Treatment options in oncology

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Anti-cancer treatment modalities

- ✔ Surgery
- ✔ Radiation therapy
- ✔ Drug therapy-anti-cancer drugs:
  - cytotoxic drugs
  - hormone therapy
  - cytokines,
  - targeted therapy: monoclonal antibodies & "small molecules"

- ✔ Drug that protect against side effects of chemotherapy

Goals of cancer chemotherapy

- Palliative
  - Increased survival
  - Symptom relief/Improved quality of life
- Curative
- Adjuvant/Neoadjuvant (induction chemotherapy)
  - Disease free survival (DFS) as end point in adjuvant chemotherapy

Adjuvant/neoadjuvant chemotherapy with proven efficacy

Adjuvant:

-Breast cancer

-Colon cancer (Dukes` C2; i.e. positive regional lymph nodes)

Neoadjuvant:

-Osteogenic sarcoma

- Gastric Adenocarcinoma

Groups of cytotoxic drugs and mechanism of action

Major Groups of Cytotoxic Drugs

- ✔ Alkylating Agents & Platinum Analogs
- ✔ Antimetabolites
- ✔ Topoisomerase (I,II) interactive agents
- ✔ Antimicrotubule Agents

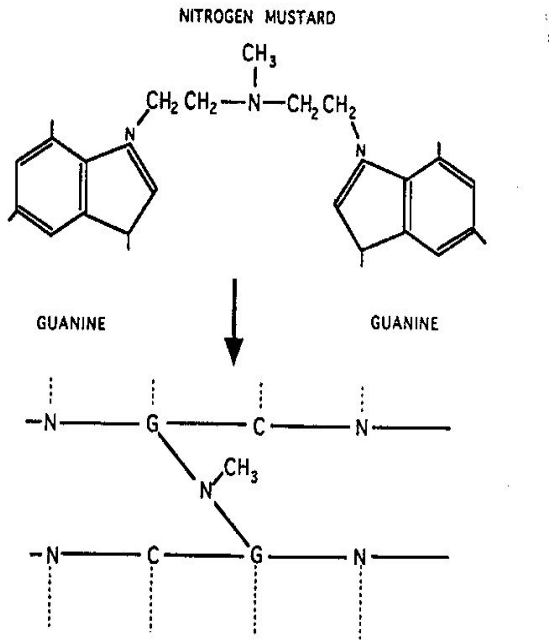
Alkylating agents

- The parent drug (prodrug) is activated to form an “active drug”, which has an alkylating group.
- The “active drug”, which is positively charged, binds covalentely to various macromolecules at nucleophylic sites.
- The biological effect results mainly from alkylation of DNA bases (particularly the electron-rich N-7 position of guanine) and formation of DNA adducts.

Alkylating **agents**

DNA alkylation produces a variety of defects - double-and single-stranded breaks

Bifunctional alkylating agent form interstrand DNA crosslinking, which disrupt DNA replication and transcription.



FORMATION OF AN INTERSTRAND DNA CROSSLINK

Commonly used alkylating agents

- ✔ Cyclophopsphamide (cytoxan)
- ✔ Ifosfamide

The prodrug is activated by CYT-P-450 dependent metabolism in the liver.

- ✔ Chlorambucil (leukeran)

Side Effects of Cyclophosphamide

- **Nausea and vomiting are dose-related:**
- **> 90% for >1500 mg/m2,**
- **60-90% for 750-1500 mg/m2,**
- **30-60% for < 750 mg/m2 or oral;**

- **Myelosuppression**

- **Hemorrhagic cystitis (up to 40%) with high-dose and/or long term therapy - severe, potentially fatal**

- Alopecia (40-60%);

Side Effects of Ifosfamide

- Leukopenia
- **Nausea and/or vomiting**
- Alopecia
- **Hemorrhagic cystitis (1-10%)**
- **Encephalopathy (10-50%)**

Platinum analogs

- Cisplatin -

  Curative in testicular cancer and very active in ginecologic, GI, GU, Head and neck, lung cancers

