PRINCIPLES OF CHEMOTHERAPY

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Life cycle of human cancers relating clinical events to population doublings

- Tumor First Palpable (30 Doublings)
- Tumor First Visualized on X-ray (27 Doublings)
- 1 MG
- 130 MG
- 10^6 (1 MG)
- 10^9 (10 G)
- 10^10
- 10^12
- 1 KG = death
- Tumor causes first symptoms

Logarithmic graph showing the exponential growth of tumor cells and mass over the number of doublings.
Gomperzian growth

<table>
<thead>
<tr>
<th>Years</th>
<th>Cell number</th>
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<tbody>
<tr>
<td>0</td>
<td>1</td>
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<tr>
<td>0.109</td>
<td>10</td>
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<tr>
<td>0.229</td>
<td>$10^2$</td>
</tr>
<tr>
<td>0.360</td>
<td>$10^3$</td>
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<tr>
<td>0.506</td>
<td>$10^4$</td>
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<tr>
<td>0.670</td>
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<td>0.858</td>
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<tr>
<td>1.078</td>
<td>$10^7$</td>
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<tr>
<td>1.343</td>
<td>$10^8$</td>
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<tr>
<td>1.674</td>
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<td>2.120</td>
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<td>2.801</td>
<td>$10^{11}$</td>
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<tr>
<td>4.306</td>
<td>$10^{12}$</td>
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</table>
Fractional cell kill in rapidly growing (A) and slowly growing (B) tumors
Proposal for a new model of breast cancer metastatic development

Demicheli, Annals of Oncology 8:1075 (1997)
Four ways of giving chemotherapy

1. Induction treatment for advanced cancer - 1° or salvage, no alternatives
2. Adjunct to local methods of treatment - adjuvant chemotherapy
3. Primary treatment for localized cancer - neoadjuvant chemotherapy
4. Direct instillation into sanctuaries of specific regions affected by cancer
1. **Induction chemotherapy**

- No alternative therapy exists - inoperable or metastatic
- Often use combinations of drugs with different mechanisms of action
- Define response as: complete, partial, stable disease or progression
- Stable disease may prolong survival - concept of cancer as a chronic disease
Response of patient #16 with ca of cervix to 13-cis-RA/ Carboplatin/Taxol

Tumor initiating cells – resistance and recurrence

- **Tumors from Stem cells**
  - Heterogenous cancer
  - Increased metastatic potential

- **Tumors from late progenitor cell**
  - Homogenous cancer
  - Less metastatic potential

**Therapy is effective against cancer stem cells, and the tumor is eliminated.**

**The tumor initially shrinks, but the self-renewing CSCs regenerate the tumor.**

**Cancer stem cell specific therapy**

**Tumor regression**

**Conventional cancer therapy**

**Tumor relapse**
Endocrine and growth factor regulation of normal and malignant mammary epithelial cells
2. Adjuvant chemotherapy

- Tumor volume is at minimum or unmeasurable
- Treatment of micrometastatic or invisible disease
- Increase cure rate over that of surgery alone - e.g. breast ca.
- Major endpoint: relapse-free survival
Primary breast tumors metastasize to bone marrow

Braun, et al., NEJM 342:525, 2000
Patients with bone marrow micrometastases at diagnosis have worse survival.
Survival advantage of adjuvant chemotherapy in post-menopausal women with breast cancer - a meta analysis of 9 studies

Figure 1: RFS and OS for all 3920 patients by treatment group

Frequency of cytokeratin positive cells in the bone marrow is unaffected by chemotherapy

### Comparison of Patients' Variables and Frequency of Isolated Breast Cancer Cells in Bone Marrow

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. of Patients</th>
<th>Patients With CK-Positive Cells</th>
<th>Before Therapy</th>
<th>After Therapy</th>
<th>P*</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
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<tr>
<td>Total</td>
<td>59</td>
<td></td>
<td>29</td>
<td>49</td>
<td>26</td>
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<td>Chemotherapy</td>
<td></td>
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<tr>
<td>Docetaxel/epirubicin</td>
<td>18</td>
<td></td>
<td>8</td>
<td>44</td>
<td>8</td>
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<tr>
<td>Paclitaxel/epirubicin</td>
<td>14</td>
<td></td>
<td>6</td>
<td>42</td>
<td>4</td>
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<tr>
<td>EC/CMF</td>
<td>27</td>
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<td>13</td>
<td>48</td>
<td>14</td>
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</table>

Abbreviation: EC/CMF, epirubicin, cyclophosphamide/cyclophosphamide, methotrexate, fluorouracil.

