2004 BASS Symposium

Breast Cancer Chemotherapy

Treatment, Design, & Recent Advances

Dedicated to a Beloved Friend, Dr. J.P. Hsu

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Memory ---

Dr. J.P. Hsu

- *A Gentle Boss*
- *A Sincere Mentor*
- *A Beloved Sister*
- *A Wonderful Friend*
- *A Great Human Being*

Breast Cancer – Sad Facts

- In 2004, there are 216,000 predicted new cases of female breast cancer in the US and 800,000 cases around the world.
- Approximately 30% of these patients will have metastatic breast cancer.
- Approximately 80% of the breast cancer patients will die in 10 years after diagnosis.

Outline of Presentation

- History of cancer clinical trials.
- Principle of chemotherapy.
- Risk factor and predictive models.
- Adjuvant & neoadjuvant cancer treatments.
- Dose-dense treatment.
- Statistical designs and issues.
- Summary.

Cancer Research
Historical Note

- In 1997, the NCI's Clinical Trials Program Review Group recommended to revamp the clinical trials system.
- The primary goal:
  - To accelerate the pace of clinical cancer research.
  - To enable all oncologists in the US to offer patients NCI-sponsored clinical trials.
  - To simplify and standardize procedures to participate.

Cancer Research
Historical Note

- New features of the system:
  - standardization of data collection
  - online data reporting
  - simplified informed consent
  - Established a centralized institutional review board (CIRB) process.
- Established the Cancer Trials Support Unit
  - implement a uniform system of patient registration and data collection for all trials in the network.

Cancer Research
Historical Note

- The CIRB
  - Shares responsibility for protection of research participants between the local IRB and the CIRB.
  - Results of review are distributed to the participating local IRBs via a confidential website.
  - Fifty-three phase III protocols have now gone through this process, and 139 local IRBs have participated.

CHEMOTHERAPY

Principles of treatment

1. Cell cycle : 5 phases

   G0 : “Resting cells”

   G1 : RNA and protein synthesis

   S : DNA synthesis

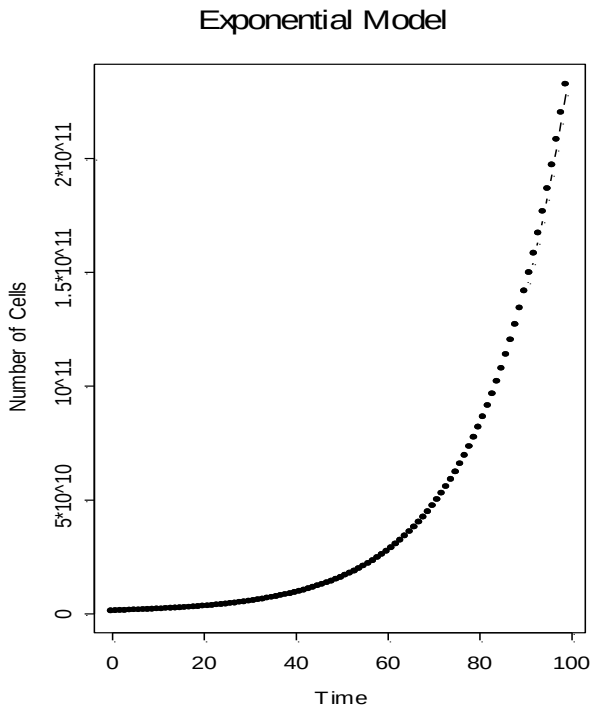
   G2 : RNA and protein synthesis

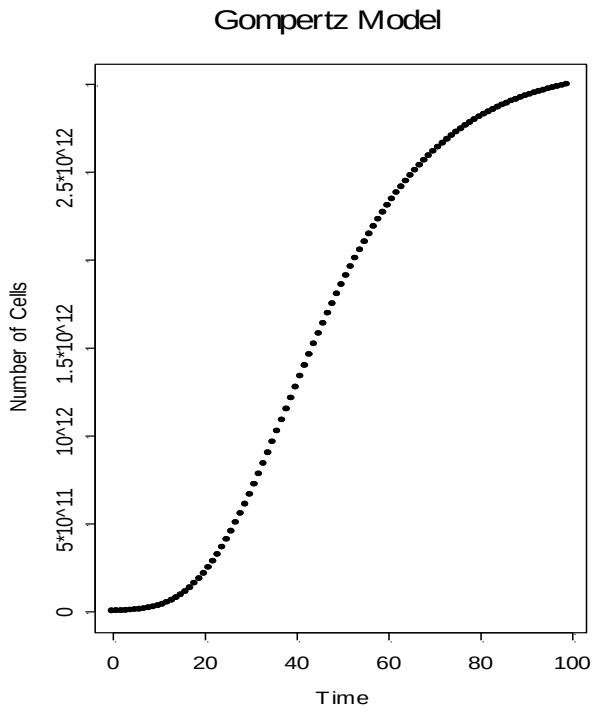
   M : Cell division (mitosis)

