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The Application of Oxaliplatin in Gastric Cancer

Mingchen Guo[1, *] **and Yunxi Yang**[2]

[1]Xi'an Tie Yi High School, Xi'an, China
[2]Shanghai Concord Bilingual School, Shanghai, China
*Corresponding author: michelle2040034280@gmail.com

Abstract:

This Gastric cancer (GC) continues to be the predominant cause of cancer-associated morbidity and mortality worldwide, with an unfavorable prognosis after delayed presentation and with high recurrence. Chemotherapy is still the cornerstone in the treatment of advanced disease, where oxaliplatin, a third-generation platinum compound, is of utmost significance. With improved safety, reduced nephrotoxicity, but greater efficacy against resistant tumors, oxaliplatin seems to have surpassed cisplatin. This review sketches out the pharmacological characteristics of oxaliplatin and its application in GC, with particular attention to combination regimens. Oxaliplatin plus fluorouracil-based chemotherapy, molecular-targeted therapy such as trastuzumab, and immune checkpoint inhibitors has been shown to have synergistic antitumor activities, improving survival and quality of life. However, the peripheral neuropathy induced by oxaliplatin and the emergence of intrinsic or acquired resistance remain important limitations of its clinical utility. The interest at present is on the mechanisms of resistance, neuroprotective strategies, and optimization of combination therapy to enhance efficacy and minimize toxicity. The future could include triple-drug therapy, new delivery routes, and a combination of targeted agents and immunotherapy. In conclusion, oxaliplatin remains the cornerstone in GC treatment with significant promise of more effective and individualized therapeutic strategies.

Keywords: Gastric cancer, oxaliplatin, combination therapy.

1. Introduction

GC ranks the most prevalent types of malignant tumors, which is a multifactorial disease with both environmental and genetic factors playing a key role in its etiology. Its incipient symptoms include vague gastrointestinal distress, episodic nausea, vomiting, and anorexia which also appear in patients without cancer. In the global cancer statistics 2024, the number of new cases and mortality from GC both

ranked fifth among malignant tumors. Data indicated under 1,000,000 new cases and within 660,000 deaths were recorded worldwide, accounting for 4.9% and 6.8% of the global total number of cases and mortality respectively [1]. Patients were usually diagnosed as being the advanced stage of GC due to the absence of concrete clinical symptoms, with a typically poor prognosis [2].

The common treatment methods for GC include surgery, radiotherapy chemotherapy, etc. of the available treatments, chemotherapy remains a cornerstone, but conventional cytotoxic drugs such as fluoropyrimidines are often accompanied by serious toxicities such as myelosuppression, gastrointestinal dysfunction, and peripheral neuropathy [2]. Moreover, intrinsic and acquired resistance—partially caused by tumor heterogeneity—also reduce the efficiency of chemotherapy.

Platinum chemotherapy drugs are vital in the treatment of advanced GC, with modest long-term survival benefit [2]. Oxaliplatin is a commonly used platinum-based chemotherapy drug for advanced GC and metastatic GC, with high safety and the ability to inhibiting the growth and spread of cancer cells. It still has some adverse impacts. Its resistance is a major factor that leads to the failure of clinical therapy and the causation of acute or chronic peripheral neuropathy during administration [3,4]. Currently, oxaliplatin is mainly used in combination with other drugs to enhance therapeutic efficacy, improve drug resistance, reduce side effects, and adapt to a wide range of applications.

This paper mainly focuses on the combination between oxaliplatin and fluorouracil-based chemotherapy, targeted drugs, and immune checkpoint inhibitors has exerted potent synergistic effects, such as prolonged survival, reduced recurrence. Parallel with this, however, are still a set of important issues which remain unresolved. The peripheral neuropathy dose-limiting toxicity that results from oxaliplatin use, as well as the onset of intrinsic and acquired drug resistance, continues to hinder its long-term clinical efficacy. Therefore, it is of theoretical and clinical importance to perform a systematic review of the pharmacologic properties of oxaliplatin, of its application in combination therapy, as well as mechanisms of resistance and toxicity, with the goal of providing data to facilitate optimization of therapeutic modalities in GC. This study aims to summarise and analyse the application of oxaliplatin and its combined therapy of the GC.

