Cell

Cancer chemotherapy

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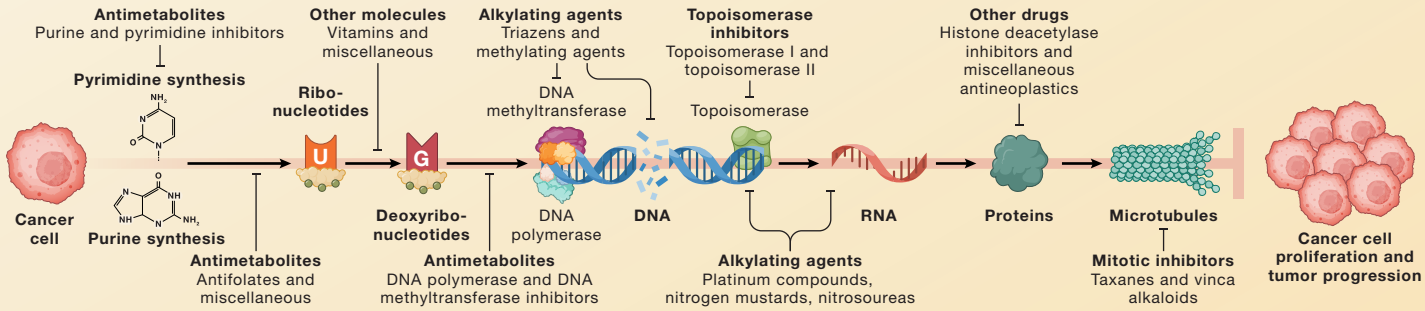
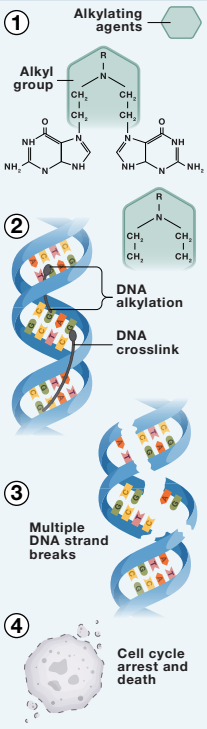


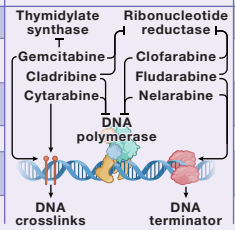
ALKYLATING AGENTS

	Drug	Therapeutic applications
Platinum compounds	Cisplatin	Bladder, testicular, ovarian, head and neck, uterus, lung cancer
	Carboplatin	Lung cancer, ovarian cancer
	Oxaliplatin	Colorectal cancer
Nitrosoureas	Carmustine	Brain tumor, lymphoma, multiple myeloma
	Lomustine	Brain and lung tumor, malignant melanoma, Hodgkin's lymphoma
	Streptozocin	Pancreatic cancer
Nitrogen mustards	Bendamustine	Chronic lymphocytic leukemia, B-cell non-Hodgkin's lymphoma, multiple myeloma
	Chlorambucil	Hodgkin's lymphoma, chronic lymphocytic leukemia, giant follicular lymphoma
	Cyclo-phosphamide	Multiple solid tumors
	Ifosfamide	Sarcoma, testicular, ovarian, bronchial, breast, pancreatic, endometrial cancer, lymphoma
	Mechlorethamine	T-cell lymphoma, B-cell lymphoma, chronic leukemia, lung cancer, medulloblastoma
	Melphalan	Multiple myeloma, ovarian cancer, neuroblastoma, melanoma, sarcoma
Triazenes	Dacarbazine	Malignant melanoma, Hodgkin's lymphoma, sarcoma
	Temozolomide	Brain tumors
	Procarbazine	Hodgkin's lymphoma



