

IRRITANTS

Drug	Information
Bleomycin	Little information is known. May cause tissue irritation.
Carboplatin	Little information is known. Protect area from sunlight.
Carmustine (BCNU)	Little information is known. May cause phlebitis.
Dacarbazine (DTIC)	Little information is known. Can cause phlebitis. Protect area from sunlight.
Ifosfamide	Little information is known. Protect area from light.
VP-16 or VM-26	Treatment is necessary if a large amount of concentrated solution extravasates. In this case, treat like vincristine or vinblastine. May cause phlebitis, urticaria, or redness.

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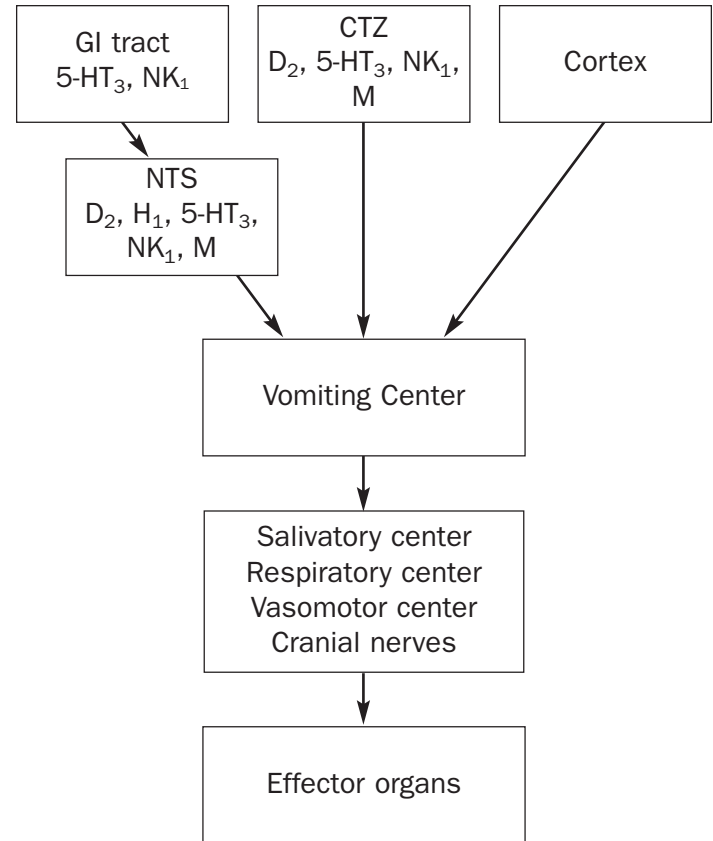
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Summary of Therapeutic Guidelines for the Use of Antiemetics From the American Society of Health-System Pharmacists

Recommendations

1. The emetic potential of the chemotherapeutic agent (Table 1) is the primary factor to consider when deciding whether to administer pharmacologic prophylaxis and which antiemetic(s) to select. (Strength of evidence = A)
2. Adult and pediatric patients receiving chemotherapeutic agent(s) with emetic potential classified as level 2 through 5 should receive pharmacologic prophylaxis against nausea and vomiting each day on which chemotherapy is given. (Strength of evidence = B) Antiemetic prophylaxis is not required when the level of emetogenicity is 1.
 - (a) Adult and pediatric patients receiving level-2 chemotherapeutic regimens can receive dexamethasone or methylprednisolone alone for prophylaxis of nausea and vomiting. (Strength of evidence = B) Prochlorperazine is also an option for adults. (Strength of evidence = D)
 - (b) Adult and pediatric patients receiving chemotherapeutic agent(s) with emetic potential of level 3 through 5 should receive a corticosteroid (dexamethasone or methylprednisolone) in combination with a 5-HT₃ receptor antagonist. (Strength of evidence = A for adults and C for pediatric patients)
 - (c) Orally and intravenously administered antiemetics are generally equivalent in efficacy and safety for both adult and pediatric patients. (Strength of evidence = B for adults and C for pediatric patients) The decision as to which formulation to use should be based on patient-specific factors and cost.
 - (d) The decision as to which 5-HT₃ receptor antagonist to use should be based on the acquisition cost of comparable doses. (Strength of evidence = A) (Tables 5 and 6) Dosage recommendations for adult and pediatric patients differ.
3. All patients receiving chemotherapy should have antiemetics available on an as-needed basis for rescue for breakthrough nausea and vomiting. (Strength of evidence = A) Patients should be educated on the appropriate administration of and expectations for therapy and should be reassured that every effort is being made to prevent symptoms. In adults, lorazepam, methylprednisolone, prochlorperazine, metoclopramide, dexamethasone, haloperidol, and dronabinol are effective. (Strength of evidence = C) In pediatric patients, chlorpromazine, lorazepam, or methylprednisolone (or dexamethasone) is recommended. (Strength of evidence = B) The choice of agent should be based on patient-specific factors (eg, anticipated adverse events, past success) and cost.

4. For the prevention of delayed emesis after cisplatin therapy in adults, dexamethasone with metoclopramide or a 5-HT₃ receptor antagonist is recommended. (Strength of evidence = A) The choice of agent should be based on patient-specific factors and cost. For delayed emesis after cyclophosphamide, doxorubicin, or carboplatin therapy, a 5-HT₃ receptor antagonist with dexamethasone is recommended. (Strength of evidence = B) Prochlorperazine in combination with dexamethasone has also been used and is available in extended-release and rectal dosage forms, but the evidence to support this combination is limited. (Strength of evidence = D) In pediatric patients, chlorpromazine, lorazepam, or 5-HT₃ receptor antagonist can be used in combination with a corticosteroid. (Strength of evidence = C)
5. Patients receiving total or hemibody irradiation (with or without concomitant chemotherapeutic agents) or single-exposure, high-dose radiation therapy to the upper abdomen should receive preventive therapy for nausea and vomiting with each day of therapy. (Strength of evidence = A) 5-HT₃ receptor antagonist should be used both in adults and in pediatric patients. (Strength of evidence = B) Oral therapy should be encouraged; however, IV therapy is an acceptable option. (Strength of evidence = B) There is no evidence to support the use of 5-HT₃ receptor antagonists 24 hours beyond the last dose of radiation.
6. If an agent is needed to treat established radiation therapy-induced emesis in adults, prochlorperazine, metoclopramide, or thiethylperazine is recommended. 5-HT₃ receptor antagonists are also an option. Chlorpromazine and lorazepam can be used in pediatric patients. (Strength of evidence = D)



CTZ = chemoreceptor trigger zone
D₂ = dopamine type 2 receptor
GI = gastrointestinal
H₁ = histamine type 1 receptor

M = muscarinic receptor
NK₁ = tachykinin neurokinin type 1 receptor
NTS = nucleus tractus solitarius
5-HT₃ = serotonin type 3 receptor

TABLE 1: STRENGTH OF EVIDENCE

- A. Strong research-based evidence (multiple relevant and high-quality scientific studies)
- B. Moderate research-based evidence (one relevant, high-quality scientific study or multiple adequate scientific studies)
- C. Limited research-based evidence (at least one adequate scientific study in patients with nausea and vomiting, published in a reputable medical journal)
- D. Panel interpretation of information that did not meet inclusion criteria as research-based evidence

TABLE 2: EMETOGENICITY OF CHEMOTHERAPEUTIC AGENTS^a

Level 1 (Less than a 10% Frequency)	Level 3 (30–60% Frequency)
Androgens	Aldesleukin ^c
Bleomycin	Cyclophosphamide IV (≤ 750 mg/m ²)
Busulfan (oral, <4mg/kg/day)	Dactinomycin (≤ 1.5 mg/m ²)
Chlorambucil (oral)	Doxorubicin hydrochloride (20–60 mg/m ²)
Cladribine	Epirubicin hydrochloride (≤ 90 mg/m ²)
Corticosteroids	Idarubicin
Fludarabine	Ifosfamide
Hydroxyurea	Methenamine (oral)
Interferon	Methotrexate (250–1000 mg/m ²)
Melphalan (oral)	Mitoxantrone (≤ 15 mg/m ²)
Mercaptopurine	
Methotrexate (≤ 50 mg/m ²) ^b	Level 4 (60–90% Frequency)
Thioguanine (oral)	Carboplatin
Tretinoin	Carmustine (<250 mg/m ²)
Vinblastine	Cisplatin (<50 mg/m ²)
Vincristine	Cyclophosphamide (>750 mg/m ² to ≤ 1500 mg/m ²)
Vinorelbine	Cytarabine (≥ 1 g/m ²)
	Dactinomycin (>1.5 mg/m ²)
	Doxorubicin hydrochloride (>60 mg/m ²)
	Irinotecan
	Melphalan (IV)
	Methotrexate (≥ 1000 mg/m ²)
	Mitoxantrone (>15 mg/m ²)
	Procarbazine (oral)
	Level 5 (More than a 90% Frequency)
	Carmustine (>250 mg/m ²)
	Cisplatin (≥ 50 mg/m ²)
	Cyclophosphamide (>1500 mg/m ²)
	Dacarbazine (≥ 500 mg/m ²)
	Lomustine (>60 mg/m ²)
	Mechlorethamine
	Pentostatin
	Streptozocin

^a The most highly emetogenic agent in the combination should be identified, and the contribution of other agents should be considered by using the following rules:

- (1) Level 1 agents do not contribute to the emetogenicity of a given regimen.
- (2) Adding one or more level 2 agents increases the emetogenicity of the combination by one level greater than the most emetogenic agent in the combination.
- (3) Adding level 3 and 4 agents increases the emetogenicity of the combination by one level per agent.

