Expert Consensus on Precision Medicine by Surgical Pharmacists for Oncology in the Perioperative Period

Issued by Guangdong Pharmaceutical Association

With the National Health Commission promoting the development of oncology pharmacists, pharmacists in China have been incorporated into the multidisciplinary team for oncology treatment, and provide necessary professional pharmacy assistance in clinical practice. Surgical pharmacists with oncology specialist skills will provide more individualized pharmacy service model, playing an important role in standardizing medication in oncology treatment[1]. They can monitor the medication of oncology patients throughout the perioperative period to ensure the safety and precision of the treatment, including medication regime formulation and adjustment, managing drug-related adverse reactions and oncologic complications, and monitoring supportive and palliative care[2]. The introduction of the concept of precision medicine in oncology treatment has led to a greater focus on how pharmacogenomic, pharmacokinetic, and pharmacodynamic differences exert significant influence on clinical outcomes and the safety and efficacy of medication [3-4]. Technological advances in precision medicine continually enhance the rationalization and personalization of medication use. Second-generation sequencing (NGS) and therapeutic drug monitoring (TDM) are gradually becoming the source of the scientific basis for medication selection and efficacy and toxicity prediction, providing referable recommendations in drug selection [5-6].

1. Rational administration of medication for perioperative anti-tumor therapy in oncology patients

1.1 Lung cancer

1.1.1 Medication therapy for non-small cell lung cancer (NSCLC): Neoadjuvant therapy: paclitaxel+ cisplatin, erlotinib, gemcitabine+cisplatin and nivolumab. Adjuvant therapy: IA: regular follow-up; IB: High-risk patients should consider adjuvant therapy; IIA and IIB: platinum-based treatment scheme, patients with EGFR-sensitive mutation can be treated with osimertinib as adjuvant targeted therapy; IIIA and IIIB: patients with EGFR-sensitive mutation after radical surgery can be treated with osimertinib or erlotinib as postoperative adjuvant therapy; Patients after radical surgery can be treated with gefitinib or erlotinib as postoperative adjuvant therapy.

1.1.2 Medication therapy for small cell lung cancer (SCLC): etoposide+cisplatin/carboplatin [7].

1.1.3 Platinum: The combination of anti-microtubule medication, anti-folate medication and pyrimidine antagonists or radiation may increase the incidence of gastrointestinal toxicity[8]. Doxorubicin and vincristine can disrupt the transport of DNA repair proteins and increase the sensitivity of cisplatin[9]. The blood concentration of paclitaxel $T_C > 0.05$ is usually recommended as the optimal interval of 26-30h[10]. Erlotinib: Cmin>500ng/mL[11], gefitinib: Cmin≥200ng/mL[12], afatinib: Cmin: 14.4-27.4ng/mL[13] and ositinib: No evidence of a relationship between exposure and efficacy[14].

1.2 Gastric cancer

1.2.1 Neoadjuvant therapy: SOX, XELOX, FOLFOX, FLOT and DOS (good physical condition).

1.2.2 Adjuvant therapy: XP and tegafur monotherapy [15].

1.2.3 The toxicity of 5-FU is related to its metabolism, usually due to the reduced activity of the key metabolic enzyme dihydropyrimidine dehydrogenase (DPYD)[16], and the optimal therapeutic window is AUC=28.03-38.94 mg·h/L[17]. Patients with UGT1A1*28 (6/7) and (7/7) genotypes should be given a lower dose of irinotecan, and those with UGT1A1*6 allele have an increased risk of grade 4 neutropenia [18].

1.3 Colorectal cancer

1.3.1 Pre-operative neoadjuvant therapy for colorectal cancer with liver and lung metastases: FOLFIRI, cetuximab, bevacizumab, mFOLFOX6 and FOLFOXIRI. Fluorouracil-based treatment scheme is recommended for patients with rectal cancer.

