CANCER PHARMACOLOGY & PHARMACOTHERAPY REVIEW

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Cancer Pharmacology and Pharmacotherapy Review is the first book devoted entirely to providing the ‘must-know’ facts on each cancer agent—including their pharmacokinetics, FDA-approved indications, toxicity, interactions, and other important information that is commonly found on board examinations and essential for any clinician or practitioner to review. The authors, an oncologist and two pharmacists, have developed a handy question-and-answer format to present the material in digestible bursts.

As the pharmacology section continues to represent a major portion of the medical oncology exam and a key component on oncology MOC exams, this portable study guide will help prepare anyone looking to fine-tune their knowledge on cancer drugs before the test. Not to mention, with recent advancements in the field of cancer treatment, it has become more cumbersome to recall and maintain essential knowledge of every cancer therapeutic—making this book not only an exam resource but also a handy quick reference for oncologists and pharmacists alike.

KEY FEATURES
• Conveniently organized and arranged by drug class and subtypes for easier recall and classification
• Includes proper dosage adjustments to account for liver and kidney dysfunction
• Features tables throughout that provide quick reference regarding FDA-approved medications
• Simplified diagrams and illustrations facilitate the pharmacokinetic processes

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Cancer Pharmacology and Pharmacotherapy Review
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Study Guide for Oncology Boards and MOC Exams

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We dedicate this book to our patients for their willingness to participate in clinical trials. Without their fortitude and willingness to participate in clinical trials, new drug discoveries and the advancement of the field of oncologic medicine would not be possible.
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Preface

In preparing for clinics, rounding, or board examinations, understanding the pharmacology of the drugs and agents can be overwhelming. In medical school and residency, it is often difficult to keep up with the mechanisms of action, kinetics, and dosing schedules of so many common medications, let alone those that are used in more rare conditions, including cancer. When residents become hematology and oncology fellows, they are forced to learn a large cohort of medications very quickly, a task that is daunting, given the ever-expanding market of new chemotherapeutic agents.

Additionally, questions on the hematology and oncology board examinations related to pharmacology represent a relatively larger percentage. This is true, given that the facts focusing on the mechanisms and side effects of these drugs do not change. Moreover, we are often asked dose-limiting side effects of medications as well as the requirements for dosage reductions related to kidney and liver failure. The University of Michigan Hematology/Oncology Fellowship Program recently published an oncology board review book, Oncology Boards Flash Review, to help solidify the knowledge one needs to have for his or her test. As a companion to this manual, we have written a similar board review book to summarize information that is most pertinent to the pharmacology of chemotherapeutic agents used by practicing hematologists and oncologists. This book contains concise summaries of the various chemotherapeutic drugs by class, pharmacology, pharmacokinetics, and toxicities and includes, to date, all of the U.S. Food and Drug Administration (FDA)-approved oncology agents available to practicing clinicians. It is our hope that fellows and practicing medical hematologists/oncologists preparing for ward rounds, outpatient clinical rotations, or for their certification or recertification examinations will find our book to be a useful tool. Our goal is to
help our readers summarize and solidify many important clinical facts and to help them build confidence in their knowledge of oncologic drugs.

The successful completion of this project was made possible by the editorial staff of Demos Medical Publishing, especially David D’Addona, acquisitions editor, and Joseph Stubenrauch, production editor.

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Traditional Chemotherapy
Microtubule Inhibitors

TAXANES AND RELATED AGENTS

What are the chemotherapy agents in the taxane class?

- Paclitaxel (Taxol®), nanoparticle albumin-bound (nab) paclitaxel (Abraxane®), docetaxel (Taxotere®), and cabazitaxel (Jevtana®)
- Ixabepilone (Ixempra®) is an epothilone
- Eribulin (Halaven®) is a halichondrin B analogue

What malignancies are each taxane FDA approved for?

**FDA-Approved Uses of Taxanes**

<table>
<thead>
<tr>
<th>Agent</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>Breast cancer, non–small cell lung cancer (NSCLC), ovarian cancer, Kaposi’s sarcoma</td>
</tr>
<tr>
<td>Nab-paclitaxel</td>
<td>Breast cancer, pancreatic cancer, NSCLC</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Breast cancer, NSCLC, prostate cancer, gastric adenocarcinoma, head and neck cancers</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>Prostate (post-docetaxel)</td>
</tr>
<tr>
<td>Ixabepilone</td>
<td>Metastatic breast cancer</td>
</tr>
<tr>
<td>Eribulin</td>
<td>Metastatic breast cancer</td>
</tr>
</tbody>
</table>

*Abbreviation: FDA, U.S. Food and Drug Administration.*
How do the taxanes work? (See Figure 1.1)

- **Summary:** More microtubule assembly occurs than disassembly, resulting in abnormal arrays or bundles of microtubules throughout the cell cycle leading to apoptosis (primarily via caspase 9 activation)

