



MiniReview

Liposomal Paclitaxel and Albumin-bound Paclitaxel (Nanovehicle Agents) for Gastric Cancer

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Abstract

Gastric cancer has the third-highest cancer-related mortality rate. Paclitaxel is a microtubule stabilizer whose systemic chemotherapy regimen is widely used in clinical practice due to its major role in the chemotherapy of advanced gastric cancer. Nanovehicles are various nanoparticles with dissolved or dispersed drugs that are currently used clinically, such as nanoparticles, liposomes, and polymeric micelles. The common nanovehicle paclitaxel formulations, such as liposomal paclitaxel and albumin-bound paclitaxel, are remarkably effective in improving biocompatibility, reducing allergic reactions, and targeting and localizing drug release. Numerous studies have indicated better anticancer activity and tolerable toxicity of nanocarrier paclitaxel compared with solvent-based paclitaxel in gastric cancer, which constitutes a trendy direction in gastric cancer treatment research. This article reviews the preparation and clinical application of paclitaxel delivery by nanovehicles in gastric cancer to provide a reference for chemotherapy in patients with advanced gastric cancer.

Keywords: gastric cancer, paclitaxel, nanovehicle, liposome, albumin

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1 INTRODUCTION

Gastric cancer is one of the common malignant tumors that kill about 300,000 people worldwide each year^[1]. In 2018, about 1 million new cases were diagnosed worldwide, ranking fifth in global malignancies and third in mortality^[2]. The development of gastric cancer is a multi-step and multi-factorial progressive process, including environmental and dietary factors, Helicobacter

pylori infection, genetic factors, precancerous lesions, etc^[3]. Early symptoms of gastric cancer are mainly epigastric pain, which is aggravated after eating, with pain patterns mostly similar to those elicited by peptic ulcers. Due to the atypical early symptoms of gastric cancer, patients are mostly in the advanced stage at the time of diagnosis, which poses a challenge for treatment^[4]. Early gastric cancer given endoscopic surgery results in 5-year

survival of over 90%, and for advanced gastric cancer (inoperable or metastatic), chemotherapy combined with optimal supportive therapy are also associated with benefits in terms of both survival time and quality of life^[5], but its 5-year survival is still less than 30%. Therefore, new strategies are urgently needed in the treatment of patients with advanced gastric cancer to prolong survival and improve their quality of life.

Paclitaxel is a diterpene alkaloid with anticancer activity, which dysregulates the balance of microtubulin and microtubulin dimer, induces microtubulin polymerization, microtubule assembly, and prevents depolymerization, thereby increasing microtubule stability, inhibiting mitosis, and inducing apoptosis in cancer cells^[6]. Paclitaxel effectively blocks the proliferation of cancer cells and is one of the most promising cytotoxic drugs for clinical applications. It is a first-line chemotherapeutic agent for patients with advanced gastric cancer with wide consensus on its effectiveness^[7]. Nevertheless, because it is difficult to dissolve in water, it needs to be dissolved in polyoxyethylene castor oil (cremophor EL) and absolute ethanol mixed solvent to increase water solubility, and cremophor EL releases histamine when degraded in vivo, resulting in different degrees of allergic reactions, and can also cause the release of granules in nerve cells and demyelinating changes and aggravate the peripheral neurotoxicity of paclitaxel^[8].

In order to reduce toxicity and improve its efficacy, new dosage forms of paclitaxel have been developed clinically in recent years. Especially, the rise of nanotechnology has brought new hope for cancer treatment. The use of nanotechnology to build a drug delivery system can effectively improve the solubility, stability, tumor targeting of drugs, and reduce their toxic side effects. In cancer treatment, some nanomaterials can easily cross many biological barriers as carriers^[9]. Chemoimmunotherapy combination therapy provides benefits such as synergistic therapeutic mechanisms, reduced drug doses, and enhanced therapeutic effects. Nanovehicles can enhance drug solubility, prolong drug circulation time, reduce systemic toxicity, and deliver drugs targeted to tumor sites^[10]. Paclitaxel delivery by nanovehicles is used in the delivery of chemoimmunotherapeutic agents due to its improved drug pharmacokinetic properties, tumor-targeted delivery capabilities, and responsive targeted drug release from the tumor microenvironment, which contributes to a superior synergistic antitumor effect and shows a potential clinical application in chemoimmunotherapy combination therapy. In addition, the unique structure and function of nanocarrier paclitaxel formulations exhibit immunomodulatory properties^[11]. In clinical applications, paclitaxel liposomes and albumin-bound paclitaxel (nab-paclitaxel) are commonly used

nanovehicle agents, and the current status of their research and clinical applications in gastric cancer are reviewed as follows.

