuropathy, and the A118G polymorphism of *OPRM1* may account for altered susceptibility to Ultracet treatment. A total of 96 patients were enrolled, and the influence of *OPRM1* A118G polymorphism on Ultracet efficacy was analyzed.

MATERIALS AND METHODS

Patients

To understand the efficacy of tramadol/acetaminophen combination tablets (Ultracet) in relieving oxaliplatin-induced painful neuropathy and the impact of the *OPRM1* A118G polymorphism on the analgesic effect of Ultracet, we examined 96 ethnic Chinese patients with adenocarcinoma of the colon, rectum, or stomach, who had received an oxaliplatin-based regimen and had experienced mild to moderate neuropathic pain. Among them, 56 patients were diagnosed as having unresectable metastatic colorectal carcinoma treated with first-line FOLFOX-4 regimen; another 28 patients with stage II/III colorectal carcinoma receiving curative surgery were treated with FOLFOX-4 in the adjuvant setting. The remaining 12 patients diagnosed as having metastatic gastric cancer were treated with first-line XELOX regimen. Administration of currently used nonopioid analgesic drugs was allowed, but the dose and frequency of these drugs remained unchanged during the Ultracet treatment period. Patients with cognitive impairment, pre-existing neuropathy, diabetes mellitus, alcoholism, brain metastasis, or history of major depression or severe anxiety, or who were currently receiving drugs that may affect the nervous system were excluded from this study. An institutional review board reviewed the study, and all patients were provided written, informed consent before initiation of study-related procedures. Characteristics of the enrolled patients are shown in Table 1.

The FOLFOX-4 regimen consisting of oxaliplatin (Sanofi-Aventis, Paris, France) 85 mg/m^2 (1-hour infusion, day 1), folinic acid (200 mg/m^2, 2-hour infusion, Day 1 and 2) before bolus 5-fluorouracil (400 mg/m^2, days 1 and 2), and infusional 5-fluorouracil (600 mg/m^2, 22-hour

Table 1. Clinical Features According to *OPRM1* Codon 118 Status in Patients With Oxaliplatin-Induced Painful Neuropathy (N=96)

Characteristics	A/A (%)	A/G or G/G (%)	*P*
All patients	30 (100)	66 (100)	
Age			.65
<50 years	10 (33.3)	19 (28.8)	
≥50 years	20 (66.7)	47 (71.2)	
Sex			.84
Male	18 (60.0)	41 (62.1)	
Female	12 (40.0)	25 (37.9)	
Body weight			.93
<50 kg	13 (43.3)	28 (42.4)	
≥50 kg	17 (56.7)	38 (57.6)	
Performance status			.91
0	14 (46.7)	30 (45.5)	
1, 2	16 (53.3)	36 (54.5)	
Primary tumor			.62
Stomach	3 (10.0)	9 (13.6)	
Colon or rectum	27 (90.0)	57 (86.4)	
Distant metastasis			.72
Presence	22 (73.3)	46 (69.7)	
Absence	8 (26.7)	20 (30.3)	
Oxaliplatin treatment			.86
Active	11 (36.7)	23 (34.8)	
Completed or discontinued	19 (63.3)	43 (65.2)	
Cycles of treatment			.70
<6	5 (16.7)	9 (13.6)	
≥6	25 (83.3)	57 (86.4)	
Concurrent use of NSAIDs			.68
Yes	4 (13.3)	11 (16.7)	
No	26 (86.7)	55 (83.3)	
Pre-treatment VAS			.76
1∼3	24 (80.0)	51 (77.3)	
4∼6	6 (20.0)	15 (22.7)	
Post-treatment VAS[a]			.02
1∼3	30 (100.0)	56 (84.8)	
4∼6	0 (0)	10 (15.2)	
Rescue analgesia requirement			.01
Required	1 (3.3)	16 (24.2)	
Not required	29 (96.7)	50 (75.8)	
Ultracet-related nausea			.78
Presence	1 (3.3)	3 (4.5)	
Absence	29 (96.7)	63 (95.5)	

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; VAS, visual analog scale.
[a] Post-treatment, 24 hours after tramadol/acetaminophen combination tablets (Ultracet) treatment.

