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Toxicity Characteristics, Effects and Coping Strategies of Ifosfamide

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Abstract. In this paper, the toxicity characteristics of Isophosphamide were discussed, and the effects of its metabolic process and side effect mechanism on patients were described in detail. The mechanism of toxicity was analyzed by molecular biology and pharmacology, so as to effectively monitor the toxic effect in tumor therapy. For decades, human beings have been exploring in the field of anti-tumor drugs. However, due to the diversity and complexity of tumorigenesis mechanisms, the same anti-tumor drug produces significantly different effects in the treatment of different types of tumors. In recent years, with the rapid development of science and technology, especially the in-depth study of tumorigenesis mechanism, people have carried out bold and in-depth exploration on some key links of tumors, such as angiogenesis inhibitors, telomerase inhibitors and the introduction of tumor suppressor genes. Although these studies are still in the initial stage, they open up new ideas for humans to eventually defeat tumors, marking a new stage in tumor treatment research. At present, there are few studies on the toxicity inhibition of ifosfamide. In this paper, studies on the toxicity characteristics, effects and coping strategies of Ifosfamide were analyzed, and it was concluded that future studies should focus on developing new formulations or administration modes to reduce the toxicity of ifosfamide while maintaining or improving its anti-tumor effect. It provides a certain reference for future research, and there are many problems about how to reduce its toxic effects cannot be solved, and future research can focus on the direction of inhibiting its toxicity.

Keywords: Ifosfamide toxicity, tumor therapy metabolic process, angiogenesis inhibitors, tumor suppressor genes.

1. Introduction

With the increasing incidence of malignant tumors, the number of cancer cases in China reaches 1.6 million every year. Due to the lack of specific early clinical manifestations, about two-thirds of patients have gone beyond radical resection at first diagnosis and have to rely on chemotherapy to improve prognosis. However, as one of the main means of tumor treatment, tumor chemotherapy has an important problem to be solved, that is, the toxic side effects of tumor chemotherapy. Due to the low biochemical selectivity of antitumor drugs, they will have toxic side effects on normal cells while killing tumor cells. It mainly includes neurotoxicity, Cardiotoxic reaction, myelosuppression, Gastrointestinal reaction,

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Urinary system toxicity [1]. Some toxic effects do not disappear quickly after drug withdrawal, and thus become a key factor in limiting the use of chemotherapy drugs, and also affect the quality of life of patients. Therefore, it is of great significance to explore how to reduce the toxic and side effects of chemotherapy to improve the anticancer effect of chemotherapy [2]. At present, chemotherapy is often combined with traditional Chinese medicine to achieve the purpose of reducing toxicity, increasing efficiency, improving clinical symptoms and improving the quality of life of patients. Its research scope mainly focuses on its anticancer mechanism and attenuated and synergistic mechanism, including inhibition of tumor proliferation, induction of tumor cell differentiation and apoptosis, regulation of oncogene expression, regulation of immune function and influence on bone marrow hematopoietic system, etc. However, few studies have been conducted on its metabolic interaction when Chinese and Western drugs are used together. The so-called metabolic drug interaction refers to the interference in the metabolic link when two or more drugs are used at the same time or in the sequence of drugs, so that the efficacy is enhanced or weakened, and the toxic side effects are produced or eliminated. The most common cause of metabolic drug interactions is the induction and inhibition of cytochrome P450.After 17 years of clinical validation in the United States from 1971, it was approved by the United States FDA in December 1988, and Isophosphamide/mesna (I/M) was listed and listed as the highest grade 1A anti-tumor drug, which is structurally similar to cyclophosphamide alkylated oxazophosphate ring drugs, and is also a precursor drug. It is converted into cytotoxic metabolites by enzymatic action in the liver. Its mechanism of action is similar to that of other alkylating agents, that is, irreversible cross-linking occurs with DNA strands and interferes with DNA synthesis. Studies in various experimental tumor systems demonstrated that I was more active than cyclophosphamide against leukemia L1210 [3]. It is also active against anthracycline and cyclophosphamide resistant Ehrlich ascites cancer. This indicates no cross-resistance with other nitrogen mustard drugs. The therapeutic effect of Yoshida ascites sarcoma in rats reached the efficacy index of cyclophosphamide. This paper aims to explore the toxicity characteristics of Ifosfamide, including its metabolic process, side effect mechanism and other effects on patients. This study will find out the plan to reduce the toxicity of Isophosphamide by studying the molecular mechanism and combining the clinical status. Besides. Through molecular biology and pharmacology, to explore the molecular mechanism of toxicity in order to monitor the toxic effects of tumor therapy. Through this study, it is expected that cancer drugs can be used more safely and the therapeutic effect can be further optimized.