1.3.2 Adjuvant chemotherapy: Not recommended for Stage I. Stage II Patients with high risk factors should be treated with oxaliplatin-based XELOX or FOLFOX, 5-FU/LV monotherapy or capecitabine;

Postoperative adjuvant chemotherapy is not recommended for patients with dMMR or MSI-H for tumor histology. Stage III: XELOX or FOLFOX, capecitabine monotherapy or 5-FU/LV; For low-risk patients (T1-3N1), XELOX can be considered as adjuvant chemotherapy for 3 months [19-20].

1.3.3 Cetuximab: Cmin>33.8mg/ml significantly prolonged OS and PFS [21]; Bevacizumab: Cmin>15.5mg/L on day 14 is associated with prolonged OS and PFS [22].

1.4 Hepatocellular Carcinoma (HCC)

1.4.1 Neoadjuvant therapy: Patients with HBV-related hepatocellular carcinoma can be given antiviral and hepatoprotective therapy at the active stage, and then undergo surgical resection after their liver function improves.

1.4.2 Adjuvant therapy: Patients with high risk of recurrence: antiviral drugs, hepatic artery intervention, systemic chemotherapy with oxaliplatin, molecularly targeted drugs, and traditional Chinese medicine treatment. Antiviral therapy and other hepatoprotective therapy for HCC: for patients with HCC complicated with HBV infection, especially those with active HBV replication, oral nucleoside and nucleotide analog antiviral therapy (entecavir, tenofovir or propofol tenofovir) should be used throughout the treatment; Direct antiviral agents (DAA) or interferon-α combined with ribavirin for patients with active HCV-related HCC; Hepatoprotective therapy: anti-inflammatory, enzyme-lowering, antioxidant, detoxifying, choleretic and hepatocyte membrane repair protection medication[23].

1.4.3 Sorafenib's therapeutic window: Cmax>3.75-4.30mg/L [24].

1.5. Breast cancer

1.5.1 Neoadjuvant therapy: For HER-2 positive breast cancer: TCbHP, THP, TCbH and AC-THP; For triple-negative breast cancer: TAC, AT, TP, AC-T and albumin paclitaxel combined with PD-1/PD-L1 inhibitors; Platinum agents can be included in the neoadjuvant therapy for patients with triple-negative breast cancer (TCb and PCb, or EC-TCb and EC-PCb), but the potential benefits and harms should be weighed when deciding to add platinum agents; Neoadjuvant chemotherapy for patients with hormone-receptor-positive breast cancer: anthracycline combined with paclitaxel: TAC, AT and AC-T; Neoadjuvant endocrine therapy for patients with hormone-receptor-positive breast cancer: AI (anastrozole, letrozole and exemestane), CDK4/6 inhibitors (piperacillin and abemaciclib), and fulvestrant.

1.5.2 Adjunctive therapy

1.5.2.1 Chemotherapy: anthracycline-based (AC and EC), anthracycline combined with paclitaxel (TAC), paclitaxel following anthracycline (AC→paclitaxel/docetaxel), anthracycline-free agents (TC and PC), capecitabine, olaparib, and albumin paclitaxe.

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1.5.2.2 Anti-HER-2 therapy: Trastuzumab for adjuvant therapy, dual-targeted therapy, and neratinib for HER-2-positive patients.

1.5.2.3 Postoperative adjuvant endocrine therapy for premenopausal patients: It can be performed after chemotherapy, and simultaneously with radiotherapy (tamoxifen excluded) and trastuzumab therapy (± other anti-HER-2 agents).

1.5.2.4 Adjuvant endocrine therapy: Tamoxifen, OFS+tamoxifen, OFS+third=generation AI; Postoperative adjuvant endocrine therapy for postmenopausal patients: The third generation AI can be recommended to all postmenopausal ER and/or PR positive patients [25].