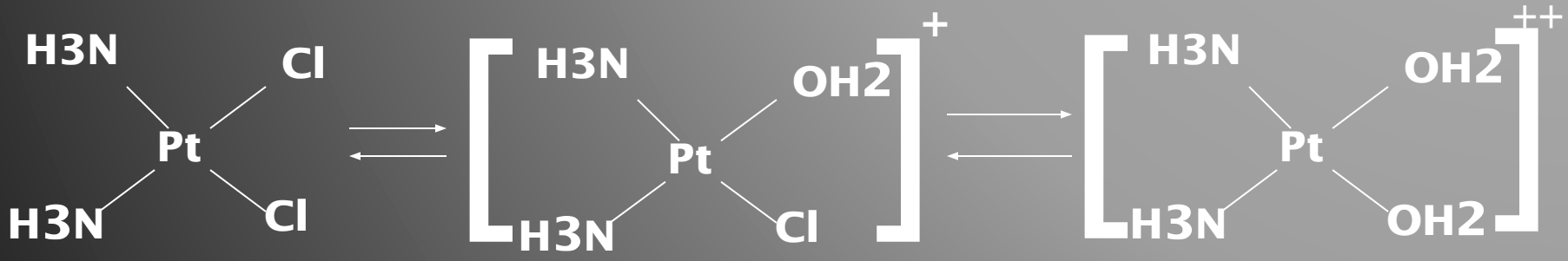
- Carboplatin

  Ovarian, lung cancer

  the difference between the cisplatin and carboplatin molecules is in the leaving groups

- Oxaliplatin
- Colorectal cancer

Activation of Cisplatin in Aqueous Soloution

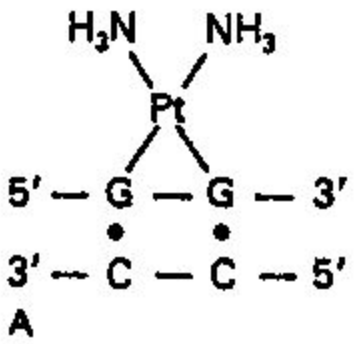


Cisplatin (dichloro)

Chloro-Aquo

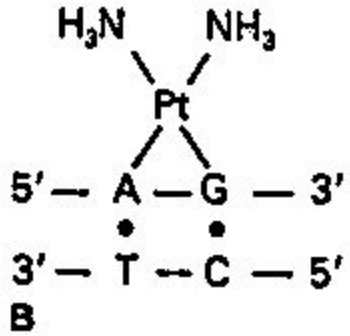
Diaquo

d(GpG) Adduct



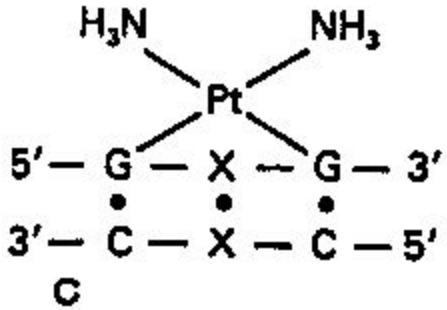
A

d(ApG) Adduct



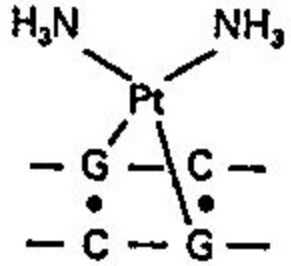
B

d(GpXpG) Adduct



C

Interstrand Crosslink



D

- This platinum-DNA adduct is repaired by the nucleotide excision repair (NER) pathway

Side Effects of CDDP

- ototoxicity (31%)
- myelosuppression
- nausea and vomiting (> 90%)
- neurotoxicity, usually peripheral neuropathies
- nephrotoxicity (28-36%)

