

Mechanisms of Action, Indications, and Toxicities of Selected Antineoplastic Agents

Drug	Mechanism of Action	Major Indications	Toxicities
Alkylating Agents			
Cyclophosphamide	Undergoes hepatic biotransformation to active metabolites that alkylate DNA; alkylation leads to miscoding of DNA and cross-linking of DNA strands	Lymphoma, mammary adenocarcinoma, sarcomas, lymphocytic leukemia	Nausea, vomiting (infrequent), moderate to severe myelosuppression, sterile hemorrhagic cystitis
Melphalan	Alkylates DNA causing miscoding and cross-linking of DNA strands	Multiple myeloma	Nausea, vomiting, anorexia, moderate myelosuppression (may be more myelosuppressive in cats)
Chlorambucil	Alkylates DNA causing miscoding and cross-linking of DNA strands; slowest-acting alkylating agent	Chronic lymphocytic leukemia, small-cell lymphoma	Nausea, vomiting, mild to moderate myelosuppression
Lomustine (CCNU)	Alkylates DNA causing miscoding and cross-linking of DNA strands; inhibits both DNA and RNA synthesis; not cross-resistant with other alkylating agents	Lymphoma, mast cell tumor, histiocytic sarcoma, CNS neoplasias, multiple myeloma	Nausea, vomiting, moderate to severe myelosuppression (may be delayed for 4–6 wk), hepatotoxicity, nephrotoxicity, pulmonary toxicity
Streptozotocin	Inhibits DNA synthesis; high affinity for pancreatic β cells	Insulinoma	Severe, potentially fatal nephrotoxicity (if given without diuresis) and hepatotoxicity, nausea (immediate and delayed), vomiting, mild myelosuppression
Dacarbazine (DTIC)	Undergoes hepatic biotransformation to active metabolites that alkylate DNA; inhibits RNA synthesis	Lymphoma, sarcomas	Severe acute nausea, vomiting, phlebitis, moderate myelosuppression, hepatotoxicity, anecdotal reports of pleural effusion in cats
Ifosfamide	Analogue of cyclophosphamide; undergoes hepatic biotransformation to active metabolites that alkylate DNA; alkylation leads to miscoding of DNA and cross-linking of DNA strands	Various sarcomas	Nausea, vomiting, myelosuppression, sterile hemorrhagic cystitis, possible nephrotoxicity
Antimetabolites			
Methotrexate	Inhibition of dihydrofolate reductase that is required for formation of tetrahydrofolate, a necessary cofactor in thymidylate synthesis; thymidylate essential for DNA synthesis and repair	Lymphoma	Nausea, vomiting, moderate myelosuppression, GI ulceration, hepatotoxicity, pulmonary toxicity
5-Fluorouracil	Pyrimidine analogue; interferes with DNA synthesis and may be incorporated into RNA to cause toxic effects	Carcinomas (systemic); cutaneous carcinomas (topical)	Systemic: nausea, vomiting, moderate myelosuppression, neurotoxicity, GI ulceration, neurotoxicity, hepatotoxicity Topical: local irritation, pain, hyperpigmentation Cannot be given to cats (fatal neurotoxicity)
Cytarabine	Pyrimidine analogue; incorporates into DNA causing steric hindrance and inhibition of DNA synthesis	Lymphoma (including CNS), leukemias; no activity in solid tumors	Nausea, vomiting, moderate myelosuppression, nephrotoxicity, hepatotoxicity

