Chapter 6
Chemotherapy for Gynecologic Cancer

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Chemotherapeutic Agents in Gynecologic Oncology

Introduction

The most commonly used agents in the treatment of gynecologic cancers are the platinums (carboplatin and cisplatin) and taxanes (paclitaxel and docetaxel). While these agents are used frequently, there are a number of other drugs employed in the recurrent setting and in the treatment of rare diseases.

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Pharmacology and Clinical Pearls

Mechanism of action, common and severe toxicities, and clinical pearls of each agent used in the treatment of gynecologic malignancies are outlined in Table 6.1.

Treatment Regimens

Regimens used for the treatment of gynecologic cancers including the drugs, dosage, and frequency are detailed in Table 6.2.

Chemotherapy-Induced Nausea and Vomiting (CINV)

Background [154–157]

Nausea /Vomiting (N/V) are two of the most feared adverse effects of chemotherapy. 70–90 % of patients will experience some form of N/V during their treatment. Since the advent of 5-Hydroxytryptamine-3 (5HT3) antagonists the incidence of vomiting has been decreased to 30 %. However, nausea still remains a significant adverse effect that can have a major impact on the treatment of gynecologic cancers.

Definitions [155, 158]

- Nausea—a feeling of sickness in the stomach characterized by an urge to vomit.
- Vomiting—an expulsion of gastrointestinal contents through the mouth.
- Acute emesis—occurs in the first 24 h after chemotherapy.
- Delayed emesis—takes place 24 h or more after chemotherapy administration.
- Anticipatory emesis—result of a learned response to chemotherapy.

TABLE 6.1. Mechanism of action, common and severe toxicities, and clinical pearls of agents used in the treatment of gynecologic malignancies.

Agent	Mechanism of action	Toxicities	Clinical pearls
Paclitaxel [1, 2]	Antimicrotuble agent; stabilizes microtubules inhibiting interphase and mitosis	• Myelosuppression • Nausea/vomiting (low risk) • Peripheral neuropathy • Arthralgia/myalgia • Hypersensitivity • Alopecia • Vascular irritant	• Should be administered prior to platinum derivatives (to avoid toxicity due to decreased paclitaxel clearance) • Premedicate with corticosteroid, H2 and H1 antagonist • Infuse through 0.22 μm in-line filter and nonsorbing administration set • Myelosuppression increased with higher doses, more frequent doses, and longer infusion times • Peripheral neuropathy increased with more frequent dosing and shorter infusion times • Dose adjust for hepatic toxicity • Drug interactions 1. Anthracyclines 2. CYP2C8, CYP3A4 inducers and inhibitors 3. P-glycoprotein inducers/inhibitors
Docetaxel [2, 3]	Antimicrotubule agent, stabilizes microtubules inhibiting interphase and mitosis	• Myelosuppression • Nausea/vomiting (low) • Peripheral neuropathy • Arthralgia/myalgia • Oncholysis, Alopecia • Hypersensitivity reactions • Fluid retention • Vascular irritant	• Should be administered prior to platinum derivatives (to avoid toxicity due to decreased clearance) • Premedicate with corticosteroid for 3 days starting the day prior to treatment to help with edema • Infuse with nonsorbing polyethylene lined (non-DHEP) tubing • Dose adjust for hepatic toxicity • Drug interactions 1. Anthracyclines 2. CYP3A4 inducers and inhibitors 3. P-glycoprotein inducers/inhibitors

(continued)

TABLE 6.1. (continued)

Agent	Mechanism of action	Toxicities	Clinical pearls
Cisplatin [2, 4]	Alkylating agent, forms DNA intrastrand and interstrand cross-links inhibiting DNA function and synthesis	• Nausea/vomiting (high risk) • Nephrotoxicity • Electrolyte depletion (potassium, magnesium) • Ototoxicity • Peripheral neuropathy • Myelosuppression • Vesicant at higher concentrations (> 0.4 mg/mL)	• Hypersensitivity may develop with prolonged (> 6 cycles) or prior exposure • Administer after taxanes • Adequate hydration prior to (1–2 L) and post infusion is recommended to prevent nephrotoxicity • Do not administer with aluminum needles or IVs • Dose adjust for renal impairment • Drug interactions 1. Aminoglycosides 2. Renal eliminated drugs 3. Loop diuretics
Carboplatin [2, 5]	Alkylating agent, forms DNA interstrand cross-links inhibiting DNA function and synthesis	• Nausea/vomiting (moderate risk) • Peripheral neuropathy • Myelosuppression • Electrolyte depletion (potassium, magnesium) • Nephrotoxicity	• Hypersensitivity may develop with prolonged (>6 cycles) or prior exposure • Administer after taxanes • Do not administer with aluminum needles or IVs • If dose calculated using estimated GFR consider capping estimated GFR at 125 mL/min to avoid toxicity • Doses calculated by target AUC via the Calvert Formula [Total dose = Target AUC × (GFR + 25)] • Drug interactions 1. Aminoglycosides 2. Renally eliminated drugs

Oxaliplatin [2, 6]	Alkylating agent, forms DNA intrastrand and interstrand cross-links inhibiting DNA function and synthesis	• Nausea/vomiting (moderate risk) • Myelosuppression • Peripheral neuropathy (acute and chronic) • Fatigue • *Vesicant*	• Hypersensitivity may develop with prolonged (>6 cycles) or prior exposure • Must be administered via central vein • Do not administer with aluminum needles or IVs • Counsel patients to avoid cold to prevent worsening of acute neuropathies/paresthesia
Irinotecan [2, 7]	Topoisomerase I inhibitor, reversibly binds to topoisomerase I stabilizing the cleavable complex resulting in double-strand DNA breaks and cell death. *S-phase specific*	• Fatigue • Nausea/vomiting (moderate risk) • Myelosuppression • Diarrhea (early and late) • Cholinergic toxicity • Alopecia • Hyperbilirubinemia	• Cholinergic symptoms and early diarrhea may be treated/prevented with atropine 0.25–1 mg • Treat late diarrhea with loperamide 4 mg PO at onset followed by 2 mg every 2 h until no bowel movement for 12 h • Patients with homozygous UGT1A1*28 allele are at increased risk for toxicity • Dose adjust for hepatic impairment • Drug interactions 1. Azole antifungals 2. Carbamazepine 3. CYP2B6, CYP3A4 inducers/inhibitors 4. Conivaptan 5. Fosphenytoin/phenytoin 6. Grapefruit juice 7. P-glycoprotein inducers/inhibitors 8. St. John's Wort

(continued)

TABLE 6.1. (continued)

Agent	Mechanism of action	Toxicities	Clinical pearls
Topotecan [2, 8]	Topoisomerase I inhibitor, binds to topoisomerase I and stabilizing the cleavable complex resulting in single-strand DNA breaks. *S-phase cell cycle specific*	• Myelosuppression • Alopecia • Fatigue • Nausea/vomiting (low risk) • Constipation • Diarrhea • Stomatitis • Vascular irritant	• Dose adjust for renal impairment • Drug interactions 1. Clozapine 2. Fosphenytoin/phenytoin 3. P-glycoprotein inhibitors
Liposomal doxorubicin [2, 9]	Topoisomerase II inhibitor; intercalates between DNA base pairs causing disruption of topoisomerase II. Chelates with iron forming complex which can produce free radicals that cause damage to DNA and cell membranes. Liposomal formulation is pegylated which increases blood circulation time	• *Palmar-plantar erythrodysesthesia* (*Hand-foot syndrome*) • Nausea/vomiting (Low risk) • Stomatitis/mucositis • Diarrhea • Myelosuppression • Discolored urine/body fluids • Infusion reaction • Vascular irritant	• Do not infuse with in-line filter • Associated with less cardiotoxicity than doxorubicin but cumulative lifetime dose should be considered • Monitor cardiac function (LVEF) at baseline and periodically during treatment • May cause radiation recall • Dose adjust for hepatic impairment • Drug interactions 1. Clozapine 2. CYP2B6 substrates 3. CYP2D6, CYP3A4 inhibitors/inducers 4. Taxanes

Doxorubicin [2, 10]	Topoisomerase II inhibitor; intercalates between DNA base pairs causing disruption of topoisomerase II. Chelates with iron forming complex which can produce free radicals that cause damage to DNA and cell membranes	• *Cardiotoxicity (acute and delayed)* • Myelosuppression • Nausea/vomiting (moderate risk) • Diarrhea • Mucositis • Alopecia • Discolored urine/body fluids • Photosensitivity • Radiation recall • Infertility • Secondary malignancy • *Vesicant*	• Increased risk of cardiotoxicity with lifetime cumulative dose >500 mg/m^2 • Baseline and periodic LVEF monitoring is recommended • Prolonging infusion time decreases risk of cardiotoxicity • Dexrazoxane may be used at a 10:1 ratio to decrease risk of cardiotoxicity • If administering continuous infusion use of a central venous line is recommended • Dose adjust for hepatic impairment. • Drug interactions 1. Clozapine 2. CYP2B6 substrates 3. CYP2D6, CYP3A4 inhibitors/inducers 4. Taxanes
Epirubicin [2, 11]	Topoisomerase II inhibitor; intercalates between DNA base pairs causing disruption of topoisomerase II. Chelates with iron forming complex which can produce free radicals that cause damage to DNA and cell membranes	• Nausea/vomiting (moderate risk) • Cardiotoxicity • Alopecia • Myelosuppression • Infertility • Mucositis • Secondary malignancy • *Vesicant*	• Increased risk of cardiotoxicity with lifetime cumulative dose >900 mg/m^2 • Baseline and periodic LVEF monitoring is recommended • Dose adjust for hepatic impairment and severe renal impairment • Drug interactions 1. Cimetidine 2. Taxanes

(continued)

TABLE 6.1. (continued)

