DRUG PROPERTIES YOU NEED TO KNOW

1. **Mechanism of action**
    a. **chemical class**
    b. **resistance**
2. Pharmacokinetics
3. Therapeutic uses
4. **Major side effects/toxicities**

DIFFERENCES ARE IMPORTANT!!!!

A 56-year-old man with non-Hodgkin's lymphoma underwent a successful course of therapy with the CHOP regimen.

1. Which of the following classes of anticancer drugs is cell cycle-nonspecific (CCNS) and used in the CHOP regimen?
    A) Alkylating agents
    B) Vinca alkaloids
    C) Antimetabolites
    D) Glucocorticoids
    E) Plant alkaloids

MECHANISM

THERAPEUTIC USES

CHOP
Cyclophosphamide
Doxorubicin
Vincristine (Oncovin)
Prednisone

A 56-year-old man with non-Hodgkin's lymphoma underwent a successful course of therapy with the CHOP regimen.

2. During the second course of treatment, this patient developed hemorrhagic cystitis. The most likely causitive agent is:
    A) Bleomycin
    B) Cyclophosphamide
    C) Doxorubicin
    D) Prednisone
    E) Vincristine

TOXICITY

NAMING CONVENTIONS

Folate analogues = **TREX**	**METHOTREXATE, PEMETREXED, PRALATREXATE**
Antimetabolites = **CITABINE** and **ARABINE**	**CAPECITABINE, CLADARABINE, CYTARABINE, FLUDARABINE, GEMCITABINE**
Platinum-containing crosslinking agents = **PLATIN**	**CISPLATIN, CARBOPLATIN, OXALOPLATIN**
Anthracycline antibiotics = **RUBICIN**	**DAUNORUBICIN, DOXORUBICIN, EPIRUBICIN, IDARUBICIN**
Nitrosoureas = **MUSTINE**	**CARMUSTINE (BCNU), LOMUSTINE (CCNU)**
Taxanes = **TAXEL**	**PACLITAXEL, CABAZITAXEL, DOCATAXEL**
Antibiotics = **MYCIN**	**BLEOMYCIN, MITOMYCIN**
Camptothecins = **TECAN**	**IRINOTECAN, TOPOTECAN**
Vinca alkaloids = **VIN...INE**	**VINBLASTINE, VINCRISTINE, VINORELBINE**
= **LIMUS**	**TACROLIMUS, EVEROLIMUS, TEMSIROLIMUS**
Monoclonal antibodies = **MAB**	too many to list here (there are others used as antineoplastics besides the ones you "need to know")
Signal transduction inhibitors (block the actions of tyrosine kinases) = **NIB**	**DASATINIB, ERLOTINIB, GEFITINIB, IMATINIB, LAPATANIB, NALOTINIB, PAZOPANIB, SORAFENIB, SUNITINIB**
Protein inhibitors = **IB**	**BORTEZOMIB**

DRUGS YOU NEED TO KNOW organized by chemical class = card colour

(NB: Drugs in [] are related agents, parentheses indicate alternative names)

METABOLITES & ANTIMETABOLITES

5-FLUOROURACIL [Capecitabine]
6-MERCAPTOPURINE [Azothioprine]
6-THIOGUANINE
ALLOPURINOL
CLADRABINE
CYTARABINE (ARA-C)
FLUDARABINE
GEMCITABINE
LEUCOVORIN
METHOTREXATE [Pemetrexed,Pralatrexate]

ALKYLATING AGENTS

BUSULFAN
CARMUSTINE (BCNU) / LOMUSTINE (CCNU)
CHLORAMBUCIL
CYCLOPHOSPHAMIDE [Ifosfamide]
DACARBAZINE
MECHLORETHAMINE
MELPHALAN
PROCARBAZINE
TEMOZOLAMIDE

NATURAL PRODUCTS

BLEOMYCIN
DOXORUBICIN [Daunorubicin, Idarubicin, Epirubicin, Mitoxantone]
ETOPOSIDE
IRINOTECAN / TOPOTECAN
IXABEPILONE
L-ASPARAGINASE
MITOMYCIN
PACLITAXEL [Docataxel, Cabazitaxel]
VINBLASTINE [Vinorelbine]
VINCRISTINE

