Adaptive Design for Intra Patient Dose Escalation in Phase I Trials in Oncology

Jeremy M.G. Taylor
Laura L. Fernandes

University of Michigan, Ann Arbor

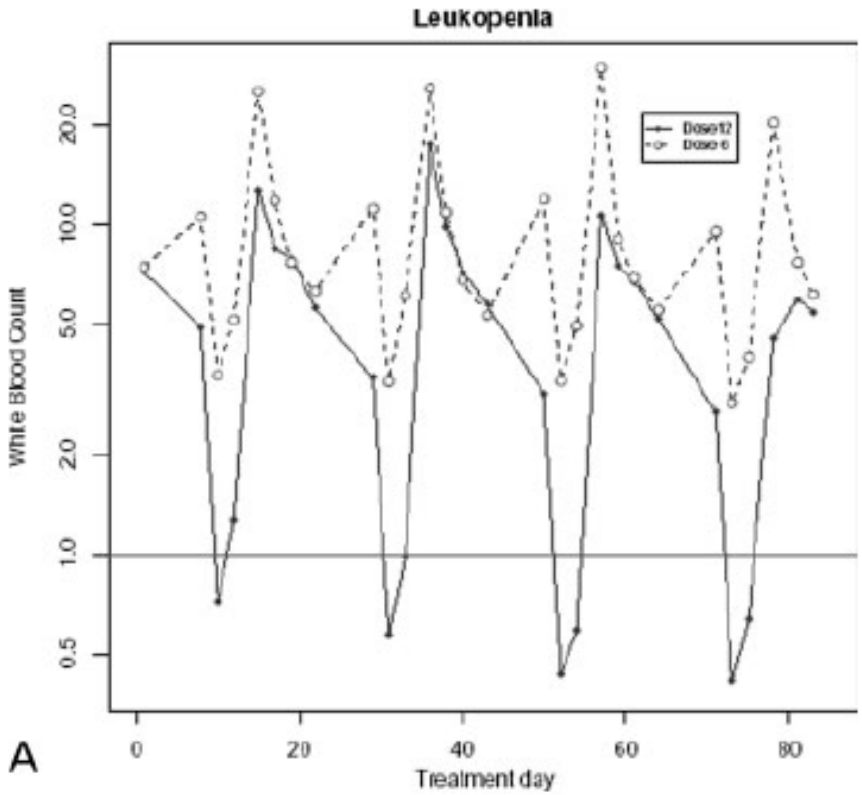
19th August, 2011

Table of Contents

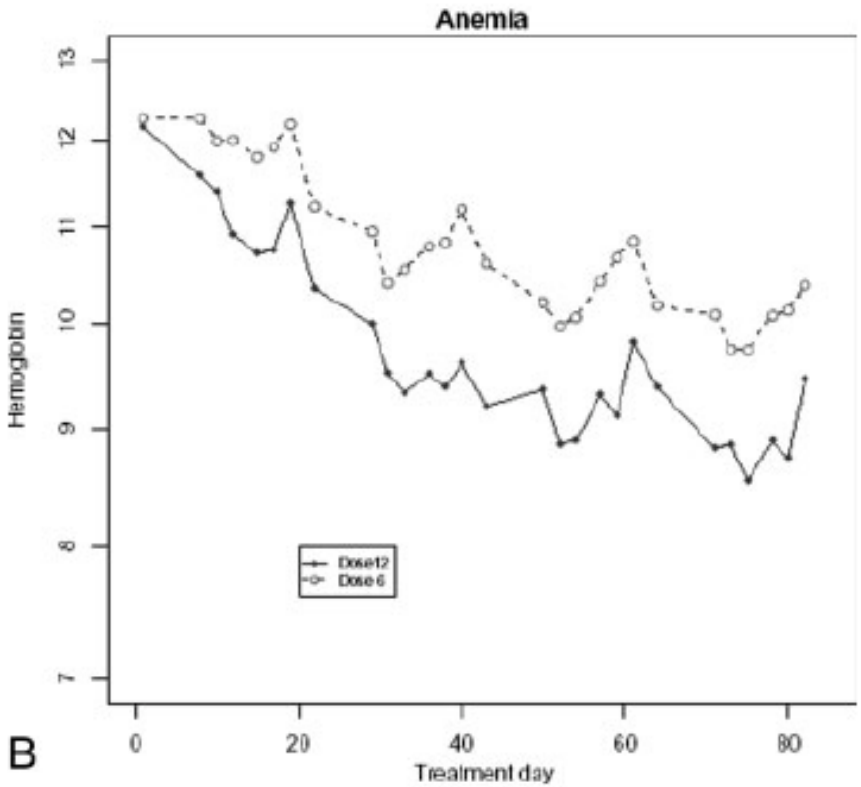
Introduction

- Many cancer therapies consist of repeated cycles of administration of a drug.
  - Typical cycle = 21 days.
- In phase I trials the goal is to find the maximum tolerated dose (MTD).
  - MTD is the dose that will be used in future studies. May lead to some severe toxicities, but the chance of toxicity is acceptably low.

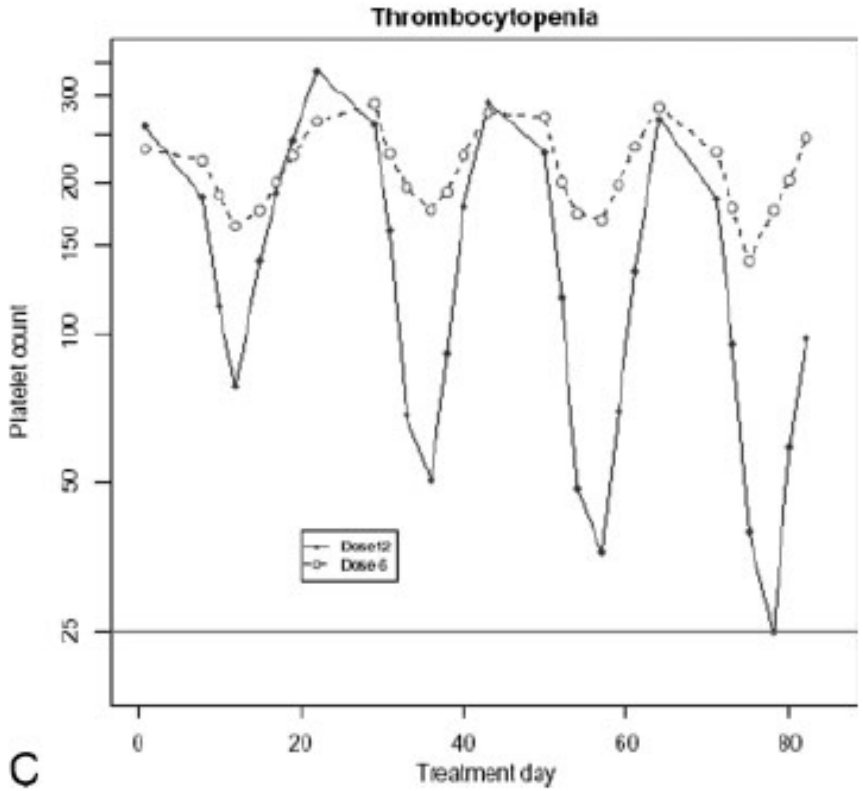
Blood count plots from phase II study



Blood count plots from phase II study



Blood count plots from phase II study



Introduction

Usual design of Phase I studies

- Use the same dose for all cycles
- Consider just one toxicity per patient
  - From any cycle
  - From the first cycle
    - Logistical problem, what to do if the patient experiences a toxicity on the third cycle?

Introduction

- A different approach
  - Allow dose to change from one cycle to the next
  - Intra-patient dose escalation
  - Gather toxicity data from all cycles
  - Current interest in this approach, LoRusso et al (2010)
  - Does require the toxicity to be linked to a specific cycle, i.e. delayed toxicities are not allowed
  - Accelerated Titration Designs already use Intra-patient dose escalation

Introduction

- This extra information may provide
  - More precise estimation of the dose-toxicity relationship
  - Enable a better selection of the dose for the next cycle for each patient
  - Better proposed regimen at the end of the trial
  - Extra data will require more parameters in a model

Introduction

- Commentary by LoRusso et al (2010) on "Investigational Drug Steering Committee recommendations about the design of phase I studies"
- When designing a phase I study, intrapatient dose escalation is reasonable and should be encouraged in order to minimize the number of patients exposed to subtherapeutic doses of agents.
- The rules about intrapatient dose escalation must be clearly prespecified in the protocol.
- Data from patients undergoing intrapatient escalation should never be used to guide decisions about further dose level escalation or the selection of a recommended phase II dose.