1.5.3 HER-2 positive patients with BMI>30kg/m^2 have lower PFS and need TDM. Trastuzumab's therapeutic window: Cmin>20mg/mL [26]. Tamoxifen in CYP2D6 extensive metabolizers requires a reduction in drug dose[27]. A standard dose of tamoxifen is recommended for ultra-fast metabolizers and fast metabolizers[28]. Patients with slow metabolizers should have TDM with higher doses of tamoxifen or replacement with aromatase inhibitors[29]. Exemestane has been described as a therapeutic window drug for breast cancer: median Cmin=4.1ng/mL; Anastrozole: Cmin≥34.2ng/mL, and letrozole: Cmin≥85.6ng/mL;

Tamoxifen (just like endoxifen): Cmin≥5.97ng/ml[30-31].

1.6 Esophageal cancer

1.6.1 Neoadjuvant therapy: FLOT, fluorouracil-based + oxaliplatin/cisplatin, and paclitaxel+cisplatin.

1.6.2 Adjuvant therapy: For patients with esophageal adenocarcinoma who had neoadjuvant chemotherapy before surgery and completed radical surgery, the original therapy can be used for postoperative adjuvant chemotherapy. Recommended therapy: navulizumab, capecitabine+oxaliplatin, and paclitaxel+cisplatin [32].

1.6.3 High expression of PD-L1, high tumor mutational load (TMB) and MSI-H/dMMR can serve as predictors of positive efficacy [33]. Clinical application of ICIs exposure is obviously lacking in relation to efficacy or safety, and TDM has not been applied to ICIs for now [34].

1.7 Thyroid cancer

1.7.1 Adjuvant therapy: ^{131}I therapy: the serum TSH level should be increased before the removal of thyroid tissue. Serum TSH>30mU/L can significantly increase the uptake of ^{131}I by differentiated thyroid tumors.

1.7.2 Postoperative endocrine therapy for differentiated thyroid cancer: TSH suppression therapy: levothyroxine tablet (L-T4) is preferred.

1.7.3 Treatment of hypoparathyroidism

1.7.3.1 prophylactic therapy: The baseline levels of calcium, parathyroid hormone (PTH), and 25-hydroxyvitamin D3 should be obtained preoperatively.

1.7.3.2 Long-term therapy: Oral calcium, active vitamin D3 or its analogues, regular vitamin D3, PTH replacement therapy and thiazide diuretics.

1.7.3.3 Acute therapy: From intravenous to oral calcium supplementation, combined with oral active vitamin D3, and intravenous or oral magnesium supplement [35].

1.8 Cervical cancer

1.8.1 Neoadjuvant therapy: PVB and BIP.

1.8.2 Adjuvant therapy: postoperative pelvic radiotherapy+platinum-based synchronous chemotherapy±vaginal brachytherapy [36].

1.8.3 The expression of SLC5A7 and TTPA genes in patients treated with vincristine may increase the sensitivity of peripheral nerve reaction[37], and the blood concentration of vincristine≥1.57ng/ml is more likely to cause toxicity[38].

1.9 Intracranial tumor

1.9.1 Adjuvant therapy: High-grade glioma: Stupp, PCV; Anaplastic glioma: radiotherapy+temozolomide adjuvant chemotherapy, and radiotherapy+PCV chemotherapy are recommended. Glioblastoma (age≤70 years old): For patients with KPS≥60, conventional radiotherapy+synchronous and adjuvant temozolomide chemotherapy is recommended; For those with KPS<60, synchronous and adjuvant temozolomide chemotherapy±short-term radiotherapy is recommended[39].

1.9.2 The efficacy of temozolomide is associated with the genetic polymorphisms of MGMT, MMR, BER and HRR/NHEJ [40].

1.10 Pancreatic cancer

1.10.1 Neoadjuvant therapy: FOLFIRINOX, albumin paclitaxel combined with gemcitabine, and gemcitabine+Tegafur.

1.10.2 Adjuvant therapy: Tegafur monotherapy, gemcitabine combined with capecitabine, and mFOLFIRINOX. For patients with BRCA1/2 or PALB2 mutations, platinum-containing chemotherapy or combined with sequential radiotherapy are recommended, or gemcitabine combined with cisplatin (2-6 cycles) or with sequential radiotherapy and chemotherapy [41].