---

**FIGURE 1.1. Mechanism of action of microtubule inhibitors:** As a class, microtubule inhibitors interfere with microtubule dynamics and the formation of the mitotic spindle, thus preventing cell cycle progression from the G2→M phase, ultimately leading to apoptosis. Vinca alkaloids prevent microtubule assembly by binding β-tubulin and promoting depolymerization. Eribulin binds to a site near the vinca-binding site, preventing microtubule assembly and causing formation of nonproductive tubulin aggregates. Uniquely, eribulin binds only to the “plus” end of microtubules and does not affect microtubule shortening. Taxanes bind to β-tubulin on the interior surface of microtubules, promoting stabilization of the microtubule and preventing dissociation of tubulin. Epothilones have a similar mechanism of action to taxanes and occupy the same binding site; however, they interact with β-tubulin through a different molecular binding mechanism.
1. MICROTUBULE INHIBITORS

- Microtubules lengthen and shrink via attachment/detachment of α- and β-tubulin dimers. In a normal cell, there is a dynamic equilibrium of polymerization and depolymerization. This is termed dynamic instability. Taxanes block dynamic instability by binding to β-tubulin, causing less detachment of α- and β-tubulin dimers and more stability of the microtubules, leading them to be shifted to the assembled state. When more assembly occurs than disassembly, abnormal bundles of microtubules result and cellular function and replication cannot proceed.
- Cell cycle specific to the G2/M phase

How do the mechanisms of nab-paclitaxel, cabazitaxel, ixabepilone, and eribulin differ?

- Nab-paclitaxel: preferentially delivers paclitaxel out of serum and into tumor interstitium via interactions with albumin receptors. In addition, serum protein acidic that is rich in cysteine (SPARC) can be overexpressed on tumors, which nab-paclitaxel can bind to, resulting in the tumor cell rapidly internalizing paclitaxel.
- Cabazitaxel: poor affinity for the P-glycoprotein (P-gp) efflux pump, therefore active in cell lines that are resistant to paclitaxel/docetaxel and achieves greater central nervous system concentrations.
- Ixabepilone: exhibits greater potency binding to paclitaxel binding site via different molecular interactions and is not affected by mutations in β-tubulin that cause resistance to taxanes; maintains activity despite tumors overexpressing P-gp, βIII-tubulin, and microtubule assembly proteins; also enhances caspase-2-induced apoptosis.
- Eribulin: inhibits microtubule assembly without affecting disassembly by binding soluble tubulin (causing formation of aggregates) and binding to the growing (+) end of the microtubule.

What are common mechanisms of resistance to taxane therapy?

- Alterations in the α- and β-tubulin subunits can decrease the rate of polymerization into microtubules.
- Overexpression of the MDR1 gene, which encodes for a membrane P-gp efflux pump.
I. Traditional Chemotherapy

- Overexpression of βIII-tubulin and microtubule assembly proteins
- Interactions of microtubules with other cytoskeletal proteins
- Defects in apoptotic pathways

What are the common dosing ranges for each taxane?

- Paclitaxel: 50 to 200 mg/m$^2$ intravenous (IV) over 1 to 3 hours or up to 250 mg/m$^2$ IV over 24 hours every 3 weeks
- Nab-paclitaxel: 100 to 125 mg/m$^2$ IV over 30 minutes on days 1, 8, and 15 of 21- to 28-day cycle; 260 mg/m$^2$ IV over 30 minutes every 3 weeks
- Docetaxel: adult: 60 to 100 mg/m$^2$ IV over 1 hour every 3 weeks; pediatric sarcomas: 75 to 125 mg/m$^2$; 30 to 40 mg/m$^2$ IV weekly for 3 weeks every 28 days
- Cabazitaxel: 25 mg/m$^2$ IV over 1 hour every 3 weeks in combination with prednisone (10 mg orally (PO) once daily continuously)
- Ixabepilone: 40 mg/m$^2$ IV over 3 hours every 3 weeks; max body surface area (BSA) 2.2 m$^2$
- Eribulin: 1.4 mg/m$^2$ IV over 2 to 5 minutes on days 1 and 8 every 21 days

What solvents are the taxanes in and why is this important?

