ITCC INTRODUCTORY COURSE IN PAEDIATRIC DRUG DEVELOPMENT 2018

WORKSHOP 3

Simulated Pharma Teleconference

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Objectives

- To clarify basic concepts in phase I trials:
  - Dose Limiting Toxicity (DLT)
  - Maximum Tolerated Dose (MTD)
  - Recommended Phase 2 Dose (RP2D)
- To put in practice rules of dose escalation.
- To promote interaction between participants.

Outline

- Six participant centres.
- Three scenarios (i.e. phase I trials).
- Clinical cases: one per centre per trial.
- Dose escalation decisions:
  - Appendix 1 - Dose Limiting Toxicities (DLT).
  - Appendix 2 - Dose decisions: Rolling Six design.

DLT definitions

- FOR HAEMATOLOGICAL TOXICITIES:
  - CTCAE grade 4 Anemia (Life-threatening consequences).
  - Neutrophils <0.5 x10^9/L (or <500/mm^3) lasting for ≥7 days unsupported with G-CSF.
  - Platelets <25 x10^9/L (or <25,000/mm^3) lasting for ≥7 days or requiring transfusion.

- FOR NON-HAEMATOLOGICAL TOXICITIES:
  - Any non-hematologic toxicity CTCAE Grade 4.
  - Febrile neutropenia CTCAE Grade 3 or higher.
  - Increased AST (GOT) or ALT (GPT) CTCAE grade 3 or higher.
  - Increased Bilirubin grade 3 or higher.
  - Serum creatinine increased CTCAE Grade 2 or higher.
  - Diarrhoea CTCAE Grade 2 or higher persisting for ≥7 days despite optimal anti-diarrhoeal treatment.
  - Nausea and/or vomiting CTCAE Grade 2 or higher persisting for ≥7 days despite optimal antiemetic treatment.
  - Decrease in cardiac left ventricular function CTCAE Grade 2 or higher.

- OTHER:
  - Any toxicity occurring in the DLT evaluation period which delays initiation of the subsequent Cycle for >2 weeks.
  - Any CTCAE grade 5 events (death).

Common Terminology Criteria for Adverse Events (CTCAE)

Version 5.0

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

Table 1. Comparison of Decision Properties for the 3 + 3 *v* Rolling Six Design

DLT Data			Enrolling Dose Level*			
			MTD Not Exceeded		MTD Exceeded	
No. Enrolled	No. DLTs	No. Without DLT	No. With Data Pending	3 + 3	Rolling Six	3 + 3	Rolling Six
2	0, 1	Any	Any	n	n		
2	2	0	0	n − 1	n − 1		
3	0	0, 1, 2	3, 2, 1	Suspend	n		
3	≥ 2	Any	Any	n − 1	n − 1		
4	0	0, 1, 2	4, 3, 2	—	n	—	n
4	0	3	1	—	n	n	n
4	0	4	0	—	n + 1	n	n
4	1	0, 1	3, 2				
4	1	2	1				
4	1	3	1				
4	≥ 2	Any	Any				
5	0	0, 1, 2	5, 4, 3				
5	0	3, 4	2, 1				
5	0	5	0				
5	1	0, 1	4, 3				
5	1	2	2				
5	1	3, 4	1, 0	n	n	n	n
5	≥ 2	Any	Any	n − 1	n − 1	n − 1	n − 1
6	0	0, 1, 2	6, 5, 4	—	Suspend	—	Suspend
6	0	3, 4	3, 2	—	Suspend	Suspend	Suspend
6	0	5, 6	1, 0	—	n + 1	MTD	MTD
6	1	0, 1	5, 4	—	Suspend	—	Suspend
6	1	2	3	Suspend	Suspend	—	Suspend
6	1	3, 4	2, 1	Suspend	Suspend	Suspend	Suspend
6	1	5	0	n + 1	n + 1	MTD	MTD
6	≥ 2	Any	Any	n − 1	n − 1	n − 1	n − 1

Current status

Dose decision

n-1 = de-escalate

n+1 = escalate

Suspend: hold decision

MTD: maximum tolerated dose

Questions?

SCENARIO 1

- Study drug: Amsterditinib.
- Oral (tablets and solution) once daily in 28-day cycles.
- Current dose level: 0.

