Archives of
Disease in Childhood

Adaptive trial designs: what is the continual reassessment method?

Journal:	*Archives of Disease in Childhood*
Manuscript ID	edpract-2019-316931.R2
Article Type:	Research in practice
Date Submitted by the Author:	11-Oct-2019
Complete List of Authors:	Millen, Gerard; Birmingham Women's and Children's NHS Foundation Trust, Paediatric Oncology Yap, Christina; University of Birmingham College of Medical and Dental Sciences, Cancer Research UK Clinical Trials Unit, Institute of Cancer and Genomic Sciences; Institute of Cancer Research, Clinical Trials and Statistics Unit
Keywords:	Evidence Based Medicine, Oncology, Statistics

Title

Adaptive trial designs: what is the continual reassessment method?

Corresponding author

Gerard Cathal Millen, Department of Paediatric Oncology, Birmingham Children's Hospital, Steelhouse Lane, Birmingham, B4 6NH. Email: g.millen@nhs.net. Number: 01213339999

Keywords

Evidence-based medicine

Oncology

Statistics

Co-author

Christina Yap, Cancer Research UK Clinical Trials Unit, Institute of Cancer and Genomic Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, UK.

Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, SM2 5NG

Word Count excluding title page, abstract, references, figures and tables

1000 words

Adaptive trial designs: what is the continual reassessment method?

Early phase trials provide crucial information about new medicines that allow them to be taken forward into larger confirmatory studies. Paediatric early phase studies are becoming more common, particularly in the era of precision therapy. There are almost 600 active paediatric phase I/II trials listed on clinicaltrials.gov. Conventionally, early phase dose-escalation trials use rule-based designs such as the 3+3 to guide dose decisions. A trial is considered to have a rule-based design if pre-defined rules are used to guide decisions to escalate, continue or de-escalate based on the observed toxicities at the current dose.

Though it is well established that model-based design is generally superior to rule-based design, its uptake remains low. Trials with a model-based design use statistical models to guide decisions on which dose levels to give the next patient(s), based on the targeted toxicity level and previous information. In this article, we review one of the most commonly used model-based designs, the continual reassessment method.

The goal of any phase I study is to find a recommended dose of a new therapy to advance in subsequent studies. This can be defined in different ways; one of the most common being the maximum tolerated dose (MTD). One key question is: “What level of toxicity is acceptable based on the expected benefits of treatment?” The MTD is defined as the dose expected to cause a degree of medically undesirable dose-limiting toxicity (DLT) in an

acceptable specified proportion of participants. The latter is referred to as the target toxicity level (TTL). This level will differ depending on the expected benefits of the treatment as well as the severity of the expected toxicity for the specific intervention. This relationship is illustrated in figure 1.

With rule-based 3+3 design, cohorts of three patients are treated at each dose level and decisions on escalation or de-escalation are based on the number of patients with DLTs at the current dose. If 0/3 patients experience DLTs, the dose is escalated to the next level. If 1/3 DLT is observed, 3 further patients will be recruited and escalation happens if no further DLT is observed. If ≥2/3 DLTs are observed, the dose is de-escalated to the next level. Depending on factors such as the number of dose levels and the starting dose, many patients may receive sub-therapeutic doses without any toxicities. Other drawbacks are highlighted in table 1.[1]

What is the continual reassessment method?

The continual reassessment method is a form of model-based trial design that was first proposed in 1990 to obtain the MTD.[2] Unlike rule-based approaches, a continual reassessment method utilises a statistical model to estimate the relationship between dose and DLT risk. With a Bayesian approach, it integrates accumulated observed data in the trial as well as prior information from clinicians and past studies, to recommend a dose with estimated DLT risk closest to the TTL to the next cohort/patient. The model learns as the trial progresses as the data from every patient already enrolled is included to recommend the best MTD estimate for the next patient. Since its introduction, numerous modifications