1.10.3 The molecular target of gemcitabine is nucleotide reductase1 (RRM1), and it increased expression and activity serve as a marker of gemcitabine resistance[42].

2. Perioperative infection, blood pressure, blood volume and nutrition management

2.1 Management of preoperative infection prevention medication

2.1.1 Perioperative antibiotic management: Prophylactic use of antibiotics plays an important role in reducing the chance of infection in surgery, organ transplantation, and cancer chemotherapy [43]. Intravenous administration is usually recommended. It is necessary to maintain an effective concentration at the surgical site before the contamination occurs and cover the entire surgical process. It can be administered once before clean surgery with an operation time of < 2h. If the surgery exceeds three hours or two times the half-life of the drugs used, or the blood loss in adults exceeds 1500ml, an additional dose should be administered intraoperatively. The duration of prophylaxis should not exceed 24 hours, and the contamination/cardiac surgery can be extended to 48 hours. Organ transplantation such as heart, lung, and liver can be extended to 72 hours[44-45] .

2.1.2 Principles of classified infection prevention and treatment of perioperative malignancy: Follow the guiding principles of clinical application of antibacterial drugs issued by the National Health Commission of China in 2015[46].

2.2 Management of postoperative anti-infection medication

2.2.1 Types and prevention strategies of postoperative infection in common tumor patients

2.2.1.1 Postoperative surgical site infection (SSI): It often occurs in the surgical site, the deep space of surgical field adjacent to the surgical organ and the entrance wounds[47], and the pathogen is usually a colonizing bacterium of the skin [48]. In general, bacterial infection in biofilm can not be recognized by standard clinical microbiological tests alone, and it should be combined with clinical manifestations [49].

2.2.1.2 Negative pressure drainage therapy for SSI: It can remove excess edema of the tissue and promote the formation of granulation tissue [50], reduce local toxins and bacteria, increase periwound blood flow and lymphatic drainage, reduce interstitial edema and stimulate local cell proliferation[51].

2.2.1.3 Drainage therapy for SSI: Postoperative stress, ischemia-reperfusion and tissue repair can lead to sterile inflammation, and increase leukocytes in abdominal drainage fluid., so it cannot be used directly as an indicator of infection to evaluate the patient's condition[52]. Placement of a single mediastinal drain via the abdominal cavity during thoracic surgery can significantly reduce postoperative pain and pleural effusion, without increasing the occurrence of postoperative infection[53].

2.2.1.4 Management of perioperative urinary tract infections: Enterobacteriaceae is the most common pathogen in urinary tract infection, and candida albicans, enterococcus and pseudomonas aeruginosa are more prevalent in ICU[54-55]. Systemic antimicrobials should not be routinely used to prevent urinary tract infections. Bladder irrigation with or without antimicrobials is recommended for urinary tract infections caused by obstruction[56].

2.2.1.5 Management of intravenous placement-related infections: Coagulase-negative staphylococcus is the most common bacteria responsible for bloodstream infections associated with intravenous placement, followed by staphylococcus aureus, enterococcus, and streptococcus, but there is a tendency to change to gram-negative bacteria[57]. Clinically, the initial treatment plan is usually empirical therapy, which depends on the severity of the disease, the risk factors of infection and the possible pathogens associated with the specific endovascular devices [58]. Recommended antimicrobials based on pathogen types: G^+: vancomycin or daptomycin; G^-: β-lactam/β-lactamase inhibitor combination or carbapenems ± aminoglycosides; Fungal: echinocandin[59].

2.2.1.6 Pressure sore-associated infection: Repeated inflammatory irritation and dirt exposure may cause further deterioration of pressure sore infection, which can develop from local to systemic infection[60]. In general, impregnated dressings with antibacterial properties such as silver sulfadiazine, furacilin and ethacridine can be applied locally[61].

