In summary, the two papers show that the low-affinity liver isoform of glucose transporter is found in cells that primarily export glucose, such as those cells involved with transepithelial glucose transport or gluconeogenesis, whereas the high-affinity erythrocyte/brain transporter is found in cells that primarily take up glucose from plasma. Important and novel aspects of these studies include the demonstration of two types of transporters coexisting in the kidney, the type and density correlating with direction of transport (influx or efflux) and energy requirements, and the localization of a liver-type glucose carrier to the basolateral membrane of differentiated small intestinal surface cells, confirming their role in nutrient absorption. Unquestionably, a new and useful research tool for studying transmembrane glucose transport has been added to the investigator's armamentarium.

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TREATMENT OF HEPATOCELLULAR CARCINOMA

Venook AP, Stagg RJ, Lewis BJ, Chase JL, Ring EJ, Maroney TP, Hohn DC. Chemoembolization for hepatocellular carcinoma. J Clin Oncol 1990;8:1108-1114.

ABSTRACT

Fifty-one patients with unresectable hepatocellular carcinoma were treated by embolization of the hepatic artery with Gelfoam powder, contrast material and three chemotherapeutic agents (doxorubicin, mitomycin, cisplatin). Twelve patients (24%) had a partial response with a decrease in the tumor diameter by at least 50%, 13 patients (26%) had only minor responses, 12 (24%) had stabilization of disease and the remainder had progressive disease. Tumor liquefaction was noted on computed tomographic scanning in 70% of patients, and 23 of 34 patients with elevations in serum alpha-fetoprotein values had a greater than 50% reduction following treatment. The median patient survival time from treatment was 207 days. Most patients experienced transient pain, fever, nausea and elevations in serum aminotransferase activities as a result of therapy. Ascites developed in 14 patients. There were two treatment-related deaths: one from tumor hemorrhage and one from liver failure. Chemoembolization therefore appears to have significant activity in patients with hepatocellular carcinoma and is relatively well tolerated.

Franco D, Capussotti L, Smadja C, Bouzari H, Meakins J, Kemeny F, Grange D, et al. Resection of hepatocellular carcinoma: results in 72 European patients with cirrhosis. Gastroenterology 1990;98:733-738.

ABSTRACT

This study reports the results of resection in 72 cirrhotic patients with hepatocellular carcinoma from Europe. One and 3 year survival rates were 68% and 51% respectively. Survival was significantly higher in Child's class A than in class B or C patients. Patients with a thickly encapsulated tumor lived longer than those with an infiltrating tumor and also had a significantly lower recurrence rate. There was no relationship between the size of the tumor or the presence of symptoms and survival. These data suggest that good results can be achieved by resection of hepatocellular carcinoma in European cirrhotic patients. A thickly encapsulated tumor and good liver function are the main determinants of low cancer recurrence and high survival.

COMMENTS

HCC is one of the most common cancers worldwide, although it occurs relatively infrequently in the developed Western world (1). Typically HCC is seen at an advanced stage with extensive intrahepatic disease and metastases to lung, bone, adrenal gland or regional lymph nodes. It is also usually associated with significant liver disease, particularly cirrhosis (2). Because of this late presentation and association with cirrhosis, HCC has a grave prognosis, with survival times being measured in weeks to months. No effective therapy has been available for advanced HCC, although surgical resection has been considered potentially curative if carried out at an early stage. Within the past few years, a significant shift in emphasis has occurred with the attempt to diagnose HCC at an early, asymptomatic

phase using various screening techniques in high-risk individuals.

The two papers summarized above represent the two extremes of treatment for HCC. The first, by Venook and colleagues from San Francisco, describes the palliative use of chemoembolization for advanced, symptomatic HCC, whereas the second paper describes the results of resection for small, asymptomatic HCC in two European centers. Venook et al. described embolization of the hepatic artery feeding the tumor with a Gelfoam plug mixed with contrast material and three chemotherapeutic agents (doxorubicin, mitomycin and cisplatin) in 51 patients with HCC. The authors emphasize that they injected enough Gelfoam into the artery to cause stagnation of flow but not total occlusion. Thus they were able to administer this therapy to each patient on several occasions. The best response noted was a greater than 50% decrease in diameter of the tumor. This occurred in 24% of patients. Tumor liquefaction was noted in 70% of cases, and serum α-fetoprotein (AFP) levels fell by half in 68% of patients in whom it was elevated.