2. Goal of a drug:

   To interrupt the cell cycle

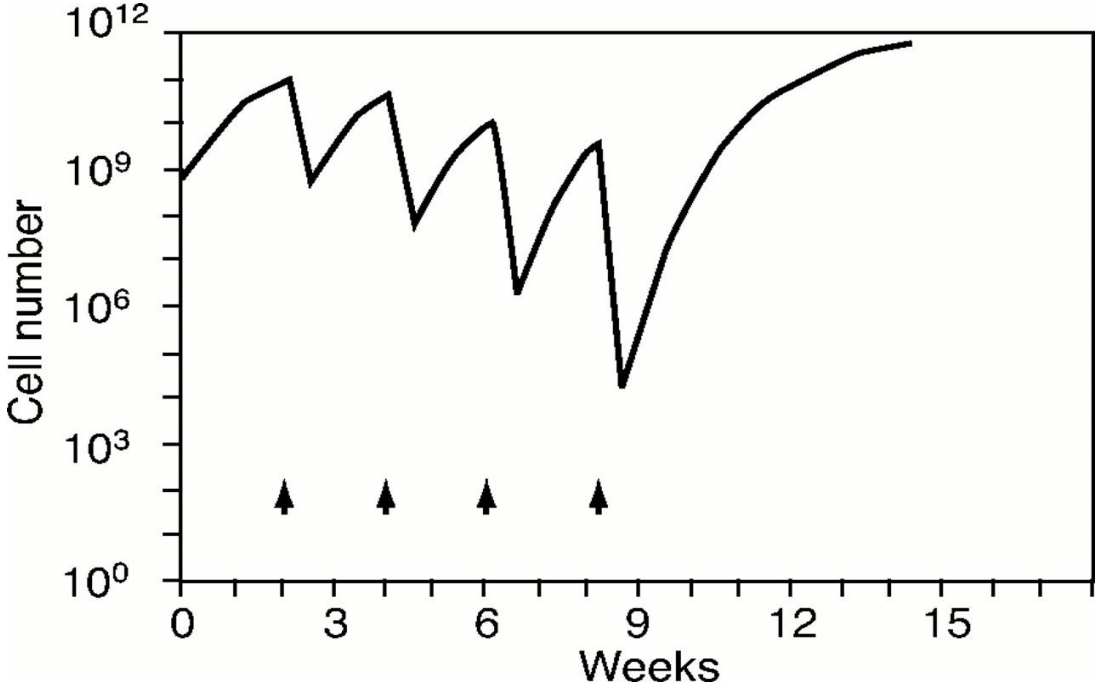
Cell Growth Models





Basis of Chemotherapy

Growth and Kill Model



Anti-Cancer Drug
Classification

- Chemotherapy
  - Alkylators, Antibiotics, Antimetabolites, Topoisomerases inhibitors, Mitosis inhibitors, etc.
- Hormonal therapy
  - Steriods, Anti-estrogens, Anti-androgens, LH-RH analogs, Anti-aromatase agents.
- Immunotherapy
  - Inteferon, Interleukin-2, Vaccines.

Breast Cancer Chemotherapy
Agents

A few frequently used chemo agents:

- Tamoxifin
- Taxanes
  - Paclitaxel, Docetaxel
- Capcitabine, Vinorelbine, Gemcitabine.

