Anticancer drugs

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Anticancer drugs

- cancer
  - malignant neoplasm, malignant tumor
  - uncontrolled proliferation
    - escaped from the mechanism normally regulating the cell growth
  - dedifferentiation and loss of function
  - benignant or malignant features
    - invasiveness
    - metastasis
  - genesis of cancer
    - procarcinogen factors
    - transformation of proto-oncogenes→oncogenes
    - inactivation of tumor-suppressor genes

- anti cancer therapy
  - difficult task
  - selective toxicity?
    - structural, functional features of human cells (unlike bacterias)
    - m.o.a:
      - damage DNA or DNA synthesis→inducing apoptosis

General purposes of anticancer therapy

- kill/remove malignant cells
  - cytotoxic drugs
    - chemotherapeutic agents
    - targeted cytotoxic agents (AB linked to toxins or radioactive agents)
  - surgery
  - irradiation

Anticancer drugs

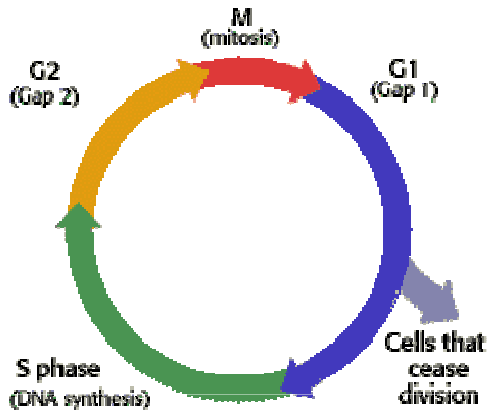
- Resistance to anticancer drugs
  - temporary resistance
    - pharmakokinetic resistance
      - isolated organs, (CNS)
      - no penetration of anticancer drugs
    - cell kinetic resistance
      - cell cycle (phase)
  - permanent resistance
    - primary
      - solid tumors' „ab ovo" resistance
    - secundaer (acquired)
      - decreased influx of anticancer drugs
        - doxorubicine, vinblastin
      - altered metabolizing pathways
        - antimetabolites
      - increased protecting factors (gluthatione)
      - receptor down regulation
      - rapid repair of drug induced lesions
        - alkylating agents

Drugs used in cancer chemotherapy

- Cytotoxic drugs
  - alkylating agents
    - form covalent bonds with DNA and impede replication
  - antimetabolites
    - block metabolic pathways in DNA synthesis
  - cytotoxic antibiotics
    - substances of microbal origin, that intercalate into the cell DNA
  - plant derivatives
    - affect microtubule function
- Hormones
    - drugs, that suppress hormone secretion or antagonise hormone action
- Miscellaneous agents
- Supportive therapy

Drug action based on cell cycle

- Phase specific agents
  - M phase
    - vinca alkaloids
  - S phase
    - cytarabine, methotrexate, 5-FU



- Cycle specific agents
  - acting all stages of the cycle
    - alkylating agents, dactinomycin, cisplatin

- Cycle non-specific agents
    - bleomycin, nitros-ureas

Anticancer drugs

- Adverse effects
  - bone marrow toxicity – myelosuppression!
  - impaired wound healing
  - loss of hair (alopecia)
  - damage to GIT epithelium
  - depression of growth (children)
  - sterility/infertility
  - teratogenicity

Alkylating agents

- mechanism of action:
  - form covalent bonds with DNA (nucleofilic subst.)
    - carbonium ion (C atom with 6e^-) – highly reactive
    - e^- donors –DNA - (amine-, hydroxyl-, sulfhydril group)
  - bifunctional
    - two alkylating groups
  - action
    - interchain cross linking – defective replication!
    - intrastrand linking, chain breakage/termination
  - mainly in S phase, G_2 phase (triggering apoptosis)
- unwanted effects:
  - myelosuppression
  - infertility (men)
  - incr. risk of non-lymphocytic leukaemia

Alkylating agents

- Nitrogen mustards
  - originated from „mustard gas” (Ist WW)
  - bis-chlorethyl-amine derivatives
    - intramolecular cyclisation→ethylene immonium→ reactive carbonium ion!!!→REACTIVITY!

