ANNALS OF SURGERY
Vol. 221, No. 6, 734–743

Adjuvant Chemotherapy Improves Survival After Liver Transplantation for Hepatocellular Carcinoma

Kim M. Olthoff, M.D.,* Michael H. Rosove, M.D.,† Christopher R. Shackleton, M.D.,* David K. Imagawa, M.D., Ph.D.,* Douglas G. Farmer, M.D.,* Petronella Northcross, R.N.,† Anita L. Pakrasi, R.N.,* Paul Martin, M.D.,† Leonard I. Goldstein, M.D.,† Abraham Shaked, M.D., Ph.D.,* and Ronald W. Busuttil, M.D., Ph.D.*

From the Departments of Surgery and Medicine,† UCLA School of Medicine, Los Angeles, California*

Objective
The aim of this study was to evaluate the effect of postoperative adjuvant chemotherapy on the recurrence rate and survival of patients after orthotopic liver transplantation (OLT) for hepatocellular carcinoma (HCC).

Summary Background Data
Historically, liver transplantation for HCC has yielded poor long-term survival. Multimodality therapy has been initiated in an effort to improve survival statistics.

Methods
Twenty-five patients were placed on 6 months of intravenous fluorouracil, doxorubicin, and cisplatin after OLT. Risk factors, recurrence rates, and survival rates were analyzed and compared with historic controls.

Results
Overall long-term survival in the protocol patients was 46% at 3 years, improved over our historic controls of 5.8% at 3 years ($p = 0.0001$). Overall recurrence rate was 20% ($n = 4$). Possible risk factors, such as tumor size, vascular invasion, multifocality, capsular invasion, and tumor differentiation, were not found to be significantly predictive of survival. Three patients with long-term, disease-free survival had tumors > 5 cm. Side effects from chemotherapy were common, but rarely severe.

Conclusions
This study suggests that adjuvant chemotherapy after transplantation for HCC can provide long-term cure and may improve survival, even in patients with stage III and IV disease.

Primary hepatocellular carcinoma (HCC) remains one of the most common tumors worldwide, with an incidence as high as 30 per 100,000 men in certain high-risk regions.[1] Early detection is difficult, yet crucial for successful treatment. Patient prognosis is poor, with most series reporting a 3- to 6-month median survival for unresectable tumors after the onset of symptoms.[2] Partial hepatic resection remains the mainstay of therapy for lesions confined to one lobe and has a 5-year survival rate ranging from 25% to 39%.[2] However, resectability is limited by tumor characteristics, such as multifocality, bilobar lesions, large central lesions, and associated cirrhosis. Attempts at resection in patients with cirrhosis are associated with high perioperative mortality and high recurrence because of the limited functional reserve of the remaining liver and the frequent multifocality of the disease.

Orthotopic liver transplantation (OLT) for unresectable HCC offers the advantages of removal of the entire liver, thereby eliminating the problem of multifocality or bilobar involvement, and replacement with a functional liver, allowing patients with advanced cirrhosis to be treated. Unfortunately, early studies with OLT for HCC demonstrated high recurrence rates and disappointing long-term survival of 18% to 30% at 5 years.[2,3] Although this may be viewed as a success from an oncologic viewpoint, these survivals clearly are not acceptable for liver transplantation, where donor resources are limited and OLT for benign disease offers a 5-year survival rate of 65% to 75%. However, there are many instances of long-term survivors from HCC, and therefore, OLT continues to be pursued as a therapeutic option. In an effort to improve survival statistics, several institutions have initiated adjuvant chemotherapy protocols.[4–7] In 1989, the Dumont-UCLA Transplant Program initiated a protocol of intensive postoperative adjuvant chemotherapy, including doxorubicin, cisplatin and fluorouracil. The aim of this report is to review the results of the first 25 patients enrolled in this protocol. In addition, we compared these results to the previously reported survival of HCC patients who underwent transplants at UCLA before the introduction of this protocol.[8]

PATIENTS AND METHODS

Between February 1989 and June 1994, 26 patients were enrolled in this center's protocol for adjuvant chemotherapy after OLT for HCC. The protocol was approved by the UCLA Human Subject Protection Committee, and informed consent was obtained from each patient. Criteria for inclusion in the study included the following: surgically unresectable HCC; no evidence of extrahepatic spread by chest and abdominal computed tomography scans, bone scan, and ultrasound; no prior chemotherapy; and no significant cardiac disease by echocardiogram. Preoperative histologic diagnosis was not considered necessary for enrollment. All patients underwent OLT, although one patient did not receive any postoperative chemotherapy because of multi-organ failure and fungal sepsis, and therefore, was excluded from the study, leaving 25 patients for further evaluation.

