Drug Delivery in Oncology

An Introduction to The Systemic Therapy of Cancer

Workshop on Modeling in Oncology
Fields Institute 2005

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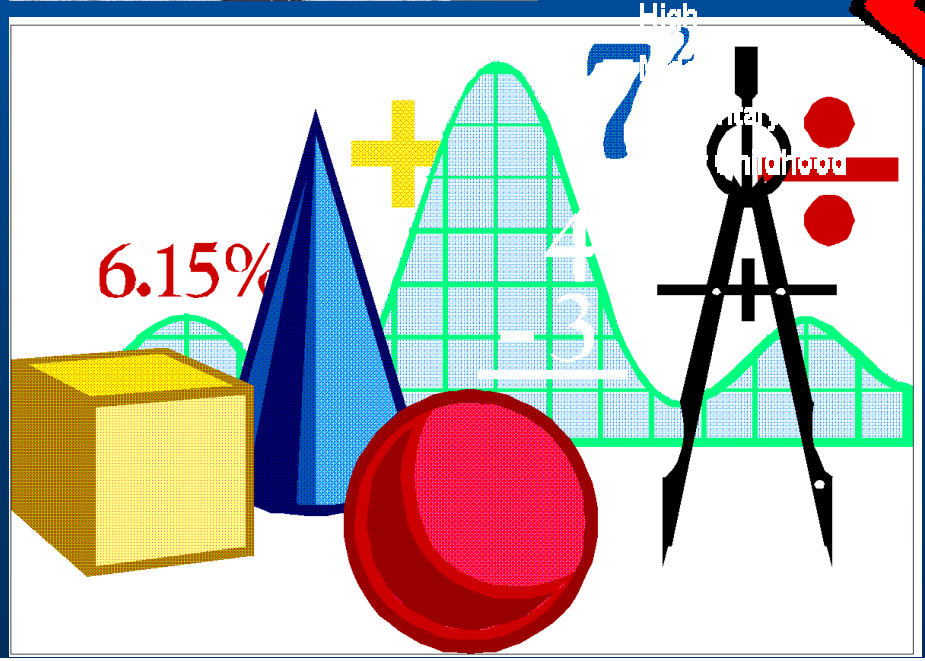


MATHEMATICS
is one of the essential emanations
of the human spirit, a thing
to be valued in and for itself,
like art or poetry.

OSWALD VEBLEN 1924

For Don Knuth with admiration and respect.
Hermann Zapf. 18 January 2002

The Mathematics of Cancer

Cancer as a Disease

- Uncontrolled exponential growth of mutated cell [monoclonal].
- Induced by genetic mutations in host cells.
- Inheritance of certain genes can alter risk.
- Environmental influences alter genetic mutation rates.
- Most cancers increase in incidence with age.