Agent	Mechanism of action	Toxicities	Clinical pearls
Gemcitabine [2, 12]	Pyrimidine antimetabolite inhibits DNA synthesis in *S-phase*. Phosphorylated intracellularly to its active metabolites, gemcitabine diphosphate and gemcitabine triphosphate	• Myelosuppression • Nausea/vomiting (low risk) • Rash • Diarrhea • Alopecia • Transient flu-like symptoms • *Hemolytic uremic syndrome*	• Increasing infusion time >60 min increases toxicity • Drug interactions 1. Bleomycin 2. Fluorouracil
Vinorelbine [2, 13]	Antimicrotubule agent; inhibits the formation of microtubules preventing cell replication. *M phase specific*	• Myelosuppression • Peripheral neuropathy • Constipation • *Paralytic ileus/intestinal obstruction* • Fatigue • Nausea/vomiting (minimal risk) • Alopecia • *Vesicant*	• Consider placing patient on bowel regimen • Dose adjust for hepatic impairment • Drug interactions 1. Substrates of CYP3A4 2. Azole antifungals 3. Phenytoin
Vinblastine [2, 14]	Antimicrotubule agent; inhibits the formation of microtubules preventing cell replication. *M phase specific*	• Myelosuppression • Hypertension • Alopecia • *Constipation* • Peripheral neuropathy • Nausea/vomiting (minimal risk) • *Vesicant*	• Dose adjust for hepatic impairment • Consider placing patient on bowel regimen • Drug interactions 1. CYP3A4 and P-glycoprotein substrates 2. Induces P-glycoprotein 3. Itraconazole 4. Voriconazole 5. Erythromycin

Vincristine [2, 15]	Antimicrotubule agent; inhibits the formation of microtubules preventing cell replication. M and S phase specific	• Alopecia • Myelosuppression • Nausea/vomiting (minimal risk) • Cranial nerve dysfunction • *Constipation* • *Paralytic ileus/intestinal perforation* • Peripheral neuropathy • Foot drop/gait changes • *Vesicant*	• Consider placing patient on bowel regimen • Drug Interactions 1. CYP3A4 and P-glycoprotein substrates 2. Itraconazole 3. Voriconazole
Methotrexate [2, 16]	Folate antimetabolite; binds to and inhibits dihydrofolate reductase decreasing formation of reduced folates and thymidylate synthetase inhibiting DNA synthesis, repair and cell replication. *S phase specific*	• Myelosuppression • Alopecia • Nausea/vomiting (low to minimal risk) • Mucositis	• Leucovorin given with some regimens to mitigate hematologic and gastrointestinal side effects • *Elimination reduced in patients with ascites and/or pleural effusions* • Dose adjust for renal and hepatic impairment • Drug interactions 1. Substrates of P-glycoprotein 2. Probenecid 3. Salicylates 4. Hydantoin anticonvulsants 5. Nonsteroidal anti-inflammatory drugs (NSAIDs)
Dactinomycin [2, 17]	Binds to guanine DNA base inhibiting DNA, RNA, and protein synthesis	• Alopecia • Nausea/vomiting (moderate risk) • Increased pigmentation • Rash • Myelosuppression • *Vesicant*	• Adjust dose for hepatic impairment • Drug interactions 1. NSAIDs 2. Salicylates

(continued)

TABLE 6.1. (continued)

Agent	Mechanism of action	Toxicities	Clinical pearls
Cyclophosphamide [2, 18]	Alkylating agent; forms cross-links between strands of DNA inhibiting DNA synthesis. Prodrug that requires activation by liver	• Nausea/vomiting (moderate risk) • Alopecia • *Secondary malignancy* • Infertility • *Hemorrhagic cystitis* (rare at doses use for gynecologic malignancy) • Myelosuppression	• Increase fluid intake during treatment to prevent bladder toxicity • Mesna may be given with higher doses (≥1,000 mg/m^2) to prevent/treat hemorrhagic cystitis • Oral doses should be taken in morning with plenty of fluid • Drug interactions 1. CYP2B6 substrates 2. Nalidixic acid
Altretamine [2, 19]	Alkylating agent; not fully characterized	• Myelosuppression • Peripheral neuropathy • Nausea/vomiting (moderate risk)	• Available as 50 mg capsule • Drug interactions 1. Monoamine oxidase inhibitors 2. NSAIDs 3. Pyridoxine
Capecitabine [2, 20]	Pyrimidine antimetabolite; Prodrug of fluorouracil, activated by liver and tissue to active form which inhibits thymidylate synthetase inhibiting DNA and RNA synthesis. *G1 and S phase specific*	• Nausea/vomiting (low risk) • Myelosuppression • Mucositis • Diarrhea • *Palmar plantar erythrodysesthesia (Hand-foot syndrome)* • Photosensitivity	• Take within 30 min of meal • Swallow tablets whole • Contraindicated in known deficiency of dihydropyrimidine dehydrogenase (DPD) • Not recommended for CrCl <30 mL/min • Dose adjust for renal and hepatic impairment • Drug interactions 1. CYP2C9 inhibitor 2. Warfarin 3. Folic acid 4. Leucovorin

Fluorouracil [2, 21]	Pyrimidine antimetabolite; inhibits thymidylate synthetase inhibiting DNA and RNA synthesis. *G1 and S phase specific*	• Vascular irritant • *Palmar-plantar erythrodysesthesia* • Nausea/vomiting (Low risk) • Photosensitivity • Myelosuppression	• Contraindicated in known deficiency of dihydropyrimidine dehydrogenase (DPD) • Drug interactions 1. Inhibits CYP2CP 2. Dapsone 3. Trimethoprim 4. Hydantoin anticonvulsants 5. Levamisole
Ifosfamide [2, 22]	Alkylating agent; cross-linking strands of DNA inhibiting protein and DNA synthesis	• *Hemorrhagic cystitis* • Alopecia • Nausea/vomiting (High to moderate risk) • Myelosuppression • Encephalopathy (confusion, somnolence, dizziness) • Infertility • Secondary malignancy	• Must be administered with Mesna (at least 60 % of ifosfamide dosage) to prevent hemorrhagic cystitis • Adequate hydration, dose fractionation may be used to decrease hemorrhagic cystitis • Neurotoxicity increased in patients with hypoalbuminemia, renal dysfunction, and history ifosfamide induced encephalopathy • Neurotoxicity may be treated with methylene blue • Dose adjust for renal impairment • Drug interactions 1. CYP2A6, CYP2C19, and CYP3A4 substrates 2. CYP2C9 inducer 3. Conivaptan 4. St. John's wort 5. Telithromycin

(continued)

TABLE 6.1. (continued)

Agent	Mechanism of action	Toxicities	Clinical pearls
Melphalan [2, 23]	Alkylating agent; Cross-links strands of DNA inhibiting DNA and RNA synthesis	• Myelosuppression • Nausea/vomiting (minimal risk) • Secondary malignancy (risk as high as 11 %)	• Administer oral formulation on empty stomach • Dose adjust for renal impairment
Pemetrexed [2, 24]	Folate antimetabolite, inhibits folate dependent enzymes involved in DNA and RNA function and synthesis, thus inhibiting cell function and replication	• Fatigue • Nausea/vomiting • Myelosuppression	• Do not give when CrCl <45 mL/min • Must give with vitamin B12 1,000 mcg subQ every 9 weeks and folic acid 400–1,000 mcg PO daily started 1 week prior to initial dose • Give dexamethasone 4 mg PO BID for 3 days starting 24 h prior to each dose • Drug interactions 1. NSAIDs
Dacarbazine [2, 25]	Exact mechanism unknown, suggested to have alkylating effect as well as antimetabolite activity	• Nausea/vomiting (High risk) • Diarrhea • Flu-like syndrome • Alopecia • Photosensitivity • Rash • Vascular irritant	• Dose adjust for renal impairment • Drug interactions 1. CYP1A2 and CYP2E1 substrates
Temozolomide [2, 26]	Prodrug which is nonenzymaticaly converted to alkylating agent. Bonds to DNA leading to double strand breaks and cell death	• Nausea/vomiting (moderate risk) • Myelosuppression • Fatigue • Alopecia • Constipation	• Capsules should be taken with a full glass of water • Food decreases absorption • Do not crush, break or chew capsule • Administer on empty stomach at bedtime to avoid nausea/vomiting

Pazopanib [2, 27]	Tyrosine kinase inhibitor, decreases activity of vascular endothelial growth factors (VEGF), platelet-derived growth factor receptors, cytokine receptor, interleukin-2 receptor inducible T-cell kinase, leukocyte-specific protein tyrosine kinase, and transmembrane glycoprotein receptor tyrosine kinase	• Hypertension • Fatigue, insomnia, hemiparesis • Hair color change • Hand-foot skin reaction • Rash/skin depigmentation • Diarrhea • Nausea/vomiting (minimal risk) • Myelosuppression • Hepatotoxicity	• Administer 1 h before or 2 h after a meal • Do not crush or chew tablet • If receiving steroids monitor for *Pneumocystis Jiroveci* and consider prophylaxis • Dose adjust for hepatic impairment • Drug interactions 1. CYP3A4 and P-glycoprotein substrates 2. CYP3A4 strong inhibitors—consider decreasing dose by at least 50 % 3. CYP3A4 strong inducers - do not use 4. Avoid grapefruit juice
Etoposide [2, 28, 29]	Topoisomerase II inhibitor, activity results in DNA strand breaks. *S-phase specific*	• Nausea/vomiting (low risk) • Myelosuppression • Alopecia • *Secondary malignancy* • Infusion reaction/hypersensitivity • Vascular irritant	• Do not crush, open or chew capsules • Dose adjust for renal impairment • Drug interactions 1. CYP3A4 and P-glycoprotein substrates
Bleomycin [2, 30]	Antitumor antibiotic, binds to DNA leading single and double strand breaks and decreased DNA, RNA, and protein synthesis	• Vascular irritant • Hypersensitivity reaction • *Pulmonary dysfunction* • Hyperpigmentation • Mucositis • Acute febrile reaction	• Complete pulmonary function tests prior to initiation and consider monitoring every 2 cycles or as clinically indicated • Risk factors for pulmonary toxicity include smoking, prior radiation, and concurrent oxygen administration • Dose adjust for renal impairment

TABLE 6.2. Common gynecologic oncology treatment regimens [31–153].

