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Research Progress on Anti-tumor Mechanism of Artesunate Combined Drugs

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Abstract: Artesunate (ART) is a semi-synthetic artemisinin derivative of hemiterpene lactones, which is widely used in clinical antimalarial therapy. In recent years, studies have shown that artesunate also has anti-inflammatory, anti-tumor, anti-fibrosis, antiviral, antibacterial, immunomodulatory and other pharmacological activities. Artesunate can play an anti-tumor role by inhibiting tumor cell proliferation, invasion and migration, promoting tumor cell apoptosis and blocking cell cycle. At the same time, when combined with other anti-tumor drugs, it can enhance the anti-tumor efficacy, shorten the duration of administration, reduce the dose and adverse reactions. In this paper, the main keywords of "artesunate", "pharmacology", "anti-tumor" and "combined drug" were searched and integrated in Pubmed, Web of Science and CNKI electronic databases to review the anti-tumor mechanism of artesunate combined with other drugs in recent 5 years. The prospect of clinical application of artesunate as an antitumor drug was prospected to provide some theoretical basis for further rational development and utilization of artesunate and new drug research and development.

Keywords: Artesunate; Anti-tumor; Drug combination; Action mechanism.

1. Introduction

Cancer is a major global public health problem and a major contributor to the global disease burden due to its high morbidity and mortality [1-3]. At present, surgical treatment, chemotherapy, radiotherapy, targeted therapy, immunotherapy and other methods are mainly used in the clinical treatment of cancer [4-7], but chemotherapy drugs will have adverse effects on liver and kidney function, and there is a large difference between individuals treated with drugs, which is prone to drug resistance and poor prognosis, so it is necessary to find safer and effective anti-tumor drugs.

ART is a derivative of artemisinin, which has the characteristics of rapid action, low toxicity and resistance[8]. In addition to its pharmacological effects of anti-malaria, anti-inflammation, anti-virus and anti-fibrosis, ART has also been widely used in anti-tumor. Many studies have shown that ART can be used in the treatment of gastric cancer, liver cancer, breast cancer, colorectal cancer and other cancers, and has significant therapeutic effect. ART can specifically inhibit the growth of cancer cells and exert anti-tumor effects by inhibiting angiogenesis, inhibiting the invasion and migration of cancer cells, inducing cell cycle arrest, and regulating signal transduction [9-12].

The generation of drug resistance and the accumulation of dose-related toxicity are the main shortcomings of chemotherapy drugs in the treatment of cancer. Therefore, it is necessary to find drugs that can improve efficiency and reduce toxicity in dealing with drug resistance, and the combination of drugs can enhance the therapeutic effect of each other, prevent the occurrence of drug resistance, reduce the dose used in each single treatment and reduce the adverse reactions of chemotherapy drugs and molecular targeted drugs.

This review aims to provide a theoretical basis for the further development of ART combined therapy by summarizing the anti-tumor mechanism of ART combined with other drugs, alleviating pain for patients, and providing certain ideas for the research and development of new drugs.

2. Artesunate Combination

2.1. Alkylating agents

Alkylating agents [13-14] belong to cytotoxic drugs, also known as biological alkylating agents, which can form carbocation ions or other compounds with active electrophilic groups in the body, and then covalently bind with electron rich groups (such as amino, sulfhydryl, hydroxyl, carboxyl, phosphoric acid, etc.) in biological macromolecules in cells. Make it inactive or make the DNA molecules break, resulting in the death of tumor cells. Alkylating agents are representative drugs such as camustine, nitrogen mustard hydrochloride, cyclophosphamide and Milfarran, which have become important drugs for cancer chemotherapy. Alkylating agents are easy to synthesize and have important value in tumor treatment, but their selectivity is poor, adverse reactions are large, and drug resistance is easy to occur. The alkylating agent, Temozolomide, combined with artesunate and phosphatidylcholine to form targeted liposomes, reduces the effective dose and toxic effects of temozolomide, and provides a new therapeutic method for the clinical treatment of drug-resistant glioblastoma [15].

