A review of research progress of antitumor drugs based on tubulin targets

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Abstract: Microtubules exist in all eukaryotic cells and are one of the critical components that make up the cytoskeleton. Microtubules play a crucial role in supporting cell morphology, cell division, and material transport. Tubulin modulators can promote microtubule polymerization or cause microtubule depolymerization. The modulators interfere with the mitosis of cells and inhibit cell proliferation. Tubulin mainly has three binding domains, namely, paclitaxel, vinca and colchicine binding domains, which are the best targets for the development of anticancer drugs. Currently, drugs for tumor therapy have been developed for these three domains. However, due to its narrow therapeutic window, poor selectivity, and susceptibility to drug resistance, it has severely limited clinical applications. The method of combined medication, the change of administration method, the modification of compound structure, and the research and development of new targets have all changed the side effects of tubulin drugs to a certain extent. In this review, we briefly introduce a basic overview of tubulin and the main mechanism of anti-tumor. Secondly, we focus on the application of drugs which developed based on the three domains of tubulin to various cancers in various fields. Finally, we further provide the development progress of tubulin inhibitors currently in clinical trials.

Keywords: Tubulin; inhibitor; modulator; clinical trials

Tubulin

Composition

Microtubules, which are mainly composed of α- and β-tubulin, are highly conserved and ubiquitous in eukaryotic cells (1). α- and β-tubulin consist of 450 amino acids, and both have a 40% amino acid sequence homology, which makes their three-dimensional structures similar. Microtubules all have a hollow tubular structure that consists of a positive end and a negative end (2). The positive end provides a faster growth speed and a slower dissociation speed; meanwhile, the negative end provides a slower growth speed and a faster dissociation speed. The negative end is usually fixed, while the positive end enters the surrounding cytoplasm by adding subunits that bind to guanosine-5'-triphosphate (GTP) (3). Besides the major α- and β-tubulins, seven tubulins have been identified in eukaryotes, namely α-, β-, γ-, δ-, ε-, ζ-, and η –tubulin (3,4). γ-tubulin exists mainly around centrioles, promoting nucleation of intracellular microtubules, and controlling the replication process of the mitotic spindles (5). ε- and δ-tubulin, as newly discovered members of the centrosome tubulin superfamily, maintain the microtubule cytoskeleton structure (6).

Dynamics

The microtubules in the cell can be rapidly aggregated and

deaggregated. This characteristic is known as the dynamic or dynamic instability of the microtubules, and mainly occurs on the ends of the microtubules (7). Therefore, this dynamic instability refers to the depolymerization and growth changes of the microtubule ends. The dynamics and the specific functions of microtubules are regulated primarily by microtubule-binding proteins, tubulin post-translational modifications, and tubulin subtypes (8,9). Among them are microtubule polymerase, microtubule depolymerase, acetylation, tyrosination/detyrosination, depolymerized proteins, and microtubule splicing proteins (10,11). GTP hydrolysis is an energy source that regulates the dynamic instability of microtubules. When tubulin is added to the end of the microtubule, the tubulin-bound GTP is hydrolyzed into tubulin-GDP and inorganic phosphate Pi (12). The Pi is then dissociated from the microtubules, leaving a microtubule core composed of GDP and microtubules (13). Microtubule ends that contain the tubulin-binding GTP or GDP-Pi are stable for depolymerization. At the same time, the release of tubulin-GDP and inorganic phosphate Pi induces the change in conformation of the tubulin molecules, allowing for the creation of the microtubule polymer. The polymer created by this is unstable, which causes the microtubules to be damaged or shortened (14). The conformational changes of microtubule ends that are driven by GTP hydrolysis provide an ideal structure for various microtubule-binding proteins to precisely regulate the dynamic instability of the microtubules (12).

Mechanism of action

When the cell is in the pre-division phase, the microtubules present in the cytoplasm and depolymerize to form tubulin and enter the nuclear region of the cell to polymerize into a spindle (15). The spindle can then pull the chromosome to the two poles of the two daughter cells during mitosis, completing cell proliferation. Tubulin regulators can affect the dynamic properties of microtubules, promote the polymerization of microtubules, or cause the depolymerization of microtubules, interfering with the mitosis of the cells and inhibiting cell proliferation (16). It is because of these dynamic characteristics of disintegration and aggregation in microtubules that eukaryotic cells can complete mitosis. Disrupting the dynamic circulation of microtubules will affect the mitotic process of tumor cells, inhibiting the growth of tumor cells or inducing their apoptosis (17). Therefore, microtubules have become

important targets for anticancer drugs.