have been proposed to improve safety such as increasing the size of dosing cohorts and reducing the chance of large increases in dose in the early stages of a study.[3]

continual reassessment method designs are particularly attractive in paediatric trials as it is exceptionally rare for a drug to be trialled in children prior to similar studies in adults. The toxicity seen in adults can be used to estimate the likely toxicity across the tested doses in children to inform an appropriate starting dose and the statistical model. In practice, if we observe patients experience DLT at the current dose, the model will assess if it has underestimated the risk of DLTs and may then reduce the dose for the next cohort if so. If patients do not experience DLT, the opposite may occur. The trial continues until pre-defined stopping criteria are met such as a pre-specified maximum number of enrolled patients or sufficient patients being dosed at the proposed MTD.[4,5]

Consider Figure 2 from the VIOLA trial. The VIOLA trial was a phase I study looking at the treatment of adult patients with relapsed AML post allogeneic stem cell transplant. The prior curve shows that the study team initially over-estimated the risk of DLTs. As the trial progressed and more patients were treated without DLTs, the model reduced its DLT risk estimates, resulting in the updated curves shown.

A good example of a paediatric trial which used the continual reassessment method is a trial of selumetinib in patients with recurrent or refractory low grade glioma[6].

Benefits of continual reassessment method over rule-based designs

A large number of studies have compared continual reassessment method design to rule-based designs and a number of benefits have been identified, including the ability to identify the recommended Phase II dose more accurately. One key advantage is the flexibility to accommodate potential deviations from the plan as seen in the VIOLA trial.[7] Key features are summarised in table 1.[1,8,9]

	Rule-based designs	**Model-based designs**
Target DLT rate	Unclear	Clearly defined and can be flexibly chosen
Patients treated at the optimal dose	(relatively) few	(relatively) many
Patients treated at subtherapeutic doses	(relatively) many	(relatively) few
Utilisation of available data	Poor	Efficient
Extension to more complex questions	Difficult & dubious	Smooth & straightforward
Deviations from the plan (e.g. other doses, different number of patients on a dose)	Hard or impossible to incorporate	Easily accommodated

Table 1: Summary of some key features of rule-based and model-based designs[1]

Concerns about continual reassessment method trials

There are some concerns about continual reassessment method studies that currently limit their use. All model-based designs account for less than 10% of current phase I studies. They are undoubtedly more complex to design/run, requiring active input from a trial statistician.

This can increase the up-front costs prior to securing funding which can deter some clinicians.[10]

Whilst most early phase researchers are readily familiar with the 3+3 design which is simple and easy to implement, there can be perceived fears around the "black-box" of model-based designs. However, it is straightforward to make the "black-box" transparent using the concept of "Dose Transition Pathways" to understand possible courses of action in a trial that implements a model-based design – both at the design and conduct stage.[11]

Some researchers have raised concerns about the safety of continual reassessment method trials. As highlighted in Table 1, continual reassessment method studies are safer and more ethical than rule-based designs by treating more patients at a dose more likely to be effective whilst protecting them against excessive doses. Safety mechanisms can be built-in to limit risks such as increased dose cohorts and avoid skipping of untried doses in escalation. Crucially, these safety mechanisms do not reduce the flexibility or efficiency of the studies. Furthermore, the observation of safety data from the first patient in a study may be required before any other patients can be dosed in that cohort due to several past phase I trial disasters. [5,10,11]

Conclusion

Early phase clinical trials are essential components of evidence-based medicine. Due to relatively small patient numbers, it is vital that trials are designed in the most efficient way possible. continual reassessment method has been shown to have many advantages over

conventional trial designs including efficiency and efficacy for patients. Despite this, uptake remains low with relatively unfounded fears about the complexity of designing and running them.

Footnotes

Contributors: GCM wrote and revised the initial manuscript. CY wrote, reviewed and revised the manuscript prior to submission. Both authors approved the final manuscript.

Competing interests: None declared

Funding: CY is funded by Cancer Research UK Grant No. C22436/A15958

Provenance and peer review: Commissioned; externally peer reviewed.