Unfortunately, chemoembolization was associated with significant complications, including two treatment-related deaths and severe morbidity in some cases, with fever, pain, nausea and vomiting and the development of liver failure. It is not clear, then, whether patients derived any real benefit from this therapy. The authors suggest that the mean survival time of patients in this study (7 mo) was prolonged beyond that of historical controls. Transcatheter arterial embolization (TAE) is an established mode of therapy for HCC in some centers and appears to prolong survival marginally (3). The premise for using this treatment is that HCC derives all or most of its blood supply directly from the hepatic artery, whereas the remainder of the liver depends on the portal vein for most of its blood supply. However, the effect of TAE has not been subjected to controlled clinical trials. The intraarterial infusion of chemotherapeutic agents at the time of embolization may have theoretical benefits, but most of the effect may be caused by occlusion of the blood supply of the tumor (4).

Most reports of resection of small HCCs from cirrhotic livers have come from Japan, Taiwan and China, where this tumor occurs frequently (5). The report by Franco and colleagues describes their experience with 72 patients at two hospitals, one in northern Italy and the other in France. In most cases, the tumor was detected at routine screening by ultrasound examination or serum AFP measurement in asymptomatic patients. The authors found that patients with Child class A cirrhosis had a significantly better prognosis after surgery and that the tumor was less likely to recur if it was of the slowly expanding type with a thick capsule. Deaths after the operation occurred in 7% of the patients, mostly caused by bleeding esophageal varices. The patients had other complications after the operation related to their cirrhosis, including ascitic fluid leaking through the abdominal wall (19%) and the development of liver failure (8%). On follow-up after surgery, HCC recurred in 16 patients (22%).

Although both reports are positive in tone, they serve to emphasize the dismal outlook for patients with HCC. Although long-term survival is possible after surgical resection, it remains to be proven whether the use of screening programs to detect HCC at an early stage actually improves the prognosis of this condition or whether their reported success is caused by lead-time bias. Thus small HCCs may represent a very early stage of disease that might take as long as several years before clinical symptoms appear. The apparent prolongation of survival may simply represent this same interval that the tumor would have taken naturally before clinical appearance.

Liver transplantation has also been considered to be a curative modality of therapy in some patients with HCC that is found incidentally at the time of surgery (6). Other investigators have chosen to use other means of local destruction of small tumors in cirrhotic livers, such as local injection of alcohol (7). This appears to be able to destroy viable tumors less than 3 cm in diameter and is associated with minimal morbidity and mortality.

Traditional systemic or regional chemotherapy has not proven effective in HCC. Response rates of 8% to 42% have been reported (8, 9). These rates are not dissimilar from those found by Venook in the study described above. Order et al. have described some complete responses to targeted radiation therapy with radiolabeled antiferritin (8, 9). Responses to this treatment appeared to be better in patients who did not have elevated serum AFP values. However, preliminary results of a controlled trial have not confirmed the efficacy of this imaginative approach (10). Further study of chemoembolization is warranted, perhaps in patients with less advanced disease who have the potential for better responses. Other means of targeting chemotherapy to the liver or to the tumor directly should be explored. Lipiodol is an oil-based contrast agent that appears to be taken up and trapped specifically in HCC tissue. This phenomenon has proved to be useful for radiological imaging of HCC. However, Lipiodol appears to have some direct antitumor effect when injected into the hepatic artery and has also been mixed with chemotherapeutic agents with some promising results (10). Lipiodol has also been used to target radioiodine to HCC (Dusheiko GM, Personal communication).