IMMUNOSUPPRESSANTS

CYCLOSPORINE, TACROLIMUS
PREDNISONE, DEXAMETHASONE
EVEROLIMUS, TEMSIROLIMUS

THERAPEUTIC PROTEINS ("BIOLOGICS")

ALEMTUZUMAB
L-ASPARAGINASE
BEVACIZUMAB
CETUXIMAB / PANITUMUMAB
DENILEUKIN DIFTITUX
ERYTHROPOIETIN [Darbepoietin, MPEGepoietin]
FILGRASTIM [PEGFilgrastim]
INTERFERON α
INTERLEUKIN 2
INTERLEUKIN 11
INTERLEUKIN-12
RITUXIMAB [Ibritumomab, Tositumomab]
ROMIPLOSTIM
SARGRAMOSTIM (GM-CSF)
TRASTUZUMAB
TUMOUR NECROSIS FACTOR α

MISCELLANEOUS

ARSENIC TRIOXIDE
BEXAROTENE
BORTEZOMIB
CISPLATIN [Carboplatin, Oxaloplatin]
ERLOTINIB, GEFITINIB
HYDROXYUREA
IMATINIB [Dasatinib, Nilotinib]
LAPATINIB
MESNA
PAZOPANIB, SUNITINIB
SORAFENIB
THALIDOMIDE
TRETINOIN
VORINOSTAT

ACTION (label colour)	SITE	MECHANISM	DRUG
Prevent DNA synthesis	I. Block nucleotide synthesis (both purines and pyrimidines)	Inhibit dihydrofolate reductase	Methotrexate Pemetrexed Pralatrexate
	II. Block purine synthesis	"Pseudofeedback inhibition" of PNP and PRPP	6-Mercaptopurine 6-Thioguanine
	III. Block pyrimidine synthesis	Inhibit thymidylate synthase	Capecitabine 5-Fluorouracil Pemetrexed Pralatrexate
	IV. Block generation of deoxyribonucleotides	Inhibit ribonucleotide reductase	Cytarabine Fludarabine Gemcitabine Hydroxyurea
	V. Block DNA synthesis	Inhibit DNA polymerase	Cladarabine Cytarabine Fludarabine Gemcitabine
Disrupt DNA, prevent DNA repair and/or interfere with RNA synthesis	I. Crosslink DNA	Alkylating agents	Busulfan Carmustine (BCNU) Chlorambucil Cyclophosphamide Dacarbazine Ifosfamide Lomustine (CCNU) Mechlorethamine Melphalan Mitomycin Procarbazine Temozolamide
		Miscellaneous	Carboplatin Cisplatin Oxaloplatin
	II. Intercalate or form adducts with DNA	Anthracycline antibiotic (and related agents)	Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantone
	III. Cause DNA strand breaks	Free radical generation	Bleomycin
		Form topoisomerase II-DNA complexes	Etoposide
		Inhibit topoisomerase I	Irinotecan Topotecan
		Generate H_2O_2 (??)	Procarbazine

Interrupt mitosis	I. Disrupt spindle formation	Terminate spindle assembly	Vinblastine Vincristine Vinorelbine
		Enhance spindle formation	Paclitaxel Ixabepilone
Immune system modulators	I. **Immunosuppressives**	Glucocorticoids	Dexamethasone Prednisone
		Antibiotics	Cyclosporine Tacrolimus
		Antibodies	Alemtuzumab Denileukin diftitux Ibritumomab Rituximab Tositumomab
	II. **Immune system stimulants** (hematopoietic agents listed under supporting agents)	Cytokines	Interleukin 2 Interferon α Tumour necrosis factor α
Target altered proteins or processes	I. Target mutated or over-expressed proteins	Block bcr-abl	Dasatinib Imatinib Nilotinib
		Block HER2	Lapatanib Trastuzumab
	II. Block growth factors or growth factor receptors (anti-VEGF listed under Prevent angiogenesis)	Block EGFR	Cetuximab Erlotinib Gefitinib Lapatanib Panitumumab
		Decrease FGF production	Interferon α
	III. Target altered processes (blocking mTOR listed under prevent angiogenesis)	Deplete asaparagine	L-asparaginase
		Inhibit 26S proteosome	Bortezomib
		Inhibit HDAC	Vorinostat

