Journal of Surgical Oncology Supplement 3:100–103 (1993)

Regional Cancer Chemotherapy for Advanced Stage Hepatocellular Carcinoma

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KEY WORDS: **hepatoma, platinum, liver transplant**

INTRODUCTION

The conventional treatment for hepatocellular carcinoma (HCC) has been surgical resection, typically by segmentectomy, lobectomy, or trisegmentectomy. The large majority of patients, however, cannot have their tumors resected, either because of underlying cirrhosis and liver damage, making resection hazardous, or because of the multifocal or bilobar spread of the hepatoma. In those patients with resectable tumors, the recurrence rates and survival have been found to depend mainly on stage of disease [1,2]. The best results have been with TNM stage I disease, with stage II and resectable stage III disease typically having < 30% survival at 3 years. Factors adversely influencing prognosis have included diffuse disease, multifocal primaries, vascular invasion, and lymph node involvement.

Causes of Recurrence After Resection

The evidence from liver transplantation specimens indicates that much clinically evident hepatoma is either multifocal or widespread. This suggests that disease that has been diagnosed by angiography, ultrasound, magnetic resonance imaging (MRI) or computed tomography (CT) scan consistently underestimates the amount of spread of disease in the liver. Thus, there is a reasonable probability of undetected residual microscopic disease in the remaining liver, which would account for the high recurrence rates.

Liver Transplantation

The results of liver transplantation for stages I and II HCC have been very encouraging, with high 3- and 5-year survival rates [1,2]. However, for stage IVA and to a lesser extent for stage III disease, recurrence rates in the new liver and in other organs still remain very high. For stage IVA, there are few 2-year survivors. The causes of these high recurrence rates are not immediately apparent. Likely explanations include the presence of microscopic metastases at the time of transplantation for advanced stage disease, vascular invasion with seeding of the blood stream during surgical manipulation, and the effect of immunosuppression in enhancing the growth of occult microscopic disease.

Chemotherapy of HCC

A considerable literature on single and combination drug chemotherapy for HCC has recently been reviewed [3]. In summary, no consistent response rates of > 20% nor impact on survival have been demonstrated. There is, thus, no standard chemotherapy treatment for HCC that can be justified by published response rates. Although earlier studies suggested that doxorubicin was a useful agent, subsequent reports have not substantiated this [3].

In contrast to the responses for systemically delivered chemotherapy, many groups have reported > 40% response rates for several agents and combinations of agents when delivered regionally [3–6]. The principle underlying this concept is that whereas approximately 80% of the oxygen-carrying blood to the normal liver is delivered via the portal vein, HCCs derive their blood supply primarily from an arterial supply, usually through a neo-vasculature. This permits the selective delivery of drugs to the tumor with a relative sparing of the normal liver. Even damage to the hepatic artery does not necessarily compromise the residual liver, at least when the residual liver is normal.

REGIONAL CHEMOTHERAPY FOR HCC

The selective nutrition of tumors in the liver from the hepatic artery rather than the portal vein has given rise to several approaches for selectively interfering with tumor growth by local means. These have included direct hepatic artery ligation, embolization or thrombosis of the hepatic artery, or intermittent obstruction of the hepatic

Accepted for publication October 30, 1992.

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artery. While responses have been reported with obstruction of the hepatic artery alone, they have normally been of relatively short duration. In addition, this type of treatment can be difficult and may be associated with hepatic decompensation, in the presence of chronic hepatitis or cirrhosis, particularly if the main portal vein is obstructed.

Arterial Chemotherapy

Several agents have been reported to induce tumor responses when injected or infused into the hepatic artery. These include 5-fluorouracil (5-FU), 5-FUdR, mitomycin C, doxorubicin, neocarzinostatin, and cis-platinum. Few studies have reported an impact on survival, however. A large number of studies, most notably from Japan, have reported consistently higher response rates in the region of 50%, with single or combination drugs when combined with some form of embolizing agent given into the hepatic artery. These agents have included collagen, starch, glass beads, degradable starch microspheres, the poppy seed oil Lipiodol (Ethiodol), gelatin, and even blood clots. Most studies have not been randomized, so that it is not usually easy to determine the effect of the embolizing agent on the chemotherapy with which it is mixed. In addition, the mechanical obstruction due to the embolizing agent is often short lived. Some agents, such as Lipiodol, essentially cause no hepatic arterial obstruction, or at least only a very transient one.