2.2. Anti-tumor antibiotics

Anti-tumor antibiotics [16] are chemicals produced by microorganisms with anti-tumor activity and are an important category of chemotherapy drugs for malignant tumors. According to their structure, antitumor antibiotics can be divided into anthracycline, enediyne, macrolides, glycopeptides and benzodipyrrole, represented by mitomycin, epirubicin, doxorubicin, bleomycin and doxorubicin magnitude. This class of drugs can play an anticancer role by interfering with nucleic acid and protein synthesis, but their clinical use is limited because of their powerful side effects, such as anthracyclines, which can cause cardiac side effects [17]. At present, most anti-tumor antibiotic drugs are in a

period of rapid development, which can reduce their resistance and reduce adverse reactions by combining with other drugs, and improve the quality of life of patients. Studies [18] have shown that ART and doxorubicin have a synergistic effect, which can enhance the apoptotic cell death of leukemia T cells. Doxorubicin combined with ART can reduce the toxicity of each drug and has a significant therapeutic effect on breast and colon cancer [19].

2.3. Platinum metals

Platinum-based anti-tumor drugs [20-21] have been widely used in the single or combined treatment of a variety of clinical tumors, and are currently the most widely used anti-tumor drugs in clinical practice. The main representative drugs include cisplatin, carboplatin, oxaliplatin and other bivalent platinum. After entering the nucleus, bivalent platinum drugs can form adduct with DNA, inhibit DNA replication and transcription, induce DNA damage, activate ATR pathway and trigger cycle arrest regulated by P53 and apoptosis factors, thus inducing mitochondrial regulated Caspase-dependent and non-dependent apoptosis pathways, inducing tumor cell apoptosis and exerting anti-tumor effects [22]. However, bivalent platinum drugs have serious side effects such as ototoxicity, nephrotoxicity and cardiotoxicity during treatment, which are dose-dependent [23]. At present, platinum drugs are mainly used in combination with other anti-tumor drugs to reduce the side effects and drug resistance, and improve the anti-tumor effect of this drug. The combination of ART and platinum drugs can effectively induce autophagy death and apoptosis, block the cell cycle, have significant anti-tumor effect in vivo, and greatly improve the safety of drugs, especially reduce the renal toxicity of platinum drugs [24]. The combination of ART and cisplatin has a synergistic effect, which can significantly improve the anti-lung cancer efficacy of ART used alone [25]. At the same time, the combination of ART and carboplatin also has a synergistic effect, which can play an anticancer role by enhancing apoptosis [26].

2.4. Anti-metabolism

Anti-metabolic drugs [27] are a class of anti-tumor drugs that work by interfering with essential biochemical processes. Most of these drugs are nucleoside analogues, which can specifically interfere with nucleic acid metabolism, inhibit the division and proliferation of tumor cells, and eventually lead to the death of tumor cells. Including thymidylate synthase inhibitors, DNA polymerase inhibitors, dihydrofolate reductase inhibitors, purine nucleotide synthesis inhibitors and so on. Common anti-metabolic representative drugs include 5-fluorouracil, methotrexate, cytarabine, etc. Among them, 5-fluorouracil is widely used in the treatment of colon cancer and breast cancer, but it has serious toxic effects on the heart, so combination therapy is often used clinically to reduce the toxic side effects caused by its single use [28]. The combination of ART and 5-fluorouracil can reduce the adverse reactions caused by 5-fluorouracil and synergically inhibit the proliferative activity of cancer cells, providing a new treatment option for patients with colorectal cancer [29]. ART combined with cytarabine can be used in the treatment of acute myeloid leukemia [30-32].

2.5. Others

Erlotinib, a tyrosine kinase inhibitor of the epidermal growth factor receptor, binds to the adenosine triphosphate binding pocket of mutated EGFR, impedes EGFR phosphorylation and thus inhibits downstream signaling pathway activation, and is currently mainly used in the treatment of non-small cell carcinoma. The combination of ART and erlotinib has a synergistic inhibitory effect on tumor cells [33]. Sorafenib, a multi-kinase inhibitor, is currently the standard chemotherapy drug for the treatment of advanced liver cancer, but its efficacy is limited and drug resistance is easy to occur. The combination of ART and sorafenib has a synergistic effect, and the combination of the two drugs can significantly enhance the inhibition of tumor [34].

