PRINCIPLES OF CANCER TREATMENT AND CHEMOTHERAPY

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PRINCIPLES OF CANCER TREATMENT
Principles of cancer treatment. I.

* first goal of cancer treatment = eradicate cancer
Principles of cancer treatment. II.

* with primary goal not accomplished → palliation, amelioration of symptoms and preservation of quality of life, while striving to extend life
Principles of cancer treatment. III.

* "primum non nocere" not guiding principle of cancer therapy;

* with cure possible, treatment be undertaken despite certainty of severe and perhaps life-threatening toxicities;

- every cancer treatment: potential to cause harm and producing toxicity without benefit ("therapeutic index" of many interventions quite narrow, with most treatments given to point of toxicity);

* conversely, with cure impossible and palliation being primary goal → careful attention to minimizing toxicity of potentially toxic treatments
Principles of cancer treatment. IV.

* irrespective of clinical scenario, guiding principle of cancer treatment be “primum succerrere”, "first hasten to help“;

- radical surgical procedures, large - field hyperfractionated radiation therapy, high - dose chemotherapy and maximum tolerable doses of cytokines (e.g., interleukin, IL - 2) used in certain settings, where 100% of pts experience toxicity and side effects from intervention and only a fraction of pts experience benefit;

- one of challenges of cancer treatment = using various treatment modalities alone and together to maximize chances for pt benefit
Principles of cancer treatment. V.

* cancer treatments divided into four main types:
  - surgery;
  - radiation therapy (including photodynamic therapy = with endoscopes and fiber optic catheters to deliver light and intravenously - administered photosensitizers);
  - chemotherapy (including hormonal therapy and molecularly targeted therapy), and
  - biologic therapy (including immunotherapy and gene therapy)

photodynamic therapy
Principles of cancer treatment. Vbis. Photodynamic therapy (PDT)

* PDT uses drug (called “photosensitiser”, e.g., Tookad, bacterio - chlorophyll derivative absorbing light at 763 nm) activated by light, usually from laser;
  - activated drug kills cells around light fibre, by producing Reactive Oxygen Species (ROS), powerful forms of oxygen which can either kill cells directly or attack blood vessels which supply cells;
  - in photochemical terms, photosensitiser ↑ energy levels (from ground low energy at higher energy state, when activated by laser light)
Principles of cancer treatment. VI.

* modalities often used in combination, with agents in one category can act by several mechanisms;
  - e.g., chemotherapy agents can induce differentiation and antibodies (a form of immunotherapy) used to deliver radiation therapy;
* surgery and radiation therapy as “local treatments” (though their effects can influence behavior of tumor at remote sites);
  - chemotherapy and biologic therapy as “systemic treatments”
Principles of cancer treatment. VII.

* “medical oncology” = study of tumors including treatment approaches = multidisciplinary effort with surgery -, radiotherapy - and internal medicine - related areas of expertise;

[treatments of pts with hematologic malignancies often shared by hematologists and medical oncologists]
CANCER CELLS
Principles of cancer treatment. VIII.

* in many ways, cancer attempts to mimic a normal organ to regulate its own growth;

- however, cancers have not set appropriate limit on how much growth be permitted;

* normal organs and cancers share property of having:

- 1) population of cells in cycle and actively renewing, and

- 2) population of cells not in cycle
Principles of cancer treatment. X.

* in cancer, not dividing cells heterogeneous;
- some: too much genetic damage to replicate (but also defects in death pathways permitting their survival);
- others, starving for nutrients and oxygen, and
- others, out of cycle but poised to be recruited back into cycle and expand if needed (i.e., "reversibly growth arrest");

* while severely damaged and starving cells unlikely to kill pt, cells reversibly not in cycle capable of replenishing tumor cells physically removed or damaged by radiation and chemotherapy.
Principles of cancer treatment. XI.

* “cancer stem cells” fraction (whose properties still being elucidated) among cells reversibly not in cycle capable of replenishing tumor cells (? new target for therapies retarding their ability to reenter cell cycle)
Principles of cancer treatment. XII. Therapeutic implications of cancer stem cells (CSC)

* CSC (grey) self-renew and differentiate within tumors to form additional cancer stem cells and non-tumorigenic cancer cells (orange), with limited proliferative potential (as tumor grows, these cells either undergo limited benign growth or form disseminated malignancies);

- therapies that kill, induce differentiation or prevent metastasis of CSC → potential cures while therapies killing primarily non-tumorigenic cancer cells shrink tumors, but will not cure pt because CSC regenerate tumor → prospectively identifying and characterizing CSC → possible to identify more effective therapies
GOMPertzian Growth
Principles of cancer treatment. XIII.