2.2.2 PK/PD of anti-infection drugs: According to the characteristics of PK/PD, antibacterials can be divided into the time/concentration-dependent types[62]. For time-dependent antibacterials, the clinical efficacy can be enhanced by increasing *f*% T>MIC. It is recommended that the daily dose should be administered several times and/or the infusion time be prolonged[63]. For concentration-dependent antibacterials, the clinical efficacy can be enhanced by increasing Cmax in the blood, and a single daily dose is generally recommended[64]. The high distribution volume of lipophilic antibacterials in the body leads to a better inhibitory concentration in the lung epithelial lining fluid[65], and the permeability of cerebrospinal fluid is higher than that of hydrophilic drugs, but most drugs can enter during meningitis[66].

2.2.3 Use of antibacterials in special conditions
2.2.3.1 Hypoproteinemia: The free state of ceftriaxone, teicoplanin and daptomycin, which are high-protein binding antibacterials, increases in the state of hypoproteinemia. The concentration of these antibacterials in a free state is initially higher, but they are quickly cleared in the body, resulting in a smaller amount of storage of bound drugs, a shorter half-life, and less overall drug exposure. Such patients need human albumin supplements to improve the pharmacokinetics and efficacy of drugs [67].

2.2.3.2 Renal insufficiency: Antibiotics therapy in the first 48h is key to the clinical outcome of infectious diseases. The dosage adjustment of antibacterials based on renal function can be delayed according to clinical manifestations, and the use of adequate antibacterials with a broad therapeutic index will improve the prognosis of infected patients [68].

2.2.4 Genetic testing in anti-infection therapy: Genetic testing for pathogenic species and drug resistance: mNGS method can detect all infected DNA and RNA viruses, parasites, fungi, and bacteria in a single test, and has advantages in the detection of meningitis, acute respiratory infections, sepsis, and drug resistance [69]. Antibiotics-related genetic testing: The variation of some drug transporters involved in the cellular transport of antibacterials may be associated with individual differences in clearance rate and action of these drugs [70].

2.2.5 Anti-infection drugs and TDM : β-lactams: f%T>MIC: 40-70%; Aminoglycosides: Cmax≥8-10×MIC; Linezolid: Cmin: 2-7mg/L; Ticoranine: infections without complication: Cmin≥10-20mg/L, for severe staphylococcal infection: Cmin≥20-30mg/L; Voriconazole: Cmin≥0.5-5mg/L is associated with the improved clinical outcome, and Cmin≥5mg/L is associated with hepatotoxicity and neurotoxicity[71-72]; Vancomycin: Cmin: 10-15mg/L, adult severe MRSA infection: 10-20mg/L.[73]

2.3 Blood pressure management
2.3.1 ACEI/ARB should be discontinued before surgery and reused as soon as possible after surgery [74]. For adults undergoing non-cardiac surgery, there is no upper limit of blood pressure recommended to start treatment. Intraoperative arterial pressure management should be individualized [75]. After surgery, patients' specific target range of blood pressure should be set according to baseline preoperative blood pressure and clinical manifestations, and the frequency of postoperative monitoring should be clinically evaluated for high or low postoperative blood pressure.

2.3.2 Intraoperative hypotension events are common, which are associated with kidney and brain damage and the increased possibility of death in high-risk patients. Preventive measures include using vasopressors to increase arterial pressure, positive inotropic drugs and atropine to increase heart rate, or crystalloids, colloids or blood products to replenish blood volume [76].

2.4 Blood volume management
2.4.1 Perioperative intravenous infusion therapy is used to restore and maintain body water, electrolyte and organ perfusion to achieve homeostasis. However, inappropriate fluid infusion is detrimental to the