Side Effects

- Carboplatin
- Myelosuppression
- Nausea and vomiting

- Oxaliplatin
- neuropathy, sensory
- Myelosuppression

Antimetabolites

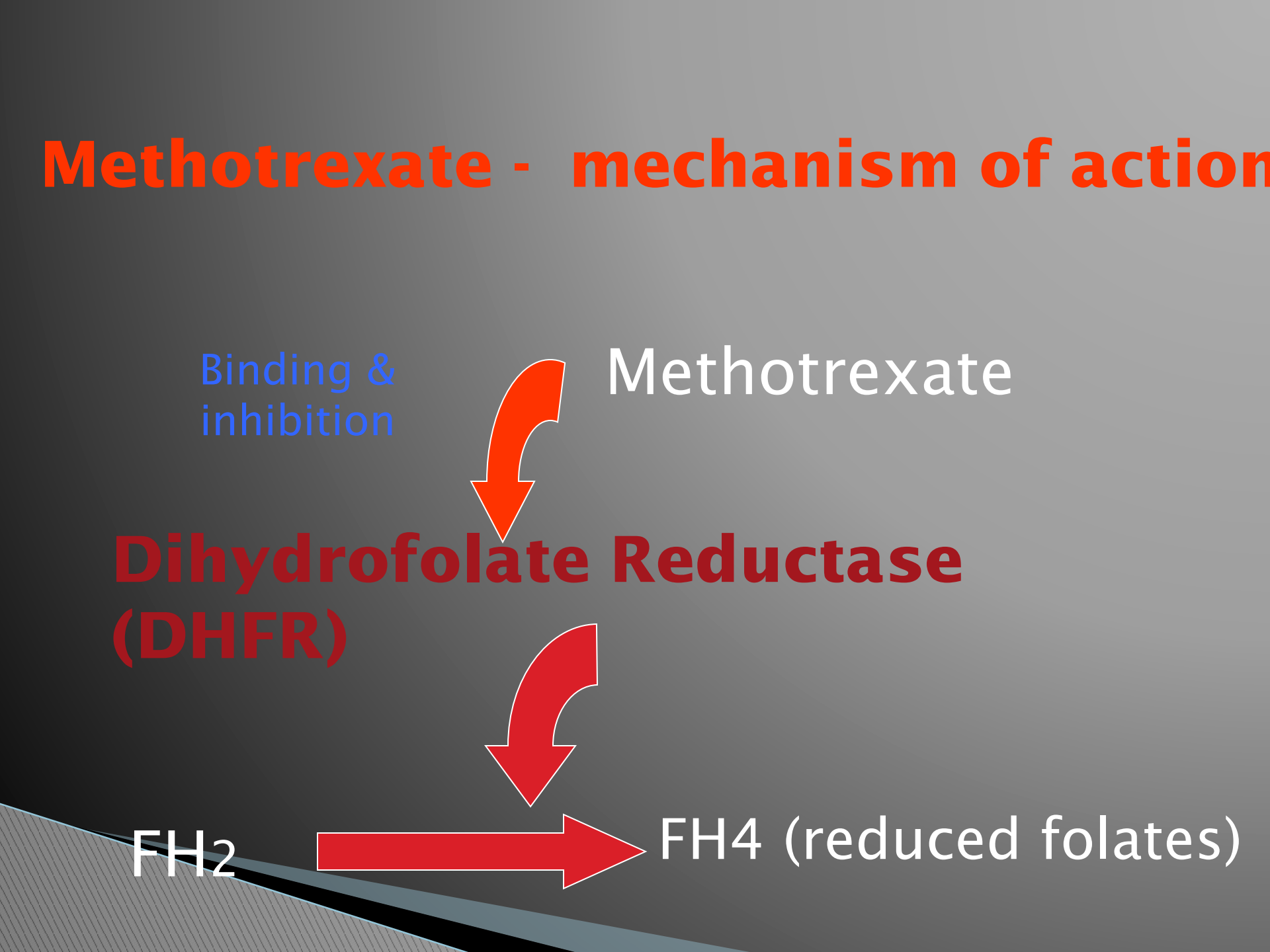
- Antimetabolites are antineoplastic agents that are **structurally and chemically similar to naturally occurring compounds**, required for synthesis of purines, pyrimidines, and nucleic acids.

- These drugs interfere with DNA synthesis by **competitive inhibition of a key enzyme** in the purine or pyrimidine synthesis pathway or by **incorporation** into the DNA or RNA molecules.