Many of the therapeutic approaches described above appear to be of marginal benefit and therefore need to be studied in controlled trials. This has rarely been done in the Far East, where many patients are available for such studies. In the United States and Europe, controlled trials of larger numbers of patients will almost certainly require the cooperation of many medical centers. For such multicenter controlled trials to be contemplated, however, investigators need to have a format for planning and executing such trials. At a recent conference on HCC held at the National Institutes of Health in Bethesda, Maryland, investigators began discussing such cooperative efforts. Many felt that much of the

HCC terminology needs to be standardized first. For example, what is an "incidental HCC"? Is this the same as a "small" HCC or an "asymptomatic HCC"? What tumor diameter should be used to define small HCC? Both 3 cm and 5 cm have been proposed. It was emphasized that not all HCCs are the same in biological behavior. They may vary depending on histological type (the fibrolamellar type is slower growing with a better prognosis), on cause (hepatitis B reactivation may occur in association with chemotherapy), on whether cirrhosis is present and perhaps on whether serum AFP values are elevated. In any trial these factors should be assessed, and perhaps patients enter into studies stratified according to some of these variables. Better means of assessing the response to therapy need to be used. One very promising approach is the use of a computer program, developed at Johns Hopkins Hospital, to measure tumor volume (10).

In summary, therapies that may significantly benefit patients with HCC are being developed. Their worth will eventually need to be tested in controlled clinical trials requiring large numbers of patients. In the developed Western world, where HCC is relatively uncommon, such trials may need to be conducted in multiple centers using standardized terminology and methodology.

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MORE ON GLUCOSE TRANSPORTERS: THE ACINAR ORGANIZATION FOR HEPATIC GLUCOSE TRANSPORT

Tal M, Schneider DL, Thorens B, Lodish HF. Restricted expression of the erythroid/brain glucose transporter isoform to perivenous hepatocytes in rats: modulation by glucose. J Clin Invest 1990;86:986-992.

ABSTRACT

The "erythroid/brain" glucose transporter (GT) isoform is expressed only in a subset of hepatocytes, those forming the first row around the terminal hepatic venules, while the "liver" GT is expressed in all hepatocytes. After 3 d of starvation, a three- to fourfold elevation of expression of the erythroid/brain GT mRNA and protein is detected in the liver as a whole; this correlates with the expression of this GT in more hepatocytes, those forming the first three to four rows around the hepatic venules. Starvation-dependent expression of the erythroid/brain GT on the plasma membrane of these additional hepatocytes is lost within 3 h of glucose refeeding; however, by immunoblotting we show that the protein is still present. Its loss from the surface is possibly explained by internalization.

COMMENTS

Transport of glucose across the plasma membrane of mammalian cells can occur by a secondary active transport process such as in the small intestine or by facilitated diffusion. Facilitated diffusion of glucose is mediated by a family of related transport proteins having different tissue distribution and diverse regulation. To date, five functional facilitated diffusion transport systems and a pseudogene have been identified (Table 1). These proteins vary in size from 492 amino acids to 524 amino acids (1). Among the five functional forms a 39% to 65% identity and a 50% to 76% similarity exists. Twenty-six percent of the residues are identical in all five forms, whereas 13% are conservative substitutions (1). Two species of facilitated diffusion glucose transporters have been found in the liver, a less abundant erythroid/brain form or glut-1 and the main liver form or glut-2. These forms differ considerably in the Michaelis constant (K_m) for glucose. Glut-1 has a K_m of 1 to 2 mmol/L and thus is saturated at physiological concentrations of serum glucose (about 5 mmol/L). In contrast, glut-2 has a K_m of 15 to 20 mmol/L. Therefore hepatic glucose homeostasis is subserved by the low-affinity liver isotype or glut-2.

The two rat liver isoforms respond differently to conditions of fasting and refeeding and to experimental diabetes and insulin replacement. These different patterns of response led investigators to propose that these transporters are regulated by different mechanisms (2). In this paper, the authors, using polyclonal antibodies that specifically recognize either glut-1 or glut-2, immunolocalized the hepatocytes expressing these transporters. They observed that under control conditions, glut-2 was expressed in all hepatocytes. In contrast,