Cl- dissociation

  - cyclophosphamide
    - inactive→metabolized in the liver→active! (aldophosphamide)
    - non enzymatic transformation
      - acrolein – haemorrhagic cystitis
        - increase fluid intake!!!
        - sulfhydril donors (mesna, N-ACC)
      - phosphoramide mustard – cytotoxic effect
    - appl.: iv., im., p.o.
    - pronounced effect on lympocytes (immunsuppressant)
      - lymphomes, leukaemia
    - a.e.:
      - nausea, vomiting
      - bone marrow depression
  - estramustine
    - combination of chlormethine and oestrogen
    - cytotoxic and hormonal action
    - appl.: prostata cancer
  - chlorambucil

Alkylating agents

- Nitrosureas
  - lomustine, carmustine
    - lipid soluble
    - cross the blood-brain barrier
    - appl.: tumors in CNS (brain, meninges)
    - adv. eff.:
      - bone marrow depression (3-6 weeks)
      - acustic damage
      - alopecia
- Busulfan
  - selective effect on bone marrow (granulocytes, platelets, red cells)
  - no effect on lymphoid tissue, GIT
  - applied in CGL

Alkylating agents

- Platinum compounds
  - cisplatin
    - water soluble
    - planar coordination of central Pl surrounded by Cl^- and NH_2 → reactive complex (Cl^- dissociates)
    - cross linking between N7 - O6 guanine
    - appl.: solid tumors
      - testis, ovary
    - slow intravenous injection, infusion
    - a.e.:
      - nephrotoxicity
        - hydration
      - nausea, vomiting
        - ondansetron, tropisetron
      - tinnitus, hearing loss
  - carboplatin
    - derivative of cisplatin
    - decreased adverse effect profile
    - myelotoxic

- Dacarbazine derivatives
  - prodrug, activated in the liver
  - temezolimide (carmustin)
    - clinical use: malignant glioma

Antimetabolites

- block or subvert pathways of DNA synthesis

- Folate antagonists
  - folate (FH4) are essential in purin nucleotides synth. (DNA synthesis)!
  - methotrexate
    - structure
      - pteridine ring-PABA-glutamic acid – (resembl. to folate)
    - inhibitis DHFR (no FH_2, FH_4) – cofactor of thymidylate synthase (dUMP→dTMP) – DNA synthesis
    - adm.: orally, iv., i.m.,
    - low lipid solubility – no pass to CNS – intrathecal administration (lumbar punction)
    - adverse effects
      - bone marrow depression
      - damage the epithelium of GIT
      - nephrotoxicity
    - AD: Leucovorin (synthetic folate analogue)
    - clinical use: AML

- Pyrimidine analogues
  - Fluorouracil (5-FU)
    - structural analogue of uracil
    - converted to FdUMP (fraudulent nucleotide)
    - interaction with thymidilate synthase → no dTMP / incorporation into the DNA
    - parenteral application (breast cancer, colorectal cancer)
    - adverse effects:
      - GIT epithelium damage
      - cerebellar disturbances

Antimetabolites

- Cytarabine
  - cytosin arabinoside (citidine+carbohydrate)
  - transformed to CATP (cytosin arabinozide triphosphate)
  - inhibits DNA polymerase – applied at lymphomas
  - adverse effects:
    - bone marrow depression
    - nausea, vomitting

- Gemcitabine
  - new analogue of cytarabine
  - decreased adverse effect profile
  - combination with cisplatin (solid tumors)

- Purine analogues

  - Fludarabine
    - triphosphate form inhibits DNA polymerase
  - Pentostatin
    - inhibits adenosine desaminase
    - adenosine $\not\rightarrow$ inosine
  - Azathioprim
    - 6-MP (6-mercaptopurine) → 6TG (fraudulent nucleotide) – structural analogue of guanin
    - inhibits HGPRT
      - inhibiting purin synthesis
      - chain terminator (fraudulent nucleotide)
    - eliminated by xanthin oxydase
      - allopurinol – reduced th. dose (when coapplied)
    - clinical use: leukaemia, lymphoma

Cytotoxic antibiotics

- Anthracyclines
  - Doxorubicine
    - cytotoxic actions
      - direct binding on DNA
        - inhibits AMP kinase – p53 suppression – apoptosis
        - intercalation – inhibits replication
    - intravenous infusion
    - myeloid leukemias
    - a.e.:
      - cardiac damage
        - free radicals↑
        - dysrythmias
  - Dactinomycin
    - intercalating between guanosine-cytosine pairs
    - blocking DNA dependent RNA synthesis
  - Bleomycin
    - glycopeptide AB derivative
    - effects
      - produces free radicals – DNA damage (chain fragmentation)
      - intercalates into the DNA – chain termination
    - M phase, G2 phase, G0 phase
    - clinical use
      - germline cancer
    - a.e.: pulmonary fibrosis

Cytotoxic antibiotics

- Mitomycin
  - similar function, like alkylating agents (cross-linking of DNA)
  - binding to O6 of guanine
  - a.e.:
    - myelosuppression

- Hydroxycarbamide
  - hydroxyurea – urea analogue
  - inhibits ribonucleotide reductase
  - ribonucleotides $\not\rightarrow$ desoxyribonucleotide
  - clinical use: leukaemia

