The Relationship between TUBB3 Gene Expression and Chemotherapy of Advanced Gastric Cancer with Docetaxel

Wei Zhao, Xin Shi, Zhiliang Cong, Liang Guo*

The Fourth People's Hospital of Jinan City, Taishan Medical College, Shandong, China, 250031

Keywords: TUBB3 gene expression; Chemotherapy; Docetaxel; Gastric cancer

Abstract: To investigate the relationship between the expression of beta-tubulin III and the efficacy of docetaxel in advanced gastric cancer. Pathological data of patients with advanced gastric cancer treated with docetaxel-based chemotherapy regimen were examined by immunohistochemical PV9000 method. The relationship between the expression of beta-tubulin III and the efficacy and adverse reactions of chemotherapy was analyzed. Patients with TUBB3 (-) expression were better than those with TUBB3 (+). The most common adverse reactions were bone marrow suppression and digestive tract reaction. The patients with TUBB3 (-) expression were well tolerated after symptomatic support treatment. There was no significant difference in toxic and side effects between TUBB3 (+) group and TUBB3 (-) group. This study shows that the expression of TUBB3 may be a predictor of the efficacy of docetaxel-based chemotherapy regimens in the treatment of advanced gastric cancer.

1. Introduction

The incidence of gastric cancer is very high in many countries all over the world, and the number of deaths caused by gastric cancer ranks second among all the deaths caused by malignant tumor. Paclitaxel extracted from Taxus plants is a highly effective and natural anti-tumor substance. It can play an anti-tumor role by inducing and promoting the polymerization of tubulin and inhibiting its depolymerization. Docetaxel can induce and promote tubulin polymerization and inhibit microtubule depolymerization more effectively than taxol. With the extensive application of paclitaxel in the treatment of advanced gastric cancer, the therapeutic effect and adverse reactions of paclitaxel in different patients are quite different. To explore the biological indicators related to the chemosensitivity of docetaxel, and predict the sensitivity of patients to the chemosensitivity accurately according to the individual differences of patients before chemotherapy, so as to formulate individualized chemosensitivity plan. In this paper, immunohistochemical method was used to study the relationship between the expression of beta-tubulin III and the efficacy of paclitaxel chemotherapy in advanced gastric cancer. The sensitivity of chemotherapeutic drugs was predicted, which could be used to guide the clinical use of drugs in advanced gastric cancer, improve the efficiency of drugs, and provide theoretical basis for the individualized treatment of cancer.

2. Research subjects and evaluation criterion

2.1 Research subjects

The subjects were 72 patients with advanced gastric cancer, including 53 males and 19 females. The median age was 57 years old. All patients were confirmed as gastric cancer by gastroscopic biopsy or pathological specimens after operation. The pathological specimens were well preserved. There were complete imaging data such as gastroscopy, CT, MRI, B-mode ultrasonography, chest X-ray and bone scan. All patients belonged to stage IV. There were 7 highly differentiated adenocarcinomas, 21 moderately differentiated adenocarcinomas and 41 poorly differentiated adenocarcinomas. All patients received docetaxel-based chemotherapy regimens and met the following inclusion criteria: (1) pathologically proven gastric cancer; (2) no previous chemotherapy;

  DOI: 10.25236/ibmc.2019.006

(3) Karnofaky score > 70, expected survival > 4 months; (4) There is at least one measurable lesion in order to evaluate the therapeutic effect after chemotherapy; (5) Check the function of cardiopulmonary, liver and kidney before chemotherapy, and there is no obvious contraindication of chemotherapy, so it can tolerate chemotherapy. (6) Chemotherapy cycle is more than 3 cycles.

2.2 Chemotherapy protocol

In this study, all patients received docetaxel-based chemotherapy regimen, the specific chemotherapy regimen is: docetaxel 75mg/m2, D1 static point, combined with cisplatin 75mg/m2, D1-3 static point, every three weeks for a course of treatment. In order to prevent or reduce the most common serious adverse reactions of docetaxel, such as fluid retention and allergic reaction, oral dexamethasone tablets were given for three consecutive days on the day before chemotherapy, on the day of chemotherapy and on the second day of chemotherapy at a specific dose of 8 mg/bid. Diphenhydramine hydrochloride 40 mg intramuscular injection and cimetidine 0.6 g intravenous injection were given 30 minutes before administration, and 5-HT3 receptor antagonists were used as routine drugs to prevent nausea and vomiting before treatment.