* tumors follow Gompertzian growth curve;
- growth fraction of neoplasm starts at 100% with first transformed cell and declines exponentially over time until time of diagnosis, with tumor burden of $1 \times 10^9$ (1 cubic cm) tumor cells (growth fraction usually $\sim 1 - 4\%$);

* thus, peak growth rate occurs before detectable tumor
XIV. Gompertzian tumor growth

* growth fraction of tumor ↓ exponentially over time *(top)*;

* growth rate of tumor peaks before clinically detectable *(middle)*;

* tumor size ↑ slowly, goes through exponential phase and slows again as tumor reaches size at which limitation of nutrients or auto - or host regulatory influences occurs *(below)*;

- maximum growth rate at 1 / e (= .367), point at which tumor is ~ 37% of its maximum size *(marked with X)*;

- tumor detectable at burden of ~ $10^9$ (1 cm$^3$) and kills pt at burden of ~ $10^{12}$ (1 kg) cells;

* efforts to treat tumor and ↓ its size can result in ↑ in growth fraction and growth rate
TUMOR ANGIOGENESIS
Principles of cancer treatment. XV.

* key feature of successful tumor = ability to stimulate development of new supporting endothelial cells and stroma through angiogenesis and production of proteases to allow invasion through basement membranes and normal tissue barriers
Principles of cancer treatment. XVI. Angiogenesis

* = new capillary formation from preexisting postcapillary vessels to supply $O_2$ and nutrients to tumor;
* essential for tumor growth ($>1 - 2 \text{ mm}^3$) and metastasis (continuity with existing vasculature and easier entering into circulation)
CELL RECRUITMENT
Principles of cancer treatment. XVII.

* specific cellular mechanisms promote entry or withdrawal of tumor cells from cell cycle;

- e.g., when tumor recurs after surgery or chemotherapy, frequently → accelerated growth and ↑ growth fraction ("cell recruitment");

* pattern similar of regenerating organs;

- e.g., partial resection of liver → recruitment of cells into cell cycle (→ resected liver volume replaced);

- similarly, chemotherapy - damaged bone marrow ↑ growth to replace cells killed by chemotherapy
Principles of cancer treatment. XV.

* usually, cancers do not recognize limit on their expansion, with some, infrequent exceptions:
  - e.g., Monoclonal Gammopathy of Uncertain Significance (MGUS) = clonal neoplasm with intrinsic features that stop growth before lethal tumor burden reached (but a fraction of pts progresses to develop fatal multiple myeloma, probably due to accumulation of additional genetic lesions);
  - elucidation of mechanisms regulating this "organ - like" behavior of tumors may provide additional clues to cancer control and treatment
a) multiple myeloma (MM) arises from normal germinal-centre B cell, with 30 - 50% of malignant MM arising from benign plasma-cell neoplasm. Monoclonal Gammopathy of Undetermined Significance (MGUS);

- initially, MM confined to bone marrow (intramedullary), but with time tumor acquires ability to grow in extramedullary locations (e.g., blood, pleural fluid and skin);
- some of these extramedullary MM establish immortalized cell;

* transition of MGUS to intramedullary MM manifested by \( \uparrow \) no. of MM cells at multiple foci, associated angiogenesis and osteolytic bone destruction.
b) low proliferative index in pt with MGUS (right red surface staining for syndecan identifies ~ 10% plasma cells, none staining for brown nuclear proliferation marker Ki67);

c) bone - marrow biopsy stained for CD34, identifying endothelial cells (↑ vascularity in MM);

d) skull X - ray shows classic 'punched - out' lytic bone lesions (although skull lesions asymptomatic, extensive vertebral involvement causes compression fractures, resulting in pain and loss of height: 5 cm on average by time of diagnosis);

e) peripheral blood smear identifies circulating plasma cells in pt with plasma - cell leukemia
PRINCIPLES OF CHEMOTHERAPY
PRINCIPLES OF CHEMOTHERAPY

* medical oncology = subspecialty of internal medicine caring for and designing treatment approaches to pts with cancer, in conjunction with surgical and radiation oncologists;

