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Trial of the correlation between cytochrome oxidase CYP3A4 with the susceptibility of paclitaxel-based regimen for advanced gastric cancer*

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Abstract *Objective:* The aim of the study was to investigate the relationship between susceptibility of paclitaxel-based regimen and gene polymorphisms of cytochrome oxidase CYP3A4 for advanced gastric cancer. *Methods:* Peripheral venous blood sample of 53 advanced gastric cancer patients were enrolled to test the mutation of CYP3A4 gene by denaturing high performance liquid chromatography (DHPLC) and DNA sequencing. The relation between the efficacy of paclitaxel-based regimen and CYP3A4 gene polymorphisms was further analyzed. *Results:* DHPLC indicated that among the 53 patients, 21 cases showed biomodal type (mutation) and 32 cases were of unimodal type (wild-type). Sequencing results showed that the deletion mutation was found at the 27th basic group of C in exon 10 of CYP3A4 gene. The response rate (RR) and disease control rate (DCR) of wild-type group were 40.6% and 84.4%, while in mutation group they were 33.3% and 85.7%, respectively, with no significances between the two groups ($P > 0.05$). Of all 53 cases, the median progression-free survival (PFS) was 6.5 months (95% CI: 3.576–9.424 months), and the median overall survival (OS) was 11.0 months (95% CI: 6.955–15.045 months). The median PFS and OS in wild-type group had no differences compared with those in mutation group (7.0 months vs. 7.0 months, $P > 0.05$; 10.0 months vs. 14.0 months, $P > 0.05$). Between wild-type and mutation groups, the median PFS of patients applied with oxaliplatin containing regimen and the median OS in patients applied with/without oxaliplatin had no significant differences ($P > 0.05$), while the median PFS in patients received non-oxaliplatin regime had statistical differences ($P = 0.024$). The median PFS and OS in patients receiving 3-drug or 2-drug regimes had no correlation with CYP3A4 gene polymorphisms. The adverse effects in the two groups were mild, mainly in grades 1–2. The common adverse effects were anorexia, nausea/vomiting and leucopenia. *Conclusion:* Deletion mutation was located in the 27th basic group of C in exon 10 of CYP3A4 gene. Paclitaxel-based regime has a trend to prolong the OS of advanced gastric cancer with mutation type.

Key words denaturing high performance liquid chromatography (DHPLC); CYP3A4; gastric cancer; paclitaxel

Gastric cancer is one of the most common malignant tumors of alimentary tract in the world, and the morbidity and mortality of diseases are in the third place. Although in the past few decades, we have made certain achievements in the field of preventive and early diagnosis of gastric cancer. But most patients have been in advanced stage when visiting their physicians, and lost the opportunity to surgery. Chemotherapy is an important means of treatment of advanced cancer and it can alleviate the problem and prolong survival time of the patients. However, due to the highly heterogeneous of gastric cancer, patients make different sensitivities of the same chemotherapy. In recent years, with pharmacogenomics research advance in chemotherapy drugs mechanism, we found that chemotherapy drugs on the killing effect of tumor cells and toxicity were significantly associated with specific single nucleotide polymorphism (SNP) and/or gene expression. SNP determines the differences between individual and susceptibility to disease/sensitivity to drugs [1–2].

Cytochrome P450 (CYP) is an important drug metabolic enzyme. According to the sequence homologies, it can be divided into different families and subfamilies. Members of the subfamilies of CYP3A can catalysis oxidize and peroxide many drugs. Many drugs are the substrate, such as paclitaxel.

To investigate the relationship between susceptibility

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of paclitaxel-based regimen and gene polymorphisms of subfamilies of CYP3A, peripheral venous blood samples were enrolled to test the mutation of CYP3A4 gene by denaturing high performance liquid chromatography (DHPLC) and DNA sequencing. And the relation between the efficacy of paclitaxel-based regimen and CYP3A4 gene polymorphisms was further analyzed.