Introduction

- Data from patients undergoing intrapatient escalation should never be used to guide decisions about further dose level escalation or the selection of a recommended phase II dose.
- What does this last comment mean?
- The data is complicated so don't use it.
- My thought, The data is complicated, but we have a way to untangle it and use it to help make conclusions.

General goals of Phase I trials

- Find MTD
- Treat patients at doses which may be efficacious
- Limit the number of toxicities for patients in the trial
- Gain experience at a specific dose that will be recommended for future use
- Learn something about dose response relationships

Table of Contents

Method

Setting and notation

- Patient i receives a maximum of six cycles (k=1...6) in a regimen.
- A patient is assigned a dose $d_{i,k}$ from five possible dose levels $S_1 \ldots S_5$
- $Y_{i,k} = 1$ if toxicity on k^{th} cycle for patient i
- $Y_{i,k} = 0$ if no toxicity on k^{th} cycle for patient i
- Stop giving drug on future cycles if $Y_{i,k} = 1$

Requirements of a model

- Correlation between $Y_{i,j}$ and $Y_{i,k}$
- Allow possible cumulative effect of dose
- $p_{i,k} = P(Y_{i,k} = 1)$

A possible model, Random effects

- Simon et al 1997, Legedza and Ibrahim 2000
- $logit(p_{i,k}) = a_i + \beta d_{i,k} + \gamma D_{i,k}$
- $a_i \sim N(\alpha, \sigma^2)$
- $D_{i,k}$ is cumulative dose
- 4 parameters
- We didn't use this

Markov Model, MM

$$log\left(1-p_{i,k}\right) = -\alpha\left[d_{i,k} - \rho d^{\ddagger}_{i,k-1}\right]^{+} - \beta D_{i,k-1} d_{i,k}$$

- $p_{i,k}$ probability of toxicity on cycle k for patient i given no prior toxicity
- $d_{i,k}$ dose assigned on cycle k for patient i
- $d^{\ddagger}_{i,k-1} = \max_{j=1\ldots k-1}(d_{i,j})$
- $D_{i,k-1} = \sum_{m=1}^{k-1} d_{i,m}$ cumulative dose

Markov Model contd, Special cases

$$p_{i,k} = 1 - exp\left(-\alpha\left[d_{i,k} - \rho d^{\ddagger}_{i,k-1}\right]^{+} - \beta D_{i,k-1} d_{i,k})\right)$$

- $d_{i,k} = 0 \Rightarrow \mathrm{P}(\text{no toxicity}) = 1$
- $P(toxicity|d_1 = S_5) \leq P(toxicity|d_1 = S_4, d_2 = S_5)$

Markov Model contd, Special cases

$$p_{i,k} = 1 - exp\left(-\alpha\left[d_{i,k} - \rho d^{\ddagger}_{i,k-1}\right]^{+} - \beta D_{i,k-1} d_{i,k})\right)$$

- $k = 1 \Rightarrow$ P(no toxicity) $= 1 - p_{i,1} = exp(-\alpha d)$
- $\rho = 0, \beta = 0 \Rightarrow$ P(no toxicity) $= exp(-\alpha d)$ on every cycle
  - Independent "hits" on each cycle
- $\rho = 1, \beta = 0 \Rightarrow$ P(no toxicity) $= 1$ for $k = 2, 3, ..., K$ if dose does not change
  - Each person has a "frailty" which will be exposed on cycle 1

Markov Model contd, interpretation of parameters

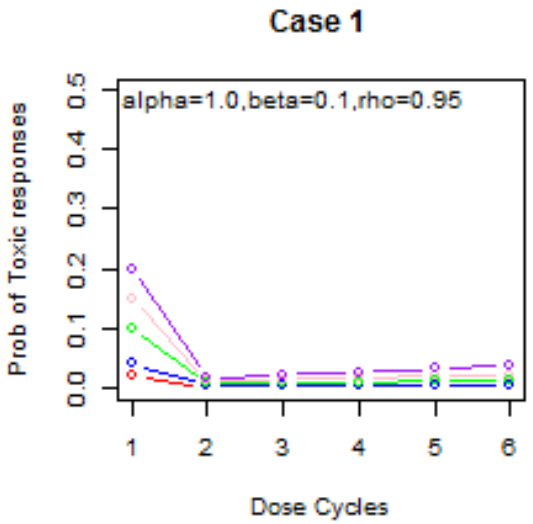
- $(\alpha > 0)$ controls for the non-cumulative effect of the current dose on causing toxicity
- $(\beta \geq 0)$ controls the effect of cumulative dose on the probability of observing a toxicity.
- $(0 \leq \rho \leq 1)$
  - Allows for frailty and correlation
  - Accounts for the effect of the maximum dose administered to the subject in the past.
  - A subject surviving a dose in the past is less like likely to experience a toxicity in the future, if given the same dose.