- Paclitaxel: Cremophor® EL (use non–polyvinyl chloride [PVC] tubing, bag, and connectors; 0.2 to 1.2 micron in-line filter required)
- Nab-paclitaxel: delivered in an amorphous, nanoparticle form to overcome insolubility in aqueous solutions (no cremophor or polysorbate 80; no special tubing; in-line filter is not recommended)
- Docetaxel: polysorbate 80 (use non-PVC tubing, bag, and connectors; in-line filter not recommended)
- Cabazitaxel: polysorbate 80 (use non-PVC tubing, bag, and connectors; 0.2 to 1.2 micron in-line filter required)
- Ixabepilone: cremophor (use non-PVC bag, tubing, and connectors; 0.2 to 1.2 micron in-line filter)
- Eribulin: does not contain solvents such as cremophor or polysorbate 80 (non-PVC equipment, in-line filter not required)
1. MICROTUBULE INHIBITORS

– Cremophor leads to immediate hypersensitivities (monitor patient’s vital signs every 15 minutes during infusion; reactions usually occur within the first 10 minutes of infusion)

– Polysorbate 80 leads to delayed hypersensitivities such as fluid accumulations

**Are the taxanes metabolized/eliminated renally or hepatically?**

- All four taxanes are extensively metabolized hepatically
- All four taxanes (except eribulin) do not appear to require dose adjustments for renal dysfunction

**Are there drug interactions with any of the taxanes?**

Taxanes should be administered prior to platinum derivatives to limit myelosuppression and enhance efficacy

- Paclitaxel: affected by CYP3A4 and CYP2C8 inhibitors/inducers, P-gp inhibitors; sequence doxorubicin/epirubicin prior to paclitaxel as paclitaxel can increase the maximum concentration (Cmax) and decrease clearance of these agents resulting in profound neutropenia and stomatitis; sequence paclitaxel prior to cyclophosphamide to reduce myelosuppression
- Nab-paclitaxel: not well characterized; assumed to be similar to paclitaxel
- Docetaxel: affected by CYP3A4 inhibitors/inducers, radiotherapy (radiation recall and radiosensitization); sequence doxorubicin/epirubicin/vinorelbine/topotecan before docetaxel to reduce profound neutropenia
- Cabazitaxel: affected by CYP3A4 inhibitors/inducers
- Ixabepilone: affected by CYP3A4 inhibitors/inducers
- Eribulin: a CYP3A4 inhibitor and weak inhibitor of P-gp; thus will affect substrates of CYP3A4 and P-gp

**What are the class adverse effects of the taxanes?**

- Infusion reactions
- Myelosuppression
I. Traditional Chemotherapy

- Neuropathy
- Alopecia (generally full body)
- Myalgia
- Fatigue

What are the most common adverse effects of each taxane?

- Paclitaxel: myelosuppression (more thrombocytopenia), cardiovascular and hypersensitivity reactions (characterized by hypotension, dyspnea, flushing, and rash), peripheral sensory neuropathy, central nervous system (CNS) effects from dehydrated alcohol, alopecia, skin reactions, bradycardia, and radiation recall

- Nab-paclitaxel: myelosuppression (less thrombocytopenia), peripheral sensory neuropathy (appears more reversible than paclitaxel), alopecia, edema, skin rash, hypersensitivity (rare), and ocular disturbances (blurred vision and photopsia)

- Docetaxel: fluid retention (peripheral edema, generalized edema, pleural effusions, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention due to ascites), myelosuppression (more than paclitaxel), cutaneous reactions, less cardiotoxicity than paclitaxel, peripheral neuropathy, conjunctivitis, lacrimation, stomatitis/mucositis, diarrhea, hepatotoxicity, and myalgias/arthralgias

- Cabazitaxel: myelosuppression, febrile neutropenia, fatigue, urinary tract infections, dehydration, less hypersensitivity reactions, diarrhea, acute renal failure (from diarrhea/dehydration), less peripheral neuropathy, less alopecia, minimal fluid retention, minimal onychodystrophy

- Ixabepilone: peripheral neuropathy, CNS effects (high concentration of dehydrated alcohol), radiation recall, myelosuppression, less hypersensitivity, constipation, stomatitis/mucositis, anorexia, alopecia, and arthralgias/myalgias

- Eribulin: peripheral neuropathy, myelosuppression, febrile neutropenia, QT prolongation, anorexia, arthralgias/myalgias, decreased liver function, and alopecia
1. MICROTUBULE INHIBITORS

What is the difference in the side effect profile between weekly dosing and dosing every 3 weeks of paclitaxel and docetaxel?

**Differences in Side Effect Profile Between Weekly Dosing and Dosing Every 3 Weeks of Paclitaxel and Docetaxel**

<table>
<thead>
<tr>
<th>Weekly</th>
<th>Every 3 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td></td>
</tr>
<tr>
<td>Nail/skin changes</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td>Edema</td>
<td>More alopecia (total body loss)</td>
</tr>
<tr>
<td>Neuropathy (but delayed)</td>
<td>Myalgia</td>
</tr>
<tr>
<td>Generally better tolerated</td>
<td><em>Continuous infusion:</em> more myelosuppression, mucositis, diarrhea, febrile neutropenia, possibly less neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td></td>
</tr>
<tr>
<td>Tear duct changes</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td>Nail/skin changes</td>
<td>Mucositis</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>Myalgia</td>
</tr>
</tbody>
</table>

What are the premedications required?

