SELECTIVE THERAPY OF HEPATIC CANCERS

USING MICROSHERES

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Regional chemotherapy is based on the premise that many chemotherapeutic agents display a steep dose response for toxicity and for therapeutic effect. Regional chemotherapy administration represents a means to generate increased drug exposure in the region where the tumor resides, while maintaining a lower drug exposure at the level of dose-limiting normal host tissues elsewhere in the body. Thus, even in circumstances where systemically administered chemotherapy is relatively ineffective, regional chemotherapy may improve the likelihood of response by the generation of much greater drug exposure. With sufficient regional selectivity, dose-limiting toxicity should be manifested by the normal tissues of the region infused and not by tissues elsewhere in the body. In this regard, regional chemotherapy has similarities to radiation therapy, but may be more selective in those situations where tumor and normal tissue in the treated region differ significantly in intrinsic drug sensitivity and blood supply.

Of all the forms of regional chemotherapy practiced, experience has been greatest with intra-arterial therapy and this has been most extensively applied to the treatment of primary and metastatic cancer in the liver, with a history going back more than 20 years. Pharmacokinetic analyses outlining the crucial elements and potential drug exposure increase with intra-arterial drug infusions have been carried out by Eckman et al (1), Chen and Gross (2), and Collins and Dedrick (3). Combining the advantage gained through the total body clearance (TBC) relative to regional blood flow (Q) plus that gained by regional extraction (E), the general equation defining the regional advantage of intra-arterial infusion is:

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\text{Regional advantage} = 1 + \frac{\text{TBC}}{Q (1-E)}
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Based on radiographic appearances using contrast angiography, it has been customary to regard tumors as being either hypo- or hyper-vascular relative to normal liver. As tumor nodules grow, the evoked new capillary bed develops at the periphery, so that the most vascularized area is the outer shell of the nodule (4). Although the central core of many tumor nodules in the liver is hypovascular, the periphery of the tumor nodules is generally hypervascular relative to normal liver, as demonstrated by
nuclear tomographic scans after hepatic-arterial injection of Tc99m-macro-aggregated albumin (TcMAA) (5). The microvascular pattern is consistent with the distribution of tumor cell viability and growth, the central core of the tumor often being necrotic while the peripheral rim of actively proliferating tumor cells has an excellent blood supply. The presence or absence of a hypovascular core appears to relate more to the size of the tumor nodule than to tumor type. Nodules less than 8 cm. in diameter are uniformly hypervascular, whereas those greater than 9 cm. in diameter display a hypovascular core and a hypertensive rim as ascertained by radionuclide tomographic angiography. The density of vessels in the hypervascular regions of tumor nodules appears to be twofold to sixfold greater than in normal liver. These observations regarding regional blood flow (Q) and relative capillary density suggest a number of methods whereby tumor hypervascularity can be used for selective therapeutic advantage.

Microspheres of 40-80 μm diameter, when injected as a homogeneous suspension into the hepatic artery, should lodge in the hepatic-arterial microvasculature in direct proportion to regional blood flow throughout that watershed (6). As mentioned above, the hepatic-arterial injection of TcMAA with nuclear tomography provides a means to determine the relative blood flow distribution between normal liver and tumor nodules within liver and, thus, to monitor selective delivery of therapeutic microspheres to tumor (5,6). One method for decreasing hepatic-arterial blood flow is the use of microparticulates or microspheres. At sufficiently high doses, approximating 90 million biodegradable starch microspheres (40-μm diameter, Pharmacia, Uppsala, Sweden), hepatic-arterial blood flow can be totally blocked in about 25% of patients (7). By 30 minutes after hepatic-arterial tree as ascertained by contrast angiograms. In the remaining 75% of patients, hepatic-arterial flow decreases by 80% and arterial-venous shunting occurs. Thus, the use of the hepatic-arterial starch microspheres may be an additional method to deliver more drug to tumors within the liver.

The concurrent hepatic-arterial injection of a suspension of starch microspheres in a drug solution has the potential of temporarily holding the drug solution in the hepatic-arterial capillary bed, thus allowing more time for the higher drug concentration to move into surrounding tissue. Carmustine and mitomycin have been examined in conjunction with starch microspheres given via the hepatic artery (7,8). These agents were chosen due to their rapid tissue uptake and mechanism of action as alkylating agents. Because of increased drug delivery to the liver and hepatic tumor, systemic drug exposure was reduced up to 90% for carmustine (7) and 70% for mitomycin (8) when the drug was given with starch microspheres versus drug injection alone. In hypervascular regions of tumors, more drug solution should be held up as compared to the drug entrapment in less vascular regions of normal liver. As the microspheres are digested, their diameter progressively decreases (from 40 μm initially) and the drug column moves distally into the capillary bed. Due to complete dissolution of the starch microspheres, subsequent doses can be administered without destroying access to the tumor microcirculation. These studies have prompted the initiation of phase II clinical trials of hepatic-arterial carmustine and mitomycin with starch microspheres.

REFERENCES