Tumor Growth

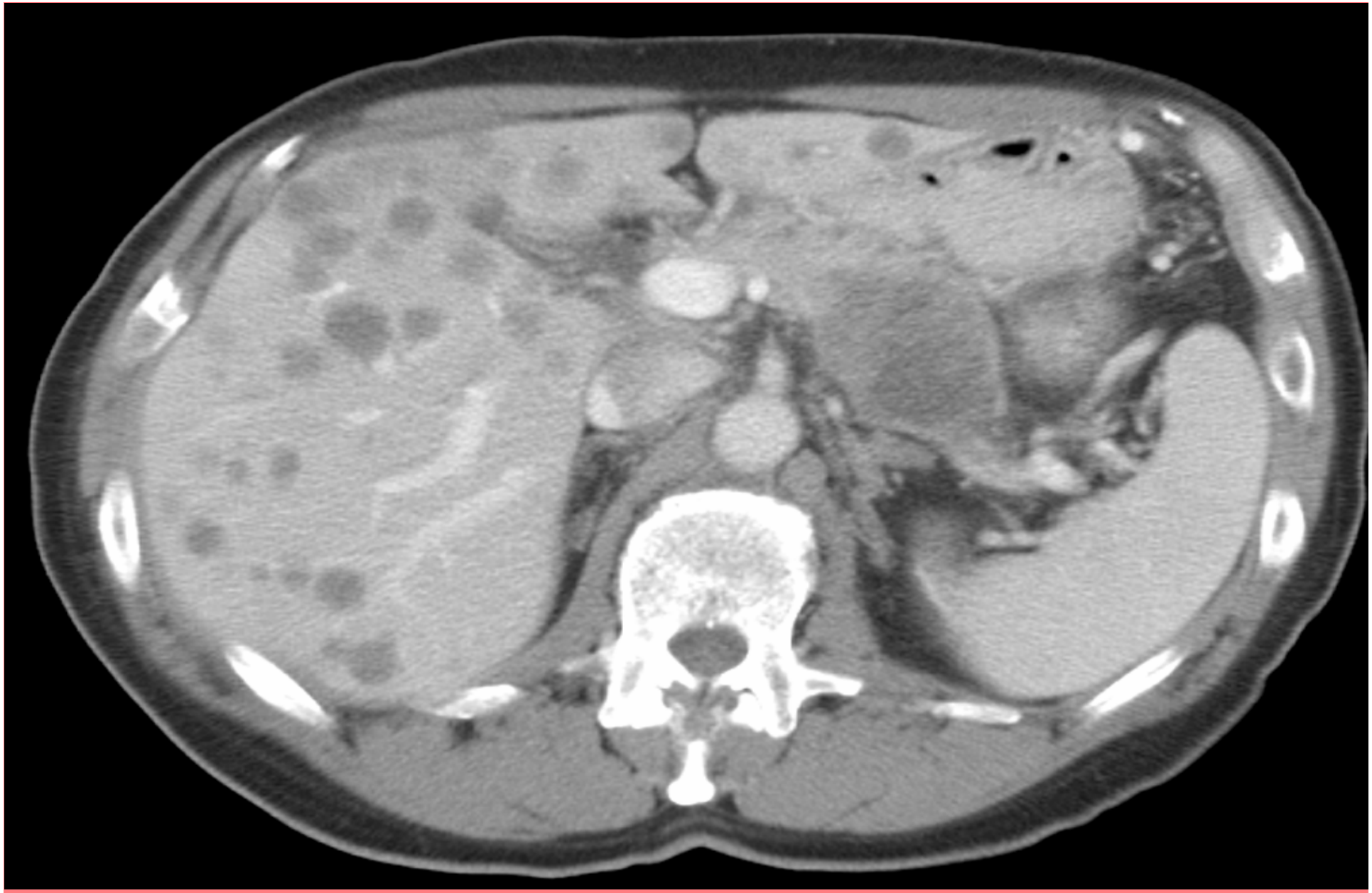
- Growth of tumors dependent upon rates of proliferation and death.
- Rates of proliferation important in response to therapy.
- Not all cells are actively cycling.
- Doubling times typically around 2 months.
- Rate of growth does not increase over time.

Tumors as Clonal Populations

- Cancers are monoclonal [derived from a single cell]
- Theoretically to eradicate a tumor all cells must be killed
- However …
  - Not all cells are actively cycling
  - Not all cells in tumor can repopulate.
  - Genetic instability leads to high mutation rates.

What is a Tumor?

- Mass of cells derived from a single cell [monclonal].
- Blood vessels, inflammatory [immune] cells.
- Tumor 1 cm in size has 1 billion [10^9] cells
  - 30 doublings [$1024 = 10^3 = 2^{10}; 10^9 = 2^{30}$]
- Tumor 10 cm in size has 1,000 billion [10^{12}] cells
  - Additional 10 doublings.



Tumor in the body and tail of pancreas with liver metastasis

The Systemic Treatment of Cancer

Systemic Therapy
How Do We Give It?

- Intravenous administration.
  - Bolus administration
  - Continuous infusion.
- Oral administration.
- Direct installation - site specific
  - Peritoneal cavity [ovarian cancer]
  - Hepatic perfusion [colorectal cancer]
  - Central nervous system, bladder.

Systemic Therapy
How Do We Give It?

- Basic issue in drug delivery is [small] therapeutic index
- Close to lethal toxicity so …
  - Need to minimize pharmacological variability
    - Dosing on basis of body surface area.
    - Intravenous rather than oral administration.
    - Iterative process.
  - Need to reduce risk of toxicity
    - Infusional therapy.
    - Regional therapy.
    - Antidotes

Kinetics of Tumor Growth

Skipper's Laws:

- Assumes doubling time of proliferating cancer cells is constant
- Assumes fractional cell kill, i.e. same proportion of cells is killed with each dose of drug
- So if 99% cells are killed per cycle, then a tumor burden of 10^{11} cells will be reduced to < 1 cell in 6 cycles:

  10^{11} -> 10^{9} -> 10^{7} -> 10^{5} -> 10^{3} -> 10^{1} -> 0.1

Systemic Therapy
Why do we give it?