*χ² test for contingency tables; P < .05 was considered statistically significant. The number of patients with CK-positive cells before chemotherapy was compared with that after chemotherapy.

Braun, et al, JCO 18:80, 2000
3. Primary chemotherapy

- Meant to shrink tumor prior to surgery - neoadjuvant
- Presenting tumor is a biologic marker of response
- Largest tumor mass - least favorable kinetics for response to chemotherapy - slowest dividing
- Assume metastases have more favorable response kinetics
- Poor response quickly directs Rx to alternate method
- Able to categorize prognosis by degree of response
- Removal of residual tumor and analysis of viability directs prognosis, eg. testicular ca
- Treat to CR + 2 more cycles defines a fraction of patients with significant cure rate w/o alternate Rx
Mammographic complete response to neoadjuvant chemotherapy – opportunity to observe tumor response

Prechemotherapy mammogram (A) reveals malignant lesion (arrow). Postchemotherapy mammogram (B) shows a mammographic complete response.

Jones RL, Smith IE. Lancet Oncology. 7:869, 2006
4. Special uses of chemotherapy

• **Rationale**: highest concentration of drug against target tumor, spare nl. tissue, systemic effects

• **Sites**:
  – spinal fluid - by LP or Omaya reservoir - leukemia, lymphoma - therapeutic
  – pleural, pericardial space to control effusions - palliative
  – carotid artery - head and neck ca, brain tumors - therapeutic or sensitizing w/ RT
  – intraperitoneal - ovarian, gastric
  – Hepatic artery catheter – direct treatment of metastatic lesion
  – liposomal drugs - 3 day intravascular $T_{1/2}$
# Classification of Cytotoxic Agents

<table>
<thead>
<tr>
<th>Alkylating Agents</th>
<th>Anti-Metabolites</th>
<th>Mitotic Inhibitors</th>
<th>Antibiotics</th>
<th>Others</th>
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</thead>
<tbody>
<tr>
<td>BUSULFAN</td>
<td>CYTOSINE</td>
<td>ETOPOSIDE</td>
<td>BLEOMYCIN</td>
<td>L-ASPARAGINASE</td>
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<tr>
<td>CARMUSTINE</td>
<td>ARABINOSIDE</td>
<td>TENIPOSIDE</td>
<td>DACTINOMYCIN</td>
<td>HYDROXYUREA</td>
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<tr>
<td>CHLORAMBUCIL</td>
<td>FLOXURIDINE</td>
<td>VINBLASTINE</td>
<td>DAUNORUBICIN</td>
<td>PROCARBAZINE</td>
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<tr>
<td>CISPLATIN</td>
<td>FLUOROURACIL</td>
<td>VINCRIStINE</td>
<td>DOXORUBICIN</td>
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<tr>
<td>CYCLOPHOSPHAMIDE</td>
<td>MERCAPTOPURINE</td>
<td>VINDESINE</td>
<td>MITOMYCIN-C</td>
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<tr>
<td>IFOSFAMIDE</td>
<td>METHOTREXATE</td>
<td>TAXOIDS</td>
<td>MITOXANTRONE</td>
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<tr>
<td>MELPHALAN</td>
<td></td>
<td></td>
<td>PLICAMYCIN</td>
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</table>
SITES OF ACTION OF CYTOTOXIC AGENTS

Cell cycle level

Antibiotics

Antimetabolites

S (2-6h)

G2 (2-32h)

M (0.5-2h)

Alkylating agents

Vinca alkaloids

Mitotic inhibitors

Taxoids

G1 (2-∞h)

G0
SITES OF ACTION OF CYTOTOXIC AGENTS

Cellular level

DNA synthesis

DNA transcription

DNA duplication

Intercalating agents

Antimetabolites

Alkylating agents

Mitosis

Spindle poisons
SITES OF ACTION OF CYTOTOXIC AGENTS

- Purine synthesis
- Pyrimidine synthesis
- Ribonucleotides
- Deoxyribonucleotides
- Nucleic acids
- Proteins
- Enzymes
- Microtubules
- Alkylating agents
- Antibiotics
- Etoposide
- L-asparaginase
- Vinca alkaloids
- Taxoids
Goldie-Coldman Hypothesis