2 PACLITAXEL LIPOSOMES

With the merits of high encapsulation rates, good targeting, and low toxicity, liposomes have been widely studied as carriers for combined chemoimmunotherapy. Hydrophilic therapeutic agents can be encapsulated within liposomes, hydrophobic therapeutic agents can be encapsulated in lipid bilayers, and therapeutic agents can also be loaded within liposomes or on the surface of liposomes through charge interactions with lipids or chemical linkage with lipid molecules^[12]. The paclitaxel liposomes encapsulate the water-insoluble paclitaxel in the liposomal bilayer, eliminating the use of polyoxyethylene-substituted castor oil mixed with anhydrous ethanol as a solubilizer that is prone to serious allergic reactions, which improves the safety of clinical use of paclitaxel and reduces adverse reactions while maintaining the unique efficacy of paclitaxel^[13]. The drug encapsulated in liposomes is not metabolized and inactivated in the plasma, decreasing the volume of drug distribution and reducing drug accumulation in normal tissues^[14]. Phospholipids and cholesterol are key components of liposome preparation, and liposomes improve product performance by increasing the solubility of ingredients, improving their bioavailability, enhancing intracellular uptake, and altering pharmacokinetics^[15]. Based on liposome delivery systems, paclitaxel liposomes can enhance the therapeutic efficacy of anticancer drugs by increasing the exposure of tumor cells to the drug and reducing the damage to normal tissues, using the phenomenon of the enhanced permeability and retention effects or the principle of targeting^[16]. Paclitaxel liposomes feature unparalleled merits, including the ability to carry hydrophobic payloads, ease of synthesis, good manufacturing control, and excellent biocompatibility, and have antitumor efficacy comparable to that of conventional paclitaxel^[17]. In addition, allergic reactions are important adverse events in paclitaxel drug therapy and can lead to death in severe cases. Studies have revealed a high incidence of allergic reactions of 8-14% during paclitaxel-based chemotherapy. However, drug-related allergic reactions are low in paclitaxel liposome applications^[18].

Paclitaxel liposomes include targeted liposomes, environmentally responsive liposomes, dual drug carriers, and flexible liposomes. Targeted paclitaxel liposomes are most commonly used in clinical settings to promote cellular uptake of drugs, selectively accumulate in mitochondria, cause a release of cytochrome C, and activate pro-apoptotic proteins by targeting delivery to trigger a waterfall reaction of cystathionin 9 and cystathionin 3, which inhibits the activity of anti-

apoptotic B lymphocytoma-2 protein and therefore enhances apoptosis by acting on the mitochondrial pathway^[19].

Han et al.^[20] found that paclitaxel liposomes showed no significant improvement in clinical efficacy in the first-line treatment of patients with progressive gastric cancer, but significantly reduced adverse reactions during treatment. Lu et al.^[21] observed the clinical efficacy and adverse effects of paclitaxel liposome combined with capecitabine in the treatment of 34 cases of advanced gastric cancer, and the results showed that paclitaxel liposome plus capecitabine was better tolerated in clinical application and was an optimal regimen for the first-line treatment of advanced gastric cancer, which merits further promotion. Hong et al.^[22] investigated the clinical efficiency of paclitaxel liposomes combined with capecitabine in the treatment of gastric cancer and the effect on patients' multiple tumor marker protein chip levels, and the results showed that paclitaxel liposomes plus capecitabine significantly reduced patients' multiple tumor marker protein levels, improved quality of life, and reduced local recurrence rate, distal metastasis rate, and mortality. In addition, to prevent possible allergic reactions to paclitaxel, pretreatment consisting of intravenous dexamethasone 5-10mg, intramuscular diphenhydramine 50mg, and intravenous cimetidine 300mg was given 30min before paclitaxel liposome treatment^[23].

The application of paclitaxel liposomes in gastric cancer is more established, with tumor and lymph node targeting, and the concentration in lymph nodes is 200% higher than that of ordinary paclitaxel injection, which is considered more effective for patients with gastric cancer with abdominal or peritoneal lymph node metastasis.

