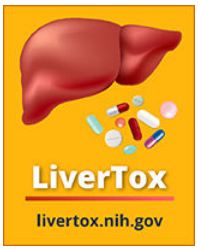
U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Antineoplastic Agents. [Updated 2024 Mar 7].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/



Antineoplastic Agents

Updated: March 7, 2024.

OVERVIEW

The antineoplastic agents or anticancer drugs represent a large and diverse class of medications. They generally have limited but important uses, and often have significant hepatotoxicity.

The antineoplastic agents are not easily classified. Historically, they are categorized as (1) alkylating agents, (2) antimetabolites, (3) natural products, (4) hormones and antagonists, and (5) miscellaneous. In recent years, however, the miscellaneous group has come to include some of the most important agents. Anticancer agents can also be classified by indication (lymphoma, leukemia, melanoma, solid tumor), mechanism of action (such as alkylating agents, antibiotics, biological response modifiers, antiandrogens, topoisomerase inhibitors or protein kinase inhibitors), chemical structure (folic acid analog, platinum coordination complex, purine or pyrimidine analog, monoclonal antibody) or as cytotoxic or nonspecific vs noncytotoxic or targeted. The classification used in LiverTox represents a mixture of these systems, which generally follow those given in modern pharmacology textbooks.

Almost all antineoplastic agents have some degree of hepatotoxicity, and the liver injury is usually due to direct, intrinsic toxicity. The typical manifestation is an elevation in liver enzymes or bilirubin during therapy that reverses rapidly with stopping treatment or dose modification. This type of hepatotoxicity is dose related and generally self-limiting, but can be severe, progressive and even fatal as can occur with sinusoidal obstruction syndrome or acute toxic hepatic injury. The antineoplastic agents often have a narrow toxic-therapeutic ratio, although the usual dose limiting toxicity is myelosuppression. Nevertheless, liver injury also can be dose limiting, which generally becomes clear in early dose finding studies. For this reason, many antineoplastic agents acquire a reputation for hepatotoxicity based upon premarketing studies, but are later found to be reasonably well tolerated and only rare causes of clinically significant liver injury when given in lower doses. Antineoplastic agents that are well known to cause significant direct hepatotoxicity when given in moderate to high doses (particularly when used in myeloablation before hematopoietic cell transplantation) include busulfan, melphalan, cyclophosphamide, dacarbazine, cytarabine, fluorouracil, carboplatin and L-asparaginase. At lower doses, these agents are well tolerated.

Some antineoplastic agents can also cause idiosyncratic liver injury due to immunologic or metabolic idiosyncrasy. Thus, typical drug induced cholestatic liver injury can occur in rare instances after therapy with cyclophosphamide, azathioprine, mercaptopurine, melphalan and temozolomide. Acute hepatocellular injury can occur with flutamide, bicalutamide and thalidomide. Steatohepatitis can occur with L-asparaginase, methotrexate and tamoxifen (although this pattern may be due to direct toxicity rather than idiosyncratic injury). Selected anticancer agents have also been linked to immunoallergic hepatitis or to autoimmune hepatitis-like injury. A distinctive autoimmune pattern is found in rare instances after monoclonal antibody therapies or with the protein kinase inhibitors. The pathogenesis of these immune reactions is not always well

understood. Finally, some antineoplastic agents can cause reactivation of hepatitis B, exacerbations of chronic hepatitis C, or lead to decompensation of an preexisting cirrhosis.

A classification of the antineoplastic agents with listing of individual agents is given below. There has been a steady increase in development of innovative antineoplastic agents in recent years and between 5 and 10 new anticancer agents are approved yearly. The hepatotoxicity of these recently introduced agents has not always been well defined. The following links are to individual drug records for the antineoplastic agents; those that are not underlined have yet to be added.