^b When methotrexate and cytarabine are coadministered intrathecally to pediatric patients, the level of emetogenicity is increased to level 3.

^c Corticosteroids should not be used as antiemetics.

TABLE 3: ADVERSE EFFECTS OF ANTIEMETIC AGENTS

Medication	Adverse Effects ^a
<i>Antihistamines</i> diphenhydramine hydroxyzine	Most common: sedation, dry mouth, constipation Less common: confusion, blurred vision, urinary retention
<i>Belladonna alkaloid</i> scopolamine	Most common: dry mouth, drowsiness, impaired eye accommodation Rare: disorientation, memory disturbances, dizziness, hallucinations
<i>Benzamides</i> benzquinamide metoclopramide trimethobenzamide	Most common: sedation, restlessness, diarrhea (metoclopramide), agitation, central nervous system depression Less common: extrapyramidal effects (more frequent with higher doses), hypotension, neuroleptic syndrome, supraventricular tachycardia (with IV administration)
<i>Benzodiazepines</i> lorazepam	Most common: sedation, amnesia Rare: respiratory depression, ataxia, blurred vision, hallucinations, paradoxical reactions (weeping, emotional reactions)
<i>Butyrophenones</i> droperidol, haloperidol	Most common: sedation, hypotension, tachycardia Less common: extrapyramidal effects, dizziness, increase in blood pressure, chills, hallucinations
<i>Cannabinoids</i> dronabinol	Most common: drowsiness, euphoria, somnolence, vasodilation, vision difficulties, abnormal thinking, dysphoria Less common: diarrhea, flushing, tremor, myalgia
<i>Corticosteroids</i> dexamethasone methylprednisolone	Most common: gastrointestinal upset, anxiety, insomnia Less common: hyperglycemia, facial flushing, euphoria, perineal itching or burning (with dexamethasone, probably secondary to vehicle and rate of injection)
<i>Phenothiazines</i> prochlorperazine promethazine chlorpromazine thiethylperazine	Most common: sedation, lethargy, skin sensitization Less common: cardiovascular effects, extrapyramidal effects, cholestatic jaundice, hyperprolactinemia Rare: neuroleptic malignant syndrome, hematologic abnormalities
<i>Serotonin Antagonists</i> ondansetron granisetron dolasetron	Most common: headache, asymptomatic prolongation of electrocardiographic interval Less common: constipation, asthenia, somnolence, diarrhea, fever, tremor or twitching, ataxia lightheadedness, dizziness, nervousness, thirst, muscle pain, warm or flushing sensation on IV administration Rare: transient elevations in serum transaminases

^a Most common = >10%, less common = 1–10%, rare = <1%. Based on FDA-approved labeling and generalized to the drug class.

TABLE 4: ONSET AND DURATION OF EMESIS

Chemotherapeutic Agent	Onset of Emesis after Administration (hr)	Duration of Emesis (hr)
Aldesleukin	0–6	N.A. ^a
Androgens	48–100 ^b	Variable
Asparaginase		
or pegaspargase	1–3	N.A.
Bleomycin	3–6	N.A.
Busulfan	N.A.	N.A.
Carboplatin		
(200–400 mg/m ²)	2–6	1–48
Carmustine	2–6	4–24
Chlorambucil (oral)	48–72	N.A.
Cisplatin	1–6	>24
Cladribine	N.A.	N.A.
Corticosteroids	N.A.	N.A.
Cyclophosphamide ^c	6–12	6–36
Cytarabine (>1000 mg/m ²)	6–12	3–5
Dacarbazine ^d	2–6	6–24
Dactinomycin	2–6	12–24
Daunorubicin	2–6	<24
Docetaxel	N.A.	N.A.
Doxorubicin	2–6	6–24
Etoposide	3–6	6–12
Fludarabine	N.A.	N.A.
5-Fluorouracil	3–6	3–6
Gemcitabine	N.A.	N.A.
Hydroxyurea	6–12	N.A.
Ifluridine	N.A.	N.A.
Ifosfamide	3–6	6–12
Interferon-alfa	N.A.	N.A.
Irinotecan	2–6	6–12
Lomustine	3–6	6–12
Mechlorethamine	0.5–2	6–24
Melphalan (oral)	6–12	N.A.
Mercaptopurine	4–8	N.A.
Methotrexate	4–12	3–12
Mitomycin	2–6	18–24
Mitoxantrone (<15 mg/m ²)	N.A.	N.A.
Paclitaxel	N.A.	N.A.
Pentostatin	N.A.	N.A.
Procarbazine (oral) ^b	24–27	Variable
Semustine	3–6	6–12
Streptozocin	2–6	12–24
Teniposide	3–6	6–12
Thioguanine	4–8	N.A.
Thiotepa	6–12	Variable
Vinblastine	4–8	N.A.
Vincristine	4–8	N.A.

^a Not available ^b Development of tolerance possible ^c High dose

^d Characteristically, vomiting lessens with each subsequent dose when dacarbazine is given over five days

TABLE 5: STANDARD DOSAGES AND COSTS OF ANTIEMETICS FOR MANAGEMENT OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING IN ADULTS

Agent	Dosage	Cost/Dose (\$) ^a	Cost/Day (\$) ^a
Prophylaxis			
Ondansetron ^b	24 mg p.o. (tablet or suspension) 30 min before chemotherapy	38.46	^c
	8 mg i.v. 30 min before chemotherapy	48.90	
Granisetron ^b	2 mg p.o. 30 min before chemotherapy	82.56	
	10 µg/kg i.v. 30 min before chemotherapy	121.77 ^d	
Dolasetron ^b	100–200 mg p.o. 30 min before chemotherapy	66.00	
	1.8 mg/kg or 100 mg i.v. 30 min before chemotherapy	149.88	
Dexamethasone ^e	20 mg p.o. 30 min before chemotherapy	1.60	
	20 mg i.v. 30 min before chemotherapy	3.08	
Treatment			
Lorazepam	1–2 mg p.o. or sl q 6 hr	0.19–0.38	0.76–1.52
	1–2 mg i.m. or i.v. q 6 hr	5.19–10.30	20.76–41.52
Prochlorperazine	5–20 mg p.o. q 6 hr	2.54–2.16	2.16–8.64
	5–20 mg i.m. or i.v. q 6 hr	1.10–4.38	4.40–17.52
	25 mg rectally q 12 hr	3.39	6.78
	15–30 mg (extended-release capsule) p.o. q 12 hr	1.64–3.28	3.28–6.00
Metoclopramide	2 mg/kg i.v. q 2–4 hr for 2–5 doses; for delayed nausea and vomiting, 0.5 mg/kg or 30 mg i.v. q 4–6 hr for 3–5 days	3.94	7.88–19.70
	2 mg/kg p.o. q 2–4 hr for 2–5 doses; for delayed nausea and vomiting, 0.5 mg/kg or 30 mg p.o. q 4–6 hr for 3–5 days	0.51	1.02–2.55
Dexamethasone	10–20 mg p.o. q 4–6 hr	0.80–1.60	3.20–9.60
	10–20 mg i.v. q 4–6 hr	2.33–4.22	9.32–27.96
Haloperidol	1–4 mg p.o. q 6 hr	0.20–0.80	0.80–3.12
	1–4 mg i.m. or i.v. q 6 hr	0.75–3.00	3.00–12.00
Dronabinol	5–15 mg/m ² (~5–20 mg) p.o. q 3–6 hr	5.87–22.49	23.48–179.92

^a 1998 Red Book

^b For use with chemotherapeutic agents having an emetogenic potential of level 3, 4, or 5

^c Not applicable

^d For a 70 kg patient

^e For use with chemotherapeutic agents having an emetogenic potential of level 2, 3, 4, or 5
Not recommended for use with aldesleukin

TABLE 6: STANDARD DOSAGES AND COSTS OF ANTIEMETICS FOR MANAGEMENT OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING IN PEDIATRIC PATIENTS