Materials and methods

Patients

A total of 53 cases of peripheral venous blood samples of advanced gastric cancers treated with paclitaxel-based regimens were enrolled into this study. All the patients came from Department of Abdomen Medical Oncology, Fujian Province Cancer Hospital (China) from October 2009 to March 2011. Inclusion criteria for the patients were as follows: (1) Diagnosing gastric cancer by the pathological histology or cytological diagnosis; (2) Imageology and other auxiliary examinations confirmed that they could not be surgical resection and relapse or metastasis after operation; (3) No important viscera dysfunction, no central nervous system metastatic lesions, and no completely intestinal obstruction; (4) Treated with paclitaxel-based regimens (≥ 1 cycle), and the chemotherapy regimens included paclitaxel, paclitaxel + oxaliplatin, paclitaxel + leucovorin/fluorouracil, paclitaxel + raltitrexed, paclitaxel + S-1, paclitaxel + oxaliplatin + leucovorin/fluorouracil, and paclitaxel + oxaliplatin + S-1. The median chemotherapy cycles was 4 cycles. Of all 53 cases, 34 cases were males and 19 were females; the median age was 49 (22–78) years; and pathological type was adenocarcinoma, clinical stage was IV.

Reagents and instruments

DNA extraction kit from QIAGEN, Germany; TaqDNA polymerase from ROCHE, Switzerland; Nucleic acid protein detector (GENOVA) from JENWAY, England; Cycler Thermal Cycier from BIO-RAD DNA ENGINE, USA; DHPLC from TRANSGENOMIC, USA.

Methods

Extracting genome DNA

Collected peripheral venous blood samples before chemotherapy (anti-freeze with EDTA), extract genome DNA with DNA extraction kit, quantified with nucleic acid protein detector, and –20 ℃ saved standby.

Designing and synthesizing PCR primers

CYP3A4 includes 13 exons and 12 introns, the structure zone which mainly controls the transcription and expression is the 5' coding region, designed primers for all the coding region. The primer design is failure, because the nucleotide fragment of exon 1 is too long. So we designed the primer sequences of the other 12 exons (5' to 3'). Because the nucleotide fragment of exon 13 is too long, we divided it into four segments amplification. Those primers were compounded by AXYGEN, USA (Table 1).

The PCR reaction system and conditions

PCR reaction system 50 μL, included 0.2 mmol/L dNTP, 1.5 mmol/L Mg^{2+}, template DNA 100 ng, TaqDNA polymerase 1.25 U, upstream and downstream primers were 0.2 μmol/L respectively. PCR reaction condition: pre-degeneration for 10 min and degeneration for 40 s in 94 ℃, annealing for 45 s in 55 ℃, extension for 35 s in 72℃, 35 circulations, then extension for 10 min in 72 ℃. PCR products were detected by 1% agarose gel electrophoresis (included 0.5 μg/mL ethidium bromide).

Testing the mutation of CYP3A4 gene by DHPLC

Tested the mutation of the amplified PCR product by WAVE DHPLC invented by the American Transgenomic Corporation, the solid phase column was alkylated C18, the bridge molecules was TEAA, and the main components of elution buffer was acetonitrile. Finally, we tested the mutation of the CYP3A4 gene in the best separated temperature which came from the software theoretical temperature curve.