Cervical cancer: locally advanced		
Chemotherapy regimen	Chemotherapy regimens details	References
Cisplatin + RT	Cisplatin 40 mg/m^2 IV day 1 Q1 week × 6 weeks Concurrent radiotherapy 55–75 Gy	[31–34]
Cisplatin + 5-FU + RT	Cisplatin 70 mg/m^2 IV day 1 5-FU 1,000 mg/m^2/day continuous IV days 1–4 Q3w × 2 cycles Concurrent radiotherapy 49.3 Gy Followed by cisplatin 70 mg/m^2 IV day 1 5-FU 1,000 mg/m^2/day continuous IV days 1–4 Q3w × 2 more cycles	[35]
Cervical cancer: recurrent or metastatic first line		
Cisplatin + paclitaxel	Cisplatin 50 mg/m^2 IV day 1 Paclitaxel 135 mg/m^2 IV day 1 Q3w	[36, 37]
Carboplatin + paclitaxel	Carboplatin AUC = 6 IV day 1 Paclitaxel 175 mg/m^2 IV day 1 Q3w	[38]
Cisplatin + topotecan	Cisplatin 50 mg/m^2 IV day 1 Topotecan 0.75 mg/m^2/day IV days 1–3 Q3w × 6 cycles	[37, 39]
Cisplatin + paclitaxel + bevacizumab	Cisplatin 50 mg/m^2 IV day 1 Paclitaxel 135–175 mg/m^2 IV day1 Bevacizumab 15 mg/kg IV day 1 Q3w	[40]

Cisplatin + gemcitabine	Cisplatin 50 mg/m^2 IV day 1 Gemcitabine 1,000 mg/m^2/day IV days 1, 8 Q3w	[37]
Cisplatin	Cisplatin 50 mg/m^2 IV day 1 Q3w	[39]
Carboplatin	Carboplatin AUC = 5–7.5 IV day 1 Q3w	[41]
Paclitaxel	Paclitaxel 135–175 mg/m^2 IV day 1 Q3w	[42]
Cervical cancer: recurrent or metastatic second line		
Bevacizumab	Bevacizumab 15 mg/kg IV day 1 Q3w	[43]
Docetaxel	Docetaxel 75 mg/m^2 IV day 1 Q3w	[44]
5-FU	5-FU 370 mg/m^2/day IV push days 1–5 Leucovorin 200 mg/m^2 IV push days 1–5 Q4w OR 5-FU 1,000 mg/m^2/day continuous IV infusion days 1–5 Q4w	[45]
Gemcitabine	Gemcitabine 800 mg/m^2 IV days 1, 8, 15 Q4w	[46]
Ifosfamide	1.5 g/m^2/day IV days 1-5 Mesna 300 mg/m^2 IV 0 h, 4 h, 8 h, d1–5 Q4w	[47, 48]
Irinotecan	Irinotecan 125 mg/m^2 IV days 1, 8, 15 & 22 Q6w	[49]
Mitomycin	Mitomycin 10–15 mg/m^2 IV push day 1 Q4-6w	[50]
Topotecan	Topotecan 1.5 mg/m^2/day IV days 1–5 Q3–4w or Topotecan 3–4 mg/m^2/d IV days 1, 8, 15 Q4w	[51, 52]

(continued)

Table 6.2. (continued)

Cervical cancer: locally advanced		
Chemotherapy regimen	Chemotherapy regimens details	References
Endometrial cancer: hormonal therapy for recurrent, metastatic, or high-risk endometrial cancer		
Hormonal regimen	Hormonal regimen details	References
Medroxyprogesterone	Medroxyprogesterone 200–1,000 mg po daily days 1–14 Q28d	[53]
Tamoxifen	Tamoxifen 20 mg po bid	[54]
Megestrol acetate	Megestrol 80 mg po bid OR Megestrol 800 mg po daily in divided doses	[55, 56]
Megestrol/tamoxifen	Megestrol 80 mg po bid × 3 weeks alternative with tamoxifen 20 mg po bid	[57]
Letrozole	Letrozole 2.5 mg po daily	[58]
Anastrozole	Anastrozole 1 mg po daily	[59]
Endometrial cancer: adjuvant for recurrent, metastatic, or high-risk endometrial cancer		
Cisplatin + doxorubicin	Doxorubicin 60 mg/m^2 IV day 1 Cisplatin 50 mg/m^2 IV day 1 Q3w	[60, 61]
Cisplatin + doxorubicin + paclitaxel	Doxorubicin 45 mg/m^2 IV day 1 Cisplatin 50 mg/m^2 IV day 1 Paclitaxel 160 mg/m^2 IV day 2 Q3w	[62]
Carboplatin + paclitaxel	Paclitaxel 175 mg/m^2 IV day 1 Carboplatin AUC 5-7 IV day 1 Q4w	[63–65]
Weekly paclitaxel + carboplatin	Paclitaxel 80 mg/m^2 IV days 1, 8, 15 Carboplatin AUC = 2 IV days 1, 8, 15 Q3w	[66]

Carboplatin +docetaxel	Carboplatin ACU = 6 IV day 1 Docetaxel 60 mg/m^2 IV day 1 Q3w Carboplatin AUC = 6 IV day 1 Docetaxel 75 mg IV day 1 followed by radiation Q3w	[65, 67, 68]
Cisplatin	Cisplatin 50–60 mg/m^2 IV day 1 Q3w	[69, 70]
Carboplatin	Carboplatin 360–400 mg/m^2 IV Q3-4w	[71, 72]
Doxorubicin	Doxorubicin 45–60 mg/m^2 IV day 1 Q3w	[73]
Liposomal doxorubicin	Liposomal doxorubicin 40–50 mg/m^2 IV day 1 Q3w	[74]
Paclitaxel	Paclitaxel 175–250 mg/m^2 IV day 1 Q3w	[75, 76]
Weekly docetaxel	Docetaxel 36 mg/m^2 IV days 1, 8, 15 Q3w	[77]
Bevacizumab	Bevacizumab 15 mg/kg IV day 1 Q3w	[78]
Cisplatin + ifosfamide (for carcinosarcoma)	Cisplatin 20 mg/m^2/day IV days 1–4 Ifosfamide 1.5 g/m^2/day IV days 1–4 Mesna 120 mg/m^2 IV loading dose followed by 1.5 g/m^2/day IV days 1–4 Q3w	[79, 80]
Ifosfamide + paclitaxel (for carcinosarcoma)	Ifosfamide 1.6 g/m^2/day (1.2 g/m^2/day if patients received prior radiation) IV days 1–3 Paclitaxel 135 mg/m^2 IV over 3 h day 1 Mesna 2 g IV over 12 h days 1–3 Q3w × 8 cycles	[81]

(continued)

TABLE 6.2. (continued)

Cervical cancer: locally advanced		
Chemotherapy regimen	Chemotherapy regimens details	References
Ifosfamide (for carcinosarcoma)	Ifosfamide 2.0 g/m^2/day (1.2 g/m^2/day if patients received prior radiation) IV days 1–3 Mesna 2 g IV over 12 h days 1–3 Q3w × 8 cycles	[81]
Uterine sarcoma: hormonal therapy for endometrial stromal sarcoma		
Hormonal regimen	Hormonal regimen details	References
Medroxyprogesterone	Medroxyprogesterone 500–1,000 mg po daily	[82]
Megestrol acetate	Megestrol 160 mg po daily	[83, 84]
Letrozole	Letrozole 2.5 mg po daily	[85]
Anastrozole	Anastrozole 1 mg po daily	[85]
GnRH analog	Optimal dose unknown	
Uterine sarcoma: chemotherapy		
Gemcitabine + docetaxel	Gemcitabine 900 mg/m^2 IV over 90 min days 1, 8 Docetaxel 75–100 mg/m^2 IV day 8 Q3w Dose reduced by 25 % for patients with prior history of pelvic radiation	[86–89]
Doxorubicin + ifosfamide	Doxorubicin 50–75 mg/m^2 IV day 1 Ifosfamide 5 g/m^2 IV over 24 h day 1 Mesna 6 g/m^2 IV over 36 h day 1 Q3w Dose reduced by 25 % for patients with prior history of pelvic radiation	[90, 91]

Doxorubicin + dacarbazine	Doxorubicin 60 mg/m^2 IV day 1 Dacarbazine 250 mg/m^2 IV days 1–5 Q3w Dose reduced by 25 % for patients with prior history of pelvic radiation	[92]
Gemcitabine + dacarbazine	Gemcitabine 1,800 mg/m^2 IV over 180 min day 1 Dacarbazine 500 mg/m^2 IV Q2w	[93, 94]
Gemcitabine + vinorelbine	Vinorelbine 25 mg/m^2 IV day 1 Gemcitabine 800 mg/m^2 IV over 90 min days 1, 8 Q3w	[95]
Doxorubicin	Doxorubicin 60 mg/m^2 IV day 1 Q3w	[92]
Epirubicin	Epirubicin 75 mg/m^2 IV day 1 Q3w	[96]
Gemcitabine	Gemcitabine 1,000 mg/m^2 IV days 1, 8, 15 Q4w	[97]
Ifosfamide	Ifosfamide 1.5 g/m^2/day IV days 1–5 Q3w	[98]
Liposomal doxorubicin	Liposomal doxorubicin 50 mg/m^2 IV day 1 Q4w	[99]
Paclitaxel	Paclitaxel 175 mg/m^2 IV day 1 Q3w	[100, 101]
Temozolomide	Temozolomide 50–75 mg/m^2 po daily week 1–6 Q8w	[102]
Dacarbazine	Dacarbazine 1,200 mg/m^2 IV day 1 Q3w	[94]

(continued)

Table 6.2. (continued)

Cervical cancer: locally advanced		
Chemotherapy regimen	Chemotherapy regimens details	References
Vinorelbine	Vinorelbine 30 mg/m^2 IV day 1 Q2w	[103]
Pazopanib	Pazopanib 800 mg po daily	[104]
Ovarian, fallopian tube, or primary peritoneal carcinoma: primary chemotherapy for Stage II–IV		
Paclitaxel+carboplatin	Paclitaxel 175 mg/m^2 IV over 3 h day 1 Carboplatin AUC=5–7.5 IV day 1 Q3w×6 cycles	[105]
Docetaxel+carboplatin	Docetaxel 60–75 mg/m^2 IV day 1 Carboplatin AUC=5–6 IV day1 Q3w×6 cycles	[106]
Paclitaxel+cisplatin	Paclitaxel 135 mg/m^2 IV over 24 h day 1 Cisplatin 75–100 mg/m^2 IV day 2 Q3w×6 cycles	[107]
Paclitaxel IV+cisplatin IP+ paclitaxel IP	Paclitaxel 135 mg IV over 3 h or 24 h day 1 Cisplatin 75–100 mg/m^2 IP day 2 Paclitaxel 60 mg/m^2 IP day 8 Q3w×6 cycles	[108]
Paclitaxel D1,8, 15+carboplatin	Paclitaxel 80 mg/m^2 IV over 1 h days 1, 8, 15 Carboplatin AUC=6 IV day 1 Q3w×6 cycles	[109]
Paclitaxel+carboplatin+ bevacizumab	Paclitaxel 175 mg/m^2 IV day 1 Carboplatin AUC=5–7.5 IV day 1 Q3w×6 cycles + Bevacizumab 15 mg/kg IV day 1 (C2–22)	[110]