Intra-Lesional Injections

A large literature exists on the direct injection of ethanol into small HCCs [7]. This appears to be a rather safe modality of treatment, and high response rates have been reported. However, since only a single lesion or small numbers of lesions can realistically be injected, the incidence of new hepatomas occurring in the cirrhotic livers that have been injected is quite high. Multiple treatments are normally given several times a month, but the treatment is cheap and can be done in an outpatient setting under ultrasonography guidance, and for small lesions at least, high response rates are reported. For other malignancies, there is a long history of intra-lesional injection, particularly for melanoma, for which BCG and polyI:polyC injections have been reported to produce high rates of single lesion involution. It is probable that for any tumor, including HCC, direct injection of irritants will do the same. The limitation of this technique is that it cannot be performed adequately for large or multiple lesions.

HORMONAL THERAPIES

The high male to female incidence of HCC and the presence of receptors for androgens, epidermal growth factor (EGF), transforming growth factor alpha (TGFα), and glucagon in HCC has led to the idea that growth factor or hormonal manipulation may alter growth. Recent reports on the use of tamoxifen have led to a suggestion of an effect on survival, but no objective response rates of tamoxifen alone have been reported. Anti-androgen and luteinizing hormone releasing hormone (LHRH) antagonist therapies are currently under investigation in controlled clinical trials in the EORTC, but no benefit has been so far reported. More hormonal agents are likely to be tested in the next few years.

At the University of Pittsburgh Liver Transplant Department, 29 patients were recently treated with tamoxifen 20 mg bid orally. Inclusion criteria were failure of prior chemotherapy or inability to give chemotherapy because of underlying liver disease, usually due to Child's class C cirrhosis. Of 29 patients treated, 28 are currently evaluable for response. There were no responders, and average time to progression has been 3 months. In this series of patients with advanced disease, no activity for tamoxifen has been found.

COMBINATION REGIONAL CHEMOTHERAPY FOR ADVANCED STAGE HCC

From 1990 to 1992, 83 patients at the University of Pittsburgh were enrolled in a study with a protocol investigating the role of doxorubicin and cis-platinum in the treatment of advanced stage HCC. All patients had biopsy proven HCC. Patients were excluded who had liver failure, non-correctable coagulopathy, or encephalopathy. The regimen consisted of doxorubicin 4 mg/m^2 and cis-platinum 100 mg/m^2 mixed in 100 ml normal saline and administered into the hepatic artery for 30 minutes. Usually only a right or left hepatic artery infusion was given, unless there was massive bilobar disease, in which case occasional patients had the proper or common hepatic artery cannulated. Cycles were repeated every 28 days for a minimum of three treatments (evaluable for response). Interferon-alpha was also administered subcutaneously as 3 million units three times a week continuously throughout the treatment. This was included in the regimen because of its synergistic cytotoxicity with both doxorubicin and cis-platinum and because of its action in suppressing virus hepatitis. Forty-eight patients are currently evaluable for response, of whom 29 have achieved greater than 50% reduction in the product of two perpendicular diameters of their tumors, measured by CT scan, to produce a *60% response rate*. An additional five patients with fibrolamellar HCC were also treated, of whom none had a response. In a large experience of 83 patients treated on or off protocol, 3 had chemotherapy-induced hepatic decompensation. An additional six had chemotherapy-induced worsening of their liver function, which, however, stabilized. Abdominal pain was seen in only five patients and fever in two. A transient chemical hepatitis was seen in 24 patients, which almost invariably disappeared within 10 days of treatment. This high response rate was also associated with an increased patient

survival in those patients who responded compared with those who did not [6]. For non-responding patients, the 50% survival was reached at 6 months. However, in responding patients, there was one death at 3 months and one at 12 months. All other responding patients are currently alive, with the longest survivor currently at 26 months.

Several new conditions were introduced with this protocol. These included full systemic doses of chemotherapy given into the hepatic artery; an escalating dose approach was used to limit hepatic decompensation; therapy was based primarily upon use of cis-platinum; systemic interferon was added; repeated long-term treatments were used, because of the often long doubling times; embolization was omitted, to permit repeated regular re-treatments. Because of initial experience of hepatic dysfunction with the chemotherapy, and our inability to predict tolerance to this chemotherapy, an escalating dosage approach was taken. The first treatment was given at 50% of the calculated dose, the second at 75%, and the third and subsequent treatments at 100% of calculated dose.