Legends

Figure 1: An illustration of the relationship between dose level and the probability of toxicity and activity. A target toxicity level (the proportion of patients in which it is considered acceptable to have medically undesirable side effects) of 20% will result in a maximum tolerated dose at dose level 3 (MTD_1), which gives an activity rate (the proportion of patients who demonstrate efficacy) of 45%. A target toxicity level of 40% will result in a maximum tolerated dose at dose level 5 (MTD_2), which gives an activity rate of 70%. The stars indicate the activity at dose level 3 and 5. In this example, as the dose increases, the activity increases but so does the toxicity.

Figure 2: This figure shows the evolution in the estimates of the probabilities of DLTs through successive patient cohorts in the VIOLA trial which utilised a continual reassessment method design. The dose-toxicity curves reduced through the first 4 cohorts as no DLTs were observed before increasing again in cohorts 5 and 6 when DLTs occurred. The MTD was declared at dose level 3 as it had an estimated DLT risk closest to the target toxicity level of 20%. Adapted from: Combination Lenalidomide and Azacitidine: A Novel Salvage Therapy in Patients Who Relapse After Allogeneic Stem-Cell Transplantation for Acute Myeloid Leukemia[7]

References

1 Adaptive Designs Working Group of the MRC Network of Hubs for Trials Methodology Research. A quick guide why not to use AB designs. http://www.methodologyhubs.mrc.ac.uk/files/6814/6253/2385/A_quick_guide_why_not_to_use_AB_designs.pdf (accessed 15 Mar 2019).

2 O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. *Biometrics* 1990;**46**:33–48.

3 Piantadosi S, Fisher JD, Grossman S. Practical implementation of a modified continual reassessment method for dose-finding trials. *Cancer Chemother Pharmacol* 1998;**41**:429–36. doi:10.1007/s002800050763

4 Garrett-Mayer E. The continual reassessment method for dose-finding studies: a tutorial. *Clin Trials J Soc Clin Trials* 2006;**3**:57–71. doi:10.1191/1740774506cn134oa

5 Wheeler GM, Mander AP, Bedding A, *et al.* How to design a dose-finding study using the continual reassessment method. *BMC Med Res Methodol* 2019;**19**. doi:10.1186/s12874-018-0638-z

6 Banerjee A, Jakacki RI, Onar-Thomas A, *et al.* A phase I trial of the MEK inhibitor selumetinib (AZD6244) in pediatric patients with recurrent or refractory low-grade glioma: a Pediatric Brain Tumor Consortium (PBTC) study. *Neuro-Oncol* 2017;**19**:1135–44. doi:10.1093/neuonc/now282