Table 1 Exon primer sequences of CYP3A4

Exons	Primer sequences
Exon 2F	5'-CGCTGTGACTTGATTTCTGTTTC-3'
Exon 2R	5'-CTACCTGAGATTTGGGCTGTTC-3'
Exon 3F	5'-CCTCCTCTGTTTTCTCTTATTTCC-3'
Exon 3R	5'-TCTCTCTGTTTGTAGTTAGGTTGAC-3'
Exon 4F	5'-AGTCTGGCTTCCTGGGTTG-3'
Exon 4R	5'-GCTCTGTGAACTGTATCAATGTC-3'
Exon 5F	5'-GCCCATCACCCAGTAGACAG-3'
Exon 5R	5'-GCTCAAATTCAGTGGACTACCC-3'
Exon 6F	5'-CTGGTGGGGACAGGTATAAAATAAG-3'
Exon 6R	5'-CTACTTACTCTTTCAAGGTGACAGG-3'
Exon 7F	5'-GGCACCTGATAACACCTTCTG-3'
Exon 7R	5'-TGATGGTCACACATATCTTCAAATG-3'
Exon 8F	5'-TTTCCTACAGCAGTCTTTCCATTC-3'
Exon 8R	5'-CTGACTCATTCTCATATCTCCTTCC-3'
Exon 9F	5'-GAGCCATCTCACATGATAGCC-3'
Exon 9R	5'-CACAAGTAGCCCTCAGAAACAC-3'
Exon 10F	5'-AAATGTCTTTCCTCTCCTTTCAGC-3'
Exon 10R	5'-AGCCTTCCTACATAGAGTCAGTG-3'
Exon 11F	5'-TATCCAAATCTGTTTCGTTCTTTCC-3'
Exon 11R	5'-ATTATACAACCACATGACTGTCCTG-3'
Exon 12F	5'-ACCAGATTCAGCAAGAAGAACAAG-3'
Exon 12R	5'-AAGCACCCTTAAAGATCACAGATG-3'
Exon 13F1	5'-TGTCTCACTCACTTTGATGCTATAC-3'
Exon 13R1	5'-TCTACCTCCTCACACTGATTTGG-3'
Exon 13F2	5'-GAATAGAACTCTGAAATGAAGATGGG-3'
Exon 13R2	5'-CGCCAACAGTGATTACAATGAC-3'
Exon 13F3	5'-TATAGAACTGAATGAGAACCAACAAG-3'
Exon 13R3	5'-CCTCAGCCTCCTGTGTAGTG-3'
Exon 13F4	5'-GGTGGATCGCCTGAGGTC-3'
Exon 13R4	5'-GACCAATCGACTGTTTTTTATTAAG-3'

DNA sequencing

According to the DHPLC result, we took the different peak types of PCR products to Japanese Takara Corporation for DNA sequencing.

Efficacy and adverse reactions evaluation

Evaluation RECIST 1.1 standard into complete remission (CR), partial response (PR), stable disease (SD) and progressive disease (PD), CR + PR statistics efficiency response rate (RR), CR + PR + SD to calculate disease control rate (DCR). Evaluation of adverse reactions was in accordance with the NCI CTC 4.0. There were 0–4 grades adverse reactions.

Follow-up

All cases accepted at least one time of follow-up (8 weeks/time). They were followed up by several methods, including clinical attendance, letters and telephones. They were followed up until death or June 20th 2012. Follow-up time ranged from 2 to 46 months, with the median follow-up time of 16 months. None of them was withdrawing. The progression-free survival (PFS) and overall survival (OS) were calculated since the time of chemotherapy to the time of PD and death respectively.

Statistical analysis

Statistical analysis was performed using SPSS 16.0 statistical software. The Chi square test or Fisher exactly probabilistic method were used to compare count data. Kaplan-Meier test was performed to compare the PFS and OS. A $P < 0.05$ was considered significant.

Results

DHPLC screening

DHPLC indicated that among the 53 patients, all the samples were unimodal type in the un-denaturation temperature of 50 ℃. Under the partly denaturation temperature, exon 10 showed that the bimodal type and the unimodal type of amplification products. And the other exons only showed the unimodal type. The unimodal type stands for homozygous chain. The bimodal type stands for heterogeneous double chains, and it presents there were mutation heterogeneous double chains. Among the 53 patients, 21 cases were bimodal type, and 32 cases were unimodal type. In the same DHPLC operating condition, the mutant peak pattern of exon 10 of different PCR products looked the same. And it showed that there was single type of mutation of exon 10.

DNA sequencing

Choosing the samples of the unimodal type and the bimodal type to DNA sequencing. The result showed that 27th base in exon 10 of the unimodal type CYP3A4 gene was cytosine (C), but the bimodal type was deletion mutation. We verified that the bimodal type was C deletion mutation in the 27th base through gene Bank (Fig. 1).