Paclitaxel + carboplatin + bevacizumab	Paclitaxel 175 mg/m^2 IV day 1 Carboplatin AUC = 5–7.5 IV day 1 Q3w × 6 cycles + Bevacizumab 15 mg/kg IV day 1 (C2-18)	[111]
Ovarian, fallopian tube, or primary peritoneal carcinoma: platinum-sensitive, first-relapse		
Paclitaxel + carboplatin	Paclitaxel 175 mg/m^2 IV day 1 Carboplatin AUC = 5–6 IV day 1 Q3w	[112, 113]
Gemcitabine + carboplatin	Gemcitabine 1,000 mg/m^2 IV days 1, 8 Carboplatin AUC = 4 IV day 1 Q3w	[114]
Gemcitabine + carboplatin + bevacizumab	Gemcitabine 1,000 mg/m^2 IV days 1, 8 Carboplatin AUC = 4 IV day 1 Bevacizumab 15 mg/kg IV day 1 Q3w	[115]
Gemcitabine + cisplatin	Gemcitabine 600–750 mg/m^2 IV days 1, 8 Cisplatin 30 mg/m^2 IV days 1, 8 Q3w	[116, 117]
Docetaxel + carboplatin	Docetaxel 75 mg/m^2 IV day 1 Carboplatin AUC = 5 IV day 1 Q3w	[118]
Paclitaxel D1,8, 15 + carboplatin	Paclitaxel 80 mg/m^2 IV over 1 h days 1, 8, 15 Carboplatin AUC = 6 IV day 1 Q3w	[109]
Docetaxel D1,8,15 + carboplatin	Docetaxel 35 mg/m^2 IV days 1, 8, 15 Carboplatin AUC = 2 IV days 1, 8, 15 Q4w	[119]

(continued)

Table 6.2. (continued)

Cervical cancer: locally advanced		
Chemotherapy regimen	Chemotherapy regimens details	References
Liposomal doxorubicin + carboplatin	Liposomal doxorubicin 30 mg/m^2 IV day 1 Carboplatin AUC = 5 IV day 1 Q4w	[120]
Carboplatin	Carboplatin AUC = 5–6 IV day 1 Q3w	[112, 114, 121]
Bevacizumab	Bevacizumab 15 mg/kg IV day 1 Q3w	[122]
Ovarian, fallopian tube, or primary peritoneal carcinoma: platinum-resistant or subsequent recurrence		
Docetaxel	Docetaxel 75–100 mg/m^2 IV day 1 Q3w Or Docetaxel 30 mg/m^2 IV days 1, 8, 15 Q4w	[123, 124]
Weekly paclitaxel	Paclitaxel 80 mg/m^2 IV days 1, 8, 15 Q4w	[125]
Gemcitabine	Gemcitabine 600–1,000 mg/m^2 IV days 1,8, 15 Q4w	[126–128]
Etoposide (oral)	Etoposide 50 mg/m^2 po days 1–21 Q4w	[129]
Altretamine	Altretamine 260 mg/m^2 po days 1–14 Q4w	[130]
Bevacizumab	Bevacizumab 15 mg/kg IV day 1 Q3w	[122, 131, 132]
Nab-paclitaxel	Nab-paclitaxel 260 mg/m^2 IV day 1 Q3w	[133]

Oxaliplatin	Oxaliplatin 130 mg/m^2 IV day 1 Q3w	[134]
Liposomal doxorubicin	Pegylated liposomal doxorubicin 40 mg/m^2 IV day 1 Q4w	[135–137]
Topotecan	Topotecan 1.25 mg/m^2 IV days 1–5 Q3–4w Or Topotecan 3–4 mg/m^2 IV days 1, 8, 15 W3-4w	[135, 138–140]
Vinorelbine	Vinorelbine 30 mg/m^2 IV days 1, 8 Q3w	[141]
Pemetrexed	Pemetrexed 900 mg/m^2 IV day 1 Q3w	[142]
Ifosfamide	Ifosfamide 1,000–1,200 mg/m^2/day IV days 1–5 Mesna 200 mg/m^2/day IV 0 h, 4 h, 8 h, days 1–5 Q4w	[143]
Capecitabine	Capecitabine 2,000 mg/m^2/day po in two divided doses, days 1–14 Q3w	[144]
Irinotecan	Irinotecan 250–300 mg/m^2 IV day 1 Q3w	[145]
Tamoxifen	Tamoxifen 20 mg po bid	[146]
Anastrozole	Anastrozole 1 mg po daily	[147]
Letrozole	Letrozole 2.5 mg po daily	[148–150]
Leuprolide acetate	Leuprolide 3.75 mg im Q4w	[151]
Megestrol acetate	Megestrol 800 mg po daily × 28 days followed by 400 mg po daily	[152, 153]

- Breakthrough emesis occurs despite prophylactic antiemetics.
- Refractory emesis failure to respond to prevention or intervention in the previous cycle.

Alternative Etiologies [159]

- Medications (opioids, antimicrobials).
- Surgery/radiation.
- Electrolyte imbalances/dehydration.
- Gastrointestinal: obstruction, gastroparesis, constipation.
- Psychological (anxiety, anticipatory).
- Brain metastasis.

Complications [157, 158]

- Metabolic imbalances.
- Decreased performance status.
- Nutrient depletion/Anorexia.
- Wound dehiscence.
- Esophageal tears.
- Noncompliance with treatment.
- Aspiration.
- Decreased quality of life.

Risk Factors [154, 157, 158, 160, 161]

Patient Related

- Age—increased risk in younger patients.
- Gender—increased risk for females.
- History of alcohol use—decreased with prior use.
- History of CINV.
- History of vertigo/motion sickness.
- Non-chemotherapy related etiologies.
- History of nausea/vomiting with pregnancy.

Chemotherapy Related

- >90 % = High risk.
- 31–90 % = Moderate risk.
- 10–30 % = Low risk.
- <10 % = Minimal risk.

See Table 6.3 for CINV risk for agents used to treat gynecologic cancers.

TABLE 6.3. Chemotherapy induced nausea/vomiting (CINV) risk by agent.

Risk category	Agents
High risk (>90 %)	Cisplatin
	Dacarbazine
	Doxorubicin >60 mg/m^2
	Ifosfamide ≥2 g/m^2/dose
Moderate risk (31–90 %)	Carboplatin
	Dactinomycin
	Doxorubicin <60 mg/m^2
	Epirubicin ≤90 mg/m^2
	Ifosfamide <2 g/m^2/dose
	Irinotecan
	Melphalan
	Methotrexate ≥250 mg/m^2
	Oxaliplatin
	Temozolomide
Low risk (10–30 %)	Docetaxel
	Liposomal doxorubicin
	Etoposide
	Fluorouracil
	Gemcitabine
	Mitomycin
	Paclitaxel
	Pemetrexed
	Topotecan
Minimal risk (<10 %)	Bevacizumab
	Bleomycin
	Vinblastine
	Vincristine
	Vinorelbine

Therapeutic Options [2, 160, 168]

High Therapeutic Index Agents

Used primarily for prevention first line breakthrough. Dosing outlined in Table 6.4.

- 5HT3 receptor antagonists:

  Agents: Ondansetron, Palonosetron, Granisetron, Dolasetron.
  Adverse effects: headache, constipation, QT prolongation.

- Corticosteroids.

  Agents: Dexamethasone, Prednisone, Methylprednisolone.
  Adverse effects: hyperglycemia, insomnia, hypertension, immunosuppression.

Table 6.4. High therapeutic index antiemetic common dosing.

Agent	Pre-chemotherapy	Post-chemotherapy
Ondansetron	8–16 mg IV/PO 30 min prior to	8 mg PO TID × 3 days
Dolasetron	100 mg IV/PO 30 min prior to	100 mg PO daily × 3 days
Granisetron	1 mg IV/PO 30 min prior to; 34.3 mg transdermal patch applied 24–48 h prior to	1–2 mg PO BID × 3 days
Palonosetron	0.25 mg IV 30 min prior to	
Dexamethasone w/ aprepitant 125 mg PO	12 mg IV/PO 30 min prior to	8 mg PO daily × 3 days
Dexamethasone w/ fosaprepitant 150 mg IV	12 mg IV/PO 30 min prior to	8 mg day 2, 8 mg PO BID days 3 and 4
Dexamethasone w/o aprepitant	8-20 mg IV/PO 30 min prior to	8 mg PO BID × 3 days
Aprepitant	125 mg PO 1 h prior to	80 mg PO × 2 days
Fosaprepitant	150 mg IV 30 min prior to	

- Neurokinin-1 receptor antagonists.

  Agents: Aprepitant, Fosaprepitant.
  Adverse effects: headache, hiccups, fatigue.
  Moderate inhibitor and inducer of CYP3A4, weak inducer of CYP2C9.

Low Therapeutic Index Agents

Used primarily for breakthrough N/V. Dosing outlined in Table 6.5.

- Phenothiazines.

  Agents: Prochlorperazine, Promethazine.
  Adverse effects: sedation, anticholinergic effects, extrapyramidal side effects.

- Metoclopramide.

  Adverse effects: sedation, extrapyramidal side effects, diarrhea.

TABLE 6.5. Low therapeutic index antiemetic common dosing.

Agent	Dosing
Promethazine	6.25–25 mg IV/PO q6h prn 25 mg PR q6h prn
Prochlorperazine	5–10 mg IV/PO q6h prn 25 mg PR q6h prn
Metoclopramide	0.5–2 mg/kg IV q4h prn (must give w/diphenhydramine 25 mg IV q6h to prevent extrapyramidal side effects) 10–40 mg PO q6h prn
Olanzapine	2.5–5 mg PO qHS
Alprazolam	0.5–2 mg PO prior to chemotherapy
Lorazepam	1–2 mg IV/PO prior to chemotherapy 0.5–2 mg PO q4h prn N/V
Haloperidol	1 mg IV q4h PRN
Dronabinol	5–10 mg PO q3h prn
Nabilone	1–2 mg PO q12h prn

- Olanzapine.

  Adverse effects: sedation, weight gain.

- Benzodiazepines.

  Drug of choice for anticipatory N/V.
  Agents: Lorazepam, Alprazolam.
  Adverse effects: sedation, amnesia.