2. Introduction of Oxaliplatin

Oxaliplatin is a platinum-based tumor suppressor that widely used in chemotherapy treatment. It functions as a DNA synthesis inhibitor, inducing blocking replication and transcription, and ultimately triggering apoptosis. It forms adducts with DNA with fast kinetics in 15 minutes and has broad anticancer activity, low toxicity, and solubility. By using five diverse GC cell population as standards, verifying the induction of cell death, results presenting they were all sensitive to oxaliplatin [5]. Oxaliplatin exhibits superior potential as an effective therapeutic agent in the therapy of poorly differentiated GC particularly. Oxaliplatin has vital potential on inhibiting excess growth and division of a well-established human gastric cancer cell line, SGC-7901. The mechanism behind the treatment of oxaliplatin on inducing expression of GC include activation of a crucial cysteine protease for programmed cell death in mammals [6]. Furthermore, oxaliplatin reduced cell viability while triggering proptosis, immunogenic cell death, formation of reactive oxygen species that damage cell structures, collapse of mitochondrial function by opening the channels of mitochondria and activate cGMP-AMP synthase-stimulator pathway that alert immune system to have a response [7].

Oxaliplatin was originally the first platinum compound approved for administration in cisplatin-resistant disease. It has special action and resistance mechanisms compared with other platinum drugs. It is less nephrotoxic and more potent in resistant tumors compared to cisplatin by reduced recognition by DNA repair enzymes [8]. The bulky ligand inserts into the major groove of the DNA and blocks the repair proteins, the oxalate group stabilizes the complex and lowers toxicity. With combination therapy, oxaliplatin enhances effectiveness, reduces side effects, and guards against cross-resistance with cisplatin. Initially used with 5-FU for colorectal cancer, it has found usage in gastric and gastroesophageal cancers too.

3. Oxaliplatin and Its Combination Therapies

3.1 Combination of Oxaliplatin and Fluorouracil-based Drugs in GC

5-Fluorouracil (5-FU) is a kind of chemotherapeutic antimetabolite that inhibits thymidylate synthase, therefore exhaust intracellular dTTP pools which may reduce or stop DNA synthesis. It also causes cell death and can act as a chemical sensitizer. The chemotherapy regimen combining oxaliplatin with fluorouracil-based drugs is the commonly preferred chemotherapy option for GC after surgery. This regimen has excellent efficacy and safety in preventing recurrence of GC after surgery [9].

For instance, Kang et.al compared the clinical efficacy of fluorouracil and oxaliplatin combination to fluorouracil

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with irinotecan on elderly patients with advanced GC, showing the oxaliplatin group had higher scores of all dimensions of EORTC QLQ-C30 than those in the irinotecan group [10]. Furthermore, compared to the irinotecan group, the oxaliplatin group saw less side effects. For diarrhea, its incidence for oxaliplatin group is 8% which was relatively lower than irinotecan group with 18%. The incidence of peripheral neurotoxicity for irinotecan group was more than twice as much as the oxaliplatin group, with 13% and 6% respectively. The irinotecan group presented 21% incidence of leukopenia which surpasses 13% of oxaliplatin group. All results had statistically significant differences ($P<0.05$).

By contrasting fluorouracil and oxaliplatin with fluorouracil and cisplatin, Guo et al.'s study examines the recent therapeutic effect and prediction of disease development for patients with GC [11]. For the oxaliplatin group, the overall incidence of Grade three to five adverse reactions during the treatment period was more than 20% lower than the cisplatin group. Especially the incidence of peripheral neurotoxicity in oxaliplatin group was only one third of the cisplatin group. These results were statistically significant which indicate the higher safety and reduction of incidence of side effects of using fluorouracil combined with oxaliplatin is achieved, contributing to the higher quality of life for patients.