- core skill of medical oncologist includes use of drugs expected beneficial on natural history of pt's illness or favorably influencing pt's quality of life;

- in general, curability of tumor inversely related to tumor volume and directly related to drug dose
END POINTS OF DRUG ACTION
CURABILITY
End points of drug action. I. Curability

* chemotherapy agents be used for active, clinically apparent cancer (a no. of tumors considered curable by conventional chemotherapeutic agents when disseminated or metastatic)

Small-cell lung carcinoma
Acute lymphoid and myeloid leukemia
Hodgkin's disease and high-grade lymphomas
Germ cell neoplasms (e.g., testicular seminoma and non-seminomas)
Gestational trophoblastic neoplasia
Pediatric neoplasms (e.g., Wilm's tumor)
Ovarian carcinoma
Embryonal rhabdomyosarcoma
Ewing's sarcoma
End points of drug action. II.

* with tumor localized to single site, serious consideration of surgery or radiation (these treatment modalities may be curative as “local treatments”);

* chemotherapy employed:
  - after failure of these modalities to eradicate local tumor, or
  - as part of multimodality approaches to offer primary treatment to clinically localized tumor (“neoadjuvant chemotherapy”);
  - in this event, it can allow organ preservation when given with radiation (e.g., in larynx or other upper airway sites) or sensitize tumors to radiation (e.g., to pts concurrently receiving radiation for lung or cervix cancer)
End points of drug action. III. Curability
Curability of cancers with chemotherapy
Advanced cancers possibly cured by CT and radiation

Squamous carcinoma (head and neck and anus)
Breast carcinoma
Carcinoma of uterine cervix
Non-small cell lung carcinoma (stage III)
Small-cell lung carcinoma
End points of drug action. IV. Adjuvant chemotherapy

* chemotherapy administered as adjuvant, i.e., in addition to surgery or radiation, after removing all clinically apparent disease = attempts to eliminate clinically unapparent tumor (micrometasteses) already disseminated (frequent high growth fractions in small tumors → intrinsically more susceptible to action of antiproliferative agents);

- adjuvant chemotherapy potentially curative in breast and colorectal neoplasms
End points of drug action. V. Adjuvant chemotherapy

* from above diagram, two round circles: A (no. of cancer cells in pt A) and B (no. of cancer cells in pt B);

- in both pts, surgery removed all visibly detectable cancer (e.g., pt A: large lump in right breast, ~ 4 - 5 cm in Θ; pt B had smaller lump in left breast ~ 1-2 cm in Θ);

- after surgery, both pts investigated with any tests if residual cancer could be detected, with none +, with pt A having larger amount of CC left than pt B;

- however, both amounts below "test line" → "invisible";

* both pts eligible for adjuvant treatment (e.g., chemotherapy = same treatment killing many millions of CC, with chance of cure probably better for pt B since no. of residual CC < than pt A)
End points of drug action. VI. Adjuvant chemotherapy

* although generally, the larger cancer at diagnosis, the greater chance of more cancer cells left behind, this relationship not always true;

- some pts have cancers not developing ability to migrate elsewhere (metastasize);

- other pts have cancers developing migrating ability early in their growth before found on examination or even screening (these migrating cells can grow enough to prevent additional treatment from being useful)
Curability of cancers with chemotherapy

Local cancers possibly cured with CT as adjuvant to surgery

- Breast carcinoma
- Colorectal carcinoma
- Osteogenic sarcoma
- Soft tissue sarcoma
End points of drug action.  
VIII. Conventional Dose regimens

* chemotherapy routinely used in "conventional" dose regimens, producing reversible, readily managed acute side effects (primarily transient myelosuppression ± gastrointestinal toxicity, usually nausea)
End points of drug action. IX. High - dose chemotherapy

* high - dose chemotherapy predicated on (mainly theoretical) observation that dose - response curve for many anticancer agents is rather steep, and ↑ dose produces markedly ↑ therapeutic effect;

- this, at cost of potentially life - threatening complications requiring intensive support, usually hematopoietic stem cell support from pt (autologous transplant) or (rarely) from donors matched for histo - compatibility loci (allogeneic transplant);

- definite curative potential in defined clinical settings for high - dose regimens
Curability of cancers with chemotherapy
Cancers possibly cured with "high-dose" chemotherapy with stem cell support

Relapsed leukemias (lymphoid and myeloid)
Relapsed lymphomas, Hodgkin's and non-Hodgkin's
Chronic myeloid leukemia
Multiple myeloma
End points of drug action. XI. Response

* evaluation of chemotherapeutic agent’s benefit by carefully quantitating its effect on tumor size (with using measurements to objectively decide basis for further treatment of particular pt or further clinical evaluation of drug's potential);

- complete response (CR) = disappearance of all tumor;
- partial response (PR) = ↓ by ≥ 50% in tumor's bidimensional area;
- progression of disease = ↑ of existing lesions by > 25% from baseline or from best response or development of new lesions, and
- "stable" disease = fits into none of above categories
End points of drug action.