Drug	Dosage	Cost(s) ^a		
		Per Regimen	Per Dose	Per Day
Prophylaxis				
Ondansetron	If 4–11 yr of age, 4 mg p.o. 30 min before and 4 and 8 hr after chemotherapy; may also be given as a single 12 mg dose 30 min before chemotherapy	34.65		
	If greater than 11 yr of age, 8 mg p.o. 30 min before and 4 and 8 hr after chemotherapy; may also be given as single 24 mg dose 30 min before chemotherapy	55.02		
	If greater than 3 yr of age, 0.15 mg/kg i.v. 30 min before and 4 and 8 hr after chemotherapy	146.70		
Granisetron	If ≥2 yr of age, 20–40 µg/kg i.v. 30 min before chemotherapy	34.79–69.58		
Dexamethasone	10–14 mg/m ² p.o. in single or divided doses	1.44		
	10–14 mg/m ² i.v. in single or divided doses	4.41		
Dolasetron	1.8 mg/kg p.o. 30 min before chemotherapy	49.80		
	1.8 mg/kg i.v. 30 min before chemotherapy	53.95		
Methylprednisolone	0.5–1 mg/kg p.o. 30 min before and 4 and 8 hr after chemotherapy (maximum total dose, 4 mg/kg); may also be given as single dose 30 min before chemotherapy	4.05–8.10		
	0.5–1 mg/kg i.v. 30 min before and 4 and 8 hr after chemotherapy (maximum total dose, 4 mg/kg); may also be given as single dose 30 min before chemotherapy	1.80–3.60		
Treatment				
Lorazepam	0.05 mg/kg (maximum, 3 mg) p.o. q 8–12 hr as needed		0.19	0.57–1.14
Chlorpromazine	0.05 mg/kg (maximum, 3 mg) i.v. q 8–12 hr as needed		5.19	15.57–31.14
	If >6 mo of age, 0.55 mg/kg p.o. q 4–6 hr as needed		0.07	0.28–0.42
	If >6 mo of age, 1.1 mg/kg rectally q 6–8 hr as needed (maximum of 40 mg per dose if age is <5 yr or weight is <22 kg)		3.25	9.75–13.00
	If >6 mo of age, 0.55 mg/kg i.v. q 6–8 hr as needed (maximum of 40 mg per dose if age is <5 yr or weight is <22 kg)		0.26	0.78–1.04
Methylprednisolone	0.5–1 mg/kg p.o. q 12 hr as needed		1.62–2.70	3.24–5.40
	0.5–1 mg/kg i.v. q 12 hr as needed		0.60–1.20	1.20–2.40
Dexamethasone	5–10 mg/m ² p.o. q 12 hr as needed		0.48–1.44	0.96–2.88
	5–10 mg/m ² i.v. q 12 hr as needed		1.19–2.33	2.34–4.66

^a Based on 1998 Red Book prices. For 20 kg child or child with body surface area of 0.8 m². Originally published in *Am J Health Syst Pharm*, 1999;56:729-764 ©1999, American Society of Health-System Pharmacists, Inc. All rights reserved. Reprinted with permission (R2152).

Summary of Guidelines for the Use of Antiemetics: Evidence-Based Clinical Practice Guidelines From the American Society of Clinical Oncology (ASCO)

- I. Chemotherapy-Induced Emesis
 - A. Acute Emesis (vomiting occurring 0 to 24 hours after chemotherapy)
 1. Antiemetic Agents: Highest Therapeutic Index
 - a. Serotonin Receptor Antagonists
 - i. Agent equivalence

At equivalent doses, serotonin receptor antagonists have equivalent safety and efficacy and can be used interchangeably based on convenience, availability, and cost.
 - ii. Drug dosage

Established, proven doses of all agents are recommended.
 - iii. Drug schedule

Single doses of antiemetics are effective and preferred for convenience and cost.
 - iv. Route of administration

At biologically equivalent doses, oral agents are equally effective and are as safe as intravenous antiemetics. In most settings, oral agents are less costly and more convenient; for these reasons, they are recommended over intravenous therapy.
 - b. Corticosteroids
 - i. Agent equivalence and route of administration

At equivalent doses, corticosteroids have equivalent safety and efficacy and can be used interchangeably.
 - ii. Drug dose and schedule

Single doses of corticosteroids are recommended.
 2. Antiemetic Agents: Lower Therapeutic Index—Dopamine Antagonists, Butyrophenones, Phenothiazines, and Cannabinoids

For chemotherapy with a high risk of emesis, selective serotonin antagonists (with dexamethasone) are recommended.
 3. Antiemetic Agents: Adjunctive Drugs—Benzodiazepines and Antihistamines

Benzodiazepines and antihistamines are useful adjuncts to antiemetic drugs but are not recommended as single agents.
 4. Antiemetic Agents: Combination of Antiemetics

It is recommended that serotonin antagonists be given with corticosteroids.
 5. Risk Factors for Acute Emesis
 - a. Patient Characteristics
 - b. Chemotherapeutic Agents
 - c. Guidelines
 - i(a). High risk: cisplatin

The combination of a 5-HT₃ antagonist plus a corticosteroid is recommended before chemotherapy.

i(b). High risk: noncisplatin

The combination of a 5-HT₃ antagonist plus a corticosteroid is recommended before chemotherapy.

ii. Intermediate risk

A corticosteroid is suggested for patients being treated with agents of intermediate emetic risk.

iii. Low risk

It is suggested that for patients being treated with agents of low emetic risk, no antiemetic be routinely administered before chemotherapy.

iv. Combination chemotherapy

It is suggested that when combination chemotherapy is given, the patient be given antiemetics appropriate for the chemotherapeutic agent of greatest emetic risk.

v. Multiple consecutive days of chemotherapy

It is suggested that antiemetics appropriate for the risk class of the chemotherapy, as outlined above, be administered for each day of the chemotherapy.

B. Delayed Emesis (vomiting occurring >24 hours after chemotherapy)

1. Antiemetic Agents

a. Single Agents

- i. Corticosteroids
- ii. Metoclopramide and serotonin receptor antagonists

b. Combinations of Agents

2. Risk Factors for Delayed Emesis

- a. Patient Characteristics
- b. Chemotherapeutic Agents
- c. Guidelines

i(a). High risk: cisplatin

For all patients receiving cisplatin, a corticosteroid plus metoclopramide or plus a 5-HT₃ antagonist is recommended for the prevention of delayed emesis.

i(b). High risk: noncisplatin

A prophylactic corticosteroid as a single agent, a prophylactic corticosteroid plus metoclopramide, and a prophylactic corticosteroid plus a 5-HT₃ antagonist are regimens suggested for the prevention of delayed emesis.

ii. Intermediate – low risk

No regular preventive use of antiemetics for delayed emesis is suggested for patients receiving these chemotherapeutic agents.

C. Anticipatory Emesis

1. Prevention

Use of the most active antiemetic regimens appropriate for the chemotherapy being given to prevent acute or delayed emesis is suggested. Such regimens must be used with the initial chemotherapy, rather than after assessment of the patient's emetic response to less effective treatment.

2. Treatment

If anticipatory emesis occurs, behavioral therapy with systematic desensitization is effective and is suggested.

D. Special Emetic Problems

1. Emesis in Pediatric Oncology

The combination of a 5-HT₃ antagonist plus a corticosteroid is suggested before chemotherapy in children receiving chemotherapy of high emetic risk.

2. High-Dose Chemotherapy

A 5-HT₃ antagonist plus a corticosteroid is suggested.

3. Vomiting and Nausea Despite Optimal Prophylaxis in Current or Prior Cycles

It is suggested that clinicians (1) conduct a careful evaluation of risk, antiemetic, chemotherapy tumor, and concurrent disease and medication factors, (2) ascertain that the best regimen is being given for the emetic setting, (3) consider adding an anti-anxiety agent to the regimen, and (4) consider substituting a dopamine receptor antagonist, such as high-dose metoclopramide, for the 5-HT₃ antagonist (or add the dopamine antagonist to the regimen).

II. Radiation-Induced Emesis

A. Risk Factors for Radiation-Induced Emesis

1. Guidelines

a. High Risk: Total Body Irradiation

A serotonin receptor antagonist should be given with or without a corticosteroid before each fraction and for at least 24 hours after.

b. Intermediate Risk: Hemibody Irradiation, Upper Abdomen, Abdominal-Pelvic, Mantle, Cranial Radiosurgery, and Craniospinal Radiotherapy

A serotonin receptor antagonist or a dopamine receptor antagonist should be given before each fraction.

c. Low Risk: Radiation of the Cranium Only, Breast, Head and Neck, Extremities, Pelvis, and Thorax

Treatment should be given on an as-needed basis only. Dopamine or serotonin receptor antagonists are advised. Antiemetics should be continued prophylactically for each remaining radiation treatment day.