3.2 Combination of Oxaliplatin and Targeted Therapies in GC

The combined therapy of oxaliplatin and targeted drugs has emerged as a novel mean for managing HER2-positive GC. HER2- positive GC is a kind of GC characterized by HER2 overexpression. The ToGA trial initially established the current standard therapy regimen using trastuzumab with capecitabine or 5-FU with oxaliplatin for the advanced stomach and gastroesophageal junction cancer. While cisplatin was first used, oxaliplatin is now the lead drug due to its better safety profile and similar efficacy outcomes [12]. Preclinical data have shown that oxaliplatin has the ability to enhance the antitumor immune response through stimulation of an immune mechanism where effector cells recognize and kill target cells coated with antibodies that are bound to specific antigens on the target cell's surface, also known as antibody-dependent cellular cytotoxicity (ADCC) and induction of immunogenic cell death (ICD), which is a kind of cell death that can activate immune response by releasing tumor antigens, when used in combination with trastuzumab. This oxaliplatin and trastuzumab combination helps to potentiate the immune system to destroy and kill the tumor cells, hence providing justification for the combination strategy as a therapeutic option for HER2-positive GC [12,13]. The combination is a promising new development in therapeutic strategy optimization in advanced GC, especially in patients with HER2 overexpression.

In a single prospective clinical trial, the combination of oxaliplatin with trastuzumab, a humanized monoclonal antibody that blocks HER2 activation. Six cycles of treatments resulted in significant serum tumor marker levels decrease along with increase of T-lymphocyte subsets, therefore showing a combined effect: cytotoxic and immunomodulating effects [14]. The serum tumor marker level of cancer antigen 19-9 showed a substantial decline, dropping from 60.5 U/mL to 26.4 U/mL ($P<0.01$). Additionally, the level of carcinoembryonic antigen reduced to less than half of the previous level, with 6.1ng/mL after treatment ($P<0.01$). For T-lymphocyte subsets, CD4+ / CD8+ ratio was increased sharply by 1.5 times and percentage of CD3+ grew up from 62.5% to 70.0% ($P<0.05$). All results presented a better immune response is acquired in patients.

3.3 Combination of Oxaliplatin and Immune Checkpoint Inhibitors in GC

Oxaliplatin not only can trigger cytotoxicity effect directly GC cells, but also ICD. During this process, during tumor cells will release endogenous cell like damage-associated molecular patterns (DAMPs). These signals initiate sterile inflammation. Tumor cells express abnormal self-protein, or TAA, is vital to activation of dendrite cells and T cells, and thus amplify anti-tumor immune response. This vaccination redesigns TME to create an immune-permissive microenvironment that maximizes the efficacy of combination therapies, particularly immune checkpoint inhibitors like PD-1 inhibitors. Despite the fact that PD-1 inhibitors have been reported to be ineffective following single administration in treating advanced GC, they increase the antitumor activity and tumor regression significantly in combination with oxaliplatin, and promising results from clinic trials [15].

Clinical data shows that, in comparison to therapy with cisplatin, treatment with oxaliplatin helps patients stay longer without the disease getting worse, a period known as progression-free survival (PFS). This observation indicates its superior effect on therapeutic efficacy. Another recent Meta-analysis confirms that the mixing of oxaliplatin and a PD-1 inhibitor shows the best results, giving the highest probability of PFS (99.3%) [16]. These findings suggest the increased clinical efficacy of the regimen. In addition, survival benefits are much more pronounced in some subgroups, i.e., MSI-H tumors or PD-L1 high-expressing patients, thereby highlighting the significance of

biomarkers in selecting patients who are able to receive therapy. Besides these encouraging results, such issues as immune-related adverse effects and drug resistance are potential constraints to the broader use of this combination. Future studies are aimed at optimizing biomarker-targeted regimens, minimizing accompanying toxicities, and investigating multi-drug regimens, such as oxaliplatin in combination with other immune checkpoint agents or other targeted drugs.