3. Anti-tumor Mechanism of Artesunate Combineddrugs

3.1. Induced iron death of tumor cells

Studies have shown that the combination of ART and sorafenib more significantly inhibited the proliferation of HepG2 cells and in vivo tumors, and the combination therapy induced lipid peroxidation and iron death compared with drug alone. ART can enhance the sensitivity of hepatocellular carcinoma cells to sorafenib and has a synergistic anticancer effect when combined with sorafenib. Combined therapy can reduce the synthesis of GSH and increase the production of ROS, thus reducing mitochondrial potential and damaging mitochondrial function. The activation of cathepsin B/L and the degradation of ferritin were induced. The two synergistically reduce the expression of TFRC along with the degradation of FTL and FTH, promoting liver cancer cells towards iron death [35].

3.2. Induction of tumor cell apoptosis

Baicalein is a kind of flavonoid compound. Both ART and baicalein have anticancer effect, and they have synergistic effect when used together. Compared with single therapy, combination therapy increased the cleavage of caspase 3 and PARP in liver cancer cells and increased the expression of DNA damage inducing factor (GADD45A), TNF-α and TNF-receptor-associated factor 3 (TRAF3). Reduce liver cancer cell activity to induce apoptosis [36].

The combination of ART and temozolomide to form targeted liposomes can improve the sensitivity of U251-TR glioma to temozolomide. Targeted liposomes inhibited MGMT protein expression by interfering with Wnt/β-catenin, while enhancing DNA damage, which synergistically enhanced the pro-apoptotic effect. Liposomes can deliver drugs deep into tumors through the blood-brain barrier, and can effectively reduce the effective dose of temozolomide and reduce the toxic effects of temozolomide [15].

The combination of ART and cisplatin can inhibit the proliferation of A549 cells. Compared with the single treatment of ART and cisplatin, the combination treatment can increase the expression of p21, decrease the expression of cyclinB1 and p34, increase the expression of p53 and Bax, and decrease the expression of Bcl-2. Enhance the activities of caspase-3, caspase-7 and caspase-9, and synergically regulate the activity of P38/JNK/ERK1/2 MAPK pathway, inducing cell apoptosis [25].

Both ART and carboplatin can inhibit the activity of A549 cells, and the combination of the two can significantly enhance the apoptosis rate of tumor cells. The combination of low concentration ART and carboplatin showed a synergistic effect, which significantly inhibited cell proliferation, promoted cell cycle arrest in G2 /M phase, increased the

expressions of Bax, p21, p53 and Caspase-3, and decreased the expressions of Bcl-2 and Cyclin B1. It plays a synergistic role in non-small cell lung cancer by enhancing mitochondria-dependent apoptosis [26].

Both ART and 5-fluorouracil had inhibitory effects on HCT116 cells, and the antitumor activity of ART combined with 5-fluorouracil was significantly higher than that of 5-fluorouracil alone. Combined use of the two decreased PCNA, Ki-67, and Bcl-2 levels, and increased Cleaved caspase-3 levels. ART significantly enhanced the sensitivity of tumor cells to 5-fluorouracil and increased the apoptosis of tumor cells [29].

ART and ginsenoside Rg3 synergistically reduce the survival rate of sorafenib resistant HepG2 liver cancer cells, significantly increase cell ROS, inhibit the phosphorylation of STAT3 and its upstream kinase Src, reduce the level of STAT3, down-regulate the protein levels of Mcl-1 and Bcl-2 in HepG2 cells, and induce cell apoptosis. It also inhibited the growth of HepG2-SR tumor in mice [37].

ART alone inhibited the activity of C918 cells and significantly increased ROS levels, LDH release, caspase-3, caspase-9, and IL1b and IL18 levels. ART inhibits the activity of C918 cells by inhibiting MALAT1/YAP signaling pathway. However, the combination of Vitipofen and ART can enhance the inhibitory effect of ART on C918 cells [38].

Bortezomib is a proteasome inhibitor, which is mainly used in the treatment of hematological malignancies such as multiple myeloma and lymphoma. Hu et al. [39] showed that the IC50 of ART and bortezomib acting alone on MV4-11 cells for 48h was 1.44 μg/ml and 8.97 nmol/L, respectively, and both had significant inhibitory effects on MV4-11 cells. When the two methods were used in combination, the proliferation inhibition rate of the cells was higher than that of the method of drug alone. The combination of the two drugs also significantly increased the apoptosis rate of the cells, and the mechanism was that the two drugs up-regulated the expression of cleaved Caspase-3, Bim, and LC3B, and down-regulated the expression of Bcl-2. The combination of the two drugs can synergistically inhibit proliferation and promote apoptosis.