- Treating advanced (not resectable) disease
- After potentially curable local treatment (adjuvant)
- Primary therapy for localized cancer (neoadjuvant)
- To prevent cancer occurring.

Goals of therapy

#1. Cure the patient.

Established cancers reliably cured by chemotherapy

- Testicular Cancer, Lymphoma, Pediatric tumors

#2. Control the cancer.

(>50% remissions)

- Small cell lung cancer, Ovarian cancer, Leukemia, Hormonal therapy of prostate cancer.

(30-50% remissions)

- Non-small cell lung cancer, Bladder, Breast and Colorectal cancer

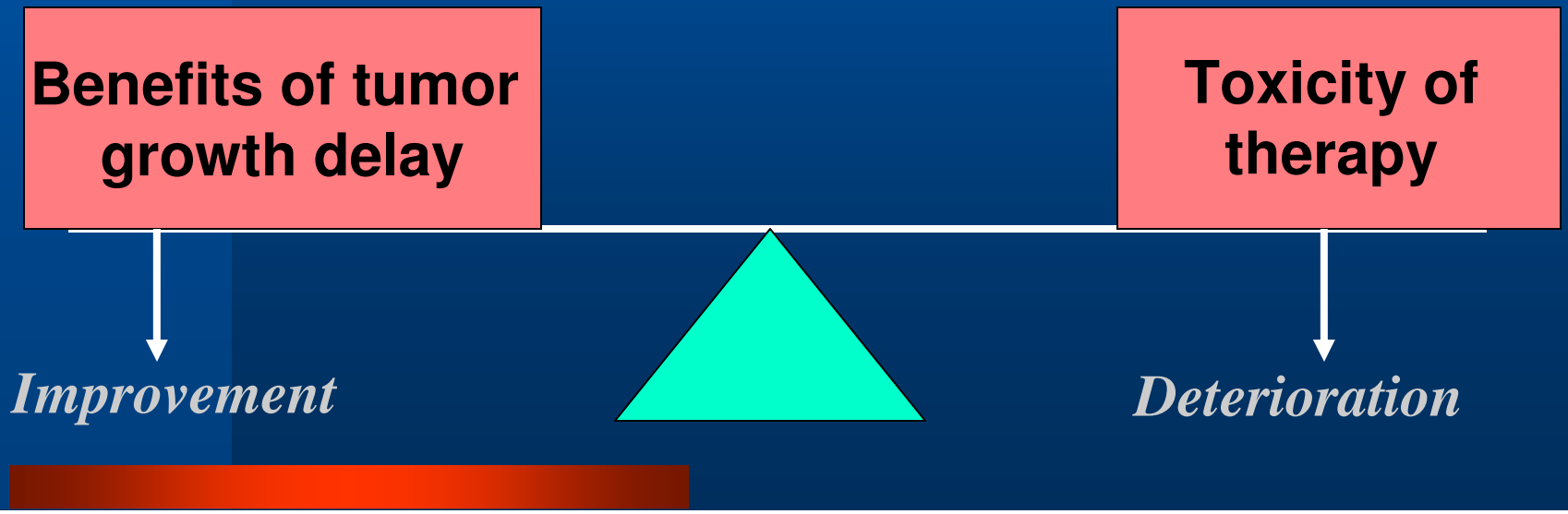
(<10% remissions)

- Pancreatic cancer, Liver cancer, Kidney cancer

Acceptability of toxicity is inversely proportional to likelihood and magnitude of expected benefit.

Palliative Effects of Chemotherapy

- Chemotherapy may shrink the tumor, provide relief of symptoms and lead to improvement.
- Chemotherapy may cause toxicity which leads to deterioration.