2.3 Evaluation criterion

Evaluation of the efficacy of chemotherapy: Perfect CT, B-mode ultrasonography, MRI and bone scan after 3 cycles of chemotherapy to evaluate the efficacy. According to the evaluation criteria of RECIST solid tumors, CR was divided into complete remission (CR): the tumors disappeared completely, no new lesions appeared, and the tumor markers were normal and maintained for 4 weeks. Partial remission (PR): the total length of lesions decreased by more than 30%, did not reach CR and maintained for 4 weeks without new lesions; stability (SD): the total length of lesions decreased but did not reach PR or increased but did not reach PD; progress (PD): the total length of lesions increased by more than 20%, or one or more new lesions appeared. The total effective rate (RR) is equal to the complete remission rate plus partial remission rate (CR+PR). Adverse reactions were evaluated according to the general criteria for toxicity assessment established by NCI in the United States. The main adverse reactions observed in the experimental study were leukopenia caused by bone marrow suppression, mainly in Grade 1 and 2. The incidence and severity of leukopenia were related to dosage. Detailed evaluation criteria were as follows:

Table1. General criteria for toxicity assessment of United States NCI

Adverse reactions	Level 1	Level 2	Level 3	Level 4	Level 5
Total leukopenia	3.0-4.0×10^9/L	2.0-3.0×10^9/L	1.0-2.0×10^9/L	<1.0×10^9/L	Death
Nausea	Loss of appetite without changing dietary habits	Oral intake decreased, no significant weight loss, dehydration or malnutrition required intravenous infusion	Intake of calories or insufficient fluids orally requires intravenous infusion tube feeding or TNP	Life in danger	Death
Vomit	One episode in 24 hours	2-5 episodes within 24 hours, requiring intravenous infusion less than 24 hours	Within 24 hours, seizures occurred more than 6 times, requiring intravenous infusion or TPN more than 24 hours.	Life in danger	Death

3. Test results of observed subjects

The expression of TUBB3 in pathological specimens of all advanced gastric cancer patients included in this study was detected by immunohistochemistry. The results showed that the positive expression rate of TUBB3 was 35.48% and the negative expression rate was 64.52%. The patients

were grouped according to gender, nationality, age and degree of tissue differentiation, and the expression of TUBB3 was tested by Chi-square test. The results showed no statistical significance ($P < 0.05$).

3.1 Chemotherapeutic effect

Among 72 patients, there were 1 CR, 34 PR, 19 SD and 16 PD. The total effective rate (RR) was 51.72%, the disease control rate was 79.73%, and the progress rate was 21.97%. The effective rate of TUBB3 (+) was lower than that of TUBB3 (-); the control rate of TUBB3 (+) was 65.54% lower than that of TUBB3 (-) 79.5%; the progress rate of TUBB3 (+) was 42.24% higher than that of TUBB3 (-) 14.7%; all patients were divided into effective (CR + PR) and ineffective (SD + PD) groups for statistical analysis, the results showed significant difference ($P < 0.05$). The comparison of TUBB3 expression with chemotherapeutic efficacy is shown in Table 2.

Table 2. Comparison of TUBB3 expression with chemotherapeutic efficacy

	Effective (CR+PR)	Invalid (SD+PD)	χ^2	P value
TUBB3(+)	7(31.82%)	15(68.18%)	5.35	0.021
TUBB3(-)	25(62.50%)	15(37.50%)		

3.2 Toxic side effects

As a result of pretreatment before chemotherapy, none of the selected patients had fluid retention and allergic reactions. The main adverse reactions were nausea and vomiting caused by digestive system toxicity and leukopenia caused by bone marrow suppression. There were 51 cases of nausea, no grade 4 or 5 adverse reactions; 24 cases of vomiting, no grade 3, 4 or 5 adverse reactions; 35 cases of leukopenia, no grade 5 adverse reactions, symptomatic support treatment were able to tolerate and successfully complete the treatment. Because of fewer cases and little difference among different levels, some cells were merged. The expression of TUBB3 in patients was compared with the occurrence of toxic and side effects. There was no statistical difference between the two groups.

4. Conclusions

A large number of experimental studies in breast cancer and lung cancer have confirmed that the cause of drug resistance to docetaxel is the high expression rate of beta-tubulin III. With the wide application of docetaxel in gastric cancer, it is more and more important to find indicators that can predict the chemosensitivity of docetaxel. In this study, the expression of beta-tubulin III in 72 cases of advanced gastric cancer was detected by immunohistochemistry. The results showed that the positive staining was localized in the cytoplasm of normal cells and tumor cells, showing yellow or brown granules. As a result of pretreatment before chemotherapy, no fluid retention and allergic reaction occurred in 72 patients. The main toxic side effects were leukopenia caused by bone marrow toxicity and nausea and vomiting caused by digestive system toxicity. Statistical analysis of the occurrence of toxic and side effects showed that there was no significant difference between the patients with positive expression of beta-tubulin III and negative expression of beta-tubulin III. The patients could tolerate and complete the treatment after symptomatic supportive treatment.

Acknowledgement

Study on the pharmacological effects and adverse reactions related gene markers of Docetaxel, 201401072

References

[1] Bianjilai. Capecitabine for maintenance therapy in patients with advanced gastric cancer after postoperative adjuvant chemotherapy [J]. Drugs and Clinical, 2011, 1(9): 125-126.

[2] Song W S, Cho W H, et al. Proximal tumor location and fluid-fluid levels on MRI predict resistance to chemotherapy in stage IIB osteosarcoma [J]. Clin Orthop Relat Res, 2014, 472(6):1911-1920.

[3] Jin Maolin. The development and application of chemotherapy for gastric cancer [J]. Clinical Oncology of China, 2010, 27 (10): 792-798