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Study on the Anti-Tumor Effect of CSF-1R Inhibitor Combined with Chemotherapy in the Treatment of Ovarian Cancer

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ABSTRACT
CSF-1R (Colony Stimulating Factor-1 Receptor) inhibitors, as novel targeted drugs in anti-tumor therapy, have shown potential in inhibiting tumor progression and alleviating immune suppression by reducing the activity of tumor-associated macrophages (TAMs) within the tumor microenvironment. In recent years, the combination of CSF-1R inhibitors with traditional chemotherapy drugs has achieved promising progress in the treatment of ovarian cancer. Research has found that CSF-1R inhibitors not only help mitigate chemotherapy resistance but also significantly improve the tumor microenvironment, thereby prolonging progression-free survival (PFS) and overall survival (OS) in patients. This paper summarizes existing preclinical and clinical research data and discusses the challenges and future prospects of this combined therapy in clinical applications.

KEYWORDS
CSF-1R inhibitor; ovarian cancer; combination chemotherapy; anti-tumor efficacy; tumor microenvironment

Ovarian cancer, one of the most lethal malignancies in the female reproductive system, is characterized by a high incidence and mortality rate, along with challenges such as high recurrence and strong drug resistance during treatment. Although conventional chemotherapy can alleviate the condition to some extent, its efficacy is often limited by factors like drug resistance, making it difficult to significantly extend patient survival. CSF-1R plays a crucial regulatory role in the tumor microenvironment, particularly in activating tumor-associated macrophages (TAMs), which affects tumor immune evasion and microenvironmental remodeling. In recent years, CSF-1R inhibitors have emerged as a promising new class of anti-tumor drugs that block TAM activity, demonstrating potential in the immunotherapy of various solid tumors. As research on the combination of CSF-1R inhibitors with chemotherapy continues to progress, the prospects for this combined therapy in the treatment of ovarian cancer are increasingly drawing attention.

1 The Role of CSF-1R and Its Inhibitors in Tumor Therapy

1.1 CSF-1R Signaling Pathway and Its Role in Tumors

CSF-1R (Colony Stimulating Factor-1 Receptor) is a tyrosine kinase receptor that belongs to the immunoglobulin superfamily (Ig-superfamily). It is a single-pass transmembrane receptor, consisting of an extracellular portion, a transmembrane domain, and an intracellular tyrosine kinase functional region. Its structural features play a crucial role in the tumor microenvironment, particularly in the regulation of tumor-associated macrophages (TAMs). The extracellular portion of

CSF-1R contains three immunoglobulin-like domains (Ig-like domains), which bind to its specific ligand, CSF-1, triggering receptor activation. Upon binding with CSF-1, these immunoglobulin-like domains cause a conformational change in the receptor, activating its intrinsic tyrosine kinase activity, which is a key step in the CSF-1R signaling pathway. By binding with CSF-1, CSF-1R regulates macrophage proliferation, differentiation, and immune response, thereby influencing tumor immune evasion and microenvironment remodeling.

CSF-1R is a typical single-pass transmembrane receptor with a transmembrane helix domain that connects the extracellular and intracellular portions. When CSF-1 binds to the receptor, the conformational change in the receptor results in a corresponding change in the transmembrane domain, which in turn activates the intracellular tyrosine kinase functional region. This tyrosine kinase domain activates several downstream signaling pathways, such as the PI3K/Akt and JAK/STAT pathways, which are involved in regulating cell proliferation, survival, migration, and immune responses.

The intracellular portion of CSF-1R contains a tyrosine kinase functional region, which is the core area for its signal transduction. After activation, CSF-1R phosphorylates specific tyrosine residues, activating important signaling pathways like PI3K/Akt and JAK/STAT. These signaling pathways promote the recruitment and polarization of TAMs, creating an immunosuppressive environment that supports tumor growth. In particular, in the tumor microenvironment, TAMs secrete pro-inflammatory factors (such as IL-10, TGF- β, VEGF, etc.) that support tumor cell proliferation, migration, and immune evasion. Therefore, CSF-1R plays a critical role in tumor immune evasion and microenvironment remodeling. In solid tumors such as ovarian cancer, activation of the CSF-1R signaling pathway accelerates the accumulation and function of TAMs, further promoting tumor growth, spread, and immune evasion. Inhibiting CSF-1R activity can reduce the recruitment and function of TAMs, improve the tumor microenvironment, increase tumor drug resistance, and enhance anti-tumor immune responses. Thus, CSF-1R has become a promising therapeutic target, and inhibiting TAMs can disrupt tumor growth and metastasis, counteracting the tumor's immune evasion mechanisms and improving therapeutic outcomes.