All 25 patients had HCC as one of their primary indications for transplantation; however, 21 patients had significant associated disease, including alcoholic cirrhosis (6), chronic active hepatitis C (8), chronic active hepatitis B (4), and cryptogenic cirrhosis (3). One patient had a prior resection for HCC, which recurred. Incidental tumors were not included in this protocol. All patients underwent extensive preoperative screening, as is routine for all liver transplant patients.

Of the 25 patients, 17 were men and 8 were women. Age range was 19 to 69 years, with a mean age of 54 ± 11.4 years. Fourteen patients were white, six were Asian, and five were Hispanic. Serum alpha fetoprotein was elevated in 21 patients. Four patients were hepatitis B surface antigen positive.

When a donor organ became available, the patient was taken to the operating room, with a "backup" recipient in house. A complete exploratory laparotomy was performed to evaluate the resectability of the tumor and to look for evidence of metastatic disease. The hepatectomy and implantation of the donor organ then were performed in the standard fashion. The explanted liver was completely assessed by pathology for tumor size, location, focality, vascular invasion, capsule penetration, tumor differentiation, and lymph node metastases. The patients were then classified according to the pathological tumor-node-metastasis (pTNM) staging system (Table 1).

All patients received maintenance immunosuppression with corticosteroids, cyclosporine, and azathioprine, or FK506. Rejection episodes were treated with pulse steroids, and taper and steroid-resistant episodes were treated with OKT3 monoclonal antibody.

Intravenous chemotherapy via a central venous catheter was initiated once the patient was stable postoperatively with adequate hepatic and renal function, and adequate blood counts. Fluorouracil was given as a continuous intravenous infusion at 75 to 150 mg/day. Doxorubicin (22.5–37.5 mg/m^2) and cisplatin (40–60 mg/m^2) were given every 3 weeks, the dosage determined

Presented at the 106th Annual Session of the Southern Surgical Association, December 4–7, 1994, Palm Beach, Florida.
Supported by the Dumont Foundation, the Joanne Barr Memorial Liver Transplant Foundation, and the Torino Fellowship.
Address reprint requests to Ronald W. Busuttil, M.D., Ph.D., Director, Dumont-UCLA Transplant Center, UCLA Department of Surgery, 10833 Le Conte Ave, Los Angeles, CA 90024.
Accepted for publication January 18, 1995.

by the development of significant side effects. Doses were reduced or held for significant leukopenia or worsening renal function. Patients were monitored closely as outpatients until the 6 months of chemotherapy was completed. Thereafter, the patients were observed for follow-up on a regular basis, with routine post-OLT blood work, serial alpha fetoprotein levels, and computed tomography scans, when indicated. Echocardiograms were initially done after every 100 mg/m^2 of doxorubicin, and were increased to every 50 mg/m^2 in the most recent patients.

Actuarial survival and disease-free survival were calculated using the Kaplan-Meier product limit estimate. Comparison between groups was done using log-rank analysis. Tumor characteristics as predictors of survival were analyzed using a stepwise Cox regression model. Calculations were performed using SPSS (SPSS, Inc., Chicago, IL) advanced statistical module software.

RESULTS

Operative Findings and Pathologic Classification

A total of 27 liver transplants were performed in 25 patients. One patient required retransplantation for hepatic artery thrombosis and another for poor graft function due to ischemic damage of the donor graft.

At the time of operation, no patient had gross evidence of extrahepatic disease, except for one patient with extension of tumor to the peritoneum, which was completely excised with the liver. Twenty patients had associated cirrhosis on histology. Tumor size ranged from 2 cm to 20 cm at the greatest diameter. Vascular invasion was seen in eight patients, with three patients having portal vein thrombosis at the time of OLT. There was penetration of the capsule in five patients. No patient had lymph node involvement by tumor. Tumor differentiation was well-differentiated (n = 8), moderately differentiated (n = 5), poorly differentiated (n = 2), mixed (n = 2), cholangiohepatoma (n = 1), sclerosing (n = 1), fibrolamellar (n = 1) and nondesignated (n = 5). Seven patients had unifocal tumors and 18 had multifocal tumors. The final pTNM staging was I (n = 0), II (n = 6), III (n = 8), IVA (n = 10), and IVB (n = 1).