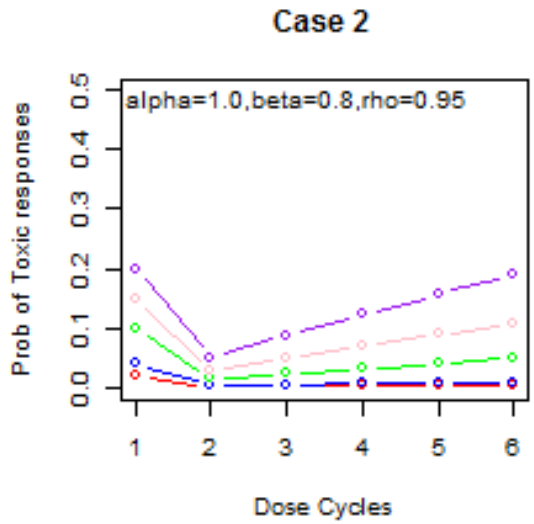
Model Flexibility

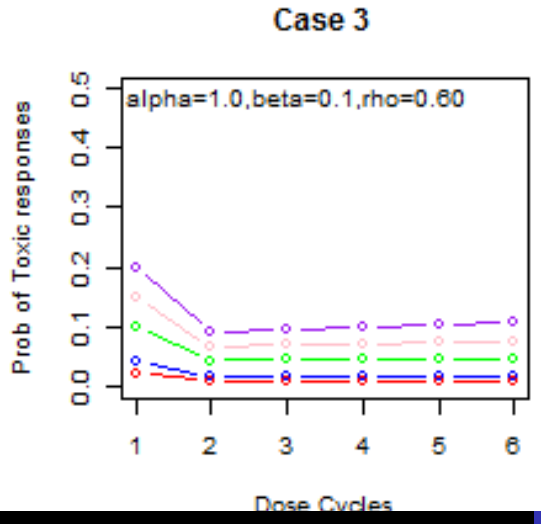
		α	β	ρ
Four scenarios	Case 1	1.0	0.1	0.95
	Case 2	1.0	0.8	0.95
	Case 3	1.0	0.1	0.60
	Case 4	0.3	0.8	0.95

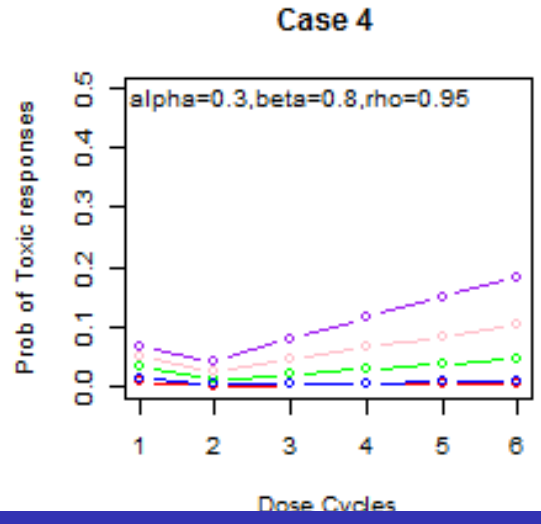
Assume a subject receives the same dose from $S1 \ldots S5$ for all 6 cycles.