4. Toxic and Side Effects of Oxaliplatin

Oxaliplatin mainly cause neurological damage. This side effect limits how much of the drug can be used. This issue can appear soon after treatment or gradually develop with long-term use and accumulation of drugs in the body. Acute neuropathy, present in 85–95% of patients, is due in large part to sodium channel dysfunction and calcium chelation, resulting in cold-induced paresthesia, numbness, and tingling. While reversible, these symptoms can temporarily impact daily functions and compromise compliance [17]. Chronic neuropathy, found in about half of patients, is the result of cumulative DRG neuronal injury, including mitochondrial injury, oxidative stress, and DNA injury. It manifests clinically as chronic sensory impairment, gait instability, and muscle weakness, which all severely affect quality of life. Unlike cisplatin nephrotoxicity, oxaliplatin neuropathies are at least partially reversible but this can take several months. Assessment typically relies on clinical grading scales such as NCI-CTCAE and patient-reported measures like the EORTC QLQ-CIPN20, though the lack of standardized biomarkers complicates mechanistic studies [18]. Current management is limited to dose modification, treatment interruption, and symptomatic care, while preventive strategies such as calcium–magnesium infusions or neuroprotective agents remain inconclusive. Because OIPN frequently necessitates dose reduction or suspension of administration, continued research into its mechanisms and interventions is indicated to improve the safety and long-term administration of oxaliplatin GC.

5. Resistance Mechanism of Oxaliplatin in GC Cells

The inherent or acquired drug resistance within tumor cells is a key link leading to treatment failure and tumor progression. There are several possible mechanisms of oxaliplatin resistance including reduced the time for drug action, enhanced DNA damage repair ability and changes in apoptosis regulatory genes [19].

Methyltransferase-like 3 (METTL3) is a key enzyme, mainly for adding a methyl group through N6-methyladenosine (m6A) RNA methylation. Its functions include regulate cell cycle and apoptosis, particularly its alteration of m6A is essential for transforming of epithelial cells into mesenchymal cells, spreading of GC cells and forming secondary tumors. Tumor tissues of patients with GC contains considerable amount of METTL3, the objective response rate after receiving oxaliplatin chemotherapy is reduced and the progression-free survival period is shorter, suggesting it may act as a predictor for drug resistance. Wang et al. demonstrated that METTL3 knockdown induced oxaliplatin-resistant GC cell death and allowed higher sensitivity to oxaliplatin [20]. In addition, the mechanisms of correction for DNA damage were significantly activated in oxaliplatin-resistant GC cells. METTL3 knockout effectively inhibited the DNA repair pathway, indicating that this makes GC cells more sensitive to oxaliplatin by blocking the DNA repair process. As a result, targeting METTL3 may increase the therapeutic effect for patients.

6. Conclusion

In conclusion, the combination therapies of oxaliplatin show better therapeutic effect and alleviate side effects than using oxaliplatin for treatment alone. Of different combination therapies, the chemotherapy drug fluorouracil combined with oxaliplatin shows the higher quality of life and well-being for patients. The targeted drug trastuzumab combined with oxaliplatin, which indicates HER2-positive advanced GC is well treated. Additionally, oxaliplatin combined with trastuzumab increase the potential of antitumor response. Combination of oxaliplatin and PD-1 inhibitors demonstrate synergistic efficacy and rank highest in survival and response outcomes, underscoring their strong therapeutic potential in GC.

Nonetheless, neurotoxicity is the dose-limiting toxicity that comes in both an acute and a chronic presentation with the ability to damage the quality of life in patients but being reversible in most instances. In addition, the primary mechanisms and pathways of oxaliplatin resistance are not fully explained and unraveled. Researchers from all over the world are still working to completely understand and explore it.

Research focus should now be directed towards reversal of resistance and prevention of neuropathy, i.e., with neuroprotective agents or enhanced dosing regimens. Triple-drug therapies—i.e., oxaliplatin combined with fluorouracil, targeted therapy, and immunotherapy—can result in even more therapeutic activity and lower recurrence when combination regimens are prolonged. Novel agents like bispecific antibodies, oncolytic viruses, or individ-

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ualized nanomedicine delivery systems seek to further improve tumor targeting and systemic toxicity reduction. In conclusion, oxaliplatin remains a cornerstone in GC therapy with favorable prospects for even better, individualized, and more tolerable regimens.

Authors Contribution

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

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