Antineoplastic Agents

- Alkylating Agents
  - Altretamine, Bendamustine, Busulfan, Carmustine, Chlorambucil, Cyclophosphamide, Dacarbazine, Ifosfamide, Lomustine, Lurbinectedin, Mechlorethamine, Melphalan, Procarbazine, Streptozocin, Temozolomide, Thiotepa, Trabectedin
  - Platinum Coordination Complexes
    - Carboplatin, Cisplatin, Oxaliplatin
- Antibiotics, Cytotoxic
  - Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitomycin, Mitoxantrone, Plicamycin, Valrubicin
- Antimetabolites
  - Antifolates: Methotrexate, Pemetrexed, Pralatrexate, Trimetrexate
  - Purine Analogues: Azathioprine, Cladribine, Fludarabine, Mercaptopurine, Thioguanine
  - Pyrimidine Analogues: Azacitidine, Capecitabine, Cytarabine, Decitabine, Floxuridine, Fluorouracil, Gemcitabine, Trifluridine/Tipracil
- Biologic Response Modifiers
  - Aldesleukin (IL-2), Denileukin Diftitox, Interferon Gamma
- Histone Deacetylase Inhibitors
  - Belinostat, Panobinostat, Romidepsin, Vorinostat
- Hormonal Agents
  - Antiandrogens: Abiraterone, Apalutamide, Bicalutamide, Cyproterone, Enzalutamide, Flutamide, Nilutamide
  - Antiestrogens (including Aromatase Inhibitors): Anastrozole, Exemestane, Fulvestrant, Letrozole, Raloxifene, Tamoxifen, Toremifene
  - Gonadotropin Releasing Hormone Analogues: Degarelix, Goserelin, Histrelin, Leuprolide, Relugolix, Triptorelin
  - Peptide Hormones: Lanreotide, Octreotide, Pasireotide
- Monoclonal Antibodies
  - Alemtuzumab, Atezolizumab, Avelumab, Belantamab, Bevacizumab, Blinatumomab, Brentuximab, Cemiplimab, Cetuximab, Daratumumab, Dinutuximab, Dostarlimab, Durvalumab, Elotuzumab, Enfortumab, Gemtuzumab, Inotuzumab Ozogamicin, Ipilimumab, Mogamulizumab, Moxetumomab Pasudotox, Necitumumab, Nivolumab, Ofatumumab, Olaratumab, Panitumumab, Pembrolizumab, Pertuzumab, Polatuzumab Vedotin, Ramucirumab, Rituximab, Sacituzumab Govitecan, Teclistamab, Tisotumab Vedotin, Tositumomab, Trastuzumab, Trastuzumab Deruxtecam, Trastuzumab Emtansine, Tremelimumab
- Protein Kinase Inhibitors
  - Abemaciclib, Acalabrutinib, Adagrasib, Afatinib, Alectinib, Alpelisib, Asciminib, Axitinib, Binimetinib, Bortezomib, Bosutinib, Brigatinib, Cabozantinib, Carfilzomib, Ceritinib, Cobimetinib, Copanlisib, Crizotinib, Dabrafenib, Dacomitinib, Dasatinib, Duvelisib, Enasidenib, Encorafenib, Entrectinib, Erdafitinib, Erlotinib, Fedratinib, Futibatinib, Gefitinib, Gilteritinib, Glasdegib,

Ibrutinib, Idelalisib, Imatinib, Infigratinib, Ivosidenib, Ixazomib, Lapatinib, Larotrectinib, Lenvatinib, Lorlatinib, Midostaurin, Mobocertinib, Momelotinib, Neratinib, Nilotinib, Niraparib, Olaparib, Olutasidenib, Osimertinib, Pacritinib, Palbociclib, Pazopanib, Pemigatinib, Pexidartinib, Ponatinib, Regorafenib, Ribocicib, Ripretinib, Rucaparib, Ruxolitinib, Selumetinib, Sonidegib, Sorafenib, Sunitinib, Talazoparib, Tivozanib, Trametinib, Trilaciblib, Umbralisib, Vandetanib, Vemurafenib, Vismodegib, Zanubrutinib

- Taxanes
  - Cabazitaxel, Docetaxel, Paclitaxel
- Topoisomerase Inhibitors
  - Etoposide, Irinotecan, Teniposide, Topotecan
- Vinca Alkaloids
  - Vinblastine, Vincristine, Vinorelbine
- Miscellaneous
  - Asparaginase (Pegaspargase), Belzutifan, Bexarotene, Cedazuridine, Eribulin, Everolimus, Hydroxyurea, Ixabepilone, Lenalidomide, Mitotane, Omacetaxine, Pomalidomide, Selinexor, Tagraxofusp, Tazemetostat, Tebentafusp, Telotristat, Temsirolimus, Thalidomide, Venetoclax

ANNOTATED BIBLIOGRAPHY

References updated: 01 May 2019

Zimmerman HJ. Hepatotoxic effects of oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 673-708.

(Expert review of hepatotoxicity of cancer chemotherapeutic agents published in 1999).

DeLeve LD. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, p. 541-67.

(Review of hepatotoxicity of cancer chemotherapeutic agents published in 2013).

Wellstein A. General principles in the pharmacotherapy of cancer. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 1161-6.

(Textbook of pharmacology and therapeutics).