Consensus on the Pharmaceutical Care for Anti-Tumor Drugs Taxanes (2022)

Working Group on the Development of Chinese Expert Consensus on the Pharmaceutical Care for Anti-Tumor Drugs Taxanes

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Catalog

1 Background

Due to their remarkable biological activity and unique mechanism of action, antitumor drugs taxanes are widely used in the treatment of various malignant tumors such as lung, breast, ovarian and head and neck cancers, and play an irreplaceable role in tumor drug therapy. Since the discovery of Paclitaxel in 1963 and the determination of its chemical structure in 1971, paclitaxel synthesis methods and formulation processes have been continuously updated and improved in order to overcome the problems of low yield and difficulties in drug formulation. The differences in the structure and formulation of antitumor drugs taxanes have led to different pharmacokinetics, pharmacodynamics and toxicological characteristics of different drugs, resulting in many discrepancies in the workings of drug configuration, clinical use and pharmaceutical care. With the increase in dosage forms, rational use of antineoplastic drugs taxanes has received more and more clinical attention. At present, there are no guidance documents for pharmaceutical care of antitumor drugs taxanes at home and abroad, and there is a lack of pharmaceutical care pathways or norms for antitumor drugs taxanes based on multi-link and multidisciplinary evidence-based support. Therefore, experts from the Cancer Pharmacists Branch of Chinese Pharmacists Association, together with multidisciplinary experts from around China and under the guidance of the National Cancer Center reached the *Chinese Expert Consensus on the Pharmaceutical Care for Anti-Tumor Drugs Taxanes* to promote the rational use of antitumor drugs taxanes and provide reference and reference for pharmacists to carry out pharmaceutical service of this type of drugs.

2 Purpose of Consensus Development

To provide a basis for decision making and implementation of pharmaceutical services for antitumor drugs taxanes in China, and to guide the clinical practice of pharmacists related to the field of clinical diagnosis and treatment of cancer.

3 Drugs included in the Consensus

The antitumor drugs taxanes included in this consensus include: Paclitaxel Injection, Paclitaxel Liposome for Injection, Paclitaxel for Injection (Albumin Bound), Paclitaxel Polymeric Micelles for Injection and Docetaxel Injection.

4 Scope of Consensus

This consensus applies to pharmacists working with antineoplastic drugs taxanes in all medical institutions and pharmacies.

5 Process and Methodology of Consensus Development

5.1 Methodology of Consensus Development

The writing and development process of this consensus was referred to the WHO Guideline Development Manual published in 2015. The expert consensus recommendations were formed using the Delphi method, i.e., after identifying consulting experts according to the expert selection criteria, expert opinions were collected in a structured manner, and the Kendall harmonization

coefficients and significance were statistically calculated to form conclusions with high consistency and reliability, thus determining the expert consensus recommendations.

5.2 Consensus Registration

This consensus has been registered on the International Practice Guidelines Registry Platform (http://guidelines-registry.cn/) (registration number IPGRP2022CN151).

5.3 Consensus Working Group

This Consensus Working Group consists of consensus guiding experts, compiling experts, external review experts, executive authors and secretarial team. The consensus working group covers experts in different fields such as pharmacy, medicine, nursing, and methodology.

6 Related terminology (see Appendix I for details)

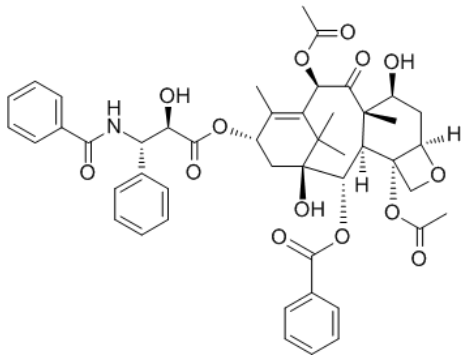
7 Glossary of terms (see Appendix II for details)

8 Taxanes and the properties of the different preparations

8.1 Chemical structures

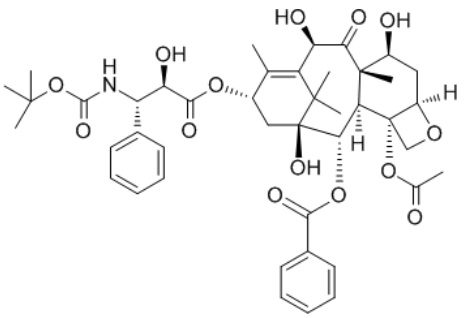
The antitumor drugs of the taxanes class are divided into two categories: paclitaxel and docetaxel; paclitaxel is diterpenes alkaloids with the chemical name of 5β,20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate-2- benzoate 13-(2R,3S)-N-benzoyl-3-phenylisoserine ester, and its structural formula is shown in Figure 1.

Docetaxel is a derivative of paclitaxel, which is formed by the substitution of acetoxy group on C10 of the parent nucleus of paclitaxel by a hydroxyl group and the substitution of benzoyl group on N of C13 side chain by tert-butoxycarbonyl group. The chemical name is [2aR-(2aα,4β,4aβ,6β,9α,(αR′,βS′),11α,12,2aα,12bα)]-β-[[(1,1- dimethylethoxy)carbonyl]amino]-α-carbonyl benzenepropanoic acid [12b-acetoxy-12- benzoyloxy-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,6,11-trihydroxy 4a,8,13,13-tetramethyl-5-oxo-7,11-methylene-1H-cyclodecapentaeno[3,4]benzo[1,2-b]oxetan-9-yl] ester, whose structural formula is shown in Figure 2.



Molecular formula: $C_{47}H_{51}NO_{14}$ Molecular weight: 853.9

Figure 1 Chemical structure formula of paclitaxel



Molecular formula: $C_{43}H_{53}NO_{14}$ Molecular weight: 807.88

Figure 2 Chemical structure formula of docetaxel

8.2 Pharmacological Effects

The active component of paclitaxel injection, paclitaxel liposome for injection, paclitaxel for injection (albumin bound) and paclitaxel polymeric micelles for injection are all paclitaxel, whose anti-tumor mechanism of action is to stabilize the microtubule system by promoting the aggregation of microtubule protein dimers and inhibiting microtubule depolymerization, thereby inhibiting the normal dynamic reorganization of the microtubule network, which is essential for cell function during interphase and mitosis. At the same time, paclitaxel can cause abnormal arrangement of microtubule bundles throughout the cell cycle and cell mitosis to produce multiple stellate bodies, affecting tumor cell division.

Docetaxel Injection significantly reduces the number of free tubules by promoting the polymerization of

tubules into stable microtubules and inhibiting their depolymerization, and its binding to microtubules does not change the number of protofilaments.

8.3 General information and pharmaceutical characteristics of different preparations of taxanes

Related information is detailed in Tab 1.

Tab 1 General information and pharmaceutical characteristics of different preparations of taxanes

Generic name of drug	Characteristic	Accessories	Formulation characteristics	Grain size	Drug-time curve characteristics	Plasma protein binding rate	Half-life and clearance	Excretion
Paclitaxel Injection	Colorless to slightly yellowish viscous clear liquid	Polyoxyethyl castor oil, ethanol	Paclitaxel is the first generic injectable form to be approved for marketing	Not applicable	Biphasic decline	89%～98%	The average elimination half-life is 3 to 50 h	Mainly excreted through feces (>90%)
Paclitaxel liposome for injection	Off-white or light-yellow lump, slightly fishy smell of lecithin	Lecithin, cholesterol, threonine, glucose	Paclitaxel-embedded preparations in lipid particles	The average particle size is about 0.8 μm	Biphasic decline, three-compartment model	89%～98%	The average elimination half-life is 5.3-17.4 h	Mainly excreted in the feces, only a small amount of prodrug is excreted in the urine
Paclitaxel for injection (albumin-bound)	White to yellow lyophilized lumps or powder	Human Albumin	Nanoparticles made of Paclitaxel and human albumin	The average particle size is about 130 nm	biphasic decline	94%	In the dose range of 80-300 mg/m², the mean overall clearance was 13-30 L/h/m², and the mean terminal phase half-life was 13-27 h.	Fecal excretion of paclitaxel accounts for approximately 20% of the total dose

Paclitaxel polymer Micelles for injection	White to light Yellow lyophilized lumps or powder	Monomethoxy polyethylene glycol 2000 polypropylene cross-ester (53:47) copolymer, anhydrous disodium hydrogen phosphate, sodium dihydrogen phosphate	Polymeric Micelles as Drug carriers for novel nano formulations	18 to 20 nm	biphasic decline	89%～98%	The mean elimination half-life was 16.6 to 19.8 h over the dose range of 175 to 435 mg/m^2	Mainly excreted through feces
Docetaxel Injection	Yellow to brownish yellow viscous liquid, some products are equipped with special solvents	Polysorbate 80, citric acid (contained in some products), ethanol (contained in some products)	Docetaxel was the first injectable form approved for marketing	Not Applicable	Three-room mode	＞95%	In the dose range of 20-115 mg/m², the total clearance was 21 L/h/m², and the alpha, beta and gamma half-lives were 4 min, 36 min and 11.1 h, respectively.	Mainly excreted through feces, the amount excreted through feces is about 75% of the given dose

9 Storage and transportation of drugs

Paclitaxel injection should be stored and transported under 25℃ away from light; paclitaxel for injection (albumin-bound type) should be stored and transported away from light within the temperature range of 20℃~30℃; paclitaxel liposome for injection and paclitaxel polymer micelles for injection should be stored and transported away from light at 2℃~8℃; docetaxel injection needs to be stored and transported away from light, and the temperature for storage and transport varies among different manufacturers.

10 Administration of drugs

10.1 Prescription Review

10.1.1 Indications and dosage

National Medical Products Administration (NMPA) approved indications for paclitaxel antitumor drugs and their dosages are shown in

Tab 2.

Tab 2 Indications, usage and dosage of anti-tumor drugs taxanes

Drug Name	Indications	Usage and Dosage
Paclitaxel Injection (2021-1-8 Edition)	First-line and follow-up treatment for progressive ovarian cancer	1. For patients with untreated ovarian cancer, the following therapies are recommended as an option, once every 3 weeks (1) Intravenous drip of 175 mg/m² for > 3 h and cisplatin 75 mg/m² (2) Intravenous drip of 135 mg/m² for > 24 h and cisplatin 75 mg/m² For patients with ovarian cancer who have already received chemotherapy, the recommended regimen is 135 mg/m²or 175 mg/m² ivgtt for > 3 h, once every 3 weeks
	1. Adjuvant therapy for lymph node positive breast cancer patients after standard adriamycin-containing regimen combined with chemotherapy 2. Patients with metastatic breast cancer who have failed combination chemotherapy or recurred within 6 months of adjuvant chemotherapy	1. Adjuvant regimen for lymph node-positive breast cancer: dose 175 mg/m², ivgtt drip > 3 h, every 3 weeks, 4 courses, sequential after adriamycin-containing combination chemotherapy 2. Effective regimen for patients with metastatic disease who have failed initial chemotherapy or who have relapsed within 6 months of adjuvant chemotherapy: 175 mg/m² ivgtt drip > 3 h. once every 3 weeks
	First-line treatment for patients with non-small cell lung cancer	175 mg/m² ivgtt for > 3 h. once every 3 weeks
	Second-line treatment of AIDS-associated Kaposi's sarcoma (Kaposi's sarcoma).	135 mg/m^2, ivgtt > 3 hours, once every 3 weeks; or 100 mg/m^2, ivgtt > 3 hours (dose strength 45-50 mg/m^2 /w), once every 2 weeks
Paclitaxel liposome for injection (2015-11-25 edition)	First-line chemotherapy for ovarian cancer and later treatment of metastatic ovarian cancer, as first-line chemotherapy, also in combination with cisplatin	Commonly used dose is 135-175 mg/m²
	For follow-up treatment of patients with breast cancer who have had standard chemotherapy containing adriamycin or for patients with recurrence	
	First-line chemotherapy in combination with cisplatin for patients with non-small cell lung cancer who cannot be treated with surgery or radiation	
Paclitaxel for injection (Albumin-bound) (Version 2020-09-21)	Indicated for the treatment of metastatic breast cancer that has failed combination chemotherapy or breast cancer that has recurred within 6 months after adjuvant chemotherapy. Unless clinically contraindicated, prior chemotherapy should include an anthracycline anticancer agent	Recommended dose 260 mg/m² ivgtt over 30 min. once every 3 weeks

