Chemotherapy Drug Sequencing

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Objectives

- Discuss rationale for chemotherapy sequencing
- Describe adverse events with improper sequencing
- Evaluate common regimens and discuss sequencing

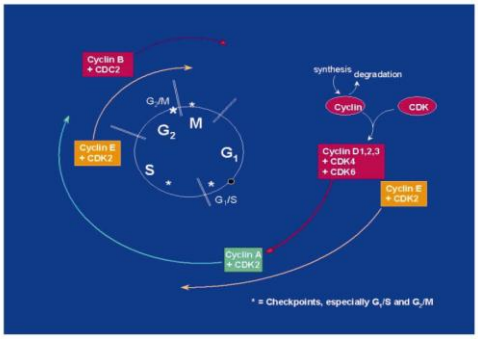
Background

- First attempt at systemic treatment of cancer was in 1943
- Expansion of understanding of cancer has led to development of chemotherapeutic agents
- Chemotherapeutic agents differ in
  - Mechanisms of action
  - Toxicity
  - Activity

Background

- Individual agents have not increased cure rates in majority of malignancies
- Concept of combination chemotherapy to treat metastatic disease was breakthrough
- Chemotherapy sequencing increasingly apparent in treatment

Cell Cycle



Drug Resistance Updates 2000; 3: 335-336

Rationale for Combination Chemotherapy

Table I History of combination chemotherapy

	Model	Concept
Skipper and Schabel[17,18]	Leukemia L1210 mouse model	Fractional or log-kill
Luria and Delbruck[19]	Bacterial mutations altered virus sensitivity to virus resistance	Tumor resistance
Goldie and Coldman[21,23]	Mathematical model applying a spontaneous mutation rate	Individual drug resistant mutant clones all ready exist
DeVita[2,3] and others[25,26]	Various: multidrug resistance,[27] thymidylate synthase[30]	Biochemical synergy
Norton and Simon[10,31]	Gompertzian mathematical model of tumor growth kinetics	Dose-density
Shah and Schwartz and others	Cell physiology and cell cycle	Cell cycle mediated drug resistance

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Biochemical Synergy

- Synergy
  - Greater than expected additive effect of individual drugs when combined
  - Multiple sites in pathways can be attacked
  - Multiple cellular maintenance and function of essential repair mechanisms are altered
- Antagonism
  - Less than expected additive effect of individual drugs when combined

Misconceptions

- Common misconception is agents have been tested as part of a chemotherapy regimen
- Several agents are metabolized via the CYP450 system
  - Doxorubicin
  - Docetaxel
  - Paclitaxel
- Many agents have cell cycle-specific mechanisms of action
- Drug information extrapolated from published single agent data to all in agents in same class

Cone Health Cancer Center Clinical Pearls

- Administer vesicants → irritant → nonvesicants
- Vesicants are irritating and could increase the risk of vein fragility if given last
- Monoclonal antibodies typically administered first
- If no specifics, administer according to clinical trial

Pay Your Taxes First

- Taxanes act by stabilizing microtubules
  - Causing a G2/M cell cycle arrest followed by apoptosis
- Taxanes should be administered prior to platinums
  - 33% reduction in paclitaxel clearance when cisplatin given prior to paclitaxel
  - No increase in efficacy
  - Increased myelosuppression
- Carboplatin and paclitaxel have failed to demonstrate similar pharmacokinetic results

Regimens Lacking Clinical Data

Sequence		Rationale	Evidence
5-FU	Cisplatin	Maximum synergistic activity; less toxicity	In vitro only
Gemcitabine	Docetaxel	Synergistic effect (antagonistic in opposite)	In vitro only
Irinotecan	Docetaxel	Significant myelosuppression with this combination, but not related to sequence	--
Paclitaxel	Irinotecan	Less kinetic interactions; less hepatotoxicity	Trend pharmacokinetic changes, no clinical relevance evaluated; sequence had no effect
5-FU	Cisplatin	Maximum synergistic activity; less toxicity	In vitro only; murine only