Plots


Case 1
alpha=1.0,beta=0.1,rho=0.95
Prob of Toxic responses
0.0 0.1 0.2 0.3 0.4 0.5
1 2 3 4 5 6
Dose Cycles


Case 2
alpha=1.0,beta=0.8,rho=0.95
Prob of Toxic responses
0.0 0.1 0.2 0.3 0.4 0.5
1 2 3 4 5 6
Dose Cycles


Case 3
alpha=1.0,beta=0.1,rho=0.60
Prob of Toxic responses
0.0 0.1 0.2 0.3 0.4 0.5
1 2 3 4 5 6
Dose Cycles


Case 4
alpha=0.3,beta=0.8,rho=0.95
Prob of Toxic responses
0.0 0.1 0.2 0.3 0.4 0.5
1 2 3 4 5 6
Dose Cycles

Estimation

- During the trial or at the end of the trial
- Adaptive, uses all available data at that time
- Bayesian using WinBugs
- Likelihood = $\prod_{i=1}^{I} \prod_{k=1}^{k_i} p_{i,k}(\alpha, \beta, \rho)^{Y_{i,k}} (1 - p_{i,k}(\alpha, \beta, \rho))^{(1-Y_{i,k})}$
- Priors
  - $\alpha \sim LogNormal(1, 0.2^2)$
  - $\beta \sim LogNormal(\mu_\beta = (30 * S_3)^{-1}, (3\mu_\beta)^2)$
  - $\rho \sim Uniform(0.8, 1)$

Table of Contents

Single Trial with 30 subjects

- True values (α, β, ρ) are used to generate data and calculate the probability of toxicity at each of the cycles for five different fixed dose regimens.
- 30 subjects are generated in each of the 50 simulated trials.

1. 3 subjects receive six cycles of dose 1
2. 3 subjects receive six cycles of dose 2
3. 10 subjects receive six cycles of dose 3
4. 10 subjects receive six cycles of dose 4
5. 4 subjects receive six cycles of dose 5

Parameter estimates

	$\hat{\alpha}(MSE)$	$\hat{\beta}(MSE)$	$\hat{\rho}(MSE)$
Case 1	0.975(0.004)	0.106(0.002)	0.915(0.002)
True values	1.0	0.1	0.95
Case 2	1.025(0.005)	0.630(0.181)	0.886(0.004)
True values	1.0	0.8	0.95
Case 3	1.017(0.004)	0.465(0.232)	0.872(0.074)
True values	1.0	0.1	0.60
Case 4	0.798(0.250)	0.723(0.028)	0.899(0.003)
True values	0.3	0.8	0.95

Comparison with single toxicity measure and CRM

- $V_i = 0$ if no toxicity on any cycle
- $V_i = 1$ if toxicity on any cycle
- CRM model
  - $logit(P(V_i = 1|d_i)) = 3 + w * d_i$
  - Bayesian estimation with $w \sim Normal(1, 0.3^2)$ prior.
- Calculate $P(V_i = 1)$
  - From true Markov model
  - From estimate Markov model
  - From estimated CRM

Results - Bias

Average of posterior means

	Case 1			Case 2		
Prob	True	CRM	MM	True	CRM	MM
$P(V=1\|S_1)$	0.026	0.027	0.028	0.030	0.043	0.036
$P(V=1\|S_2)$	0.052	0.052	0.057	0.069	0.087	0.078
$P(V=1\|S_3)$	0.137	0.129	0.147	0.233	0.247	0.233
$P(V=1\|S_4)$	0.216	0.197	0.227	0.406	0.408	0.380
$P(V=1\|S_5)$	0.298	0.270	0.309	0.584	0.578	0.521

Results - MSE and SD

	Case 1		Case 2	
	CRM	MM	CRM	MM
MSE	0.0003	0.0001	0.0009	0.0001
of	0.0008	0.0001	0.0024	0.0002
point	0.0029	0.0005	0.0069	0.0024
estimate	0.0049	0.0010	0.0077	0.0084
	0.0067	0.0017	0.0053	0.0173
Average	0.017	0.006	0.026	0.008
SD	0.029	0.013	0.042	0.015
of	0.053	0.031	0.073	0.048
posterior	0.066	0.047	0.078	0.079
distribution	0.075	0.067	0.064	0.103

Sequential selection of doses

Current condition of a potential trial involving 30 subjects.
Matrix with subject outcomes - Dose(Toxicity)

Subject	Cycle1	Cycle2	Cycle3	Cycle4	Cycle5	Cycle6
1	$S_2(0)$	$S_2(0)$	$S_2(0)$	$S_2(0)$	$S_2(0)$	$S_3(0)$
2	$S_2(0)$	$S_2(0)$	$S_2(0)$	$S_2(0)$	?(?)	
3	$S_3(1)$					
4	$S_3(0)$	$S_3(0)$	?(?)			
5	?(?)					