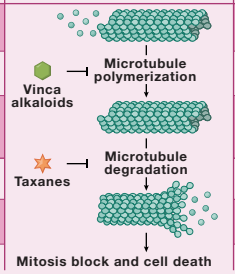
ANTIMETABOLITES

	Drug	Therapeutic applications
Pyrimidine antagonists	Fluorouracil	Colorectal, breast, stomach, pancreatic, head and neck cancer
	Capecitabine	Colorectal, breast and gastric cancer
	Floxuridine	Digestive system cancers
Purine antagonists	6 - mercaptopurine	Acute lymphoblastic or lymphocytic leukemia
	Thioguanine	Acute myeloblastic or lymphoblastic leukemia
Antifolates	Methotrexate	Leukemia, breast, skin, head and neck, lung, uterine cancer
	Pemetrexed	Non-squamous non-small cell lung cancer, malignant pleural mesothelioma
	Pralatrexate	T-cell lymphoma
Enzyme Inhibitors	Cladribine	Hairy cell leukemia
	Fludarabine	B-cell chronic lymphocytic leukemia
	Gemcitabine	Pancreatic, lung, ovarian, breast cancer
	Clofarabine	Acute lymphoblastic leukemia
	Nelarabine	T-cell lymphoblastic leukemia and lymphoma
	Cytarabine	Acute myeloid and other leukemias



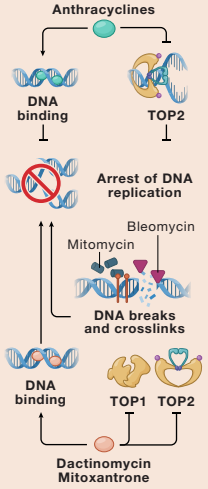
MITOTIC INHIBITORS

	Drug	Therapeutic applications
Taxanes	Cabazitaxel	Metastatic castration-resistant prostate cancer
	Docetaxel	Breast, lung, prostate, stomach, head and neck cancer
	(Nab) Paclitaxel	Breast, ovarian, lung and pancreatic cancer, AIDS-related Kaposi's sarcoma
Vinca alkaloids	Vinblastine	Hodgkin's lymphoma, testicular and breast cancer, Kaposi's sarcoma
	(Liposome) Vincristine	Leukemia,lymphoma, neuroblastoma, sarcomas
	Vinorelbine	Lung cancer and breast cancer



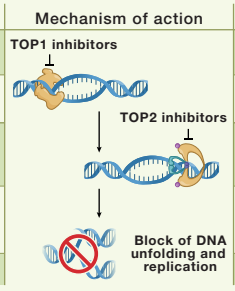
ANTI-TUMOR ANTIBIOTICS

	Drug	Therapeutic applications
Anthracyclines	Daunorubicin	Leukemia
	(Liposomal) Doxorubicin	Several solid tumors and hematological malignancies, AIDS-Kaposi's sarcoma
	Epirubicin	Several solid tumors and hematological malignancies
	Idarubicin	Acute myeloid/lymphoid leukemia
	Valrubicin	Bladder cancer
Non-Anthracyclines	Bleomycin	Squamous cell and testicular carcinoma, lymphoma, pleural effusion
	Dactinomycin	Several solid tumors
	Mitomycin-C	Stomach, pancreatic, breast, bronchial carcinoma, solid tumors
	Mitoxantrone	Prostate cancer, leukemia, non-Hodgkin's lymphoma, breast cancer, hepatocellular carcinoma



TOPOISOMERASE INHIBITORS

	Drug	Therapeutic applications
TOP1 Inhibitors	(Liposomal) Irinotecan	Colorectal, small-cell lung, pancreatic cancer
	Topotecan	Ovarian cancer, small cell lung cancer, cervical cancer
TOP2 Inhibitors	Etoposide (VP-16)	Lung, testicular and ovarian cancer, lymphoma, acute myeloid leukemia
	Mitoxantrone	Prostate, liver and breast cancer, leukemia, non-Hodgkin's lymphoma
	Teniposide	Leukemia



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SnapShot

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Antineoplastic drugs: Main concepts

Before the mid-1900s, the treatment of cancer was based mainly on the adoption of surgery or cautery for the eradication of non-invasive tumor lesions, while no effective therapeutic options were available for patients with advanced or metastatic diseases. Only after the Second World War, the first active ingredients with anticancer properties were discovered and adopted for the effective treatment of tumors. Since the late '40s, different classes of chemotherapeutic drugs have been used alone, in combination with other agents or in association with traditional surgery or radiation therapy.[1]

Despite the development of novel effective strategies for the treatment of tumors, including the introduction of targeted therapy and immunotherapy, chemotherapy still plays crucial roles in the fight against cancer alone or in combination with other regimens.

At present, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved several antineoplastic agents able to arrest tumor progression through direct or indirect mechanisms.[2,3] These drugs are classified into the following categories according to their mechanisms of action: alkylating agents, antimetabolites, mitotic inhibitors, topoisomerase inhibitors, and antitumor antibiotics plus a more heterogeneous group of agents with unknown or miscellaneous anticancer activities. Overall, chemotherapeutic drugs arrest the growth of tumors preventing the production of nucleotides, inhibiting key enzymes involved in the maintenance, duplication and transcription of DNA, or blocking proteins and cell structures fundamental for the duplication of cancer cells.