A Randomized Perspective Study of Cis-Platinum and Doxorubicin Plus or Minus Lipiodol Infused Into the Hepatic Artery for Advanced Staged HCC

A current ongoing study at the University of Pittsburgh compares cis-platinum and doxorubicin with or without Lipiodol. Currently, 46 evaluable patients have been enrolled in the study, 23 in each arm. There have been 14/23 responders in the Lipiodol arm (61%) and 12/23 responders in the solution arm (52%). This is not yet statistically significant. Interestingly, we again see a survival advantage for responders in both groups. There is a 25% mortality for responders at 1 year compared with a 75% mortality for non-responders. Currently, no major advantage has been found for the addition of Lipiodol in this study.

SPECIAL PROBLEMS ASSOCIATED WITH CHEMOTHERAPY OF HCC

Most types of tumor tend to arise in an otherwise basically healthy body. However, HCC usually arises on the basis of chronic hepatitis or cirrhosis, and thus in a diseased major organ. The organ concerned, namely the liver, is also the main site of detoxification of xenobiotics, and this poses special hazards in the treatment with cytotoxic chemicals of patients with HCC. In addition, the sequelae of portal hypertension and splenomegaly are particular concerns for chemotherapists. These include bleeding from esophageal varices and the possibility of their exacerbation, splenomegaly-associated thrombocytopenia, and splenomegaly-associated leukopenia. The recent availability of granulocyte colony stimulating factor has vastly increased the margin of safety with leukopenia. Curiously, we rarely encounter dramatic drops in platelet count, despite low platelet starting levels. The reasons for this are unclear. In addition, the decreased synthetic function is often associated with hypo-prothrombinemia, and the decreased catabolic functions of the liver are associated with an inability to detoxify the chemotherapeutic agents, resulting in an often dangerous increase in plasma half-life. Finally, the decreased hepatic reserve in an already damaged liver appears to render the liver particularly sensitive to further damage by chemotherapeutic agents, often resulting in at least transient increases in bilirubin and sometimes permanent hepatic decompensation.

CHEMOTHERAPY FOR HCC: SOME SPECIFIC CONSIDERATIONS

Intrinsic Drug Resistance

It has been known for over 50 years that chronic injury to the liver results in a resistance to toxicity induced by a variety of chemical agents [8]. Subsequently, it was shown that polycyclic hydrocarbon carcinogens and other carcinogens could induce both tumors as well as resistance to toxic damage. It then became apparent that resistance to inhibitors of growth was an innate property of carcinogen-induced hepatocellular carcinomas, both in vivo and in vitro. This has been associated with an altered biochemical pattern of the hepatomas, which includes a decrease in phase I enzymes, including cytochromes p-450 and mixed function oxygenases; an increase in several phase II enzymes, including UDP-glucuronyl transferase, glutathione-S-transferases, gamma-glutamyl transferase; and an increase in some other detoxifying enzymes, including epoxide hydrolase and DT-diaphorase. Increases in expression of specific genes associated with drug resistance have also been found, including increased mRNA levels for multiple drug resistance gene 1, metalathionein, gamma-glutamyl transpeptidase, glutathione-S-transferase π, epoxide hydrolase, and the heat shock cognate genes. Thus, it is not surprising that systemic chemotherapy has failed to produce consistent meaningful response rates for this disease. Probably a whole new generation of drugs is needed, which does not depend upon cytotoxicity for their mechanisms of action. In the interim, a rational approach for increasing the drug concentration is either regional injection of chemotherapy, increasing the concentration of cytotoxic chemotherapy directly in the region of the tumor, or else continuous infusion into the hepatic artery. There is little literature on the latter modality for HCC, however.

Tumor Doubling Times

The reported doubling times for human hepatomas is quite variable, ranging from 30 to over 300 days. This has strong implications for cancer chemotherapy. For a tumor with a doubling time of 30 to 90 days, only a small fraction of the cells will be in the DNA synthesis part of

the cell cycle on the day of chemotherapy. Thus, only a small fraction of the cells will be in the sensitive phase of the cell cycle. A practical consequence of this is that multiple repeated treatments will be required to impact on a greater proportion of the cells in the tumor. A correlate of this is that embolization, although it may obstruct the blood supply temporarily, can also interfere with repeated regular re-treatments. This needs to be taken into account in the design of regimens for HCC.