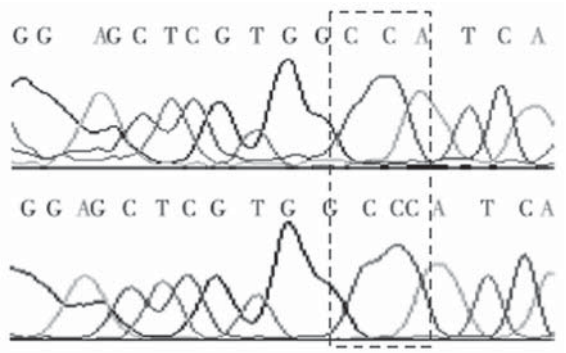

Fig. 1 DNA sequencing in exon 10 of CYP3A4 gene

Efficacy

Short-term efficacy

Of 53 cases, 13 cases in PR, 14 cases in SD, 5 cases in PD, the RR and DCR were 40.6% and 84.4% in the wild-type group; 7 cases in PR, 11 cases in SD, 3 cases in PD, the RR and DCR were 33.3% and 85.7% in the mutation group. Two groups had no CR case, and with no significances between the two groups ($P > 0.05$).

Long-term efficacy

At the end of the follow-up time, the median PFS (mPFS) was 6.5 months (95% CI: 3.576–9.424 months), the median OS (mOS) was 11.0 months (95% CI: 6.955–15.045 months) of the 53 patients. Of the 32 wild-type patients, the mPFS was 7.0 months (95% CI: 2.295–11.708 months), and the mOS was 10.0 months (95% CI: 7.925–12.075 months). Of the 21 mutation patients, the mPFS was 7.0 months (95% CI: 5.321–8.679 months), and the mOS was 14.0 months (95% CI: 12.928–15.072 months). The median PFS and OS in wild-type group had no differences compared with those in mutation group ($P > 0.05$). For further analysis, in the mutation group, 5 cases received 3-drug regimen and 9 cases received 2-drug regimen, the mPFS and mOS had no differences between the two regimens (5.0 months vs. 6.5 months, $P > 0.05$; 9.0 months vs. 10.5 months, $P > 0.05$). In the wild-type group, 9 cases received 3-drug regimen and 21 cases received 2-drug regimen, the mPFS and mOS also had no differences between the two regimens (4.5 months vs. 6.0 months, $P > 0.05$; 12.5 months vs. 15.0 months, $P > 0.05$). For further analysis between patients applied with/without oxaliplatin, the mPFS was 5.0 months (95% CI: 1.323–8.677 months), the mOS was 11.0 months (95% CI: 6.305–15.659 months) of the 22 wild-type patients received oxaliplatin containing regimen; the mPFS was 6.0 months (95% CI: 1.659–18,341 months), the mOS was 11.0 months (95% CI: 0.153–21.847 months) of the 10

wild-type patients without oxaliplatin containing regimen. The mPFS was 7.0 months (95% CI: 4.769–9.231 months), the mOS was 13.5 months (95% CI: 8.766–18.234 months) of the 15 mutation patients received oxaliplatin containing regimen; the mPFS was 1.5 months, the mOS was 3.5 months (95% CI: 0–7.101 months) of the 6 mutation patients without oxaliplatin containing regimen. Between wild-type and mutation groups, the mPFS of patients applied with oxaliplatin containing regimen and the mOS in patients applied with/without oxaliplatin had no significant differences ($P > 0.05$), while the median PFS in patients received non-oxaliplatin regimen had statistical difference ($P = 0.024$; Fig. 2–5).

Adverse events

All the adverse effects were well tolerated, and the main was 1–2 grades. The incidence of 3–4 grades was < 10%. The common adverse effects were anorexia, nausea/vomiting, leucopenia and hepatic dysfunction. Only one wild-type patient happened mild gastrointestinal bleeding and 2 cases happened anaphylaxis to paclitaxel, while the mutation patients had no these adverse events (Tables 2 and 3).