Paclitaxel polymer micelles for injection (2021-10-26 edition)	This product in combination with platinum is indicated for the first-line treatment of patients with epidermal growth factor receptor (EGFR) mutation-negative and mesenchymal lymphoma kinase (ALK)-negative, non-surgically resectable locally advanced or metastatic non-small cell lung cancer (NSCLC)	Cycle 1: 230 mg/m^2, ivgtt for ≥3 h; followed by cisplatin 70 mg/m^2. 2nd dose after 3 weeks Cycle 2 and subsequent cycles: If the patient had a neutrophil nadir ≥ 1.0×10^9 /L after cycle 1 dosing, along with a platelet nadir ≥ 80×10^9 /L, and no grade II-ivgtt non-hematologic toxicity occurred, 300 mg/m^2 was given ivgtt for ≥ 3 h; then cisplatin 70 mg/m^2 was given once every 3 weeks.
Docetaxel Injection (Version 2020-8-31)	1. Applicable to the treatment of locally advanced or metastatic breast cancer Docetaxel in combination with trastuzumab for the treatment of metastatic breast cancer patients with HER2 gene overexpression who have not received prior chemotherapy for metastatic breast cancer 3. Docetaxel combined with adriamycin and cyclophosphamide for postoperative adjuvant chemotherapy in lymph node-positive breast cancer patients	1. In adjuvant chemotherapy for lymph node positive breast cancer that is operable, the recommended dose is: adriamycin 50 mg/m²and cyclophosphamide 500 mg/m²given for 1 h, followed by docetaxel 75 mg/m^2 every 3 weeks for 6 cycles 2. The recommended dose of docetaxel for the treatment of patients with locally advanced or metastatic breast cancer is 100 mg/m². In first line, docetaxel 75 mg/m² combined with adriamycin 50 mg/m^2 In combination with trastuzumab, the recommended dose of docetaxel is 100 mg/m^2 once every 3 weeks and trastuzumab once weekly
	Indicated for the treatment of locally advanced or metastatic non-small cell lung cancer, even after failure of cisplatin-based chemotherapy	For the treatment of non-small cell lung cancer, the recommended dose for previously untreated patients is docetaxel 75 mg/m^2 and an immediate intravenous infusion of cisplatin 75 mg/m² over 30-60 min For patients who have failed prior platinum-containing therapy, the recommended dose of docetaxel is 75 mg/m^2 as monotherapy
	Docetaxel in combination with prednisone or prednisolone for hormone-refractory metastatic prostate cancer	The recommended dose is docetaxel 75 mg/m^2 every 3 weeks, with continuous oral prednisone or prednisolone 5 mg twice daily
	Docetaxel in combination with cisplatin and 5 fluorouracil for the treatment of advanced gastric adenocarcinoma, including adenocarcinoma of the	The recommended dose is docetaxel 60 mg/m² infused for 1 h, followed by cisplatin 60 mg/m² infused for 13 h (both on d1 only) and 5-fluorouracil infused for 5 d at the end of the cisplatin infusion at a daily dose of 600 mg/m²ivgtt for 24 h. once every 3 weeks

10.1.2 Off-label use

Taxanes have been recommended by many domestic and international diagnosis and treatment guidelines for cancers because of their confirmed efficacy, involving the treatment of lung cancer, pancreatic cancer, ovarian cancer, bile duct cancer and so on. Due to the delayed updating of drug instructions, there are many off-label uses recommended by the guidelines. In the course of clinical application, the principles of safe, effective, economical and rational drug use should be adhered to, and the drug instructions and related diagnosis and treatment guidelines should be followed for rational use. In special circumstances, such as the absence of effective or better treatment means, patients' informed consent should be obtained before off-label uses of these drugs with evidence-based principles [1]. (See Tab 3 Off-label use of taxanes （As of October 2022）Tab 3 for details)

Tab 3 Off-label use of taxanes（As of October 2022）

Drug name	Indication	Dosage	Source of evidence
Paclitaxel for injection （ 2021-1-8 version）	Cervical cancer	Concurrent chemoradiotherapy: 1. Cisplatin + paclitaxel: cisplatin 50 ~ 70 mg/m^2, paclitaxel 135 ~ 175 mg/m^2, d1 and d29 combined radiotherapy (RT) 2. Cisplatin + paclitaxel (weekly): cisplatin 25 ~ 30 mg/m^2, paclitaxel 60 ~ 80 mg/m^2, d1, d8, d15, d22, d29 and d36 combined radiotherapy Neoadjuvant chemotherapy: 1. Paclitaxel + cisplatin Systemic chemotherapy: 1. Pembrolizumab + cisplatin (carboplatin) + paclitaxel ± bevacizumab (for PD-L1 positive tumors) 2. cisplatin (carboplatin) + paclitaxel + bevacizumab 3. Topotecan + paclitaxel + bevacizumab 4. PalcitaxelPaclitaxel monotherapy	1.National Health Commission《 Cervical cancer diagnosis and treatment guidelines》（2022 version） 2.NCCN clinical practice guidelines ： cervical cancer（2022.V1）
	Gastric cancer	Monotherapy: Paclitaxel 80mg/m^2, ivgtt, d1, 8,15, repeated every 28 days; Paclitaxel 135 to 250 mg/m^2, ivgtt, d1, repeated every 21 days; Paclitaxel ivgtt80 mg/m^2, ivgtt, once a week and repeated every 28 days Two-drug regimen: 1. Ramolumab 8 mg/kg ivgtt, d1, 15; Paclitaxel 80 mg/m^2 ivgtt, d1, 8,15, repeated every 4 weeks 2. Paclitaxel 45-50 mg/m^2, ivgtt, d1; Capecitabine 625 to 825 mg/m^2, orally, d1-5, twice a day, once a week for 5 weeks 3. Paclitaxel 45-50 mg/m^2 ivgtt, d1; Fluorouracil 300 mg/m^2, ivgtt, d1-5, once a week for 5 weeks Systemic therapy for metastatic or locally advanced cancer (local therapy is not applicable): paclitaxel ± cisplatin or carboplatin 1. Paclitaxel 135 ~ 200 mg/m^2, ivgtt, d1; Cisplatin 75 mg/m^2 ivgtt, d1, repeated every 21 days	1.National Health Commission《Gastric cancer diagnosis and treatment guidelines》（2022 version） 2.Chinese Society of Clinical Oncology （ CSCO ）《Gastric cancer diagnosis and treatment guidelines》（2022 version） 3. NCCN clinical practice guidelines ： Gastric cancer（2022.V2）

		2. Paclitaxel 90 mg/m^2, ivgtt, d1; Cisplatin 50 mg/m^2 ivgtt, d1, repeated every 14 days 3. Paclitaxel 200 mg/m^2, ivgtt, d1; Carboplatin AUC=5, ivgtt, d1, repeated every 21 days Preoperative chemotherapy: Paclitaxel 50 mg/m^2, d1, combined with carboplatin AUC=2, d1, intravenous infusion for 5 weeks	
	Nasopharyngeal carcinoma	Recurrent, unresectable, or metastatic disease: 1. Cisplatin or carboplatin + paclitaxel 2. Paclitaxel monotherapy	1.Chinese Society of Clinical Oncology（CSCO）《Guidelines for diagnosis and treatment of nasopharyngeal carcinoma》（2022 version） 2.NCCN clinical practice guidelines：Head and neck cancer（2022.V2）
	Head and neck cancer	Systemic therapy for primary cancer + concurrent radiotherapy: 1. Carboplatin + paclitaxel 2. Cisplatin + paclitaxel induction/Sequential systemic therapy: paclitaxel + cisplatin +5-FU Recurrent, unresectable, or metastatic (and without surgery or radiotherapy options): 1. Cisplatin or carboplatin + docetaxel or paclitaxel 2. Pembrolizumab + platinum (cisplatin or carboplatin) + paclitaxel 3. Cisplatin or carboplatin + docetaxel + cetuximab 4. Palcitaxel monotherapy First-line treatment for relapsed metastatic squamous cell carcinoma (non-nasopharyngeal carcinoma): Paclitaxel + platinum 1. Paclitaxel 175 mg/m^2 ivgtt, d1; Cisplatin 75 mg/m^2, ivgtt, d1, and repeated every 3 weeks for 4-6 cycles 2. Paclitaxel 200 mg/m^2 ivgtt, d1, 8; Carboplatin AUC=2.5 ivgtt, d1, 8, repeated every 3 weeks for 4-6 cycles Second-line or salvage treatment for relapsed metastatic squamous cell carcinoma (non-nasopharyngeal carcinoma) : Paclitaxel 80 mg/m^2 ivgtt, d1, 8,15, repeated every 4 weeks	1. Chinese Society of Clinical Oncology（CSCO）《Head and neck cancer diagnosis and treatment guidelines》（2022 version） 2. NCCN clinical practice guidelines：Head and neck cancer（2022.V2）

		Paclitaxel 80 mg/m^2 ivgtt, d1, 8, 15, repeated every 4 weeks	
	Esophageal carcinoma	Concurrent chemotherapy regimen: 1. Paclitaxel 45-60 mg/m^2 ivgtt, d1; Cisplatin 20 to 25 mg/m^2 ivgtt, d1 or carboplatin AUC=2 ivgtt, d1, repeated weekly 2. Paclitaxel + fluorouracil or capecitabine or tegfur Preoperative neoadjuvant therapy: Paclitaxel + cisplatin (TP) (recommended for squamous cell carcinoma) 1. Paclitaxel 150 mg/m^2 ivgtt, d1, cisplatin 50 mg/m^2 ivgtt, d1, repeated every 2 weeks 2. Paclitaxel 135 mg/m^2 ivgtt infusion, d1; Cisplatin at 70 mg/m^2, ivgtt, d1, and repeated every 3 weeks Postoperative adjuvant therapy: Paclitaxel + cisplatin (TP) (recommended for squamous cell carcinoma): paclitaxel 150 mg/m^2 ivgtt, d1; Cisplatin 50 mg/m^2, ivgtt, d1, and repeated every 2 weeks First-line treatment for advanced disease: 1. Platinum drugs + paclitaxel ① Paclitaxel 135 ~ 175 mg/m² ivttt for 3 h, d1; Cisplatin 75 mg/m² ivgtt, d1, repeated every 3 weeks ② Paclitaxel 90 ~ 150 mg/m² ivgtt for 3 h, d1; Cisplatin 50 mg/m² ivgtt, d1, repeated every 2 weeks ③ Paclitaxel 90 mg/m² ivgtt, d1; Carboplatin AUC=5 ivgtt , d1, repeated every 3 weeks 2. Immunotherapy +TP regimen ① Camrelizumab + paclitaxel + cisplatin (recommended for squamous cell carcinoma) Camrelizumab 200 mg ivgtt, d1; Paclitaxel 175 mg/m^2 ivgtt, d1; Cisplatin 75 mg/m^2 ivgtt, d1, repeated every 3 weeks ② Triprilimab + paclitaxel + cisplatin (recommended for squamous cell carcinoma) Terrelizumab 240 mg ivgtt, d1; Paclitaxel 175 mg/m^2 ivgtt, d1;	1.National Health Commission《Guidelines for diagnosis and treatment of esophageal cancer》（2022 version） 2. Chinese Society of Clinical Oncology（CSCO）《Guidelines for diagnosis and treatment of esophageal cancer》（2022 version） 3. NCCN clinical practice guidelines：Esophageal carcinoma and gastroesophageal junction carcinoma（2022.V4）

		Cisplatin 75 mg/m^2 ivgtt, d1, repeated every 3 weeks Terrelizumab 240 mg ivgtt, d1; Paclitaxel 175 mg/m^2 ivgtt infusion, d1; Cisplatin ivgtt at 75 mg/m^2, d1, and repeated every 3 weeks ③ Sintillimab + paclitaxel + cisplatin (recommended for squamous cell carcinoma) Sindillimab (3mg/kg, body weight ≤60kg; 200mg, weight > 60kg) ivgtt, d1; Paclitaxel 175 mg/m^2 ivgtt infusion, d1; Cisplatin ivgtt at 75 mg/m^2, d1, and repeated every 3 weeks 3. Palcitaxel monotherapy ① Paclitaxel 130~175 mg/m^2 ivgtt, d1, repeated every 3 weeks ② Paclitaxel 80mg/m^2 ivgtt, d1, 8,15,22, repeated every 4 weeks 4. Small-molecule targeted drugs +TP regimen 9. Anrotinib 10mg, po, d1~14; Paclitaxel 135 mg/m^2 ivgtt infusion, d1; Cisplatin was administered ivgtt 60-70 mg/m^2, d1-3, and repeated every 3 weeks Late second-line and after-line treatment: 1. Paclitaxel 175 mg/m^2 ivgtt infusion, d1, repeated every 3 weeks 2. Paclitaxel 80mg/m^2 ivgtt infusion, d1, 8,15,22, repeated every 4 weeks 3. Paclitaxel 80mg/m^2 ivgtt, d1, 8,15, repeated every 4 weeks	
	Bladder cancer	First-line treatment of metastatic urothelial carcinoma of the bladder: 1. Platinum tolerance (PS score 0~1 or glomerular filtration rate > 50~60 ml/min): paclitaxel + cisplatin + gemcitabine Recommended usage: Paclitaxel 80 mg/m^2 ivgtt infusion, d1, d8; Cisplatin 70 mg/m^2 ivgtt, d1 or d2; Gemcitabine 1000 mg/m^2 ivgtt, d1, d8, repeated every 3 weeks 2. Platinum intolerance (PS score of 2 or glomerular filtration rate of 30-60 ml/min): paclitaxel + gemcitabine Recommended usage: Paclitaxel 80 mg/m^2 ivgtt infusion, d1, d8; Gemcitabine 1000 mg/m^2 ivgtt, d1, d8, repeated every 3 weeks	1.National Health Commission《Guidelines for diagnosis and treatment of bladder cancer》（2022 version） 2.NCCN clinical practice guidelines：Bladder cancer（2022.V2）