**Premedications Required for Taxanes**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Premedication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>Dexamethasone 20 mg IV, diphenhydramine 50 mg IV, and famotidine 20 mg IV</td>
</tr>
<tr>
<td>Nab-paclitaxel</td>
<td>None required</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>1. Dexamethasone (8 mg PO twice daily for 3 days starting 1 day prior to treatment)</td>
</tr>
<tr>
<td></td>
<td>2. Prostate cancer: dexamethasone (8 mg PO at 12 hr, 3 hr, and 1 hr prior to the docetaxel infusion)</td>
</tr>
<tr>
<td></td>
<td>3. Simplified: 20 mg IV dexamethasone</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>Dexamethasone 10 mg IV, diphenhydramine 50 mg IV, and famotidine 20 mg IV</td>
</tr>
<tr>
<td>Ixabepilone</td>
<td>Diphenhydramine 50 mg IV and famotidine 20 mg IV</td>
</tr>
<tr>
<td>Eribulin</td>
<td>None</td>
</tr>
</tbody>
</table>
10 I. Traditional Chemotherapy

What is the emetogenicity level of the taxanes?

- All six agents are categorized as low

Are the taxanes vesicants or irritants?

- Paclitaxel: irritant with vesicantlike properties
- Nab-paclitaxel: irritant
- Docetaxel: irritant
- Cabazitaxel: irritant
- Ixabepilone: irritant
- Eribulin: nonvesicant/nonirritant
VINCA ALKALOIDS

What are the chemotherapy agents in the vinca alkaloid class?

- Vincristine (Oncovin®)
- Liposomal vincristine (Marqibo®)
- Vinblastine (Velban®)
- Vinorelbine (Navelbine®)

What malignancies are each vinca alkaloid FDA approved for?

<table>
<thead>
<tr>
<th>Agent</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine</td>
<td>Acute lymphoblastic leukemia (ALL), Hodgkin’s (HL) and non-Hodgkin’s lymphoma (NHL), Wilms’ tumor, neuroblastoma, rhabdomyosarcoma</td>
</tr>
<tr>
<td>Liposomal vincristine</td>
<td>ALL</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>HL and NHL, testicular cancer, breast cancer, Kaposi’s sarcoma, histiocytosis, choriocarcinoma</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Non–small cell lung cancer</td>
</tr>
</tbody>
</table>

*Abbreviation:* FDA, U.S. Food and Drug Administration.

How do the vinca alkaloids work? (See Figure 1.1)

- Derived from the Madagascar periwinkle plant (*Catharanthus roseus*)
- Binds to β-tubulin, which prevents polymerization and therefore inhibits microtubule assembly/promotes disassembly (reminder: taxanes prevent the disassembly of microtubules)
- Cell cycle specific to the G2/M phase
- Liposomal vincristine is a sphingomyelin/cholesterol liposome–encapsulated formulation of vincristine sulfate
I. Traditional Chemotherapy

What are the common mechanisms of resistance to vinca alkaloid therapy?
- Overexpression of the mdr-1 gene, which encodes for a membrane P-gp efflux pump
- Alterations in the α- and β-tubulin subunits

What are the common dosing ranges for each vinca alkaloid?
- Vincristine: 1.4 mg/m² (capped at 2 mg; exception EPOCH)
- Liposomal vincristine: 2.25 mg/m² IV over 1 hour once every 7 days (no cap)
- Vinblastine: 4 to 7.4 mg/m² every 7 to 14 days
- Vinorelbine: 20 to 30 mg/m² every 7 days

Are the vinca alkaloids metabolized/eliminated renally or hepati-
cally?
- All four are extensively metabolized hepatically
- All four vinca alkaloids do not appear to require dose adjustments for renal dysfunction

Are there drug interactions with any of the vinca alkaloids?
- Vincristine and liposomal vincristine: CYP3A4 and P-gp inhibitors/inducers
- Vinblastine: CYP3A4, CYP2D6, and P-gp inhibitors/inducers
- Vinorelbine: CYP3A4 and CYP2D6 inhibitors/inducers

What are the most common adverse effects of each vinca alkaloid?
- Vincristine and liposomal vincristine: constipation, ileus, loss of deep tendon reflex, peripheral neuropathy, jaw pain, syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- Vinblastine: myelosuppression, alopecia, hypertension (due to autonomic dysfunction), malaise, SIADH, less peripheral neuropathy

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• Vinorelbine: myelosuppression, granulocytopenia, peripheral neuropathy, constipation, aspartate transaminase (AST)/alanine transaminase (ALT) elevation, alopecia, SIADH, less peripheral neuropathy than vincristine but more than vinblastine

What is the emetogenicity level of the vinca alkaloids?
• All four agents are categorized as low

Are the vinca alkaloids vesicants or irritants?
• All four are vesicants