Discussion

CYP450 is an important drug phase I metabolic enzymes, widely participates hydroxyl, oxidation, reduc-

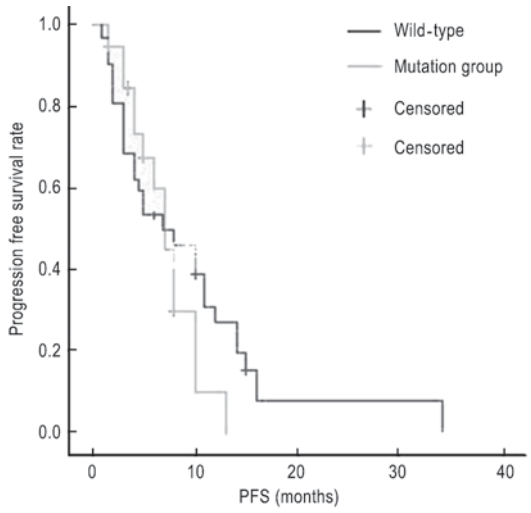

Fig. 2 The PFS curves of 53 cases of CYP3A4 wild-type and mutation groups

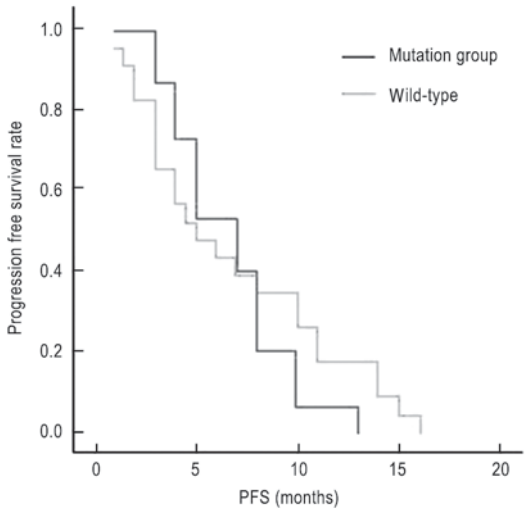

Fig. 4 The PFS curves of received oxaliplatin containing regimen of CYP3A4 wild-type and mutation groups

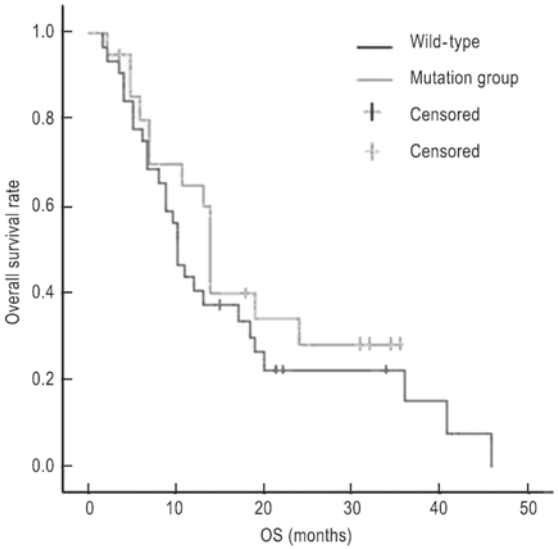

Fig. 3 The OS curves of 53 cases of CYP3A4 wild-type and mutation groups

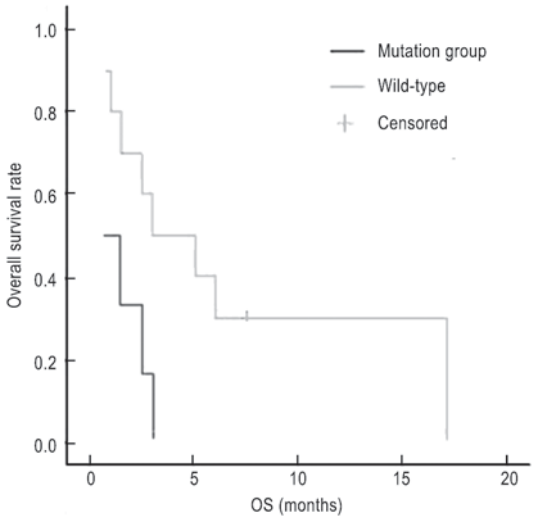

Fig. 5 The OS curves of without oxaliplatin regimen of CYP3A4 wild-type and mutation groups