- Tumor cells acquire spontaneous mutations that result in specific drug resistance between $10^3$-$10^6$ cell stage
- Detectable tumors are at least $10^9$ cells
- Tumors at diagnosis have drug resistant clones - # depends on individual mutation rate
- Despite response with PR or CR, resistant clone expands
- Small tumors have resistant clones
- Give multiple drugs at once or cycle non-crossresistant regimens
Clonal evolution of tumors
DRUG RESISTANCE

EXTRACELLULAR

INTRACELLULAR

PGP_{170} ATP

ATP

Drug

Plasma Membrane
Combination chemotherapy

- Single drugs do not cure cancer - need combinations of drugs for durable responses
- Combinations developed based on biochemical actions - ineffective
- Combine effective drugs from different classes of drugs that have demonstrated efficacy individually
Accomplishes 3 important objectives:
  – provides maximal cell kill within range of toxicity tolerated for each drug
  – provides a broader range of coverage of resistant cell lines in a heterogeneous tumor population
  – prevents or slows development of new resistant clones
Principles for selecting drugs for most effective combination

• Select only drugs known to be partially effective when used alone - ones producing some fraction of CR preferable
• When several drugs in a class available, select ones whose toxicities do not overlap with toxicities of other drugs in combination - broadens range of side effects but limits lethal side effects to same organ - maximize dose intensity
Use drugs in optimal dose and schedule

- give combinations at constant intervals - extending time between treatments allows regrowth of tumor
- inter-treatment interval should be shortest possible for recovery of most sensitive tissue - usually bone marrow
- omission of a drug from combination may allow growth of clone sensitive to that drug alone but resistant to all other drugs
- arbitrary reduction of dose of an effective drug may reduce dose below threshold of effectiveness and lose chance of cure
SIDE EFFECTS OF CHEMOTHERAPY

Cognitive effects
Mucositis
Nausea/vomiting
Diarrhea
Cystitis
Sterility
Myalgia
Neuropathy
Alopecia
Pulmonary fibrosis
Cardiotoxicity
Local reaction
Renal failure
Myelosuppression
Phlebitis
Complications of chemotherapy

Bone marrow suppression

- Storage compartment - able to supply mature cells to circulation for 8-10 days
- Nadir blood counts 10-14 days after chemo, recover by 21 days - rationale for q 3 week chemo
- Colony stimulating factors shorten recovery by a week
- Prior chemo, RT, shorten time to neutropenia and thrombocytopenia, effects of chemo more severe
- Nadir sepsis - abx, isolation, G/GM-CSF, RBC tx - positive blood cx - 2 week antibiotic course
Complications of chemotherapy

Pulmonary toxicity

Drugs reported to induce toxicity:

- alkylating agents: busulfan, cytoxan, chlorambucil, melphalan
- nitrosoureas: carmustine (BCNU), lomustine (CCNU)
- antibiotics: Bleomycin - most common, mitomycin-C
- antimetabolites: methotrexate, azathioprine, mercaptopurine, Ara-C
- miscellaneous: decarbazine, vinblastine
Complications of chemotherapy

Pulmonary toxicity (cont.)

Mechanisms:
- trigger formation of superoxide radicals, $\text{H}_2\text{O}_2$, OH radicals
- immune activation - prostaglandins, thymocyte activation (mtx), PMN alveolitis (Bleo), eosinophils (procabazine, bleo, mtx)
- collagen deposition, fibrosis (bleo, cytoxan)
- inactivation of antiprotease system
Complications of chemotherapy

Pulmonary toxicity (cont.)

- Predisposing factors
  - age >60
  - prior RT to lungs
  - simultaneous O₂ >35%
  - decreased creatinine clearance (drug retained)
- Signs and symptoms
  - develop over weeks to months
  - dyspnea, “velcro” rales
  - dry cough - not hemoptysis
  - decreased DLCO
Complications of chemotherapy

Cardiac toxicity

- Anthracyclines - increasing cardiotoxicity with cumulative doses - lifetime threshold 550 mg/m²
- mediastinal RT - additive risk factor
- can be acute or subacute
- Pathology: mitochondrial swelling, disruption of myofibrils, disruption of sarcoplasmic reticulum, vacuolization
- cardiomyopathy, decreased systolic function, exercise response
- liposomal formulation - no toxicity to 1200mg/m²
Complications of chemotherapy