		Second-line treatment options for metastatic bladder urothelial carcinoma (failure of platinum-based chemotherapy, or failure of immune checkpoint inhibitor therapy): 1. Paclitaxel monotherapy 2. Gemcitabine + paclitaxel Third-line treatment for advanced or metastatic urothelial carcinoma of the bladder: 1. Paclitaxel monotherapy 2. Gemcitabine + paclitaxel	
	Small cell lung cancer	Second-line treatment of recurrent small cell lung cancer ≤6 months: Paclitaxel monotherapy	1. Chinese Society of Clinical Oncology（CSCO）《Guidelines for diagnosis and treatment of small cell lung cancer》（2022 version） 2. NCCN clinical practice guidelines：Small cell lung cancer（2023.V1）
	Melanoma	Advanced skin melanoma Treatment: Paclitaxel 175 mg/m^2 d1± carboplatin AUC=5 ± bevacizumab 5 mg/kg d1, 15, repeated every 4 weeks	National Health Commission《Guidelines for melanoma diagnosis and treatment》（2022 version）
Paclitaxelfor injection（albumin-bound）（2020-09-21version）	Locally advanced or metastatic non-small cell lung cancer	First-line treatment: 1. Two-drug regimen containing cisplatin or carboplatin: ① Albumin paclitaxel + carboplatin: 100 mg/m^2, d1, 8,15; Carboplatin AUC=5-6, d1, repeated every 3 weeks ② Albumin paclitaxel + cisplatin: 100 mg/m^2, d1, 8,15; Cisplatin 75mg/ m^2, d1, repeated every 3 weeks 2. Combined with immunotherapy regimen: ① Albumin paclitaxel + carboplatin + Pabolizumab :100 mg/m^2, d1, 8,15; Carboplatin AUC=5, d1; Pabolizumab 200mg, d1, every 21 days (for non-squamous cell carcinoma) ② Albumin paclitaxel + carboplatin + tirelizumab :100 mg/ m^2, d1, 8,15; Carboplatin AUC=5, d1; Tirelizumab 200mg, d1, every 21 days (for squamous cell carcinoma)	1.Chinese Society of Clinical Oncology（CSCO）《Guidelines for diagnosis and treatment of non-small cell lung cancer》（2022 version） 2.NCCN clinical practice guidelines：small cell lung cancer（2022.V5） 3.Drug instruction approved by FDA

		③ Albumin paclitaxel + carboplatin combined with Attilizumab (for non-squamous cell carcinoma) ④ Albumin paclitaxel + carboplatin combined with triprilimab (for squamous cell carcinoma)	
	Metastatic pancreatic cancer	125 mg/m^2, intravenous infusion 30-40 min, d1, 8,15; Gemcitabine 1000 mg/m^2, intravenous infusion 30 to 40 min, d1, 8,15, repeated every 4 weeks	1.National Health Commission《 Pancreatic cancer Diagnosis and treatment guidelines》（2022 version） 2. NCCN clinical practice guidelines： Pancreatic cancer（2022.V1） 3. Drug instruction approved by FDA
	Platinum-sensitive or platinum-resistant recurrent ovarian cancer	Platinum sensitive: Paclitaxel (albumin-bound) ± carboplatin Platinum resistance: Paclitaxel (albumin-bound) ± bevacizumab	1.National Health Commission《 National Health Commission ovarian cancer diagnosis and treatment standards》（2022 version） 2. Chinese Society of Clinical Oncology（CSCO）《Ovarian cancer diagnosis and treatment guidelines》（2022 version） 3. NCCN clinical practice guidelines： Ovarian cancer includes fallopian tube cancer and primary peritoneal cancer（2022.V5）
	Metastatic melanoma	Paclitaxel (albumin-bound) 260 mg/m^2 d1± carboplatin AUC=5, ± bevacizumab 5 mg/kg D1/15, repeated every 4 weeks	National Health Commission《Guidelines for melanoma diagnosis and treatment》（2022 version）
	Esophageal carcinoma	Advanced first-line treatment: Paclitaxel (albumin-bound) 125 mg/m^2 ivgtt, d1, 8; Cisplatin 75 mg/m^2 ivgtt, d1, repeated every 3 weeks Late second-line and after-line treatment: Paclitaxel (albumin-bound) 100 to 150 mg/m^2 ivgtt, d1, 8, repeated every 3 weeks	National Health Commission《Guidelines for diagnosis and treatment of esophageal cancer》（2022 version）
	Gastric cancer	Second-line and after-line treatment options: Paclitaxel (albumin-bound) 100 mg/m^2 ivgtt, d1, 8,15, repeated every 28 days	Chinese Society of Clinical Oncology（CSCO）《Gastric cancer diagnosis and treatment guidelines》（2022 version）
	Endometrial	Monotherapy for postoperative adjuvant chemotherapy or	1.National Health Commission《Guidelines for diagnosis

	carcinoma	palliative chemotherapy	and treatment of endometrial cancer》（2022 version） 2.NCCN clinical practice guidelines：Uterine cancer（2022.V1）
Docetaxel for Injection（2020-8-31version）	Nasopharyngeal carcinoma	Induction Therapy/Sequential Systemic Therapy: 1. Docetaxel monotherapy 2. Docetaxel + cisplatin Recurrent, unresectable, oligo-metastatic, or metastatic disease (without surgical or RT options): Cisplatin or carboplatin + docetaxel	NCCN clinical practice guidelines：Head and neck cancer（2022.V2）
	Head and neck cancer	Induction/sequential systemic therapy or postoperative chemotherapy: 1. Docetaxel monotherapy Recurrent, unresectable, or metastatic cancer (without surgical or RT options): 1. Cisplatin + docetaxel + Cetuximab 2. Pembrolizumab + platinum (cisplatin or carboplatin) + docetaxel 3. Docetaxel monotherapy Locally advanced squamous cell carcinoma of the head and neck: Docetaxel + cisplatin + fluorouracil First-line treatment for relapsed metastatic squamous cell carcinoma (non-nasopharyngeal carcinoma): 1. Docetaxel 75 mg/m^2, ivgtt infusion, d1, 8; Cisplatin 75 mg/m^2, ivgtt, d1, repeated every 3 weeks for 4 to 6 cycles Second-line or salvage treatment for relapsed metastatic squamous cell carcinoma (non-nasopharyngeal carcinoma): Docetaxel 28 mg/m^2 ivgtt, d1, 8, 15, repeated every 4 weeks	1.Chinese Society of Clinical Oncology（CSCO）《Head and neck cancer diagnosis and treatment guidelines》（2022 version） 2. NCCN clinical practice guidelines：Head and neck cancer（2022.V2） 3. Drug instruction approved by FDA
	Small cell lung cancer	Second-line treatment of recurrent small cell lung cancer ≤6 months: Docetaxel monotherapy	1.Chinese Society of Clinical Oncology（CSCO）《Guidelines for diagnosis and treatment of small cell lung cancer》（2022 version） 2.NCCN clinical practice guidelines：small cell lung cancer（2023.V1）

	Cervical cancer	Monotherapy for second-line chemotherapy for squamous cell carcinoma, adenocarcinoma, or adeno-squamous cell carcinoma	1. Cervical cancer diagnosis and treatment guideline（2021 version）（Chinese Anti-Cancer Association gynecological tumor professional Committee） 2. NCCN clinical practice guidelines：Cervical cancer（2022.V1）
	Esophageal carcinoma	Preoperative neoadjuvant therapy: 1. Fluorouracil + folinate + oxaliplatin + docetaxel (FLOT) (for adenocarcinoma only) Fluorouracil 2600mg/m^2, continuous intravenous infusion t, 24h, d1; Calcium folinate 200mg/m^2 ivgtt, d1; Oxaliplatin 85mg/m^2, ivgtt infusion, d1; Docetaxel 500 mg/m^2, ivgtt infusion, d1, repeated every 2 weeks, 4 cycles before surgery, 4 cycles after surgery, a total of 8 cycles 2. Docetaxel + Cisplatin + fluorouracil (DCF) (recommended for squamous cell carcinoma) Docetaxel 70 mg/m^2, ivgtt, d1; Cisplatin 70 mg/m^2, ivgtt drip, d1; Fluorouracil 750 mg/m^2, ivgtt drip, d1-5, repeated every 3 weeks Late first-line treatment: Platinum +5-FU/CF+ docetaxel 1. Docetaxel + Cisplatin + fluorouracil (Modified DCF) (recommended for adenocarcinoma) Docetaxel 40 mg/m^2, ivgtt, d1; Cisplatin 40 mg/m^2, ivgtt infusion, d3; Calcium folinate 400 mg/m^2, ivgtt infusion, d1; Fluorouracil 40mg/m^2, ivgtt drip, d1, then 2000 mg/m^2, continuous ivgtt drip, 24h, d1-2, repeated every 2 weeks 2. Oxaliplatin +5-FU+ docetaxel: oxaliplatin 85 mg/m^2, ivgtt infusion, d1; Fluorouracil 1200 mg/m^2, continuous intravenous infusion, 24 h, d1-2; Docetaxel 50mg/m^2, ivgtt, d1, repeated every 2 weeks 3. Carboplatin +5-FU+ docetaxel: Carboplatin AUC=6, ivgtt infusion, d2; Fluorouracil 1200 mg/m^2, continuous intravenous infusion, 24 h, d1-3; Docetaxel 70mg/m^2, ivgtt, d1, repeated every	1.National Health Commission《Guidelines for diagnosis and treatment of esophageal cancer》（2022 version） 2. Chinese Society of Clinical Oncology（CSCO）《Guidelines for diagnosis and treatment of esophageal cancer》（2022 version） 3. NCCN clinical practice guidelines：Esophageal carcinoma and gastroesophageal junction carcinoma（2022.V4）

		2 weeks 4. Docetaxel 75~100 mg/m², ivgtt drip, d1, repeated every 2 weeks Late second-line and after-line treatment: Docetaxel 75 to 100 mg/m², ivgtt, d1, repeated every 2 weeks	
	Ovarian/fallopian tube/primary peritoneal cancer	Epithelial ovarian cancer: 1. Postoperative adjuvant therapy, docetaxel 60-75 mg/m^2 intravenous infusion for 1 h, followed by carboplatin AUC= 5-6 intravenous infusion for 1 h, d1. The dose was repeated every 3 weeks for 3 to 6 cycles 2. Platinum-sensitive recurrence was treated with single drug or combined with carboplatin 3. Monotherapy for platinum resistance recurrence	1.Chinese Society of Clinical Oncology （ CSCO ）《Ovarian cancer diagnosis and treatment guidelines》（2022 version） 2.NCCN clinical practice guidelines ： Ovarian cancer includes fallopian tube cancer and primary peritoneal cancer（2022.V5）
	Malignant germ cell tumor/sex cord stromal tumor	Ovarian cancer of germ cell origin: 1. Palliative care for recurrent malignant germ cell tumors: docetaxel ± carboplatin 2. Recurrent cable stromal tumor: Docetaxel monotherapy	NCCN clinical practice guidelines ： Ovarian cancer includes fallopian tube cancer and primary peritoneal cancer（2022.V5）
	Endometrial carcinoma	Postoperative adjuvant chemotherapy or palliative chemotherapy: docetaxel ± carboplatin (for patients contraindicated with paclitaxel)	1.National Health Commission《Guidelines for diagnosis and treatment of endometrial cancer》（2022 version） 2.NCCN clinical practice guidelines ： Uterine cancers（2022.V1）
	Gastric cancer	Common first-line treatment options: 1. Docetaxel 75 mg/m^2, ivgtt infusion, d1; Cisplatin 75 mg/m^2, ivgtt, d1; 5-FU 1000 mg/ (m^2·d) continuous intravenous drip for 24 h, d1-5, repeated every 21 days (DCF) 2. Docetaxel 60 mg/m^2, ivgtt infusion, d1; Cisplatin 60 mg/m^2, ivgtt, d1; 5-FU 600 mg/ (m^2·d) continuous intravenous drip for 24 h, d1-5, repeated every 21 days (mDCF) Postoperative adjuvant chemotherapy commonly used regimens: 1. The drug was administered by body surface area for 14 consecutive days with 7 days rest; Docetaxel 40 mg/m^2, repeated every 21 days Common schemes of neoadjuvant chemotherapy:	1.National Health Commission《Gastric cancer diagnosis and treatment guidelines》（2022 version）2.Chinese Society of Clinical Oncology（CSCO）《Gastric cancer diagnosis and treatment guidelines》（2022 version） 3.NCCN clinical practice guidelines ： Gastric cancer（2022.V2） 4.Drug instructions approved by FDA

		Docetaxel 50 mg/m^2, ivgtt, d1; Oxaliplatin 100 mg/m^2, ivgtt infusion, d1; Tetrahydrofolic acid 200 mg/m^2, ivgtt infusion, d1; 5-FU 2600 mg/m^2 was given ivgtt for 24 h and repeated every 21 days Palliative chemotherapy: Capecitabine plus docetaxel Second line and posterior line treatment commonly used: Docetaxel 75 to 100 mg/m^2 ivgtt, d1, repeated every 21 days Perioperative chemotherapy: Fluorouracil 2600 mg/m^2, intravenous infusion for 24 h, d1; Folinic acid 200 mg/m^2, ivgtt infusion, d1; Oxaliplatin 85 mg/m^2, ivgtt infusion, d1; Docetaxel 50 mg/m^2, ivgtt infusion, d1, repeated every 14 days Systemic therapy for metastatic or locally advanced cancer (local therapy is not applicable): 1 Docetaxel 70 to 85 mg/m^2, ivgtt infusion, d1± Cisplatin 70 to 75 mg/m^2, ivgtt infusion, d1, repeated every 21 days 2. Docetaxel 40 mg/m^2, ivgtt infusion, d1; Folinic acid 400 mg/m^2, ivgtt infusion, d1; Fluorouracil 400 mg/m^2, ivgtt infusion, d1; Fluorouracil 1000 mg/m^2, continuous infusion for 24 hours, D1-2 cisplatin 40 mg/m^2, intravenous infusion, d3, repeated every 14 days 3. Docetaxel 50 mg/m^2, ivgtt infusion, d1; Oxaliplatin 85 mg/m^2, ivgtt infusion, d1; Fluorouracil was administered at 1200 mg/m^2 for 24 h, d1-2, and repeated every 14 days 4. Docetaxel 75 mg/m^2, ivgtt infusion, d1; Carboplatin AUC=6, ivgtt infusion, d1; Fluorouracil was administered at 1200 mg/m^2 for 24 hours, D1-3, repeated every 21 days 5. Docetaxel 35 mg/m^2, ivgtt infusion, d1, 8; Irinotecan 50 mg/m^2, ivgtt infusion, d1, 8, repeated every 21 days	
	Bladder cancer	Docetaxel monotherapy is indicated for second-line treatment (failure of platinum-based chemotherapy or immune checkpoint	1National Health Commission《Guidelines for diagnosis and treatment of bladder cancer》（2022 version）

		inhibitor treatment) or third-line treatment in patients with advanced or metastatic uroepithelial carcinoma of the bladder	2.NCCN clinical practice guidelines：bladder cancer（2022.V2）
Paclitaxel liposome for injection （ 2015-11-25 version）	Non-small cell lung cancer	First-line treatment: 1. Two-drug regimen containing cisplatin or carboplatin: ① Paclitaxel liposome + carboplatin: 135-175 mg/m^2, d1; Carboplatin AUC=5~6, d1, repeat every 3 weeks ② Paclitaxel liposome + cisplatin: 135-175 mg/m^2, d1; Cisplatin 75 mg/m^2, d1, repeated every 3 weeks	Chinese Society of Clinical Oncology （ CSCO ）《Guidelines for diagnosis and treatment of non-small cell lung cancer》（2022 version）
	Esophageal carcinoma	Advanced first-line treatment: Camrelizumab + Apatinib + Nedaplatin + paclitaxel liposomes: Camrelizumab 240 mg ivgtt, d1; Paclitaxel liposome 150 mg/m^2 ivgtt, d1; Nedaplatin 50 mg/m^2 ivgtt, d1; Apatinib 50 mg, po, d1-3, repeated every 2 weeks	Chinese Society of Clinical Oncology （ CSCO ）《Guidelines for diagnosis and treatment of esophageal cancer》（2022 version）

10.1.3 Special populations

According to the instructions of taxane antitumor drugs and related studies, the specific use of various special populations is detailed in Tab 4.