infusion immediately after bolus 5-fluorouracil, days 1 and 2) was administered every 2 weeks. The XELOX regimen consisting of oxaliplatin (130 mg/m^2, day 1) and capecitabine (Roche, Basel, Switzerland) (1000 mg/m^2 twice daily, days 1-14) was administered every 3 weeks. Ultracet (Janssen Korea, Kyunggi-Do, South Korea) was administered orally at 1 tablet every 6 hours. For patients experiencing undesirable pain control or breakthrough pain, rescue analgesia with 1 tablet of Ultracet was administered every 6 hours according to a previously published article.[12] A detailed neurological history was obtained including possible risk factors for the development of peripheral neuropathy (eg, diabetes mellitus, alcohol abuse, central nervous system diseases, prior history of neurotoxic drug use, or neuropathy). Pain severity was assessed and scored using a visual analog scale (VAS) before and 24 hours after the administration of Ultracet.

Examination of the OPRM1 *A118G and C17T Polymorphisms*

Genomic DNA, extracted from patients' leukocytes via 0.5 mL whole blood using standard phenol-chloroform procedures, was subjected to *OPRM1* polymorphism testing. The *OPRM1* A118G polymorphism was examined using the method previously described.[19] Briefly, DNA was extracted from patients' white blood cells using standard phenol-chloroform procedures. Then 0.1 μg genomic DNA, forward primer 5′-GAT GAG CCT CTG TGA ACT AC-3′ and reverse primer 5′-CAA TCA CAT ACA TGA CCA GG-3′, were used for polymerase chain reaction (PCR) amplification. Initial denaturation was carried out at 94°C for 5 minutes. Cycling conditions were: primer annealing at 60°C for 1 minute, polymerization at 72°C for 1 minute, and strand separation at 94°C for 1 minute. Thirty-five cycles were carried out. A final polymerization step of 72°C for 10 minutes was carried out to complete the elongation processes. A negative (no DNA) control was run with each PCR analysis. The size of the PCR product was 523 bp. After amplification, the PCR products were sequenced directly.

The C17T polymorphism of *OPRM1* is the second most common coding region variant of the human mu-opioid receptor gene in Caucasian populations.[20] In the current study, *OPRM1* C17T polymorphism was also examined using these PCR products and direct sequencing results. The prevalence of *OPRM1* C17T polymorphism was analyzed, and the influence of this polymorphism on the analgesic efficacy of Ultracet was evaluated.

Statistical Analysis

All statistical analyses were performed using the SPSS software system (SPSS for Windows, version 14.0, SPSS Inc., Chicago, Ill). The correlations between different *OPRM1*-118 genotypes and clinical characteristics, response, and the requirement for rescue analgesia to Ultracet treatment were analyzed with chi-square test. The genotype was dichotomized into the wild-type homozygote (AA) and the combination of the G allele variants (AG + GG) as previously described.[17] To assess the efficacy of Ultracet for relieving oxaliplatin-induced painful neuropathy, we used the Wilcoxon signed rank test to compare the VAS scores obtained before and 24 hours after Ultracet treatment. To assess the value of the A118G polymorphism of *OPRM1* in predicting Ultracet efficacy, we used a general linear model with repeated measures that included 118 AA and AG + GG genotypes. *P* values $<.05$ were considered statistically significant.