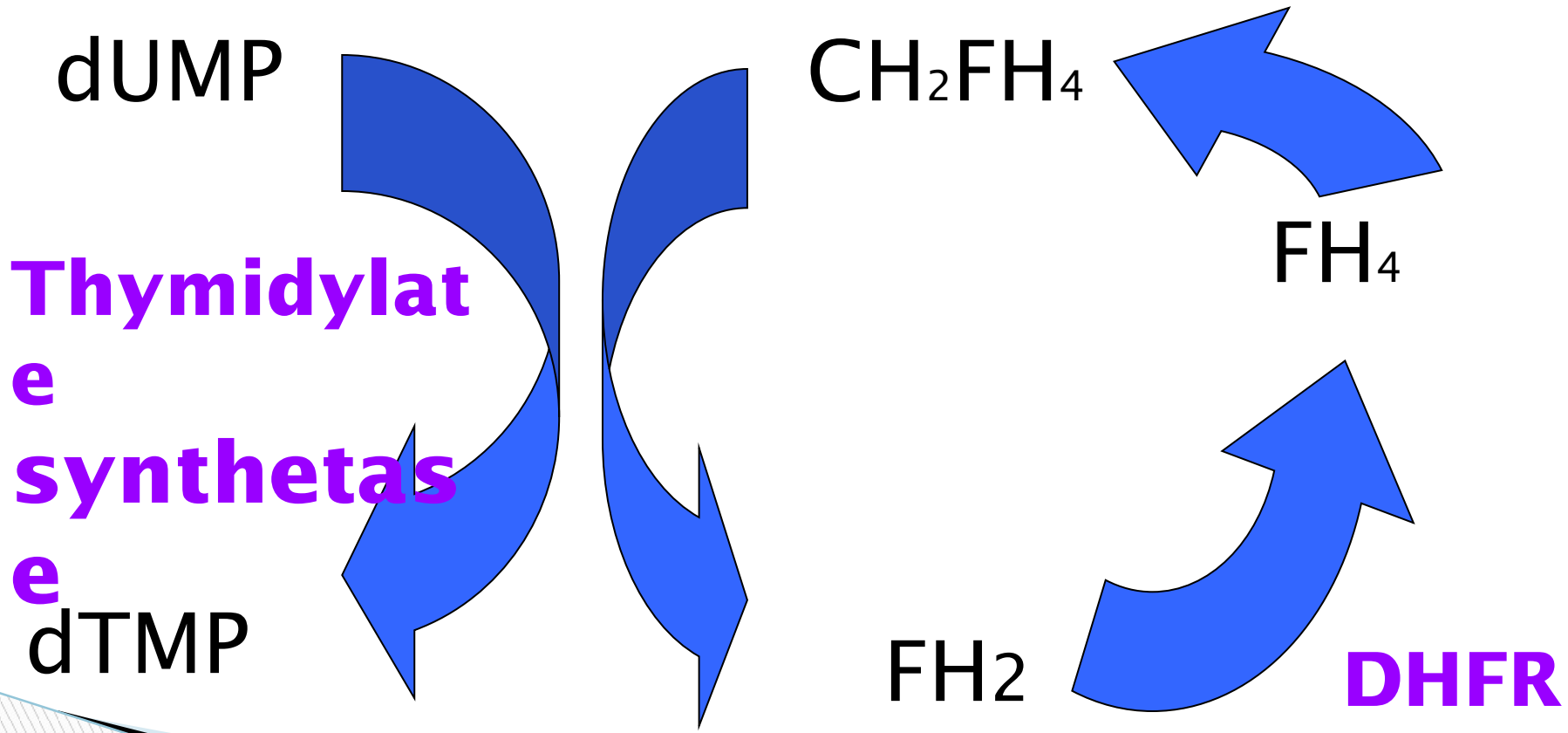
Antimetabolites & analogs

- ✔ Methotrexate…….. Folic acid
- ✔ 5-Fluorouracil…… Uracil
- ✔ Cytosine arabinose…… Deoxycytosine
- ✔ Gemcitabine…….. Deoxycytosine
- ✔ Pemetrexed …… Pyrrolopyrimidine
- ✔ 6-Mercaptopurine…… Hypoxantine
- ✔ 6-Thioguanine…… Guanine

Methotrexate - mechanism of action



Reduced Folates and Thymidylate synthetase (TS)



5 Fluorouracil (5FU)

5FU undergoes **intracellular activation** to the following active nucleotides:

- **-fluorodeoxyuridine monophosphate (**FdUMP):

  This nucleotide inhibits **Thymidylate synthetase (TS)** and, therefore, inhibits DNA synthesis (competitive inhibition of a key enzyme).

- **-5-fluorouridine triphosphate (**FUTP):

  This nucleotide undergoes incorporation into RNA and, therefore, causes RNA damage.

Cell cycle specific and non cell cycle specific drugs

- Alkylating agents and platinum analogs are non cell cycle specific
- Antimetabolites are S-phase specific.

