Chemotherapy (chemo) is the specific systematic treatment administered in oncological practice for malignant neoplasms in order to destroy chaotically dividing abnormal cells. Chemo is a part of anticancer treatment along with radiotherapy, immunotherapy and surgery. The drugs used in chemotherapeutic protocols cannot be purchased over the counter; they can be taken with prescription only. Cancer drugs influence and actions are directed to the malignant cell reproduction, cure, control, palliation or chemoprevention.

Definition and Background of Chemotherapy Drugs

Chemotherapy is the treatment of disease by the use of chemical substances, especially the treatment of cancer by cytotoxic and other drugs. It may be used before a potentially curative surgical treatment (neoadjuvant) to reduce the size of a tumor considered difficult to resect with healthy margins. This is in contrast with adjuvant chemotherapy, which is drug treatment after surgery.

Chemotherapy may be used alone or in combination with radiation therapy (Lymphomas).

Oncologists administer neoadjuvant therapy with the objective of reducing tumor size. Reduction of tumor mass decreases the extent and invasiveness of a surgery and makes it easier for the surgeon to distinguish between normal and cancerous tissue. In tumors
Initially diagnosed as non-operable or of borderline respectability, shrinking of the cancerous lesion can enable surgery and allow for adequate clean margins. The neoadjuvant chemotherapy not only facilitates the procedure but can also improve postoperative recovery and the long-term outcome for the patient.

Neoadjuvant chemotherapy is usually given for inoperable breast, colorectal and lung cancers and it is a treatment option for many other solid tumors. It is also used in some types of advanced childhood neoplasias such as ruptured Wilms’ tumors, osteogenic sarcoma and embryonal rhabdomyosarcomas.

There is a very important disadvantage of neoadjuvant therapy: If the neoplasm is antitumor drug-resistant, then the size of the malignant mass would not shrink. Moreover, it would grow intensively and spread metastasis into surrounding tissues and organs with the blood flow and through the lymph system.

Adjuvant chemotherapy is another potentially curative treatment. It is administered to reduce cancer recurrence. This method is directed toward destroying malignant cells that may be left behind after radical surgery.

Also, there is a complex treatment conducted together with other methods of anticancer cure (chemoradiation).

Chemotherapy is frequently used as a combination of drugs is usually administered for different types of malignant neoplasms.

Antitumor drugs intake routes:

- Oral (by mouth)
- Intramuscular or subcutaneous (injection)
- Intravenous (IV)
- Intra-arterial (into the arteries)
- Intraleisonal (into the tumor)
- Intrapertoneal (into the peritoneal cavity)
- Intrathecal (into the spinal fluid)
- Topical (applied to the skin)

Side Effects of Chemotherapy Drugs

All of them trigger side effects, such as:

- Low blood count (most of the anticancer drugs oppress the growth and proliferation of all cells of the body, targeting especially rapidly reproducing cells, such as the intestinal mucosal lining and blood).
- Alopecia as an after-effect of the radiotherapy.
- Nausea, vomiting and diarrhea are frequent in patients undergoing chemotherapy.
- Anorexia.
- Skin rash, mouth sores, photosensitivity of the skin are the symptoms reflecting the grade of toxicity of the chemo.
- Infertility occurs in most of the cases for both men and women. That is why those who can afford to keep their semen or eggs in special banks until their complete recovery, are able to conceive and bear a baby later in their lives.
- Elevated liver tests take place due to the high toxicity of some chemo agents. The liver is exposed to the chemical components of the anticancer
drug, causing lysis of hepatocytes.

USMLE-relevant NOTE: Cancer drugs are immune suppressors, thus they render the body unable to react to live vaccines. Live vaccines are: MMR (Measles-Mumps-Rubella), Varicella (chickenpox), Varicella zoster (shingles).

Daily dosages of chemotherapeutic agents are calculated according to the weight and height of the patient and stage of the malignant process.

Classification of Chemotherapy Drugs

Chemotherapeutic agents can be subgrouped regarding their mechanism of action, chemical structure and similarity to other drugs:

- Antimetabolites (cell-cycle-specific agents that affect DNA synthesis)
- Plant Alkaloids
- Topoisomerase Inhibitors
- Antitumor Antibiotics
- Alkylating Agents
- Nitrosoureas
- Steroids

Antimetabolites

This group of cancer drugs is administered in order to substitute affected DNA and RNA blocks to normal building blocks of DNA and RNA, on the stage of replication of the chains.