SCENARIO 2

- Study drug: Utrechtumumab.
- Intravenous once every 2 weeks.
- One cycle = 4 weeks.
- Current dose level: 3.

SCENARIO 3

- Study drug: Rotterdamidomide.
- Oral drug (capsules and solution) administered twice daily, 3 weeks on & 1 week off, in 28-day cycles.
- Current dose level: 1.

Dose Escalation Decisions

SCENARIO 1

- Study drug: Amsterditinib.
- Oral (tablets and solution) once daily in 28-day cycles.
- Current dose level: 0.

SCENARIO 1

- Clinical cases:
  - No DLTs in 5 patients
  - Patient #4 is not evaluable for DLTs: “C1 D21”

Table 1. Comparison of Decision Properties for the 3 + 3 *v* Rolling Six Design

No. Enrolled	DLT Data: No. DLTs	No. Without DLT	No. With Data Pending	Enrolling Dose Level*: MTD Not Exceeded: 3 + 3	MTD Not Exceeded: Rolling Six	MTD Exceeded: 3 + 3	MTD Exceeded: Rolling Six
2	0, 1	Any	Any	n	n		
2	2	0	0	n − 1	n − 1		
3	0	0, 1, 2	3, 2, 1	Suspend	n		
3	0	3	0	n + 1	n + 1		
3							
3							
3							
4						—	n
4						n	n
4						n	n
4						—	n
4						—	n
4						n	n
4	≥ 2	Any	Any	n − 1	n − 1	n − 1	n − 1
5	0	0, 1, 2	5, 4, 3	–	n	–	n
5	0	3, 4	2, 1	–	n	n	n
5	0	5	0	–	n + 1	n	n
5	1	0, 1	4, 3	–	n	–	n
5	1	2	2	n	n	–	n
5	1	3, 4	1, 0	n	n	n	n
5	≥ 2	Any	Any	n − 1	n − 1	n − 1	n − 1
6	0	0, 1, 2	6, 5, 4	—	Suspend	—	Suspend
6	0	3, 4	3, 2	—	Suspend	Suspend	Suspend
6	0	5, 6	1, 0	—	n + 1	MTD	MTD
6	1	0, 1	5, 4	—	Suspend	—	Suspend
6	1	2	3	Suspend	Suspend	—	Suspend
6	1	3, 4	2, 1	Suspend	Suspend	Suspend	Suspend
6	1	5	0	n + 1	n + 1	MTD	MTD
6	≥ 2	Any	Any	n − 1	n − 1	n − 1	n − 1

SCENARIO 1

Decision: the dose can be escalated

SCENARIO 1: Learning points

- Paediatric phase I trials usually start at 80% of the approved adult dose adjusted according to body surface area or weight.

- The **paediatric RP2D** ranged **between 90 – 130% of the equivalent adult dose** in 13 out of 19 (69%) paediatric phase I trials.
  - Paoletti et al. EJC. 2013

SCENARIO 2

- Study drug: Utrechtumumab.
- Intravenous once every 2 weeks.
- One cycle = 4 weeks.
- Current dose level: 3.

SCENARIO 2

- Two DLTs:
  - Patient #2: diarrhoea grade 2 lasting ≥7 days
  - Patient #5: elevated ALT and AST grade 3 (one missed dose)

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No. Enrolled	DLT Data: No. DLTs	No. Without DLT	No. With Data Pending	Enrolling Dose Level*: MTD Not Exceeded: 3 + 3	MTD Not Exceeded: Rolling Six	MTD Exceeded: 3 + 3	MTD Exceeded: Rolling Six
2	0, 1	Any	Any	n	n		
2	2	0	0	n − 1	n − 1		
3	0	0, 1, 2	3, 2, 1	Suspend	n		
3	0				1		
3	1						
3	1						
3	≥ 2				1		
4	0					—	n
4	0					n	n
4	0				1	n	n
4	1					—	n
4	1					—	n
4	1					n	n
4	≥ 2				1	n − 1	n − 1
5	0					–	n
5	0					n	n
5	0				1	n	n
5	1	0, 1	4, 3	–	n	–	n
5	1	2	2	n	n	–	n
5	1	3, 4	1, 0	n	n	n	n
5	≥ 2	Any	Any	n − 1	n − 1	n − 1	n − 1
6	0	0, 1, 2	6, 5, 4	—	Suspend	—	Suspend
6	0	3, 4	3, 2	—	Suspend	Suspend	Suspend
6	0	5, 6	1, 0	—	n + 1	MTD	MTD
6	1	0, 1	5, 4	—	Suspend	—	Suspend
6	1	2	3	Suspend	Suspend	—	Suspend
6	1	3, 4	2, 1	Suspend	Suspend	Suspend	Suspend
6	1	5	0	n + 1	n + 1	MTD	MTD
6	≥ 2	Any	Any	n − 1	n − 1	n − 1	n − 1