Chemotherapy

Nineteen patients completed the full 6 months of chemotherapy. All but one patient required brief interruptions for neutropenia or gastrointestinal symptoms. Of the six patients who did not complete their course, three were taken off treatment because of poor graft function (two patients underwent retransplantation and one patient is awaiting retransplantation), two patients stopped their therapy at 4 months for personal reasons, and one patient had the final dose of cisplatin held because of orthostatic hypotension and syncope.

Nearly all the patients had some side effect from the chemotherapy, but few were severe (Table 2). The most frequent side effect was neutropenia, occurring in 21 of 25 patients (84%). Severe neutropenia was treated with granulocyte colony-stimulating factor and interruption of the chemotherapy. There were three episodes (one in each of three patients) of hospitalization for neutropenic fever; these were successfully treated with granulocyte colony-stimulating factor and intravenous antibiotics. Gastrointestinal symptoms, stomatitis, headache, and parasthesias also were encountered, but uncommon. Some platinum doses also were omitted because of azotemia. Catheter complications included one episode of catheter sepsis requiring removal, and one superior vena cava thrombosis requiring anticoagulation. There were two episodes of doxorubicin cardiomyopathy; one was very mild, with global hypokinesis and a left ventricular ejection fraction of 50% to 55% after 133 mg/m^2; the other was severe, with a left ventricular ejection fraction of <30% after 263 mg/m^2, which may have been a contributing factor to the patient's death. After these complications, we increased the frequency of echocardiograms to every 50 mg/m^2 of doxorubicin.

Recurrence and Survival

Of the 25 patients entered into the study, 14 are alive and free of disease, with a follow-up of 6 to 70 months (median 33 months). One patient is alive with recurrent disease, occurring 11 months after an OLT for an aggressive hepatoma, which had recurred after a prior resection. The causes of death in the remaining ten patients were recurrent tumor (n = 4), recurrent hepatitis B (n = 2), massive upper gastrointestinal bleed with pulmonary emboli (n = 1), sepsis (non-neutropenic, occurring after completion of chemotherapy (n = 2), and multisystem organ failure with doxorubicin cardiomyopathy (n = 1). Recurrence of tumor occurred at 9, 11, 11, 12, and 23 months. Sites of recurrence were lung (n = 1), liver (n = 1), both liver and lung (n = 2), and retroperitoneal/mediastinal nodes (n = 1). Overall recurrence rate was 20%. Overall actuarial survival rates for all 25 patients at 6 months and 1, 2, and 3 years were 96.0%, 77.7%, 55.1%, and 46.0%. Tumor-free survival rates at 6 months and 1, 2, and 3 years were 96.0%, 63.2%, 53.0%, and 46% (Fig. 1). When risk factors, such as tumor size greater than 5 cm, vascular invasion, multifocality, capsular invasion, and tumor differentiation, were entered as covar-