MTX (Methotrexate, common brands: Trexall, Rasuvo)

Table: "Methotrexate." by Wikipedia:

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<tr>
<th>Pharmacokinetic data</th>
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<tbody>
<tr>
<td>Bioavailability</td>
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<td>Protein Binding</td>
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<td>Metabolism</td>
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<td>Biological half-life</td>
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<tr>
<td>Formula</td>
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<tr>
<td>Molar Mass</td>
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</table>
MTX is an “antineoplastic” or “cytotoxic” anti-cancer drug, regarded as antimetabolite, which interferes with DNA synthesis of the cells.

**MTX is prescribed for these types of malignant tumors:**

- Acute lymphoblastic leukemia
- Choriocarcinoma, chorioadenoma and gestational trophoblastic diseases
- Breast cancer
- Meningeal cancer, soft tissue sarcoma (desmoid tumors, aggressive fibromatosis)
- Bladder cancer
- Central Nervous System (CNS) lymphoma
- Gestational trophoblastic disease
- Head and neck cancer (certain types)
- Lung cancer
- Mycosis fungoides (a type of cutaneous T-cell lymphoma) advanced stages
- Advanced Non-Hodgkin lymphoma
- Osteosarcoma that has not spread
- Non-cancerous conditions such as psoriasis and rheumatoid arthritis, Crohn’s disease, dermatomyositis/polymyositis, ectopic pregnancy, systemic lupus erythematosus and Takayasu arteritis.

**Ways of administration of MTX:**

- Intravenous infusion
- Intramuscular
- Intraventricular or intrathecal infusion

**Fluorouracil (5-FU, common brands: Efudex, Carac, Fluoroplex)**

Table: “Fluorouracil.” by Wikipedia:

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<td>Bioavailability</td>
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<td>8—12 %</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Intracellular and hepatic (CYP-mediated)</td>
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</table>
Fluorouracil (5-FU) is the most often used anticancer drug (antimetabolite), which affects DNA synthesis. 5-FU may be administered together with radiotherapy; causes common side effects as any other chemotherapeutic agents.

The types of cancer where 5-FU is prescribed:

- Breast cancer
- Head and neck cancers (advanced stages)
- Anal cancer
- Stomach cancer and colon cancer
- Some non-melanoma skin cancers

Mercaptopurine (6-MP, common brands: Purinethol, Purixan)

Table: "Mercaptopurine." by Wikipedia:

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<td>Molar mass</td>
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Mercaptopurine (6-MP) is an antimetabolite ("antineoplastic" or "cytotoxic") administered for the treatment of acute lymphoblastic leukemia (ALL). 6-MP is taken in the form of tablets.

Thioguanine (6TG, common brands: Tabloid) & Cytarabine (Ara-C, common brands: DepoCyt)

6TG (Thioguanine) is an antimitabolite ("antineoplastic" or "cytotoxic") chemotherapy drug. Acute myelogenous leukemia (induction, consolidation and maintenance) is an indication for the administration of 6TG. However, in chronic myelogenous leukemia, it is not preferred. 6TG is in the pill form, prescribed according to the anthropological data of the patient.

Table: "Thioguanine." by Wikipedia:

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<td>Bioavailability</td>
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<td>Formula</td>
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<td>Molar mass</td>
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</table>
**Ara-C (Cytarabine)** is an antimetabolite ("antineoplastic" or "cytotoxic") cancer drug. This type of chemotherapeutic remedy is successfully used in different **types of leukemia**:

- Acute and chronic myelogenous leukemia (**AML** and **CML**)
- Acute lymphocytic leukemia (**ALL**)
- Lymphoma
- Meningeal leukemia and lymphoma, which affects the lining of the brain and spinal cord.

**Table**: "Cytarabine." by Wikipedia:

<table>
<thead>
<tr>
<th><strong>Pharmacokinetic data</strong></th>
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<tr>
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<td>Molar mass</td>
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**Antitumor Antibiotics**

This type of drugs is used **in order to stop replication of cancerous DNA** inside the affected cells.

**Dactinomycin** (trade name: **Cosmegen**)
Dactinomycin is an antitumor antibiotic ("antineoplastic" or "cytotoxic"). It's taken in the intravenous form with caution, as it can cause a damage to the surrounding tissue. It may be used for:

- Wilms' tumor
- Ewing's sarcoma
- Childhood Rhabdomyosarcoma
- Ovarian (germ cell) cancer
- Gestational trophoblastic neoplasm
- Metastatic testicular tumors
- Sarcomas, carcinomas and adenocarcinomas
- Soft tissue sarcoma and osteosarcoma.