SCENARIO 2

Decision:

- **Dose level 3: de-escalate**
- **Dose level 2: MTD**

SCENARIO 2: Learning points

- Dose-limiting toxicity (DLT):
  - **Adverse event** presumably **related** to the study drug that are considered **unacceptable** because of their severity and/or irreversibility
- DLTs are:
  - Defined before beginning the trial.
  - Protocol specific.
  - Determined tipically in the first cycle.
  - Graded according to standardised criteria (CTCAE).
  - Applicable only in patients with a certain drug exposure.

SCENARIO 2: Learning points

- Limitations of using DLTs:
  - The definitions are often heterogeneous between trials.
  - “Classic” DLTs are based on the toxicity profile of cytotoxic agents.
  - Current phase I trials mainly evaluate molecular targeted agents which display a different toxicity profile.
  - Delayed toxicities are normally not considered in the definition of the MTD/RP2D.

Bautista et al. EJC. 2017

SCENARIO 2: Learning points

- Maximum Tolerated Dose:
  - Highest dose level at which <33% of cases experience a DLT: i.e. maximum one DLT for every 6 cases.
  - The MTD is not always reached.

- Recommended Phase 2 Dose:
  - It's never higher than the MTD.
  - It takes into consideration issues like tolerability, drug combinations, etc

SCENARIO 3

- Study drug: Rotterdamidomide.
- Oral drug (capsules and solution) administered twice daily, 3 weeks on & 1 week off, in 28-day cycles.
- Current dose level: 1.

SCENARIO 3

- One DLT (patient #1): febrile neutropenia.
- Patient #3 not evaluable for DLTs.

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No. Enrolled	DLT Data			Enrolling Dose Level*			
				MTD Not Exceeded		MTD Exceeded	
	No. DLTs	No. Without DLT	No. With Data Pending	3 + 3	Rolling Six	3 + 3	Rolling Six
2	0, 1	Any	Any	n	n		
2	2	0	0	n − 1	n − 1		
3	0	0, 1, 2	3, 2, 1	Suspend	n		
3							
3							
3							
3							
4							n
4							n
4							n
4							n
4							n
4							n
4							n − 1
5							n
5							n
5							n
5	1	0, 1	4, 3	–	n	–	n
5	1	2	2	n	n	–	n
5	1	3, 4	1, 0	n	n	n	n
5	≥ 2	Any	Any	n − 1	n − 1	n − 1	n − 1
6	0	0, 1, 2	6, 5, 4	—	Suspend	—	Suspend
6	0	3, 4	3, 2	—	Suspend	Suspend	Suspend
6	0	5, 6	1, 0	—	n + 1	MTD	MTD
6	1	0, 1	5, 4	—	Suspend	—	Suspend
6	1	2	3	Suspend	Suspend	—	Suspend
6	1	3, 4	2, 1	Suspend	Suspend	Suspend	Suspend
6	1	5	0	n + 1	n + 1	MTD	MTD
6	≥ 2	Any	Any	n − 1	n − 1	n − 1	n − 1

SCENARIO 3

Decision:

- **Hold decision about dose escalation**
- **Enrol one more case in current dose level**

SCENARIO 3: Learning points

- Means to expedite phase I trials:
  - Patient selection
  - Backfill cohorts
  - Dose escalation methods: rolling 6 design, model-based designs, etc
  - Alternative endpoints: e.g. Optimal Biological Dose

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Many thanks