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Current Perspective

Eligibility of patients with renal impairment for Phase I trials: Time for a rethink?

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Abstract Since the inception of Phase I clinical trials in cancer, patients with renal dysfunction have commonly been excluded from participation because of a poor outlook. Most cancer drugs are approved with limited information on the pharmacokinetics and/or pharmacodynamics of the drugs in patients with renal dysfunction, and no formal renal dysfunction study is ever undertaken. Patients with asymptomatic mild to moderate renal dysfunction pose an increasingly frequent challenge for clinicians. In this paper, we discuss that a subset of patients with asymptomatic mild to moderate renal impairment might be appropriately entered into selected Phase I trials. This will provide physicians timely data of the new agents in this patient population and increase patients' access to experimental treatments.

1. Introduction

The number of patients with renal dysfunction is increasing worldwide [1]. This is a large and growing problem particularly among ageing populations. Characterising the safety and pharmacokinetics of new drugs in patients with renal dysfunction is important because renal dysfunction is regularly encountered among patients with advanced cancer. Cancer patients often have varying degrees of renal impairment, either due to underlying disease process or as a consequence of nephrotoxic effect of the cytotoxic agents. Renal dysfunction is associated with decreased renal clearance, altered absorption, plasma protein binding, distribution and biotransformation of the drugs [2]. Traditionally, the majority of Phase I studies of novel agents in oncology have excluded patients with moderate to severe renal dysfunction mainly due to safety concerns. Exclusion of patients with renal dysfunction is typically based on the serum creatinine. In routine practice, renal function is mostly assessed on the basis of the serum creatinine level. However, creatinine clearance (GFR) provides a more accurate assessment of renal function and can be calculated from the serum creatinine, 24-h urine collection and isotopic methods [3]. Although

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there is no standard cut off for renal function, serum creatinine within 1.5 times the upper limit of normal is mostly required to be eligible for a Phase I study. Excluding patients with renal dysfunction from Phase I studies results in a significant handicap in the future clinical practice because of lack of safety or pharmacokinetic information in such patients.

Patients with renal dysfunction are generally considered to be in a poor physical condition. Therefore, it is believed that these patients may not be able to complete the evaluable period for dose limiting toxicity of the study. Patients with renal dysfunction are also thought to be at increased risk of certain toxicities and may even add to the potential adverse events associated with the study drug. The symptoms and signs of renal dysfunction may also make it difficult to differentiate them from drug-related adverse events. Therefore, a separate Phase I study with selected agents, has been performed for such patients to determine the safety profile, drug exposure/pharmacokinetics or maximally tolerated dose (MTD) [4].

Renal clearance in human has been predicted successfully by using physiologically based allometric procedures [5]. The data on the accurate prediction of human renal clearance specifically for new anticancer agents are limited and may complicate extrapolation from preclinical to clinical studies. Paine et al. observed that there exists a good correlation between human and dog renal clearance of 36 commonly used drugs after correcting for differences in plasma protein binding [6]. Adjustment of the standard drug dosage in patients may be necessary because of renal dysfunction and interspecies differences to avoid excessive accumulation of the drug and/or its active metabolite.

We propose that it is time to reconsider routine exclusion of asymptomatic patients with only moderate renal dysfunction from Phase I oncology trials. The newer targeted agents in development generally have a wider therapeutic index. Patients with asymptomatic mild to moderate renal dysfunction might have a better outlook (than previously perceived) depending upon other prognostic factors such as age, control of systemic disease and performance status. The survival of renal dysfunction patients may still be measured in years [7]. The prognosis of cancer patients with renal dysfunction may not be worse than that of patients with normal renal function [8,9]. Most patients with renal dysfunction are not on any specific drugs which are metabolised by the cytochrome P450 system. In reality, symptoms from renal dysfunction can be differentiated from potential drug-related toxicities without much difficulty. Patients with asymptomatic renal dysfunction might not have increased drug-related adverse events with the agents that are predominantly eliminated via other routes, and therefore, less likely to complicate assessment of toxic effects. Multiple Phase I trials conducted exclusively in cancer patients with renal dysfunction, have reinforced the notion that the MTD in these patients is either the same or up to 25% lower than the previously established MTD [4,10,11]. To further illustrate the point, imatinib was originally granted accelerated approval for the treatment of advanced or metastatic gastrointestinal stromal tumour in 2002. The first prospective pharmacokinetic study of imatinib in patients with renal dysfunction was completed in 2005 (results published in 2008) [12]. Imatinib was well tolerated up to 800 daily by patients with renal dysfunction. The most frequently reported adverse events across all cohorts/dose levels were mild to moderate in severity and hence, no dose modification was recommended for such patients.

The National Cancer Institute (NCI) Organ Dysfunction Working Group is actively involved in evaluating promising agents in patients with renal or hepatic dysfunction. The US Food and Drug Administration (FDA) may request dedicated pharmacokinetic and safety studies in renal (organ) dysfunction patients at the time of drug approval based on the available data in the new drug application [13]. The FDA has developed guidances on the design, conduct, analysis and reporting of organ dysfunction studies [14]. These guidelines recommend that a pharmacokinetic study be carried out during the development of a drug, which is likely to be used in patients with impaired renal function and when renal dysfunction is likely to significantly alter the pharmacokinetics of the drug. For example, the FDA approved eribulin (November, 2010) and regorafenib (September, 2012), and recommended a post marketing dedicated renal dysfunction study in subjects with renal impairment [15,16]. As these studies are still ongoing for several years, inadequate information in the drug label about the dose for renal dysfunction patients remains a significant concern to the treating physician and highlights a major limitation of the current approach. Moreover, most cancer drugs are approved with limited information on the pharmacokinetics and/or pharmacodynamics of the drugs in patients with renal dysfunction, and no formal renal dysfunction study is ever undertaken. Table 1 presents dosage adjustment information as per FDA approved drug label for the anticancer agents that have been approved between 2012 and 2014.

In this era of targeted therapies, we suggest that it is time to reconsider and include patients with renal impairment in Phase I oncology trials of agents with low renal clearance. A more prudent approach would be to accrue normal renal function patients at a particular dose level first to determine the safety and pharmacokinetics. After establishing the safety and following dose escalation, patients with moderate renal dysfunction would be enrolled at that dose level to determine the safety and pharmacokinetics. This would provide