Table: “Dactinomycin.” by Wikipedia:

<table>
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<th>Pharmacokinetic data</th>
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<tbody>
<tr>
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<td>Biological half-life</td>
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<td>Formula</td>
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<td>Molar mass</td>
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</table>

Doxorubicin (common brands: Doxil, Adriamycin)
**Doxorubicin** is an anthracycline antibiotic ("antineoplastic" or "cytotoxic"). This drug is vesicant that requires careful administration; it exists in intravenous form as well. Doxorubicin was originally made from the bacteria *Streptomyces peucetius*.

This cancer drug is widely used in oncology as the list of the diseases it may cure is quite extended:

- Acute lymphoblastic leukemia (ALL)
- Acute myeloblastic leukemia (AML)
- Thymomas
- Thyroid cancer
- Bone sarcoma
- Uterine sarcoma
- Soft tissue sarcoma
- Wilms’ tumor
- Waldenström macroglobulinemia
- Transitional cell bladder cancer
- Breast cancer
- Endometrial cancer
- Gastric cancer
- Head and neck cancer
- Hodgkin lymphoma
- Non-Hodgkin lymphoma
- Multiple myeloma
- Neuroblastoma
- Ovarian cancer
- Small Cell Lung cancer
- Liver cancer
- Kidney cancer

**Table:** "Doxorubicin." by Wikipedia:

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<tr>
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<td>Protein binding</td>
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<tr>
<td>Metabolism</td>
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<tr>
<td>Biological half-life</td>
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</tbody>
</table>
Bleomycin (trade name: **Blenoxane**)

**Bleomycin** is an antitumor antibiotic (“antineoplastic” or “cytotoxic”), which is taken intravenously and intrapleurally.

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**Table:** "Bleomycin." by Wikipedia:

<table>
<thead>
<tr>
<th>Pharmacokinetic data</th>
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<td>Excretion</td>
<td>Renal (60—70 %)</td>
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**Chemical and physical data**

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<tr>
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<tbody>
<tr>
<td>Formula</td>
<td>$C_{27}H_{29}NO_{11}$</td>
</tr>
<tr>
<td>Molar mass</td>
<td>543.52 g/mol</td>
</tr>
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</table>

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Ball-and-stick model of the bleomycin molecule.

**Bleomycin is indicated for the most aggressive malignant tumors:**

- Squamous cell cancers
- Melanoma
- Sarcoma
- **Testicular cancer**
- **Ovarian cancer**
- **Hodgkin’s lymphoma**
- Non-Hodgkin’s lymphoma

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<tbody>
<tr>
<td>Formula</td>
<td>$C_{55}H_{84}N_{17}O_{21}S_{3}$</td>
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<tr>
<td>Molar mass</td>
<td>1415.551 g/mol</td>
</tr>
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</table>
Plant Alkaloids

Plant alkaloids attack cancer cells during various phases of division.

- Vinca alkaloids: Vincristine, Vinblastine and Vinorelbine.
- Taxanes: Paclitaxel and Docetaxel.
- Podophyllotoxins: Etoposide and Tenisopide.
- Camptothecin analogs: Irinotecan and Topotecan.

**Vinca alkaloids**

Vinca alkaloids are obtained from the Madagascar periwinkle plant. They are naturally occurring or semi synthetic nitrogenous bases extracted from the pink periwinkle plant *Catharanthus roseus*. Vinca alkaloids were discovered in the 1950’s by Canadian scientists Robert Noble and Charles Beer.

There are four major vinca alkaloids in clinical use: Vinblastine (VBL), vinorelbine (VRL), vincristine (VCR) and vindesine (VDS), but only VCR, VBL and VRL are approved for use in the United States. From 2008, there is also a new synthetic vinca alkaloid, vinflunine that is currently approved in Europe for medicinal treatment.

The main mechanism of vinca alkaloids cytotoxicity is their interactions with tubulin and disruption of microtubule function, particularly of microtubules comprising the mitotic spindle apparatus, directly causing metaphase arrest. Vinca alkaloids and other antimicrotubule agents also have an effect on both non-malignant and malignant cells in the non-mitotic cell cycle, because microtubules are involved in many non-mitotic functions.

**VCR** has been approved to treat acute leukemia, rhabdomyosarcoma, neuroblastoma, Wilm’s tumor, Hodgkin’s disease and other lymphomas.

