

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

Anticancer drugs (part 3)
By
Dr. Mohammad Salem Hareedy
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Miscellaneous anticancer drugs

1-Hydroxyurea: it **inhibits** the enzyme **ribonucleotide diphosphate reductase**, a rate limiting step in DNA synthesis. It is used for **treatment of myeloproliferative disease**. Hydroxyurea treats **sickle cell anemia**. Hydroxyurea is used in **chronic myelogenous leukemia** & in **mouth cancers**.

2-Protein tyrosine kinase inhibitors e.g., imatinib

It targets a **protein kinase** called BCR-ABL tyrosine kinase (in Philadelphia chromosome) which is implicated in **chronic myeloid leukemia**.

3-Epithelial growth factor receptor (EGFR) inhibitors e.g., gefitinib

EGFR is essential for the growth and differentiation of epithelial cells. In epithelial cancers, overexpression or mutational activations of the EGFR is a common finding and may create a dependence on EGFR signaling in these tumors. It is used in **non-small cell lung cancer and colon cancer**.

4- All trans retinoic acid (tretinoin)

- It is **closely related to vitamin A**. It is a differentiation inducer used for treating **acute myelogenous** & acute promyelocytic leukemias.
- Tretinoin binds to and activates certain protein receptors in cells, including cancer cells. This may slow the growth of cancer cells and change how these cells look and act.
- Adverse effect: **Retinoic acid syndrome**

Retinoic acid syndrome (also referred to as **differentiation syndrome**) is a potentially **life-threatening complication** in children treated for acute promyelocytic leukemia (APL) with all-trans retinoic acid.

The release of inflammatory cytokines causes the syndrome.

Retinoic acid syndrome typically occurs around 7 days after beginning treatment and is characterized by **respiratory distress, fever, pulmonary infiltrates, and weight gain**. **Pericardial effusion, hypotension, cardiac failure, and renal failure** can also occur.

5-Immunomodulators e.g. Thalidomide used in **multiple myeloma**.

6-Biological response modifiers e.g., interferon-alfa & interleukin-2

They enhance the immunological response to neoplastic cells or directly bind to receptors on tumor cells (cytotoxicity)

They were used in renal cell carcinoma and melanoma.

Interferon alpha is used in

- 1. AIDS-related Kaposi's Sarcoma**
- 2. Follicular lymphoma**
- 3. Hairy cell leukemia**
- 4. Chronic myelogenous leukemia**
- 5. Cervical intraepithelial neoplasms**
- 6. Condyloma acuminata (genital wart)**

Targeted anticancer drugs (monoclonal Abs)

Target	Drug (monoclonal Abs)	Therapeutic use
CD20	Rituximab , Obinutuzumab, Ofatumumab	Non-Hodgkin lymphoma CLL
HER2	Trastuzumab , Pertuzumab,	Breast cancer, gastric cancer
PD-1/PD-L1	Pembrolizumab, Nivolumab, Atezolizumab	Melanoma , NSCLC, various solid tumors
VEGF/VEGFR	Bevacizumab , Ramucirumab	Colorectal cancer , NSCLC, glioblastoma
EGFR	Cetuximab , Panitumumab, Amivantamab	Colorectal cancer , NSCLC
CD30	Brentuximab vedotin	Hodgkin lymphoma, ALCL
CD38	Daratumumab, Isatuximab	Multiple myeloma
CTLA-4	Ipilimumab	Melanoma
TROP2	Sacituzumab govitecan	Triple-negative breast cancer (TNBC)
CD19/CD3	Blinatumomab	Acute lymphoblastic leukemia (ALL)

Specific toxicities of anticancer drugs

Toxicity	Drug(s)
Renal	Cisplatin*, methotrexate
Pulmonary	Bleomycin*, busulfan, procarbazine
Cardiac	Doxorubicin, daunorubicin
Neurologic	Vincristine*, cisplatin
Immunosuppressive	Cyclophosphamide, methotrexate
Other	Cyclophosphamide (hemorrhagic cystitis); procarbazine (leukemia); asparaginase* (pancreatitis)

*Less BMS: “marrow sparing”

Specific toxicities of anticancer drugs

- ❑ **Hemorrhagic cystitis** induced by **cyclophosphamide**.
- ❑ Excess fluid intake and use of **acetylcysteine** or neutralizing agents like mercaptoethanesulfonate (**mesna**) reduce this toxicity.

