

The background of the slide features a sunset landscape. The sky transitions from a deep blue at the top to a bright orange and yellow near the horizon. In the foreground, there are dark silhouettes of mountains and a large saguaro cactus on the right side. In the background, a city skyline with several skyscrapers is visible against the sky.

Why We Need to Study Schedule Dependence

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Background

- Cancer drug development
 - Rich set of examples for the rewards of assessing schedule dependence
 - Few categories of medication have a narrower therapeutic index and a greater potential for causing harmful side effects than antineoplastic drugs
 - Antitumor activity of certain chemotherapeutic agents is highly schedule dependent



Background

- Schedule dependent drugs
 - Dose fractionated over several days can produce a different antitumor response or toxicity profile compared with the same dose given over a shorter time period



Background

- Cancer drug development
 - Significant challenges for optimizing scheduling and sequencing
 - Complexity of molecules utilized
 - Small molecules with relatively short half-lives
 - Biologics and pegylated compounds with long half-lives
 - Combinations of drugs
 - Synergy due to biochemical interactions
 - Different mechanisms of resistance
 - Non-overlapping toxicities



Reasons Why Schedule Would Matter

- Reach a certain level of drug exposure
- Saturate a receptor
- Avoid an anticipated toxicity
- Sequence the timing of delivering cytotoxic agents before providing an agent that damages blood vessels that feed the tumor
- Stimulate tumor proliferation before administering a cytotoxic
- And others.....



Dose Scheduling Examples

- Cytosine arabinoside
- Methotrexate
- 5 Fluorouracil
- Etoposide
- Taxanes
- Herceptin + std chemotherapy
- Angiogenesis inhibitors + std chemotherapy



Examples - antimetabolites

- Cytosine arabinoside
 - Inactive unless given as a prolonged infusion or on a multiple day administration schedule
- Methotrexate
 - Toxicity related to duration of time at a plasma concentration adequate to inhibit dihydrofolate reductase
- 5 Fluorouracil
 - Toxicity depends on its administration schedule, with weekly bolus doses producing more myelosuppression and infusion of several days producing greater GI toxicity

Example - etoposide

- Etoposide
 - As a single agent, preclinical and clinical findings suggested duration of exposure of neoplastic cells to etoposide is important in producing maximal antitumor activity
 - In one of the first definitive demonstrations of etoposide scheduling dependence in clinical oncology, investigators demonstrated markedly increased efficacy in small cell lung cancer when an identified total dose of etoposide was administered by a 5 day divided dose schedule rather than a 24 hour infusion (Slevin et al 1989)



Example - etoposide

- Etoposide
 - PK analysis showed that both schedules produced similar overall drug exposure (as measured by AUC) but that the divided dose schedule produced twice the duration of exposure to an etoposide plasma concentration of > 1 mcg/ml
 - In combination with cisplatin, there was no difference in efficacy with duration of exposure



Example – anti VEGF

- Anti-Vascular Endothelial Growth Factor (VEGF)
 - Potential benefit of targeting and killing both endothelial and neoplastic cells to enhance survival in multiple types of cancers
 - Combining anti-VEGF treatment with contemporary cytotoxic agents or by using broad spectrum multi-targeted agents that block VEGF and other growth-factor pathways in both cell types



Example – anti VEGF

- Anti-Vascular Endothelial Growth Factor (VEGF)
 - 1996 proposed that combining antiangiogenic therapies with cytotoxic therapies would have significant synergistic effects because it allows targeting of both the malignant cell compartment and the vascular stroma
 - 2001 proposed that anti-VEGF can “normalize” tumor vasculature, and allow an increase and/or more uniform delivery of drugs and oxygen
 - Recent successes of antiangiogenic agents have taught us important lessons about the significance of the target, timing and dosage of agent

Challenges to Consider for the Modeling and Simulation Expert

- In Oncology
 - Individual variation in extent and progression of disease (often life-threatening and lethal consequences if left untreated)
 - Often test drugs at the top of the therapeutic window and the toxicity profile
 - Use combined modalities with drugs, surgery, radiation



Challenges to Consider for the Modeling and Simulation Expert

- In Oncology
 - Individual variation (efficacy and toxicity) in response to treatment
 - Need breaks in therapy to allow recovery from toxicity
 - Utilize supportive care agents to attenuate toxicity (e.g., nausea, anemia, neutropenia)
 - Can also contribute their own toxicity profile



Questions to the Modeling and Simulation Expert

- There are a large number of dose scheduling scenarios that could be tested
- Not enough patients, time or money to evaluate all of them
- How can we change the shape of the therapeutic window with scheduling?
- How can modeling help select the right schedule for the phase 3 trial?
- What data sets do we need for the modelers?



Questions to the Modeling and Simulation Expert

- How can we model the impact of scheduling on toxicity? Do we assess pharmacodynamic marker of anemia, neutropenia or clinical symptom such as neurotoxicity
- How can we model the impact of scheduling on efficacy? Do we assess imaging biomarker such as tumor size, functional metabolic activity, or clinical endpoint such as survival



Questions to the Modeling and Simulation Expert

- Example – angiogenesis inhibitor + standard chemotherapy
 - What's the right sequence?
 - Sequentially AI then std chemo or concurrently or AI after standard chemotherapy?
 - Variety of angiogenesis inhibitors – is it agent specific or can we extrapolate to a class of agents? Specific chemotherapies or can we generalize? Specific tumors? Stage of tumor?
 - Quantitative or qualitative answers?
 - Do we extrapolate to the phase 3 setting? Perform small scale clinical trial(s) first?



Questions to the Modeling and Simulation Expert

- What about the more unique compounds?
 - Pegylated
 - Drugs attached to antibodies
 - Drugs stuck to nanoparticles or in liposomes
- What types of data are needed for the modeler? Are there new tools to help with modeling the schedules?



Questions to the Modeling and Simulation Expert

- When should we rely on models instead of clinical data?
 - To plan phase 3 schedules?
 - In adaptive designs to deal with safety signals that may be schedule dependent, or that emerge during a phase 3 trial?
 - To extend the population to children in marketed drugs?