Another characteristic of VCR that has been reported is treating several non-malignant hematologic disorders such as refractory autoimmune thrombocytopenia, hemolytic uremic syndrome and thrombotic thrombocytopenic purpura.

VCR’s most common side-effects are: Peripheral neuropathy, suppression of bone marrow activity, constipation, nervous system toxicity, nausea and vomiting.

**VBL** has been used as an integral part of medicinal treatment regimens for testicular carcinoma and both Hodgkin and non-Hodgkin lymphomas. It is also used in breast cancer and germ cell tumors.

Side-effects of VBL consist of toxicity to white blood cells, nausea, vomiting, constipation, dyspnea, chest or tumor pain, wheezing and fever. It is also rarely associated with increased antidiuretic hormone secretion.

**VRL** has similar action and side effects as VBL.

**Taxanes**

Also a plant derivative, the principal mechanism of action of the taxane class of drugs is the disruption of microtubule function. Microtubules are essential to cell division, and taxanes stabilize GDP-bound tubulin in the microtubule, thereby inhibiting the process of cell division as depolymerization is prevented. Thus, in essence, taxanes are mitotic inhibitors. In contrast to the taxanes, the vinca alkaloids prevent mitotic spindle formation through inhibition of tubulin polymerization. Both taxanes and vinca alkaloids
are, therefore, named spindle poisons or mitosis poisons, but they act in different ways. Taxanes are also thought to be radiosensitizing.

**Paclitaxel** (Taxol) and **docetaxel** (Taxotere) are widely used as chemotherapy agents against breast cancer, particularly when unresponsive to other chemotherapeutic agents.

**Podophyllotoxins: Etoposide and Teniposide.**

Teniposide is a semisynthetic derivative of podophyllotoxin from the rhizome of the wild mandrake (*Podophyllum peltatum*).

Teniposide causes dose-dependent single- and double-stranded breaks in DNA and DNA-protein cross-links. The substance has been found to act as an inhibitor of topoisomerase II, since it does not intercalate into DNA or bind strongly to DNA. The cytotoxic effects of teniposide are related to the relative number of double-stranded DNA breaks produced in cells, which are a reflection of the stabilization of a topoisomerase II-DNA intermediate.

In the US, it is approved for the second-line therapy of acute lymphocytic leukemia (ALL) in combination with other antineoplastic drugs. In Europe, it is also approved for the treatment of Hodgkin’s lymphoma, generalized malignant lymphoma, reticulocyte sarcoma, acute leukemia, primary brain tumours (glioblastoma, ependymoma, astrocytoma), bladder cancer, neuroblastoma and other solid tumours in children.

The drug is contraindicated during pregnancy and lactation, in patients with severe liver or kidney impairment or severely impaired haematopoiesis.

Teniposide, when used with other chemotherapeutic agents for the treatment of ALL, results in severe bone marrow suppression. Other common side effects include gastrointestinal toxicity, hypersensitivity reactions, and reversible alopecia.

Also a topoisomerase II inhibitor, Etoposide is used for cancers such as Kaposi’s sarcoma, Ewing’s sarcoma, lung cancer, testicular cancer, lymphoma, nonlymphocytic leukemia, and glioblastoma multiforme. It is often given in combination with other drugs (such as bleomycin in treating testicular cancer). It is also sometimes used in a conditioning regimen prior to a bone marrow or blood stem cell transplant.

**Camptothecin analogs: Irinotecan and Topotecan.**

Both synthetic, water-soluble analogs of the natural chemical compound camptothecin (extracted from the bark of the tree *Camptotheca acuminata*). They are topoisomerase inhibitors.

**Topotecan** was approved for use in:

- Ovarian cancer (FDA May 1996).
- Cervical cancer (FDA June 2006).
- Small cell lung carcinoma (SCLC) (FDA Oct 2007).

**Experimental use**

As of 2016 experiments were under way for Neuroblastoma, Brainstem glioma, Ewing’s sarcoma and Angelman’s syndrome (16 topoisomerase inhibitors unsilence paternal UBE3A). In addition, topotecan is experimentally treating Non-small cell lung cancer, Colorectal Cancer, Breast cancer, Non-Hodgkin Lymphoma, Endometrial cancer, and Oligodendroglioma.
Side effects

- Myelosuppression, specifically neutropenia, leukopenia, anemia, and thrombocytopenia
- Diarrhea, nausea, vomiting, stomatitis, and constipation
- Increased susceptibility to infections
- Asthenia

Irinotecan

Irinotecan, sold under the brand name Camptosar among others, is a medication used to treat colon cancer and small cell lung cancer and experimentally in its liposome form to treat pancreatic cancer. For colon cancer it is used either alone or with fluorouracil. For small cell lung cancer it is used with cisplatin. It is given by slow injection into a vein.