Tab 4 Drug recommendations for taxane antitumor drugs in special population

Drug name	Patients with liver insufficiency	Patients with renal insufficiency	Elderly patients	Lactating woman	Pregnancy
Palcitaxel for Injection	When liver function is impaired, dosage should be adjusted according to the degree of liver function impairment and the infusion time of drugs, referring to the instructions	It is suggested to combine with clinical practice.	It can be used, but has a higher incidence of myelosuppression, neuropathy, and cardiovascular adverse reactions	Contraindicated, interrupt breastfeeding if used	Contraindicated
Palcitaxel liposome for Injection	Use with caution	It is suggested to combine with clinical practice.	No experimental data are available，It is suggested to combine with clinical practice.	Contraindicated，interrupt breastfeeding if used	Insufficient data with potential risk. It is suggested to combine with clinical practice.
Palcitaxel for Injection（albumin bound）	For patients with mild liver dysfunction (Tbil > 1 ULN to ≤1.5 ULN, and AST≤10 ULN), there is no need to adjust the dose, that is, 260 mg/m^2 can still be used. 200 mg/m^2 is recommended for moderate and severe hepatic dysfunction (Tbil > 1.5 to ≤5 ULN and AST≤10 ULN) If Tbil > 5uln or AST > 10uln, Contraindicated	Patients with mild and moderate renal dysfunction (Crcl≥30 mL/min to < 90 mL/min) need not adjust the dosage; Severe renal dysfunction and end-stage renal disease (Crcl < 30 mL/min), it is suggested to combine with clinical practice.	Some clinical trials have shown no increase in the incidence of adverse events in older adults. However, meta-analyses have shown a higher incidence of nasal bleeding, diarrhea, dehydration, fatigue, and peripheral edema in older adults aged 65 years and older. Therefore, caution is recommended	Not recommended. If used, it is recommended to stop breastfeeding within 2 weeks after use of this product and the last dose	Contraindicated
Paclitaxel polymeric Micelles for	Use with caution in patients with mild liver	Use with caution in patients with mild renal	Safety data do not show significant differences,	It is not recommended to use. If it has been used, it is	Contraindicated

Injection	insufficiency without dose adjustment; It is not recommended for patients with moderate or severe liver insufficiency	insufficiency without dose adjustment. In combination with cisplatin, the patient's cisplatin tolerance should be considered. It is not recommended for patients with moderate or severe renal insufficiency	use with caution, no dose adjustment	recommended to use this product in lactating female patients Stop breastfeeding within two weeks after the last medication	
Docetaxel for Injection	For ALT and/or AST > 1.5 ULN and ALP > 2.5 ULN, 75 mg/m^2 is recommended. Tbil > ULN and/or ALT and AST > 3.5 ULN accompanied by ALP > 6 ULN are generally not recommended, and no reduction is recommended	It is suggested to combine with clinical practice.	The incidence of adverse reactions was relatively higher without special guidance. It is not recommended for use in conjunction with other antitumor agents in elderly patients aged over 70 years	Contraindicated, interrupt breastfeeding if used	Contraindicated

P.S.: ALT: alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; Tbil: total bilirubin; ULN: normal upper limit; Crcl: Creatinine clearance

10.1.4 Contraindication

The contraindications of Taxane-derived drugs are listed in Tab 5.

Tab 5 The contraindications of Taxane-derived drugs

Drug	Contraindication
Paclitaxel Injection	①A history of severe hypersensitivity reactions to cremophor EL ②Baseline neutrophil counts of < 1,500 cells/mm^3
Paclitaxel Liposome for Injection	①A history of severe hypersensitivity reactions to Taxane-derived drugs ②Baseline neutrophil counts of < 1,500 cells/mm^3

Paclitaxel for Injection （Albumin Bound）	①Baseline neutrophil counts of < 1,500 cells/mm^3 ②A history of severe hypersensitivity reactions to Paclitaxelor human serum albumin
Paclitaxel Polymeric Micelles for Injection	① A history of severe hypersensitivity reactions to Paclitaxel and other component in prescription. ②Baseline neutrophil counts of < 1,500 cells/mm^3
Docetaxel Injection	①A history of severe hypersensitivity reactions to docetaxel or to other excipients. ②Baseline neutrophil counts of < 1,500 cells/mm3 ③Pregnant women ④Patients with severe damage to liver function ⑤Contraindications of other drugs should be concerned in the situation of drug combination.

10.1.5 Premedication Regimen

According to the official instruction, guideline and clinical actual circumstances of medication, the contraindications of Taxane-derived drugs are summarized in Tab 6.

Tab 6 Premedication Regimen

Drug	Purpose	Regimen
Paclitaxel Injection	Reduce the incidence of hypersensitivity reactions	Dexamethasone[b] 20mg (i.g. 8 mg twice daily) starting 30-60min prior to administration or 20mg (p.o. 20 mg) starting 30-60min 12h/6h prior to administration; Diphenhydramine(i.m.50 mg)[c];Cimetidine (i.g. 300mg) or Ranitidine[d](i.g. 50mg) starting 30-60min prior to administration
Paclitaxel Liposome for Injection	Reduce the incidence of hypersensitivity reactions	Dexamethasone[b](i.g. 5-10mg); Diphenhydramine(i.m.50 mg)[c];Cimetidine[d] (i.g. 300mg)starting 30min prior to administration
Paclitaxel for Injection（Albumin Bound）	None	No need
Paclitaxel Polymeric Micelles for Injection	None	No need
Docetaxel Injection	Reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity react ions	Dexamethasone 16 mg per day (e.g., 8 mg twice daily) for 3 days starting 1 day prior to Docetaxel Injection administration[b].

a Derived from official drug instruction

b See Clinical problem1

c See Clinical problem2

d See Clinical problem3

10.1.6 Drug interaction

1）Interaction between Taxane-derived drugs and Western Medicines

Taxane-derived drugs are metabolized by liver Cytochrome P450 proteins (CYP450) 2C8 and 3A4 enzymes. Some drugs could have effect on taxane-derived drugs through inducing and inhibiting these metabolic enzymes or metabolized by these enzymes. According to the official instructions and related references, the drug interaction of Taxane-derived drugs were summarized in Tab 7. It is noted that monitoring of adverse reactions , dosage adjustment and other measures should be concerned when applying these drug simultaneously[1].

Tab 7 Interaction between Taxane-derived drugs and Western Medicines*

Drug	Interactive drug	Cause	Reference	UpToDate Risk Ratings	Advice
Paclitaxel Injection	Vaccines (Live)	Paclitaxel may enhance the adverse/toxic effect of Vaccines (Live).	Drug instruction of Paclitaxel Injection	X	Avoid combination
	Sorafenib	Sorafenib may enhance the adverse/toxic effect of Paclitaxel	Drug instruction of Sorafenib	X	Avoid combination
	Anthracyclines	Paclitaxel may enhance the adverse/toxic effect of Anthracyclines. Paclitaxel may increase the serum concentration of Anthracyclines. Paclitaxel may also increase the formation of toxic anthracycline metabolites in heart tissue.	Ma li *et al*.[2] Iqbal, M. *et al*.[3]	D	Use Anthracyclines then Paclitaxel
	Blood Pressure Lowering Agents	Enhance the hypotensive effect of Hypotension-Associated Agents	UpToDate	C	Monitor therapy
	CYP2C8, CYP3A4 Inducers or Inhibitors	Decrease or increase the serum concentration of PACLitaxel	Drug instruction of Paclitaxel Injection	C	Monitor therapy
	Ketoconazole	Ketoconazole (CYP3A4 Inhibitors (Strong)) may increase the serum concentration of PACLitaxel by interfering P-glycoprotein (MDR1) efflux transporter.	Drug instruction of Paclitaxel Injection	C	Monitor therapy
	Verapamil	CYP3A4 Inhibitors (Moderate)，it can reduce 50% clearance of paclitaxel and increase the serum concentration of PACLitaxel	Drug instruction of Paclitaxel Injection	C	Monitor therapy
	Deferiprone	Deferiprone may enhance the neutropenic effect of Deferiprone.	UpToDate	D	Consider therapy modification
Docetaxel Injection	Vaccines (Live)	Docetaxel may enhance the adverse/toxic effect of Vaccines (Live)	UpToDate	X	Avoid combination

	Tofacitinib	Docetaxel may enhance the immunosuppressive effect of Tofacitinib	UpToDate	X	Avoid combination
	Denosumab	Denosumab may enhance the immunosuppressive effect of Docetaxel	UpToDate	D	Consider therapy modification
	Dronedarone	Dronedarone may increase the serum concentration of Docetaxel.	UpToDate	D	Consider therapy modification
	Deferiprone	Docetaxel may enhance the neutropenic effect of Deferiprone	UpToDate	D	Consider therapy modification
	CYP3A4 Inhibitors (Strong)	CYP3A4 Inhibitors (Strong) may increase the serum concentration of Docetaxel	1.UpToDate 2.Engels, F. et al.[4]	D	Consider therapy modification
	Amphotericin B	Docetaxel may enhance the adverse/toxic effect of Amphotericin B.	UpToDate	C	Monitorhe adverse reactions of amphotericin B
	Olaparib	Docetaxel may enhance the myelosuppressive effect of Olaparib.	UpToDate	C	Monitorhe adverse reactions of Olaparib
	Sorafenib	Sorafenib may increase the serum concentration of Docetaxel	UpToDate	C	Monitor adverse reactions of Docetaxel
Paclitaxel Liposome for Injection	Cisplatin	Pharmacokinetic data showed that if paclitaxel liposomes were given after the administration of cisplatin, the clearance rate of paclitaxel liposomes would be reduced by about 30%. Besides, the severity of bone marrow toxicity would be aggravated.	Drug instruction of Paclitaxel Liposome	—	Combinative administration should be avoidedin addition to using paclitaxel followed by cisplatin
	Ketoconazole	Ketoconazole may increase the serum concentration of Paclitaxel Liposome	Drug instruction of Paclitaxel Liposome	—	Monitor adverse reactions of Paclitaxel Liposome
Paclitaxel for	Vaccines (Live)	Paclitaxel（Albumin Bound）may enhance the	UpToDate	X	Avoid combination

Injection（Albumin Bound）		adverse/toxic effect of Vaccines (Live)			
	Sorafenib	Sorafenib may enhance the adverse/toxic effect of Paclitaxel（Albumin Bound）	UpToDate	X	Avoid combination
	Tacrolimus (Topical)	Paclitaxel（Albumin Bound）may enhance the immunosuppressive effect of Tacrolimus (Topical)	UpToDate	X	Avoid combination
	Tofacitinib	Paclitaxel（Albumin Bound）may enhance the immunosuppressive effect of Tofacitinib	UpToDate	X	Avoid combination
	Cladribine	Paclitaxel（Albumin Bound）may enhance the immunosuppressive effect of Cladribine.	UpToDate	X	Avoid combination
	Upadacitinib	Paclitaxel（Albumin Bound）may enhance the immunosuppressive effect of Upadacitinib	UpToDate	X	Avoid combination
	Deferiprone	Paclitaxel（Albumin Bound）may enhance the neutropenic effect of Deferiprone	UpToDate	D	Consider therapy modification
	Denosumab	Denosumab may enhance the immunosuppressive effect of Paclitaxel（Albumin Bound）	UpToDate	D	Consider therapy modification
	Palifermin	Palifermin may enhance the adverse/toxic effect of Paclitaxel（Albumin Bound）	UpToDate	D	Consider therapy modification
	Amphotericin B	Paclitaxel（Albumin Bound）may enhance the adverse/toxic effect of Amphotericin B	UpToDate	C	Monitor the adverse reactions of amphotericin B
	Clozapine	Clozapine may enhance the adverse/toxic effect of Paclitaxel（Albumin Bound）	UpToDate	C	Monitor the adverse reactions of Clozapine
	Olaparib	Paclitaxel（Albumin Bound）may enhance the myelosuppressive effect of Olaparib	UpToDate	C	Monitor the adverse reactions of Olaparib
	CYP2C8, CYP3A4 Inducers or Inhibitors	CYP2C8, CYP3A4 Inducers or Inhibitors may increase or decrease the serum concentration of PACLitaxel (Protein Bound).	UpToDate	C	monitoring of exposure to paclitaxel (albumin binding type)
	CYP3A, CYP2C	CYP3A, CYP2C Inducers or Inhibitors may	Drug instruction of	—	Monitor the adverse