ANTIEMETIC AGENTS, DOSES, AND ADMINISTRATION SCHEDULE

Antiemetic Agent (trade name)	Dose Range	Schedule (for acute chemotherapy-induced emesis, unless otherwise noted)	Evidence (type and grade)
Agents with highest therapeutic index			
<i>Serotonin receptor antagonists</i>			
Dolasetron (Anzemet®)	100 mg or 1.8 mg/kg IV	One time, before chemotherapy	I, A
Dolasetron (Anzemet®)	100 mg PO	One time, before chemotherapy	II, A
Granisetron (Kytril®)	1 mg or 0.01 mg/kg IV	One time, before chemotherapy	I, A
Granisetron (Kytril®)	2 mg PO	One time, before chemotherapy	I, A
Ondansetron (Zofran®)	8 mg or 0.15 mg/kg IV	One time, before chemotherapy	I, A
Ondansetron (Zofran®)	Oral doses vary (12–24 mg/d) (8 mg doses usually used in delayed or RT emesis)	One time, before chemotherapy (two to three times daily in delayed or RT emesis)	II, B
Tropisetron (Navoban®)	5 mg IV	One time, before chemotherapy	III, B
Tropisetron (Navoban®)	5 mg PO	One time, before chemotherapy	III, B
<i>Corticosteroids</i>			
Dexamethasone (Decadron®)	20 mg IV	One time, before chemotherapy	II, B
Methylprednisolone (Medrol®)	40 mg to 125 mg	One time, before chemotherapy	V, D
Agents of lower therapeutic index			
<i>Dopamine receptor antagonists</i>			
Metoclopramide (Reglan®)	2 mg/kg to 3 mg/kg IV	Before chemotherapy and 2 hours after chemotherapy	I, A
Metoclopramide (Reglan®)	20 mg to 0.5 mg/kg PO for delayed emesis or RT	Two to four times a day for delayed emesis	IV, D
Prochlorperazine (Compazine®)	10 mg to 30 mg IV	Every 3 to 4 hours	II, B
Prochlorperazine (Compazine®)	10 to 20 mg PO	Every 3 to 4 hours	III–IV, C

HIGH EMETIC RISK: CHEMOTHERAPEUTIC AGENTS AND

GUIDELINES FOR ACUTE AND DELAYED EMESIS

Acute Emetic Category	Chemotherapy Agent (trade name)	Guideline for Acute Emesis	Guideline for Delayed Emesis	Evidence (type and grade)	
				Acute Emesis	Delayed Emesis
High: cisplatin	Cisplatin (<i>Platinol</i> [®] , Bristol-Myers Oncology, Princeton, NJ)	Pretreatment: 5-HT ₃ antagonist plus a corticosteroid	Oral corticosteroid plus oral metoclopramide (or plus an oral 5-HT ₃ antagonist) <i>Dexamethasone</i> 8 mg, twice daily for 3 to 4 days, plus either <i>Metoclopramide</i> 30–40 mg, two to four times per day for 2–4 days, or 5-HT ₃ antagonists at doses in previous table, for 2–3 days (guideline for all agents in this class, except cisplatin) <i>Dexamethasone</i> 8 mg, twice daily for 2–3 days, plus either <i>Metoclopramide</i> 30–40 mg, two to four times per day for 2–3 days, or 5-HT ₃ antagonists at doses in previous table, for 2–3 days	I, A	I, A
High: noncisplatin	Dacarbazine (<i>DTIC-Dome</i> [®] , Bayer, West Haven, CT) Actinomycin-D (<i>Cosmegen</i> [®] , Merck, Whitehouse Station, NJ) Methotrexate (<i>Mustargen</i> [®] , Merck) Streptozotocin (<i>Zanosar</i> [®] , Pharmacia & Upjohn, Kalamazoo, MI) Altretamine (<i>Hexalen</i> [®] , US Bioscience, Westconshohocken, PA) Carboplatin (<i>Paraplatin</i> [®] , Bristol-Myers Oncology) Cyclophosphamide (<i>Cytosan</i> [®] , Bristol-Myers Oncology) Lomustine (<i>CeeNU</i> [®] , Bristol-Myers Oncology) Carmustine (<i>BiCNU</i> [®] , Bristol-Myers Oncology) Daunorubicin (<i>Cerubidine</i> [®] , Bedford Laboratories, Bedford, OH) Doxorubicin (<i>Adriamycin</i> [®] , Pharmacia & Upjohn) Epirubicin (<i>Ellence</i> [®] , Pharmacia & Upjohn) Idarubicin (<i>Idamycin</i> [®] , Pharmacia & Upjohn) Cytarabine (<i>Cytosar-U</i> [®] , Pharmacia & Upjohn) Ifosfamide (<i>Ifex</i> [®] , Bristol-Myers Oncology)			II–III, A–B (range for agents below in this class)	III–IV, B–D (range for agents below in this class)

INTERMEDIATE EMETIC RISK: CHEMOTHERAPEUTIC AGENTS

AND GUIDELINES FOR ACUTE AND DELAYED EMESIS

Acute Emetic Category	Chemotherapy Agent (trade name)	Guideline for Acute Emesis	Guideline for Delayed Emesis	Evidence (type and grade)	
				Acute Emesis	Delayed Emesis
Intermediate	Irinotecan (<i>Camptosar</i> [®] , Pharmacia & Upjohn) Mitoxantrone (<i>Novantrone</i> [®] , Immunex, Seattle, WA) Paclitaxel (<i>Taxol</i> [®] , Bristol-Myers Oncology) Docetaxel (<i>Taxotere</i> [®] , Aventis, Strasbourg, France) Mitomycin (<i>Mutamycin</i> [®] , Bristol-Myers Oncology) Topotecan (<i>Hycamtin</i> [®] , SmithKline Beecham, Philadelphia, PA) Gemcitabine (<i>Gemzar</i> [®] , Lilly, Indianapolis, IN) Etoposide (<i>VePesid</i> [®] (VP-16), Bristol-Myers Oncology) Teniposide (<i>Vumon</i> [®] , Bristol-Myers Oncology)	Pretreatment: a corticosteroid (such as dexamethasone 4–8 mg by mouth, given once before chemotherapy)	No regular preventative use of antiemetics for delayed emesis	III–IV, B–D (range for agents in this class)	V, D (applies to all agents in this class)

NOTE: Individual patients may require treatment similar to that recommended for high-emetic-risk agents. Combinations of agents in this class are not well studied, but they may occasionally cause more emesis for some patients, requiring treatment similar to that recommended for high-emetic-risk agents.

LOW EMETIC RISK: CHEMOTHERAPEUTIC AGENTS AND

GUIDELINES FOR ACUTE AND DELAYED EMESIS

Chemotherapy Agent (trade name)	Guideline for Acute Emesis	Guideline for Delayed Emesis	Evidence (type and grade)	
			Acute Emesis	Delayed Emesis
Vinorelbine (<i>Navelbine</i> ®, Glaxo Wellcome, Research Triangle Park, NC)	No routine pretreatment antiemetics	No regular preventative use of antiemetics for delayed emesis	V, D (applies to all agents in this class)	V, D (applies to all agents in this class)
5-Fluorouracil (various manufacturers)				
Methotrexate (various manufacturers)				
Thioguanine (<i>Tabloid</i> ® Thioguanine, Glaxo Wellcome)				
Mercaptopurine (<i>Purinethol</i> ®, Glaxo Wellcome)				
Bleomycin (<i>Blenoxane</i> ®, Bristol-Myers Oncology)				
L-Asparaginase (<i>Elspar</i> ®, Merck)				
Vindesine (<i>Eldisine</i> ®, Lilly)				
Vinblastine (<i>Velban</i> ®, Lilly)				
Vincristine (<i>Oncovin</i> ®, Lilly)				
Busulfan (<i>Myleran</i> ®, Glaxo Wellcome)				
Chlorambucil (<i>Leukeran</i> ®, Glaxo Wellcome)				
Melphalan (<i>Alkeran</i> ®, Glaxo Wellcome)				
Hydroxyurea (<i>Hydrea</i> ®, Bristol-Myers Oncology)				
Fludarabine (<i>Fludara</i> ®, Berlex, Wayne, NJ)				
Cladribine (<i>Leustatin</i> ®, Ortho Biotech, Raritan, NJ)				
Tamoxifen (<i>Nolvadex</i> ®, Zeneca, Wilmington, DE)				

NOTE: Individual patients may require treatment similar to that recommended for intermediate-emetic-risk agents. Combinations of agents in this class are not well studied, but they may occasionally cause more emesis for some patients, requiring treatment similar to that recommended for intermediate-emetic-risk agents.

<i>Risk Categories</i>	<i>Area Receiving Radiation</i>	<i>Antiemetic Guideline</i>	<i>Evidence (type and grade)</i>
High risk	TBI	Before each fraction: 5-HT ₃ antagonist	II, III/B,C
Intermediate risk	Hemibody irradiation	Before each fraction: 5-HT ₃ antagonist or dopamine receptor antagonist	II, III/B
	Upper abdomen		
	Abdominal-pelvic		
	Mantle		
	Cranium (radiosurgery)		
	Craniospinal		
Low risk	Cranium only	As-needed basis: dopamine receptor or 5-HT ₃ antagonist	IV, V/D
	Breast		
	Head and neck		
	Extremities		
	Pelvis		
	Thorax		

Reprinted from the ASCO Guidelines on Antiemetics appearing in *J Clin Oncol*. 1999;17:2971-94. With permission from the author.

Summary of the American Society of Clinical Oncology (ASCO) Guidelines for the Use of Colony-Stimulating Factors (CSFs)

Guidelines for CSF Primary Administration

General Circumstances

Primary administration of CSFs was shown to reduce the incidence of FN [febrile neutropenia] by approximately 50% in the three major randomized trials in adults in which the incidence of FN was greater than 40% in the control group. The value of primary CSF administration has not been clearly established in less myelosuppressive regimens, and the cost benefit of primary versus secondary administration for the majority of initial chemotherapy regimens is unproven. It is recommended that primary administration of CSFs be reserved for patients expected to experience levels of FN that are at least comparable to or greater than those seen in control patients in these randomized trials, ie, an expected incidence $\geq 40\%$. Thus, for previously untreated patients receiving most chemotherapy regimens, primary administration of CSFs cannot be recommended.