Dose escalation restrictions

- Start at S_2
- Need experience of 4 cycles of S_k before trying S_{k+1}
- No skipping doses within a patient

Design Rules

Three probabilities are calculated based on posterior mean for $p_{i,k}$, doses already given and possible future doses for subject i.

- A:(Next Cycle$|d) = 1 - \prod_{j=c}^{c} (1 - p_{i,j})$
- B:(Future Cycles$|d, ..d) = 1 - \prod_{j=c}^{6} (1 - p_{i,j})$
- C:(All Cycles$|d_{i,1}, ..d_{i,c-1}, d, ..d) = 1 - \prod_{j=1}^{6} (1 - p_{i,j})$

Choose the dose $d_{i,c}$ based on

- C is closest to 0.3
- A<0.15
- B<0.4

Summary of results

- Accrue 30 patients sequentially, no delays
- true $\theta = (1.0, 0.1, 0.95)$ was used to generate the responses at each cycle

Summary of subjects and doses assigned.

	Cycle1	Cycle2	Cycle3	Cycle4	Cycle5	Cycle6	Total
S_1	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
S_2	2(0)	2(0)	2(0)	2(0)	1(0)	0(0)	9(0)
S_3	21(2)	1(0)	0(0)	0(0)	1(0)	1(0)	24(2)
S_4	7(2)	20(3)	1(0)	2(0)	0(0)	7(0)	37(5)
S_5	0(0)	3(0)	20(0)	19(1)	20(0)	14(0)	76(1)
Total	30(4)	26(3)	23(0)	23(1)	22(0)	22(0)	146(8)

Summary of results

- True $\theta = (1.0, 0.1, 0.95)$
- At the end of the study
  $\hat{\theta} = (\hat{\alpha} = 1.010, \hat{\beta} = 0.070, \hat{\rho} = 0.912)$.
- What would be the recommended dose at the end of the study?
- May want to limit the number of changes in dose

Estimated P(Toxicity) for different regimens

Regimen	True Prob	Prob Estimate
$S_1S_1S_1S_1S_1S_1$	0.026	0.029
$S_2S_2S_2S_2S_2S_2$	0.052	0.059
$S_3S_3S_3S_3S_3S_3$	0.138	0.151
$S_4S_4S_4S_4S_4S_4$	0.216	0.231
$S_5S_5S_5S_5S_5S_5$	0.298	0.313
$S_5S_5S_5S_4S_4S_4$	0.235	0.252
$S_4S_4S_4S_3S_3S_3$	0.155	0.170
$S_3S_3S_3S_2S_2S_2$	0.066	0.078
$S_2S_2S_2S_1S_1S_1$	0.029	0.035
$S_1S_1S_1S_2S_2S_2$	0.048	0.053
$S_2S_2S_2S_3S_3S_3$	0.122	0.131
$S_3S_3S_3S_4S_4S_4$	0.198	0.212
$S_4S_4S_4S_5S_5S_5$	0.278	0.292

Possible conclusion from the study

- We could recommend regimens that have probability of toxicity on the entire regimen close to 0.3 and the escalation $S_4 S_4 S_4 S_5 S_5 S_5$ regimen could be a good possibility.

