Designs for Partially-Ordered Phase I Trials : Combinations of Agents and Groups of Patients

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Novel designs for new types of studies

- LoRusso, Boerner and Seymour (2010) report on a workshop on Phase I studies, organized by the NIH Clinical Trials Design Taskforce
- Develop consensus recommendations for the optimal design of phase I studies:
  - efficient trial designs
  - *phase I drug combinations*
  - appropriate statistical and correlative endpoints.

Clinical Cancer Research, 16:1710-1718

Overviews of clinical and design issues for combinations

- Verweij, Disis and Cannistra (2010) Phase I Studies of Drug Combinations
  - JCO, Vol 28, No 30 (October 20): pp 4545-4546

- Hamberg and Verweij (2009) Phase I Drug Combination Trial Design:Walking the Tightrope
  - JCO, Vol 27, No 27 (September 20): pp 4441-4443

Example 1. Combination of bortezomib and vorinostat

Toxicity increases →

Toxicity increases ↑

	Vorinostat			
Bortezomib	100 mg 1x per day	100 mg 2x per day	200 mg 2x per day	300 mg 2x per day
1.6				
1.3				
1.0				

Jones et al. (2012) J Thorac Oncol. 2012;7: 1683–1690

Example 2. On-going study at UVa

- Phase I trial of a toll-like receptor (TLR) agonists with or without a form of incomplete Freund's adjuvant (IFA) for the treatment of melanoma.

Toxicity increases →

Toxicity increases ↑

	IFA		
Doses of TLR	0	V1	V6
1600			
400			
100			
25			

- IRB######; FDA approved
- Wages and Conaway (2013, to appear) Pharmaceutical Statistics

Not all combinations need to be options

- Study designed at UVA for pancreatic cancer pts

	B1	B2	B3	B4	B5
A4					
A3					
A2					
A1					

- Perotti et al. (2010)

	Ridaforolimus			
Cap	25	37.5	50	75
1800				
1650				

J Clin Oncol 2010, 28:4554-4561

Compare to single agent trials

- Same:
  - Need to do the dose allocation sequentially
- Different
  - Is there one MTD or are there multiple MTDs?
  - Toxicity probabilities follow a partial order

Illustrate 'partial order' with example 1

- Know some orderings among DLT probabilities
  - B 1.0, V 100 mg 1x day less toxic than all others

	Vorinostat			
Bortezomib	100 mg 1x per day	100 mg 2x per day	200 mg 2x per day	300 mg 2x per day
1.6				
1.3				
1.0	Least			

Illustrate 'partial order' with example 1

- Know some orderings among DLT probabilities
  - B 1.6, V 200 mg more toxic than B 1.3, V 200 mg

	Vorinostat			
Bortezomib	100 mg 1x per day	100 mg 2x per day	200 mg 2x per day	300 mg 2x per day
1.6			Less	More
1.3				
1.0				

Illustrate 'partial order' with example 1

- Know some orderings among DLT probabilities
  - B 1.3, V 100 mg 2x per day more toxic than B 1.0, V 100 mg 2x per day

	Vorinostat			
Bortezomib	100 mg 1x per day	100 mg 2x per day	200 mg 2x per day	300 mg 2x per day
1.6				
1.3		More		
1.0		Less		

Illustrate 'partial order' with example 1

- May not know some orderings among DLT probabilities
  - B 1.3, V 100 mg 1x day or B 1.0, V 100 mg 2 x day?

	Vorinostat			
Bortezomib	100 mg 1x per day	100 mg 2x per day	200 mg 2x per day	300 mg 2x per day
1.6				
1.3	??			
1.0		??		

Illustrate 'partial order' with example 1

- May not know some orderings among DLT probabilities
  - B 1.0, V 300 mg or B 1.6, V 200 mg 2 x day?

	Vorinostat			
Bortezomib	100 mg 1x per day	100 mg 2x per day	200 mg 2x per day	300 mg 2x per day
1.6			??	
1.3				
1.0				??