Table 1. PATIENT CHARACTERISTICS AND PATHOLOGIC FINDINGS

Patient No.	Age (yrs)	Preoperative AFP	pTNM	Tumor Size (cm)	Cirrhosis*	Focality	Vascular Invasion	Status	Follow-up (mos)	Cause of Death
1	19	5	IVA	4	1	U	1	Alive	70	
2	62	105	II	2	1	M	0	Alive	60	
3	50	3490	IVA	17	1	M	0	Dead	7	Nocardia pneumonia
4	62	71	IVA	6	1	M	1	Dead	8	Recurrent hepatitis B
5	46	8	IVA	9	0	M	0	Dead	17	Recurrent tumor—9 mos
6	54	18580	III	9	1	M	1	Alive	42	
7	52	19	IVA	7	1	M	0	Dead	33	Recurrent tumor—23 mos
8	54	151	III	4.5	1	M	1	Alive	39	
9	60	NA	II	12	0	U	0	Dead	24	Recurrent tumor—12 mos
10	59	4430	III	3.7	1	M	0	Dead	9	Gastrointestinal bleed, pulmonary embolus
11	63	3840	IVA	2.2	1	M	1	Dead	12	Recurrent tumor—11 mos
12	64	27900	IVA	6	1	M	1	Dead	2.5	Sepsis, multiple organ failure
13	69	64	II	8	1	U	0	Alive	34	
14	68	88645	II	12	0	U	0	Alive	33	
15	56	8	III	3	1	M	0	Alive	29	
16	45	3000	I	2	1	U	0	Dead	13	Recurrent hepatitis B
17	65	42	IVA	4	1	M	0	Dead	9	Cardiomyopathy
18	36	6000	IVA	10	0	M	1	Alive (R)	19	
19	59	44	III	3.8	1	M	0	Alive	18	
20	68	220	III	5	1	M	0	Alive	16	
21	49	340	IVA	4	1	M	0	Alive	13	
22	59	38	II	5	1	U	0	Alive	9	
23	51	NA	IVA	11	1	U	1	Alive	9	
24	41	5	III	20	0	M	0	Alive	8	
25	48	990	III	5	1	M	0	Alive	6	

R = recurrent tumor.
* 1 = present, 0 = not present.

iates in a stepwise Cox regression model, none were found to be significantly predictive of survival.

The overall survival was compared with the survival of 17 patients who underwent OLT for HCC at UCLA between May 1984 and December 1988 before introduction of the adjuvant protocol.[8] Tumor size in this early group ranged from 0.5 to 15 cm. Four patients died in the first 3 months from nontumor-related causes, and recurrence of tumor occurred in 67% of the remaining patients (n = 8). Overall actuarial survival rates at 6 months and 1, 2, and 3 years were 58.8%, 35.3%, 17.7%, and 5.8%. Using log-rank analysis, survival was significantly better in the protocol adjuvant chemotherapy group than in the historic controls (p = 0.0001, Fig. 2).

There are 16 patients on the current protocol with follow-up greater than 2 years after transplant. Of these, seven are alive and free of disease. Three of these patients had tumors greater than 5 cm (8, 9, and 12 cm), two had vascular invasion (including one with portal vein thrombosis), four had multifocal tumors, one had capsular invasion, and six had associated cirrhosis. The pTNM stages of these seven patients were II (n = 3), III (n = 3), and IVA (n = 1). Of the 16 patients with long-term follow-up, four had recurrent disease (25%), three of whom had initial tumors greater than 5 cm (7, 9, and 12 cm); one had vascular invasion with portal vein thrombosis; three had multifocal tumors; three had capsular penetration; and two had associated cirrhosis. The pTNM stages of these four patients were II (n = 1), IVA (n = 2), and IVB (n = 1).

There are nine patients with less than 2 years of follow-up. Of these, seven are alive and free of disease. One patient had recurrent disease at 11 months, but remains alive, and the other was the patient who died from multiorgan failure and cardiomyopathy.

DISCUSSION

Hepatocellular carcinoma remains one of the most difficult tumors to treat. Early disease is diagnosed infrequently, and survival after the onset of symptoms is extremely poor. There have been many modalities applied

Table 2. SIDE EFFECTS OF ADJUVANT CHEMOTHERAPY

Side Effect	N*	%
Neutropenia	21	84
Gastrointestinal symptoms—nausea, vomiting, diarrhea	11	44
Stomatitis/mucocitis	10	40
Parasthesias	4	16
Headache	3	12
Alopecia	2	8
Decrease LVEF	2	8
Line complications SVC thrombosis, pain, infection	3	12

* Total N = 25.
LVEF = left ventricular ejection fraction; SVC = superior vena cava.

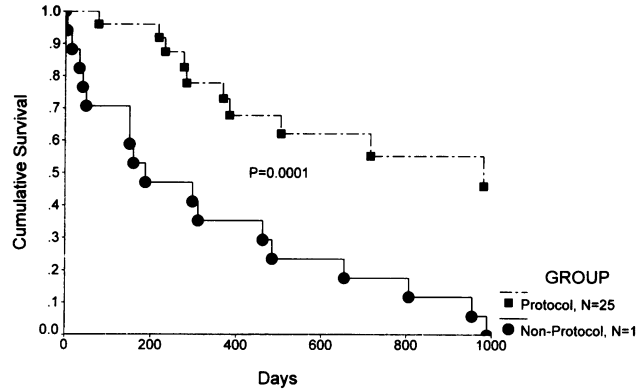

Figure 2. Overall actuarial survival of 25 protocol patients and 17 nonprotocol patients. Overall actuarial survival rates at 1, 2, and 3 years for protocol patients were 78%, 55%, and 46%, respectively. Overall actuarial survival rates for nonprotocol patients were 35%, 18%, and 5.8%, respectively, for the same time intervals (p = 0.0001).