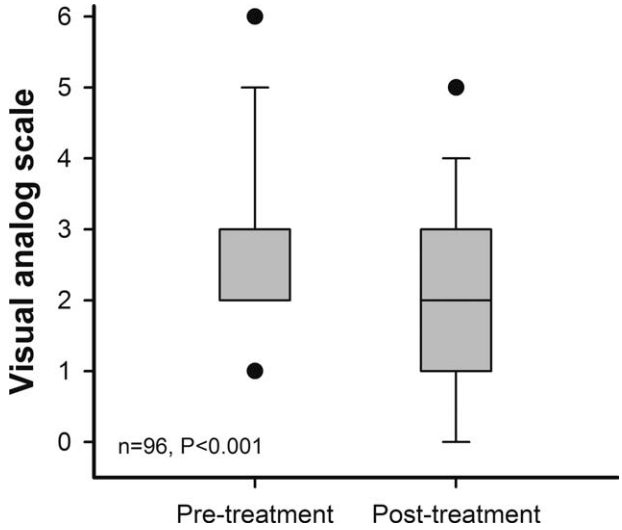

Figure 1. Ultracet was effective in relieving oxaliplatin-induced painful neuropathy. A total of 96 patients were analyzed. Ultracet was administered at 1 tablet orally every 6 hours, and the visual analog scale (VAS) scores were obtained before and 24 hours after Ultracet treatment. The mean pre-treatment and post-treatment VAS sores were 3.1 and 2.1, respectively ($P < .001$; Wilcoxon signed rank test).

RESULTS

Ultracet Is Effective in Relieving Oxaliplatin-Induced Painful Neuropathy

A total of 96 patients with adenocarcinoma, including colorectal (n = 84) and gastric (n = 12) carcinomas, who developed mild (VAS 1-3) to moderate (VAS 4-6) painful neuropathy after being treated with oxaliplatin-based chemotherapy were analyzed. No differences were found in clinical characteristics, including age, sex, body weight, performance status, location of primary tumor, presence of distant metastasis, and cycles of oxaliplatin treatment in patients with or without OPRM1 A118G polymorphism (Table 1). Ultracet was administered orally at 1 tablet every 6 hours. As shown in Figure 1, the mean pre-treatment and post-treatment VAS scores were 3.1 and 2.1, respectively ($P < .001$), indicating that Ultracet is effective in the management of oxaliplatin-induced painful neuropathy.

A Significantly Higher Prevalence of OPRM1 *A118G Polymorphism Has Been Identified in Chinese Population, but No C17T Polymorphism Was Found*

Because A118G polymorphism of *OPRM1* is associated with functional change of the mu-opioid receptor and reduced analgesic efficacy to opioid agents,[15-17] we wondered whether this polymorphism also contributes to altered efficacy of oral Ultracet treatment. Representative PCR-direct sequencing patterns of different *OPRM1*-118 genotypes are shown in Figure 2. The allelic frequency of the variant (118G) allele was 39.6%. The prevalence of *OPRM1* codon 118 AA, AG, and GG genotypes was 31.3% (n = 30), 58.3% (n = 56), and 10.4% (n = 10), respectively, which is similar to a previous study in Singapore.[21] Compared with Caucasian populations, a significantly higher prevalence of 118G allele variants was demonstrated in our cases (68.7% vs 21.1%).[19] In contrast, the C17T polymorphism of *OPRM1*, the second most common coding region variant of the human mu-opioid receptor gene in Caucasian populations, has not been found in the patients enrolled in this study, indicating the existence of ethnic differences in *OPRM1* genotypes.

OPRM1 *A118G Polymorphism Leads to a Reduced Analgesic Efficacy for Ultracet*

Compared with the AA genotype (wild-type), patients with 118G allele variants (AG or GG genotypes) in *OPRM1* had a significantly reduced response to Ultracet treatment, which is consistent with previous findings.[15-17] As shown in Figure 3, the pre-treatment and post-treatment VAS scores for patients with G allele variants were 3.1 and 2.6, respectively; however, for patients with AA genotype, pre-treatment and post-treatment VAS scores were 3.0 and 0.9, respectively ($P < .001$). In addition, patients with G allele variants had a higher percentage of moderate pain (VAS 4-6) after being treated with Ultracet (0 vs 15.2%; $P = .02$) (Table 1). We subsequently

