Commentary (Perry): Chemotherapy Dosing in the Setting of Liver Dysfunction

July 01, 2005
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The article by Eklund, Trifilio, and Mulcahy begins to address the difficulties involved in dealing with a special patient population—those with impaired hepatic function. The issues involved in dealing with abnormal liver function are distinct from those encountered with end-stage renal disease (to be discussed in the August issue of ONCOLOGY); hepatic function due to tumor may improve with successful therapy, while for dialysis patients, their renal disease is considered permanent. As Eklund and colleagues suggest, we do not have uniform criteria for dose modifications in liver disease. For hepatic dysfunction, levels of serum bilirubin, transaminases, albumin, and the extent of liver involvement on scans have all been used, with a resulting lack of standardization. Abnormal liver function tests are almost always an exclusion criterion for phase I through phase III randomized clinical trials studies, so few, if any, patients have been studied in the original registration studies. Looking at subpopulations comes later, if at all. It is essential to understand the etiology of the liver disease, with the understanding that extrahepatic biliary obstruction due to chemosensitive tumors may respond rapidly to full-dose chemotherapy, particularly if the goal is a complete response and potential cure. I believe it is important to recognize that patients with severely altered renal function have a backup, in the form of dialysis (a proximate lifesustaining measure), that patients with hepatic failure do not. Patients with hepatic failure, therefore, are more likely to have poorer survival. For patients with Childs-Pugh grade A (well-compensated) disease, 1-year survival is 100% and 2-year survival is 85%. For those with grade B disease (significant functional compromise), the 1- and 2-year survival rates drop to 80% and 60%, respectively, while for grade C disease (decompensated), the 1- and 2-year rates are 54% and 35%, respectively.

Rationale for Treatment
I would submit that treatment of cancer in the adjuvant setting cannot be defended in this setting of hepatic failure, and only treatment of metastatic disease seems reasonable. But the cost of a few months of additional survival must be weighed against the likelihood of increased side effects and, perhaps, increased morbidity and mortality due to increased toxicity. Treatment of tumors that are very responsive to chemotherapy (Hodgkin's and non-Hodgkin's lymphomas, germ cell tumors, small-cell lung cancer) seems most likely to end in a favorable result, while treatment of most metastatic solid tumors (breast cancer, non-small-cell lung cancer, colorectal cancer) may buy only increased side effects and no survival advantage. The other side of the coin is response to therapy. If few or no patients respond to modified (reduced) doses, is it ever worthwhile to treat such patients who will almost certainly experience toxicity? We also have a paucity of data on this risk/benefit aspect of therapy. Chemotherapy-Associated Toxicity
As the toxicity produced by chemotherapeutic agents themselves may cloud the issue, a working knowledge of the potential side effects of the agents used it critical.[1,2] New combinations may produce unexpected toxicities as well.[3] It is also important to note that radiation therapy to the kidney, as in the treatment of nephroblastoma, may produce abnormal liver function tests and scans.[4] Eklund et al do not discuss ifosfamide, the nitrosoureas, cytarabine, mercaptopurine, thioguanine (Tabloid), and mitoxantrone (Novantrone), although most of these agents are less commonly used and do not have a role in the treatment of the "responsive" tumors listed above. Hepatologist Paul King and I have attempted to record existing guidelines elsewhere.[1,2] General Treatment Principles
In summary, I suggest several general principles:
(1) Look for reversible causes of liver dysfunction (biliary stones, extra hepatic biliary obstruction,
etc).
(2) Review all the patient's medications for hepatotoxic drugs.
(3) Know the metabolism and excretion of the proposed drugs.
(4) Know the prognosis of any underlying liver disease.
(5) When possible, pick drugs with alternate routes of metabolism.
(6) Modify doses appropriately.
(7) Recognize that new drug combinations may produce unexpected toxicity.
(8) Report the results (responses and toxicities) to increase our database.

Disclosures:
The author has no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

References:

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