recovery of the organism. Insufficient infusion (inadequate renal perfusion) or excessive infusion (renal interstitial edema) can cause acute kidney injury. In addition, the use of limited fluid infusion will cause insufficient perfusion of the wound and anastomosis, which may result in a higher infection rate at the surgical site. During this period, improving fluid management can reduce complications, shorten hospital stay and improve prognosis [77]. Usually, carbohydrate infusion is recommended for surgical patients until two hours before surgery, which may help improve patients' metabolism and reduce insulin resistance, anxiety, nausea, and vomiting, with transition to oral rehydration as soon as possible after operation [78]. The adjustment of postoperative blood volume needs to be based on the amount of loss caused by the operation process. Total rehydration during the perioperative period of gastrointestinal surgery = physiological requirements (normal daily basic requirements) + cumulative losses (caused by preoperative fasting, nausea, vomiting, and bowel cleansing) + additional losses (intraoperative blood loss, evaporation of fluid from surgical wounds or airways, intraoperative urine volume, sweating, etc. [79]).

2.4.2 Glucose solution(g)+insulin(U)+potassium chloride (GIK) is often used as perioperative rehydration fluids, which can provide fluid and energy supplement for postoperative patients. For patients with hyperglycemia, the normal range of "insulin(U): glucose(g) ratio" in infusion is 1:4-5. The ratio is often adjusted according to the blood glucose level: If the blood glucose level is 6.7~10mmol/L, the ratio is 1:3; If the blood glucose level is 10~15mmol/L, the ratio is 1:2-3; If the blood glucose level >15mmol/L, the ratio is 1:2[80-81].

2.5 Nutrition management

2.5.1 Poor nutritional status is common in cancer patients. Severe malnutrition occurs in 50%-80% of cancer patients, reducing the quality of life and survival rate and impeding oncologic treatment [82]. NRS 2002 recommends a nutrition plan for inpatients with a total score ≥3; For those whose score is temporarily < 3, nutritional risk screening can be repeated periodically[83-84]. An oral diet should be started early for patients undergoing esophagogastrectomy and intrathoracic anastomosis. Those at high risk of anastomotic leak require the placement of a jejunal feeding tube [85].

2.5.2 Preoperative nutrition management: Normal feeding cannot meet the body's energy requirements; Malnutrition or nutritional risk exists; It is estimated that patients cannot be fed for more than 5 days druing the perioperative period, or the estimated energy intake is less than 50% of the required amount. Patients undergoing major surgery with malnutrition or serious nutritional risk for more than 7 days should be given 7-14 days of nutritional treatment before surgery. Patients with serious nutritional risk are advised to delay the operation.

Postoperative nutrition management: Patients with nutritional risk or malnutrition who cannot meet nutritional requirements in postoperative oral feeding should consider postoperative nutrition management. For patients whose 50% of energy requirements cannot be met by postoperative oral feeding and enteral nutrition for more than 7 days, enternal nutrition (EN) combined with parenteral nutrition (PN) is recommended. Early postoperative (within 24 hours) to start tube feeding is recommended for patients with malignant tumors of the head and neck or abdomen, patients with significant perioperative malnutrition, and patients whose postoperative oral intake of nutrition is expected to be insufficient or difficult. During chemotherapy: in patients with malnutrition or nutritional risk, when daily energy intake is less than 60% of the requirement for more than 1-2 weeks or expected not to be able to eat for 7 days or more, or when inadequate intake induces weight loss. Protein intake should exceed 1g/(kg·d) and is recommended to reach 1.5-2.0g/(kg·d) [86].

3. Perioperative management of blood glucose, blood clots, pain, nausea, and vomiting

3.1 Blood glucose management

3.1.1 Strict control of blood glucose levels <8.3mmol/L can reduce the risk of infection at the surgical site [87]. Patients with HbA1c >8% or blood glucose levels >13.9mmol/L (severe hyperglycemia) should postpone surgery. If the patient's fasting hyperglycemia >11.1mmol/L, pre-mixed insulin should be given preoperatively [88-89]. Perioperative blood glucose control is more lenient for special groups such as elderly people over 75 years old, patients whose life expectancy is <5 years (such as cancer), patients with combined cardiovascular and cerebrovascular diseases, moderate to severe liver and kidney insufficiency population, patients at high risk of hypoglycemia, patients with mental or intellectual disabilities, and patients be given parenteral nutrition. Usually, the target range is fasting blood glucose or preprandial blood

glucose of 6.1-7.8mmol/L, and random blood glucose of 7.8-10.0mmol/L two hours after meals or when unable to eat.