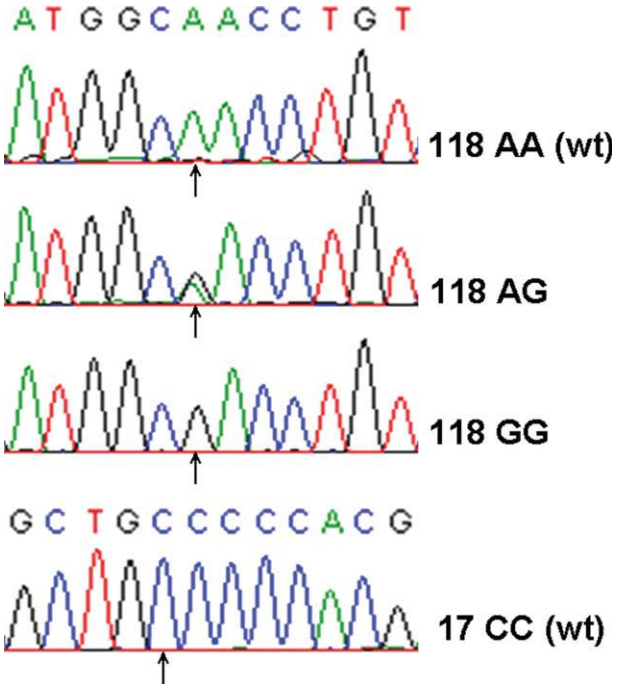

Figure 2. Representative polymerase chain reaction (PCR)-direct sequencing patterns of different *OPRM1* genotypes examined by patients' blood samples are shown. Genomic DNA obtained from patients' leukocytes was subjected to PCR amplification. Forward primer 5′-GAT GAG CCT CTG TGA ACT AC-3′ and reverse primer 5′-CAA TCA CAT ACA TGA CCA GG-3′ were used for PCR amplification. The size of the PCR product was 523 bp. After amplification, the PCR products were sequenced directly.

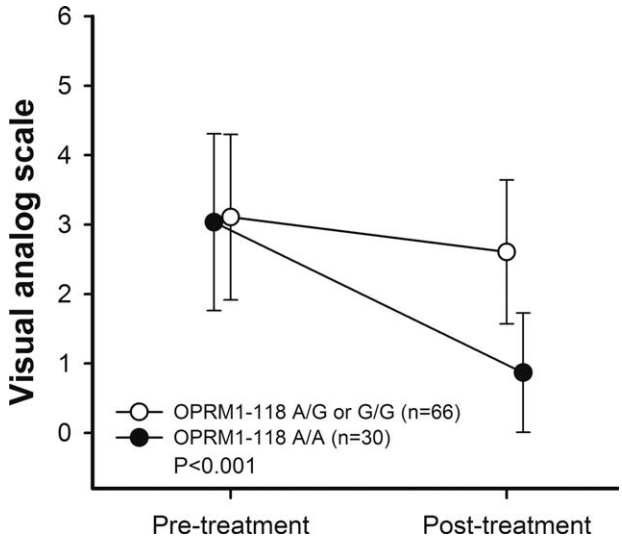

Figure 3. Patients with the 118G allele variants had a reduced analgesic response to Ultracet treatment. The pre-treatment and post-treatment VAS sores for patients with G allele variants (AG + GG) were 3.1 and 2.6, respectively; however, for patients with homozygous AA genotype, the pre-treatment and post-treatment VAS sores were 3.0 and 0.9, respectively ($P < .001$; general linear model with repeated measures), indicating that the *OPRM1* A118G polymorphism may affect individual sensitivity to Ultracet treatment.

proposed that this polymorphism, by functional effects that may affect the efficacy of opioids, might account for a higher incidence of breakthrough pain and a higher need for pro re nata analgesics. As shown in Table 1, the requirement for rescue analgesia was also significantly higher for patients with G allele variants (3.3% vs 24.2%; $P = .01$), indicating that the *OPRM1* A118G polymorphism may affect individual sensitivity to Ultracet treatment. In the current study, only a minority of patients received concurrent NSAIDs (diclofenac, celecoxib, or ibuprofen), and the percentage of patients receiving these drugs was very similar in both *OPRM1* genotype groups (13.3% vs 16.7 %; $P = .68$) (Table 1); therefore, the influence of concurrent NSAID treatment in patients with different *OPRM1* genotypes could be neglected.

DISCUSSION

Opioids have long been misguidedly considered ineffective for the treatment of neuropathic pain[22]; however, in properly selected patients, opioids may be a good option for treating painful neuropathy. For example, the benefit of oxycodone in treating diabetic neuropathy has been demonstrated,[23] and the use of tramadol may effectively relieve pain and allodynia in patients with polyneuropathy.[24] In the current study, we demonstrated that Ultracet, a tramadol/acetaminophen combination tablet, is effective in relieving oxaliplatin-induced painful neuropathy. The mean pre-treatment and post-treatment VAS scores are 3.1 and 2.1, respectively ($P < .001$, Fig. 1), indicating that Ultracet plays a role in the management of chemotherapy-induced peripheral neuropathy.