Options for combination agent trials: Convert to a single agent design

- Guess at the orderings that are unknown: lay out a 'complete' ordering
  - Can use a single agent design (e.g. CRM)
  - Perotti (2010) (used 3 + 3)

	Ridaforolimus			
Cap	25	37.5	50	75
1800				
1650				

Options for combination agent trials: Convert to a single agent design

- Advice on how to do this:
  - Korn E, Simon R . Using the tolerable-dose diagram in the design of phase I combination chemotherapy trials. J Clin Oncol. 1993;11(4):794-801.
  - Kramar, A., Lebecq, A., Candahl, E. Continual reassessment methods in phase I trials of the combination of two drugs in oncology. Statistics in Medicine Volume 18, Issue 14, pages 1849–1864, 30 July 1999
  - Le Tourneau, C. , Lee J., Siu, L. (2009) Dose Escalation Methods in Phase I Cancer Clinical Trials. J Natl Cancer Inst 2009;101:708 – 720

Convert to complete ordering

- Advantages
  - Simple
  - Good design options to choose
  - *If* complete ordering is ‘correct’, good properties in determining MTD if ‘good’ design is used.
- Disadvantages
  - May have very poor properties if ordering is incorrectly specified

A second option for combination agent trials:

- Mathematical model for the proportion of DLT's at each dose combination
- References
  - Thall et al. (2003, Biometrics 59, 487-496)
  - Wang and Ivanova (2005, Biometrics 61, 217–222)
  - Yin and Yuan (2009, App. Stat. 58, pp. 211–224)
  - Braun and Wang (2010, Biometrics, 66:805-12)
- Presentation by Dr. Thall

Extending the CRM to partial orders

Toxicity increases →

	Vorinostat			
Bortezomib	100 mg 1x per day	100 mg 2x per day	200 mg 2x per day	300 mg 2x per day
1.6				
1.3				
1.0				

Toxicity increases ↑

References:

Wages, N. , Conaway, M. and O'Quigley, J. (2011), Biometrics, 1555-63

Wages, N. , Conaway, M. and O'Quigley, J. (2011), Clin Trials, 380-389

Wages, N. and Conaway, M. (2013, to appear) Pharm. Statistics

CRM for Partial Orders

- Intuition: If we knew which one was the ‘correct’ order, we could just use usual CRM
  - Same idea as converting the problem to a single agent case
  - Technically, it is a little more complicated than that, but this serves well for intuition about how the method works
- Different from choosing a single ordering in that
  - allows the data to help guide which is the correct order
  - Our estimate of the ‘correct’ order can change throughout the study.

Extending the CRM to partial orders

- Consider a set of complete orderings consistent with the partial ordering
- Example:

Toxicity increases →

Toxicity increases ↑

	Vorinostat			
Bortezomib	100 mg 1x per day	100 mg 2x per day	200 mg 2x per day	300 mg 2x per day
1.6	[6]	[9]	[11]	[12]
1.3	[3]	[5]	[8]	[10]
1.0	[1]	[2]	[4]	[7]

Extending the CRM to partial orders

- Consider a set of complete orderings consistent with the partial ordering
- Example:

Toxicity increases →

	Vorinostat			
Bortezomib	100 mg 1x per day	100 mg 2x per day	200 mg 2x per day	300 mg 2x per day
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1.3	[2]	[5]	[8]	[11]
1.0	[1]	[4]	[7]	[10]

↑ Toxicity increases

How to choose complete orders?

- Clinical knowledge
- Using advice of
  - Korn and Simon (1993)
  - Kramar (1999)
  - Le Torneau et al. (2009)
- Generic set of 6 orderings
  - Wages and Conaway, 2013, Pharm Stat

Partial Order CRM

- Once you have the set or complete orders
- Apply CRM ordering by ordering
  - Choose the ordering most consistent with the data
  - Apply usual CRM method to this one ordering
  - Next patient goes on the dose combination recommended by CRM

How well does this identify the MTD?

- Wages, Conaway and O'Quigley (2011)
- Wages and Conaway (2013)
- Harrington, J., Wheeler, G., Sweeting,M. Mander A. and Jodrell, D. (2013) Adaptive designs for dual-agent phase I dose-escalation studies. Nature Reviews Clinical Oncology 10, 277-288 (May 2013)

General properties

- Better performance than methods that rely on a single guess at the ordering (if that guess is incorrect)
  - Particularly true if use 3 + 3.
- Usually identifies MTD (slightly) less often than when true ordering is known
  - Performance is often similar to single agent CRM where true ordering is known

Implementation

- R package ('POCRM') available
- http://cran.r-project.org/web/packages/pocrm/
  - For single trial
  - For simulation
  - Documentation at this site
  - Also: Wages and Varhegyi (2013, Computer Methods and Programs in Biomedicine)

Summary of methods for combinations of agents

- Several options for exploring combinations of agents
  - Don’t need to restrict attention to fixing one agent and escalating the other
  - No need to specify how exactly these combinations will be ordered
  - Although you can use this information if this is known