Side Effects of Chemotherapy

- Grade 3 or 4 toxicity are most concerned.
- Common toxicities:
  - Neutropenia
  - Anemia, nausea/vomiting
  - Diarrhea, Alopecia
  - Peripheral Neuropathies
  - Mucositits
  - Arthralgia/myalgia

Chemotherapy Side Effects
Causes

- Anticancer drugs kill fast growing cells
  - blood cells progenitors
  - cells in the digestive tract
  - reproductive system
  - hair follicles
- Other tissues affected
  - heart and lungs
  - kidney and bladder
  - nerve system

Chemotherapy

Strategies of administration

- Monotherapy
- Combination chemotherapy
  - Combined effect > ind. effect + ind. toxicity
  - Goal: maximize efficacy & minimize toxicity
- Adjuvant chemotherapy
  - Apply when no evidence of cancer
  - Goal: prevention of recurrence
- Neoadjuvant chemotherapy
- Combined modality chemotherapy :
  - Chemotherapy + radiotherapy + surgery
  - Goal: obtain higher response rate

Chemotherapy for Metastatic Breast Cancer

- **Single agent**: often used for women with good performance status.
- **Combination**: usually reserved for patient with symptomatic disease requiring a quicker response.
  - US Oncology trial showed the combination of capecitabine and docetaxel improves RR, TTP, & OS compared with docetaxel alone.
  - ECOG – 1193 with doxorubicin and paclitaxel did not improve survival.

Chemotherapy for Metastatic Breast Cancer

- ***Relapsed after adjuvant therapy***: recommended for combination chemotherapy like docetaxel/capecitabine.
  - Capecitabine is recommended for older women with very indolent disease, with no treatment for a long time, and prefer good quality of life.
  - Anthracycline-based regimens are commonly utilized in women without prior adjuvant chemotherapy.

Chemotherapy for Metastatic Breast Cancer

- ***Sequential or Concurrent***:
  - The decisions regarding sequencing depend on the side-effect profiles of various agents.
  - No consensus.

Chemotherapy for Metastatic Breast Cancer *(Pt. with ER/PR-, Her2-, >50 yrs)*

Clinical Situation	Combo.	Seq.
Asymptomatic patients with bone metastases	23%	77%
Asymptomatic patients with several small lung metastases	30%	70%
Asymptomatic patients with several small hepatic metastases	38%	62%
Patients with bone metastases with moderate pain requiring oral narcotics	50%	50%
Very symptomatic patients with visceral metastases	85%	15%

Chemotherapy for Metastatic Breast Cancer *(Combination chemo)*

Agent	**Adjuvant chemotherapy**		
	No prior Rx	AC-paclitaxel (> 2yrs)	AC (>2 yrs.)
AC	29%	-	-
FAC/FEC	26%	6%	3%
Capecitabine/docetaxel	16%	64%	61%
AT (either taxane)	16%	3%	6%
Platinum agent/docetaxel	3%	9%	9%
Capecitabine/paclitaxel	-	3%	6%

Chemotherapy for Metastatic Breast Cancer *(Seq. single agent after adj AC chemo)*

Agent	1st line	2nd line	3rd line
Docetaxel	65%	30%	3%
Paclitaxel	20%	2%	2%
Capecitabine	8%	33%	23%
Vinorelbine	-	20%	33%
Gemcitabine	2%	8%	35%
Doxorubicin	5%	5%	2%
Cyclophosphamide	-	-	2%
Platinum	-	2%	-

Chemotherapy
Strategies to maximize effect

- Chemotherapy spaced out over a long time
  - 4 to 12 + months
  - Aim: gradually lower the number of cells
- Chemotherapy repeated
  - 3 or 4 weekly
  - Aim: wait for another cell-cycle / phase
- Continuous infusion
  - 1 to 5 + days
  - Aim: for drugs being “phase specific.”

Breast Cancer
Risk Factors

Key factors:

- Age
  - Risk increases with age.
- Reproductive risk factors
  - Higher risk: early menarche &/ late menopause, late pregnancy.
- LCIS & DCIS increase risk of invasive cancer.
- Prior history & family history of breast cancer.
- Genes.
- Environmental & life style factors.

Breast Cancer
Risk Estimation Model (1)

Gail, M., *et al.*, *"Projecting Individualized Probabilities of Developing Breast Cancer for White Females Who Are Being Examined Annually," JNCI, 1989.*

- Based on BCDDP *(Breast Cancer Detection Demonstration Project)* database
  - To estimate breast cancer incidence rates.
  - Assume a piecewise baseline hazard rates.
  - Case-control method.
  - For both invasive and *in situ* breast cancer.