Table 2 The adverse events of 21 cases of CYP3A4 mutation group [*n* (%)]

Adverse effects	Grading	
	Grades 1–2	Grades 3–4
Anorexia	2 (9.5)	1 (4.8)
Nausea vimiting	2 (9.5)	2 (9.5)
Fatigue	3 (14.3)	1 (4.8)
Constipation	0 (0)	0 (0)
Diarrhea	0 (0)	0 (0)
Leukopenia	1 (4.8)	2 (9.5)
Thrombocytopenia	1 (4.8)	0 (0)
Hepatic dysfunction	2 (9.5)	0 (0)
Renal damage	0 (0)	0 (0)
Gastrointestinal bleeding	0 (0)	0 (0)

Table 3 The adverse events of 32 cases of CYP3A4 wild-type group [*n* (%)]

Adverse effects	Grading	
	Grades 1–2	Grades 3–4
Anorexia	7 (21.9)	0 (0)
Nausea vimiting	0 (0)	0 (0)
Fatigue	1 (3.1)	2 (6.3)
Constipation	0 (0)	0 (0)
Diarrhea	0 (0)	0 (0)
Leukopenia	9 (28.1)	2 (6.3)
Thrombocytopenia	0 (0)	0 (0)
Hepatic dysfunction	2 (6.3)	0 (0)
Renal damage	0 (0)	0 (0)
Gastrointestinal bleeding	1 (3.1)	0 (0)

tion, hydrolysis and the other drug phase I reaction *in vivo*. CYP3A is an important member of CYP450 family which is in the human chromosome 7 q21.3–22.1. CYP33A4, CYP3A5, CYP3A7 and CYP3A43 are the main subtypes involved in the metabolism of drugs. About 60% metabolism of drugs through the CYP3A, these includes many chemotherapy drugs, such as paclitaxel, vincristine and irinotecan, etc. CYP3A4 accounts for 25% of total CYP450 enzyme in human liver, and it is an important drug metabolizing enzyme of cytochrome P450 enzyme family 3. There is distinctly individual difference of CYP3A4 enzyme activity between wild-type and mutation type [3]. And genetic or environmental factors can lead to the mutation of CYP3A4, and it can causes the difference of enzyme activity between individuals. There is significant differences of many metabolism and effect from catalysis by that enzyme. So that it showed that different drug efficacy and adverse events between individuals. To further understand it, we carried out this study. Currently, scholars have found that CYP3A4 gene has several mutant alleles in exons 5, 7, 9 and 12, and the mutation frequency is very low in Chinese population [4]. Our study found that deletion mutation was located in the 27th basic group of C in exon 10 of CYP3A4 gene, that is codon 294 became Gln → Asn, and it leaded to the change of amino acid residue (glutamine → aspartic acid, CAA → AAT). Consequently, which changed the amino acid type and sequence of the polypeptide chain. Deletion mutation often makes the error result of the polypeptide chain.

Paclitaxel is one kind of antineoplastic drug which is from the bark of yew. It shows the antitumor activity through being inhibitor of microtubule disassembly, as promoters of tubulin assembly, and inhibiting mitosis. The V325 trial establishes the status of the yew drugs in chemotherapy for gastric cancer [5]. Huang *et al* [6] find that paclitaxel-base regimen for advanced gastric cancer, the RR is 17%–23% in one-drug regimen, and the RR is 50%–60% in combination regimens. The mOS is 11–12 months. For the other regimens invalidly, there still be valid. The RR is 22%–44% and the mOS is 10 months. Lin *et al* [7] find that paclitaxel first-line treats advanced gastric cancer, the RR, DCR, mOS and mPFS are 39.1%, 69.6%, 7.5 months and 4.1 months respectively. For the paclitaxel-base combined regimen, the RR, DCR, mOS and mPFS are 47.3%–60.0%, 89.2%–92.6%, 11.4–11.7 months and 6.6–7.2 months respectively. Japan and South Korea carry out a number of studies on paclitaxel + S-1 regimen as first-line treatment for advanced gastric cancer [8–10], the results confirm that there is high objective response rate and effectively prolonging the mOS from this combined regimen. Lee [11] and Baize *et al* [12] have reported that paclitaxel-base regimen can effectively bring benefit to the advanced gastric cancer. Oxaliplatin is the third generation of platinum antitumor drug after cisplatin and carboplatin. It is different from cisplatin structure, and many studies confirm that it is inhibitor for many tumors *in vivo* and *in vitro*. It is reported that there is 10%–35% oxaliplatin combined regimens for advanced gastric cancer. And it can effectively bring benefit to the RR and mOS [13]. Cunningham *et al* [14] have reported that oxaliplatin can take the place of cisplatin for advanced gastric cancer and has a good survival benefit. In this study, the mPFS was 6.5 months (95% CI: 3.576–9.424 months), and the mOS was 11.0 months (95% CI: 6.955–15.045 months) of the 53 patients. The mPFS and mOS are significantly longer than those of the V325 trial (mPFS: 6.5 months vs. 5.6 months, mOS: 11.0 months vs. 9.2 months). The advanced gastric cancer patients were significantly benefited from paclitaxel-base combined regimens.