Tubulin Binding Agents

Vinca Alkaloids:

- ✔ Vincristine (Oncovin)
- ✔ Vinblastine
- ✔ Vinorelbine (Navelbine)

Taxanes:

- ✔ Paclitaxel (Taxol)
- ✔ Docetaxel (Taxotere)

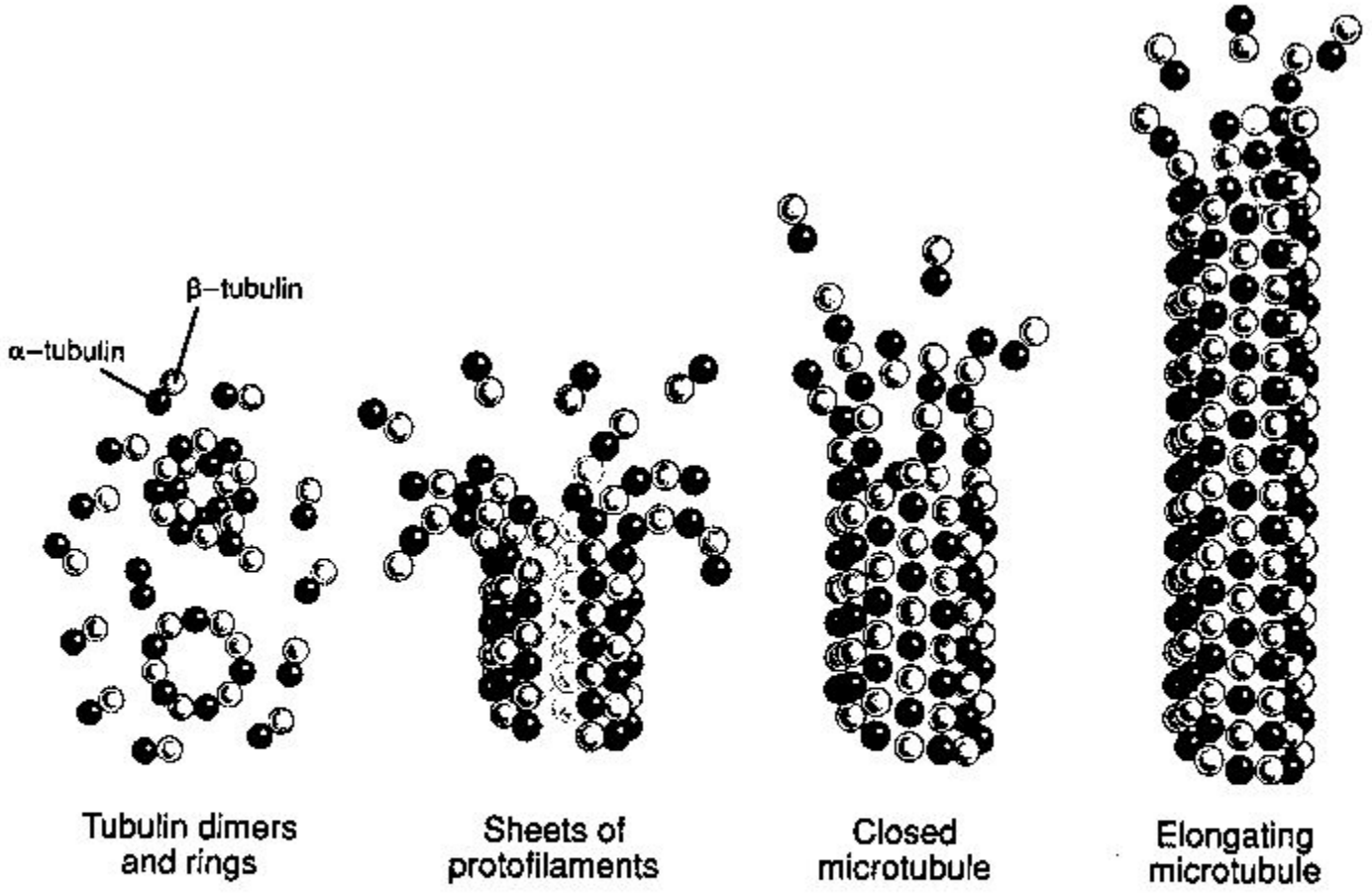


FIGURE 3.