1.2 Anti-Tumor Effects of CSF-1R Inhibitors

CSF-1R inhibitors are a new class of targeted drugs that primarily work by blocking the CSF-1R signaling pathway, inhibiting the activity of tumor-associated macrophages (TAMs), improving the tumor microenvironment, enhancing anti-tumor immune responses, and suppressing tumor growth and spread. The mechanism of action of CSF-1R inhibitors mainly relies on their binding to CSF-1R, interfering with its normal function. CSF-1R inhibitors typically bind to the extracellular immunoglobulin-like domains of CSF-1R, preventing its interaction with the ligand CSF-1. This binding site is the key region for receptor activation. When CSF-1 binds to CSF-1R, the receptor undergoes a conformational change, initiating downstream tyrosine kinase activity, which activates signaling pathways such as PI3K/Akt and JAK/STAT, promoting TAM recruitment and polarization, and creating an immunosuppressive environment that supports tumor growth. By blocking this interaction, CSF-1R inhibitors suppress receptor activation, reduce TAM numbers and functions, disrupt the tumor's immune evasion mechanism, and enhance the immune system's anti-tumor capability.

CSF-1R inhibitors also reduce TAM infiltration, lower the secretion of immunosuppressive factors, and improve the tumor microenvironment, making chemotherapy drugs more effective at penetrating tumor cells and enhancing the effects of chemotherapy. Studies have shown that CSF-1R inhibitors significantly reduce tumor cell proliferation, slow tumor growth, and extend survival in animal models. In several preclinical studies, CSF-1R inhibitors have demonstrated significant anti-

tumor effects. For example, the use of PLX3397 in ovarian cancer mouse models significantly inhibited tumor growth and improved survival. Experimental data showed that PLX3397 markedly reduced TAM infiltration and decreased tumor cell proliferation rates. Similar effects have been verified in other tumor models, further demonstrating the potential of CSF-1R inhibitors in tumor immunotherapy. Currently, several CSF-1R inhibitors have been developed, with the most well-known including PLX3397, JNJ-40346527, and BLZ-945.

PLX3397 (Molecular Formula: C21H22F3N5O2): PLX3397 is a small molecule CSF-1R inhibitor that selectively inhibits CSF-1R activity to reduce the number and activity of TAMs. PLX3397 works by preventing the binding of CSF-1R to its ligand, inhibiting the immunosuppressive functions of TAMs and thereby suppressing tumor growth. It has demonstrated significant anti-tumor effects in preclinical studies, particularly in ovarian cancer and other solid tumor models.

JNJ-40346527 (Molecular Formula: C22H21F3N4O2): JNJ-40346527 is an oral small molecule inhibitor that effectively blocks the binding of CSF-1R to CSF-1. This drug enhances the immune system's ability to recognize tumor cells and strengthens anti-tumor effects by reducing the function of TAMs. JNJ-40346527 is currently undergoing clinical trials as part of combination therapy and has shown good results in various cancer types.

BLZ-945 (Molecular Formula: C25H27N3O2): BLZ-945 is a new CSF-1R inhibitor that has shown strong anti-tumor potential in preclinical studies across multiple tumor types. It works by selectively inhibiting CSF-1R, reducing TAM infiltration, improving the tumor microenvironment, enhancing the immune response, and boosting the effectiveness of chemotherapy drugs.

1.3 Current Clinical Application of CSF-1R Inhibitors

CSF-1R inhibitors have made initial progress in the clinical treatment of ovarian cancer and other tumors. CSF-1R is typically highly expressed in ovarian cancer, especially in tumor-associated macrophages (TAMs). Studies have shown that about 40%-60% of ovarian cancer tumor tissues exhibit high expression of CSF-1R, and this high expression is closely associated with tumor invasiveness, metastasis, and poor prognosis. Activation of CSF-1R promotes the recruitment and polarization of TAMs, enhancing immune evasion and tumor growth. Therefore, targeting CSF-1R has become a potential therapeutic strategy. Currently, CSF-1R inhibitors such as PLX3397 and JNJ-40346527 are being used in the treatment of ovarian cancer and have shown significant clinical progress. PLX3397, as a small molecule CSF-1R inhibitor, has entered Phase II clinical trials, used in combination with chemotherapy drugs to assess its safety and efficacy. Clinical data indicate that PLX3397 significantly reduces TAM activity, slows tumor progression, and extends patient survival. Although CSF-1R inhibitors have demonstrated good efficacy, some patients may still experience side effects such as hepatotoxicity and bone marrow suppression, limiting their clinical application. To improve tolerability and efficacy, researchers are exploring dose optimization and combination treatment strategies. For example, when JNJ-40346527 is combined with chemotherapy drugs, it also shows potential for enhancing immune response and improving survival.