Paclitaxel Polymeric Micelles for Injection	Inducers or Inhibitors	interfere the metabolic process of paclitaxel polymeric micelles.	Paclitaxel Polymeric Micelles for Injection		reactions of Paclitaxel Polymeric Micelles
	Ketoconazole	Ketoconazole may inhibit the metabolic process of paclitaxel polymeric micelles.	Drug instruction of Paclitaxel Polymeric Micelles for Injection	C	Monitor the adverse reactions of Paclitaxel Polymeric Micelles

Note: Classifications of the drug's interaction risk rating is derived from UpToDate database. (Risk Rating C: Monitor therapy; Risk Rating D: Consider therapy modification; Risk Rating X: Avoid combination)

2） Interaction between Taxane-derived drugs and Chinese Medicines

The interactions between Taxane-derived drugs and traditional Chinese Medicines (TCM) should be concerned in case of differences in efficacy caused by pharmacokinetic changes of Taxane-derived drugs. More importantly, synergistic toxic effects of taxane-derived drugs and TCM needs attention. Many evidences proved that addition of compound Kushen injection (20mL, q.d.) during the chemotherapy of Paclitaxel injection (135~175 mg/m^2, q3w) may cause more severe of myelosuppression and high incidence of Grade II neurotoxicity. The potential mechanism may be related to the liver drug enzymes (CYP2C8 and CYP3A4 etc.) which involves in the metabolism of Paclitaxel.In vitro studies have confirmed that compound Kushen injection can affect the metabolism of paclitaxel by affecting CYP2C8[5].Anti-tumor TCM injection (Kanglaite injection, Aidi injection, Brucea javanica oil emulsion injection, cinobufacini capsule, lentinan for injection, Kangai injection, Xiaoaiping injection) could effect CYP3A4,which should be noted when using Paclitaxel synchronously[6].

3）Interaction between pre-treatment drugs and other medicines

To prevent the occurrence of severe allergic reactions, pre-treatment is usually required before the administration of Taxane-derived drugs. Common pre-treatment drugs include dexamethasone, diphenhydramine (or alternative medicine) and cimetidine (or ranitidine). Clinically, the interaction of this type of drugs should also be concerned (see Tab 8).

Tab 8 Interaction between pre-treatment drugs and other medicines*

Drug name	Need modification	Incompatibility
Dexamethasone	Rifampicin, Ritonavir, Sorafeni,Thalidomide,Indinavir,Barbiturate,Phenytoin,salicylic acid, blood anticoagulant, Oral hypoglycemic agents and etc.	Procaine and etc.
Diphenhydramine	Metoclopramide, Metoprolol, Barbiturate, Sulfacetamide sodium, Sodium Amimosalicylate, Central depressant, MAO Inhibitors, Heparin, Adrenergic neuron blocking drugs and etc.	Meglumine Adipiodone, Meglucamine Iothalamate, Inosine, Thiopental Sodium, Cefuroxime Sodium, CefuroximeAxetil, Cefoperazone sodium, Cephalothin Sodium, Ceftazidime, Cefotiam and etc.
Cimetidine	Mephalon, Clozapine, Chlorpromazine, Quinine, Ciprofloxacin+theophylline, Imipramine, Epirubicin, Adizolam, Amitriptyline, Diltiazem (dosage adjustment), Metformin (dosage adjustment), Vardenafil, Felodipine (dosage adjustment), Sulfonylurea, Propranolol, Lidocaine (dosage adjustment), Tamoxifen (Interval-dose), Methadone, Nifedipine (dosage adjustment) and etc.	/
Ranitidine	Sulfonylureas, Triazolam, Tamoxifen (Interval-dose), Pancreatin (dosage adjustment), Ornidazole, magnesium oxide and etc.	/

*Derived from instructions

4）The order of medication

The order of medication is listed in Tab 9

Tab 9 The order of medication of Taxane-derived drugs and other anti-tumor drugs

Combination	Prior	Posterior	Evidence
Paclitaxel/ Cisplatin	Paclitaxel	Cisplatin	Using Paclitaxel after cisplatin may decline the clearance of Paclitaxel and exaggerate the myelosuppression【Paclitaxel Injection instruction】
Paclitaxel/ Doxorubicin	Doxorubicin	Paclitaxel	Initial administration of paclitaxel followed by doxorubicin resulted in a significant decrease in doxorubicin clearance with blood concentration of doxorubicin and its product of metabolism【DOXOrubicin for Injection instruction 】
paclitaxel/ cyclophosphamide	cyclophosphamide	paclitaxel	Initial administration of paclitaxel followed by cyclophosphamide could aggravate myelosuppression【 Cyclophosphamide for Injection instruction 】
docetaxel/ doxorubicin/ cyclophosphamide	cyclophosphamide	docetaxel	In the treatment of breast cancer, initial administration of doxorubicin/cyclophosphamide after 1h followed by docetaxel is required.【Docetaxel for Injection instruction 】
Docetaxel/ Trastuzumab	Trastuzumab	Docetaxel	Trastuzumab administration should be followed by initial dose of Docetaxel administered as an intravenous infusion after one day. And Docetaxel should be administered immediately after intravenous infusion of trastuzumab if the initial dose is well tolerated.【Docetaxel for Injection instruction】
Docetaxel/ Trastuzumab/ Pertuzumab	Trastuzumab/ Pertuzumab	Docetaxel	Trastuzumab and Parstuzumab should be administered sequentially (in any order), following completion of Docetaxel.【Pertuzumab for Injection instruction】
Docetaxel/ cisplatin/ fluorouracil	Docetaxel	cisplatin，then fluorouracil	In a phase III randomized controlled clinical trial, the commonly used dose schedule for head and neck squamous cell carcinoma treatment is docetaxel 75 mg/m^2 infusion for 1h followed by followed by cisplatin 100 mg/m2 infusion for 0.5~3 hours. Then, fluorouracil was given at 1000 mg/m^2/d for 4days consecutively[7].

10.2 Configuration of drugs

Taxane antitumor drugs should be centrally configured in the intravenous drug dispensing center, and the whole configuration process follows the Guidelines for the Construction and Management of the Intravenous Drug dispensing Center and the Operation Quality Management Specification of intravenous cytotoxic Drugs in Medical Institutions. Specific drug configuration operation and related requirements are as follows:

1) Manual configuration

The configuration methods of paclitaxel injection, paclitaxel liposomes for injection, paclitaxel for injection (albumin binding type/albumin-bound), paclitaxel polymer micelle for injection and docetaxel injection are shown in Tab 10 (docetaxel injection is slightly different due to different manufacturers and preparations).**Error! Reference source not found.**

Docetaxel injection with a special solvent: Remove the docetaxel injection from the refrigerator, and keep the vial upright at room temperature[8, 9]. Place in biosafety cabinet for 5 min. After disinfecting the syringe with 75% ethanol(A 20mL syringe is recommended.)**Question 3**[9-11], slowly inject 1.5 ml of special solvent along the wall of the bottle (Tilt the docetaxel bottle by 60°, hold the syringe in your right hand, stick the inclined surface of the needle close to the 1/2 of inner wall of the bottle, and slowly inject the solvent along the bottle wall[10]**Question 3**).Gently shake and mix evenly (It is recommended to turn the vial slowly clockwise for 30s to avoid violent shaking. And keep the bottle in the biosafety cabinet for at least 20min. After observing that the drug was completely dissolved, hold the disinfected bottle of Docetaxel injection in your left hand so that the bottle is at a 45° angle with the operating table. Using the needle stem and glue plug plane vertical needle left direction method (needle oblique plane to the left) stabbed into the bottle. Finally, use a syringe to draw as much as possible, inject the liquid into 0.9% sodium chloride solution or 5% glucose injection 250 ml, gently shake the mixture evenly[8]See Clinical Problem 5 for details.

Docetaxel injection without special solvent: Leave the medicine at room temperature for 5 minutes after removing it from the refrigerator. Take the required volume of drug directly injected into 250ml 0.9% sodium chloride injection or 5% glucose injection (the final concentration of liquid should not exceed 0.74 mg / ml), shake gently and mix evenly

Tab 10 Configuration requirements for yew-class antitumor drugs

	Paclitaxel injection	Paclitaxel liposomes for injection	Paclitaxel was used for injection (Albumin-binding type)	Paclitaxel polymer micelles for injection	Docetaxel Injection
Menstruum	0.9% sodium chloride injection, or 5% glucose injection, or 5% glucose plus 0.9% sodium chloride injection, or 5% glucose Ringer's solution	5% glucose injection	0.9% sodium chloride injection	0.9% sodium chloride injection	5% glucose or 0.9% sodium chloride
Collocation	The liquid was extracted and injected into 100~500 ml 0.9% sodium chloride injection, or 5% glucose injection, or 5% glucose plus 0.9% sodium chloride injection, or 5% glucose in Ringer's solution	After adding 5% glucose injection into the drug, it was placed in a special oscillator and shaken to dissolve. After it was completely dissolved, the mixture was transferred to 250-500 m l 5% glucose injection.	Take 20 ml of 0.9% sodium chloride and inject it slowly along the inner wall of the bottle (> 1 min) dto avoid foam, and let it stand for more than 5 min. Then turn gently or slowly upside down (> 2 min) and let stand for 15 min. Finally, the required amount of liquid was pumped into an empty sterile 0.9% sodium chloride injection bag.	Slowly pour 5ml 0.9% sodium chloride injection into the bottle along the wall and leave for at least 10 mi. Shake slowly and gently or invert up and down until the freeze-dried powder (block) is completely dispersed., Extract required liquid into 0.9% sodium chloride sterile injection bag dilute for reserve use.	Different configuration methods are different, see the above.
Configuration concentration	0.3~1.2 mg/ml		5 mg/ml		Original research drug: 0.74 mg / ml
Finished product traits	Colourless clarification of liquid	Milk white suspension	Milk-white, homogeneous liquid without visible microparticles	A homogeneous, transparent liquid with an emulsion	Colourless clarification of liquid
Stability after the configuration	It can be kept stable for 27 h at room temperature and under indoor light.	It was stable at room temperature (25℃) and indoor light for 24 h.	The suspension in the bottle can be stored for 8 h at 2~8℃under the condition of avoiding light; Suspended liquid in the infusion bag after dispersion and dissolution: it can be stored for 8	Data is insufficient, so it is recommended to use it immediately.	Original drug: Preinjection can be stored at 2~8℃ for 8 h, but it is recommended to use it immediately after preinjection configuration. The injection solution can be

			h at room temperature (20~25℃) and indoor light.		stored at room temperature for 4 h.

A: It is recommended to add 10 ml in the instruction manual, but it is reported that the physical stability indicators are more reliable by adding 15 ml of solvent.[11];

b: Oscillation frequency: 20 Hz, amplitude: 7 cm in X axis, 7 cm in Y axis, 4 cm in Z axis;

c: The instructions require vibration for 5 min, but the actual work found that paclitaxel liposomes for injection needed 15 minutes of vibration to completely dissolve., And there is literature[11, 12]reported the particle size and sealing rate have the best effect when shaken for 15 min;

d: Avoid injecting 0.9% sodium chloride injection directly into lyophilized blocks or powder to avoid foam.

2) Intelligent intravenous drug dispensing robot configuration (hereinafter referred to as robot) The robot has the whole process quality control system, its configuration process in hundred sterile fully closed negative pressure chamber. It can realize closed loop detection control configuration process, ensure finished aseptic and accurate dosage. At the same time, it can reduce the unavoidable occupational damage and drug cross contamination during manual operation.

The configuration conditions and methods of yew antitumor drugs are different. In order to ensure the complete dissolution and accurate configuration of the drugs, the configuration conditions and methods should be tested when using the robot configuration. The configuration of the intelligent intravenous drug deployment robots of different manufacturers is different.

10.3 The infusion of drugs

The infusion requirements of taxane drugs are different due to the different dosage forms and production processes, and the detailed infusion requirements are shown in Tab 11.**Error! Reference source not found.** Paclitaxels are non-DNA binding foaming drugs, and the extravasation can cause blebbing, ulceration, or necrosis of the skin or mucosa. According to the Prevention and Treatment of Chemotherapy extravasation, the vascular condition of the patients should be fully evaluated before the infusion, and the appropriate infusion method should be selected, so as to prevent the extravasation of the drugs. In case of extravasation, please dispose of it immediately according to the procedures in the above standards. For the discomfort caused by the extravasation of paclitaxel drugs (without albumin-bound dosage forms), 150 U/ml hyaluronidase agent should be used as an antidote/antagonist. According to the assessed amount of extravasation drug, 1ml of exudate was treated with 1ml of hyaluronidase and subcutaneously injected at the exudate site in 5 times clockwise. Subsequently, necessary measures such as dry hot compress, raising the affected limb and 50% magnesium sulfate wet compress should be adopted[13].