Dose Intensity

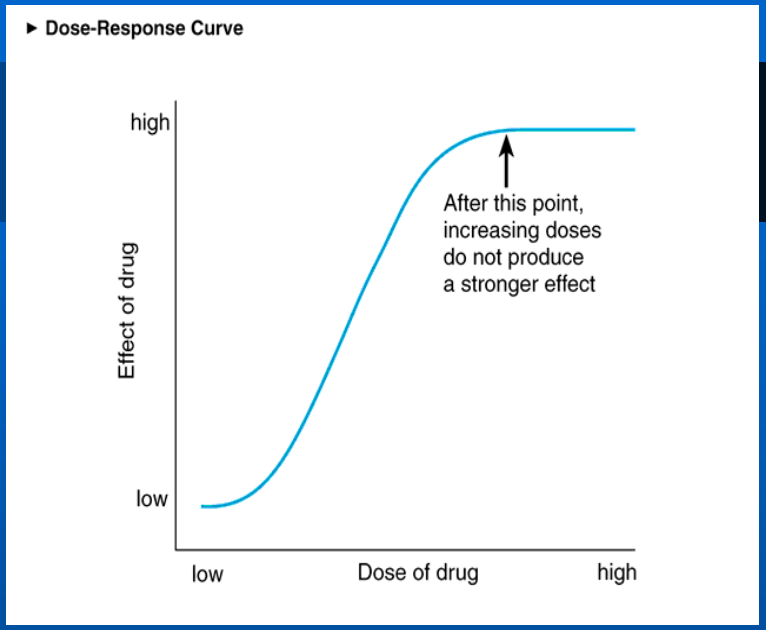
Rationale:

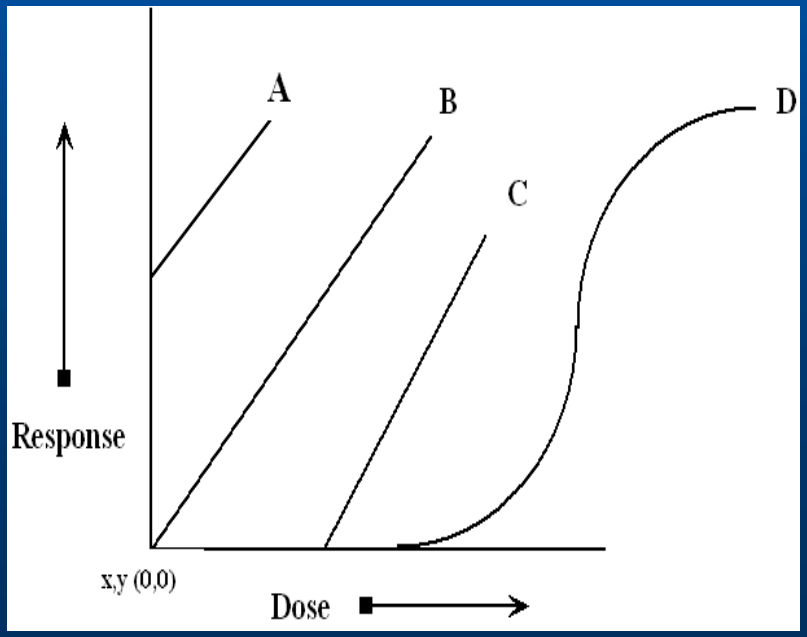
- More is better [in vitro]

However…..

- Disease and drug specific
- Toxicity will increase
- Depends on goals of therapy

Poorly understood and characterized in patients





Combination Chemotherapy

Rationale:

- minimize resistance
- maximize synergy/additivity
- avoid drugs of overlapping toxicity
- cytokinetic considerations
- biochemical considerations

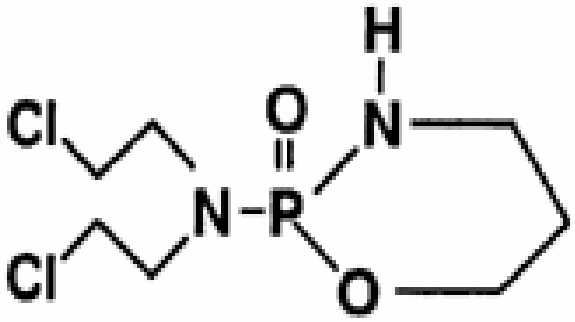
Types of systemic therapy.

- Chemotherapy [cytotoxic therapy]
- Hormonal therapy
  - Breast and prostate cancers
- Immune therapy
  - Interferon, Interleukin-2
- 'Molecular' or 'Targeted' therapies
  - EGFR, VEGF, mTOR.

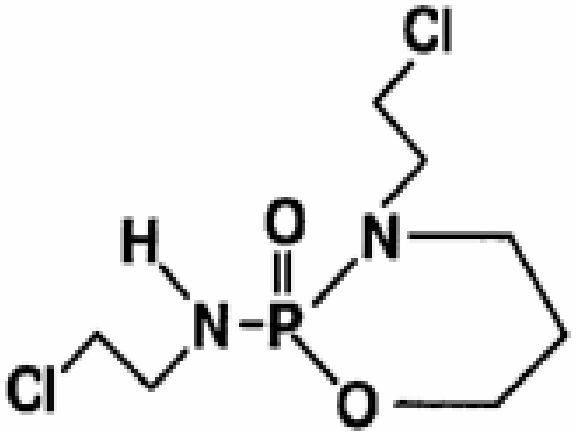
Types of systemic therapy.