Proposed pathway of microtubule polymerization in vitro. Prior to polymerization, tubulin exists as oligomeric rings and free dimers. Polymerization starts with opening of the rings and joining of protofilaments laterally and at the ends. The cylindrical microtubule structure forms when 13 protofilaments join side-by-side. After formation, a steady state is reached, at which new dimers are added to one end and dimers are removed at the other end. [Adapted from Schiff and Horwitz.[4]]

Vinca Alkaloids

Mechanism of action:

binding to specific site on tubulin with **prevention of polymerization**, inhibition of microtubule assembly and mitotic spindle formation (leading to metaphase arrest)

Mechanism of action of taxanes

- Bind to polymerized tubulin (beta subunit of microtubules)
- Binding is reversible and stabilize the microtubules against depolymerization (induce tubular polymerization), thereby disrupting normal microtubule dynamics (halts mitosis) and lead to arrest at G2/M phase.

Hormone therapy

Hormone therapy in breast cancer: antiestrogens and aromatase inhibitors

- 2/3 of all post-menopausal breast cancers are hormone-sensitive, expressing estrogen- and/or progesterone-receptors (ER/PgR)
- Estrogens can stimulate cancer growth through binding to specific nuclear estrogen receptors (ER)
- Cancer regression can be achieved by
  - Blocking estrogen receptors with an **antiestrogen such as tamoxifen,faslodex**
  - Effectively suppressing estrogen synthesis with **aromatase inhibitors** such as letrozole (femara) or anastrazole (arimidex) –through blocking conversion of androstenedione to estrone .

Non steroidal=Type II=reversible:

- Anastrazole (Arimidex)
- Letrozole (Femara)

Steroidal=Type I=irreversible:

- Exemestane (Aromasin)

Target therapy

Rituximab (Mabthera)

- Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen.

- Active as single agent in CD-20 positive NHL and synergistic with chemotherapy in NHL.

Tyrosine kinase inhibitors

TKI

- **The HER2 protein is a transmembrane thyrosine kinase** that is a member of the epidermal growth factor.
- HER2 is a growth factor receptor.
- HER2 is overexpressed in 20-30% of human breast cancers (in the majority, HER2 overexpression is caused by amplification of the HER2 gene).
- Overexpression of HER 2 is associated with worse prognosis in breast cancer.

Trastuzumab (Herceptin)

- A recombinant humanized monoclonal antibody that binds with the extracellular domain of the HER2 cell-surface receptor, thereby inhibiting the growth of breast tumor cells that overexpress HER2.

- It is active in breast cancer only in HER 2 positive pts, especially in combination with chemotherapy, both in metastatic disease and as adjuvant therapy in HER 2 positive tumors.