3 NAB-PACLITAXEL

Nab-paclitaxel refers to the use of nanotechnology such as ultrasound and high-pressure homogenization, where albumin acts as a nanovehicle to carry paclitaxel. It enhances the drug delivery and bioavailability of paclitaxel with the help of natural albumin^[24]. Nab-paclitaxel enables albumin to carry paclitaxel out of circulation more rapidly, cross endothelial cells through receptor-mediated cytotocytosis, and concentrate more in tumor tissue through high tumor permeability and retention effects, consistently exhibiting pharmacokinetic benefits^[25]. Albumin in nab-paclitaxel binds to acidic cysteine-rich protein receptors highly expressed by tumor cells, resulting in higher concentrations of paclitaxel in tumor tissue^[26]. Compared with solvent-based paclitaxel (sb-paclitaxel), nab-paclitaxel has the following advantages: (1) it provides higher paclitaxel concentrations in a shorter period of time (30min vs. 3h for sb-paclitaxel); (2) it obviates the requirements for

hormonal pretreatment, eliminates the need for dosing to prevent allergic reactions, and is considered the drug of choice in combination immunization regimens; (3) it enhances the transport of paclitaxel across endothelial cells as well as enables greater delivery of paclitaxel to tumors; (4) It uses endogenous albumin transport pathways, including receptor-mediated cytotocytosis, to cross the endothelial cell monolayer into the tumor^[27].

Nab-paclitaxel may provide more survival benefits in gastric cancer peritoneal metastases. Intraperitoneal paclitaxel chemotherapy has been proven effective for peritoneal metastases^[28]. Kinoshita compared the difference in efficacy between different approaches of administration of nab-paclitaxel and sb-paclitaxel, and the results demonstrated that at the same dose, the application of nab-paclitaxel treatment resulted in a significant reduction in subcutaneous tumor size, ascites weight, and peritoneal load compared with sb-paclitaxel. The antitumor effect of nab-paclitaxel after intravenous administration is comparable to that after intraperitoneal administration in terms of administration approaches. Intravenous nab-paclitaxel is a new option for peritoneal dissemination targeted therapy for gastric cancer^[29]. *In vitro* studies confirmed that nab-paclitaxel increased mitotic spindle-associated phosphoproteins, independent of baseline levels of phosphotaxin, while inducing mitotic cell death by increasing the expression of cleaved-PARP and caspase-3. After two weeks of albumin-conjugated paclitaxel, oxaliplatin, or epoetin treatment, the mean *in vivo* local tumor growth inhibition rates were 77, 17.2, and 21.4%, respectively^[30].

Nab-paclitaxel enhances trastuzumab efficacy in human epidermal growth factor receptor 2 (HER2) positive gastric cancer patients. In HER2-positive gastric cancer NCI-N87 cells, the bacterial semi-inhibitory concentrations in paclitaxel, nab-paclitaxel, and trastuzumab / nab-paclitaxel were 0.24 ± 0.08 , 0.13 ± 0.03 , and 0.048 ± 0.01 , respectively, and trastuzumab / nab-paclitaxel induced higher apoptosis rates and significant G2/M blockade^[31]. In tumor-bearing mice, trastuzumab / nab-paclitaxel treatment for 4 weeks resulted in significantly smaller tumor volumes than paclitaxel and nab-paclitaxel. Trastuzumab / nab-paclitaxel mediates targeted therapy and enhances antitumor efficacy, and is, therefore, considered a potential novel therapeutic agent for HER2-positive gastric cancer^[32]. Bando et al.^[33] evaluated the efficacy and safety of nab-paclitaxel adjuvant therapy as first-line chemotherapy for advanced gastric cancer, with median progression-free survival and overall survival of 9.63 and 14.60 months, respectively, the objective remission rate of 58.9% and disease control rate of 87.7%, confirming the similarity of nab-paclitaxel with sb-paclitaxel in overall survival. Sb-paclitaxel is available as one of the standard second-line chemotherapy