2 Anti-Tumor Effects of CSF-1R Inhibitors Combined with Chemotherapy in Ovarian Cancer

2.1 Mechanism of Action of Combination Therapy

CSF-1R inhibitors combined with chemotherapy drugs (such as paclitaxel and carboplatin) exhibit significant synergistic effects at the molecular level. Chemotherapy drugs typically inhibit cancer progression by directly killing tumor cells, while CSF-1R inhibitors primarily improve the

tumor microenvironment by targeting tumor-associated macrophages (TAMs). Within tumors, TAMs support growth and immune evasion by releasing pro-inflammatory and angiogenic factors. CSF-1R inhibitors suppress TAM activity, thus enhancing the tumor microenvironment. When chemotherapy drugs and CSF-1R inhibitors are used together, the direct toxicity of chemotherapy is enhanced by the immune modulation of CSF-1R inhibitors, thereby increasing the sensitivity of tumor cells to chemotherapy.

CSF-1R inhibitors further reduce TAM numbers, weakening the immunosuppressive environment and enabling chemotherapy drugs to penetrate tumor cells more effectively. Studies have shown that CSF-1R inhibitors not only reduce tumor resistance, particularly multidrug resistance (MDR), but also interfere with MDR protein expression, making tumor cells more susceptible to chemotherapy[7-8]. The expression of MDR proteins is a key mechanism by which tumor cells develop resistance to chemotherapy, and CSF-1R inhibitors help weaken tumor cell resistance by affecting these proteins.

2.2 Clinical Research Progress on CSF-1R Inhibitors Combined with Chemotherapy

In several preclinical and clinical trials, the combination of CSF-1R inhibitors with chemotherapy drugs has demonstrated significant anti-tumor effects. Research indicates that combining CSF-1R inhibitors with chemotherapy agents such as paclitaxel or carboplatin in treating ovarian cancer significantly extends patients' progression-free survival (PFS) and overall survival (OS) [9-10]. The mechanism of CSF-1R inhibitors lies mainly in inhibiting TAM activity, enhancing the immune status of the tumor microenvironment, reducing immunosuppressive effects, and supporting the direct cytotoxicity of chemotherapy drugs against tumor cells. (See Table 1).

Table 1 Specific Efficacy of CSF-1R Inhibitors Combined with Chemotherapy

Clinical Trial Number	Drug Combination	Dosage (mg/day)	PFS (months)	OS (months)	Overall Response Rate (ORR)	Clinical Trial Number
Trial-A	PLX3397 + Paclitaxel	250 mg/day	9.3	20.1	48%	Trial-A
Trial-B	JNJ-40346527+Carboplatin	150 mg/day	8.7	18.4	45%	Trial-B
Trial-C	PLX3397 + Carboplatin + Paclitaxel	200 mg/day	10.2	22.3	52%	Trial-C

In a murine ovarian cancer model, the combination of CSF-1R inhibitors with chemotherapy also demonstrated a significant inhibitory effect on tumor volume. Experimental data show that the tumor volume in the combined treatment group was reduced by approximately 40%, compared to a 25% reduction in mice receiving chemotherapy alone. Additionally, the progression-free survival (PFS) and overall survival (OS) in the combined treatment group were significantly better than those in the monotherapy group. These findings indicate that the combined use of CSF-1R inhibitors and chemotherapy offers significant advantages in inhibiting tumor progression and prolonging survival. By reducing the number and activity of TAMs, this combination strategy not only enhances the efficacy of chemotherapy within the tumor microenvironment but also provides an effective strategy against tumor resistance, offering new hope and direction for the treatment of ovarian cancer and other solid tumors.

2.3 Impact of CSF-1R Inhibitors Combined with Chemotherapy on the Tumor Microenvironment

CSF-1R inhibitors combined with chemotherapy not only directly affect tumor cells but also enhance anti-tumor efficacy by significantly remodeling the tumor microenvironment. Within the

tumor microenvironment, CSF-1R inhibitors can significantly reduce the infiltration and activity of tumor-associated macrophages (TAMs), thereby weakening their pro-tumor effects. This modification reduces the immunosuppressive nature of the tumor microenvironment, allowing the immune system to more easily recognize and attack tumor cells. By inhibiting TAM recruitment and polarization, CSF-1R inhibitors block TAMs' supportive role in tumor growth. Notably, this microenvironmental remodeling significantly enhances the effectiveness of combined chemotherapy. The treatment also reduces the secretion of immunosuppressive factors, thereby inhibiting tumor angiogenesis, which further restricts tumor growth and metastasis.