XII. Surrogate markers of efficacy

* newer evaluation systems (especially for biological agents) will utilize temporal, unidimensional measurements (as “surrogate markers”, instead of “response”, with intent similar in rigorously defining evidence for activity of agent in assessing its value to pt), e.g.:

- time of stable disease;

- time to disease progression
* with cure not possible, chemotherapy undertaken for palliating adverse effects of tumor;

- usually, tumor-related symptoms are pain, weight loss or some “local symptoms” related to tumor’s location and effect on normal structures;

- pts treated with palliative intent be aware of diagnosis and limitations of proposed treatments, have access to supportive care and suitable performance status (according to evaluation algorithms, e.g., Karnofsky or Eastern Cooperative Oncology Group, ECOG, scores
End points of drug action. XIV. Palliation. II.
ECOG Performance Status

* PS0 = without symptoms;

- PS1 = mild symptoms not requiring treatment;

- PS2 = symptoms requiring some treatment;

- PS3 = disabling symptoms, but allowing ambulation for > 50% of day;

- PS4 = ambulation < 50% of day;

* only PS0 - PS3 pts usually considered suitable for palliative (noncurative) treatment (with curative potential, even poor - performance status pts be treated, with prognosis inferior to that of good - performance pts treated with similar regimens)
Curability of cancers with chemotherapy
Advanced cancers responsive with useful palliation, not cure, by chemotherapy

Bladder carcinoma

Chronic myeloid and lymphocytic leukemia

Hairy cell leukemia

Gastric carcinoma

Cervix and endometrial carcinoma

Soft tissue sarcoma

Head and neck cancer

Breast carcinoma

Colorectal carcinoma

Renal carcinoma
**End points of drug action. XVI. Palliation. IV.**

* support provided by primary caregiver (important perspective) in accessing palliative and hospice-based options critical in providing basis for pts to make sensible choices;

* it may bring pts and their families facing incurable cancer = given limited value of chemotherapeutic approaches at some point in natural history, palliative care or hospice-based approaches (prominent attention as a valuable therapeutic plan = meticulous and ongoing attention to symptom relief, family, psychological and spiritual support) = optimizing quality of life rather than attempting to extend it becomes valued intervention;

- pts facing impending progression of disease in life-threatening way frequently choose to undertake (toxic) treatments of little to no potential value
CANCER DRUGS
OVERVIEW
AND PRINCIPLES FOR USE
Cancer drugs: overview and principles for use. I.

* cancer drug treatments of 4 broad types:

1) conventional chemotherapy agents = (historically) from empirical observation that "small molecules" (usually, with MW < 1500 Da) cause major regression of experimental tumors in animals (these agents mainly target DNA structure or segregate DNA as fixed chrs in mitosis)
Cancer drugs: overview and principles for use. II.

2) targeted agents = "biological" agents (= small molecules or Abs inhibitors of “critical signaling pathways”) designed and developed to interact with defined molecular targets expressed by tumor cells (“successful tumors” activate biochemical pathways leading to uncontrolled proliferation through action of, e.g., oncogene products, loss of cell cycle inhibitors or loss of cell death regulation) with acquiring capacity to replicate chrs indefinitely, invade, metastasize and evade immune system);

- targeted therapies seek to capitalize from biology the aberrant cellular behavior as basis for therapeutic effects
Cancer drugs: overview and principles for use. IIbis. Signaling pathways
Cancer drugs: overview and principles for use. III.

3) hormonal therapies (first form of targeted therapy) capitalize biochemical pathways of estrogen and androgen function and action (therapeutic basis for approaching pts with tumors of breast, prostate, uterus and ovarian origin);

4) biologic therapies = often macromolecules with particular target (e.g., interferons and interleukins) having capacity to orchestrate or regulate host immune response to kill tumor cells (thus, biologic therapies include not only Abs but cytokines and gene therapies)
Cancer drugs: overview and principles for use. IV.