Special Circumstances

Clinicians may occasionally be faced with patients who might benefit from relatively nonmyelosuppressive chemotherapy but who have potential risk factors for FN or infection because of bone marrow compromise or comorbidity. It is possible that primary CSF administration may be exceptionally warranted in patients at higher risk for chemotherapy-induced infectious complications, even though the data supporting such use are not conclusive. Such risk factors might include the following: pre-existing neutropenia due to disease, extensive prior chemotherapy, or previous irradiation to the pelvis or other areas containing large amounts of bone marrow; a history of recurrent FN while receiving earlier chemotherapy of similar or lesser dose-intensity; or conditions potentially enhancing the risk of serious infection, eg, poor performance status and more advanced cancer, decreased immune function, open wounds, or already-active tissue infections. This is not meant to be an all-inclusive list; it is anticipated that, depending on the unique features of the clinical situation, there will be instances when the administration of a CSF will be appropriate outside of uses recommended in other guidelines.

Guidelines for Secondary Prophylactic CSF Administration

In the setting of many tumors exclusive of curable tumors (eg, germ cell tumors), dose reduction after an episode of severe neutropenia should be considered as a primary therapeutic option. No published regimens have demonstrated disease-free or overall survival benefits when the dose of chemotherapy was maintained and secondary prophylaxis was instituted. In the absence of clinical data or other compelling reasons to maintain chemotherapy dose-intensity, physicians should consider chemotherapy dose reduction after neutropenic fever or severe or prolonged neutropenia after the previous cycle of treatment.

Guidelines for CSF Therapy

Afebrile Patients

Current evidence supports the recommendation that CSFs should not be routinely used for patients with neutropenia who are afebrile. The strength of this recommendation has increased with the trial reported in 1997.

Febrile Patients

The collective results of the eight trials provide strong and consistent support for the recommendation that CSFs should not be routinely used as adjunct therapy for the treatment of uncomplicated fever and neutropenia. Uncomplicated fever and neutropenia are defined as follows: fever of ≤ 10 days in duration; no evidence of pneumonia, cellulitis, abscess, sinusitis, hypotension, multiorgan dysfunction, or invasive fungal infection; and no uncontrolled malignancies. The eight trials have consistently shown a decrease in the duration of neutropenia of less than 500/ μL , but clinical benefit has not consistently accompanied the decreased duration of neutropenia.

Certain patients with fever and neutropenia are at higher risk for infection-associated complications and have prognostic factors that are predictive of poor clinical outcome. The use of a CSF for such high-risk patients may be considered, but the benefits of a CSF in these circumstances have not been proven. These factors include profound (ANC $< 100/\mu\text{L}$) neutropenia, uncontrolled primary disease, pneumonia, hypotension, multiorgan dysfunction (sepsis syndrome), and invasive fungal infection. Age greater than 65 years and posttreatment lymphopenia may also be high-risk factors but have not been consistently confirmed by multicenter trials.

Guidelines for Use of CSFs to Increase Chemotherapy Dose-Intensity

In the absence of more trials demonstrating a favorable effect on overall survival, disease-free survival, quality of life, or toxicity, there is no justification for the use of CSFs to increase chemotherapy dose-intensity or schedule or both outside of a clinical trial. This application of CSF use remains the domain of appropriately designed clinical investigation.

Guidelines for Use of CSFs as Adjuncts to Progenitor-Cell Transplantation

CSFs are recommended to help mobilize PBPCs and after PBPC infusion. Mobilized PBPCs have largely replaced bone marrow-derived cells for use in autologous transplantation. Side effects associated with mobilization and subsequent apheresis are usually limited and include constitutional symptoms and a decrease in platelets and other hematopoietic elements, especially after mobilization with combinations of chemotherapeutic agents and a CSF. The optimal dose of CSFs and chemotherapeutic agents is the subject of ongoing investigations, but a higher (10 $\mu\text{g}/\text{kg}/\text{d}$) dose of G-CSF in the setting of mobilization may yield greater content of CD34+ progenitor cells in the PBPC product, as documented in patients with hematologic malignancies and in patients with rheumatoid arthritis. Although the optimal method of mobilization needs further investigation, especially in heavily pretreated patients, administration of G-CSF, either alone or in combination with GM-CSF, or after the use of chemotherapeutic agents, generates PBPCs, leading to rapid hematopoietic recovery, shorter hospitalization, and possibly reduced costs. Further investigations are necessary to assess the potential risks, especially that of secondary hematologic malignancies associated with the use of combining chemotherapeutic agents and CSFs. The role of CSF-mobilized donor bone marrow in the autologous transplant setting is also under assessment.

Guidelines for Use of CSFs in Patients With Acute Leukemia and Myelodysplastic Syndromes

Acute Myeloid Leukemia

CSF use can be considered in this setting if benefits in terms of possible shortening of hospitalization outweigh the costs of CSF use. Several studies have shown that CSF administration can produce modest decreases in the duration of neutropenia

when begun shortly after completion of the initial days of chemotherapy of the initial or repeat induction. Beneficial effects on end points such as duration of hospitalization and incidence of severe infections have been variable and modest, although patients 55 years of age or older are most likely to benefit from CSF use. No study has yet demonstrated significant improvement in complete response rates or long-term outcome. Thus, while there seems to be minimal risk associated with the use of CSFs in this situation, the choice of whether or not to use the CSF is likely to be determined by cost considerations. In a nutshell, the cost of the cytokine must be balanced against any possible shortening of hospitalization associated with the slightly more rapid marrow recovery, as, for example, in patients 55 years of age or older. It is not known from the published data whether the CSFs significantly accelerate recovery to ANC of 100 to 200/mm³. In most patients, regenerating counts of this level are sufficient to protect against infection so as to permit safe discharge of patients from hospital.

There is no evidence that CSFs given either before or concurrently with chemotherapy for *priming effects* are of benefit, and their use in this fashion cannot be recommended outside the setting of the clinical trial.

There seems to be more profound shortening of the duration of neutropenia after *consolidation chemotherapy* for patients with AML in remission. Although the randomized studies did not address this issue, it is likely that this will be associated with decreased rates of hospitalization and possibly shorter durations of hospitalization in such patients. No benefit has been demonstrated in terms of prolongation of complete response duration or overall survival; however, the available evidence indicates that the CSFs can be recommended after the completion of consolidation chemotherapy.

Myelodysplastic Syndromes (MDS)

CSFs can increase the ANC in neutropenic patients with MDS. Data supporting the routine, long-term, continuous use of CSFs in these patients are lacking. Intermittent administration of CSFs may be considered in a subset of patients with severe neutropenia and recurrent infection.

Acute Lymphoblastic Leukemia (ALL) (Note. This topic is new to the guideline.)

The data are sufficient to recommend G-CSF administration begun after completion of the first few days of chemotherapy of the initial induction or first postremission course, thus shortening the duration of neutropenia of less than 1,000/mm³ by approximately 1 week. Effects on the incidence and duration of hospitalization and the acquisition of serious infections are less consistent. Although there was a trend for improved complete response rates in one large study, particularly in older adults, there was no prolongation of disease-free or overall survival in any of the trials. G-CSF can be given together with the continued corticosteroid/antimetabolite therapy, which is a feature of many ALL regimens, without evidence that such concurrent therapy prolongs the myelosuppressive effects of the chemotherapy. As in AML, it is not known from the published data whether the CSFs significantly accelerate recovery to ANC of 100 to 200/mm³. In most patients, regenerating counts of this level are sufficient to protect against infection so as to permit safe discharge of patients from the hospital. The use of G-CSF for children with ALL was associated with small benefits in days of antibiotic use or in-hospital days, although a small amount of additional costs was incurred, after the costs of the CSFs were taken into consideration. Cost estimates of CSFs for adults with ALL have not been reported.

Leukemia in Relapse (Note. This topic is new to the guideline.)

The available data are not sufficient to recommend either for or against the use of CSFs in patients with refractory or relapsed ALL. Few controlled studies have evaluated CSFs in patients with relapsed or refractory acute leukemia. The available data suggest shortening of the duration of neutropenia but are inadequate to comment on any effects on infectious complications and, in particular, on whether there may be an adverse effect on response rates in some patients with myeloid malignancies because of a stimulatory effect on leukemia growth in a situation in which there is less of a guarantee that chemotherapy will produce sufficient cytoreduction. Therefore, there is no evidence that CSFs are of important benefit in patients with refractory or relapsed myeloid leukemia, and they should be used judiciously or not at all in such patients.

Guidelines for Use of CSFs in Patients Receiving Concurrent Chemotherapy and Irradiation

CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In the absence of chemotherapy, in patients receiving radiation therapy involving large fields, therapeutic use of CSFs may be considered if prolonged delays secondary to neutropenia are expected.

Guidelines for Use of CSFs in the Pediatric Population

In the absence of conclusive pediatric data, the guidelines recommended for adults are generally applicable to the pediatric age group. However, optimal CSF doses have yet to be determined. Further clinical research into the use of these factors in support of chemotherapy and PBPC transplantation in the pediatric age group should be given high priority.