- ❑ **Neuropathy** due to **vinca alkaloids** (**vincristine & vinblastine**), **taxanes** (like **paclitaxel**) and **thalidomide** (used to treat myeloma). It may be mild not to lead to **discontinue therapy** except if severe leading to motor impairment or severe paresthesias.

- ❑ **Bleomycin toxicity: Edema** of the interphalangeal joints, hardening of the palmar and plantar skin. The more serious are **anaphylactic, or serum-sickness like reaction**, and **fatal pulmonary fibrotic** reactions.

- ❑ **L-asparagenase** induced **pancreatitis**

- ❑ **Procarbazine** is associated with a risk of **causing secondary, therapy-related acute myeloid leukemia** or other cancers, often linked to high doses or prolonged use

Summary anticancer drugs

Drug	Mechanism	Uses	Side Effects
Cyclophosphamide	Alkylating agent—attacks guanine N7—dysfunctional DNA	Non-Hodgkin, ovarian, breast cancer, neuroblastoma	BMS, hemorrhagic cystitis (mesna , traps acrolein and is protective)
Cisplatin	Alkylating agent—cross-links DNA strands	Testicular, ovarian, bladder, lung cancer	Nephrotoxicity (use amifostine); neurotoxicity (deafness)
Procarbazine	Alkylating agent	Hodgkin	BMS, leukemogenic
Doxorubicin	Intercalator, forms free radicals, inhibits topoisomerase	Hodgkin, breast, endometrial, lung, and ovarian cancers	BMS—delayed CHF (dexrazoxane is an iron-chelating agent preventing the formation of free radicals; it is not a free radical “trapper”)

Definition of abbreviations: BMS, bone marrow suppression; CCS, cell-cycle specific
 CHF= congestive heart failure

Drug	Mechanism	Uses	Side Effects
Methotrexate (CCS)	Antimetabolite—inhibits DHF reductase (S phase)	Leukemias, lymphomas, breast cancer; rheumatoid arthritis, psoriasis	BMS, leucovorin (folinic acid) rescue
5-Fluorouracil (CCS) Capecitabine (oral)	Pyrimidine antimetabolite (S phase) bioactivated to inhibit thymidylate synthetase	Breast, ovarian, head, and neck cancer—topical for basal cell cancer and keratoses; colorectal cancer	BMS
6-Mercaptopurine (CCS)	Purine antimetabolite (S phase) bioactivated by HGPRT transferase	Acute lymphocytic leukemia; immunosuppression	BMS
Bleomycin (CCS)	Complexes with Fe and O ₂ → DNA strand scission (G ₂ phase)	Hodgkin, testicular, head, neck, skin cancer	Pneumonitis, pulmonary fibrosis
Vinblastine (CCS) Vincristine	↓ Microtubular polymerization—spindle poisons (M phase)	Vinblastine—Hodgkin, testicular cancer, Kaposi Vincristine—Hodgkin, leukemias, Wilms	BMS Neurotoxicity
All-trans retinoic acid (ATRA)	Differentiating agent, promotes differentiation of promyelocytes	Acute myelogenous leukemia (AML), M3	“Differentiation syndrome” with respiratory distress, pleural and pericardial effusions, CNS symptoms

Definition of abbreviations: BMS, bone marrow suppression; CCS, cell-cycle specific

Acute promyelocytic leukemia (APL) = M3

Thank
You