- Butyrophenones.

  Agents: Haloperidol
  Adverse effects: sedation, constipation, arrhythmias, extrapyramidal side effects.

- Cannabinoids.

  Agents: Dronabinol, Nabilone.
  Adverse effects: sedation, abnormal thinking, palpitations, tachycardia, euphoria.

General Principles of Treatment [155, 160, 161, 165]

- Primary goal is prevention of CINV.
- Agents are chosen based upon chemotherapy regimen.
- Consider toxicity of antiemetics used.
- Always provide "rescue" medication for breakthrough CINV.

Treatment Recommendations [160, 161, 165, 169, 170]

High Risk Chemotherapy

- Acute Emesis Prevention.

  5HT3 antagonist + Dexamethasone + Neurokinin 1 antagonist +/– lorazepam +/– H2 blocker or proton pump inhibitor.

- Delayed Emesis Prevention.

  If fosaprepitant 150 mg: dexamethasone 8 mg PO day 2 then 8 mg PO BID days 3–4.
  If aprepitant day 2–3: dexamethasone 8 mg PO days 2–4.

Moderate Risk Chemotherapy

- Acute Emesis Prevention.

  5HT3 antagonist + dexamethasone +/– Neurokinin 1 antagonist +/– lorazepam +/– H2 blocker or proton pump inhibitor.

- Delayed Emesis Prevention.

  5HT3 antagonist monotherapy for 2–3 days, OR.
  Dexamethasone monotherapy for 2–3 days, OR.
  Neurokinin 1 antagonist (if used day 1) + dexamethasone.

Low Risk

- Prior to chemotherapy.
  Dexamethasone PO/IV, OR.
  Metoclopramide PO/IV, OR.
  Prochlorperazine PO/IV, OR.
  +/– Lorazepam and/or H2 blocker or proton pump inhibitor.

Minimal Risk

- No prophylaxis recommended.

Multiday Chemotherapy Regimens

- Consider emetogenic potential of each day.
- 5-HT3 antagonist should be administered daily for moderately or highly emetogenic chemotherapy.

- Dexamethasone should be given daily prior for moderately or highly emetogenic chemotherapy.
- Prevent delayed emesis with 2–3 days of prophylaxis following chemotherapy.
- Palonosetron or transdermal granisetron may be used in lieu of daily 5HT3 dosing.
- Dosing of Aprepitant beyond 3 days has been shown to be safe and effective in phase II trials.
- Repeat doses of palonosetron have been studied and shown to reduce CINV.

Breakthrough Emesis

- Add agent from different class.
- PO administration often unfeasible due to emesis.
- Routine administration of "rescue" medication should be considered.
- Multiple concurrent agents in alternating schedules.
- Reevaluate for alternative etiologies.
- Change regimen for next cycle.

Chemotherapy-Induced Diarrhea

Introduction [171–173]

Many chemotherapy agents can cause damage to the intestinal mucosa ultimately resulting in diarrhea. If not managed properly chemotherapy-induced diarrhea can result in treatment delays, dose reductions, and serious complications that may be fatal. Most agents for the primary treatment of gynecologic oncology do not commonly cause diarrhea but a number of agents used for recurrence or rare tumor types are known to cause diarrhea.

Pathogenesis [171–178]

- Direct damage to intestinal mucosa (fluorouracil, capecitabine, Irinotecan late-onset, doxorubicin, gemcitabine, dacarbazine).
- Cholinergic stimulation (Irinotecan acute-onset).
- Inhibition of vascular endothelial growth factor (pazopanib).
- Dihydropyrimidine dehydrogenase (DPD) deficiency and thymidylate synthetase gene (TYMS) polymorphism can increase severity of diarrhea with fluorouracil and capecitabine.
- Irinotecan is metabolized by the enzyme uridine diphospho-glucuronosyltransferase 1A1 (UGT1A1).
- Patients that are heterozygous or homozygous for UGT1A1*28 may be at increased risk for diarrhea.

Signs and Symptoms [171–173, 179]

- Increase in number of stools or ostomy output.
- Dehydration.
- Renal insufficiency.
- Electrolyte abnormalities (hypokalemia, metabolic acidosis, hyponatremia, or hypernatremia).
- Fatigue.
- Decreased quality of life.
- Noncompliance with treatment.

Evaluation [171–173, 179]

- Determine onset and duration.
- Assess for alternative etiologies (infection, medication, radiation, diet, colitis, etc.).
- Consider testing for DPD deficiency, TYMS variants, or UGT1A1 polymorphism.
- Determine severity (Table 6.6).
- Identify causative agent.

Table 6.6. Severity/grade of chemotherapy-induced diarrhea.

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >6 stools per day over baseline; incontinence; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

Therapeutic Options [2, 162–164, 167, 171–173, 179, 180]

General Principles

- Treat any alternative/underlying etiologies.
- Provide supportive care in the form of hydration and electrolyte repletion.
- Severe cases may require delays or dose reduction of chemotherapy.
- Scheduled doses of antidiarrheal are usually necessary to control symptoms.
- Once controlled medications can be titrated to maintain control.

Nonpharmacologic Treatment

- Avoid diarrhea inducing foods (dairy, spicy foods, alcohol, caffeine, high fiber).
- Discontinue all laxative, stool softeners, or promotility agents.
- Aggressive oral hydration (8–10 glasses per day).
- Small frequent meals.

Pharmacologic Treatment

- Loperamide.
  - Rapid onset of action.

  Formulation

  Tablet: 2 mg.
  Capsule: 2 mg.
  Solution: 1 mg/7.5 mL, 1 mg/5 mL.
  Suspension: 1 mg/7.5 mL.

  Dose

  Standard dose: 4 mg PO after initial loose stool, 2 mg PO every 4 h or after subsequent loose stool.
  High dose: 4 mg PO after initial loose stool, 2 mg PO every 2 h until diarrhea free for 12 h.
  Maximum dose (16 mg/day) listed in drug references may be exceeded.

- Diphenoxylate and atropine.
  - Rapid onset of action.

  Formulation

  Tablet: diphenoxylate 2.5 mg/atropine 0.025 mg.
  Solution diphenoxylate 2.5 mg/atropine 0.025 mg per 5 mL.

  Dose: 5 mg diphenoxylate every 6 h until diarrhea controlled.

- Deodorized tincture of opium.
  - Contains 10 mg/mL of morphine.
  - Doses are expressed in milligrams of morphine.
  - Dose: 6 mg (0.6 mL) PO every 6 h.
  - Use with caution.

- Paregoric.
  - Contains 0.4 mg/mL of morphine.
  - Dose: 5–10 mL PO every 6 h.
- Octreotide.
  - Somatostatin analog.
  - Best used for complicated or refractory chemotherapy induced diarrhea.

Dose

100–150 mcg subQ three times daily; may increase dose up to 500 mcg three times daily.
25–50 mcg/h IV infusion.

Treatment Recommendations [172, 173, 180]

Uncomplicated Diarrhea

- Grade 1–2 with no complicating signs or symptoms.
- Nonpharmacologic therapy.
- Hold chemotherapy for grade 2 until symptoms resolve.
- Initiate standard dose loperamide and reevaluate in 12–24 h.
- If symptoms resolve you may discontinue treatment after 12 h with no loose stool.
- If symptoms persist increase to high dose loperamide, consider antibiotics, and reevaluate in 12–24 h.
- If diarrhea persists discontinue loperamide, complete more comprehensive workup and begin octreotide or other second line agent.
- If at any time the patients show worsening diarrhea or develop complication, they should be treated as such.

Complicated Diarrhea

- Grade 3–4 or Grade 1–2 with cramping, nausea/vomiting, decrease performance status, fever, sepsis, neutropenia, bleeding, or dehydration.
- Admit patient to hospital.

- Give supportive care (IV hydration/electrolytes) and non-pharmacologic treatment.
- Start octreotide and antibiotics as needed.
- Hold all chemotherapy until symptoms resolve, restart at a reduced dose.

Peripheral Neuropathy

Introduction [181–183]

Peripheral neuropathy is an often overlooked but serious adverse effect that is common in patients with gynecologic cancers. Over 2/3 of gynecologic oncology patients my experience some form of peripheral neuropathy. Onset may result in the need for dose reductions or treatment delays potentially effecting treatment outcomes as well as patient's quality-of-life.

Risk Factors [1–6, 15, 182–186]

- Diabetes.
- Preexisting neuropathy.
- History of alcohol abuse.
- Nutritional deficiencies.
- Metabolic abnormalities.
- Paraneoplastic disorders.
- Tumor compression or infiltration.
- Chemotherapy use (Table 6.7).

Definitions [179]

- Peripheral neuropathy: a disorder characterized by inflammation or degeneration of the peripheral sensory nerves.
- Paresthesia: abnormal cutaneous sensations of tingling, numbness, pressure, cold and warmth experienced in the absence of stimulus.

Table 6.7. Chemotherapy agents commonly causing peripheral neuropathy.

Drug	Onset dosage	Incidence	Notes
Cisplatin	300 mg/m^2	28–100 %	Worsens in combination with taxane May progress after discontinuation
Oxaliplatin	Acute: any Persistent: 500 mg/m^2	Acute: 65–80 % Persistent: 43 %	Acute neuropathy, transient and triggered by cold Persistent neuropathy similar to cisplatin
Carboplatin	600–800 mg/m^2	6–42 %	Less neurotoxic than other platinums Worsens in combination with taxane
Paclitaxel	100–1,000 mg/m^2	57–83 %	Worsens in combination with platinum Increased incidence with short/frequent infusions
Docetaxel	400 mg/m^2	11–64 %	Less severe neurotoxicity compared to paclitaxel Worsens in combination with platinum
Vincristine	Onset: 4 mg/m^2 Motor dysfunction: >6 mg/m^2		May cause autonomic neuropathy Motor neuropathy more common
Altretamine		31 %	Generally reversible upon discontinuation

- Instrumental activities of daily living (ADL): preparing meals, shopping, using the telephone, etc.
- Self-care ADL: bathing, dressing and undressing, feeding self, using toilet, taking medications, not bedridden.

Clinical Manifestations [181–184, 186, 187]

- Sensory symptoms (paresthesia, numbness, pain) are most common.
- Motor symptoms (weakness, loss of tendon reflexes) are uncommon.