2. Pharmacological Action of Ifosfamide

Isophosphamide is a cytotoxic drug belonging to the Oxyammonia phoscyclic cytotoxic drugs. Chemically, it is related to nitrogen mustard and is a synthetic analogue of cyclophosphamide. Ifosfamide is not active in vitro; it is selectively activated by microsomal enzymes in the liver. At the same time, its nitrogen and phosphorus ring C-4 atoms are hydroxylated. Thus, the primary metabolite 4-hydroxy-isocyclophosphamide is formed, and its isomer isaldophosphamide is in dynamic equilibrium [4]. The spontaneous decomposition of isoaldehyde phosphamide into acrolein and the alkylated metabolite isocyclophosphamide mustard. Acrolein is the main cause of urinary toxicity of ifosfamide. Another metabolic pathway is the oxidation and dealkylation of the side chain of vinyl chloride. The cytotoxic effects of isoaldephosphoramide are due to the interaction of its alkylated metabolites with DNA. The first attack point is the phosphodiester bond of DNA. Alkylation results in the breaking and cross-linking of DNA strands. In the cell cycle, passage through the G2 phase is blocked. Its cytotoxicity is not cell cycle specific. Cross-resistance of this product cannot be ruled out, mainly referring to structurally related cell growth inhibitors such as cyclophosphamide, but also including other alkylating agents. On the other hand, it has been reported that IFosfamide often remains effective against tumors that are resistant to cyclophosphamide or that have recurred after treatment with cyclophosphamide. After entering the body, ifosfamide is mainly metabolized into a series of active metabolites by cytochrome P450 enzyme system. The key metabolites include acrolein, phosphamide nitrogen mustard and so on. These metabolites not only exert anti-tumor activity, but also become important factors leading to toxicity [5].

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3. The side Effects of Ifosfamide and its Internal Molecular Mechanism

3.1. Side effects

3.1.1. Acute toxicity

The LD5o value (intraperitoneal injection) in mice ranges from 520-760 mg/kg, while in rats it is 150-300 mg/kg. Repeated intravenous use of doses of 100 mg/kg or higher can lead to toxic symptoms in rats.

3.1.2. Long-term toxicity

Consistent with clinical adverse effects, long-term toxicity tests showed damage to the lymphopoietic system, gastrointestinal tract, bladder, kidney, liver, and gonads. As an alkylating agent, isocyclophosphamide is a genotoxic substance with corresponding mutagenicity. In long-term studies in rats and mice, ifosfamide has been shown to have carcinogenic effects.Reproductive toxicity isocyclophosphamide has embryonic toxicity and teratogenic effects. Teratogenic effects were observed in all three animals (mice, rats, domestic immunizations) at doses of 3-7.5 mg/kg.