Table of Contents

Discussion

Possible rules for deciding on future doses

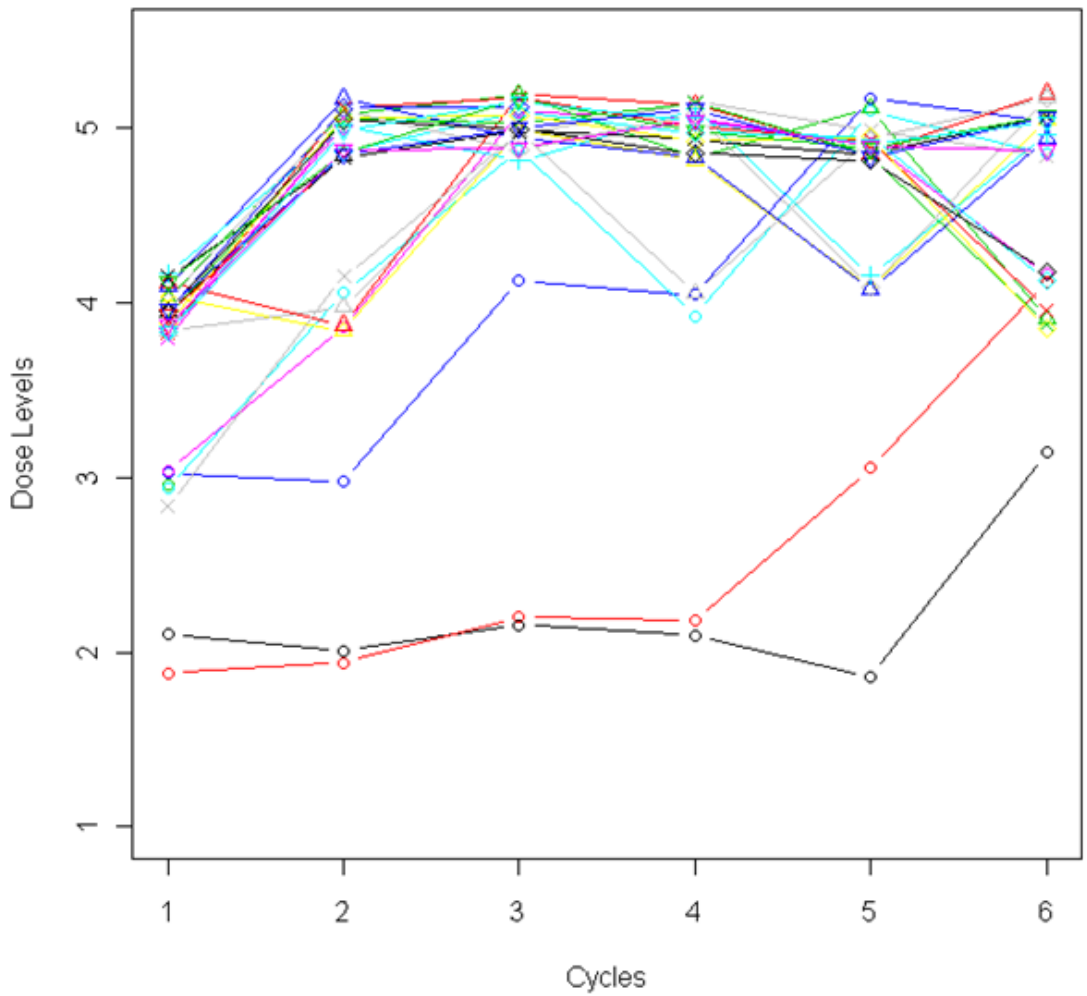
- A,B,C criteria with different cut-offs
- Choose $p_1^*, p_2^*, ..., p_6^*$ such that
  - $1 - \prod_{k=1}^{6}(1 - p_k^*) =$ target toxicity level
  - For cycle k choose $d_{i,k}$ st $\hat{P}(Y_{i,k} = 1|d_{i,k})$ is close to p_k^*
- Maximize $\Sigma_{k=1}^{6} d_{i,k}(1 - Y_{i,k})$