- Autonomic symptoms are rare (typically caused by vinca alkaloids).
- Symmetrical "glove and stalking" distribution.
- Starts distally in fingers and toes and moves proximally.
- Symptoms may progress after discontinuation of offending agent.
- Resolution usually occurs within 3 months but may persist.

Evaluation [179, 182, 183, 185]

- Patients receiving neurotoxic agents should be questioned on the presence of peripheral neuropathy at each encounter.
- Grade severity of symptoms and effect on functioning (Table 6.8).
- Evaluate for the presence of pain.
- Neurophysiologic testing is inconsistent and often unnecessary.
- Need for interventions should be based upon severity of symptoms, and patient preference.
- Referral to neurologist, physical/occupational therapy, or pain specialist may be needed.

Prevention [2, 182–190]

Chemotherapy Selection

- For patients at high risk avoid chemotherapy regimens commonly associated with peripheral neuropathy.
- Use docetaxel instead of paclitaxel.
- Carboplatin use is preferred over cisplatin.
- Avoid dose-dense paclitaxel.
- Extend duration of paclitaxel infusion.
- Avoid vinca alkaloids.

TABLE 6.8. Peripheral neuropathy severity/grading.

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	–	–
Peripheral neuropathy	Asymptomatic; observation; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death

Pharmacologic Prevention

- No treatment is proven to prevent the onset of chemotherapy-induced peripheral neuropathy.
- Use of prophylactic medications cannot be recommended for routine use.
- Amifostine.
  - Multiple randomized trials and a meta-analysis failed to show benefit.
  - Not recommended due to lack of evidence and potential toxicity.
- Glutathione.
  - Meta-analysis of five trials showed no benefit for cisplatin-induced peripheral neuropathy.
  - Small trial of patient receiving oxaliplatin showed decreased grade II–IV neuropathy with glutathione use.
- Vitamin E.
  - Patients having received 300 mg/m^2 of cisplatin or more have shown decreased incidence and severity of peripheral neuropathy with vitamin E 400 international units daily during and 3 months following discontinuation of cisplatin.
  - Due to antioxidant effect there is theoretical concern about potential to decrease chemotherapy efficacy.
  - Further study evaluating efficacy and safety is needed.
- Erythropoietin.
  - Animal studies suggest potential for prevention with cisplatin and docetaxel-induced peripheral neuropathy.
  - Study of patients receiving paclitaxel and erythropoietin for anemia suggests decreased peripheral neuropathy.
  - Risks of erythropoietin currently outweigh potential benefits for prophylaxis in patients being treated with curative intent or those without anemia.

- IV calcium and magnesium.
  - Early trials in patient receiving infusion of calcium and magnesium with oxaliplatin showed potential benefit.
  - Randomized placebo controlled trial of 353 patients showed no difference in acute or cumulative neurotoxicity.
  - Expert consensus is to avoid use.
- Glutamine and acetyl-L-carnitine.
  - Conflicting data from small trials with a variable design.
  - Further study needed to determine benefit.
- Serotonin-norepinephrine reuptake inhibitors.
  - Venlafaxine has been shown to decrease oxaliplatin-induced acute peripheral neuropathy.
  - No information regarding efficacy for chronic neuropathy.
  - Not recommended due to limited evidence.

Treatment

General Principles [2, 182, 183, 185, 187]

- Treat any underlying neuropathy or metabolic abnormalities that may cause neuropathy.
- Chemotherapy may be switched to an agent that causes less CIPN (i.e., paclitaxel to docetaxel) if clinically appropriate.
- Dose reduction or discontinuation of offending agent may be necessary.

Pharmacologic Treatment

- There are no approved medications for the treatment of CIPN.
- Most medications available have been approved based upon their ability to treat pain in patients with diabetic neuropathy.
- A variety of agents have been used (Table 6.9).

TABLE 6.9. Agents commonly used for chemotherapy-induced peripheral neuropathy pain.

Drug	Dose	Adverse effects
Duloxetine	Starting: 20–30 mg/day Maximum: 120 mg/day	Nausea, xerostomia, constipation, diarrhea
Gabapentin	Starting: 100–300 mg nightly Maximum: 1,200 mg TID	Somnolence, dizziness, nausea, diarrhea, edema, discoordination
Lidocaine 5 % patch	3 Patches daily	Rash
Opioids	Variable	Constipation, nausea, vomiting, sedation, respiratory depression
Pregabalin	Starting: 25–50 mg TID Maximum: 200 mg TID	Dizziness, somnolence, xerostomia, edema, blurred vision, decreased concentration
Tramadol	Starting: 50 mg 1–2/day Maximum: 100 mg q6h or q8h for elderly	Dizziness, constipation, nausea, somnolence, seizure, serotonin syndrome
Tricyclic antidepressants	Variable	Anticholinergic effects, cardiovascular effects, dizziness, somnolence

- Motor weakness and loss of light touch and proprioception are not treatable with medication.
- Start with low dose and titrate to doses that maximize symptom control while limiting side effects.
- A trial of 2–8 weeks should be given to determine efficacy.
- Addition of a second agent with a different mechanism of action may be necessary.
- Dietary supplements such as acetyl-L-carnitine, glutamine, vitamin E, and glutathione have been studied but efficacy has not been established.

Nonpharmacologic Treatment

- Acupuncture.
- Neurostimulation.
- Massage.
- Meditation.
- Occupational/physical therapy.

Febrile Neutropenia

Introduction [191, 192]

Febrile neutropenia (FN) is one of the major dose-limiting toxicities of chemotherapy regimens used in patients with gynecologic oncology. It often requires hospitalization and broad spectrum antibiotics. Without prompt recognition and treatment, FN is associated with substantial morbidity, mortality, and cost. This section reviews some key points of management of FN and common drugs used in the clinical practice.

Definitions [193]

- Neutropenia: absolute neutrophil count (ANC) $<0.5\times10^9$/L or ANC $<1\times10^9$/L with predicted decrease to $\leq0.5\times10^9$/L with the next 48 h.
- Febrile neutropenia: ANC $<0.5\times10^9$/L and a single oral temperature of $\geq$38.3 °C (101 °F) or $\geq$38.0 °C (100.4 °F) for at least an hour.

Risk Factors [194]

- Patient related.
  - Neutropenia.
  - Type of malignancy (hematologic malignancies have higher risk).
  - Asplenic.
  - Genetic factors.
- Chemotherapy regimen related.
- Immune system dysfunction.
- Corticosteroids and other lymphotoxic agents.
- Other defects in host defense.

Microbiology [193, 195]

- Bacterial infection (80–85 %).
- Most common bacterial pathogen for febrile neutropenia has changed over the past two decades from gram-negative to gram-positive organisms.
- Extended-spectrum β-lactamase (ESBL)-producing *E. coli* and Klebsiella species are emerging.
- Gram-negative organisms:
  - *E. coli.*
  - Klebsiella spp.
  - "SPICE" organisms: Serratia, Pseudomonas spp, indole-positive Proteus species, *Citrobacter freundii, Enterobacter cloacae*.
- Gram-positive organisms:
  - Staphylococcus species (most coagulase negative).
  - Streptococcus species.
  - Enterococci.
- Polymicrobial.
- Fungal infection.
  - Candida species.
  - Aspergillus species.
  - Others.
- Other infections: viral.

Diagnosis and Workup [193, 195]

- Diagnosis: Fever and ANC $<0.5 \times 109$/L.
- Workup:
- History.
- Complete physical exam (rectal exam not recommended due to a risk of transient bacteremia).
- Two sets of blood cultures and any site-specific culture (i.e., port-a-cath, PICC line; results often negative).
- Chest X-ray.

- CBC with differential.
- Chemistry including liver and renal function.

Initial Risk Assessment [193, 194, 196]

Low Risk

Outpatient status at time of development of fever.

- No acute comorbidity.
- Anticipated short duration of profound neutropenia.
- Good performance status (PS 0–1).
- No hepatic insufficiency.
- No renal insufficiency
  OR
- MASCC Risk index score ≥21 (see Table 6.10).

High Risk

Inpatient status at time of development of fever.

- Significant medical comorbidity or clinically unstable.
- Anticipated prolonged profound neutropenia (ANC ≤0.1 × 109/L and ≥7 days).
- Hepatic insufficiency (AST/ALT ≥5 × UNL).
- Renal insufficiency (CrCL <30 ml/min).
- Uncontrolled/progressive cancer.
- Pneumonia or other complex complications.
- Alemtuzumab.
- Mucositis grade 3–4.
  OR
- MASCC Risk index score <21 (see Table 6.10).

Primary Prophylaxis [193, 194]

Low risk: Not recommended (included most solid tumor patients).

High Risk: Consider fluoroquinolones prophylaxis (levofloxacin is preferred).

TABLE 6.10. MASCC scoring index for evaluation of febrile neutropenia [196].

Characteristic	Score
Illness extent (choose 1 item below)	
No symptoms	5
Mild symptoms	5
Moderate symptoms	3
No hypotension (SBP ≥90 mmHg without pressors)	5
No chronic obstructive pulmonary disease	4
Solid tumors (if have hematologic malignancy—no previous fungal infection)	4
No dehydration	3
Outpatient at onset of fever	3
Age <60 yo (does not apply for patients ≤16 yo)	2

Therapeutic Options [193, 194]

Common antibiotic and antifungal treatments are outline in Tables 6.11 and 6.12.

Low Risk Patients

- Patients can be managed in home, ambulatory clinic, or hospital.
- Both IV and/or oral antibiotics are reasonable.
- Close monitoring before and after antibiotics administration, especially within the first 72 h, is required.
- Anti-pseudomonas antibiotics should be used the first line.
- If oral antibiotics are chosen, ciprofloxacin plus amoxicillin/clavulanate are the first line therapy.

High Risk Patients

- Patients should be managed in the hospital setting.
- IV antibiotics is required.
- Monotherapy with anti-pseudomonas antibiotics can be used as the first line for uncomplicated patients.
- Details of drug dose and spectrum (see Tables 6.11 and 6.12).
- Add site-specific evaluation and therapy when indicated.

Table 6.11. Common antibiotics used for FN [2, 194].