3.3. Synergistic interaction

The combination of ART, venettok and cytarabine was used in the treatment of acute myeloid leukemia. While inducing apoptosis, Vinettok combined with cytarabine increased the binding of Mcl-1 and Bim, inhibiting part of apoptosis. However, ART can up-regulate Noxa and replace Bim bound to Mcl-1, causing Bim to dissociate and recruit E3 ubiquitin ligase to degrade Mcl-1, reversing the drug resistance of Mcl-1/p-Chk1 treated by cytarabine and vinettok [31].

Li et al. [40] showed that the IC50 values of solafenib acting alone on HepG2 and Huh7 cells were 5.93-8.51μm and 7.11-17.11μm, respectively. The IC50 values of HepG2 and Huh7 cells treated by ART alone were 63.28-99.85 μM and 344.70-1,099 μM, respectively. The sensitivity of these cells to ART treatment was low. When the two drugs treated the cell line at a constant ratio (1:10 for HepG2 and 1:50 for Huh7), the combination significantly inhibited the growth of tumor cells without significantly enhanced hepatotoxicity compared with the single drug. The combined use of the two can significantly reduce the expression of VEGFR2 protein, synergistically play an anti-angiogenic role, and enhance the apoptosis of tumor cells.

ART has heme-dependent anti-tumor activity, and histone deacetylase inhibitors (HDACi) can promote heme synthesis in red blood cells, and the combination of the two has a synergistic anti-tumor effect. The combination of drugs can effectively reduce the activity of Huh-7, Hep3B, HCT116, A549 and PANC-1 cells. ART consumes free heme, weakens the negative feedback inhibition of ALAS1, promotes the expression of ALAS1 protein, and enhances the sensitivity of tumor cells to ART [41].

Wu et al. [42] showed that ART could promote the sensitivity of liver cancer cells to sorafenib. The combination of ART and sorafenib can inhibit tumor growth, and sorafenib can reduce the expression of p-RAF1 and P-ERK1/2 in RAF/MAPK pathway, but has no effect on PI3K/AKT/mTOR pathway. However, ART can inhibit the expression of p-AKT and p-mTOR in PI3K/AKT/mTOR pathway, but has no inhibitory effect on RAF/MAPK pathway. The combination of ART and ART can significantly reduce the expression of p-mTOR and p-ERK and promote the expression of c-PARP and p-PARP, thus promoting the apoptosis of liver cancer cells.

3.4. Others

Both oxaliplatin and ART have certain inhibitory effects on tumor. Studies have shown that their complex OPA can directly inhibit the proliferation of human colon cancer cells and inhibit the immunomodulatory activity of macrophage TREM2 in vivo. OPA prevents tumor growth in vivo by reducing the number of CD206 and CX+3 CR1 immunosuppressive macrophages; It also promotes the increase and infiltration of immunostimulated dendritic cells, cytotoxic T cells, and natural killer cells, and inhibits tumors by shaping the immunosuppressive microenvironment [43].

4. Summary and Prospect

Cancer has become the most important disease burden in the world. Currently, drug therapy is the main treatment for cancer, but the single use of chemotherapy drugs has great harm to human body, more adverse reactions and easy to produce drug resistance. In recent years, drug combination has become a research hotspot because of its advantages of synergistic effect, reducing effective dose and adverse reactions. ART has anti-tumor activity, and its toxic side effects are small, few adverse reactions, can be used as a combination of drug choice. Many studies have shown that ART can be used in combination with common anti-tumor drugs such as alkane, anti-tumor antibiotics, and anti-metabolic drugs to significantly enhance their anti-tumor activity, reverse drug resistance, reduce toxic side effects, and provide a new treatment plan for tumor patients. However, most of the studies on ART combined drug use are in the basic experimental stage, and the clinical studies are relatively few. Its safe dosage and whether it has toxic and side effects need to be further explored. At the same time, due to the complex tumorigenesis mechanism, involving multiple factors and signaling pathways, the anti-tumor mechanism of ART has not been fully defined. In addition, due to the different types of tumors, the administration methods are also different, and whether the anti-tumor effects of ART under different administration routes are significantly different. Therefore, the anti-tumor mechanism of ART combined drug use needs to be further studied, and clinical research should be strengthened at the same time to lay a foundation for the clinical application of combined therapy with anti-tumor drugs.

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