to the treatment of HCC, including chemotherapy and radiation; however, these remain palliative at best. Complete surgical ablation of the tumor remains the treatment of choice, offering the best long-term, disease-free survival. Survival at 5 years after hepatic resection for all hepatomas has been reported to range from 12% to 49%.[2,9] If the tumor is small (less than 5 cm), 5-year survival may be as high as 60%.[10] On the other hand, tumor multiplicity and vascular invasion have been reported to have a significant negative impact on survival after resection.[9]

Unfortunately, many tumors are not diagnosed until they reach an advanced stage and are not easily amenable to resection. It is estimated that less than 30% of patients who are diagnosed with HCC are considered resectable, and of those who undergo resection, up to 60% will have recurrent disease.[2,11] Many of these patients also have associated cirrhosis, markedly increasing the difficulty of a resection, with postoperative morbidity as high as 40% and perioperative mortality between 10% and 25%.[2,9,11-13] These dismal results led hepatobiliary surgeons to search for a better approach to HCC, especially when found in association with cirrhosis. Liver transplantation seemed to emerge as a logical extension of the partial hepatic resection, offering a more radical oncologic approach to the tumor and allowing for replacement of poorly functioning hepatic parenchyma with a normal liver. However, liver transplantation has its own inherent disadvantages, including a perioperative mortality rate of 10% to 20%, high expense, and limited donor supply. Recurrence rates have been reported as high as 65%.[2] In addition, immunosuppression may cause enhancement of tumor growth, with tumor doubling times of less than 50 days in most patients with recurrent tumor after OLT, as reported by Yokoyama et al.[14]

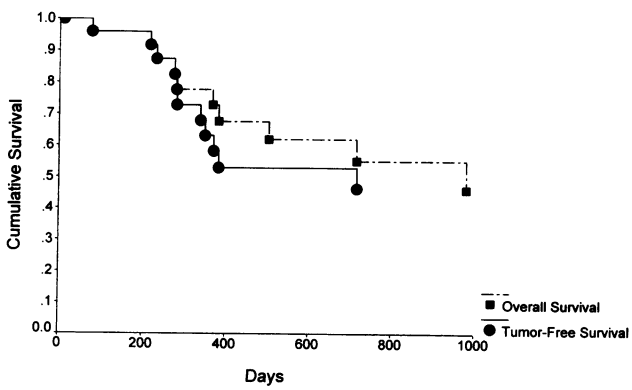

Figure 1. Overall actuarial survival and tumor-free survival in 25 protocol patients.

In 1983, the National Institutes of Health Consensus Conference on liver transplantation stated that primary hepatic malignancy not amenable to surgical resection may be an indication for transplantation, despite a strong likelihood for recurrence.[15] More than 10 years later, OLT for hepatoma remains a controversial issue, and criteria still are being defined. There is little disagreement that OLT for tumors that are less than 5 cm, unifocal, encapsulated, incidental, without vascular invasion, or of the fibrolamellar variant offer an excellent chance at long-term survival. Unfortunately, some of these characteristics cannot be defined until the hepatectomy is done, and most patients do not fit within these guidelines at the time they are referred for transplantation. Therefore, survival after OLT has been disappointing. In a review of recent literature, long-term survival