Vascular Access and Flow

Repeated instillation of toxic drugs into the hepatic artery or its branches often results in intimal damage. Usually this is minor or transient, but can induce thrombosis, which can negatively impact on the safety of resection and occasionally of transplant. Often, aberrant blood vessels feed the tumor, which are not always easily accessed by the vascular radiologist. In addition, reverse flow in the liver consequent on portal hypertension can result in centrifugal blood flow, with limited amounts of chemotherapy being delivered to the tumor. Often, the hepatoma is bilobar or diffusely involving many lobes. It is difficult to know the optimal means of infusing chemotherapy in these circumstances. The choices include infusing chemotherapy only into the proper or common hepatic artery, in the hope of drug accessing all of the tumor, although that in turn will depend upon the vagaries of the blood supply to the various tumor nodules; splitting the tumor dose among the various branches of the hepatic artery; or administering chemotherapy to specific arteries on sequential courses of chemotherapy. Our own practice is to try to concentrate the chemotherapy on the largest area of tumor initially, and not to treat the whole liver, in order to decrease the likelihood of hepatic decompensation. If there is bilobar disease, we will subsequently alternate sides for treatment. This also has the effect of increasing the concentration of chemotherapy on the tumor nodule being treated. The vagaries of blood flow can also result in back flow of chemotherapy into the mesenteric artery, gastric arteries, or blood vessels feeding the gall bladder. Consequences of this include abdominal pain from bowel irritation, exacerbation of peptic ulcer disease, or chemical cholecystitis.

COMBINED MODALITY THERAPY FOR HCC

Given the high recurrence rates for advanced stages of HCC after either resection or transplantation, and the high response rates being seen by many groups for aggressive regional chemotherapy, it would seem reasonable to combine these approaches. Studies with preoperative neo-adjuvant or post-operative adjuvant chemotherapy for resectable HCC have been published from Japan, with conflicting results. No large or multi-center study has yet been published. At the University of Pittsburgh, we recently started a program of neo-adjuvant chemotherapy with a minimum of three cycles of intra-arterial doxorubicin and cis-platinum prior to placing patients on a waiting list for their liver transplant. Patients then continue their monthly treatment cycles until a donor liver is found. So far, 11 patients have been treated with this combination who have a minimum of 12 months follow-up post-transplant, or who have died. One patient died of recurrent disease within 12 months. One patient developed newly recurrent disease, giving a 91% 1-year survival. During the same period of time and under the identical immunosuppressant regimen with the novel agent FK506, an additional 14 patients were transplanted without prior neo-adjuvant chemotherapy. This was not given either because of patient refusal or (usually) poor liver function and Child's class C cirrhosis. Nine of these patients developed recurrences within 12 months of transplant (64% recurrence rate at 1 year), and eight had died with tumor recurrence in 1 year (43% 1-year survival). This small pilot experience is encouraging [9], but a randomized study will be needed to test this idea formally.

REFERENCES

1. Ringe B, Pchlmayr R, Wittekind C, Tusch G: Surgical treatment of hepatocellular carcinoma: experience with liver resection and transplantation in 198 patients. World J Surg 15:270–285, 1991.
2. Iwatsuki S, Starzl TE, Sheahan DG, Yokoyama I, Demetris AJ, Todo S, Tzakis A, Van Thiel DH, Carr BI, Selby R, Madariaga J: Hepatic resection versus transplantation for hepatocellular carcinoma. Ann Surg 214:221–229, 1991.
3. Lotze MT, Flickinger JC, Carr BI: Hepatobiliary neoplasms. In DeVita V, Hellman K, Rosenberg S (eds): "Principles and Practice of Oncology," 4th ed. 1992.
4. Onohara S,Kobayashi H, Ito HY, et al.: Intra-arterial cis-platinum infusion with sodium thiosulfate protection and angiotensin II induce hypertension for treatment of hepatocellular carcinoma. Acta Radiol. 29:197–202, 1988.
5. Kajanti M, Rissanen P, Virkkunen P, et al.: Regional intra-arterial infusion of cis-platin in primary hepatocellular carcinoma. Cancer 58:2386–2388, 1986.
6. Carr BI: High objective response rates of advanced hepatocellular carcinoma to intra-arterial therapy. Proc ASCO 11:470, 1992.
7. Livraghi T, Festi D, Monti F, Salmi A, Vettori C: US-guided percutaneous ethanol injection of small hepatic and abdominal tumors. Radiology 161:309–312, 1986.
8. Carr BI: Pleiotropic drug resistance in hepatocytes induced by carcinogens administered to rats. Cancer Res 47:5577–5583, 1987.
9. Carr BI, Selby R, Madariaga J, Iwatsuki S, Starzl TE: Prolonged survival of transplantation and cancer chemotherapy of advanced stage hepatocellular carcinoma. Transplant Proc 25(1):1128–1129, 1993.