The most significant adverse effects of irinotecan are severe diarrhea and extreme suppression of the immune system.

Topoisomerase inhibitors are often divided according to which type of enzyme it inhibits.

- Topoisomerase I inhibitors: irinotecan, topotecan, camptothecin and lamellarin D all target type IB topoisomerases,
- Topoisomerase II inhibitors: etoposide (VP-16), teniposide, doxorubicin, daunorubicin, mitoxantrone, amsacrine, ellipticines, aurantricarboxylic acid, and HU-331, a quinolone synthesized from cannabidiol.

Classical alkylating agents

The nitrogen mustards were the first alkylating agents used medically, as well as the first modern cancer chemotherapies. Goodman, Gilman, and others at Yale began studying nitrogen mustards at Yale in 1942, and, following the sometimes dramatic but highly variable responses of experimental tumors in mice to treatment, these agents were first tested in humans late that year. Use of methyl bis (B-chloroethyl)emine hydrochloride (mechlorethamine, mustine) and tris (B-chloroethy) amine hydrochloride for Hodgkin’s disease lymphosarcoma, leukemia, and other malignancies resulted in striking but temporary dissolution of tumor masses.

Alkylating agents are a class of chemotherapy drugs that bind to DNA and prevent proper DNA replication. They have chemical groups that can form permanent covalent bonds with nucleophilic substances in the DNA. Alkylating agents are used as part of chemotherapy in different types of cancers.

Many of the agents are known as “Classical alkylating agents”. These include true alkyl groups, and have been known for a longer time than some of the other alkylating agents. Examples include melphalan and chlorambucil.

The following three groups are almost always considered “classical”.

- Nitrogen mustards
  - Cyclophosphamide
  - Mechlorethamine or mustine (HN2) (trade name Mustargen)
  - Uramustine or uracil mustard
  - Melphalan
  - Chlorambucil
  - Ifosfamide
Here are some specifics about nitrogen mustards, nitrosoureas and alkylsulfonates:

**Cyclophosphamide** requires activation by the CYP450 system in the liver. The most active metabolite is 4-hydroxycyclophosphamide. It treats lymphoma, multiple myeloma, leukemia, ovarian cancer, breast cancer, small cell lung cancer, neuroblastoma, and sarcoma. As an immune suppressor it is used in nephrotic syndrome and following organ transplant.

Common side effects include low white blood cell counts, loss of appetite, vomiting, hair loss, and bleeding from the bladder. Other severe side effects include an increased future risk of cancer, infertility, allergic reactions, and pulmonary fibrosis.

**Melphalan**

Melphalan chemically alters through alkylation of the DNA nucleotide guanine, and causes linkages between strands of DNA. This chemical alteration inhibits DNA synthesis and RNA synthesis, functions necessary for cells to survive. These changes cause cytotoxicity in both dividing and non-dividing tumor cells.

It is used to treat multiple myeloma, ovarian cancer and Amyloid light-chain amyloidosis.

**Chlorambucil**

Chlorambucil, sold under the brand name Leukeran among others, is a chemotherapy medication used to treat chronic lymphocytic leukemia (CLL), Hodgkin lymphoma, and non-Hodgkin lymphoma. For CLL it is a preferred treatment. It is given by mouth.

Common side effects include bone marrow suppression. Other serious side effects include an increased long term risk of further cancer, infertility, and allergic reactions. Use during pregnancy often results in harm to the baby.

**Carmustine** (bis-chloroethylnitrosourea, BCNU, BiCNU) is a medication used mainly for chemotherapy and sometimes for immunosuppression before organ transplantation. It is a nitrogen mustard β-chloro-nitrosourea compound used as an alkylating agent. As a dialkylating agent, BCNU is able to form interstrand crosslinks in DNA, which prevents DNA replication and DNA transcription.

It is used in the treatment of several types of brain cancer (including glioma, glioblastoma multiforme, medulloblastoma and astrocytoma), multiple myeloma and lymphoma (Hodgkin’s and non-Hodgkin).