Drug name	Dose	Adverse effects	Comments	Dose adjustment due to renal dysfunction
Gram-positive active antibiotics				
Vancomycin	15 mg/kg IV Q12h; c.diff: 125 mg PO Q6h	Rash, red man syndrome	Not effective for vancomycin-resistant enterococcus (VRE)	Yes
Linezolid	600 mg IV/PO BID	Thrombocytopenia, Serotonin syndrome (rare), peripheral neuropathy (long-term use)	Effective for MRSE and VRE Cautious for when used during immunosuppressive chemotherapy	No
Daptomycin	6 mg/kg IV daily	Myositis and rhabdomyolysis	Check CK prior to start treatment and once a week thereafter Not effective for pneumonia due to inactivation by pulmonary surfactactant Effective for MRSA and VRE	Yes
Dalfopristin/ quinopristin	7.5 mg/kg IV Q8h	Myalgia, arthralgia	Effective for VRE, but not effective for *Enterococcus faecalis* Less common use due to its side effects Central line access required	No
Ceftaroline	600 mg IV Q12h	Uncommon	Has both gram-positive and negative activity including MRSA Not effective for *Enterococcus faecalis* Seroconversion of Coombs' test	Yes
Gram-negative active antibiotics (including pseudomonas)				
Pipercillin/ tazobactam	4.5 g IV Q6h	Allergy	Empiric drug choice for FN Active for most gram-positive, negative and anaerobe organisms Not recommended for meningitis False positive for galactomannan test	Yes

Cefepime	2 g IV Q8h	Uncommon	Empiric drug choice for FN Active for most gram-positive, negative organisms Not effective for anaerobes and Enterococcus spp. Recommended for suspected/proven CNS infection	Yes
Imipenem/ cilastatin sodium	500 mg IV Q6h	Nausea/vomiting; seizure	Empiric drug choice for FN Active for most gram-positive, negative and anaerobe organisms Preferred for ESBL or serious Enterobacter infections May lower seizure threshold for CNS tumor/infection or renal insufficiency	Yes
Meropenem	1 g IV Q8h (2 g IV Q8h for meningitis)	Uncommon, seizure	Empiric drug choice for FN Active for most gram-positive, negative and anaerobe organisms Preferred for ESBL or serious Enterobacter infections May lower seizure threshold for CNS tumor/infection or renal insufficiency	Yes
Ceftazidine	2 g IV Q8h	Uncommon	Not effective for anaerobes and Enterococcus spp. Less common use for FN due to increasing resistance at some centers	Yes
Other antibiotics				
Ciprofloxacin	500–750 mg PO BID or 400 mg IV Q8h	QTc prolongation	Minimal gram-positive coverage Not effective for anaerobes Oral combination with amoxicillin/clavulanate or clindamycin for low risk patients	Yes
Levofloxacin	500–750 mg PO/ IV daily	QTc prolongation	More gram-positive coverage in addition to gram-negative organisms Not effective for anaerobes Drug of choice of prophylaxis for selective high risk patients	Yes
Aminoglycoside	Varies with different agents	Renal toxicity, ototoxicity	Effective mainly for gram-negative organisms Synergistic effect when used with beta lactams for *S. aureus* and Enterobacter spp. Reserve for severe infections Pharmacokinetic monitoring is required	Yes

TABLE 6.12. Common antifungals used for FN [2, 194].

Drug name	Dose	Adverse effects	Comments	Dose adjustment due to renal dysfunction
Fluconazole	400 mg IV/PO daily	Minimal	Effective for many Candida spp Variable activity against *Candida glabrata*, but not effective for *Candida krusei* Not effective for molds	Yes
Voriconazole	6 mg/kg IV Q12h × 2, then 4 mg/kg IV Q12h; or 200 mg po bid	QTc prolongation; drug interactions with CYP3A4 substrates	Effective for Candida and Aspergillus species Not effective for Zycomycetes Primary therapy for invasive aspergillosis Use with caution with IV form in patients with renal dysfunction	No
Posaconazole	Prophylaxis: 200 mg PO TID Treatment: 200 mg PO QID followed by 400 mg PO BID	QTc prolongation drug interactions with CYP3A4 substrates	Effective for Candida and Aspergillus and some Zycomycetes spp Administer with a full meal or liquid nutritional supplements PPIs can decrease absorption of posaconazole Use with caution with IV form in patients with renal dysfunction	No
Amphotericin B deoxycolate	0.5–1.5 mg/kg IV Q24h	Infusion reaction, renal toxicity, electrolyte wasting	Effective for Candida and Aspergillus and some Zycomycetes spp Prehydration Premedication with acetaminophen, antihistamine, and meperidine	Yes

Liposomal amphotericin B	3–10 mg/kg IV Q24h	Less infusion reactions and nephrotoxicity, electrolyte wasting than plain amphotericin B	Effective for Candida and Aspergillus and some Zycomycetes spp Prehydration Premedication with acetaminophen, antihistamine, and meperidine	Yes
Amphotericin B lipid complex	5 mg/kg IV Q24h	Less infusion reactions and nephrotoxicity, electrolyte wasting than plain amphotericin B	Effective for Candida and Aspergillus and some Zycomycetes spp Prehydration Premedication with acetaminophen, antihistamine, and meperidine	Yes
Amphotericin B colloidal dispersion	5 mg/kg IV Q24h	Substantial infusion reactions, nephrotoxicity, electrolyte wasting	Effective for Candida and Aspergillus and some Zycomycetes spp. Prehydration Premedication with acetaminophen, antihistamine, and meperidine	Yes
Caspofungin	70 mg IV once followed by 50 mg IV Q24h	AST/ALT elevation (less common)	Effective for Candida and Aspergillus spp only Not effective for Zycomycetes Primary therapy for invasive Candida infection Salvage therapy for aspergillosis	No, but does adjustment is required for liver dysfunction
Micafungin	Treatment: 100 mg IV Q24h Prophylaxis: 50 mg IV Q24	Uncommon	Effective for Candida and Aspergillus spp only Not effective for Zycomycetes Primary therapy for invasive Candida infection	No
Anidulafungin	200 mg IV once followed by 100 mg IV Q24h	Uncommon	Effective for Candida and Aspergillus spp. only Not effective for Zycomycetes Primary therapy for invasive Candida infection	No

Clinically Unstable Patients

- Empiric treatment: broad spectrum β-lactam (meropenem, imipenem/cilastatin, pipercillin/tazobactam plus an aminoglycoside and vancomycin).
- Strongly consider adding fluconazole and echinocandin antifungal if patient not on antifungal prophylaxis.
- Consider additional stress dose of hydrocortisone, especially for patients with septic shock.

Indications for Antibiotics with Gram-Positive Coverage

- Clinically apparent, serious, catheter-related infection.
- Blood culture positive for gram-positive bacteria prior to final identification and susceptibility test.
- Known colonization with penicillin/cephalosporin-resistant pneumococci, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococus.
- Severe mucositis.
- Hypotension or septic shock without identified pathogen (clinically unstable).
- Soft tissue or skin infection.

Follow-Up [193]

- Changes of empiric antibiotics should be based on clinical and microbiology data.
- If infection is identified, then change antibiotics to appropriate coverage for the site and the drug susceptibility of the pathogen.
- If vancomycin or other gram-positive coverage antibiotics are part of the initial empiric therapy, it can be discontinued after 2 days without evidence of infection.
- After initial empiric standard regimen, antibiotics for hemodynamically unstable patients should be expanded to

include coverage for persistent gram-negative, gram-positive, anaerobic bacteria and antifungals.
- Empiric antifungals can be considered for patients with persistent fever over 4–7 days of broad spectrum antimicrobials and with no identified source of fever.

Treatment Duration [194]

- For fever of unknown origin, initial antibiotic therapy should continue until ANC $\geq 0.5 \times 109$/L and increasing.
- For documented infection, continue antibiotics at least to ANC $\geq 0.5 \times 109$/L; however, a full course of therapy can also be based on the infection site and pathogen. Can consult with institutional infectious disease specialist.
- Skin/soft tissue: 7–14 days.
- Bloodstream infection (uncomplicated).
  - Gram-positive: 7–14 days.
  - Gram-negative: 10–14 days.
  - *S. aureus*: at least 2 weeks after first negative blood culture, treatment course can be prolonged with the involvement of endovascular structure.
  - Yeast: at least 2 weeks after the first negative blood culture.
- Sinusitis/bacterial pneumonia: 10–21 days.
- Invasive fungal infection:
  - Candida: at least 2 weeks after the first negative blood culture.
  - Mold: (e.g., Aspergillus): at least 12 weeks.
- Viral infection.
  - HSV/VZV: 7–10 days.
  - Influenza: at least 5 days, maybe prolonged until symptom resolution in immunocompromised patients.

Extravasation

Background [197]

Extravasation causes 0.5–6 % of adverse events associated with chemotherapy administration. Based on the characteristics and potential tissue damage, chemotherapy agents can be classified as irritant, vesicant and nonirritant, non-vesicant. However, it is often controversial regarding which drugs are vesicants or irritants. Because of limited clinical trial data, treatment for extravasation may vary from institution to institution.

Definitions [198]

- Irritant: An agent which may cause a local inflammatory reaction, but without tissue necrosis.
- Vesicant: An agent which may cause severe tissue necrosis.

Table 6.13 compares and contrasts irritants and vesicants.

Risk Factors [197]

- Vein physiology—fragile, small, sclerotic veins, blood flow, and vessel size.
- Pharmacologic—duration and amount of chemotherapy exposure, drug administration sequence (see Table 6.13).
- Physiologic—superior vena cava syndrome, peripheral neuropathy, lymphedema, phlebitis.

TABLE 6.13. Comparison of irritant and vesicant.

	Irritant	Vesicant
Physiology	Local inflammatory reaction	Tissue injury and/or necrosis
Duration of injury	Short-term	Longer, or permanent
Symptoms	Burning, tender, erythema	Burning, itching, blistering, pain
Blood return	Intact	No

- Radiologic—previous local irradiation.
- Mechanical—needle insertion technique, injection site, multiple venipuncture attempts.

Prevention [197–200]

- Use of central venous catheter if possible.
- Careful administration with frequent checking of blood return.
- IV sites should be started from as distant from hand, dorsum of the foot, or any joints as possible.
- Do not administer chemotherapy distal from a recent venipuncture site.
- Consider using hot compress to dilate veins before administration.
- Educate patients to report any pain, tingling, burning symptoms.
- Monitor IV sites frequently during infusion.

Clinical Management [199, 200]

General Management Protocol (see Table 6.14)

- Stop infusion.
- Aspirate any drugs via intravenous cannula.
- Do not flush the line.
- Instill antidotes if available.
- Remove the catheter.
- Cold or warm packs as recommended.
- Consider taking a picture of the site with extravasation and mark the border.
- Monitor the site for 24 h, at 1 and 2 weeks and as necessary for redness, swelling, pain, ulceration and necrosis.
- Early surgery for severe and large amount of extravasation when necessary.