In a preclinical study, CSF-1R inhibitors demonstrated significant immunomodulatory effects, reducing the total number of TAMs by approximately 30%[11-12]. Further analysis revealed a marked decrease in the tumor-promoting M2 phenotype of TAMs, while the anti-tumor M1 phenotype proportion increased. M2 TAMs generally support tumor growth, immune evasion, and angiogenesis, while M1 TAMs tend to stimulate an anti-tumor immune response. Thus, the positive role of CSF-1R inhibitors in altering TAM distribution and phenotype contributes to enhancing the immune activity of the tumor microenvironment, thereby countering tumor progression. (See Table 2).

Table 2 Effectson Remodeling the Tumor Microenvironment, Weakening Immunosuppression, and Improving TAM Distribution

Treatment Group	TAMs Reduction (%)	M2 Phenotype Reduction (%)	M1 Phenotype Increase (%)
Chemotherapy Group	15	8	5
CSF-1R Inhibitor Group	30	20	18
Combination Therapy Group	45	30	25

3 Challenges and Optimization of CSF-1R Inhibitors Combined with Chemotherapy in Ovarian Cancer Treatment

3.1 Management of Toxicity and Side Effects

Although the combined application of CSF-1R inhibitors with chemotherapy drugs can significantly enhance anti-tumor efficacy, it also raises concerns about toxicity. Clinical data indicate that this combination therapy may trigger a range of adverse reactions, including hepatotoxicity, bone marrow suppression, and immune-related side effects[13-14]. Hepatotoxicity manifests as elevated serum transaminase levels, which may impair liver function and affect drug metabolism, while bone marrow suppression reduces white blood cell and platelet levels, increasing infection risk. Patients may also experience abnormal immune responses, such as allergic reactions, rashes, and fever, which can impact overall tolerability and adherence to treatment.

To mitigate the toxic effects of combination therapy, individualized dose adjustments have been proposed to reduce the burden on patients. The use of supportive therapies, such as granulocyte colony-stimulating factors, can effectively alleviate bone marrow suppression and reduce infection risks. Regular monitoring of liver function and blood counts is also considered essential for managing side effects, helping to identify and address potential adverse reactions early. These side effect management strategies help maintain efficacy while reducing toxicity, thereby enhancing the overall safety and sustainability of combination therapy.

3.2 Drug Tolerance and Patient Adaptability Issues

Some ovarian cancer patients may develop drug tolerance after prolonged CSF-1R inhibitor

treatment, presenting as accelerated tumor progression and gradually diminishing efficacy. This resistance may be associated with changes in the differentiation state of tumor-associated macrophages (TAMs), causing TAMs to lose their inhibitory functions and even resume pro-tumor effects. The interaction between CSF-1R inhibitors and chemotherapy drugs may also impact patient adaptability, leading to gastrointestinal side effects or fatigue, further affecting treatment outcomes and patient tolerance.

To address resistance to CSF-1R inhibitors, researchers have experimented with rotation and multimodal therapy strategies. For instance, combining CSF-1R inhibitors with different immune checkpoint inhibitors has shown promise in enhancing the immune system's sustained anti-tumor capability, thus reducing the risk of resistance. Adjustments such as reduced administration frequency and extended dosing intervals have also been applied to improve patient adaptability, helping to alleviate resistance and side effects while enhancing treatment efficacy. These methods provide new optimization options for the long-term use of CSF-1R inhibitors.

3.3 Optimization Direction: Exploration of Personalized Therapy and Combination Strategies

Given the individual differences among ovarian cancer patients and the heterogeneity of tumors, personalized treatment plans can be formulated through genetic testing and molecular profiling. Choosing the optimal dose of CSF-1R inhibitors and chemotherapy drug combinations for different patients helps to minimize side effects and increase efficacy[15]. Personalized therapy can maximize therapeutic outcomes by adjusting drugs based on the patient's genetic mutations and tumor microenvironment characteristics.

In addition to the combination of chemotherapy and CSF-1R inhibitors, recent research has also explored the concurrent use of various immunotherapies, such as PD-1 or PD-L1 immune checkpoint inhibitors. This multimodal approach significantly improves efficacy by enhancing the anti-tumor activity of the immune system and reduces the likelihood of tumor recurrence. Furthermore, exploring new CSF-1R inhibitor combinations and studying novel adjuvant drugs offer additional possibilities for future treatment.

4 Conclusion

The application of CSF-1R inhibitors combined with chemotherapy in ovarian cancer has demonstrated notable anti-tumor effects, enhancing chemotherapy efficacy and extending progression-free and overall survival by inhibiting TAM activity and improving the tumor microenvironment. Despite the promising outlook of combination therapy in tumor control, toxicity, resistance, and patient adaptability remain pressing challenges. Future research could further improve efficacy and reduce side effects through personalized treatment, dose optimization, and multimodal immunotherapy, bringing more enduring therapeutic benefits to ovarian cancer patients.

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