Table 1. Studies Related to Nab-paclitaxel in Gastric Cancer

Authors	Stage	Intervention Drugs	Disease Type
Sasaki et al. ^[35]	Phase II	Nab-ptx 260mg/m ²	Unresectable / metastatic or recurrent GC
Bando et al. ^[33]	Phase II	Nab-ptx 100mg/m ²	Unresectable / metastatic or recurrent GC
Katsaounis et al. ^[36]	Phase II	Nab-ptx 150mg/m ²	Unresectable / metastatic or recurrent GC
Sato et al. ^[37]	Phase II	Nab-ptx 180mg/m ²	Unresectable / metastatic or recurrent GC
Watson et al. ^[38]	Phase II	Nab-ptx 150mg/m ² plus FOLFOX4	Resectable GC, HER2-
Shitara et al. ^[32]	Phase III	Nab-ptx 260mg/m ²	Unresectable / metastatic or recurrent GC

Notes: Nab-ptx, nab-paclitaxel; GC, gastric cancer; FOLFOX4, 5-fluorouracil, leucovorin, and oxaliplatin

regimens for advanced gastric cancer. Takashima et al.^[34] studied the efficacy and safety of nab-paclitaxel compared with sb-paclitaxel in the second-line treatment of patients with advanced gastric cancer and showed that nab-paclitaxel was indistinguishable from sb-paclitaxel (HR=0.97, 95% CI = 0.76 to 1.23). Concurrently, studies have suggested that nab-paclitaxel plus tegafur and / or oxaliplatin regimens are more effective and tolerable in terms of adverse events, suggesting that nab-paclitaxel may provide an alternative third-line treatment option for patients with advanced gastric cancer.

Nab-paclitaxel exhibits a non-inferior overall survival to sb-paclitaxel in the treatment of patients with different stages of gastric cancer and has a better safety profile (Table 1).

4 OTHER PACLITAXEL NANOVEHICLES

Other paclitaxel nanovehicles include paclitaxel micelles and paclitaxel nanocrystals. Paclitaxel micelles consist of a central hydrophobic core and a hydrophilic shell, and polymeric micelles with hydrophilic properties prolong circulation by avoiding uptake by the reticuloendothelial system^[39]. Paclitaxel was self-assembled and loaded using functionalized polyethylene glycol-poly(lactic acid) to form nanomicelles with a particle size of 20nm and showed significantly increased cytotoxicity due to enhanced accumulation in gastric cancer cells. Folic acid-modified phospholipid-encapsulated paclitaxel nanocrystals are a novel nanoformulation with high drug content, good stability, and tumor cell targeting properties using paclitaxel as a model drug and nanocrystals as a formulation form^[40]. The injectable volume in and adjacent to gastric cancer lesions is restricted, and the high drug content characteristics of nanocrystals meet the requirements for drug content of the formulation for peritumoral injection in gastric cancer. Gastric cancer cells mostly highly express folic acid receptors, and folic acid modification facilitates improved uptake of nanocrystals by tumor cells. Research in animal models of gastric cancer has indicated that folic acid-modified phospholipid-encapsulated paclitaxel nanocrystals exhibit good tumor-shrinking effects in

association with their ability to persist in the injected local area, compared to sb-paclitaxel which is more readily absorbed into the bloodstream via the local circulation^[41].

In spite of the effectiveness of paclitaxel micelles and paclitaxel nanocrystals in gastric cancer confirmed by cellular experiments and animal experiments, their efficacy remains unidentified.

5 CONCLUSION

With the continuous expansion of nanotechnology in the field of pharmacology, paclitaxel delivery by nanovehicles has become one of the most favored anticancer drugs for the treatment of solid tumors in clinical practice, with proven efficacy in various solid tumors and its expanding application in gastric cancer^[42]. This article reviews the mechanism of action and the application of liposomal paclitaxel, nab-paclitaxel, and other types of paclitaxel nanovehicles in gastric cancer for their clinical application. Paclitaxel delivery by nanovehicles offers benefits such as enhanced drug bioavailability and reduced toxic reactions in gastric cancer, with wide clinical promise, but there are still many pressing issues to be addressed. Concurrently, no uniform clinical criteria for the selection of paclitaxel nanovehicles have been established, and more evidence-based medical references are required from large samples with long follow-up randomized controlled studies.

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Conflicts of Interest

The authors declared no conflict of interest.

Author Contribution

Liu M was responsible for writing, and original-draft. Gao N was responsible for reviewing. Wang X was responsible for supervision. All authors contributed to the manuscript and approved the final version.

Abbreviation List

HER2, Human epidermal growth factor receptor 2

Nab-paclitaxel, Albumin-bound paclitaxel
Sb-paclitaxel, Solvent-based paclitaxel

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