was only 18% to 45% at 5 years. Penn recently reported the results of the Cincinnati Transplant Tumor Registry, collecting data from liver transplant centers around the world.[3] Patients with "usual hepatomas," excluding incidental and fibrolamellar tumors, had a recurrence rate of 39% and a 5-year overall survival of 18%. Of the 365 patients transplanted for HCC, only 34 (9%) survived tumor free for more than 2 years, and another 21 had recurrences after 2 years. Haug et al. reported a 25% recurrence rate and a 3-year survival rate of 42% in 24 patients with HCC, 36% if tumors less than 3 cm were excluded. Survival at 3 years for patients with cirrhosis was only 32%.[16] The results of 61 liver transplants for HCC were reported by Ringe et al. Of these cases, 60% were associated with cirrhosis and 67% were associated with tumors greater than 5 cm. Five-year survival was 15.2%.[9] Pichlmayr recently presented survival statistics for 70 patients with stage III and IVA tumors. Five-year survival was 25% in these groups, compared with 70% to 80% in stage I and II disease.[17] The Pittsburgh experience showed a strong correlation to tumor stage, with an overall 5-year survival rate of 35.6%, but only 10.9% for stage IVA. Tumor size, bilobar involvement, and vascular invasion were independently associated with poor survival rates.[18]

Despite these results, many series report occasional long-term survival despite poor prognostic factors. Therefore, it seems that cure is possible, and patients with advanced tumors should not be excluded from transplantation. Instead, attempts at improving therapy should be undertaken. To this end, multimodality therapy recently has been introduced into the liver transplant field, and several centers have reported their early results (Table 3). The rationale used by investigators for multimodal adjuvant chemotherapy include the following: 1) control of tumor growth during the waiting period; 2) elimination of tumor cells that are disseminated during the manipulation of the tumor; and 3) control of micrometastatic deposits that are present postoperatively. Stone et al. reported results from a pilot study of 20 patients treated with combined modality therapy using preoperative, intraoperative, and postoperative doxorubicin and OLT. Seventeen of these patients (85%) had tumors greater than 5 cm. Three-year survival was 59% and tumor-free survival was 54%.[4] Bismuth performed preoperative chemoembolization with ethiodized oil, doxorubicin, and gelatin sponge as well as postoperative fluorouracil and doxorubicin. Twenty patients underwent OLT and the explanted tumors showed greater than 50% necrosis in approximately half of the specimens. Long-term survival statistics were not available.[19] Cherqui et al. also has employed preoperative chemoembolization, but has added preoperative radiotherapy, in addition to postoperative systemic chemotherapy with mitoxantrone. Only nine patients were entered into the study; however, seven had advanced stage IVA tumors. Three-year actuarial survival was 64% (follow-up 7–45 months).[6] Carr et al. reported the Pittsburgh experience of preoperative treatment with intraarterial doxorubicin and cisplatin and subcutaneous alpha-interferon, as well as 12 months of postoperative chemotherapy. Results are promising, with an 82% 1-year disease-free survival, but follow-up still is too short to draw any conclusions.[5] Schwartz has reported the Mount Sinai protocol incorporating preoperative chemoembolization with intraoperative and postoperative systemic chemotherapy. Ten patients with tumors 5 cm or greater were enrolled and transplanted, and nine are alive without recurrence at 3 months to 2 years posttransplant.[7]

In our current study, postoperative chemotherapy was employed in an attempt to eliminate micrometastases that might be present at the time of OLT, or that are shed from manipulation of the tumor. Although no chemotherapeutic regimen has been shown to be curative in HCC without surgical resection, their effectiveness may, in theory, be increased if the tumor burden is removed and only microscopic deposits remain.

The majority of the patients enrolled in our study had advanced disease; 14 patients (56%) had tumors greater than 5 cm, 20 patients (80%) had stage III and IV disease, and 72% had multifocal tumors. Long-term 3-year actuarial survival was 46%. This survival is markedly improved over our historic controls.[8] In this study, there were three Asian patients with hepatitis B who died from recurrent hepatitis (n = 2) or recurrent tumor (n = 1). Jurim et al. have reported about this subgroup of patients, demonstrating extremely high hepatitis B recurrence rates (72%) and a 3-year survival of only 32%.[20] If these patients were removed from this current study, 3-year actuarial survival of the protocol patients would be 55%.