3.2 Thrombosis management

3.2.1 The American Society of Clinical Oncology recommends that patients undergoing major cancer surgery should be given thromboprophylaxis before surgery and continue for at least 7-10 days postoperatively. Patients undergoing major abdominal or pelvic surgery with high-risk features should be considered for prophylaxis for up to 4 weeks to reduce the incidence of venous thromboembolism [91]. Both malignant tumors and surgery will increase the risk of venous thromboembolism. Prophylaxis commonly includes mechanical prevention and medication. Cancer patients undergoing surgery are usually treated with medicine, such as heparin and low-molecular-weight heparin. The mechanical methods include intermittent pneumatic compression. For patients with cancer and severe renal impairment (creatinine clearance <30mL/min), unfractionated heparin is usually preferred to low-molecular heparin, while for long-term thromboprophylaxis, low-molecular heparin is recommended [92].

3.3 Pain management

3.3.1 Perioperative pain management mode: Thoracic surgery is the most severe postoperative pain [93]. and NSAIDs, acetaminophen, gabapentin, pregabalin, ketamine and opioids can be given for analgesia [94]. Pain after laparoscopic surgery: paracetamol and NSAIDs are used to treat mild to moderate pain, and opioids for severe pain. Dexamethasone, ketamine, and dexmedetomidine can increase the effectiveness of the above medication [95]. NSAIDs can reduce pain 24 hours after brain surgery [96].

3.3.2 Except remifentanil, most opioids are metabolized by cytochrome P450 enzymes. Codeine, hydrocodone, oxycodone and tramadol are metabolized by CYP2D6 enzymes into active metabolites. Fentanyl and sufentanil are metabolized by CYP3A4 enzymes [97]. Codeine and tramadol: CYP2D6 should not be used for ultra-fast metabolism, while alternative analgesics should be used for slow metabolism. Hydrocodone: CYP2D6 moderate/low metabolizers should adjust the dosage according to specific age and weight as recommended in the instructions; Oxycodone and methadone: No adequate genetic testing evidence available [98]. The trough concentrations of medicines should be monitored including morphine: 10-100ng/mL, in substitution therapy: 50-200ng/mL; buprenorphine: 1-3ng/mL; methadone: 400-600ng/mL, with an increased risk of QT interval time >450ms when above 656ng/mL [99].

3.3.3 ADRs management: NSAIDs may cause adverse reactions ranging from mild gastric irritation to severe systemic symptoms and even life-threatening allergic reactions, which can be adjusted according to their effects on COX2 and COX1[100]. For patients at high risk of gastrointestinal complications, proton pump inhibitors should be used in combination [101]. Constipation is most common among opioids. First-line treatment usually includes laxatives, increasing dietary fiber, fluid intake and exercise [102]. Naloxone is preferred if respiratory depression occurs, which is potentially fatal [103].

3.4 Nausea and vomiting management

3.4.1 Nausea and vomiting are the most common adverse events after oncologic surgery, with an incidence of 30%. Laparoscopic surgery, gynecologic surgery and other types of surgery may increase the risk of nausea and vomiting. The use of opioids in perioperative analgesia may increase the risk of nausea and vomiting in a dose-dependent manner. Clinically, 5-HT3 receptor antagonists, NK1 receptor antagonists, corticosteroids, anti-dopamines, anti-histamines and anti-cholinergics are commonly used for treatment [104]. The metabolism of 5-HT3 receptor antagonists in vivo is associated with CYP2D6[105], and aripitan is the substrate and moderate inhibitor of CYP3A4 and the inducer of CYP2C9[106]. Metoclopramide-induced extrapyramidal reactions are associated with plasma drug concentration in vivo, and its plasma exposure is also affected by CYP2D6 gene polymorphism [107-108].

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