Epidermal growth factor receptor (EGFR) as a target

EGFR

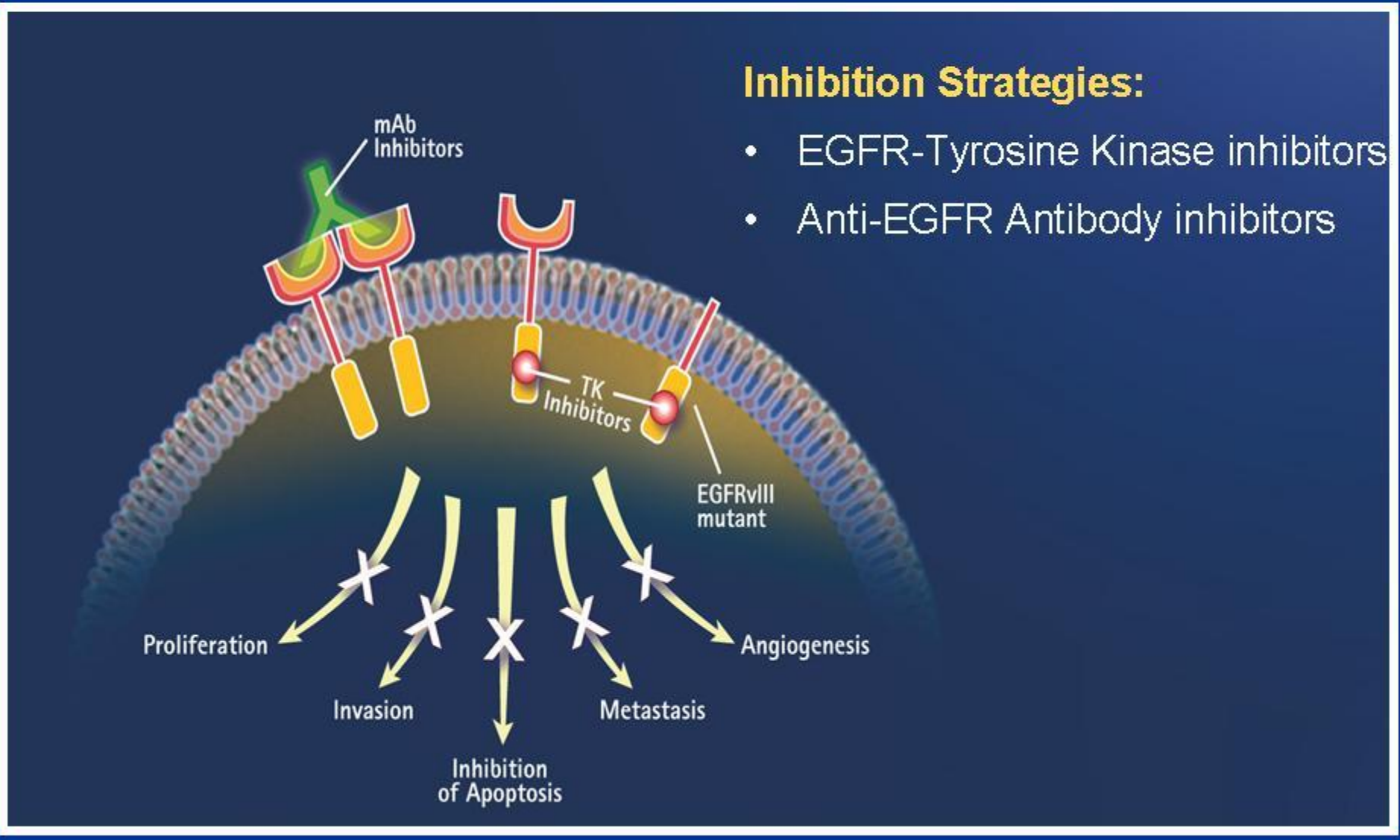
- EGFR is a 170-kd transmembrane receptor. **It has a tyrosine kinase activity.**
- It has an extracellular ligand-binding domain, a transmembrane segment and intracellular component.
- When EGF (i.e. the ligand) binds to the extracellular domain, receptors dimers are formed with activation of the extracellular tyrosine kinase domain.
- This results in autophosphorylation of downsream molecules with activation of multiple cellular functions including prpliferation and survival.
- EGFR is often overexpressed (and is often mutated) in human tumors, thus there is a good rationale for trying to inhibit the EGFR.

EGFR inhibitors

- Monoclonal antibodies: bind to the extracellular domain of the receptor.
  Example: Cetuximab (Erbitux),Panitumumab (vectibix).

- Small molecules: bind to the intracellular domain of the receptor.
  example: Erlotinib (Tarceva).

The EGFR Axis



Inhibitors of angiogenesis

Avastin (Bevacizumab)

- VEGF (vascular endothelial growth factor) , a diffusible glycoprotein produced by normal and neoplastic cells ,has been shown to have central role in the control of angiogenesis and to be essential for the development of tumor vasculature. VEGF (=ligand) binds to VEGF receptor.

- Bevacizumab (Avastin) is a humanized anti- (VEGF) monoclonal antibody. It prevents VEGF to bond to its receptor, and therefore, has an antiangiogenic effect.

- Sunitinib (Sutent) –bind to intracellular domain VEGFR

Вопросы:

- К наиболее распространенным побочным действиям циклофосфамида относятся все, кроме:

- 1. миелосупрессия
- 2. геморрагический цистит
- 3. кардиальная токсичность
- 4. энцефалопатия

- Химиотерапевтическое лечение в онкологии применяется как:

- 1.паллиация (симптоматическое лечение)
- 2. куративное лечение (излечение)
- 3. предоперационное лечение
- 4. все верно

- Основной препарат, используемый в лечении рака яичек (Testicular Cancer):

- 1. Паклитаксел (Таксол)
- 2. Метотрексат
- 3. Цисплатин
- 4. Флюроурацил (5FU)

- К ингибиторам ароматазы относятся все перечисленные препараты, кроме:

- 1.Тамоксифен
- 2.Летрозол
- 3.Фазлодекс
- 4.1,3
- 5.Экзаместен

- Трастузумаб (Герцептин) это:

- 1. анти HER-2 антитело
- 2. антиметаболит
- 3. блокатор тирозинкиназы
- 4. анти VEGF антитело