1) Hematological toxicity: proliferation and differentiation of phosphoryl stem cells, resulting in leukopenia, thrombocytopenia, etc. Patients are prone to infection and bleeding, which seriously affect the quality of life and treatment process. The hematological toxicity of ifosfamide is mainly reflected in the adverse effects on all kinds of blood cells. First, it can lead to a significant reduction of white blood cells, especially neutrophils, so that the body's immune function is significantly weakened, easy to cause a variety of serious infections, such as lung infection, urinary system infection. Second, it will cause a significant decrease in the number of platelets and increase the risk of bleeding, which may cause skin ecchymosis, mucosal bleeding, nose bleeding, etc., and even lead to life-threatening conditions such as intracranial hemorrhage in severe cases. Third, it can cause decrease of red blood cells and decrease of hemoglobin, resulting in obvious anemia symptoms in patients, such as fatigue, dizziness, palpitation, shortness of breath, etc., which seriously affects patients' daily life and activity endurance.

2) Urinary system toxicity: Acrolein has a strong irritation on the bladder mucosa, which can cause hemorrhagic cystitis. Patients may experience symptoms such as frequent urination, urgent urination, painful urination and hematuria, increasing pain and discomfort.

3) Neurotoxicity: The mechanism may involve direct damage to nerve cells or affect the metabolism of neurotransmitters. Patients may experience symptoms such as drowsiness, dizziness, and ataxia that affect daily activities and cognitive function.

4) Gastrointestinal toxicity: The most common form of nephrotoxicity caused by ifosfamide is proximal tubular dysfunction, which tends to be progressive and lead to advanced chronic kidney disease. Proximal tubular dysfunction is usually manifested as glycosuria, and may also include amino acid uria, low molecular weight proteinuria, Fanconi syndrome, hypophosphatemia, phospholuria, proximal tubular acidosis, hypokalemia, and, more rarely, hypercalcemia, high magnesiumuria, and sodium uria [6]. Fanconi syndrome is characterized by proximal tubular dysfunction (at the S3 level), and is characterized by proximal tubular dysfunction. The main manifestations are electrolyte, glucose and amino acid loss in the proximal renal tubules. Up to 1.4-5% of children treated with ifosfamide have been reported, while the incidence is much lower in adults. Tubular toxicity may be associated with metabolic acidosis in the normal anion gap (hyperchloric metabolic acidosis), resulting in proximal tubular acidosis.

3.2. Molecular mechanism

The molecular mechanism of Ifosfamide toxicity is complex. The active intermediates produced during its metabolism in vivo can directly damage genetic material such as DNA of cells and interfere with the normal division and proliferation of cells, which is one of the important reasons for the toxicity such as bone marrow suppression [7]. At the same time, these intermediates can also trigger oxidative stress, disrupt the REDOX balance within cells, and further impair cell function. In addition, ifosfamide may

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alter the physiological state and behavior of cells by affecting intracellular signal transduction pathways, thus inducing a series of adverse reactions. By means of molecular biology, the signal pathway and gene expression changes involved in toxicity were studied [8]. For example, in urinary system toxicity, the interaction of acrolein with bladder mucosal cell surface receptors and subsequent inflammatory response signaling pathways can be explored. In terms of hematological system toxicity, changes in gene expression in bone marrow hematopoietic stem cells were analyzed to reveal the specific molecular mechanism of toxicity. Further study on the molecular mechanism of its toxicity is helpful to better understand and deal with its related toxicity and provide important basis for clinical rational drug use.