Tab 11 Infusion requirements for yew-class antitumor drugs

Project	Paclitaxel liposomes for injection	Paclitaxel injection	Paclitaxel for injection (albumin-binding type)	Paclitaxel polymer micelles for injection	Docetaxel Injection
Infusion device	Disposable infusion set in line with national standards (> 10 μ m)	Disposable non-PVC infusion bottle and tube with filter (aperture 0.22 μ m)	Ordinary disposable infusion device (> 15 μ m), it is not recommended to install the filter in the infusion tube	No special requirements	
Time of infusion	3 h	The time of administration varies with different administration schemes, which are 3 h or 24 h.	30 min	3 h	1 h[20]
Matters need attention	During the infusion process, the injection site should be closely observed and alert to the possible vascular leakage and liposome sedimentation. If it is found that the lipid body is aggregated and layered under the action of gravity, it should be properly shaken to make the medicine liquid disperse evenly[14].If the liquid cannot disperse evenly after shaking, it should be stopped immediately.	During the infusion process, the injection site should be closely observed and alert to the possible vascular leakage.			

10.4 Pharmaceutical monitoring of adverse drug reactions

Because of their similar active ingredients and similar adverse reactions, they are mainly manifested as anaphylaxis, blood toxicity, neurotoxicity, muscle and arthralgia, cardiovascular toxicity, liver toxicity, liver and kidney toxicity, and digestive tract reactions ,which need to be monitored. The specific monitoring is shown in Table 12.**Error! Reference source not found.**

Table 12 Monitoring indicators related to adverse reactions of yew-class antitumor drugs

Monitoring project	Specific monitoring methods
General run of things	1. Clinical symptoms and adverse reactions should be evaluated at each follow-up visit, and the patients should be asked if they have developed any symptoms like loss of appetite, nausea, vomiting, and diarrhea' 2. Ask the patient if he have fatigue, fatigue, headache and other symptoms; 3 Ask the patient if she has paresthesia, numbness, burning, or neuropathic pain in the hand and / or feet[15]
General hematology examination	1. The blood routine was checked once or twice a week during the medication period, focusing on neutrophil and platelet counts, and on the presence of anemia 2. Regular review according to the indications
Skin or mucosa	1. Closely observe the injection site during drug administration 2. During each medical ward round, skin and mucosal examinations should be conducted to pay attention to whether the patient has skin flushing, skin itching, rash, urticaria and mucositis 3. Care for fluid retention, including edema (mainly with docetaxel injection)[16]
Muscle and joint	1. Joint and skeletal muscle examinations were performed 1 to 3 d after medication[17] 2. If it develops into chronic neuropathic pain[18-20]Regular review is required
Cardiovascular	1 Blood pressure, heart rate, and respiration were measured every 15 min within 1 h of the infusion[21] 2. Regular review of electrocardiogram, cardiac color ultrasound and myocardial enzymes spectrum, focusing on patients with cardiac risk factors[22]
Lungs	1. Regularly check blood oxygen saturation at resting or activity, as well as routine lung imaging 2. Patients with previous lung disease should have regular lung function examination
Liver	1. Check the liver function regularly[23], Blood biochemistry was checked once every 2 weeks, focusing on alkaline phosphatase, bilirubin, aspartate aminotransferase, and alanine aminotransferase 2. For patients with liver disease, liver ultrasound is reviewed regularly

Kidney	1. Regular renal function examination 2. For patients with kidney disease, renal ultrasound is reviewed regularly

10.4.1 Hematological adverse effects

Yew antitumor drugs act on tumor cells, but also damage normal hematopoietic cells in different degrees. Among them, hematological toxicity is the main dose-limiting toxicity of taxane drugs, including neutropenia, anemia, and thrombocytopenia, and the risk of occurrence is related to the type of drug, dose, and time of infusion. Different pharmacokinetic characteristics of different taxane drugs also show different safety risk characteristics in clinical practice. It has been shown that infusion time has a greater effect on myelosuppression than dose, has a greater effect on myelosuppression than dose,[24]. Moreover, the risk and severity of hematologic toxicity in docetaxel is relatively high[25];The occurrence of hematologic toxicity of albumin-bound paclitaxel is similar to the common paclitaxel[26];Paclitaxel for injection (albumin-bound type) has a lower incidence of adverse reactions to grade 4 neutropenia compared with normal paclitaxol[27]. In addition, in terms of the treatment regimen, comparing the single-weekly regimen of paclitaxel for injection (albumin-bound type) with the three-week regimen, the occurrence of hematological toxicity may be related to its specific dose[28].And the associated risk increases when combined with drugs with hemotoxic adverse reactions.

1) Neutropenia

Neutropenia refers to the peripheral blood absolute neutrophil count (ANC) is below $2.0 10^9$/ L, Neutropenic fever (FN) is the main clinical complication, which may reduce the dose or delay the treatment of chemotherapy drugs, thus reducing the clinical efficacy; or may also cause the complications such as serious infection or even death. FN is usually defined as oral temperature> 38.0℃ (axillary temperature> 38.1℃) or two consecutive oral temperature> 38℃ (axillary temperature> 37℃) within 2h with ANC <0.5 * 10^9/ L, or expected to <0.5 * 10^9/ L .

Neutropenia is the most dominant hematologic toxicity of taxane drugs in a dose-dependent manner. And a higher risk of grade 4 hematological adverse reactions in patients with elevated bilirubin or abnormal transaminase with elevated alkaline phosphatase.

This adverse reaction should be handled appropriately in accordance with the corresponding guidelines / consensus, such as the NCCN Clinical Practice Guidelines: Prevention and Treatment of Cancer-related Infection, and the NCCN Clinical Practice Guidelines: Hematopoietic Growth Factor.

2) Anemia

Anemia shows a decreased red blood cell number per unit volume, a decreased hemoglobin concentration, or a reduction of the specific red blood cell volume (HCT) to below normal levels. Common complaints include syncope, post-active dyspnea, headache, dizziness, chest pain, weakness, obvious paleness of the skin and mucous membranes, abnormal menstruation in female patients, and possible symptoms of jaundice. Cancer Related Anemia, tumor-related anemia (CRA) refers to the anemia occurring in the course of disease progression and treatment. Its incidence and severity are related to the age, tumor type, stage, course of disease, treatment regimen, drug dose and whether infection occurs during chemotherapy[29]. Taxane drugs can directly affect bone marrow hematopoiesis by blocking the synthesis of erythroid precursor cells[30, 31]. The incidence and severity of CRA may increase and worsen with increasing chemotherapy cycles.

Data from 7,324 cancer patients from 97 hospitals in China showed that the incidence of anemia in cancer patients was 49.24%, and the highest among different tumor types (62.89%), followed by gynecological tumors (60.32%) and gastrointestinal tumors (51.13%), so the

management of anemia in cancer patients should be strengthened[32]. CRA events were more common during taxane treatment, but most of them were grade 1 / 2[25, 27, 33-35]。

This adverse reaction should be treated appropriately, according to the appropriate guidelines / consensus, such as the NCCN Clinical Practice Guidelines: cancer and chemotherapy-induced anemia. In addition, iron agent supplements should refer to the relevant guidelines / consensus recommendations.

3）thrombocytopenia

Chemotherapy-induced thrombocytopenia (CIT) refers to the inhibitory effect of anti-tumor chemotherapy drugs on bone marrow megakaryocytes, resulting in platelet counts from peripheral blood less than 100×10^9/L. CIT can increase the risk of bleeding, prolong hospital stays, increase medical costs and even lead to death in severe cases. Thrombocytopenia induced by taxanes is common, but grade 3/4 is rare[25, 33, 34].

This adverse reaction should be appropriately treated according to the corresponding guidelines/consensus, such as "Chinese society of clinical oncology（CSCO）diagnosis and treatment guidelines for cancer therapy induced thrombocytopenia (CTIT)".

10.4.2 Non hematological adverse reactions

1）peripheral neuropathy

Neurotoxicity is one of the common adverse reactions of taxanes, with an incidence rate of 70%~80%. Its pathogenesis is not completely understood at present. Possible mechanisms include microtubule structure disorder, mitochondrial damage of neurons and non-neurons, axonal degeneration and calcium imbalance in the internal environment. In addition, pathological changes such as altered nerve excitability and neuroinflammation are involved in the occurrence of chemotherapy-induced peripheral neuropathy (CIPN)[36]. The clinical manifestations of neurotoxicity caused by taxanes are abnormal sensation, numbness or neuropathic pain of hands and/or feet [30]. The peripheral neuropathy is accumulative and dose-dependent, and usually worsens with the increase of the dose and the treatment time. The incidence and degree of CIPN vary with different kinds of taxanes, which may be closely related to drug dosage, infusion time and accessories[37, 38]. Among them, the cosolvent of paclitaxel injection is polyoxyethylene castor oil. Animal experiments have shown that polyoxyethylene castor oil can cause axon swelling, degeneration and demyelination, and may

extend the duration of peripheral neuropathy[38, 39]. Compared with paclitaxel injection, CIPN induced by docetaxel has a lower clinical incidence and milder symptoms [40]. Meta analysis [41] showed that paclitaxel liposome had a lower incidence of neurotoxicity than paclitaxel injection in the treatment of breast cancer ($p<0.05$). Paclitaxel for injection (albumin bound) avoids the risk of solvent-induced neuropathy by using human albumin as a carrier. However, compared with paclitaxel injection, its administration amount increased, and the infusion time was reduced, resulting in a slightly higher incidence of CIPN than that of paclitaxel injection, but its median recovery time of CIPN was far lower than that of paclitaxel injection. It is reported that the median time of peripheral neuropathy improved from grade 3 to grade 2 which induced by paclitaxel for injection (albumin bound) was 24.75 days. The median time of docetaxel injection was 37 days. The median time of paclitaxel injection was 64 days [42].

The treatment of this adverse reaction is detailed in Clinical Question 6, and appropriate treatment should be carried out by referring to the instructions or corresponding guidelines/consensus (such as "Expert consensus on the standardized management of taxane-related peripheral neuropathy" and "Guidelines for the prevention and management of chemotherapy-induced peripheral neuropathy in adult cancer survivors of ASCO").

2）anaphylaxis

①Mechanism and clinical manifestations of anaphylaxis

Patients receiving paclitaxel injection are prone to type I hypersensitivity, with an incidence as high as 30%~41%, and the incidence of severe hypersensitivity is 2%~5%[43], most of which occur 2~3 minutes after administration, almost all of them occur within the first 10 minutes of infusion, and most of them occur after the first or second infusion[44]. Generally, the symptoms include rash, skin flushing, urticaria, etc., and in severe cases, it may be manifested as chest tightness, dyspnea, hypotension, tachycardia, etc. In addition, there may be other symptoms such as angialgia, chest and limb pain[45]. The allergic reaction rate of docetaxel injection was lower than that of paclitaxel injection. Paclitaxel injection and docetaxel injection contain polyoxyethylene castor oil and polysorbide 80, respectively. Its allergic reaction is related to solvent activation of complement to produce anaphylatoxin, thereby activating basophils and mast cells, as well as the IgE mediated immune mechanism [46]. Paclitaxel liposome for injection and paclitaxel for injection (albumin bound) have relatively few allergic reactions due to

improved dosage form.

②Treatment process of anaphylaxis

First of all, ask and evaluate the patient's allergy history, explain to the patient the possible allergic reactions and countermeasures after the infusion of taxanes, and cooperate with the medical staff for pretreatment and drug infusion. Pretreatment cannot completely eliminate anaphylaxis, and close observation is still required during drug infusion. If allergic reactions occur after medication, they need to be evaluated and stratified. If mild symptoms such as flushing, rash and other skin reactions occur, treatment can be not stopped, only symptomatic treatment is required. Severe anaphylaxis characterized by dyspnea, hypotension, angioneurotic edema, and systemic urticaria requires immediate cessation of infusion and aggressive symptomatic treatment. The specific classification can be found in CTCAE version 5.0, and for specific treatment measures, refer to relevant anaphylaxis management guidelines and consensus (such as “2020 World Allergy Organization Guidelines: Severe Anaphylaxis, Expert Consensus on the Comprehensive Diagnosis and Treatment of Drug Hypersensitivity”, “2021 European Society of Allergic Reactions and Clinical Immunology (EAACI) Guidelines: Allergic Reactions”, etc.).

Patients with mild to moderate anaphylaxis can try to inject the original drug again slowly after the condition is stable. If anaphylaxis occurs again, it is recommended to use other drugs of the same type or different types of drugs instead. For severe allergic patients, the original drug is no longer recommended. After 24 hours of stable vital signs, other drugs of the same type or different types of drugs can be used under close monitoring. Among them, paclitaxel injection or docetaxel injection can be replaced by paclitaxel for injection (albumin bound).

3）Nausea、vomiting

Taxanes have low emetic risk, with an incidence of 10% to 30%. However, when used in combination, the risk level of emetic is determined by the drug with the highest risk in the combination. The program of emetic prevention should be followed by antiemetic guidelines (such as “NCCN Clinical Practice Guidelines: Antiemesis, Shanghai Expert Consensus on the Whole Process Management of chemotherapy-induced nausea and vomiting”, “Chinese Expert Consensus on the Prevention and Treatment of nausea and vomiting related to Cancer Drug Therapy”, etc.).

It is recommended to use single antiemetic drugs such as dexamethasone, type three 5-hydroxytryptamine receptor antagonist (5-HT_3RA) and metoclopramide to prevent vomiting in the single drug method of taxanes. In combination with other high-risk emetogenic drugs, a standard triple therapy of 5-HT_3RA+ neurokinin-1 receptor antagonist (NK-1 RA) + dexamethasone is generally recommended. If the patient still vomits, olanzapine can be added to the therapy. For patients with other moderate emesis risk drugs, 5-HT_3RA+ dexamethasone standard dual therapy is recommended. For patients with other high-risk factors or who still have nausea and vomiting after the previous use of this therapy, the triple therapy of "5-HT_3RA+NK-1 RA+ dexamethasone" or "5-HT_3RA+ olanzapine + dexamethasone" is recommended.

