15 Biometrical Aspects of Drug Development

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Abstract. Once the activity of a compound has been established in the laboratory (usually by use of experimental animals) the next stage of development is to bring this forward to humans in early-phase clinical trials. A pharmacokinetic study aims to establish an effective dosing regimen for the compound in order to reach concentrations within the therapeutic window as quickly as possible. The aim of the phase I trials is typically to determine a maximal safe dose with which more rigorous investigation of activity in a phase II trial can be conducted. This chapter deals with statistical issues related to the design of phase I studies.

15.1 Introduction

The design of any study is the key component for obtaining a satisfactory answer to the question posed. An important factor when considering
the design of phase III trials is the information provided from earlier-stage studies and trials. Consequently, since the development of, for example, new therapies tends to progress at the clinical stage through pharmacokinetic, phase I to phase II then to phase III trials, the sequential nature of this structure implies that reliable information from one step is important for the next. Poor experimentation at the relevant stage can clearly jeopardise the design of the next stage and, at best, results in a waste of resources and at worst may compromise patient safety. Unfortunately, the evidence provided by published reports of early-stage trials suggests that these have often not been well designed or well reported.

A phase I trial aims to determine (often from a preselected range of potential doses) the dose that can be utilised at the next stage of development and so focuses on selecting the highest practical dose, the presumption being that the greater the dose the greater the anti-disease effect will be. However, safety considerations dictate that the dose chosen for the subsequent trials should have an acceptable toxicity profile.

Phase I trials are usually small. This lack of numbers has at least two implications, one is that the final estimates of whatever statistic is to be estimated will be rather imprecise and the other is that these studies should be very carefully designed so as to maximise the information that can be obtained by optimal use of this scarce resource.

15.2 Phase I Trials

In broad terms, the aim of a phase I trial is to establish the maximum tolerated dose (MTD) of a particular compound. In some circumstances, the treatment under test may prove to be too toxic and so no MTD is established. In this case, a phase II trial would not be initiated for subsequent further testing. Underestimation of the MTD may lead to an apparent lack of efficacy at the later stages. Overestimation may lead to unacceptable toxicity (even death) in some patients. In either situation, a potentially useful compound may be shelved and opportunities for a therapeutic advance stalled.

For patients with a specific disease, one objective of treatment may be to reduce (or eradicate) the disease burden. However, it is recognised