- Chemotherapy [cytotoxic therapy] – a functional classification.
  - Alkylating agents.
  - Platinating agents.
  - Anti-metabolites.
  - Topoisomerase inhibitors.
  - Anti-mitotic agents.

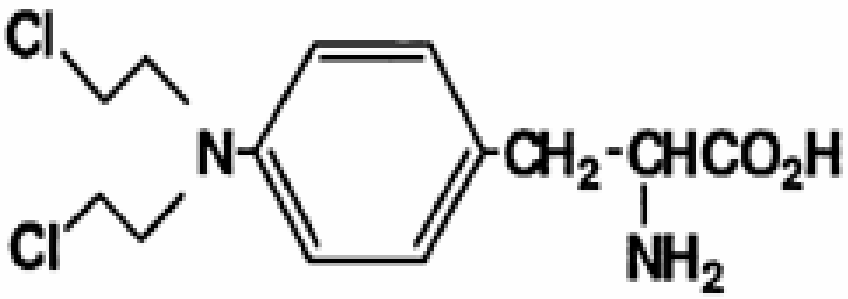
Nitrogen Mustard Alkylating Agents.



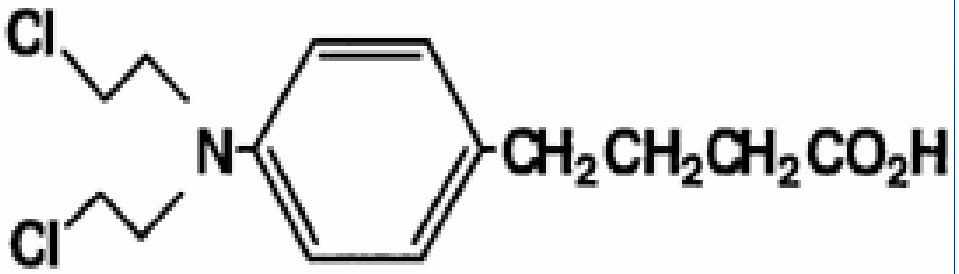
Cyclophosphamide



Ifosfamide

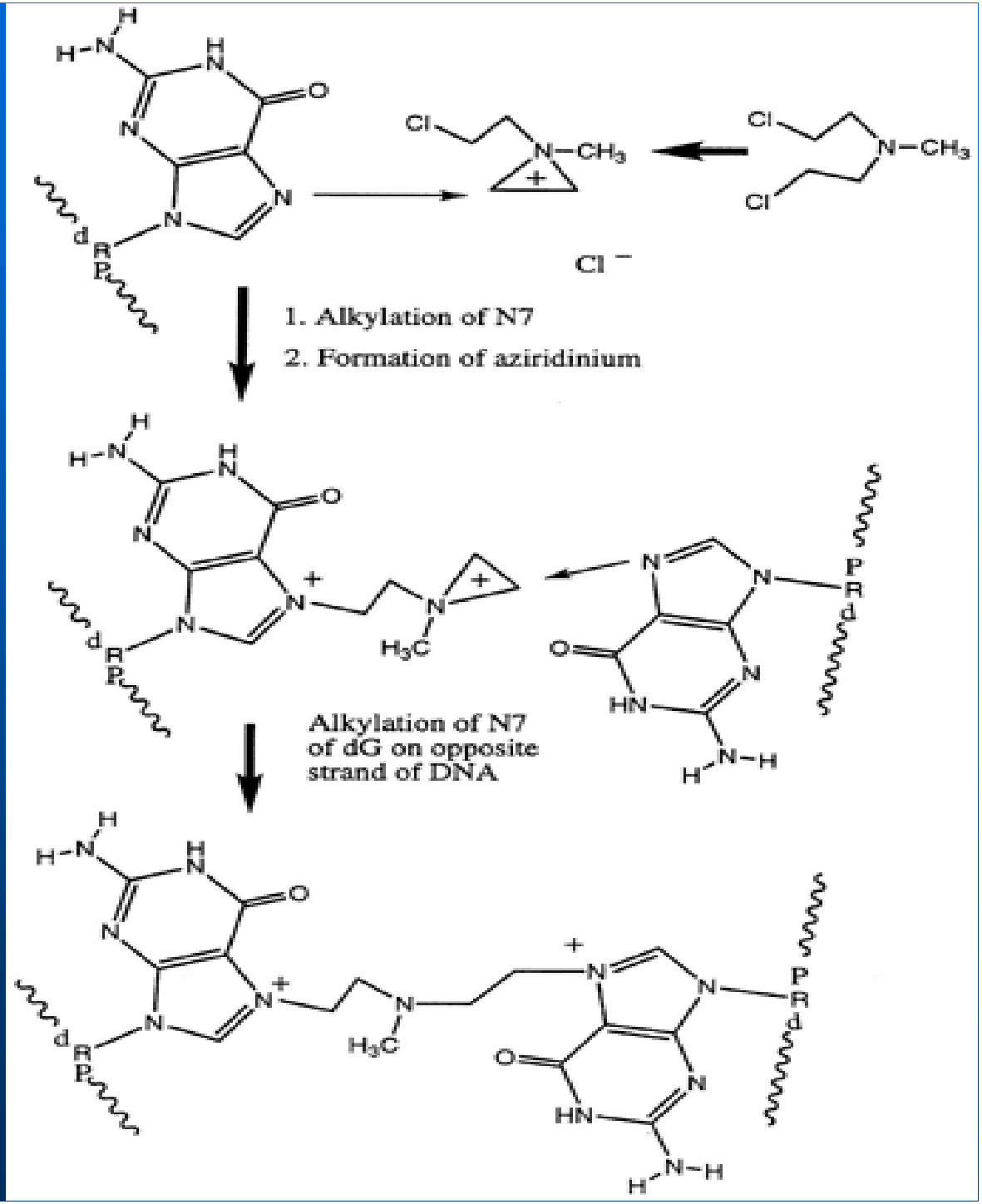


Melphalan



Chlorambucil

Inter Strand Cross Linking by Nitrogen Mustard



Complications/Toxicity

- Acute toxicities
  - vomiting, mucositis, low blood counts
- Chronic toxicities