4. Methods for mitigation of ifosfamide toxicity

4.1. Develop inhibitors targeting metabolic enzymes

Ifosfamide is mainly used for the treatment of solid tumors in clinical practice. The recommended dose of combined drug is 2.0g·m-2 for a course of 5 consecutive days. According to the conversion coefficient of human body surface area and dose of rats, the normal dose of rats was calculated to be 176mg·kg-1. Therefore, the administration dose of Ifosfamide was adjusted to 80mg·kg-1 by reference to relevant literature reports. The results showed that the injection could inhibit the activity of CYP3A4 enzyme, improve the imbalance of oxidative stress caused by isocyclophosphamide and alleviate the damage of kidney tissue caused by isocyclophosphamide [9]. Many studies have shown that the renal toxicity of IFosfamide is closely related to its metabolite chloracetaldehyde. Katarin studied the relationship between nephrotoxicity from ifosfamide and kidney development and found that the severity of nephrotoxicity depends on the ability of the kidney to metabolize chloroacetaldehyde at different developmental stages. The oxidation of chloroacetaldehyde in the body depletes glutathione, and sudha's study showed that rats with renal glutathione deficiency experienced more severe renal tubule damage after administration of IFosfamide. Combined with the research results and the metabolic pathway of isocyclophosphamide reported above, the interaction mechanism of the two can be speculated as follows: By inhibiting the activity of CYP3A4 enzyme, the plant reduces the generation of chloroacetaldehyde, the toxic product catalyzed by isocyclophosphamide via CYP3A4, and the content of chloroacetaldehyde decreases. The GSH consumed by oxidation is reduced, so that the GSH level of the kidney is increased, which plays a role in protecting the kidney. In summary, the drug interaction between Ophioglossa alba and ifosfamide can occur through the CYP pathway. Hedyotis alba injection can inhibit the activity of CYP3A4, which is the metabolizing enzyme of isocyclophosphamide, so as to reduce the production of chloracetaldehyde, and alleviate the damage to the kidney.

4.2. Drugs or substances that can reduce damage to bladder mucosa

Harmful substances such as acrolein can induce oxidative stress and produce a large number of free radicals. Glutathione, as a powerful endogenous antioxidant, can directly remove these free radicals and reduce the damage of free radicals to bladder mucosal cells. There is research has assumed a very effective protection system provided by enzymatic and non-enzymatic antioxidants in these patients. In model systems with e.g. intestinal epithelial cells or mesangial cells it has been shown that free radical scavenging enzyme (FRSE) activities are regulated by the generation of extra- and intracellular oxygen radicals [10].

5. Monitoring toxic effects using molecular biology and pharmacology

The level of toxic-related molecular markers in patients, such as sensitive markers of neuronal damage (light chain of nerve filament in cerebrospinal fluid), inflammation-related markers such as C-reactive protein, and oxidative stress markers such as malondialdehyde, were regularly monitored to assess the degree of oxidative damage.

According to the molecular characteristics of individual patients, personalized treatment plans are developed, including timely adjustment of drug dosage and combination of drugs according to the experience of doctors during treatment to reduce the risk of toxicity.

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Use pharmacological models and techniques to predict and evaluate the possible toxic effects of different treatment regimens to provide a scientific basis for clinical decision-making.

6. Conclusion

Through this period of research and reading relevant literature, this paper has a deeper understanding of the anti-tumor drug IFosfamide. As an effective anti-tumor drug, ifosfamide's clinical application is significantly affected by its toxic characteristics. In this paper, the characteristics of toxicity and strategies to mitigate toxicity were analyzed comprehensively. It is very important to effectively monitor the toxic effects in the treatment of cancer. Some measures and methods to deal with the toxic side effects of ifosfamide were summarized. The main toxicity included neurotoxicity, nephrotoxicity and cystotoxicity, which seriously affected patients' quality of life and treatment compliance. Neurotoxicity manifests in both acute and chronic forms, with the acute form usually occurring during treatment and presenting as confusion, hallucinations and seizures; Chronic forms may persist after treatment and manifest as cognitive dysfunction. Nephrotoxicity and cystitis may lead to renal failure and cystitis, requiring close monitoring and timely intervention. In addition, individualized treatment plans and close monitoring of patients' biochemical markers are essential to mitigate toxicity. Future research should focus on the development of new formulations or modes of administration to reduce the toxicity of ifosfamide while maintaining or improving its anti-tumor effect. In conclusion, the toxicity characteristics of isocyclophosphamide are problems that cannot be ignored in its clinical application. Through comprehensive management and optimization of strategies, the toxicity can be minimized and the treatment experience and quality of life of patients can be improved. Future research and clinical practice should continue to explore safer and more effective treatment options.

Authors Contributiont

All the authors contributed equally and their names were listed in alphabetical order.

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