Guidelines for CSF Dosing and Route of Administration

In adults, the recommended CSF doses are 5 µg/kg/d for G-CSF (Filgrastim) and 250 mg/m²/d for GM-CSF (sargramostim) for all clinical settings other than PBPC mobilization. In the setting of PBPC mobilization, if G-CSF is used, a dose of 10 µg/kg/d seems preferable. Outside of this indication, CSF dose escalation is not advised. Rounding the dose to the nearest vial size is an appropriate strategy to maximize cost benefit. The preferred route of CSF administration is subcutaneous.

Guidelines for Initiation and Duration of CSF Administration

The optimal timing and duration of CSF administration are still under investigation. Starting CSFs up to 5 days after PBPC reinfusion is reasonable based on available clinical data.

Special Commentary on Comparative Clinical Activity of G-CSF and GM-CSF

Guidelines about equivalency of the available recombinant preparations of G-CSF and GM-CSF cannot be proposed because there have been no large-scale, prospective, comparative trials evaluating relative CSF efficacy. The strength of evidence to support the use of G-CSF or GM-CSF varies based on the specific indication for CSF administration, eg, support after BMT or use with nontransplantation chemotherapy regimens. The panel strongly encourages additional clinical investigation that will guide clinical application of these biologically distinct molecules by addressing issues of comparative clinical activity, toxicity, and cost-effectiveness.

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Summary of the American Society of Clinical Oncology Clinical Practice Guidelines for the Use of Chemotherapy and Radiotherapy Protectants

Mesna

Guidelines for the Use of Mesna as a Urothelial Protectant

1. Mesna Use With Ifosfamide

The use of mesna is recommended to decrease the incidence of ifosfamide-associated urothelial toxicity.

a. Mesna Dosing With Standard-Dose Ifosfamide

It is suggested that the daily dose of mesna be calculated to equal 60% of the total daily dose of ifosfamide, administered as three bolus doses given 15 minutes before and 4 and 8 hours after administration of each dose of ifosfamide when the ifosfamide dose is less than 2.5 g/m²/d administered as a short infusion. For use with continuous infusion ifosfamide, mesna may be administered as a bolus dose equal to 20% of the total ifosfamide dose followed by a continuous infusion of mesna equal to 40% of the ifosfamide dose, continuing for 12 to 24 hours after completion of the ifosfamide infusion.

b. Mesna Dosing With High-Dose Ifosfamide

There is insufficient evidence on which to base a recommendation for the use of mesna with ifosfamide doses in excess of 2.5 g/m²/d. The efficacy of mesna for urothelial protection with very high-dose ifosfamide has not been proven. Based on the longer half-life of ifosfamide in these dosages, more frequent and prolonged mesna dosage regimens may be necessary for maximum protection from urotoxicity.

c. Mesna Administration by the Oral Route

Administration of the first dose of mesna intravenously (IV) at a dose equal to 20% of the total daily ifosfamide dose, followed at 2 and 8 hours by 40% weight/weight of the ifosfamide dose administered orally, may be considered an acceptable alternative to the three-dose IV mesna regimen when the total ifosfamide daily dose is less than 2.0 g/m².

2. Mesna Use With Cyclophosphamide

Mesna plus saline diuresis or forced saline diuresis is recommended to decrease the incidence of urothelial toxicity associated with high-dose cyclophosphamide in the setting of stem-cell transplantation.

3. Surveillance of Patients Receiving Ifosfamide and/or Cyclophosphamide and Mesna

There are insufficient data to make a recommendation regarding specific monitoring for hemorrhagic cystitis in patients who receive mesna to ameliorate ifosfamide- or high-dose-cyclophosphamide-associated urothelial toxicity. Recommendations for monitoring reflect the design of clinical trials involving mesna use and the opinion of the Panel.

Dexrazoxane

Guidelines for the Use of Dexrazoxane

1. Breast Cancer

a. Initial Use in Patients With Metastatic Breast Cancer

It is recommended that dexrazoxane not routinely be used for patients with metastatic breast cancer who receive initial doxorubicin-based chemotherapy.

b. Delayed Use in Patients With Metastatic Breast Cancer Who Have Received ≥ 300 mg/m² of Doxorubicin

It is suggested that the use of dexrazoxane be considered for patients with metastatic breast cancer who have received ≥ 300 mg/m² of doxorubicin in the metastatic setting and who may benefit from continued doxorubicin-containing therapy. Management of patients who have received ≥ 300 mg/m² in the adjuvant setting and are now initiating doxorubicin-based chemotherapy in the metastatic setting should be individualized, with consideration given to (1) the potential for dexrazoxane to decrease response rates, (2) the risk of cardiac toxicity, and (3) the fact that these patients were not included in the clinical trials of dexrazoxane.

c. Use in Patients Receiving Adjuvant Chemotherapy for Breast Cancer

The use of dexrazoxane in the adjuvant setting is not suggested outside of a clinical trial.

2. Other Malignancies

a. Use in Adult Patients With Other Malignancies

The use of dexrazoxane can be considered in adult patients who have received ≥ 300 mg/m² of doxorubicin-based therapy. Caution should be exercised in the use of dexrazoxane in settings in which doxorubicin-based therapy has been shown to improve survival.

b. Use in Pediatric Malignancies

There is insufficient evidence to make a recommendation for use of dexrazoxane in the treatment of pediatric malignancies.

3. Other Anthracycline Doses and Schedules

a. Use in Patients Receiving Other Anthracyclines or Other Anthracycline Dose Schedules

The current data regarding the use of dexrazoxane in patients who receive epirubicin-based therapy are insufficient to make a recommendation.

b. Use in Patients Receiving High-Dose Anthracycline Therapy

There is insufficient evidence on which to base a recommendation for the use of dexrazoxane in patients who receive high-dose anthracycline therapy.

4. Patients With Cardiac Risks

a. Use in Patients With Cardiac Risk Factors

There is insufficient evidence on which to base a recommendation for the use of dexrazoxane in patients with cardiac risk factors or underlying cardiac disease.

5. Monitoring Therapy

a. Termination of Anthracycline Therapy for Patients Receiving Dexrazoxane

Patients who receive dexrazoxane should continue to undergo cardiac monitoring. After cumulative doxorubicin doses of 400 mg/m², cardiac monitoring should be frequent. The Panel suggests repeating the monitoring study after a cumulative dose of 500 mg/m² is reached and subsequently after every 50 mg/m² of doxorubicin. The Panel recommends that the termination of dexrazoxane/doxorubicin therapy be strongly considered in patients who develop a decline in left ventricular ejection fraction to below institutional normal limits or who develop clinical congestive heart failure.

b. Dose of Dexrazoxane

It is suggested that patients who are being treated with dexrazoxane receive dexrazoxane at a ratio of 10:1 with the doxorubicin dose, administered via slow IV push or short IV infusion 15 to 30 minutes before doxorubicin administration.

Amifostine

Guidelines for the Use of Amifostine

1. Amifostine Use in Chemotherapy-Associated Complications

a. Nephrotoxicity

Amifostine may be considered for the prevention of nephrotoxicity in patients who receive cisplatin-based chemotherapy.

b. Neutropenia and Thrombocytopenia

i. Neutropenia

The Panel recommends that amifostine be considered for the reduction of neutropenia-associated events in patients who receive alkylating-agent chemotherapy. However, in the absence of clinical data supporting maintenance of the chemotherapy dose-intensity, physicians should consider chemotherapy dose reduction as an alternative to the use of amifostine.

ii. Thrombocytopenia

Present data are insufficient to recommend the use of amifostine for protection against thrombocytopenia in patients who receive alkylating-agent chemotherapy or carboplatin.

c. Neurotoxicity and Ototoxicity

Present data are insufficient to support the routine use of amifostine for the prevention of cisplatin-associated neurotoxicity or ototoxicity.

d. Paclitaxel-Associated Neurotoxicity

Present data are insufficient to support the use of amifostine for the prevention of paclitaxel-associated neurotoxicity.

2. Dose and Administration of Amifostine With Chemotherapy

In adults, the suggested dose of amifostine with chemotherapy is 910 mg/m². Amifostine is administered IV over 15 minutes, 30 minutes before chemotherapy. Administration of amifostine requires close patient monitoring, and toxicity is clearly dose-related. All patients should be treated with antiemetics before the administration of amifostine, and pretreatment with IV fluids should also be considered. Blood pressure is measured every 3 to 5 minutes during the 15-minute infusion. Amifostine is discontinued if blood pressure declines significantly or if the patient becomes symptomatic. The hypotension associated with amifostine usually occurs at the end of the infusion and is reversed with discontinuation of the amifostine, administration of saline, and placing the patient in the Trendelenburg position. There are insufficient data to recommend redosing of amifostine after chemotherapy.

3. Amifostine Use in Radiation Therapy-Associated Complications

a. Xerostomia and Mucositis

i. Xerostomia

The Panel recommends that amifostine may be considered to decrease the incidence of acute and late xerostomia in patients who undergo fractionated radiation therapy in the head and neck region.

ii. Mucositis

Present data are insufficient to recommend amifostine to prevent mucositis associated with radiation therapy.