  - cumulative organ damage - heart, lung, nerves.
- Late toxicities
  - infertility, secondary cancers.

The New Way…

Targeted Therapies

Novel targets in cancer therapy

A greater understanding of cancer biology has identified a number of potential novel approaches to cancer therapy:

- Cell Signaling
- Apoptosis and cell death
- Agents directed at tumor vasculature
- Cell cycle inhibitors
- Replicative-selective adenovirus; Gene therapy
- Differentiation agents
- Antisense oligonucleotides
- Immunostimulants; Vaccines……..

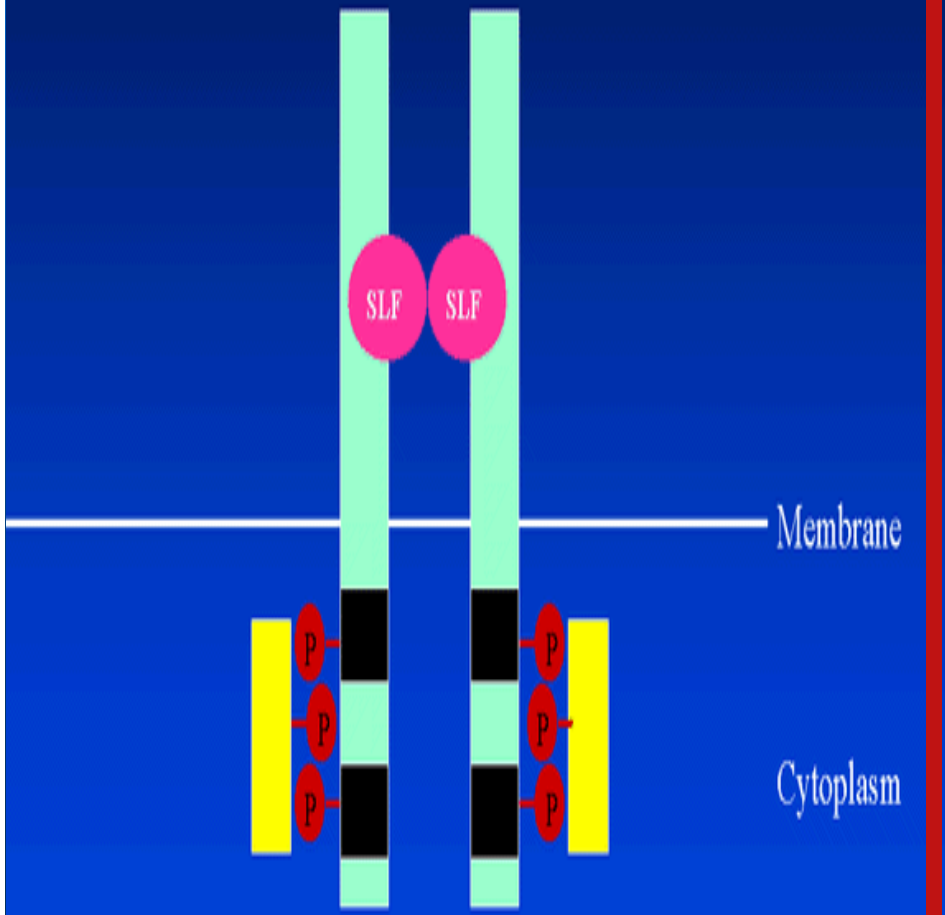
What do the new therapies look like?

