GOALS OF CANCER THERAPY:

- Destroy cancer cells or slow down their growth
- Cure cancer by destroying all cancer cells
- Reduce the chance that cancer will come back
- Prevent growth of new cancer cells
- Control the cancer by preventing spreading or destroying cancer cells that have already spread to other parts of body
- Relief of symptoms in advanced disease

TYPES OF TREATMENT:

Neoadjuvant	• To shrink tumors before radiation or surgery
Adjuvant	• After surgery or radiation to kill remaining cancer cells • Helps reduce risk of recurrence
Relapsed/ recurrent	• For cancer that comes back after treatment
Advanced/ palliative	• For metastatic cancer that has spread to other parts of the body • Symptom management
Alone	• Sometimes chemotherapy is the only modality

TUMOR KILL:

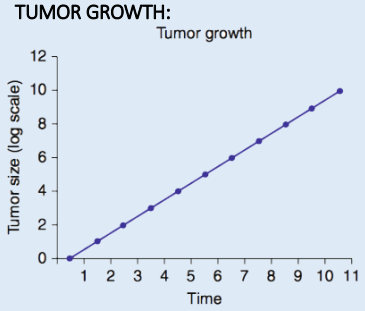
LOG-KILL HYPOTHESIS:

- A model for the effect of cytotoxic chemotherapy on tumor size
- A given dose of chemotherapy kills the same fraction of tumor cells regardless of the size of the tumor at the time of treatment
  - Magnitude of tumor cell kill is logarithmic
- Rapidly proliferating normal cells are affected → toxicity

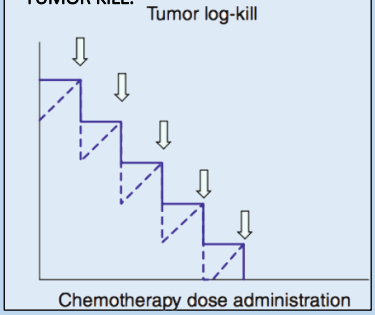
TUMOR KILL:

- Clinical experience does not always support this model
- Cure is rare in advanced care
- Recurrence in patients with early stage cancer

TUMOR GROWTH:



TUMOR KILL:



EFFICACY VS. TOXICITY:

- **Efficacy =** ideally, drugs should only work on pathways unique to cancerous cells
- **Toxicity =** most drugs affect all proliferating cells to some extent

RATIONALE FOR COMBINING CHEMOTHERAPY DRUGS:

- Often leads to better outcomes
- Additive therapeutic/anti-tumor effect
  - Kill as many cancer cells as possible
  - Different mechanisms – increase the chance of killing cancer cells regardless of where they are in cell cycle
  - Lower the chance that cancer cells will develop mutations that make them resistant to treatment – resistance may develop to single agent only
- Different dose-limiting toxicities

WHAT ARE PROTOCOLS?

- Summary of ***specific treatment regimens***
  - Include drugs on the BCCA Benefit Drug List
- Tells us;
  - Who should receive treatment
  - How they should receive treatment
  - How to monitor
- Accompanying Preprinted Orders (PPOs) and patient information handouts
- Organized by Tumor Groups (aka tumor sites)
  - 15 tumor groups
  - Supportive care protocols

PROTOCOL CODE FORMAT:

- Communication tool within health care team
- First two letters indicate the tumor group **[BR] [GI] [LY]**
  - If a tumor group has more than one site, the specific site may also be included
    - **GO OV = GO** for gynecology tumor group & **OV** for ovarian site
    - **GU P = GU** for genitourinary tumor group & **P** for prostate site
- Is treatment **[AJ]** adjuvant or **[AV]** advanced?
  - **AJ =** given after curative txt to reduce disease recurrence and improve survival
  - **AV =** palliative; used to control progression or sx of metastatic or unresectable disease
- The first 1-3 letters of the drug(s) used in the protocol complete the protocol code
  - GUP**DOC** = docetaxel
  - GIAJ**CAPOX** = capecitabine + oxaliplatin

WHY PROTOCOLS?

- In British Columbia:
  - BC Pharmacare – outpatients
  - Hospital formularies – inpatients
  - BCCA Benefit Drug List – cancer patients
- Standardized (BCCA)
- Evidence-based
- Monitoring/safety parameters
- Accountability & data collection
- Cost-effectiveness

COMPONENTS OF PROTOCOLS:

- Protocol code
- Tumor group
- Eligibility
- Exclusion criteria
- Tests
- Premedications
- Treatment
- Dose modifications
- Precautions
- BCCA consult physician
- Date of lest revision
- References

PROTOCOLS – ELIGIBILITY CRITERIA

- Disease staging
- Performance status – ECOG (Eastern Cooperative Oncology Group)
  - Estimates patient's ability to perform certain ADLs
  - Helps determine prognosis and ability to tolerate treatment
  - Used in clinical trials and in chemotherapy protocols
- Age
- Previous treatment
- Tumor markers/biomarkers
  - HER2 [breast cancer], ALK [lung cancer]
- Laboratory criteria – organ function

0 = normal activity
1 = sx & ambulatory; cares for self
2 = ambulatory > 50% of time; occasional assistance
3 - ambulatory </= 50% of time; nursing care
4 = bedridden

PROTOCOLS – EXCLUSION CRITERIA:

- Safety focused
- Often reflect clinical trial exclusion criteria
- Pre-existing conditions
- Organ status (cardiac, renal, hepatic)

TESTS:

- <u>Baseline tests:</u> to confirm eligibility criteria, establish basis of comparison
- <u>Routine tests prior to each cycle:</u> monitoring for toxicity, efficacy
- <u>As needed:</u> to investigate adverse effects
  - CBC (ANC, platelets)
  - Renal function (CrCl)
  - Liver function (AST, bili)
  - EKG, ECHO
  - Electrolytes
  - Urine protein
  - Blood pressure
  - Tumor markers

PREMEDICATIONS:
- Nausea and vomiting: SCNAUSEA protocol
- Hypersensitivity reactions: *steroids, antihistamines, H2-blocker*

SUPPORTIVE MEDICATIONS: up front in some protocols
- Prevention of febrile neutropenia: *growth factor support* (G-CSF)
  - Allow delivery of chemotherapy regimen
- Prevention of hepatitis B re-activation: *lamivudine*
- Prevention of PCP pneumonia: *co-trimoxazole*

CHEMOTHERAPY CYCLE:
- Duration of administration (ex// 5 mins vs 1 hr vs 46 hr IV)
  - Kinetics: how quickly is drug cleared?
  - Safety: adverse effects, hypersensitivity reactions
- Frequency of cycle (ex// q2week, q4h week, daily/continuous)
  - Frequently enough to kill cancer cells
  - Hematologic toxicity: recovery of counts
- Number of cycles:
  - 2 cycles → indefinitely until progression

TREATMENT – METHODS OF ADMINISTRATION:

• IV direct	• SC, IM
• IV intermittent	• Topical
• IV infusion (hospital, at home)	• IT, IP, intravesical (bladder)
• PO	• Chemoembolization

TALLman LETTERING:
- Medication safety initiative
- To help prevent errors stemming from look-alike/sound-alike drugs
- Incorporated into all protocols and PPOs

CHEMOTHERAPY DOSING:

Flat dosing	Weight-based dosing	BSA-based dosing	AUC-based dosing

• Ex// 50 mg PO daily	• Ex// 10 mg/kg	• Ex// 60 mg/m^2
		• Mosteller formula
		• Requires current **wt** & **ht** of pt
		• Average female BSA = 1.6 m^2
		• Average male BSA = 1.9 m^2
			• Calvert formula used for **carboplatin** dosing (dose = AUC (GFR + 25)
			• Strong correlation b/w total body clearance of carboplatin and GFR
			  ○ Better renal function = higher GFR
			• Target AUC of carboplatin proportional to percentage of reduction in platelet count
			  ○ Higher AUC if treatment-naïve or tolerating chemo

DOSE MODIFICATIONS:

DOSE MODIFICATIONS:
- Baseline tests +++ important
- Toxicity: ~~symptomatic ADRs or asymptomatic (routine monitoring)~~
  - Symptomatic adverse effects
  - Asymptomatic = routine monitoring
- Dose modification algorithms built into protocols
  - Decrease dose
  - Delay treatment
  - Increase cycle interval
  - Change protocols
- Allows patient to continue on treatment

HEPATIC DOSE MODIFICATIONS:
- Liver function tests:
  - Hepatocellular injury: ↑ ALT/AST
  - Presence of cholestasis: ↑ bilirubin, ↑ alk phos
- Abnormalities could be adverse effects or metastases (liver, bone)
- Pharmacodynamic and pharmacokinetic problem:
  - PD: effect of chemotherapy on the liver = hepatotoxicity
  - PK: ability of liver to metabolize chemo maybe compromised
- Dose modifications may address both PK & PD problems
  - Based on how many x ULN

RENAL DOSE MODIFICATIONS:
- Renal dysfunction could be adverse effect or separate disease
- Pharmacodynamic and pharmacokinetic problem
  - PD: effect of chemotherapy on kidney = nephrotoxicity
  - PK: ability of kidney to eliminate chemo maybe compromised
- Dose modifications may address both PK & PD problems
  - As CrCl declines, drug accumulates → smaller dose
  - < 30 mL/min → drug usually avoided
- Carboplatin protocols use AUC-based dosing
  - Consider dose re-calculation if SrCr ↑ 20% above baseline

OTHER TOXICITY DOSE MODIFICATIONS:
- Neurologic, GI, skin

ADVERSE EVENT GRADING: common Terminology Criteria for Adverse Events (CTCAE)
- Adverse events severity grading scale
- Descriptive terminology
- Designed for use in clinical trials
- Widely accepted/used in oncology treatment protocols

HEMATOLOGIC TOXICITY:
- Major dose-limiting side effect
  - Most common cause of treatment delays and dose reductions
- Rapidly growing bone marrow cells affected by chemo → myelosuppression (↓ WBC, ↓ platelet, ↓ RBC)
  - Nadir = time when lowest cell counts observed
  - Recovery = when cell numbers return to normal
    - Cycle length of 21-28 days allows for recovery from nadir

NEUTROPENIA:
- Neutrophils constitute 50-70% of circulating WBCs
- ANC = absolute neutrophil count (normal = 3-7 x 10^9 /L)
  - Measurement of total number of circulating neutrophils
- Severity and duration of neutrophil suppression related to dose, PK, administration schedule
  - Daily chemo over several days → longer, shallower nadir
  - Single chemo dose → shorter, deeper nadir
- ANC may not fully recover by next cycle
- Threshold value for dose modifications depends on protocol
  - ANC < 1.5 x 10^9/L (or even lower for other protocols)
    - Greater risk for infection

THROMOBOCYTOPENIA:
- Increased risk of bleeding
- If platelets not fully recovered, dose modification may be necessary
- Majority of BCCA protocols require threshold platelet value of 100 x 10^9 /L to proceed on time with full dose chemo
- Dose modification algorithm often combines ANC and platelets

PROTOCOLS: precautions (adverse effects, reactions, drug interactions); contact physician; date of last revision; references)