In this study, the mOS in mutation group had no difference compared with that in wild-type group (14.0 months vs. 10.0 months, $P > 0.05$), but it would had a benefit. And the mPFS and short-term efficacy also had no statistical differences. We made some analysis based on cause of the difference, such as (1): Paclitaxel is used as the substrate of CYP3A4, the cytotoxicity vanished or reduced through metabolism of CYP3A4, this phenom-

enon is called of detoxification. And paclitaxel is different from the drugs which have antineoplastic effect, such as, adriamycin, etoposide and tamoxifen, the antineoplastic effect can be further strengthened through metabolism of CYP3A4. Paclitaxel is also different from anticancer prodrugs, such as, cyclophosphamide and ifosfamide which have no antineoplastic effect. Then the intermediate products from metabolism of CYP3A4 become having antineoplastic effect. In this study, the incidence of 3–4 grades adverse effects in wild-type group was less than the mutation. This prompted wild-type CYP3A4 having stronger detoxification. (2) Many antitumor drugs are inducers or inhibitors of CYP3A4. As inducer, combining with metabolic substrate, it can improve the metabolic rate of the latter, and the latter cannot get the blood concentration playing medicinal effect. So the bioavailability is reducing. In contrast, as inhibitor, combining with metabolic substrate of CYP3A4, it can reduce the metabolic rate of the latter, and the blood concentration is rising. In this study, the two groups received different paclitaxel-base combined regimens. It would be one reason of the mPFS and mOS had no statistical differences between the two groups. (3) For further analysis, the mPFS was only 1.5 months of the mutation patients without oxaliplatin containing regimen, the mPFS was significantly lower than the oxaliplatin containing regimen. It showed that oxaliplatin + paclitaxel is effective regimen for advanced gastric cancer with mutant CYP3A4 gene. (4) The median PFS and OS in patients receiving 3-drug or 2-drug regimens had no correlation with CYP3A4 gene polymorphisms. It showed that the state of metabolic enzymes was not the only basis for patients to choose 3-drug regimen. The important basis was the performance status. (5) In this study, we tested the gene polymorphisms of CYP3A4 by DHPLC and DNA sequencing, but did not test the protein expression of CYP3A4, it also affected the study results. (6) In this study, the number of enrolled patients was limited, although the mOS had different trend between the two groups, but no statistics difference. To enlarge the sample size is a good strategy.

There are many family and subfamily members of CYP450. In this study, 53 advanced gastric cancer patients were enrolled to test the SNP of CYP3A4 gene by DHPLC. The 21 cases was mutation, and deletion mutation was located in the 27th basic group of C in exon 10 of CYP3A4 gene. But, for the advanced gastric cancer with different genotypes of CYP3A4, there were no significant differences in long-term efficacy for receiving paclitaxel combined regimens. Because of the number of enrolled patients was limited, to confirm the relation between different genotypes of CYP3A4 with drug metabolism, sensitivity and advanced effects, more works need to be done.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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