4）Muscle and joint pain

Taxane acute pain syndrome (TAPS) is clinically common and is characterized by arthralgia and myalgia that occur 1 to 3 days after chemotherapy with taxanes and last for 5 to 7 days. TAPS is related to neuropathology, and the mechanism of TAPS is still unclear. It may initially be an acute inflammatory pain and then gradually develop into chronic neuropathic pain, and it may also be related to hyperalgesia of pain receptors [18-20]. The incidence of TAPS ranges from 2.8% to 72%, and varies among different preparations. TAPS in docetaxel injection is more common than that in paclitaxel injection or paclitaxel for injection (albumin bound), and TAPS may be more common in patients with breast cancer than in non-breast cancer patients [47].

Currently, a number of drugs are available to treat TAPS, including opioids, paracetamol and nonsteroidal anti-inflammatory drugs, but the effect is not significant. Prevention may be more appropriate than treatment[48]. A retrospective study of 128 patients with breast cancer who treated with a three-week regimen of paclitaxel for injection (albumin bound) assessed possible factors influencing the development of TAPS. The results indicated that TAPS could be associated with the absence of dexamethasone at high doses of paclitaxel for injection (albumin bound), suggesting that patients receiving high-dose paclitaxel for injection (albumin bound) treatment, especially when the dose was ≥ 410 mg, dexamethasone may be given continuously for 3 days[49]. At the same time, a study evaluated the risk factors of TAPS in the case of preventive use of dexamethasone, and the results showed that the use of dexamethasone in patients younger than 55 years old would increase the risk of TAPS[50].

5）hepatic and renal function abnormity

Taxanes are mostly cleared through liver metabolism and bile excretion, so it can be seen that liver function indicators such as bilirubin and aminotransaminase are increased, but liver injury is rare[23]. For patients with abnormal liver function, the recommended dosage of taxanes is different, and the dosage should be adjusted in time according to the liver function (see Table 4 for details).

Renal metabolism of taxanes is relatively low, and the initial dose of paclitaxel for injection (albumin bound) and paclitaxel polymeric micelles for injection should not be adjusted for patients with mild to moderate renal dysfunction (estimated creatinine clearance ≥30 mL/min to < 90 mL/min).

6）Others

Other adverse reactions include fatigue, headache, alopecia, etc. Generally, there is no clear treatment recommendation. Intravenous administration of taxanes can also cause injection site reactions (including intravenous and local inflammation, drug exudation, etc.). The treatment methods refer to the treatment principles of chemotherapeutic agent extravasation.

10.4.3 Medication education for patients with adverse reactions of taxanes

Among the core competencies recommended by the American College of Clinical Pharmacy, clinical pharmacists should have the ability to communicate with patients, which means that clinical pharmacists should perform the responsibility of patient education, deliver drug and treaty-related information to patients, and improve patient compliance[51]. As for taxanes, their adverse reactions are harmful, so it is necessary to conduct adverse reactions education and patient management to avoid chemotherapy delay or dose adjustment due to adverse reactions, which may affect the therapeutic effect. The medication education for patients with adverse reactions is shown in Table 13 for details.

Table 13 Education content of drug use for patients with ADR induced by taxanes

Adverse reactions	Judgment of severity [52]	Method of treatment	Continuous monitoring method
Neutropenia	（1）grade 1: Neutrophil count (1.5 ~ < 2.0) $\times 10^9$/L （2）grade 2: Neutrophil count (1.0 ~ < 1.5) $\times 10^9$/L （3）grade 3: Neutrophil count (0.5 ~ <1.0) $\times 10^9$/L （4）grade 4: Neutrophil count < 0.5×10^9/L	Generally, ≥ grade 1 requires prompt medical treatment	Blood routine should be monitored 1~2 times a week for the first 1 month of medication, and once every 2~4 weeks after stabilization
thrombocytopenia	（1）grade 1: Platelet count (75 ~ < 100) $\times 10^9$/L （2）grade 2: Platelet count (50 ~ < 75) $\times 10^9$/L （3）grade 3: Platelet count (25 ~ <50) $\times 10^9$/L （4）grade 4: Platelet count < 25×10^9/L		
anemia	(1) Grade 1: hemoglobin (100 ~ < the lower limit of normal value) g/L, the general lower limit of normal for men is 120g/L, 110g/L for women (2) Grade 2: hemoglobin (80 ~ < 100) g/L (3) Grade 3: hemoglobin (< 80) g/L (4) Grade 4：life-threatening and requires emergency treatment		

anaphylaxis	The main manifestations were dyspnea, dizziness, hypotension and loss of consciousness, among which grade 1 and grade 2 were not objectively described in the Standard 5.0 version of the common terminology criteria for adverse events. Grade 3: symptomatic bronchial asthma; Angioedema; Hypotension; Grade 4: Life-threatening and requires urgent treatment	In general, allergic reactions need timely medical treatment	（1） Within 1 hour of medication, blood pressure, heart rate and respiration should be measured every 15 minutes （2） whether there is dyspnea, dizziness, hypotension, loss of consciousness and their degree
Peripheral sensory/motor nerve disorders	(1) Grade 1: paresthesia of hands/feet and/or decreased tendon reflexes (2) Grade 2: severe paresthesia and/or mild weakness, limited use of tools (3) Grade 3: intolerance of paresthesia and/or significant dyskinesia; Limited self-care (4) Grade 4: paralysis, requiring emergency treatment	In general, allergic reactions need timely medical treatment	Whether there are hand/foot sensory abnormalities, tendon hyporeflexia, weakness, dyskinesia, paralysis and their degree
vomiting	(1) Grade 1: vomiting 1~2 times within 24 hours, interval 5 minutes (2) Grade 2: vomiting 3~5 times within 24 hours, interval 5 minutes (3) Grade 3: vomiting ≥ 6 times within 24 hours, interval 5 minutes, tube feeding, total parenteral nutrition or hospitalization is required	(1) Grade 1 usually does not require intervention. Metoclopramide tablets may also be taken orally (except for breast cancer patients) (2) Grade 2 should be timely replenishment of fluid. If possible,	Frequency and severity of vomiting

	(4) Grade 4: Life threatening and requires urgent intervention	seek medical attention as much as possible (3) Grade 3 and above should seek medical attention immediately	
Diarrhea	It is mainly manifested by changes in the frequency and pattern of stools: (1) Grade 1: the frequency of stool increases < 4 times per day over baseline; mild increase in ostomy output compared to baseline (2) Grade 2: the frequency of stool increases < 4~6 times per day over baseline; moderate increase in ostomy output compared to baseline (3) Grade 3: the frequency of stool increases ≥7 times per day over baseline; severe increase in ostomy output compared to baseline	(1) Grade 1 recommends a light diet (2) For grade 2, antidiarrheal drugs such as loperamide or montmorillonite powder can be taken orally for symptomatic treatment, and high-fiber/lactose diet can be avoided (3) ≥ grade 3 requires prompt medical treatment	Whether the stool form changes and the frequency of stools increases [53]
Muscle and joint pain	It is manifested by obvious discomfort in muscles and joints: (1) Grade 1: mild stiffness and pain (2) Grade 2: moderate stiffness and pain, limited use of tools (3) Grade 3: severe stiffness and pain, limited self-care	Generally, ≥ grade 2 requires medical attention, pain medication, or other management	Whether there is discomfort, pain and severity in muscles and joints

Elevation of transaminase（ALT/AST）	(1) Grade 1: 1.5~3 times of the upper limit of normal value (2) Grade 2: 3~5 times of the upper limit of normal value (3) Grade 3: 5~20 times of the upper limit of normal value (4) Grade 4: 20 times of the upper limit of normal value	Generally, ≥ grade 1 requires prompt medical treatment	Transaminase (ALT/AST) was monitored once every 2 weeks for the first 2 months and once every 4 weeks after stabilization
Elevation of bilirubin	(1) Grade 1: 1~1.5 times of the upper limit of normal value (2) Grade 2: 1.5~3 times of the upper limit of normal value (3) Grade 3: 3~10 times of the upper limit of normal value (4) Grade 4: more than 10 times of the upper limit of normal value	Generally, ≥ grade 1 requires prompt medical treatment	Bilirubin was monitored once every 2 weeks in the first 2 months of administration and once every 4 weeks after stabilization
Hand-foot syndrome	The main symptoms are redness, swelling, pain, ulceration, keratosis and even numbness of hands and feet: (1) Grade 1: slight skin change (erythema, edema/hyperkeratosis), no pain (2) Grade 2: Skin changes (exfoliation, blisters, bleeding, chaps) with pain	(1) Grade 1: apply urea cream locally, take vitamin B6 orally, and continue to observe (2) Grade 2 can be temporarily applied with ointments containing hormone (such as mometasone furoate cream) and anti-infective	Whether the skin of hands and feet is red, swollen, ulcerated, keratinized, painful and its degree

	(3) Grade 3: severe skin changes (exfoliation, blisters, bleeding, chaps, edema), severe pain	ointments (such as mupirocin ointment). If possible, seek medical attention as much as possible (3) Grade 3 should seek medical attention immediately	
Oral mucositis	(1) Grade 1: asymptomatic or mild symptoms, no influence on eating, no treatment required (2) Grade 2: moderate pain, ulcer, not affecting eating, but diet adjustment is required (3) Grade 3: severe pain, ulcer, affecting eating (4) Grade 4: life threatening, requiring emergency treatment	(1) Grade 1 can contain ice cubes to maintain oral hypothermia for 30 minutes, take vitamin B6 orally, and continue to observe [54] (2) Grade 2: Lidocaine gel can be temporarily applied. If possible, seek medical attention as much as possible (3) Grade 3 and above should seek medical attention immediately	Whether the oral mucosa has erythema, ulcer, pain and its degree
Rash	The main manifestations are changes in skin color, bulging or blisters on the skin surface, etc. (1) Grade 1: covering < 10% of body surface area (2) Grade 2: covering 10%~30% of body surface area, accompanied by psychological effects, affecting instrumental daily living activities (3) Grade 3: covering ≥ 30% of body surface area, affecting self-care daily living activities	(1) Grade 1: apply paeonol locally, continue to observe (2) Grade 2 can temporarily apply ointment or cream containing hormone (such as hydrocortisone cream, desonide cream, etc.). If possible, seek medical attention as much as possible	Whether the skin has symptoms such as color change, surface swelling or blisters and their degree

	(4) Grade 4: covering the whole body, life threatening	(3) Grade 3 and above seek medical attention immediately	
Pruritus	(1) Grade 1: mild or local attack (2) Grade 2: widely distributed and intermittent, scratching causes skin changes (such as edema, papule, scratch, exudation, scab), affecting instrumental daily living activities (3) Grade 3: widespread and persistent attack, affecting self-care activities of daily living or sleep	(1) Grade 1: topical antipruritic drugs (such as calamine lotion and camphor cream) (2) Grade 2: ointment or cream containing hormone (such as dexamethasone acetate cream) can be temporarily applied. If possible, seek medical attention as much as possible (3) Grade 3: Do not handle it by yourself, and seek medical advice immediately	Whether the skin is itching and its degree
Edema in limbs	(1) Grade 1: the difference between limbs is 5%~10%, and swelling or blurred anatomical contour is found during careful examination (2) Grade 2: the difference between limbs is 10%~30%, with obvious anatomical contour blurring, skin wrinkles eliminated, affecting instrumental daily activities	Generally, ≥ grade 1 requires prompt medical treatment	Whether the limbs are swollen and the skin wrinkles are eliminated

	(3) Grade 3: difference between limbs ≥ 30%, significant anatomical contour blurring, affecting self-care daily activities		
Alopecia	(1) Grade 1: individual hair loss is less than 50%, no obvious difference is found in remote observation, but it can be seen in close observation (2) Grade 2: individual hair loss ≥ 50%, with obvious symptoms and psychological influence	(1) Grade 1：change hair style (2) Grade 2：periwig	Whether the hair is less than normal and its degree

11 Related clinical issues

11.1 Prescription review related clinical issues

Question 1: Whether the dosage of dexamethasone in preconditioning should be reduced

Recommended comments:

Existing evidence can preliminatively confirm the necessity and feasibility of dexamethasone reduction treatment, and it's suggested that whether dexamethasone reduction is used in the pretreatment scheme in prescription review should not be used as the basis for determining whether the prescription is reasonable.

Summary of the evidence:

Dexamethasone preconditioning can reduce the incidence of paclitaxel-related allergic reactions, but dexamethasone doses recommended in guidelines and instructions are not low, and adverse reactions associated with long-term corticosteroid use, including hyperglycemia and insomnia, have been well documented[55]。

As to whether glucocorticoids need to be reduced or stopped in paclitaxel preconditioning, the Guidance on Hypersensitive Reaction preconditioning of paclitaxel Preparations put forward suggestions on simplified glucocorticoid preconditioning, including dexamethasone reduction preconditioning and drug withdrawal preconditioning[43].