Tubulin modulators

Various tubulin inhibitor drugs use dynamic properties of microtubules. The colchicine compounds and various compounds acting on the colchicine-binding site and the vinblastine compounds and various compounds acting on the vinblastine-binding site can be reversely combined with tubulin to form a complex (18,19). The formed complex hinders the polymerization of other tubulins and inhibits the formation of microtubules. At the same time, microtubule polymerization inhibitors can also inhibit the formation of spindles by inducing the depolymerization of microtubules, arrest cells in the M phase, and eventually induce apoptosis. For example, compounds such as paclitaxel, epothilone, and laulimalide all promote microtubule polymerization, inhibit cell division, stop cell division in the mitotic phase (G2/M phase), and eventually cause tumor cell death by apoptosis (20).

Paclitaxel binding domain

Paclitaxel

Paclitaxel was the first member of the taxane family to be used for cancer chemotherapy (21). Paclitaxel has been widely accepted as a chemotherapeutic agent in patients with cancer and various other kinds of solid tumors. However, paclitaxel has obvious toxicity. For example, it can cause bone marrow suppression and peripheral neuropathy (22). However, in a first-line study of non-small cell lung (NSCLC), nab-paclitaxel combined with carboplatin was used, and the results showed that the combination could reduce cytotoxicity (23).

The development of nanoparticle-bound albumin paclitaxel can reduce the combination of paclitaxel and the solvent, reducing the related toxicity from the mode of administration. The incorporation of d-α-Tocopheryl polyethylene glycol (TPGS) into nanocarriers from TPGS-nanoparticles can further promote the delivery of multidrug resistance (MDR) and improve cancer treatment by changing its inherent physical and chemical properties (24). In addition to the combination of PTX and DOX, a co-encapsulated nano-drug delivery system is also used and has the potential to resolve multidrug resistance caused by a single drug without significantly affecting normal cells and tissues (25). For example, paclitaxel and gemcitabine are used in combination and administered by preparing liposomes (26). These methods provide greater flexibility for paclitaxel treatment.

Docetaxel

Docetaxel has the same effect as paclitaxel. It is an M-phase cycle-specific drug that promotes the assembly and stabilization of microtubules, preventing their disaggregation (27). However, docetaxel can cause side effects such as bone marrow suppression and allergic reactions.

In recent years, immunotherapy has shown great practical value in tumor treatment. The combination of docetaxel and PD-L1 antibodies through nanotechnology can improve the therapeutic effects and reduce systemic toxicity. Nanomedicine is a solution with great potential that can eliminate the above disadvantages and facilitate drug delivery through proper biodistribution (28).

Docetaxel therapy is the first treatment to show survival rate benefits in patients with castration-resistant prostate cancer (CRPC) (29). In prostate cancer the combination of histone deacetylase inhibitors (HDACIs) and docetaxel can synergistically inhibit the growth of cancer cells (30). The combination of gemcitabine and docetaxel has also been shown to be effective against various types of solid tumors, including sarcomas (31). Many studies have found that docetaxel promotes nuclear translocation of the transcription factor EB (TFEB) and increases its transcriptional activity. TFEB is a key nuclear transcription factor that controls lysosomal biogenesis and functions. These findings provide new insights into the regulatory mechanisms of docetaxel on lysosomes and may help to develop new potential cancer therapeutics through lysosomal inhibition (32).

Epothilones

Epothilone is a newly developed antitumor drug. Epothilone has many analogs, such as epothilone B, epothilone D, ixabepilone, sagopilone, 21-amino epothilone B, and KOS-1584 (33). Epothilones are effective in cells due to their ability to bind equally to b-tubulins I and III, giving them an advantage over taxanes (34). However, the dose-limiting toxicity of epothilone is usually accompanied by neurotoxicity and neutropenia. Ebomycin has been studied in cancer treatment and has appeared in more than 20 different studies. It has been shown to have significant activity in breast, lung, and prostate cancer and good efficacy in hormone-refractory metastatic prostate cancer and taxane-refractory ovarian cancer (35). Epothilone and its analogs will continue to play a crucial role in the future of cancer therapy (36).

Vinblastine binding domain

Vinflunine

Vinflunine belongs to the vinca alkaloids, and works by disrupting microtubule dynamics in the cell cycle. It has been approved in Europe as a second-line treatment for advanced urothelial advanced transitional cell carcinoma (TCCU). The long-term use of vinflunine can cause toxic accumulation, anemia, and neutropenia. Studies have found that in patients with advanced urothelial cancer Changchun Fluinin combined with other drugs is the best treatment option (37). Currently the most common choices for first-line chemotherapy with advanced urothelial cancer are vinflunine-gemcitabine and vinflunine-carboplatin (38). Furthermore, in patients with colon cancer, the combination of oxaliplatin and vinblastine can induce cytogenetic damage and inhibit survivin expression (39).