Pain is an early manifestation of several forms of neuropathies, including those induced by chemotherapy. In contrast to chronic cumulative neuropathy induced by cisplatin, oxaliplatin induces symptoms with cold allodynia and a rapid onset hyperexcitability early in the course of treatment.[25] Oxalate, a metabolite of oxaliplatin, has been suggested to be toxic to sodium channels, therefore; chelation of oxalate with calcium and magnesium may prevent acute toxic neuropathy.[26] Interestingly, oxaliplatin-induced mechanical hyperalgesia can be antagonized by antioxidants, supporting a role for reactive oxygen species (ROS) production in oxaliplatin-induced painful neuropathy.[27] Clinically, the use of glutathione protects against chemotherapy-induced peripheral neuropathy by defending

against oxidative injury.[28] In addition, glutathione S-transferase P1 contributes to the detoxification of cytotoxic compounds, including ROS, which may alter the efficacy and cumulative neurotoxicity of chemotherapy.[29]

In the current study, patients with *OPRM1*-118 G allele variants had a reduced analgesic effect in response to Ultracet, which is compatible with previous studies.[15-17] The pre-treatment and post-treatment VAS scores for individuals with G allele variants were 3.1 and 2.6, respectively; but for patients with the AA genotype, they were 3.0 and 0.9, respectively ($P < .001$, Fig. 3). In addition, the requirement for rescue analgesia was also higher for patients with G allele variants (3.3% vs 24.2%, $P = .01$) (Table 1). Clinically, individuals have different sensitivity to opioid drugs, suggesting potential variability in opioid receptors or their downstream effectors. Opioid receptors are the primary sites of action of opioid analgesics, which mediate multiple pharmacologic effects. Among subpopulations of opioid receptors, the mu receptor modulates predominately supraspinal analgesia,[30] and polymorphisms of the mu-opioid receptor gene may contribute to altered susceptibility to opioid drugs. For example, the A118G polymorphism of *OPRM1* increases opioid requirements in patients with pain caused by various etiologies.[15-17] In addition, the short tandem repeats in the 5′ flanking and 3′ untranslated regions of *OPRM1* have been associated with altered sensitivity to morphine-induced antinociception.[31] However, the C17T polymorphism of *OPRM1*, the second most common coding region variant of the mu-opioid receptor gene in Caucasian populations, has no influence in ligand binding or ligand-mediated signaling.[32]

In the current study, patients with different *OPRM1* genotypes were treated with similar cycles of oxaliplatin-based chemotherapy, and very similar pre-treatment VAS scores were found (3.0 and 3.1, respectively). Genetic polymorphisms of the mu-opioid receptor gene can also contribute to altered pain perception. For example, genetic variation at codon 118 of *OPRM1* has been associated with interindividual differences in pain scores of patients receiving cesarean section, and the pain scores were lowest in the AA group and highest in the GG group.[21] In another study, the A118G polymorphism of *OPRM1* was associated with increased sensitivity to pressure pain.[33] An enhanced binding affinity and potency of beta-endorphin to the GG variant of the mu-opioid receptor has been demonstrated,[19] but the potential effect of repeated, enhanced binding of beta-endorphin to the GG variant on receptor desensitization needs to be determined. In addition to physiologic changes, the contribution of *OPRM1* polymorphism to behavioral and personality differences has also been suggested.[34] The importance of these factors in determining pain perception and the effect of opioid analgesics in chemotherapy-induced painful neuropathy need further investigation.

The relationship between opioid-induced nausea and *OPRM1* genotypes remains controversial. Individuals with the homozygous AA genotype of *OPRM1* have a higher risk of developing nausea after being treated with morphine, despite a lower consumption of morphine, suggesting that a greater analgesic sensitivity accorded by the A allele is related to a higher risk of developing nausea.[21] However, another study did not show an increased occurrence of nausea in individuals with the AA genotype.[16] In the current study, the incidence of Ultracet-related nausea was quite low, and patients with different *OPRM1*-118 genotypes had a similar risk of developing nausea (3.3% vs 4.5%, $P = .78$), although patients with G allele variants had higher Ultracet consumption for rescue analgesia (Table 1). The results of the study show that the total amount of Ultracet used is unlikely to be a dominant factor in inducing nausea, because the genotypic group that used a higher amount of Ultracet was not associated with a higher risk of developing nausea.