- Targeted against a specific feature of the cancer.
  - Less [different] toxicity
  - Therapy on basis of specific features of tumor rather than histology.
- Chronic continuous therapies.

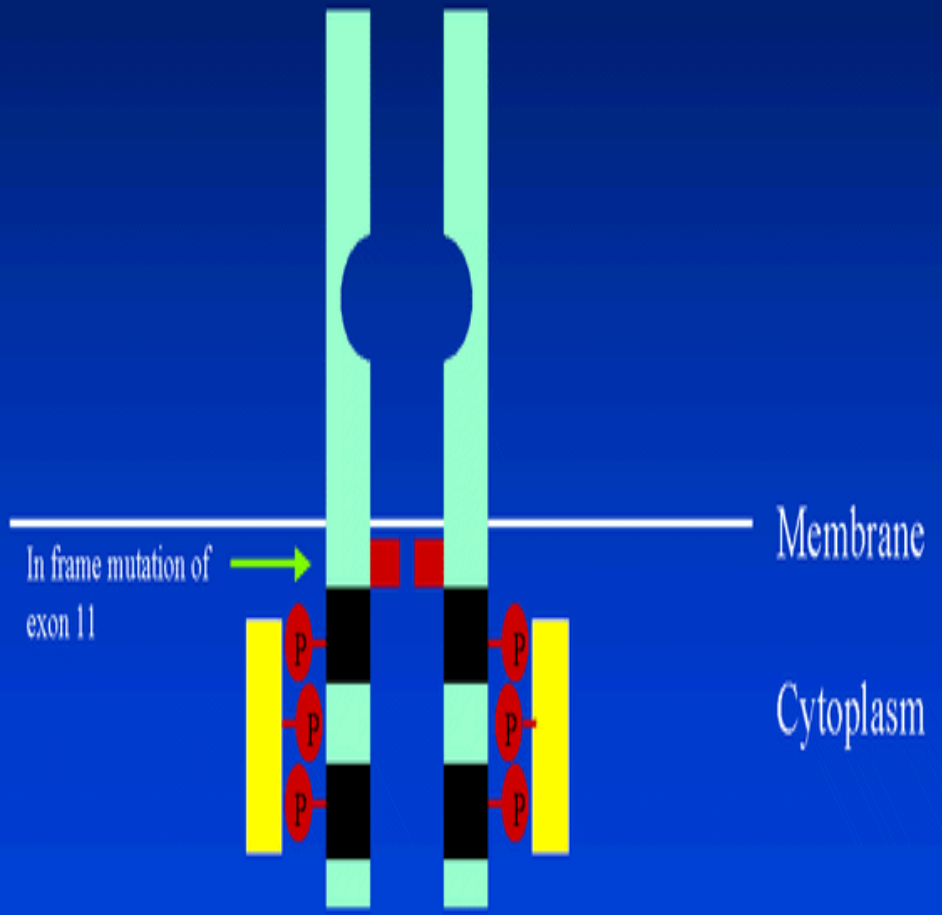
GI Stromal Tumors and c-kit

- Rare mesenchymal gut neoplasms [5000 per year]
- Resistant to XRT, chemotherapy.
- Median survival of advanced disease - 12 months.
- C-Kit: 145 Kd transmembrane glycoprotein.
- Kit protein normally expressed in.
  - Heme progenitors,Mast cells, germ cells,
  - Interstitial cells of Cajal.
- Expressed in limited number of tumors.
  - GI stromal tumors.