Vincristine

Vincristine, a natural alkaloid, was first obtained from Vinca in 1961 and was approved by the Food and Drug Administration (FDA) for clinical cancer treatment in 1963. Vincristine is highly cytotoxic during treatment (40); in an Omani study, vincristine was shown to cause neuropathy in pediatric patients of acute lymphocytic leukemia, frequent autonomic nerve attacks, and more severe cranial nerve involvement (41). Vincristine-loaded liposomes prepared by ion-pairing technology can enhance their chemical stability (42). Vincristine and β-vincristine-loaded PLGA-b-PEG nanoparticles can promote cell uptake and reduce cytotoxicity (43). Vincristine, when combined with quercetin, can be more effective in treating lymphoma through co-delivery mechanisms via nanocarriers (44).

Vinorelbine

Vinblastine is a semi-synthetic derivative of vinblastine, inhibits the polymerization of tubulin and stops cell division in the middle stage of mitosis, and is a cell cycle-specific drug. Patients receiving vinorelbine are at risk of venous stimulation, and vinorelbine can induce the extravasation of the chemotherapy port, causing infection (45). Bendamustine combined with vinorelbine is an effective treatment for autologous stem cell transplantation before the induction chemotherapy for relapsed or refractory Hodgkin's lymphoma. A study found that vinorelbine,

combined with pertuzumab for the first-line treatment of patients with HER2-positive locally advanced or metastatic breast cancer, also has high safety and effectiveness (46). At present, erlotinib and vinorelbine combined with cisplatin have been used as adjuvant treatment for patients with stage IIIA estimated glomerular filtration rate (EGFR) mutation-positive non-small cell lung cancer (EVAN) (47).

Dolastatin 10

Dolastatin 10 is a highly effective cytotoxic microtubule inhibitor. Natural synthetic analogs of dolastatin 10 have attracted great interest in cancer due to their strong *in vitro* activity and payload capacity for antibody drug conjugates (adc) (48). Studies have found that the 10-terminal thiazole moiety of dolastatin has functional group analogs. These functional groups include amines, alcohols, and thiols, which are representative structures in known conjugated drugs. These new analogs show good titers in tumor cell proliferation assays (49). After conducting a combined drug experiment on colon cancer cells, the combination of largazole and dolastatin 10 can inhibit the growth of HCT116 cancer cells, showing a synergistic effect (50,51).

Colchicine binding domain

Colchicine

Colchicine is a tricyclic alkaloid extracted from the colchicine binding site. It is an anti-inflammatory drug that primarily prevents the activation of inflammatory bodies by blocking the ability of tubulin to polymerize (52). In addition, colchicine interferes with multiple inflammatory pathways; for example, it plays a role in neutrophil adhesion and recruitment, superoxide generation, inflammasome activation, the RhoA/Rho effect kinase (ROCK) pathway, and tumor necrosis factor-alpha (TNF-α). The induction of nuclear factor kappa (NF-κ) pathway was found to reduce inflammation (53), while other research discovered that colchicine can also be used as a primary compound in potential anticancer drugs (54). Liu *et al*. found that colchicine reduced the stability of the cell skeleton in liver cancer cells and significantly reduced the ability of cells to deform. These changes make it helpful for monitoring the potential metastatic cancer cells and improving the diagnosis of cancer (55). Although colchicine works on various diseases, its use may be limited by its side effects and toxicity (52). It is advisable to carefully administer the drug

before prescribing colchicine. Pharmacokinetics should be emphasized to avoid any harmful interactions by looking for alternatives or adjusting the colchicine dose.

Podophyllotoxin

Podophyllotoxin is an effective cytotoxic agent and can be used as a primary compound for the development of antitumor drugs (56). However, its therapeutic efficacy is often limited due to side effects and developed resistance. A peptide-based podophyllotoxin conjugate has been found to have been used in treating multidrug-resistant breast cancer with the highest efficacy and minimal toxicity to solve this (57). Nanostructured lipid carriers carrying podophyllotoxin for skin targeting are also being studied *in vivo* and *in vitro* (58). Earlier studies have found that 4β-1,2,3-triazole derivatives of podophyllotoxin have stronger anticancer activity and better binding on topoisomerase II than etoposide. However, the effects of dimerization on such derivatives in anticancer activity have not been studied well. Other emerging derivatives, such as the new podophyllotoxin derivative 4β-(1,3,4-oxadiazole-2-amino-5-methyl)-4-deoxypodophyllotoxin (OAMDP) has shown to have effective antitumor activity. OAMDP can induce autophagy, cause cell-cycle arrest, and induce apoptosis (59).