The frequency of *OPRM1* A118G polymorphism varies widely across population groups. Compared with Caucasian populations,[19] a remarkably higher prevalence (68.7%) of *OPRM1* 118G allele variants, including A/G (58.3%) and G/G (10.4%), was noted in the patients in this study. Ethnic differences have a profound influence on the response and toxicity of chemotherapy. For example, because of a higher prevalence of *EGFR* mutations, gefitinib is very effective in Asian patients with nonsmall cell lung cancer.[35] The UGT1A1*28 polymorphism is rare in Asian populations, leading to a decreased risk of developing severe neutropenia after treatment with irinotecan.[36] In the current study, the prevalence of *OPRM1* codon 118 G allele variants was 68.7%, which is similar to a previous study in Singapore.[21] But in Caucasian populations, the prevalence of 118 G allele variants was only 21.1%.[19] In addition, the C17T polymorphism of *OPRM1*, the second most common coding region variant of *OPRM1* in Caucasian populations, has not been found in the patients enrolled in this study, which was consistent with a previous finding.[20] These results suggest that Asian populations might have an altered function in the mu-opioid receptor and a reduced response to opioid drugs. However, no randomized study has been conducted to

compare the efficacy of opioid treatment in different ethnic populations.

Varied CYP2D6 activity might also affect the analgesic efficacy of Ultracet. Tramadol owes its pharmacological activity through biotransformation into an active metabolite, O-demethyltramadol (M1), via cytochrome P450 2D6 (CYP2D6) in the liver.[37] M1 has remarkably higher activity than tramadol; moreover, M1 is also a potent monoamine reuptake inhibitor that may enhance the analgesic effects of tramadol through the inhibition of neuronal reuptake of noradrenaline and serotonin.[38] Interestingly, different CYP2D6 genotypes result in varied CYP2D6 activity, from very low (poor metabolizer) to extensively high (ultrarapid metabolizer),[39] and the activity of CYP2D6 significantly influences the pharmacokinetics of tramadol and M1; it is anticipated that CYP2D6 genotype may contribute to individual variability of Ultracet efficacy.

In addition to Ultracet, methadone is also effective in the treatment of chemotherapy-induced peripheral neuropathy. Methadone, a potent mu-opioid agonist, has several unique properties that make it the opioid of choice for the treatment of persistent neuropathic pain.[40] The properties of methadone that set it apart from other opioids include antagonism to receptors for *N*-methyl-D-aspartate, a known modulator of neuropathic pain.[41] Moreover, methadone may inhibit the reuptake of norepinephrine and serotonin, leading to improved analgesia in neuropathic pain.[42] In an animal model, methadone produced an analgesic effect on peripheral neuropathy induced by paclitaxel.[43] Clinically, methadone appears to be useful in the management of intractable neuropathic noncancer pain.[44] In some cases, opioid rotation is required for avoiding intolerable side effects or achieving better pain control. Clinical trials have demonstrated successful rotation to methadone from other strong opioids in the setting of intolerable side effects and inadequate analgesia despite dose escalation.[45,46] Outpatient methadone initiation and rotation have been shown to be effective and safe, with low side effect profiles for cancer pain treatment.[46] On the basis of these findings, the use of methadone with opioid rotation appears to be a good option for managing intractable neuropathic pain, including chemotherapy-induced peripheral neuropathy. Further studies are warranted.

In summary, we demonstrated that Ultracet is effective in the management of oxaliplatin-induced painful neuropathy. Asian populations have a higher prevalence of A118G polymorphism in the *OPRM1* gene. A118G polymorphism of *OPRM1*, by altered function of the mu-opioid receptor and consequential analgesic efficacy of opioid agents, could be a key determinant for decreased response to Ultracet in patients with oxaliplatin-induced painful neuropathy.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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