Cardiac toxicity

Other drugs that induce cardiac toxicity:
– mitoxanthrone, amsacrine - MI’s
– cytoxan, ifosfamide - ectopy, ST changes
– taxol - bradicardia
– vincristine, vinblastine, mitomycin-C - arrhythmias
– 5-FU, cis-platin - arrhythmias
Complications of chemotherapy

Chemical cystitis

- Drugs:
  - cyclophosphamide (cytoxan), used in solid tumors, lymphomas, bone marrow transplant conditioning;
  - ifosfamide, - dose limiting toxicity,
- Unique symptoms
  - frequency, urgency, dysuria, nocturia, microhematuria to exanguinating hemorrhage
  - timing soon after Rx
  - late sequelae - fibrosis, malignancy - TCC
Chemical cystitis (cont.)

- Etiology - acrolein, metabolically inactive breakdown product of cytoxan and ifosfamide
- Concentration of acrolein in urine, bladder damage cumulative and dose related
- Treatment of hemmorhagic cystitis:
  - stopping drug, replacing with azathioprine
  - hydration, diuretics, repletion of $K^+$
  - bladder irrigation
- Prevention - Mesna (2-mercaptoethane sulfonate) SH group complexes and neutralizes acrolein
Complications of chemotherapy

Gonadal dysfunction

- Testicular function in adult men susceptible to injury by many agents
- Primary lesion - progressive, dose related depletion of germinal epithelium lining seminiferous tubules - only Sertoli cells remain - germinal aplasia, age >45 worse
- Clinical manifestations - reduction of volume, sperm count, infertility, increased FSH
- Combination chemo with alkylators worst
Complications of chemotherapy

Gonadal dysfunction

- Frequent arrest of follicular maturation or frank destruction of ova and follicles
- Clinical: amenorheic and have post-menopausal symptoms of estrogen deficiency, elevated LH, FSH
- At least half of women treated with alkylating agents develop ovarian failure - not children
- Adjuvant chemo for breast ca.- some amenorrhea, worse with age, dose effect
Antitumor agents associated with Testicular and Ovarian dysfunction

Testicular germ cell depletion
- Definite: chlorambucil, cytoxan, busulfan, procarbazine, Nitrogen mustard, nitrosoureas
- Probable: vinblastine, adria, Ara-C, cis-platin
- Unlikely: Mtx., 5-FU, 6-MP, vincristine

Ovarian dysfunction
- Definite: cytoxan, busulfan, nitrogen mustard, L-phenylalanin mustard
- Unlikely: Mtx, 5-FU, 6-MP
- Unknown: adria, bleo, vinca alkaloid, cis-platin, Nitrosourea, Ara-C
AIM OF COMBINATION THERAPY

INCREASED EFFICACY

DIFFERENT MECHANISMS OF ACTION
Different mechanisms of action
Different mechanisms of resistance

DIFFERENT MECHANISMS OF RESISTANCE

COMPATIBLE SIDE EFFECTS

SAFETY
Molecular targets for cancer therapy

Severe acneiform rash of CI-1040 MEK inhibitor in phase I trial

Lorusso PM, et al., Journal of Clinical Oncology. 23:5281, 2005
Measuring effects on molecular targets in clinical trials

High-dose IFN2b down-regulates both pSTAT3 tyr705 (blue) and EGFR levels concurrently in tumor samples as shown in panels C and D. It was observed that pSTAT3 tyr705 negative cells (yellow arrow) exhibited higher EGFR expression level; conversely, cells denoted by the black arrow are strongly positive for pSTAT3 tyr705, but negative for EGFR.

Changes in ERK phosphorylation in PBMCs with TKI258, an Oral, Multitargeted Receptor Tyrosine Kinase Inhibitor in a patient treated at 75 mg (intermittent schedule). This patient had inhibition of ERK phosphorylation detectable at day 1, 4 h, which was maintained on day 7, and after redosing on day 15 at 4 and 24 h. pERK, phosphorylated ERK. Positive control samples are blood cells from a normal donor processed identically to clinical samples as indication of basal levels.


A Phase I Pharmacokinetic and Pharmacodynamic Study of TKI258, an Oral, Multitargeted Receptor Tyrosine Kinase Inhibitor in Patients with Advanced Solid Tumors