Breast Cancer
Risk Estimation Model (1)

- ***Comments*** on the model by Gail, M., *et al*.
  - Incorporates more risk factors than prior strategies.
  - More precise point estimate.
  - Not assume any genetic model.
  - Has been used in clinical counseling.
  - Has served as basis for patient selection in prevention trials with tamoxifen.
  - The model underestimates the absolute risk for women with genetic changes.

Breast Cancer
Risk Estimation Model (2)

Costantino, J., *et al.*, *"Validation Studies for Models Projecting Invasive and Total Breast Cancer Incidence," JNCI, 1999.*

- Based on SEER database
  - To estimate age-specific invasive breast cancer rates.
  - To estimate baseline hazard rates.
  - Include black women.
  - For invasive breast cancer only.

Breast Cancer Risk Estimation

Statistical Model

Predictive model of cancer risk

(*Gail, et al., JNCI, 1989*)

Factor	**Coeff.**	**Factor**	**Coeff.**
a. Age at menarche	0.094	e. Age (>50)	0.011
b. # prev breast biopsies	0.529	f. b x e	-0.288
c. Age at 1st live birth	0.219	g. c x d	-0.191
d. # 1st degree relative with breast cancer	0.958		

Breast Cancer Risk Estimation

Relative risk (*Gail, et al., JNCI, 1989*)

NBIOPS	AGE	
	< 50 yr	≥ 50 yr
0	1	1
1	1.698	1.273
≥ 2	2.882	1.620

AGEMEN	≥14	12-13	< 12
0	1	1.099	1.207

NUMREL	AGEFLB			
	<20	20-24	25-29	≥ 30
0	1	1.244	1.548	1.927
1	2.607	2.681	2.756	2.834
≥ 2	6.798	5.775	4.907	4.169

Total RR (same age) = RR (Table 1) × RR (Table 2) × RR (Table 3)

Breast Cancer Risk Estimation

Relative risk (*Based on Nurses' Health Study*)

NBIOPS	AGE	
	< 50 yr	≥ 50 yr
0	1	1
1	1.80	1.62
≥ 2	-	-

AGEMEN	≥14	12-13	< 12
0	1	1.05	1.10

NUMREL	AGEFLB			
	<20	20-24	25-29	≥ 30
0	1	1.16	1.33	1.54
1	1.59	1.80	2.04	2.32
≥ 2	2.52	2.81	3.12	3.48

Total RR (same age) = RR (Table 1) × RR (Table 2) × RR (Table 3)

Cancer Risk Estimation Model
Use in Practice

Use of computer program to calculate the risk of recurrence in practice (*ADJUVANT! or Mayo Clinic*).

Risk profile	**Node-Pos**	**Node-Neg**
Baseline risk of relapse	40%	31%
Risk of relapse with treatment	20%	17%
Provide the information to patients	76%	84%

Chemoprevention Trials Using Tamoxifen

- ***NSABP***: prophylactic tamoxifen with placebo (5 yr):
  - Reduce the risk of cancer for all age groups *(<50 yr: 44%, 50~59 yr: 51%, >=60 yr: 55%).*
- ***Royal Marsden Hospital*** tamoxifen prevention trial:
  - No significant difference *(p=0.8).*
- ***Italian*** tamoxifen prevention trial:
  - No significant difference *(p=0.2).*
- ***IBIS-I*** prophylactic tamoxifen trial:
  - Reduce cancer risk by *32% (p=0.013). SAE: VTE.*
- ***STAR*** trial: compare Tamoxifen with Raloxifene.

Systemic Therapy for Metastatic Breast Cancer

Key considerations:

- Prognostic factors.
- Sequence of treatment regimen:
  - Sequential single agent or
  - Concurrent combinations.

Systemic Therapy for Metastatic Breast Cancer

- Key prognostic factors:
  - Tumor size
  - Axillary node status
  - Tumor stage: *(T1: <= 2cm; T2: 2-5 cm; T3: >5 cm)*
  - Histological grade
  - Age
  - ER & PR expressions

Systemic Therapy for Metastatic Breast Cancer

- Sequential single agent & combination:
  - Single agents for patients with good PS
  - Sequencing decision may be affected by side effect profiles.
  - Docetaxel+capecitabine is an effective combination chemotherapy.