**Busulfan** is an dialkylsulfonate. Dialkylating agents can react with two different 7-N-guanine residues, and, if these are in different strands of DNA, the result is cross-linkage of the DNA strands, which prevents uncoiling of the DNA double helix. If the two guanine residues are in the same strand, the result is called limpet attachment of the drug molecule to the DNA. DNA crosslinking prevents DNA replication. Because the intrastrand DNA crosslinks cannot be repaired by cellular machinery, the cell undergoes apoptosis.

**Alkylating-like agents**
Platinum-based chemotherapeutic drugs (termed platinum analogues) act in a similar manner. These agents do not have an alkyl group, but nevertheless damage DNA. They permanently coordinate to DNA to interfere with DNA repair, so they are sometimes described as “alkylating-like”.

- **Platinum**
  - Cisplatin
  - Carboplatin
  - Nedaplatin
  - Oxaliplatin
  - Satraplatin
  - Triplatin tetranitrate

These agents also bind at N7 of guanine.

**Cisplatin**

Cisplatin is administered intravenously as short-term infusion in normal saline for treatment of solid malignancies. It is used to treat various types of cancers, including sarcomas, small cell lung cancer, squamous cell carcinoma of the head and neck and ovarian cancer, lymphomas, bladder cancer, cervical cancer, and germ cell tumors.

Cisplatin is particularly effective against testicular cancer; the cure rate was improved from 10% to 85%.

In addition, cisplatin is used in Auger therapy, a form of in-situ radiation therapy for which the heavy Platinum molecule is the enhancer.

Cisplatin can cause hypomagnesemia, hypokalemia and hypocalcaemia. It is neurotoxic, nephrotoxic and ototoxic.

**Nonclassical**

Certain alkylating agents are sometimes described as “nonclassical”. There is not a perfect consensus on which items are included in this category, but, in general, they include:

- procarbazine
- altretamine
- Some sources explicitly exclude the triazenes (dacarbazine, mitozolomide, temozolomide) from the nonclassical category. However, other sources list dacarbazine as nonclassical and some include temozolomide.
- The platinum agents are also sometimes described as nonclassical.

**Procarbazine**

When used to treat Hodgkin’s lymphoma, it is often delivered as part of the BEACOPP regimen that includes bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine (tradename Oncovin), prednisone, and procarbazine. The first combination chemotherapy developed for Hodgkin’s lymphoma (HL), MOPP also included procarbazine (ABVD has supplanted MOPP as standard first line treatment for HL, with BEACOPP as an alternative for advanced/unfavorable HL). Alternatively, when used to treat certain brain tumors (malignant gliomas), it is often dosed as PCV when combined with lomustine (often called CCNU) and vincristine.

Dose should be adjusted for kidney disease or liver disease.
**Steroids**

Common types of *steroids* used in *cancer treatment* are: hydrocortisone, dexamethasone, methylprednisolone and prednisolone. *Steroids* can be used:

- To treat the cancer itself, often alongside chemotherapy treatment
- To reduce inflammation
- To reduce the immune response, for example, after a bone marrow transplant or stem cell transplant
- To help relieve sickness when having chemotherapy
- To boost appetite

**Review Questions**

The correct answers can be found below the references.

1. **What type of leukemia is Mercaptopurine (6-MP) usually administered for?**
   
   A. Acute lymphoblastic leukemia (ALL)  
   B. Chronic lymphoblastic leukemia (CLL)  
   C. Acute myeloblastic leukemia (AML)  
   D. Chronic myeloblastic leukemia  
   E. None of above

2. **What group of chemotherapeutic agents does MTX (Methotrexate) belong to?**
   
   A. Antitumor antibiotics  
   B. Antimetabolites  
   C. Plant Alkaloids  
   D. Steroids  
   E. Topoisomerase Inhibitors

3. **Which antitumor antibiotic is frequently used in the most aggressive cancers?**
   
   A. Bleomycin  
   B. Doxorubicin  
   C. Dactinomycin  
   D. Idarubicin  
   E. None of above

**References**

- [Chemotherapy Drugs: How They Work](https://cancer.org) via American Cancer Society and cancer.org
- [A to Z List of Cancer Drugs](https://cancer.gov) via National Cancer Institute and cancer.gov
- [Chemotherapy in Cancer Treatment](https://inpractice.com) by Nancy Jo Bush, RN, MN, MA, AOCN®, FAAN via Oncology Nursing Society and inpractice.com
Methotrexate via chemocare.com

Fluorouracil via cancerresearchuk.com

Mercaptopurine via chemocare.com

Correct answers: 1A; 2B; 3A

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