Commentary (Ivy): Cancer Management in Patients With End-Stage Renal Disease

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Eneman and Philips' review, "Cancer Management in Patients With End-Stage Renal Disease," comes at a time when this issue is of critical importance to oncologists. As the authors indicate, the confluence of two factors-chronic renal replacement therapy (CRRT) lengthening lives and an aging population in general-have made the study of organ dysfunction a pressing issue.[1] The authors provide comprehensive statistics on CRRT. Age statistics also support the necessity for further study of this special population. For all types of cancer, the median age at diagnosis is 68 years, and 70% of all cancer deaths occur in people aged 65 years or older. By 2050, experts expect that more than 40% of cases will occur in this age group.[2,3] Many of these people will have end-stage organ dysfunction and limited access to care because of their comorbidities.

The authors contention that there is a paucity of information needed for optimal management is also correct. The Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) is, however, attempting to correct this knowledge deficit. To do so, CTEP is actively soliciting organ dysfunction studies in patients with renal and hepatic dysfunction. Organ dysfunction templates designed to evaluate toxicity and to measure pharmacokinetic and pharmacodynamic parameters in cohorts of patients with varying degrees of organ dysfunction have been prepared to guide investigators. They are available at [http://www.ctep.cancer.gov](http://www.ctep.cancer.gov).

Defining Treatment: Special Population

The CTEP has worked in collaboration with the US Food and Drug Administration (FDA) to define study parameters and design templates useful for patients with varying degrees of renal failure. The tools provide the parameters for studies used for regulatory review of chemotherapeutic and investigational agents. They provide essential guidance for conducting studies in patients with organ dysfunction, with the ultimate goal being determination of information that can be used in a product's complete prescribing information.


Key Components of Renal Dysfunction Studies

Extensive pharmacokinetic sampling for the agent in question as well as its active metabolites must be done to provide meaningful results leading to appropriate dosing recommendations. Should pharmacokinetic parameters correlate with an acceptable toxicity profile, they can guide future dose
recommendations in much the way that area under the concentration-time curve (AUC) is used to determine the target level for carboplatin dosing.[4] This, in fact, is a goal of these studies. Small patient cohorts are generally used, so if pharmacokinetic parameters and the target level are identified in a small study cohort (eg, 6 patients), an expanded cohort of 12 to 15 patients should be treated to validate the use of particular parameters to guide dosing.

Enzymatic activity of the CYP450 system may affect the agent of interest or its metabolites; so might concomitant medications that are CYP450 substrates, inhibitors, or inducers. In patients with organ dysfunction, active metabolic products from CYP450 interaction could be excreted via an alternative renal route, ie, different from the known primary route of elimination. Investigation of all of these possibilities is a must for organ dysfunction studies.

Finally, combination regimens remain the linchpin of cancer treatment, and many (if not most) agents will ultimately be given in combination protocols. While acknowledging that fact, it is crucial to also note that accomplishing such studies in a reasonable time frame—perhaps a licensing trial, for example—is usually very time consuming in compromised populations and, therefore, prolonged. Investigators who wish to examine combinations in organ dysfunction find that consultation with the FDA can lead to appropriate design and efficient study conduct. The FDA will ensure that the choice of regimen and the need for pharmacokinetic measurements to isolate and identify any interactions between the agents administered are included.

**Critical Priorities**

Timing is critical when conducting organ dysfunction studies for investigational agents. If these costly, time-consuming studies are initiated too early in the development process, when there is a chance that the agent may not successfully complete phase I or II trials, it is neither cost-effective nor efficient. Waiting may mean that accumulated activity data will narrow the potential cancers in which phase I organ dysfunction studies can be conducted. Delay in initiation could result in the study not being completed before FDA approval of the agent; consequently, the information may not appear in the initial prescribing information. Thus, a delicate balance exists, and investigators must determine when it is best to initiate organ dysfunction studies for those agents that have a reasonable likelihood of FDA licensing.

CTEP-sponsored organ dysfunction studies have been completed for oxaliplatin (Eloxitan)[5,6] and are close to completion for imatinib (Gleevec), ixabepilone, and bortezomib (Velcade). In the case of bortezomib, a number of dialysis patients were deemed suitable for study, making these studies feasible at an appropriate juncture and more timely than in most cases. Often, organ dysfunction studies do not include dialysis patients because they are not considered suitable candidates for investigational studies. These studies will lead to incorporation of dosing recommendations in the approved products’ complete prescribing information. All investigational agents should be considered for organ dysfunction studies at an appropriate stage of development. In the future, agents in phase III trials that have a reasonable chance of FDA approval should include organ dysfunction studies as described herein in their pivotal trials.

Eneman and Philips have done an excellent job of compiling a list of organ dysfunction studies to date. This paper stops short of being a "how to" article for the clinician, mainly because there is little clear direction or trial-confirmed information available. Certainly, the manuscript highlights a slow, steady movement toward obtaining more organ dysfunction information for antineoplastic dosing in a variety of malignant diseases. Should support from the NCI encourage researchers to continue these studies with CRRT patients enrolled in trials, perhaps the authors’ next paper will have better and more varied dosing information.

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**References:**


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