Drug	Mechanism of Action	Major Indications	Toxicities
Gemcitabine	Pyrimidine analogue; incorporates into DNA, causing steric hindrance and inhibition of DNA synthesis	Limited efficacy seen in lymphoma and various carcinomas	Mild nausea, vomiting, mild to moderate myelosuppression, pulmonary toxicity, nephrotoxicity
<i>Antibiotic Antineoplastics</i>			
Doxorubicin	Intercalates and binds to DNA, disrupting helical structure and DNA template; inhibits RNA and DNA polymerases; causes DNA topoisomerase II-mediated chain scission; generates free radicals that cause DNA scission and cell membrane damage	Lymphoma, leukemias, multiple myeloma, osteosarcoma, hemangiosarcoma, and various other sarcomas and carcinomas	Nausea, vomiting, moderate myelosuppression, hemorrhagic colitis, severe cutaneous reactions if extravasated; red urine (not hematuria), transient ECG changes and arrhythmias, nephrotoxicity, anaphylactoid reactions; Cumulative dose-related congestive heart failure in dogs; cumulative nephrotoxicity in cats
Mitoxantrone	Topoisomerase II-mediated chain scission; DNA aggregation, oxidation, and strand breakage	Lymphoma, various carcinomas	Nausea, vomiting, moderate to severe myelosuppression, diarrhea, bluish discoloration to sclera; less severe adverse effects than others in this group
Bleomycin	Mixture of glycopeptides; generates oxygen radicals that cause chain scission and fragmentation of DNA	Carcinomas	Nausea, vomiting, myelosuppression, fever, allergic reactions including anaphylaxis, hyperpigmentation, skin ulceration, pneumonitis, pulmonary fibrosis
Dactinomycin (Actinomycin D)	Intercalates and binds to DNA, disrupting helical structure and DNA template; inhibits RNA and DNA polymerases; causes DNA topoisomerase II-mediated chain scission; generates free radicals that cause DNA scission and cell membrane damage	Lymphoma, various sarcomas	Nausea, vomiting, moderate to severe myelosuppression, phlebitis; severe tissue reaction if extravasated
<i>Mitotic Inhibitors</i>			
Vinblastine	Binds to tubulin, leading to disruption of mitotic spindle apparatus and arrest of cell cycle	Lymphoma and leukemias, mast cell tumors	Mild nausea, vomiting, severe myelosuppression, neurotoxicity with high doses, inappropriate secretion of antidiuretic hormone
Vincristine	Binds to tubulin, leading to disruption of mitotic spindle apparatus and arrest of cell cycle	Lymphoma and leukemias, transmissible venereal cell tumors, various sarcomas	Mild to moderate nausea, vomiting, mild to moderate myelosuppression, severe tissue reaction if extravasated, cumulative peripheral neuropathy, constipation, paralytic ileus, inappropriate secretion of antidiuretic hormone
Vinorelbine	Binds to tubulin, leading to disruption of mitotic spindle apparatus and arrest of cell cycle	Primary lung tumors, limited efficacy in mast cell tumors	Mild nausea, vomiting, myelosuppression
Paclitaxel	Binds to tubulin, stabilizing microtubule polymer and arresting mitosis	Mammary carcinoma, squamous cell carcinoma	Myelosuppression, nausea, vomiting, hypersensitivity (when Cremor EL is used as vehicle)
<i>Miscellaneous</i>			

Drug	Mechanism of Action	Major Indications	Toxicities
Cisplatin	Reacts with proteins and nucleic acids; forms cross-links between DNA strands and between DNA and protein; disrupts DNA synthesis	Osteosarcoma, carcinomas, and mesothelioma	Intense nausea, vomiting, mild to moderate myelosuppression, potentially fatal nephrotoxicity if not given with diuresis, anaphylaxis, ototoxicity, peripheral neuropathy, hyperuricemia, hypermagnesemia; Cannot be given to cats (fulminant pulmonary edema)
Carboplatin	Reacts with proteins and nucleic acids; forms cross-links between DNA strands and between DNA and protein; disrupts DNA synthesis	Osteosarcoma, carcinomas	Mild nausea, vomiting, diarrhea, moderate to severe myelosuppression
L-Asparaginase	Inhibits protein synthesis by hydrolyzing tumor cell supply of asparagine	Acute lymphoid leukemias and lymphoma	Hypersensitivity reactions, anaphylaxis especially after repeated doses, alteration in coagulation parameters, hepatotoxicity, pancreatitis (people), potential inhibition of immune responsiveness (B and T cells)
Mitotane (o,p'DDD)	Destroys adrenal zona fasciculata and zona reticularis	Pituitary hyperadrenocorticism, palliation of adrenal cortical tumors	Nausea, vomiting, anorexia, diarrhea, adrenal insufficiency, CNS depression, dermatitis
Hydroxyurea	Inhibits conversion of ribonucleotides to deoxyribonucleotides by destroying ribonucleoside diphosphate reductase	Polycythemia vera, granulocytic and basophilic leukemia, thrombocythemia, investigational for meningiomas	Nausea, vomiting, mild myelosuppression, alopecia, sloughing of claws, dysuria
Procarbazine	Mechanism is unclear; inhibits DNA, RNA, and protein synthesis, perhaps through alkylation	Lymphoma, as part of MOPP chemotherapy protocol; brain tumors	Nausea, vomiting, myelosuppression, diarrhea
Hormones			
Prednisone	Lympholytic; inhibits mitosis in lymphocytes	Lymphoma, mast cell tumors, multiple myeloma, palliative treatment of brain tumors	Sodium retention, GI ulceration, protein catabolism, muscle wasting, delayed wound healing, suppression of hypothalamic-pituitary-adrenal axis, immunosuppression