According to the most internationally recognized guidelines for the treatments of tumors,[4,5] chemotherapeutic agents can be used as first-, second- or third-line treatments in different tumors for curative, inductive, consolidative or maintenance purposes in association with other anticancer strategies.

Of note, the administration of chemotherapy is associated with a wide range of adverse effects mainly represented by gastrointestinal disorders (nausea, vomiting, diarrhea or constipation), bone marrow suppression, weakness, hair loss, mucositis, heart problems, secondary neoplasms, etc., which reduce the compliance of patients to treatments; therefore, often it may be necessary to administer detoxifying or supportive products, including vitamins, probiotics and proper nutrition, in order to reduce the detrimental effects of chemotherapy.[6,7]

As the selection of the correct agents is still debated and this topic is often overlooked in both clinical and research settings, the present SnapShot is aimed at giving a general overview of the key chemotherapy drugs currently used in oncology.

Alkylating agents

Alkylating agents are the first category of antineoplastic drugs discovered, which completely revolutionized the treatment of tumors. This group of agents contains several active ingredients classified as nitrogen mustards, platinum compounds, nitrosoureas, triazanes, and methylating agents. Other less-used agents are alkyl sulfonates, ethyleneimines, and methylmelamines. All these drugs can alkylate nucleic acids and proteins leading to the formation of intra- and inter-strand crosslinks responsible for multiple DNA breaks occurring during DNA duplication. Both single- or double-strand DNA breaks are in turn associated with cell cycle arrest and cell death. These agents have different routes of administration and are used for the treatment of hematological and solid tumors, including brain tumors by crossing the Blood-Brain Barrier.

Antimetabolites

Antimetabolites are a class of drugs whose mechanism of action is via interfering with both DNA and RNA synthesis. This category contains: purine and pyrimidine antagonists, which are incorporated in the nascent DNA and RNA structure, thereby terminating further chain elongation or are able to interfere with enzymes involved in the production of nitrogenous bases; antifolates, which are responsible for the inhibition of ribo- and deoxyribonucleotide synthesis; and DNA polymerase and ribonucleotide reductase inhibitors, which can block different enzymes and to bind the DNA inducing crosslinks and chain termination. Besides these classes of antimetabolites there are also DNA Methyltransferase inhibitors and other drugs with non-specific mechanisms of action. These drugs can be administered intravenously or orally and are used for the treatment of almost all tumors, especially hematological tumors.

Mitotic inhibitors

Mitotic inhibitors are plant-derived agents able to induce cell cycle arrest by preventing the formation of microtubules. This category contains vinca alkaloids and taxanes; the former can bind the tubulin of microtubules inhibiting their assembly, while the latter prevents microtubule disassembly by binding the same component. At present, both natural and semi-synthetic drugs are available for the treatment of several solid tumors, including breast, lung, ovarian and prostate cancers as well as leukemia and lymphoma through intravenous administration.

Anti-tumor antibiotics

Cytotoxic antibiotics comprise two different classes of drugs, anthracycline and non-anthracycline agents. The route of administration of these drugs is intravenous and these are used for the treatment of both solid and hematological tumors. The main mechanism of action of anthracyclines is to form covalent bonds with nucleic acids and Topoisomerase-II (TOP2), thereby interfering with DNA replication. In contrast, non-anthracyclines exert different effects; while some agents (e.g. Dactinomycin and Mitoxantrone) directly interfere with topoisomerases, others induce DNA breaks (e.g. Bleomycin) or DNA crosslinks (e.g. Mitomycin). These activities hinder the correct replication of DNA.

Topoisomerase inhibitors

This category of drugs contains both Topoisomerase-I (TOP1) and Topoisomerase-II (TOP2) inhibitors obtained from plants. Among the first group, Irinotecan and Topotecan bind to TOP1 to prevent DNA unwinding, which in turn inhibits DNA replication. Similarly, Etoposide and Mitoxantrone prevent DNA replication by binding TOP2. In addition, the inhibition of Topoisomerases induces the formation of single-strand and double-strand breaks of DNA leading to the arrest of the cell cycle. These drugs can be administered intravenously or orally for the treatment of different solid tumors and Hodgkin's and non-Hodgkin's lymphomas.

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