Table 6.14. Classification of chemotherapy agents and management of extravasation.

Chemotherapy agent	Irritant or vesicant classification	Suggested extravasation management protocol
Bevacizumab	Non-vesicant/nonirritant	
Bleomycin sulfate	Non-vesicant/nonirritant (drug can be administered intramuscularly or subcutaneously)	
Carboplatin	Irritant at greater than 10 mg/mL	Cold protocol + DMSO
Cisplatin	Vesicant at high doses	Extravasation of more than 20 mL of 0.5 mg/mL concentration. If less than this, no treatment. If more, see sodium thiosulfate
Cyclophosphamide	Non-vesicant/nonirritant	
Dacarbazine	Irritant	Warm protocol
Docetaxel	Irritant potential vesicant	Cold protocol + DMSO
Doxorubicin	Vesicant	Cold protocol + DMSO OR cold protocol + dexrazoxane extravasations of less than 1–2 mL often heal spontaneously. If greater than 3 mL, ulceration often results.
Doxorubicin liposome	Irritant	Cold protocol
Epirubicin	Vesicant	Cold protocol + DMSO OR Cold protocol + dexrazoxane
Etoposide	Irritant	Warm protocol. Treatment with hyaluronidase is needed only if large amount of concentrated solution extravasates, e.g., amounts one half or more of the planned total dose of etoposide

Fluorouracil	Irritant	Cold protocol
Gemcitabine hydrochloride	Non-vesicant/nonirritant	
Ifosfamide	Non-vesicant/nonirritant	
Irinotecan	Irritant	Cold protocol
Leuprolide acetate	Non-vesicant/nonirritant	Intramuscular use only
Melphalan	Irritant	No specific recommendation
Methotrexate sodium	Non-vesicant/nonirritant	
Mitomycin	Vesicant	Cold protocol + DMSO protect extravasation from sunlight
Oxaliplatin	Irritant vesicant properties have been reported	Extravasation of moderate to high doses led to inflammation but not necrosis. Sodium thiosulfate, OR High-dose dexamethasone 8 mg BID × 10 days may be considered. avoid cold protocol
Paclitaxel	Irritant, potential vesicant	Cold protocol
Paclitaxel protein-bound	Irritant, potential vesicant	Cold protocol
Pemetrexed disodium	Non-vesicant/nonirritant	
Topotecan hydrochloride	Irritant	Cold protocol
Vinca alkaloids (vincristine, vinorelbine, vinblastine)	Vesicant	Hyaluronidase and warm protocol

Cold Protocol

- Immediately after medical treatment is completed, apply ice pack to the affected area for 15–20 min at least 4 times per day for the first 24–48 h by any of the following means:
  - Cool wash cloth.
  - Instant cool/ice pack.
- Elevate limb at all times and exercise at least every 4–6 h to reduce immobility.

Warm Protocol

- Immediately after medical treatment is completed apply warmth to the affected area for 15–20 min at least 4 times per day for the first 24–48 h by any of the following means:
  - Heating pad (K pad) on moderate setting.
  - Instant warm pack.
- Elevate and extend limb to promote circulation at all times and exercise at least every 4–6 h to reduce immobility.

Antidotes [197, 199–202]

- Sodium Thiosulfate.
  - Mix 0.4 mL of 25 % sodium thiosulfate with 2.1 mL Sterile Water for Injection (resulting in 1/6 molar solution).
  - Inject 2 mL of the sodium thiosulfate solution subQ into the extravasation site using a 25-gauge or smaller needle.
  - Follow cold protocol.
- Hyaluronidase.
  - Inject 1 mL (200 units) as five separate injections in a clockwise manner, each containing 0.2 mL of hyaluronidase, subQ around the extravasation site.
  - Change needle with each injection.

- Hyaluronidase must not be given IV; death has resulted.
- Follow warm protocol.
- DO NOT APPLY ICE.
- Dimethylsulfoxide (DMSO).
- For anthracycline extravasation management:
  - Consider for cases that may be difficult to delineate between a local infusion reaction (phlebitis, irritation) versus a small volume extravasation.
  - When opposite arm/extremity/area other than affected area is not available for IV access.
    - Begin DMSO immediately after the nurse has aspirated any residual extravasate and removed the IV device.
- Conflicting literature exists as to the benefit of this adjuvant therapy.
- Dimethylsulfoxide 99 %: Using cotton ball or small gauze pad, invert DMSO bottle to wet cotton ball or small gauze then apply topically every 6 h for 14 days or every 8 h for 7 days, leave uncovered.

- Dexrazoxane (Totect™).
  - As an alternative treatment of anthracycline extravasations.
  - Consider systemic treatment when:
    - Centrally placed venous catheter extravasations may result in extensive underlying soft tissue involvement, Large volume extravasations (when ulceration and necrosis is likely to occur),
    - Significant amount of time (>1 h) has elapsed between discovery of the extravasation and initiation of extravasation management.
    - Therapy must be initiated within 6 h of extravasation.
- Cold protocol should be held 15 min prior to infusion through 15 min after infusion.
- Recommended dose:

- Days 1 and 2: 1,000 mg/m^2 (2,000 mg max dose) IV.
- Day 3: 500 mg/m^2 (1,000 mg max dose).
- Reduce dose by 50 % for patients with a creatinine clearance less than 40 mL/min.
- Dilute in 1,000 mL 0.9 % NaCl and infuse over 1–2 h in opposite extremity/area than the one affected by the extravasation.
- On days 2 and 3, premedicate with prochlorperazine 10 mg PO or dexamethasone 12 mg PO.

Background [203]

Hypersensitivity reactions (HSRs) are most commonly seen in gynecologic oncology patients receiving platinums (carboplatin, cisplatin, and oxaliplatin) and taxanes (paclitaxel and docetaxel); however, they were reported in other agents such as liposomal doxorubicin. HSRs are often unpredictable and symptoms vary dramatically. This article focuses on carboplatin/cisplatin and paclitaxel/docetaxel HSRs and their clinical management.

Incidence [1–5, 204]

- Carboplatin: 1–6 % overall, however, incidence is up to 44 %.
- Cisplatin: 5–20 %.
- Paclitaxel and docetaxel: 10 % without premedication and 2 % with premedication.

Mechanism [203–205]

- Platinums: true allergic reactions and most acute HSR if IgE mediated activation of basophils and mast cells. Types of HSRs are outlined in Table 6.15.
- Taxanes: generally an infusion-related, but not Ig-E mediated. Often attributed to Cremophor (paclitaxel) and

TABLE 6.15. Type of hypersensitivity reaction of platinums and their characteristics.

Type of hypersensitivity reactions	Antigen	Mediated by	Mechanism	Involved in platinum hypersensitivity	Symptoms related
I	Soluble antigen	IgE	Mast cell and basophil degranulation	Carboplatin, cisplatin, oxaliplatin (most)	Early onset symptoms: itching, chest pain, rash, anaphylactic reactions
II	Cell- or matrix associated antigen	IgG, IgM	Phagocyte and NK-cell activation	Oxaliplatin	Hemolysis, thrombocytopenia
III	Soluble antigen	IgG	Immune complex, phagocyte and NK-cell activation, complement fixation	Oxaliplatin	Chronic urticaria, joint pain, proteinuria
IV	Soluble or cell-associated antigen	T-cell	Macrophage and eosinophil activation, cytotoxicity	Carboplatin, cisplatin	Delayed reactions, hours or even days after infusion

Tween 80 (docetaxel). It is the direct activation of basophils and mast cells.

Clinical Presentation and Grading [179, 203]

Severity grading of HSR is outlined in Table 6.16.

Platinum Hypersensitivity

- Often occurs following re-exposure, after the completion of the initial treatment (>6 doses).
- Symptoms can occur anytime during the infusion, or after completion of the infusion.
- Commonly HSR symptoms are more severe.
- Half of HSR are still mild but anaphylaxis can occur.

Taxane Hypersensitivity

- Often occurs during the first and second cycle of paclitaxel/docetaxel.
- Typically occurs with the first a few minutes.
- Symptoms are often milder, but anaphylaxis can still occur.

Prevention [195, 203, 204]

- Preparation for the possible HSR.
  - Obtain all necessary treatment/monitoring equipment including blood pressure monitor, IV antihistamines, IV emergent steroids (e.g., hydrocortisone), IV epinephrine, and oxygen.
- Premedication 30 min before chemotherapy (most taxanes).
  - H1 antagonist (diphenhydramine 50 mg IV).
  - H2 antagonist (ranitidine 50 mg IV or famotidine 20 mg IV).
  - Steroid (dexamethasone 20 mg IV).

TABLE 6.16. Grading of HSR.

	Grade				
	1	2	3	4	5
Hypersensitivity (allergic reaction)	Transient flushing or rash, drug fever <38.0 °C, intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤24 h	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Acute infusion reactions (cytokine release syndrome)	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilator support indicated	Death

Table 6.17. 12-Step rapid desensitization protocol for chemotherapy agents.

Step	Solution	Rate (mL/h)	Time (in minutes)	Volume infused per step (mL)
1	100-fold dilution of final target concentration	2.0	15	0.50
2		5.0	15	1.25
3		10.0	15	2.50
4		20.0	15	5.00
5	Tenfold dilution of final target concentration	5.0	15	1.25
6		10.0	15	2.50
7		20.0	15	5.00
8		40.0	15	10.00
9	Concentration was calculated by subtracting the cumulative dose administered in steps 1–8 from the total target dose	10.0	15	2.50
10		20.0	15	5.00
11		40.0	15	10.00
12		75.0	Prolonged to complete target dose	232.50

Desensitization [203, 206]

- Gradual reintroduction of small amounts of drug antigen titrating to the full dose, on prolonged infusion and premedication.
- Various desensitization protocols have been published.
- No single protocol is preferred.
- Desensitization typically takes a much longer time, but recent rapid desensitization protocols have been tested with success. Table 6.17 describes desensitization protocol from the largest study to date.
- Consider substitute with a different platinum or taxane drug.
- Cisplatin for patients with a history of severe carboplatin HSR.
- Docetaxel or nanoalbumin paclitaxel for patients with a history of severe paclitaxel HSR.
- Monitor patients closely for any signs/symptoms of breakthrough reactions during desensitization.

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