Prevent angiogenesis		Block VEGF	Bevacizumab
		Block VEGF-R	Pazopanib Sorafenib Sunitinib
		Block mTOR	Everolimus Temsirolimus
		Miscellaneous	Interleukin-12 Interferon α Thalidomide
Induce differentiation		Retinoid	Tretinoin
		Rexinoid	Bexarotene
		Miscellaneous	Arsenic trioxide

Supporting agents	I. Hematopoietic agents	Erythroid growth factors	Darbepoietin Erythropoietin Peg-epoietin
		Myeloid growth factors	Filgrastim Pegfilgrastim Sagramostim
		Megakaryocyte growth factors	Interleukin 11 Romiplostim
	II. Miscellaneous		Allopurinol Leucovorin MESNA

ORGANIZATION OF ANTINEOPLASTICS ACCORDING TO PROTEIN FUNCTION

PROTEIN	NORMAL ACTION	ANTINEOPLASTIC
L-asparaginase	Hydrolysis of asparagine to aspartic acid and ammonia	**L-ASPARAGINASE**
bcl-abl (non-receptor tyrosine kinase)	Activation of transcription factors via cascade pathway	**DASATANIB, IMATINIB, NILOTINIB**
CD20 (B-lymphocyte restricted differentiation antigen Bp35)	Transmembrane protein found on pre-B and mature B lymphocytes	**IBRITUMOMAB RITUXIMAB TOSITUMOMAB**
CD33 (gp67, p67)	Sialic acid-dependent cytoadhesion molecule expressed by monocytic/myeloid lineage cells	**GEMTUZUMAB**
CD52	CAMPATH-1 antigen; GPI-anchored protein expressed at high levels on thymocytes, lymphocytes, monocytes, and macrophages	**ALEMTUZUMAB**
Cyclophilin	Allows calcineurin activation, ultimately resulting in decreased secretion of IL-2	**CYCLOSPORINE**
Cytochrome P450	Hydroxylation of aromatic and aliphatic compounds (can activate or inactivate antineoplastic drugs)	**CYCLOPHOSPHAMIDE PROCARBAZINE DOXORUBICIN PACLITAXEL**
Dihydropyrimidine dehydrogenase	Liver and gut enzyme that degrades thymidine nucleotides	**5-FLUOROURACIL**
Dihydrofolate reductase (DHFR)	Converts dihydrofolate to tetrahydrofolate	**METHOTREXATE PEMETREXED**
DNA Polymerase	Copies DNA templates during DNA replication	**CYTARABINE GEMCITABINE**
EGFR	Binds epidermal growth factor	**CETUXIMAB, ERLOTINIB, GEFITINIB, LAPATANIB, PANITUMUMAB**
Fibroblast growth factor (FGF)	Angiogenic protein	**INTERFERON α**
FK-binding protein	Allows calcineurin activation, ultimately resulting in decreased secretion of IL-2	**TACROLIMUS**