Adjuvant Chemotherapy

- The most important recent research affecting utilization of adjuvant chemotherapy:
  - Cancer & leukemia Group B (CALGB) –9741, CALGB-9344, NSABP-B-28 and BCIRG-06
    - Randomized trial
    - Dose dense vs conventional schedule
    - Sequential vs concurrent chemotherapy
    - Trials addressing the inclusion of taxanes

Adjuvant Chemotherapy

- Six months after the initial presentation of the data, about 1/3 of U.S.-based oncologists were utilizing this approach, particularly in younger patients.
  - Patients with node-negative tumors frequently receive adjuvant chemotherapy with shorter duration compared with that in women with node-positive cancers.
  - Adjuvant chemotherapy is also used in elderly women with node-negative tumors.

Adjuvant Chemotherapy Using Taxanes

- Recent studies have integrated the taxanes into the adjuvant setting.
- For node-positive patients, the use of taxanes as adjuvant treatment are shown to be safe and beneficial.
- Docetaxel holds significant promise in the adjuvant setting.
  - Further studies are needed to determine whether it is best given sequentially to, or concurrently with, doxorubicin or epirubicin.

Adjuvant Chemotherapy Using Taxanes - *Example*

- Ravdin P. et al (2003): *Phase III comparison of docetaxel and paclitaxel in patients with metastatic breast cancer.*

Endpoint	Docetaxel	Paclitaxel	p-value
Overall RR	32%	25%	0.06
Median TTP	5.7 months	3.6 months	<0.0001
Median OS	15.4 months	12.7 months	0.03

Adjuvant Chemotherapy Using Taxanes - *Example*

- FDA recently had also approved the use of docetaxel for early breast cancer.
- Use of taxanes in adjuvant setting:
  - Docetaxel ~ 60%.
  - Paclitaxel ~ 40%.

Chemotherapy
Patient Selection

- Impact of tumor size & nodal status on choice of adj. chemotherapy

Tumor Status	2.2 cm, Node +	2.2 cm, Node -	0.8 cm, Node -
Adj. Chemo.	93%	80%	8%

Chemotherapy
Patient Selection

- Age:

Age (years)	33	43	55	65	77
Adj. Chemo.	93%	93%	98%	95%	85%

- Use of dose-dense adj. chemo. on high risk pt.

Age (years)	33	43	55	65	77
Adj. Chemo.	46%	45%	28%	29%	15%

Chemotherapy
General settings

- Neoadjuvant
  - Applied prior to operation.
- Ajuvant
  - Apply when no evidence of cancer
  - Goal: prevention of recurrence

Neoadjuvant Chemotherapy
Concept

- The concept of preoperative chemotherapy started in Dr. Fisher's laboratory in the 1980s.
  - Animal studies showed that the tumor kinetics are different when removed compared to treating it before surgery with radiation therapy, tamoxifen or cytotoxic agents.
  - These observations resulted in the concept of preoperative therapy.

Neoadjuvant Chemotherapy
Objectives

- Used in disease stage that is potentially resectable
- To reduce tumor burden
- To increase survival

- *Not a standard of treatment yet*

Neoadjuvant Therapy
Usage

- In US: neoadjuvant therapy often uses chemotherapy.
- In Europe: preoperative endocrine therapy has been extensively used in women with ER+ cancers.
- Chemotherapy and endocrine therapy have equal anti-tumor effects in patients with ER+.

Neoadjuvant Therapy
Effect

- Neoadjuvant chemo. often downstages tumors and improve chance of breast conservation.
- DFS and OS are similar to postoperative therapy.
- It is not clear whether tumor size reduction translate into more complete response.

Neoadjuvant Therapy
Strategies

- New strategies of neoadj. chemo. include dose-intensity chemo, taxanes, and combination regimens.
- It is still unknown that preoperative therapy can be used as a surrogate to determine individual benefit from systemic therapy.
- The neoadjuvant setting is also being utilized to evaluate new systemic agents and predictors of tumor response, including DNA microarray analysis.

