

Do We Have the Right Dose? Dose Adjustments for Organ Dysfunction

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Cancer patients with adequate hepatic or renal function are typically studied in clinical trials. Since most anticancer agents are cleared via hepatic or renal mechanisms, dose adjustments would be anticipated. Yet when the drug is approved, dosing modification guidelines are often lacking for patients who have varying degrees of hepatic or renal dysfunction. Therefore, oncologists may start therapy with an empirically-derived lower starting dose due to the perception that a patient with organ dysfunction would have poorer tolerability due to increased toxicity. The United States FDA and the European Medicines Agency (EMA) have developed guidances on the conduct of studies addressing the optimal dose in patients with hepatic [1,2] or renal [3,4] dysfunction. These guidance's are subjected to interpretation of whether these studies should be conducted in a cancer patient population or in healthy volunteers having hepatic or renal dysfunction. To add to the issue, growing evidence demonstrates that renal dysfunction can alter the pharmacokinetics of the drugs which are not eliminated renally [5]. Therefore, the EMA is considering a revision of the current renal dysfunction guidance [6].

With traditional cytotoxic agents, the clinical trials need to be conducted in cancer patients due to ethical and safety concerns. Conducting clinical trials in cancer patients with hepatic or renal dysfunction can prove challenging due to the overall poor health of these patients with the potential for rapid decline of performance status. Despite the challenges, multi-institutional trials have been conducted and are the gold-standard in order to facilitate accrual and provide sound dosing recommendations. Trials have been conducted in this fashion in cancer patients for bortezomib [7,8], erlotinib [9], imatinib [10,11], sorafenib [12], and tipifarnib [13]. Patients were enrolled into cohorts that were defined based on simple organ function parameters commonly available to a community oncologist. These trials were designed to provide definitive dosing recommendations with dose escalation of cohorts by not only addressing the pharmacokinetic differences but also tolerability in 54 to 150 cancer patients. This approach has lead to more sound dosing recommendations.

Many pharmaceutical companies are now conducting trials with molecularly-targeted drugs in healthy volunteers with end-organ dysfunction. Healthy volunteer studies are ethical with molecularly-targeted drugs that have minimal or no toxicity noted in toxicology studies. One may theorize that this is to minimize the number of patients or the duration of the trials in order to answer the key regulatory issue of defining a dose based on pharmacokinetic differences. Recent examples of hepatic dysfunction trials include a single-dose pharmacokinetic and tolerability assessment for axitinib [14] and bosutinib [15]. While both trials demonstrated a significant increase in exposure yet similar tolerability, these trials were only conducted with a single dose in patients with hepatic dysfunction. The pertinent clinical question of long-term tolerability remains and is necessary to be determined in order to provide clinical benefit to a patient.

While the pharmaceutical companies are trying to address the regulatory concerns in an expeditious fashion, these companies are not providing adequate long-term dosing information for oncologists.

The more prudent approach would be to utilize the single-dose healthy volunteer trials to derive a proposed dose that could be confirmed in a smaller cancer patient population utilizing just one dose per cohort with the potential for intra-patient dose alterations. Additionally, a population pharmacokinetic approach could be applied to the data to re-confirm the dosing recommendations derived from both studies. The end result would satisfy drug companies, regulatory agencies, and oncologists as the long-term tolerability of the molecularly-targeted drugs could be determined more comprehensively.

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