DOCTORAL THESIS

Developments to established dose-finding methodologies for application in trials with complex and innovative designs

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Abstract

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by Amit PATEL

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Chapter 1

Implementing the PO-TITE-CRM trial design into ADePT-DDR

1.1 Draft Structure

- Introduction
  - Basic biological background
  - Main objective of the trial
  - Introduce the new TD notation link to previous trial designs
  - Paragraph on traditional dose finding trial designs 3+3, CRM etc.
  - Methodological issues which arise due to investigating combination of drugs/varying parameters (new concept by Piers)
  - Necessity of time-to-event components for DLTs which may occur later
  - Other possible methodologies in this area which may be of use to solve this problem
  - Mini literature search will do a citation search for both methodology papers (potentially use a table/figure to summarise)
  - Detail whats to come in the chapter

- The PO-TITE-CRM Design
- PO-TITE-CRM in ADePT-DDR
- Modifications to the specification to improve operating characteristics

1.2 Introduction

Worldwide there are approximately 600,000 new cases of Head and Neck Squamous Cell Carcinoma (HNSCC) each year [1]. Of which, 12,000 occur in the UK with the most common forms of treatment being surgery, radiotherapy and/or [2]. Radiotherapy is essential for the treatment of cancer, it has been estimated that more than 40% of patients will receive radiotherapy at some point in their treatment [3]. However, despite recent advancements in radiation techniques and the use of of concomitant chemo radiotherapy, patients with solid tumours such as head and neck cancer have suboptimal cure rates [2], [4]. For those with advance HNSCC primary radiotherapy with concurrent chemotherapy is often offered but, it has not been shown to improve survival in patients aged over 70 compared to radiotherapy alone [5]. Therefore, any strategy to improve the efficacy of radiotherapy without increasing toxicity to normal tissue would have a significant impact for patients. DNA damage repair (DDR) inhibition is a potential technique which could be utilised as it potentiates the therapeutic effects of ionising radiation in cancer cells without a substantial increase in acute and late toxicity. Combining radiotherapy with DDR inhibition could improve clinical outcomes for these patients [6].

The ADePT-DDR trial is a platform trial which aims to evaluate the safety and efficacy of different DDR agents, or different immunotherapy agents and/or

DDR and immunotherapy combinations, together with radiotherapy in patients with HNSCC. The initial component of this trial is a single arm dose-finding phase Ib/IIa trial investigating the Ataxia Telangiectasis and Rad3 Related (ATR) inhibitor AZD6738 in combination with radiotherapy. ATR inhibitors block DNA repair and AZD6738 has been shown to effectively kill cancer cells in preclinical models [7].

Traditionally dose-finding trials aim to determine the maximum tolerated dose (MTD) of a treatment based on the cytotoxic assumption that toxicity increases with dose. Rule-based or 'up and down' designs achieve this by escalating and de-escalating dose dependent on the observation of severe toxicity due to the drug, commonly referred to as a dose limiting toxicity (DLT). In the case of the 3+3 design escalation continues till at least two patients in a cohort of three or six experience a DLT. More explicitly, the MTD is the dose at which $\geq$33% of patients experience a DLT [8]. Model based designs such as the continual reassessment method (CRM) [9] work on a similar principle which assumes that the probability of toxicity monotonically increases with dose. One key difference with the CRM is that it iteratively changes dose, seeking some acceptable target probability of toxicity also referred to as the MTD.

Due to the historical use of rule-based designs the majority of terminology used to describe them, and the ambiguity they raise, have been inherited by modern alternatives such as the CRM. The MTD in the context of a CRM is not the 'maximum' dose patients could tolerate but rather a dose which there would be an acceptable target probability of a DLT occurring. For example, if the target is set at 25% the MTD would be the dose at which there is a 25% probability of experiencing a DLT. Rather than using MTD the dose to be found will be referred to as the target dose (TD%%, where the %'s are replaced by the target probability), i.e. TD25 would be the dose expected to be toxic in 25% of patients.

Appendix A

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