The Development of Hepatocellular Carcinoma in Cirrhotic and Noncirrhotic Livers

To the Editor—Carcinogenesis is a multistep process; each step is a DNA mutation. These mutations, which involve the cell cycle genes, have the cumulative result of a clonal cellular growth advantage. Traditionally, because of variations in the geographic incidence of tumors, and from experimental studies, environmental and exogenous agents have been emphasized as putative carcinogens and mutagens. However, benign tumors and most cancers are not associated with an identifiable carcinogen or mutagen. If it is correct, then, to hypothesize a unique “hepatocarcinogen” responsible for the last “hit” in hepatocellular carcinogenesis?1

A darwinian approach to neoplasia in general (benign tumors are also clonal) and to cancer in particular may be useful. Cell division and DNA replication have a low but constant rate of mutation. Most such rare events are deleterious or neutral to a cell or microorganism. Rarely, however, somatic cell mutations will confer a slight growth advantage. These mutations may involve critical genes that are responsible for checkpoints or “braking” in the cell cycle. Second, third, and fourth mutations, although very rare events, are more likely to occur in this clone of cells with a selective growth advantage, ie, the source of these rare mutations is cell division itself and not an environmental mutagen. Virtually all known carcinogens are direct or indirect mitogens. Nutrients and hormones are examples of direct mitogens and are associated with some of our most common malignant neoplasms, eg, breast, bowel, and prostatic carcinoma. Toxins are indirect mitogens and selectively stimulate regeneration of those cells resistant to or unaffected by the toxin. Such is the case in hepatocellular carcinoma associated with hepatitis or alcohol.

Cell growth and regeneration have a low intrinsic rate of spontaneous mutation. Selective environments, eg, ad libitum high-fat diet, alcohol consumption, cigarette smoking, and viral infection, will maximize the frequency of such mitotic mutations and be associated with a greater incidence of malignancy.

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REFERENCE

Irradiated Blood Components

To the Editor—While I have no problem with most of the specifications outlined in the article by Przepiorka et al,1 I would take issue with the notation that irradiated components are needed for extracorporeal membrane oxygenation (ECMO).

At the University of Michigan Hospitals, in spite of not irradiating cellular blood components for patients undergoing ECMO, there have been no occurrences of transfusion-associated graft-versus-host disease (TA-GVHD) in these patients. Patients with documented immunodeficiency receive irradiated components; however, I question specifying this as a “practice parameter” for all ECMO procedures. I would be interested to know whether the authors have experienced TA-GVHD in patients undergoing ECMO, or whether this recommendation results from critical and detailed assessment of reported cases.

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REFERENCE

To the Editor—It was with great interest that we read the practice guidelines outlined by Przepiorka et al concerning the use of irradiated blood components. At the H. Lee Moffitt Cancer Center, we use irradiated cellular components for one additional indication not mentioned in the article—for patients requiring transfusion during collection of autologous peripheral blood stem cells. Patients who have been pretreated with cyclophosphamide can become sufficiently anemic and/or thrombocytopenic, requiring red blood cell (RBC) and/or platelet transfusion or requiring transfusion after their first stem cell collection. Transfused blood donor T-lymphocytes could potentially be collected along with autologous peripheral blood stem cells, frozen, thawed, and reinfused into a susceptible recipient. While we know of no studies documenting this, we believe that the risk is real and efforts should be made to reduce this risk with the use of irradiated blood.

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