Discussion

Modifying the allowed toxicity on the next cycle

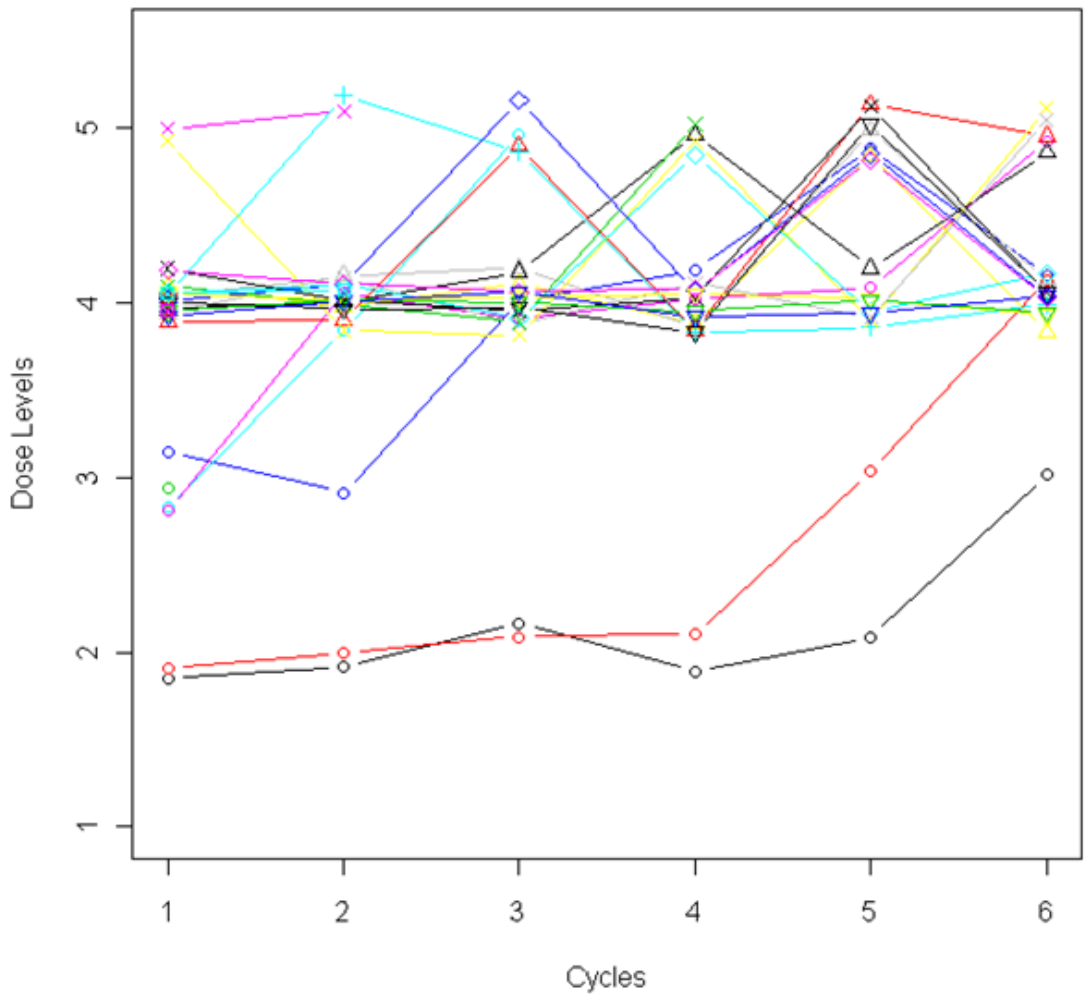
- Make P(toxicity on next cycle k) $\leq p_k^*$
- Scenario A
- $p_1^* = p_2^* = ... = p_6^* = 0.15$
- Scenario B
- $p_1^* = 0.25, p_2^* = ... = p_6^* = 0.128$

Sequence of assigned doses, scenario A



heightheight

Sequence of assigned doses, scenario B



heightheight

Discussion

Possible rules for deciding on future doses

- Dynamic programming problem
- What is the "optimal" dose at cycle k given that all future doses will be selected "optimally"

Discussion, Modelling and estimation issues

- Really need at least three parameters to allow flexibility
- Priors are important to "reduce" number of parameters with limited data. Priors stabilize the estimation early in the trial
- There will tend to be some real prior knowledge, so mildly informative priors can be used.

General goals of Phase I trials

- Find MTD -
  - A sequence of doses, not unique
- Treat patients at doses which may be efficacious
  - Possible for some cycles
- Limit the number of toxicities for patients in the trial
- Gain experience at a specific dose that will be recommended for future use
  - This is hard
- Learn something about dose response relationships

Discussion, clinical issues

- Trials with intra-patient dose escalation seem more ethical
- Some physicians like the idea of giving big doses in the first cycle, i.e. hit the cancer hard and early
- Toxicities on cycles 5 and 6 maybe not matter so much.

Discussion, clinical issues

- Will intra-patient dose escalation be accepted by physicians?
- Why not. Already doing it with Accelerated Titration designs at some institutions
- Does not involve the collection of any additional data
- Does not cause any delay in the conduct of the study

Discussion

Current clinical focus in phase I trials

- Targetted therapies
  - Toxicity rates may be lower
  - Toxicity-dose relationship probably still monotonic
- Combination of agents
  - Standard agent + new agent
- Measure "efficacy" as well as toxicity
  - Clinical efficacy
  - Modification of target biomarkers
- Combined Phase I/Phase II trials

References

- Legedza and Ibrahim, Contolled Clinical Trials, 2000
- Simon et al, J National Cancer Institute, 1997
- LoRusso et al, Clin Cancer Res, 2010