* usefulness of any drug governed by extent to which a given dose causes useful result (therapeutic effect, i.e., toxicity to tumor cells, as opposed to toxic effect);
- “therapeutic index” = degree of separation between toxic and therapeutic doses;

* really useful drugs = large therapeutic indices (usually when drug target expressed in disease - causing compartment as opposed to normal compartment)
Cancer drugs: overview and principles for use. V.

* classically, selective toxicity (= ability of drug to kill cancer cells without harming its host) of an agent for an organ governed by expression of an agent's target or by # accumulation into or elimination from compartments where toxicity experienced or ameliorated, respectively;

- for currently used chemotherapeutic agents, unfortunate property = targets present in both normal and tumor tissues (→ relatively narrow therapeutic indices)
CLINICAL TRIALS
Cancer drugs: overview and principles for use. VI. Phases of clinical trials

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Launch</th>
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<tr>
<td>Initial testing done in the lab or with animals.</td>
<td>The first step in the development of a new drug. First studies with humans. Limited to patients, who have cancer and limited treatment options. <strong>Goal:</strong> To test an initial idea to see if it has any effect.</td>
<td>Builds on results of Phase I. <strong>Goal:</strong> to see how well the treatment works against the disease.</td>
<td>Large group, sometimes thousands of patients. <strong>Goal:</strong> To see if the new treatment is better than the standard treatment for the cancer.</td>
<td><strong>Goal:</strong> To become the new standard for the cancer.</td>
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<tr>
<td><strong>Goal:</strong> 1. find the safest dose 2. most effective way to deliver a new drug 3. identify side effect</td>
<td>If treatment shows effect, and is shown to be safe enough, moves on to Phase III.</td>
<td>Participants are randomly assigned to either the new treatment or the standard treatment. <strong>Note:</strong> this is considered the most reliable and impartial way to test the new treatment.</td>
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Cancer drugs: overview and principles for use. VII.

* after demonstration of activity in animal models, conventional chemotherapeutic agents evaluated to define optimal schedule of administration in humans and arrive at drug formulation designed for given route and schedule;

* safety testing in two animal species on analogous schedule of administration defines “starting dose” for phase I trial in humans;

- usually, as fraction of dose (usually 1 / 6 - 1 / 10) causing easily reversible toxicity in more sensitive animal species;

- “escalating doses” of drug then given during human phase I trial until reversible toxicity observed
Cancer drugs: overview and principles for use. VIII.

* in humans, Dose - Limiting Toxicity (DLT) = dose conveying toxicity greater than acceptable in routine practice (allowing definition of lower Maximal Tolerated Dose, MTD = highest dose of drug not causing unacceptable side effects);

- occurrence of toxicity (if possible) correlated with plasma drug concentrations
Cancer drugs: overview and principles for use. IX.

* just lower MTD = dose suitable for phase II trials, where fixed dose administered to relatively homogeneous set of pts with particular tumor type, to define whether drug causes regression of tumor;

- "active" agent conventionally = PR rates ≥ 20 - 25% with reversible, non-life-threatening side effects (= suitable for phase III trials, assessing efficacy in comparison to standard or no therapy)
Cancer drugs: overview and principles for use. X.

* response (R, defined as tumor shrinkage) = most immediate indicator of drug effect;

* to be of clinical value, Rs must translate into “clinical benefit”, as conventionally established by beneficial effect on overall survival or at least on ↑ time to further progression of disease;

- active efforts also made to quantitate effects of anticancer agents on quality of life
Cancer drugs: overview and principles for use. XI.

* cancer drug clinical trials conventionally use toxicity grading scale:
  - grade I = not requiring treatment;
  - grade II = often requires symptomatic treatment but not life-threatening;
  - grade III = potentially life-threatening if untreated;
  - grade IV = actually life-threatening, and
  - grade V = results in pt's death
Cancer drugs: overview and principles for use. XII.

* development of “targeted agents” should proceed quite differently;

- with phase I - III trials still conducted, molecular analysis of human tumors more precisely defines “targets” expressed in pt's tumor and allows pt selection to enrich all trial phases with pts potentially responsive to agent (just by virtue of expressed target in tumor: e.g., EGFR mutations in non small cell lung cancer or c-Kit mutations in gastrointestinal stromal tumors)
Cancer drugs: overview and principles for use. XIII.