Ligand-dependent Activation of Wild-type KIT



Ligand-independent Activation of Mutant KIT (Exon 11)



STI571 (Imatinib;Gleevac)

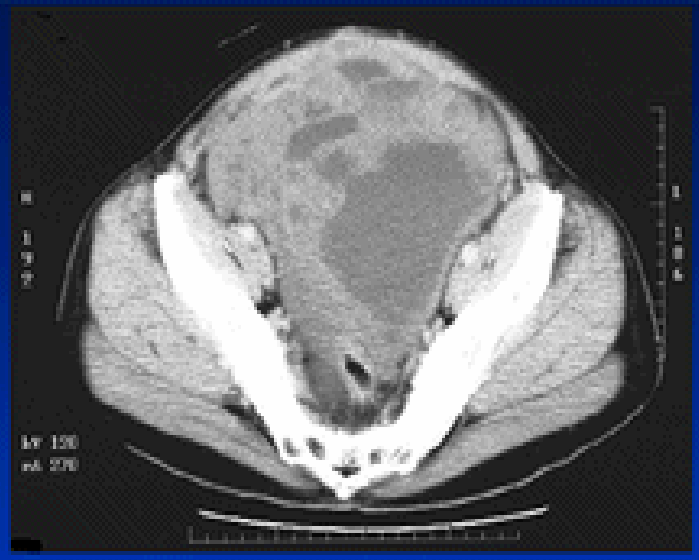
- Ø Selective tyrosine kinase inhibitor. - BCR-ABL [CML] as well as PDGF, KIT.
- Ø Inhibits phosphorylation of KIT leading to apoptosis.
- Ø Studies initiated in advanced GIST's expressing c-KIT

Best Response

	400 mg n = 44	600 mg n = 41	All pts n = 86
Partial response-n (%)	22 (50)	28 (68)	50 (59)
Stable disease-n (%)	12 (27)	10 (24)	22 (26)
Progression-n (%)	9 (21)	2 (5)	11 (13)

Pre- and Post-STI571

8/16/00



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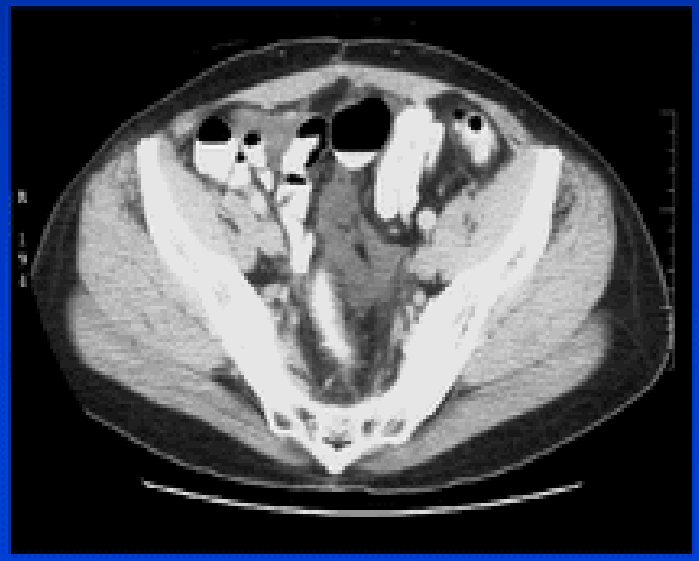

How to develop drugs?

- 1960/70's
  - screening natural products
  - development of anti-metabolites
- 1980
  - analogue development
- 1990
  - understand the disease
  - develop therapies targeted to features of cancer.
- 2000
  - major expansion of targets being tested.

Drug Development Conventional Cytotoxics

More is better - treat to maximally tolerated dose [MTD].

Phase I - define MTD, toxicity profile, pharmacokinetics, ? Any activity.

Phase II - what is the remission rate?

Phase III-compare to standard care

Drug Development
Targeted Therapy

More may not be better - treat to maximal biological effect.

Phase I - define dose, toxicity profile, pharmacokinetics, ***target effects***.

Phase II – Disease control rather than remission.

Phase III-Add to current therapies.

Summary

- Cancer is a disease of uncontrolled cell proliferation.
- Drug treatment of cancer
  - Cytotoxic Agents
    - Limited by narrow therapeutic index/ lack of selectivity.
    - Optimal dosing is critical.
  - Targeted Therapies
    - The way of the future.
    - Broader therapeutic index / more selective but…
    - Selection of appropriate patients/tumors is critical.