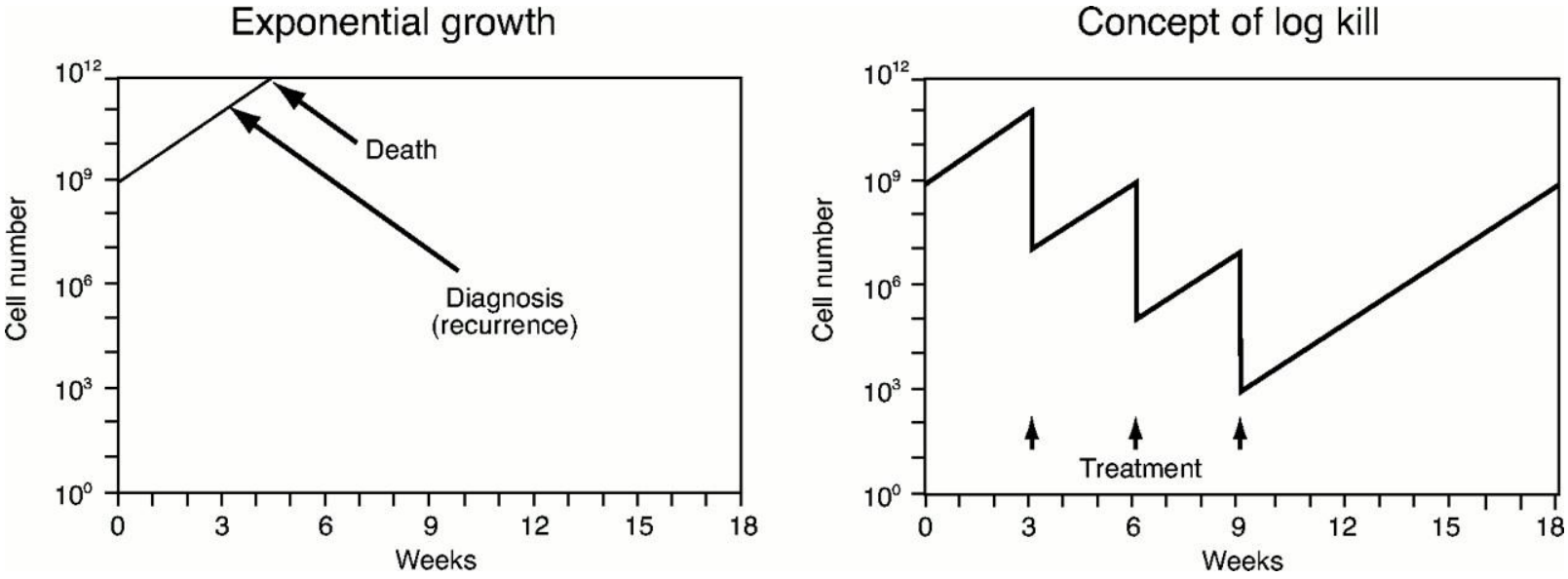
Neoadjuvant Therapy
Example

- ***Example:*** *"New Gene expression profiling for the prediction of therapeutic response to docetaxel in patients with breast cancer", Jenny C Chang, et al. The Lancet, 2003.*
- ***Findings:*** Differential patterns of expression of 92 genes correlated with docetaxel response significantly.
  - Sensitive tumors had higher expression of genes involved in cell cycle, cytoskeleton, adhesion, protein transport, protein modification, transcription.
  - Resistant tumors showed increased expression of some transcriptional and signal transduction genes.