4. Dose and Administration of Amifostine With Radiation Therapy

When given with radiation therapy, the recommended amifostine dose is 200 mg/m²/d given as a slow IV push over 3 minutes, 15 to 30 minutes before each fraction of radiation therapy. Administration of amifostine requires close patient monitoring, but side effects are fewer at this lower dose. Many patients require antiemetics. Blood pressure should be measured just before and immediately after the 3-minute amifostine infusion. The hypotension associated with amifostine at this dose is less frequent but still requires close monitoring.

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Internet Sites of Interest to the Oncology Community

Site	URL	Content
Agency for Healthcare Research and Quality	http://www.ahrq.gov/	Guidelines for acute pain management of chronic cancer pain
American Cancer Society	http://www.cancer.org/	Guidelines for breast cancer treatment in women (in conjunction with National Comprehensive Cancer Network) Recommendations for early detection of cancers of the breast, prostate, colon and rectum, and uterus
American College of Physicians	http://www.acoline.org/journals/annals/o2mar99/compend.htm	Online article discussing use of practice guideline compendiums to improve patient care Appendix including criteria for judging the quality of guidelines; listing of available guideline compendiums for preventive care Online access to clinical guidelines (eg, prostate, cancer screening, cancer prevention) limited to members
American Pain Society	http://www.ampainsoc.org/	Quality improvement guidelines for acute pain and cancer pain treatment
American Society of Clinical Oncology (ASCO)	http://www.asco.org/	Clinical practice guidelines developed by ASCO expert panels (in conjunction with the Health Services Research Department) for treatment of unresectable non-small-cell lung cancer, breast cancer and colorectal cancer surveillance, use of tumor markers in breast and colorectal cancer, use of hematopoietic colony-stimulating factors, and use of tamoxifen and raloxifene for breast cancer risk reduction Resource documents, such as criteria for facilities, personnel for administering parenteral antineoplastic therapy, and curriculum development in cancer genetics education Policy statements, including outcomes of cancer treatment for technology assessment, cancer treatment guidelines, and cancer pain assessment and treatment curriculum guidelines
American Society of Health-System Pharmacists (ASHP)	http://www.ashp.org/	ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs ASHP guidelines for managing postoperative and chemotherapy and radiation therapy-induced nausea and vomiting in adults and pediatric patients
American Society of Hematology (ASH)	http://www.hematology.org/index.cfm/	Practice guideline for diagnosis and treatment of idiopathic thrombocytopenic purpura
BC Cancer Agency	http://www.bccancer.bc.ca/cmm/#Contents/	Disease management guidelines that may be general or detailed, depending on the tumor; guidelines categorized by specific tumor groups, including breast, gastrointestinal, genitourinary, gynecologic, head and neck, lung, sarcoma, neuro-oncologic, ocular and orbital, and skin Guidelines for care of chronic ulcerating malignant skin lesions, pain control, symptom management, and nutritional care
Cancer Care Ontario Practice Guidelines Initiative (CCOPGI)	http://hiru.mcmaster.ca/ccopgi/index.html	Extensive compilation of clinical practice guidelines for treatment of gastrointestinal, genitourinary, gynecologic, head and neck, lung, neurologic, and pediatric cancers; treatment of melanoma, leukemias, lymphomas, sarcomas, anemias, hemophilia, and von Willebrand's disease; use of erythropoietin in patients who develop anemia while receiving cancer chemotherapy; use of G-CSF in patients receiving myelosuppressive chemotherapy; use of PSA in early detection of prostate cancer; and cervical cancer screening Newest guidelines, including those for use of dexrazoxane in patients receiving doxorubicin or epirubicin and use of 5-HT ₃ receptor antagonists Guidelines published in journal <i>Cancer Prevention and Control</i> and also on the Canadian Medical Association Web site (http://www.cma.ca/cpgs/index.htm)

Site	URL	Content
Cancer Therapy Evaluation Program (CTEP)	http://ctep.info.nih.gov/	Guidelines for clinical trials cooperative groups, including treatment expression and nomenclature; trials involving potentially teratogenic agents in men and women of reproductive potential; inclusion of cancer survivors, HIV-positive individuals, pregnant and breast-feeding women, and women and minorities; and monitoring of clinical trials Guidelines for investigational agents, including agent transfer and distribution, drug returns, compassionate use, accountability and storage, and submissions for clinical drug use Policy on waivers for protocol deviation Recommendations for safe handling of cytotoxic drugs
Cancer Trials (sponsored by the National Cancer Institute)	http://cancertrials.nci.nih.gov/NCL_CANCER_TRIALS/	Recommendations for developing informed consent documents for clinical trials
Centers for Disease Control and Prevention (CDC)	http://www.cdc.gov/	Guideline for prevention of intravascular device-related infection Occupational safety and health guidelines for chemical hazards Prevention and control of oral and pharyngeal cancer
Department of Health and Human Services	http://www.healthfinder.gov	Search the site using the phrase "pain management"
International Association for the Study of Pain (IASP)	http://halcyon.com/iasp	Professional site that provides clinical newsletters and pain clinic guidelines
National Comprehensive Cancer Network (NCCN)	http://www.nccn.org	Extensive compilation of clinical practice guidelines adopted by NCCN member institutions that include evaluation, management and follow-up for bladder, breast, brain, colorectal, esophageal, gastric, head and neck, renal, gastric, ovarian, prostate, testicular, and small-cell and non-small-cell lung cancers; leukemia; non-Hodgkin's lymphoma; melanoma; myeloma; sarcomas; myelodysplastic syndrome; occult primary tumors; neuroendocrine tumors; and selected pediatric malignancies Antiemetic practice guidelines
National Guideline Clearinghouse	http://www.guideline.gov/index.asp	Sponsored by AHCPR in partnership with the American Medical Association and the American Association of Health Plans Guidelines organized by disease or condition, treatment or intervention, or organization category Links to ASCO and CCOPGI guidelines United States Preventive Services Task Force guidelines including screening for colorectal, cervical, skin, bladder, gynecologic, breast, lung, prostate, testicular, ovarian, pancreatic, oral, and thyroid cancers; anemias; and hemoglobinopathies
NEUPOGEN® (Filgrastim) Product Site (sponsored by Amgen Inc.)	www.NEUPOGEN.com	Site contains detailed information on chemotherapy and neutropenia management for patients. Also provides healthcare professionals with access to valuable materials and support services.
PDQ®-NCI's Comprehensive Cancer Database	http://cancernet.nci.nih.gov/pdq.htm	Screening, prevention, and treatment summaries for breast, cervical, colorectal, endometrial, gastric, lung, oral, ovarian, prostate, skin, and testicular cancers, and neuroblastoma Summary of genetic testing for cancer risk
Society of Nuclear Medicine	http://www.snm.org/policy/guidelines_download.html	Procedure guidelines, including those for treatment of bone pain, use of radiopharmaceuticals, scintigraphy for thyroid cancer, various scintigraphy procedures (lung, bone, breast, thyroid, gallium, hepatobiliary), and tumor imaging using fludeoxyglucose F-18

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List of Generic-to-Trade Names

Generic Name	Brand Name	Generic Name	Brand Name	Generic Name	Brand Name	Generic Name	Brand Name
Aldesleukin (rIL-2)	Proleukin*	Daunorubicin Liposomal	DaunoXome*	Interferon alfa-2b	Intron A*	Tamoxifen	Nolvadex*
Alemtuzumab	Campath 1H*	Denileukin diftitox	Ontak*	Irinotecan (CPT-11)	Camptosar*	Temozolomide	Temodar*
Alitretinoin	Panretin*	Dexamethasone	Decadron*, various	Ketoconazole	Nizoral*	Teniposide	Vumon*
Altretamine	Hexalen*	Diphenhydramine	Benadryl*, various	Letrozole	Femara*	Thalidomide	Thalomid*
Aminoglutethimide	Cytadren*	Docetaxel	Taxotere*	Leuprolide acetate	Lupron*	Thioguanine	Tabloid Thioguanine*
Anastrozole	Arimidex*	Doxorubicin	Adriamycin*, various	Leuprolide acetate depot	Lupron depot*	Thiotepa	Thioplex*
Arsenic trioxide	Trisenox*	Doxorubicin HCL (liposomal injection)	Doxil*	Leuprolide Implant	Viadur*	Topotecan	Hycamtin*
Asparaginase	Elspar*	Epirubicin	Ellence*	Levamisole	Ergamisol*	Toremifene	Fareston*
Bezarotene	Targretin*	Estramustine	EmCyt*	Lomustine (CCNU)	CeeNu*	Trastuzumab	Herceptin*
Bicalutamide	Casodex*	Etoposide (VP-16)	VePesid*, various	Mechlorethamine (nitrogen mustard)	Mustargen*	Tretinoin (ATRA)	Vesanoid*
Bleomycin	Blenoxane*	Etoposide Phosphate	Etopofos*	Medroxyprogesterone	Provera*, various	Triptorelin Pamoate	Trelstar Depot*
Busulfan	Myleran*	Exemestane	Aromasin*	Megestrol	Megace*	Valrubicin	Valstar*
Busulfan Injection	Busulfex*	Fludarabine	Fludara*	Melphalan	Alkeran*	Vinblastine	Velban*, various
Capecitabine	Xeloda*	Fluoxymesterone	Halotestin*	Mercaptopurine (6-MP)	Purinethol*	Vincristine	Oncovin*, various
Carboplatin	Paraplatin*	Flutamide	Eulexin*	Methyl CCNU	Semustine*	Vinorelbine	Navelbine*
Carmustine (BCNU)	BiCNU*	Gemcitabine	Gemzar*	Methylprednisolone	Solu-Medrol*, various	Protective and Rescue Agents	
Carmustine Wafer	Gliadel*	Gemtuzumab ozogamicin	Mylotarg*	Mitomycin	Mutamycin*	Amifostine	Ethylol*
Chlorambucil	Leukeran*	Goserelin acetate	Zoladex*	Mitoxantrone	Novantrone*	Dexrazoxane	Zinecard*
Cisplatin	Platinol*	Hydrocortisone	Solu-Cortef*, various	Nilutamide	Nilandron*	Filgrastim	NEUPOGEN*
Cladribine	Leustatin*	Hydroxyurea	Hydrea*	Paclitaxel	Taxol*, Paxene*	Leucovorin	Wellcovorin*
Cyclophosphamide	Cytoxan*, various	Idarubicin	Idamycin*	Pentostatin	Nipent*	Mesna	Mesnex*
Cytarabine (Ara-C)	Cytosar-U*	Ifosfamide	Ifex*	Procarbazine	Matulane*	Sargramostim	Leukine*
Cytarabine Liposomal	DepotCyt*	Imatinib	Gleevec*	Rituximab	Rituxan*		
Dacarbazine (DTIC)	DTIC-Dome*	Interferon alfa-2a	Roferon-A*	Streptozocin	Zanosar*		