Regimens with Clinical Data

Sequence		Sequence Benefit
Gemcitabine	Cisplatin	• Increases platinum-DNA binding and lessens neutropenia • Less toxicity
Gemcitabine	Oxaliplatin	• Increases platinum-DNA binding and lessens neutropenia • Less toxic
Leucovorin	5-FU	• Stabilizes thymidylate synthase to increase 5-FU cytotoxicity and efficacy
Liposomal doxorubicin	Vinorelbine	• Decreased neutropenia • Avoidance of increased AUC of vinorelbine
Pemetrexed	Gemcitabine	• Increased efficacy
Topotecan	Carboplatin	• Less risk of neutropenia and thrombocytopenia

Breast Cancer

Regimen	Order	Rationale
Cyclophosphamide, methotrexate, 5-FU (CMF)	Doxorubicin → 5-FU → cyclophosphamide	• Vesicant 1st
Docetaxel, cyclophosphamide (TC)	Docetaxel → cyclophosphamide	• No interaction • Administer according to trial
Doxorubicin, Cyclophosphamide (AC)	Doxorubicin→ Cyclophosphamide	• Vesicant 1st
Docetaxel, doxorubicin, cyclophosphamide (TAC)	Doxorubicin→ cyclophosphamide→ Docetaxel	• Vesicant 1st • Taxanes may increase doxorubicin concentrations
Trastuzumab, docetaxel, carboplatin (TCH)	Trastuzumab→docetaxel→ carboplatin	• No interaction with trastzumab • Give taxane prior to platinum derivatives

Colon/Rectal Cancer

Regimen	Order	Rationale
Bevacizumab-FOLFOX Bevacizumab/FOLFIRI	Bevacizumab→oxaliplatin/LCV→5-FU bolus→5-FU pump Bevacizumab→ LCV/CPT-11→5-FU→ 5-FU pump	•Bevacizumab theoretically stabilizes tumor vasculature to allow chemo perfusion •Monoclonal given first at CHCC
Cetuximab-Irinotecan	No interaction	•Monoclonal given first at CHCC
Gemcitabine – oxaliplatin	Gemcitabine→oxaliplatin	•Synergistic activity •Gemcitabine increases oxaliplatin binding to DNA
5-FU – Leucovorin (Roswell Park)	LCV (1 hour) → 5-FU bolus → LCV (1 hour)	• LCV increases efficacy of 5-FU

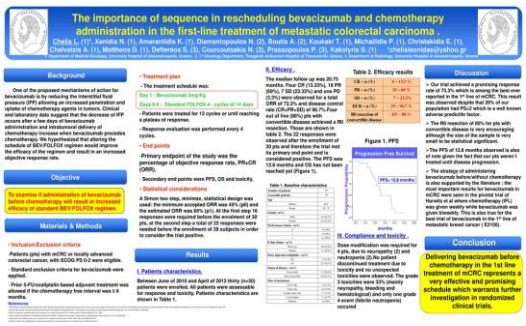
Lung Cancer

Regimen	Order	Rationale
Cisplatin/carboplatin – Etoposide	CDDP/Carboplatin→ Etoposide	• No interaction noted • May administer platinum before or after • Clinical trials vary
Carboplatin/cisplatin – paclitaxel- +/- bevacizumab	Paclitaxel → Carboplatin/cisplatin → +/- bevacizumab	• Platinum decrease renal clearance of taxanes if given 1st • Give taxane first to decrease myelosuppression and increase efficacy •Bevacizumab may be given before or after chemotherapy
Carboplatin/cisplatin – paclitaxel/bevacizumab	Paclitaxel → Carboplatin/cisplatin	• Platinum decrease renal clearance of taxanes if given 1st
Pemetrexed/cisplatin	Pemetrexed → cisplatin	• Cisplatin decreases pemetrexed clearance
Pemetrexed, bevacizumab	Bevacizumab→pemetrexed	• Monoclonal given 1st

Lymphoma/leukemia

Regimen	Order	Rationale
Bendamustine, Rituximab (TR)	Rituximab→ Bendamustine	• Monoclonal first
Cyclophosphamide, Vincristine, Prednisone (CVP) +/- Rituximab (R-CVP)	Vincristine → Cyclophosphamide→ Rituximab	• Vesicant 1st
Cyclophosphamide, Doxorubicin, Vincristine, Prednisone (CHOP) +/- Rituximab	Doxorubicin → Vincristine → Cyclophosphamide→ Rituximab	• Vesicant 1st
Mechlorethamine, Vincristine, Prednisone, Procarbazine	Mechlorethamine → Vincristine	• Vesicant 1st

Bevacizumab: First, Last, Does it Matter?



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