Dose-Dense Adjuvant Chemotherapy

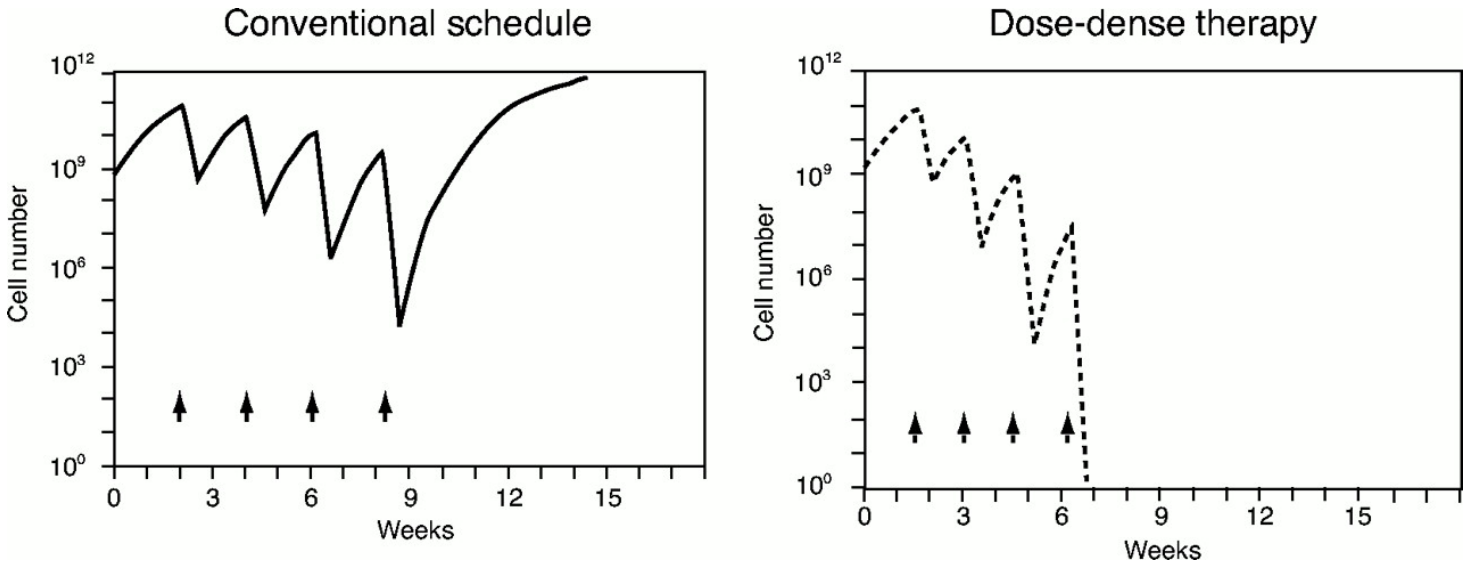
- Dose-Dense: the delivery of multiple cycles of chemotherapy using the shortest possible intervals.
- Strategy basis: theoretical model suggests the benefit of re-treatment before tumor re-growth occurs.

Dose-Dense Chemotherapy
Exponential Model



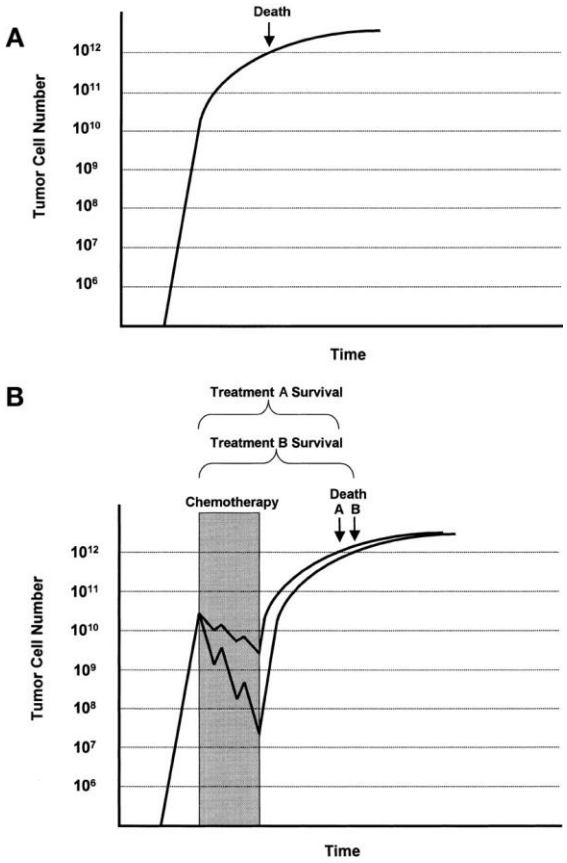
Exponential growth model: $N_t = N_0 \exp(bt)$