Glutathione peroxidase	Oxidizes glutathione	**DOXORUBICIN**
P-glycoprotein	Drug transport out of cells	Multidrug resistance
Guanylyl kinase	Converts GMP to GDP	**6-MERCAPTOPURINE** **6-THIOGUANINE**
HER2	Transmembrane protein overexpressed in breast cancer	**LAPATINIB** **TRASTUZUMAB**
Histone deacetylase (HDAC)	Removes acetyl groups from lysine residues leading to the formation of condensed and transcriptionally silenced chromatin	**VORINOSTAT**
Hypoxanthine-guanine phosphoribosyl transferase (HGPRT)	"Salvage" enzyme for recoversion of purines	**6-MERCAPRTOPURINE** **6-THIOGUANINE**
Interleukin 2 (itself an antineoplastic)	Cytokine that induces and expands a T cell response	**DENILEUKIN DIFTITUX**
mTOR	Intracellular serine/threonine kinase involved in regulation of cell proliferation and angiogenesis	**EVEROLIMUS** **TEMSIROLIMUS**
p53 gene product	Cell cycle checkpoint that is mutated in 50% of human cancers	**ALKYLATING AGENTS**
PML-RARα	Fusion protein of retinoic acid receptor and promyelocytic protein produced via translocation in APL	**ARSENIC TRIOXIDE** **TRETINOIN**
26S Proteosome	Large protein complex that degrades ubiquitinated proteins	**BORTEZOMIB**
PRPP glutamyl amidotransferase	1st committed step in purine synthesis	**6-MERCAPTOPURINE** **6-THIOGUANINE**
Purine nucleoside phosphorylase (PNP)	1st step in purine synthesis	**6-MERCAPTOPURINE** **6-THIOGUANINE**
Pyrimidine monophosphate kinase	Converts UMP to UDP	**5-FLUOROURACIL**
Ribonucleotide reductase	Reduces nucleoside diphosphates to deoxy forms	**GEMCITABINE** **HYDROXYUREA**
VEGF **VEGF-R**	Receptor for vascular endothelial growth factor (needed for angiogenesis)	**BEVACIXIMAB** **PAZOPANIB** **SORAFENIB** **SUNITINIB**
Thymidine phosphorylase	Converts capecitabine to 5-FU (preferentially in cancer cells)	**CAPECITABINE**

Topoisomerase I	Reversible nuclease that breaks phosphodiesterase bonds resulting in a transient single-strand break	**IRINOTECAN**
Topoisomerase II	Makes a temporary DNA break, then causes 2nd half of double helix to pass through the break before resealing it.	**DOXORUBICIN** **ETOPOSIDE**
Thymidylate synthase	TMP synthesis	**CAPECITABINE** **5-FLUOROURACIL** **PEMETREXED**
Tubulin	Key component of mitotic spindle and microtubules (axon transport, cytoskeleton)	**IXABEPILONE, PACLITAXEL, VINBLASTINE, VINCRISTINE**
Xanthine oxidase	Converts xanthine to uric acid	**ALLOPURINOL** **6-MERCAPTOPURINE**
Vascular endothelial growth factor (VEGF)	Angiogenic growth factor	**BEVACIXIMAB**

RENAL TOXICITY	HEPATOTOXICITY	NEUROTOXICITY	CARDIOTOXICITY	
			CHF	Other
Carmustine	Asparaginase	L-Asparaginase	Doxorubicin	Bleomycin
Cisplatin	Busulfan	Carmustine	Trastuzumab	Cisplatin
Cyclophosphamide	Carmustine	Cisplatin		Ixabepilone
Lomustine	Cyclophosphamide	Cytarabine		Nitrogen mustards
Methotrexate	6-Mercaptopurine	Etoposide		5-Fluorouracil
Vincristine	Methotrexate	5-Fluorouracil		Methotrexate
	6-Thioguanine	Ixabepilone		Paclitaxel
		Methotrexate		
		Paclitaxel		
		Procarbazine		
		Vinblastine		
		Vincristine		

RELATIVE EMETIC POTENTIAL OF ANTINEOPLASTIC DRUGS				
HIGH (>90%)	MODERATELY HIGH (60-90%)	MODERATE (30-60%)	MODERATELY LOW (10-30%)	LOW (<10%)
Cisplatin	Carmustine	L-asparaginase	Bleomycin	Busulfan
Mechlorethamine	Cyclophosphamide	Doxorubicin	Etoposide	
	Lomustine	5-Fluorouracil	Hydroxyurea	
			Melphalan	
			6-Mercaptopurine	
			Methotrexate	
			Vinblastine	