Noscapine

Noscapine is a phthalo-isoquinoline alkaloid that can easily cross the blood-brain barrier. It has been used as an antitussive medicine for many years and is highly safe (60). In recent years, noscapine has been reported to be an anticancer drug. Its anticancer effects come from its ability to force the microtubules to spend more time in the paused state, stopping mitosis and later inducing mitotic slip or mitotic mutation apoptosis. Noscapine also inhibits tumor growth by selectively blocking NF-κB, a critical transcription factor in the pathogenesis of glioblastoma, and improving tumor chemotherapy sensitivity (61). Compared with colchicine and podophyllotoxin, its toxicity is low. For example, nosine and it analogs have been shown to have no sign of neurotoxicity or immunosuppression in ovarian cancer studies research. On the other hand, noscapine has been demonstrated to have neuroprotective effects in neurodegenerative disease and stroke mouse models (62). Concerning its anti-tumor effect on human prostate cancer cell lines LNCaP and PC-3, it was found that the joint application of paclitaxel and nicardipine

can increase the percentage of apoptotic cells. These results have provided new ideas for treating prostate cancer (63).

Current clinical research

Plinabulin

Plinabulin (NPI-2358) is an anti-tubulin depolymerized vascular disrupting agent that can bind to the colchicine binding site of β-tubulin (beta-tubulin) to prevent polymerization and inhibit the effects on human tumor cell lines. It has been shown to have excellent safety in clinical trials and has yielded positive biological effects including the reduction of tumor blood flow, tumor pain, and other mechanical-related adverse events (64).

Small molecule vascular disrupting agent (VDA)

Combretastatin is a naturally occurring small allylbenzene stimulant. By binding to tubulin, it can promote microtubule depolymerization and inhibit tubulin polymerization (65). At present, different VDA have been successfully prepared, many of which have entered testing in clinical trials. The drugs that have entered the trials include: CA-4P, CA-1P, AVE8062, OXi4503, CKD-516, BNC105P, ABT-751, ZD6126, NPI-2358, MN-029, and EPC240758 (66). However, due to poor water solubility, low bioavailability, a fast metabolism rate, and systemic elimination of combretastatin A4 (CA-4), its clinical applications are limited. In a phase I study, ombrabulin (AVE8062) was used in combination with two standard taxane/platinum dual mixtures, and it was found to be feasible and with controlled overlapping toxicity. Nevertheless, it affected the efficacy of these duplexes (67).

CKD-516 is a newly developed blood vessel destroying agent. Its maximum tolerated dose (MTD), safety, pharmacokinetics, and preliminary antitumor efficacy for patients with advanced solid tumors have been determined in clinical phase I dose-escalation studies (68). ABT-751 is an oral bioavailable sulfonamide with antimitotic properties (69). Tivantinib, also known as ARQ-197, is a potent and non-ATP competitive and selective c-Met inhibitor currently under evaluation in phase 3 clinical trials for the use of liver cancer and lung cancer treatment. Preclinical studies have shown that CA-1 diphosphate (Oxi-4503) has good safety and effectiveness in clinical trials, while also being more effective than other vascular disrupting agents (70).

Inhibitor of c-MET

c-interstitial-epithelial transformation factor (c-MET) is involved in the occurrence of various tumors. Currently, many MET inhibitors have entered clinical trials, including carbotinib (XL184, BMS-907351), crizotinib (PF-02341066), MK-2461 in pancreatic cancer, Merestinib (LY2801653), Tivantinib (ARQ197), onartuzumab (MetMab), Emibetuzumab (LY2875358), rilotumumab (AMG 102), and NK4 (71).

ARQ-197 (tivantinib) is a small molecule c-Met inhibitor and has shown encouraging results in phase I and II trials; however, the most recent studies have found that tivantinib performed poorly in liver cancer and METIV-HCC III (72). Onartuzumab is a monoclonal antibody that targets the MET receptor and prevents hepatocyte growth factor (HGF) signaling. In clinical phase 3 non-small cell lung cancer trial, onartuzumab plus erlotinib did not improve clinical outcomes, with shorter OS in the onartuzumab arm, compared with erlotinib in patients with MET-positive non-small-cell lung cancer (67).

Conclusion

Microtubules are one of the crucial components that make up the cytoskeleton and exist in almost all eukaryotic cells (68). Microtubules play an essential role in all stages of cell physiological activity, including the maintenance of cell morphology, migration, mitosis, transport of intracellular materials, and signal transduction (69). Extensive research has been conducted over the past years, resulting in many highly effective tubulin modulators that function as microtubule stabilizers or microtubule destabilizers. Antitubulin agents of natural origin have three binding sites: targeted paclitaxel, vinca and, the colchicine binding domains (70). However, due to poor solubility or toxicity, many of these drugs have been restricted. Therefore, new tubulin drugs are being actively developed. In the past few years, some small molecule tubulin inhibitors and biological agents have entered clinical trials. For example, in a phase 1/2 clinical trial, rilotumab and erlotinib were used in combination to treat patients with non-small cell lung cancer (73). With a deepening understanding of tubulin, the mechanisms for treating tumors by tubulin have become increasingly clearer, and this understanding may serve as a solid foundation for the development of new drugs.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-682). The authors have no conflicts of interest to declare.

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