List of Trade-to-Generic Names

Brand Name	Generic Name	Brand Name	Generic Name	Brand Name	Generic Name	Brand Name	Generic Name
Adriamycin [®] , various	Doxorubicin	Ergamisol [®]	Levamisole	Myleran [®]	Busulfan	Taxotere [®]	Docetaxel
Alkeran [®]	Melphalan	Etopofos [®]	Etoposide Phosphate	Mylotarg [®]	Gemtuzumab ozogamicin	Temodar [®]	Temozolomide
Arimidex [®]	Anastrozole	Eulexin [®]	Flutamide	Navelbine [®]	Vinorelbine	Thalomid [®]	Thalidomide
Aromasin [®]	Exemestane	Fareston [®]	Toremifene	Nilandron [®]	Nilutamide	Thioplex [®]	Thiotepa
Benadryl [®] , various	Diphenhydramine	Femara [®]	Letrozole	Nipent [®]	Pentostatin	Trelstar Depot [®]	Triptorelin
BiCNU [®]	Carmustine (BCNU)	Fludara [®]	Fludarabine	Nizoral [®]	Ketoconazole	Trisenox [®]	Arsenic trioxide
Blenoxane [®]	Bleomycin	Gemzar [®]	Gemcitabine	Nolvadex [®]	Tamoxifen	Valstar [®]	Valrubicin
Busulfex [®]	Busulfan Injection	Gleevec [®]	Imatinib	Novantrone [®]	Mitoxantrone	Velban [®] , various	Vinblastine
Campath 1H [®]	Alemtuzumab	Gliadel [®]	Carmustine Wafer	Oncovin [®] , various	Vincristine	VePesid [®] , various	Etoposide (VP-16)
Camptosar [®]	Irinotecan (CPT-11)	Halotestin [®]	Fluoxymesterone	Ontak [®]	Denileukin diftitox	Vesanoid [®]	Tretinoin (ATRA)
Casodex [®]	Bicalutamide	Herceptin [®]	Trastuzumab	Panretin [®]	Alitretinoin	Viadur [®]	Leuprolide Implant
CeeNu [®]	Lomustine (CCNU)	Hexalen [®]	Altretamine	Paraplatin [®]	Carboplatin	Vumon [®]	Teniposide
Cerubidine [®]	Daunorubicin	Hycamtin [®]	Topotecan	Paxene [®]	Paclitaxel	Xeloda [®]	Capecitabine
Cosmegen [®]	Dactinomycin	Hydrea [®]	Hydroxyurea	Platinol [®]	Cisplatin	Zanosar [®]	Streptozocin
Cytadren [®]	Aminoglutethimide	Idamycin [®]	Idarubicin	Proleukin [®]	Aldesleukin (rIL-2)	Zoladex [®]	Goserelin acetate
Cytosar-U [®]	Cytarabine (Ara-C)	Ifex [®]	Ifosfamide	Provera [®] , various	Medroxyprogesterone	<i>Protective and Rescue Agents</i>	
Cytosan [®] , various	Cyclophosphamide	Intron A [®]	Interferon alfa-2b	Purinethol [®]	Mercaptopurine (6-MP)	Ethylol [®]	Amifostine
DaunoXome [®]	Daunorubicin Liposomal	Leukeran [®]	Chlorambucil	Rituxan [®]	Rituximab	Leukine [®]	Sargramostim
Decadron [®] , various	Dexamethasone	Leustatin [®]	Cladribine	Roferon-A [®]	Interferon alfa-2a	Mesnex [®]	Mesna
DepotCyt [®]	Cytarabine Liposomal	Lupron depot [®]	Leuprolide acetate depot	Semustine [®]	Methyl CCNU	NEUPOGEN [®]	Filgrastim
Doxil [®]	Doxorubicin HCL (liposomal injection)	Lupron [®]	Leuprolide acetate	Solu-Cortef [®] , various	Hydrocortisone	Wellcovorin [®]	Leucovorin
DTIC-Dome [®]	Dacarbazine (DTIC)	Matulane [®]	Procabazine	Solu-Medrol [®] , various	Methylprednisolone	Zincard [®]	Dexrazoxane
Ellence [®]	Epirubicin	Megace [®]	Megestrol	Tabloid Thioguanine [®]	Thioguanine		
Elspar [®]	Asparaginase	Mustargen [®]	Mechlorethamine (nitrogen mustard)	Targretin [®]	Bexarotene		
EmCyt [®]	Estramustine	Mutamycin [®]	Mitomycin	Taxol [®]	Paclitaxel		

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NEUPOGEN® (Filgrastim) INDICATIONS

Cancer Patients Receiving Myelosuppressive Chemotherapy

NEUPOGEN® is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever.

Patients With AML Receiving Induction or Consolidation Chemotherapy

NEUPOGEN® is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with AML.

Cancer Patients Receiving Bone Marrow Transplant (BMT)

NEUPOGEN® is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, eg, febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation.

Patients Undergoing Peripheral Blood Progenitor Cell Collection and Therapy (PBPC)

NEUPOGEN® is indicated for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.

Patients With Severe Chronic Neutropenia (SCN)

NEUPOGEN® is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (eg, fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

NEUPOGEN® (Filgrastim) FAIR BALANCE STATEMENTS

Cancer Patients Receiving Myelosuppressive Chemotherapy

In the phase 3 trial of NEUPOGEN® therapy following combination chemotherapy in patients (n = 207) with small-cell lung cancer, bone pain was reported in 22% of patients. In most cases, bone pain was controlled with non-narcotic analgesics such as acetaminophen.

Patients With AML Receiving Induction or Consolidation Chemotherapy

In a randomized phase 3 clinical trial, 259 patients received NEUPOGEN®, and 262 patients received placebo postchemotherapy. Overall, the frequency of all reported adverse events was similar in both the NEUPOGEN® and placebo groups (83% vs 82% in Induction 1, 61% vs 64% in Consolidation 1). Adverse events reported more frequently in the NEUPOGEN®-treated group included petechiae (17% vs 14%), epistaxis (9% vs 5%), and transfusion reactions (10% vs 5%). There were no significant differences in the frequency of these events.

Cancer Patients Receiving Bone Marrow Transplant (BMT)

In clinical trials, the reported adverse effects were those typically seen in patients receiving intensive chemotherapy followed by bone marrow transplant (BMT). In the randomized studies of BMT involving 167 patients who received study drug, the following events occurred more frequently in patients treated with NEUPOGEN® than in controls: nausea (10% vs 4%), vomiting (7% vs 3%), hypertension (4% vs 0%), rash (12% vs 10%), and peritonitis (2% vs 0%).

Patients Undergoing Peripheral Blood Progenitor Cell Collection and Therapy (PBPC)

In clinical trials, 126 patients received NEUPOGEN® for PBPC mobilization. In this setting, NEUPOGEN® was generally well-tolerated. Adverse events related to NEUPOGEN® consisted primarily of mild-to-moderate musculoskeletal symptoms, reported in 44% of patients.

Patients With Severe Chronic Neutropenia (SCN)

Bone pain was reported in approximately 33% of patients in clinical trials with NEUPOGEN® (n = 325). In most cases, bone pain was controlled with non-narcotic analgesics such as acetaminophen.

Please see accompanying full prescribing information for NEUPOGEN®.