Dose-Dense Chemotherapy
Gompertzian Model



Gompertzian Model: $N_t = N_0 \exp[\log(N_\infty / N_0)(1 - \exp(-bt))]$

Dose-Dense Chemotherapy
Schematic anti-tumor effects



Dose-Dense Adjuvant Chemotherapy

- An important example: CALGB -9741

Parameters	Dose-dense schedule	Conventional schedule	*p*-value
N	988	985	
4-years DFS	82%	75%	RR=0.74 (p=0.010)
3-years OS	92%	90%	RR=0.69 (p=0.013)

Chemotherapy
Comments on Dose & Schedule

- Oncology practices usually reduce dose in the adjuvant setting (more likely in older women.)
- Bonadonna *et al* , CALGB-8541, and CALGB-9741 demonstrated reduced disease-free and overall survival when < 85% of the planned dose was delivered in adjuvant cancer setting.
- Most study protocols use growth factor support proactively to allow for delivery of the planned dose when neutrophil counts have not recovered and the dose is scheduled.

Angiogenesis

Angiogenesis - growth of new blood vessels

- Normal angiogenesis
  - Occurs primarily during embryonic development but also in some adult physiological processes.
- Tumor angiogenesis
  - The growth of blood vessels from surrounding tissue to a tumor and is initiated by the release of chemicals by the tumor.

Antiangiogenic Therapy

- This is a targeted therapy.
- ECOG trial:
  - Treatment: capecitabile alone or combined with bevacizumab.
  - Population: heavily pretreated metastatic breast cancer patients
  - Findings: modest improvement of RR, but not TTP.

Antiangiogenic Therapy

Advantages:

- Potential for low toxicity
- Possible lack of drug resistance
- Localized response in the vasculature
- Reliance of many tumour cells on one capillary
- May be effective across a broad range of cancers

Antiangiogenic
Combined Therapy

Rationale for potential combined agents:

- Different targets for these agents.
- Lack of cross-resistance patterns.
- Lack of myelosuppression allows administration of full doses of all agents.
- Assumption of additive effects in antitumor activity.

Design of Oncology Clinical Trials
Frequently Used Designs

- Two basic designs are widely used:
  - Fixed sample size & Two-stage design.
- Common features of these designs
  - The reference standard for the results is external to the experiment
  - Endpoint may be a surrogate outcome
  - Response is known relatively soon

Design of Oncology Clinical Trials
Variations

- Scenario for anxiety:
  - Simon 2-stage procedure: 1st stage $p=0.25$, 2nd stage $p=0.4$, □=0.05, □=0.2 □ $N=(51, 16)$, $(60, 20)$.
- Three-stage.
- Multiple test procedures.
- Efficacy & toxicity combined evaluation.

Design of Oncology Clinical Trials
Flexible variations

- Sample size adjustment.
  - E.g., based on conditional power.
- Early termination of ineffective treatment.
- Early termination of unsatisfactory toxicity treatment group.
- Combination of Phase II & III trials.

Design of Oncology Clinical Trials
Conditional power

- Decision for sample size adjustment via conditional power of the Lth interim analysis *(Lan, et al 1982)*

$$CP_L(\Delta) = P(T_K > C_K | T_L, \Delta)$$

$$\Phi\Big(\Big\{ C_K - T_L t_L^{1/2} \quad (1-t_L)(N/2)^{1/2}\Delta \Big\} \times (1-t_L)^{1/2} \Big)$$

where

- $\{T_K > C_K\}$ is the critical region for the final analysis under H_0.

From Research to Practice

- ***Practical Issues:***
  - Much resources have been expended to evaluate new breast cancer treatment interventions.
  - Effort in implementation of these advances in practice is not comparable.

From Research to Practice
Example

Q: Have you read the report of CALGB-9741 in JCL, 2003?

Category	**Percentage of physician surveyed**
No	44%
Read abstract, skimmed article	24%
Read entire article	32%

From Research to Practice

- ***Possible Remedy:***
  - Continue medical education has the potential to be a useful component in the clinical research continuum.
  - Inform clinicians about available trials and emerging research findings.
  - Implement outcomes assessments to evaluate how research advances are being implemented in clinical practice.

Summary

- Great advances on cancer treatment had been made in recent years.
- Statisticians, being analytical and quantitative, have great opportunities to contribute to the design and analyses of studies.
- Many challenging issues still exist & new research are still in great demand.
- Cooperative effort with clinicians and marketing staff is essential to enhance treatment success.