* clinical trials designed that assess behavior of drug in relation to its target;
  - ideally, with known plasma concentration affecting drug target escalation to MTD may not be necessary;
  - actually, correlation of host toxicity while achieving an "optimal biologic dose" more relevant endpoint for phase I and early phase II trials with targeted agents
Cancer drugs: overview and principles for use. XIV.

* overall, valuable cancer drug treatment strategies using conventional chemotherapy agents, targeted agents, hormonal treatments or biologicals have one of two valuable outcomes, inducing:

- cancer cell death (necrosis, apoptosis, anoikis) → tumor shrinkage with corresponding ↑ in pt survival or ↑ time until disease progresses;
- cancer cell differentiation or dormancy → loss of tumor cell replicative potential and reacquisition of phenotypic properties resembling normal cells (blocking tumor cell differentiation = key feature in some leukemias)
Cancer drugs: overview and principles for use. XIV.

* **cell death** = closely regulated process;

- “necrosis” = cell death induced, e.g., by physical damage with hallmarks of cell swelling and membrane disruption;

- “apoptosis” ("programmed cell death") = highly ordered process whereby cells respond to defined stimuli by dying (and it recapitulates necessary cell death observed during ontogeny of organism);

- “anoikis” = death of epithelial cells after removal from normal milieu of substrate, particularly from cell-to-cell contact;

* cancer chemotherapeutic agents usually cause both necrosis and apoptosis
Cancer drugs: overview and principles for use. XIVbis. Necrosis

* cell death = closely regulated process;
- “necrosis” = cell death induced, e.g., by physical damage with hallmarks of cell swelling and membrane disruption
Cancer drugs: overview and principles for use. XIVter.

Apoptosis

* cell death = closely regulated process;
- "apoptosis" ("programmed cell death") = highly ordered process whereby cells respond to defined stimuli by dying (and it recapitulates necessary cell death observed during ontogeny of organism)
Cancer drugs: overview and principles for use. XIVquater.

* apoptosis characterized by chromatin condensation ("apoptotic bodies"), cell shrinkage and, in living animals, phagocytosis by surrounding stromal cells (without evidence of inflammation);

- process regulated either by a no. of signal transduction systems promoting cell's demise after certain level of insult achieved, or in response to specific cell - surface receptors mediating cell death signals;

- modulation of apoptosis by manipulation of signal transduction pathways as basis for understanding actions of drugs and designing new strategies to improve their use.
Integration of cell death responses. I.

* cell death through apoptotic mechanism requires active participation of cell;

* in response to interruption of growth factor (GF) or propagation of certain cytokine death signals (e.g., tumor necrosis factor receptor, TNF-R) → activation of "upstream" (initiator, apical caspases) cysteine aspartyl proteases (e.g., caspase 8), which directly digest cytoplasmic and nuclear proteins → activation of "downstream caspases" (effector, executioner caspases) (e.g., caspase 3);

- these cause activation of nucleases → characteristic DNA fragmentation, hallmark of apoptosis;

- chemotherapy agents creating lesions in DNA or altering mitotic spindle probably activate aspects of process by damage ultimately conveyed to mitochondria (possibly activating transcription of genes whose products produce or modulate toxicity of free radicals)]
Integration of cell death responses. II.

* as another way, membrane damage (by anticancer drugs) → activation of sphingomyelinases → production of ceramides, having direct action on mitochondria;

[- antiapoptotic protein bcl2 attenuates mitochondrial toxicity, while proapoptotic gene products (e.g., bax) antagonize action of bcl2];

- damaged mitochondria release “cytochrome C and APoptosis - Activating Factor (APAF)”, directly activating caspase 9 → propagation of direct signal to other downstream caspases through protease activation
* as further another way, Apoptosis - Inducing Factor (AIF) also released from damaged mitochondria and translocates to nucleus, binds to DNA and generates free radicals to further damage DNA;

* additional proapoptotic stimulus = bad protein, hetero - dimerizing with bcl2 gene family members to antagonize apoptosis;

- bad protein function be retarded by its sequestration as phospho - bad through 14 - 3 - 3 adapter proteins (phosphorylation of bad mediated by AKT kinase in way defining how growth factors activating AKT kinase retard apoptosis and promote cell survival)
Cancer drugs: overview and principles for use. XV.