In addition, studies have shown that reducing dexamethasone use appears to be a safer way to administer the drug in patients at high risk for steroid use[56].As for dexamethasone reduction preconditioning regimen, a retrospective study involving 3,181 patients showed that dexamethasone dose and route of administration were not correlated with hypersensitivity, and low-dose dexamethasone (10mg) preconditioning regimen may be superior to the regimen recommended in the guidelines[57]. Dong et al. compared the number of allergic reactions and other common adverse reactions among 356 patients who received two low-dose dexamethasone pretreatments, and found that the intravenous dexamethasone 10mg regimen 30 minutes before paclitaxel infusion was safer than the oral plus intravenous combination regimen. That is, dexamethasone 7.5mg orally at 10pm and dexamethasone 5.5mg intravenously 30 minutes before paclitaxel infusion[58]. Approximately 90% of paclitaxel hypersensitivity reactions (HSR) occur within the first 10 to 15 minutes of the first two infusions. Studies have confirmed that it is feasible to reduce hormone dosage by simplifying pretreatment regimen during the third cycle of administration, including dexamethasone reduction pretreatment and dexamethasone withdrawal pretreatment. Multiple studies have shown that the incidence of HSR is less than 10% for either paclitaxel alone or in combination with dexamethasone withdrawal preconditioning regimen before chemotherapy. Castro Baccarin AL et al. found that dexamethasone discontinuation was feasible in breast cancer patients receiving paclitaxel chemotherapy from week 3 to week 12, and the incidence of HSR was not significantly different from that of continuous dexamethasone

preconditioning regimen[59].In a prospective clinical study, 125 patients with stage I to III breast cancer received a preconditioning simplified regimen prior to paclitaxel therapy that included oral dexamethasone 12 mg 2 to 6 hours before infusion; if HSR did not occur in the first two cycles, dexamethasone preconditioning was discontinued at the beginning of the third cycle. It was found that the incidence of Grade 3/4 HSR was 0.8% (90% CI, 0.04% -3.7%).[60]Similarly, in a retrospective study of 81 patients, only 6.25% of patients who stopped preconditioning with dexamethasone after two cycles of chemotherapy developed HSR[61].A meta-analysis involving 637 patients in 6 studies showed that the incidence of grade 3/4 HSR was 0.44% and that of any grade HSR was 3.1%[62].

In addition, dexamethasone low-dose treatment regimen is also suitable for other taxol drugs. Jiaqi Wang et al. found that there was no significant difference in the incidence of HSR when docetaxel was administered orally 8 mg dexamethasone twice a day for 3 consecutive days, compared with the pre-treatment regimen of 5 mg intravenous injection of dexamethasone half an hour before the race, which confirmed that low-dose dexamethasone pre-treatment would not increase allergic reactions in patients receiving docetaxel chemotherapy[63]. Teng Qinghua et al. found that for breast cancer patients receiving docetaxel chemotherapy, dexamethasone is recommended to be administered twice a day, 4.5 mg each time, which can be well tolerated by patients, not only will not increase allergic reactions and other adverse reactions, but also can reduce the incidence of muscle pain, excitement or insomnia[64].

Question 2: Whether the diphenhydramine contained in the pretreatment can be replaced by promethazine

Recommended comments:

To a certain extent, promethazine can replace diphenhydramine in the pretreatment regimen, the clinical dosage is 25 ~ 50 mg, but it should not be used in ovarian cancer chemotherapy and platinum-containing chemotherapy regimen instead of diphenhydramine.

Summary of the evidence:

Diphenhydramine is one of the pre-treatment drugs prescribed in the instructions for use before chemotherapy. However, in clinical practice, promethazine is often used as a substitute for diphenhydramine. Promethazine is a phenothiazine derivative and H1 receptor blocker with antihistamine, sedative, antiemetic and anticholine pharmacological effects. Several studies have shown that no serious adverse reactions have occurred when promethazine was used instead of diphenhydramine for pretreatment. Studies show that promethazine can be used as a substitute for diphenhydramine, clinical dosage of 25 ~ 50 mg[43].In a prospective clinical study that validated the efficacy and safety of oral promethazine and dexamethasone before paclitaxel chemotherapy, patients receiving weekly or triweekly chemotherapy were given promethazine 25 mg before paclitaxel administration. HSR responses occurred in only 1% of patients in the weekly

chemotherapy group and 4% in the triweekly chemotherapy group[65]. Zhou et al used a combination of dexamethasone, promethazine, and cimetidine in a pre-treatment regimen of paclitaxel or docetaxel for patients with advanced non-small cell lung cancer. Only 1 of 78 patients developed anaphylaxis and no treatment-related death occurred[66].

Promethazine instruction manual suggests that ototoxic drugs such as cisplatin can be masked when combined with promethazine. Therefore, it is not recommended to pretreat with promethazine in combination chemotherapy with paclitaxel and cisplatin.

Question 1：Whether H2 receptor antagonists must be used in the preconditioning regimen

Recommended comments:

H2 receptor antagonists, such as cimetidine and ranitidine, are not considered as mandatory drugs for preconditioning programs. It is suggested that in prescription review, it is reasonable to judge whether H2 receptor antagonists are not used as prescriptions for preconditioning programs.

Summary of the evidence:

Polyoxyethylene castor oil and polysorbate -80 in taxol drug excipients often cause HSR, which can endanger life in severe cases. A preconditioning regimen consisting of dexamethasone in combination with H1 and H2 receptor antagonists can significantly reduce HSR. However, it is uncertain which components of a three-drug regimen consisting of dexamethasone in combination with H1 and H2 receptor antagonists are necessary to prevent these allergic reactions. Theoretically, H2 antagonists are the least effective of the three allergy prevention drugs, and H2 antagonists themselves have some sensitization[67]. Therefore, it is controversial whether H2 receptor antagonists should be used.

Studies have shown that ranitidine itself can cause adverse reactions such as abnormal transaminase levels, nausea, vomiting, rash, and HSR[68-70]. Demirkan et al. found that ranitidine caused allergic reactions in about 0.7% of infusion cases[69].Although the incidence of ranitidine HSR itself is not high, its potential harm can be very serious[71]. And studies have shown that breast cancer patients who use H2 blockers before docetaxel chemotherapy have an increased risk of hand and foot syndrome and facial erythema[72]. Cox JM et al.[73] conducted a prospective, interventionistic, non-inferiority study that compared the incidence of grade 3 HSR during paclitaxel treatment with standard and non-ranitidine pretreatments, which showed that ranitidine pretreatments without ranitidine were no worse than ranitidine pretreatments. Gelderblom reviews the work of Cox JM et al., and further suggests that paclitaxel preconditioning regimens do not require the use of H2 receptor antagonists[67]。 Foremanec et al [74]further compared the incidence of HSR in patients treated with paclitaxel in a prospective, multicenter, cohort study without H2 receptor blockers versus with two pre-chemotherapy regimens containing chlorpheniramine, dexamethasone, and H2 receptor blockers. The results showed that H2 blockers as part of a

preconditioning regimen did not have any advantage in reducing the incidence of HSR in paclitaxel-treated patients.

11.2 Admixture and infusion related clinical issues

Question 2：When dissolving paclitaxel liposomes for injection, how many milliliters of 5% glucose injection should be added first for oscillation, and how long should be shaken on a special oscillator

Recommended comments:

When dissolving paclitaxel liposomes for injection, 15 ml 5% glucose injection should be added into the original packaging container. To ensure complete dispersion of paclitaxel liposomes, it is recommended to shake for about 15 min.

Summary of the evidence:

10 ml 5% glucose injection is required to be added in the drug instructions, but incomplete suspension dispersion may occur in actual operation. Studies have shown that[11] : 15 ml of solvent should be added to the preparation of paclitaxel liposome for injection, and 15 min of oscillation can effectively ensure the stability of the drug in the suspension. It is required in the drug instructions to shake for 5 minutes. However, studies[11, 12] have shown that when shaking for 15 min, drug particle size and encapsulation rate in suspension have the best effect. Combined with the actual work and expert opinion, it is suggested that the oscillating time on the special oscillator should be about 15 minutes.

Question 3：In the admixture of Docetaxel injection, how to choose the syringe size, how to shake and mix evenly without foam

Recommended comments:

To avoid obstructed aspiration, a 20 ml syringe is recommended. After slowly turning the bottle clockwise for 30 s (avoid violent shaking), the bottle should be kept in the biosafety cabinet for no less than 20 minutes.

Summary of the evidence:

In many studies[8, 9], 20 ml syringe was recommended for extraction to avoid drug aspiration obstruction. The instructions require manual mixing inverted repeatedly for at least 45 s, and leave the mixed drug at room temperature for 5 minutes; Some studies have shown that the medicine bottle injected with special solvent is placed in the WZr-D9510 medicinal oscillator to select the unidirectional shaking mode, and taken out after shaking for 30 s[9]to mix evenly. Other studies have shown that even mixing can be achieved by placing the vial in a drug oscillator and taking it out with one-way oscillation for 15 s[75]. In addition, other studies have shown that after holding the bottle clockwise slowly for 30 s (to avoid violent shaking), the bottle should be placed upside down on a sterile towel for 5 minutes[76] to be evenly mixed. The instructions mentioned that there would still be foam after being mixed and placed at room temperature for 5 min. In practical work,

it was found that after turning the bottle slowly for 30s and standing for no less than 20 min, docetaxel could be completely and evenly mixed without foam residue. It is recommended to rotate the bottle clockwise for 30 s (avoid violent shaking), and then leave the bottle in the biosafety cabinet for at least 20 minutes.

11.3 Clinical questions related to management of adverse reactions

Question 6:

Prevention and treatment of peripheral neuropathy of taxanes antitumor drugs

Recommended comments:

Cryotherapy（performed with ice packs on hands and feet） or compression therapy can be used for prevention of peripheral neuropathy of taxanes antitumor drugs. Duloxetine remains the recommended treatment approach.

Summary of the evidence:

In prevention, frozen gloves or compression therapy can be used to prevent the occurrence of taxane-induced peripheral neuropathy. A Danish study on peripheral neuropathy in 1725 patients with early breast cancer showed that the use of frozen gloves and socks during treatment can significantly reduce the incidence of peripheral neuropathy ($p<0.0001$)[81]. A prospective self-controlled trial showed that wearing frozen gloves and socks in breast cancer patients treated with paclitaxel was effective in preventing subjective symptoms of CIPN and decreasing CIPN incidence assessed by other objective modalities [82]. A meta-analysis reported that cryotherapy could avoid dose-limiting toxicity to a certain extent and improve the full dose completion rate of chemotherapy and patient survival rate [83]. Another phase II multicenter study evaluated the effect of compression therapy using surgical gloves on the prevention of nanoparticle albumin-bound paclitaxel-induced peripheral neuropathy. The results showed that National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 2 sensory neuropathies were reported in 21.4% of the hands that wore the gloves versus 76.1% of hands that were not gloved. The incidence of motor neuropathy was 26.2% vs. 57.1%, separately [84]. At present, no consensus has been reached on drug prevention methods for patients with CIPN. The role of neurotrophic factors, vitamin B, amifostine, glutamine, glutathione and other drugs in the prevention and improvement of CIPN is controversial [85].

In treatment, duloxetine is the sole recommended treatment by the guidelines of the American Society of Clinical Oncology (ASCO) for the treatment of painful CIPN with a recommended initial oral dose of 30 mg, 1-3 times/day, and a maximum daily dose of 60 mg [86].

A phase III, randomized, double-blind, placebo-controlled, crossover trial [81] included 231 patients after chemotherapy with taxanes or oxaliplatin. Patients in the group with duloxetine administrated first had a greater reduction in mean pain (mean change in pain score of 1.06) than those in the group with placebo administrated first (mean change in pain score of 0.34) ($p=0.003$).

In addition, if duloxetine is ineffective, drug therapy such as venlafaxine, pregabalin, gabapentin or tricyclic antidepressants can be considered. Alleviation of CIPN symptoms also can be found after physical exercise, functional training, acupuncture and scrambler therapy [87].

12 Conflict of Interest Statement

All relevant personnel involved in the writing, formulation and review of the consensus have no economic and non-economic conflicts of interest directly related to this consensus, and have declared conflicts of interest in accordance with relevant requirements.

Appendix 1

Interpretation of professional terms

Pharmaceutical services: It is the services provided by pharmacists with the purpose of improving the quality of life of patients and focus on appropriate use of drugs. It is a responsible and drug-related service directly provided to the public around the established goal of improving the quality of life in the entire medical and health care process, before and during drug treatment, and at any period after recovery.

Hazardous medicinal products: Refers to drugs that can cause occupational exposure risks or hazards, that is, drugs that are genotoxic, carcinogenic, teratogenic, or have harmful effects on fertility, and can produce severe organ or other toxicity at low doses.

Aseptic operation: It refers to the operation technique of preventing microorganisms from entering the finished infusion solution and keeping sterile items and sterile areas from contamination during the preparation of intravenous drugs.

Occupational protection: In occupational work, protective measures are taken to prevent occupational exposure.

Concentration-time curve: that is, a curve drawn with plasma drug concentration as the vertical axis and time as the horizontal axis, reflecting the dynamic process of plasma drug concentration changing with time. The area under the plasma drug concentration-time curve (AUC) reflects the actual body exposure to drug after administration of a dose of the drug.

Premedication before chemotherapy: Before chemotherapy, patients are given medical operations to prevent adverse reactions such as allergic reactions, nausea and vomiting, renal function damage, and water and sodium retention.

Appendix 2

Glossary of abbreviations

Abbreviations	Full Name
ANC	Absolute Neutrophil Count
AUC	Area Under Curve
CIPN	Chemotherapy-induced Peripheral Neuropathy
CIT	Chemotherapy-Induced Thrombocytopenia
CRA	Cancer-related Anemia

CTCAE	Common Terminology Criteria for Adverse Events
EMA	European Medicines Agency
EPO	Erythropoietin
FDA	Food and Drug Administration
FN	Febrile Neutropenia
G-CSF	Granulocyte Colony-Stimulating Factor
HCT	Hematocrit
HSR	Hypersensitivity
NCCN	National Comprehensive Cancer Network
NK-1 RA	Neurokinin-1 Receptor Antagonist
NMPA	National Medical Products Administration
rhIL-11	Recombinant Human Interleukin-11
RT	Radiation Therapy
TAPS	Taxane Acute Pain Syndrome
5-HT_3RA	5-Hydroxytryptamine 3 Receptor Antagonist

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