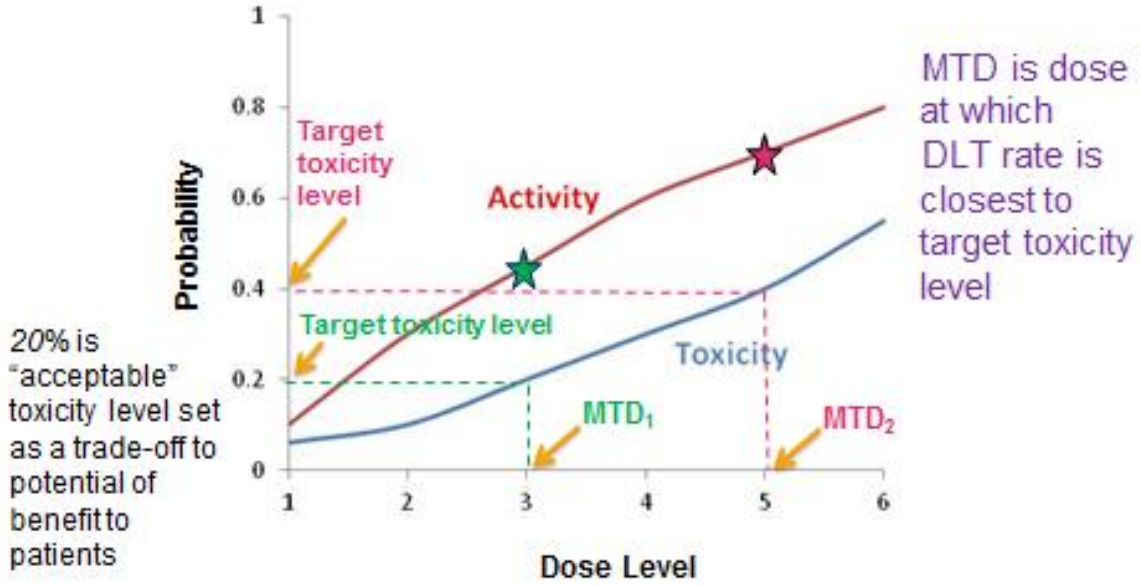
7 Craddock C, Slade D, De Santo C, *et al.* Combination Lenalidomide and Azacitidine: A Novel Salvage Therapy in Patients Who Relapse After Allogeneic Stem-Cell Transplantation for Acute Myeloid Leukemia. *J Clin Oncol* 2019;**37**:580–8. doi:10.1200/JCO.18.00889

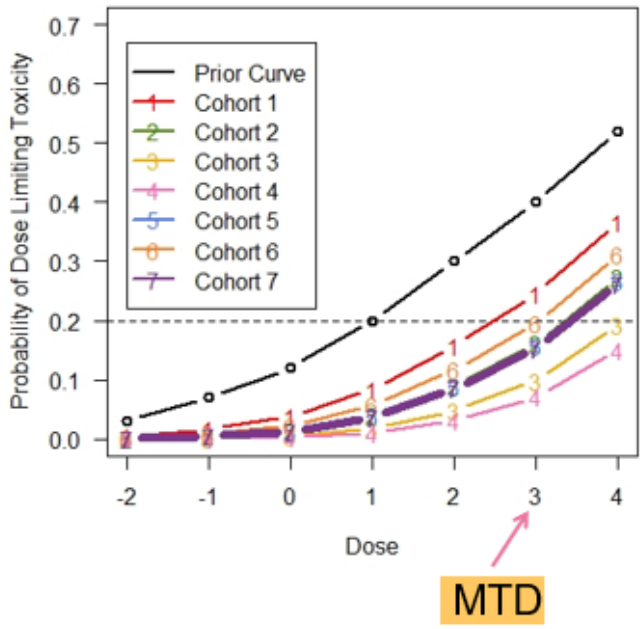
8 Boonstra PS, Shen J, Taylor JMG, *et al.* A statistical evaluation of dose expansion cohorts in phase I clinical trials. *J Natl Cancer Inst* 2015;**107**. doi:10.1093/jnci/dju429

9 Iasonos A, Wilton AS, Riedel ER, *et al.* A comprehensive comparison of the continual reassessment method to the standard 3 + 3 dose escalation scheme in Phase I dose-finding studies. *Clin Trials J Soc Clin Trials* 2008;**5**:465–77. doi:10.1177/1740774508096474

10 Love SB, Brown S, Weir CJ, *et al.* Embracing model-based designs for dose-finding trials. *Br J Cancer* 2017;**117**:332–9. doi:10.1038/bjc.2017.186

11 Yap C, Billingham LJ, Cheung YK, *et al.* Dose Transition Pathways: The Missing Link Between Complex Dose-Finding Designs and Simple Decision-Making. *Clin Cancer Res Off J Am Assoc Cancer Res* 2017;**23**:7440–7. doi:10.1158/1078-0432.CCR-17-0582





Cohort	Dose	#DLT/#patients
1	0	0/3
2	1	0/3
3	2	0/2
	3	0/1
4	3	0/2
5	3	1/3
6	3	1/3
7	3	0/4