* as general view, cancer treatments works by interaction of chemotherapeutic drug with some target, inducing "cascade" of further signaling steps;

- these signals ultimately lead to cell death by triggering an "execution phase" with activation of proteases, nucleases and endogenous regulators of cell death pathways
Cancer drugs: overview and principles for use. XVI.

* targeted agents # from chemotherapy agents in that they do not indiscriminately cause molecular lesions but regulate action of particular pathways;
  - e.g., p210^{bcr-abl} fusion protein tyrosine kinase drives chronic myeloid leukemia (CML) and HER-2/neu stimulates proliferation of a no. of breast cancers;
    - tumor described as "addicted" to function of these molecules (= without pathway's continued action, tumor cell cannot survive);
    - in this way, targeted agents alter the "threshold" tumors have for undergoing apoptosis without actually creating any molecular lesions (e.g., direct DNA strand breakage or altered membrane function)
Cancer drugs: overview and principles for use. XVII. Anoikis

* cell death = closely regulated process;
- “anoikis” = death of epithelial cells after removal from normal milieu of substrate, particularly from cell-to-cell contact
Cancer drugs: overview and principles for use. XVIIbis. Anoikis

* epithelial cells normally attached both to each other and to their matrix and undergo programmed cell death when detached from their home ground (= anoikis);

- #, cancer cells survive by autocrine or paracrine mechanisms to suppress programmed cell death, stimulate tissue invasion and promote growth of new blood vessels to supply oxygen

* autocrine (autostimulatory) mechanisms include production of TrkB protein (high affinity catalytic receptor for several "neurotrophins"), stimulated by Brain-Derived Neurotrophic Factor (BDNF), in turn activating AKT / PKB protein;

- paracrine mechanisms involve interactions with external components (e.g., immune cells, other matrices, cells of blood vessels, etc) [for simplicity, paracrine mechanisms shown as operating only in metastatic sites, but actually function in primary tumors]
Cancer drugs: overview and principles for use. XVIII.

* apoptotic mechanisms important in regulating cellular proliferation and behavior of tumor cells in vitro;

- in vivo, unclear whether (all) actions of chemotherapeutic agents causing cell death attributable to apoptotic mechanisms;

- however, changes in molecules regulating apoptosis correlated with clinical outcomes (e.g., anti-apoptotic bcl2 overexpression in certain lymphomas → poor prognosis after chemotherapy; pro-apoptotic bax expression → better outcome after chemotherapy for ovarian carcinoma);

* better understanding of relationship of cell death and cell survival mechanisms needed
DRUG RESISTANCE
Cancer drugs: overview and principles for use. XX.

* resistance to chemotherapy postulated to arise either from cells not being in appropriate phase of cell cycle (to allow drug lethality), from ↓ uptake, ↑ efflux, # metabolism of drug, or alteration of target (e.g., by mutation or overexpression);
  - e.g., p170pGP (p170 p - glycoprotein; mdr gene product) recognized from cells growing in tissue culture as mediating efflux of chemotherapeutic agents in resistant cells (in a no. of neoplasms, especially hematopoietic tumors → adverse prognosis if expressing high levels of p170PGP; modulation of this protein's function attempted by a variety of strategies)
POSSIBLE MECHANISMS OF TAXANE RESISTANCE

a) ↑↑ ↑↑ expression or inherited polymorphisms in cytochrome P450 (CYP3A4 and CYP2C8) associated with greater basal enzymatic activity → ↓ plasma concentrations of active drug;

b) efflux through trans-membrane transporters (e.g., P170 glycoprotein) ↓ taxane intracellular concentrations;

c) tubulin isoforms, mutations in tubulin proteins and loss of tubulin-stabilizing proteins (e.g., tau) contribute to microtubule destabilization;

d) dysfunction in key cell-cycle checkpoint and DNA damage repair mediators contributes to chromosomal instability and prevents induction of apoptosis by taxanes;

e) ↑ expression of antiapoptotic proteins (e.g., Bcl-2 or Thrombospondin 1, TSP1) or ↓ of negative regulator TXR1 prevent taxane-induced cell death.
Cancer drugs: overview and principles for use. XXII.

* “chemotherapeutic combinations” where drugs acting by different mechanisms combined (e.g., alkylating agent + antimetabolite + mitotic spindle blocker) more effective than single agents;
  - if possible, combinations chosen using drugs with individual toxicities to host;
  - as agents with novel mechanisms of action emerge, combinations of drugs and targeted agents maximizes chances of affecting critical pathways in tumor