Plant derivatives

- Vinca alkaloides
  - vincristin, vinblastine, vindesine, vinorelbine
    - derived from *Madagascar periwinkle*
    - binding to tubulin, inhibits microtubule polimerisation → arresting M phase
    - inhibits phagocytosis, axonal transport (
    - used in breast cancer, testicular cancer, NHL
- Taxanes
  - paclitaxel, docetaxel
    - derived from the bark of the „Pacific yew" tree
    - microtubules stabilising effect in polimerized state („freezing")
    - appl.: i.v. infusion (paclitaxel), p.o. (docetaxel)
    - clinical use.:
      - breast cancer
      - ovary cancer (paclitaxel+carboplatin)
    - a.e.:
      - neurotoxicity
      - bone marrow suppression
- Podophyllotoxins
  - etoposide
    - derived from „mandrake root"
    - inhibiting mitochondrial action,nucleoside transport
    - inhibits DNA topoisomerase II
    - a.e.:
      - nausea, vomitting
      - hair loss
- Campotechins
  - irinotecan, topotecan
    - binding and inhibiting topoisomerase I, interkaleting into DNA (DNA damage)
    - a.e.:
      - diarrhea
      - bone marrow depression

Hormones/hormone antagonists

- some tumors/neoplasms = hormone dependent/sensitive tissue

- glucocorticoids
  - prednisolone, dexamethasone
    - inhibitory effect on lymphocyte proliferation
    - combination with cytotoxic drugs
    - clinical use
      - leukaemia, lymphoma
      - ↓ICP (supportive therapy)
- oestrogenes
  - ethyniloestradiol, diethylstilbestrol
    - clinical use:
      - palliative treatment in androgen dependent prostatic tumors
      - used facilitating mammary cancer cell proliferation (stage changing) + cancer chemotherapy drug
- progestogenes
  - megestrol, medroxyprogesterone
    - clinical use
      - endometrial neoplasm
      - renal tumors

- gonadotrophin releasing hormone (GnRH) analogues
  - gosereline, busereline, triptoreline
    - inhibiting gonadotrophin and LH release
    - clinical use
      - breast cancer, prostata tumor

Hormones/hormone antagonists

- antioestrogenes
  - tamoxifen (Zitazonium)
    - clinical use
      - hormone dependent breast cancer
    - acting on oestrogene receptors (oestrogen receptor modulator)
      - inhibiting transcription of oestrogene-responsive genes
    - cardioprotective effect!
    - a.e.:
      - ↑ risk of endometrium cc.
  - aromatase inhibitors
    - anastrozole, letrozole
    - inhibits converting androstendione to androgenes and oestrogenes
    - treatment of breast cancer

- antiadrogenes
  - flutamide, cyproterone
    - prostata tumors

- adrenal hormone synthesis inhibitors
  - trilostane
    - postmenopausal breast cancer

Miscellaneous agents

- Monoclonal antibodies
  - rituximab, alemtuzumab
    - monoclonal antibody
    - binding to CD20 R of lymphocytes – activating complements
    - clinical use:
      - lymphoma, combination therapy
    - a.e.:
      - hypotension, cytokin release reaction
  - trastuzumab (Herceptin)
    - monoclonal antibody
    - binds to HER2 (human epidermal growth factor receptor 2)
      - inducing cell cycle inhibitors p21, p27
    - clinical use
      - breast cancer (HER2 overexpression)
  - Gemtuzumab + Ozogamycin

Miscellaneous agents

- imatinib mesylate
  - breaktrough in targeted chemotherapy
  - small molecule
    - inhibitor of kinases
      - receptor tyr-kinase
      - Bcr/Abl kinase (CML)
  - applied in leukaemia, GIT tumors
  - p.o.
  - PPB-high
  - a.e.:
    - fatigue, GIT symptoms, headache

- biological response modifiers
    - enhance the host's response
  - IFN-α -solid tumors, lymphomas
  - aldesleukin – recombinant IL-2 – renal tumors
  - tretionin – form of Vitamin-A - leukaemia

Supportive therapy

- analgetic drugs
  - maior analgetics
    - fentanyl (TTS), morphine
- antiemetic drugs
  - $5HT_3R$ antagonists
    - ondansetron, granisetron
  - D_2R antagonist
    - metoclopramide
- myeloprotection (GM-CSF)
  - molgramostim, sargamostim, pegfilgastrim
- steroids
  - oradexon
    - ICP↓
- hyperhydration, diuresis↑
- antidepressants, anxiolytics
  - SSRI, BDZ
- special antidotes
  - mesna, N-ACC, Leucovorin

New targets in cancer therapy

- inactivate components of oncogene signaling pathway
  - inhibitors of growth-factor receptors (Tyr-kinase receptors)
    - Tyr kinase inhibitors
  - inhibitors of anti-apoptotic factors
  - stimulating pro-apoptotic factors
  - inhibitor of adaptive proteins (Ras)

- restore function of tumore suppressor genes
  - gene therapy

- COX-inhibitors
  - selective COX-2 inhibitors (celecoxib)
    - prophylactic in mammary cancer
    - colon tumor

- p53 supplementation
  - p53 gene insertion
  - ONYX-015