Single agent trials in ordered groups

- Example. LoRusso et al. (2012) Pharmacokinetics and Safety of Bortezomib in Patients with Advanced Malignancies and Varying Degrees of Liver Dysfunction: Phase I NCI Organ Dysfunction Working Group Study NCI-6432. Clin Cancer Res; 18(10); 1–10

	Bortezomib dose (mg/ m^2)			
Hepatic function impairment	0.5	0.7	1.0	1.3
Severe				
Moderate				
Mild				
None				

- Similar example in Ramanathan et al. Phase I and Pharmacokinetic Study of Imatinib Mesylate in Patients With Advanced Malignancies and Varying Degrees of Liver Dysfunction: A Study by the National Cancer Institute Organ Dysfunction Working Group. J Clin Oncol 26:563-569.. 2008

Example 2. Radiation therapy.

- A dose escalation trial of radiation therapy

	Doses in Gy			
Life Expectancy Groups	8	10	12.5	15
Low				
High				

- IRB & FDA approval in progress

Why not run ‘parallel’ trials?

- Reversals
  - No guarantee that MTDs chosen at end of trials will reflect what is known clinically
  - Can occur that MTD (Mild) < MTD (Moderate)

- Inefficiency
  - Does not use all the available information
  - Especially true for ‘unbalanced’ groups

Options: Methods based on "isotonic regression"

- "Isotonic": statistical method for making sure that estimates line up with known orderings (no reversals)
- Wang and Ivanova (2006) Bivariate isotonic design for dose-finding with ordered groups Stat in Med, 2006; 25:2018–2026
  - Assumes only that within groups, toxicity increases as dose increases
  - For fixed dose, toxicity increases across groups

Options: Methods based on "isotonic regression"

- Yuan,Z. and Chappell,R. Isotonic designs for phase I cancer clinical trials with multiple risk groups. Clin Trials 2004 499-508
- Within each group, do separate CRM
  - Produces estimates of toxicity probabilities in each row (group)
  - If these "line up" , no adjustment
  - If there are reversals, use isotonic regression to eliminate reversals.
  - Tox prob estimates will increase across columns and across rows.

Options: Methods based on "isotonic regression"

- Example. Hypothetically, at some point on the trial, separate CRMs could give estimates:

	Bortezomib dose (mg/ m^2)			
Hepatic function impairment	0.5	0.7	1.0	1.3
Severe	0.03	0.08	0.16	0.23
Moderate	0.06	0.14	0.24	0.33
Mild	0.01	0.04	0.09	0.16

- Hypothetical isotonic estimates

	Bortezomib dose (mg/ m^2)			
Hepatic function impairment	0.5	0.7	1.0	1.3
Severe	0.045	0.11	0.20	0.28
Moderate	0.045	0.11	0.20	0.28
Mild	0.01	0.04	0.09	0.16

Option: mathematical model

- Legedza, A. and Ibrahim, J. (2001) Heterogeneity in phase I clinical trials: prior elicitation and computation using the continual reassessment method
- O'Quigley, J. and Paoletti, X (2003) Continual Reassessment Method for Ordered Groups Biometrics 59, 430–440.
- Refer to Dr. Thall presentation

Option: shift model

- O'Quigley, J. (2012) in Handbook of Statistics in Clinical Oncology, 3rd Edition. Eds Crowley, J. and Hoering, A. CRC Press

- Extension of CRM for 2 ordered groups
  - CRM in each group, but MTD shifts by Δ

Option: shift model

- Extension of CRM for 2 ordered groups
  - CRM in each group, but MTD shifts by Δ
  - Δ = 0 means MTD same in both groups
  - Δ = 1 means MTD differs by 1 category across groups
  - Δ = 2 means MTD differs by 2 categories across groups

	Doses in Gy			
Groups	8	10	12.5	15
Low				
High				

- O'Quigley, J. (2012) in Handbook of Statistics in Clinical Oncology, 3rd Edition. Eds Crowley, J. and Hoering, A. CRC Press

Shift Model

- Estimate both toxicity probabilities and shift

- Toxicity probabilities estimated with CRM-type model
- Value of Δ most consistent with the data

Option: methods based on partial orders

- Work in progress
- Similar to methods for combinations of agents
- Need to modify method to allow for MTD in each row
- Group assignment not under control of the investigator

Summary of trials done in groups

- Several options other than running parallel group trials

- Or, if you run parallel groups, ways of avoiding reversals: study findings that run counter to clinical knowledge.