Although we only experienced one mortality attributed to chemotherapy toxicity, the side effects of this regimen are not insignificant. Patients will frequently exhibit nausea, vomiting, or anorexia, and most will have at least one episode of neutropenia, requiring interruption of chemotherapy or treatment with granulocyte colony-stimulating factor. The patient who died of severe cardiomyopathy developed symptoms after a total dosage of only 263 mg/m^2, substantially lower than normally is required to produce this problem; another with mild cardiomyopathy had received only 133 mg/m^2. There is evidence that cyclosporine enhances the blood levels of anthracycline antibiotics (including doxorubicin) and increases drug transport into cells,[21,22] and therefore, any given dose may be more effective, but also more toxic. We currently employ more

Table 3. ADJUVANT THERAPY PROTOCOLS FOR ORTHOTOPIC LIVER TRANSPLANTATION AND HEPATOCELLULAR CARCINOMA

Center	Protocol	N	Recurrence	Survival (%)		
				1-Yr	2-Yr	3-Yr
Paris 1992, Bismuth et al.[20]	Preoperative chemoembolization	20	NA	71 18	49* 9†	
Pittsburgh 1993, Carr et al.[5]	Preoperative intrahepatic arterial doxorubicin, interferon, 12 months of postoperative intravenous doxorubicin	11	3/11	91	—	—
Baylor 1993, Stone et al.[4]	Preoperative doxorubicin, intraoperative dose and 20 weeks of postoperative doxorubicin	20	6/20	70	66	59
Creteil 1994, Cherqui et al.[6]	Preoperative chemoembolization and radiotherapy, postoperative systemic mitoxantrone	9	3/9	—	—	64
Mount Sinai 1994, Schwartz[7]	Preoperative chemoembolization, intraoperative and postoperative intravenous doxorubicin	10	1/9	NA	—	—
UCLA 1994, Olthoff et al. (current study)	Postoperative intravenous 5-FU, doxorubicin, cisplatin for 6 months	25	5/25	78	55	46

* Class A cirrhotics.
† Class C cirrhotics.

frequent echocardiograms on patients receiving doxorubicin as part of their routine follow-up. Concerning the frequent neutropenia, future therapy may employ routine administration of granulocyte colony-stimulating factor to prevent this troublesome side effect. There appears to be no evidence to support the claim that granulocyte colony-stimulating factor may increase rejection in the transplanted graft.[23]

The results of this study and those of the previously mentioned studies employing multimodality therapy are promising and warrant further investigation. There is a definite role for liver transplantation in the treatment of hepatocellular carcinoma, even in patients with advanced disease, and the use of adjuvant chemotherapy and hepatic artery chemoembolization may decrease tumor growth and improve survival. In this study, adjuvant chemotherapy improves survival after OLT for hepatoma when compared with historic controls. We are encouraged by these results, but must temper our enthusiasm because of the small patient numbers and the relatively short follow-up. To definitively answer the question of the benefit of adjuvant therapy, a prospective, randomized trial is necessary. Until then, the actual effects of this intervention can only be speculative.

References

1. Colombo M. Hepatocellular carcinoma. J Hepatol 1992; 15:225–236.
2. Farmer DG, Rosove MH, Shaked A, et al. Current treatment modalities for hepatocellular carcinoma. Ann Surg 1994; 219:236–247.
3. Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. Surgery 1991; 110:726–735.
4. Stone MJ, Klintmalm GBG, Polter D, et al. Neoadjuvant chemotherapy and liver transplantation for hepatocellular carcinoma: a pilot study in 20 patients. Gastroenterology 1993; 104:196–202.
5. Carr BI, Selby R, Madariaga J, et al. Prolonged Survival after liver transplantation and cancer chemotherapy for advanced-stage hepatocellular carcinoma. Transplant Proc 1993; 25:1128–1129.
6. Cherqui D, Piedbois P, Pierga J, et al. Multimodal adjuvant treatment and liver transplantation for advanced hepatocellular carcinoma. Cancer 1994; 73:2721–2726.
7. Schwartz ME. Primary hepatocellular carcinoma: transplant *versus* resection. Semin Liver Disease 1994; 14:135–139.
8. Olthoff KM, Millis JM, Rosove MH, et al. Is liver transplantation justified for the treatment of hepatic malignancies? Arch Surg 1990; 125:1261–1268.
9. Ringe B, Pichlmayr R, Wittekind C, et al. Surgical treatment of hepatocellular carcinoma: experience with liver resection and transplantation in 198 patients. World J Surg 1991; 15:270–285.
10. Chen M, Hwang T, Jeng LB, et al. Hepatic resection in 120 patients with hepatocellular carcinoma. Arch Surg 1989; 124:1025–1028.
11. Nerenstone SR, Ihde DC, Friedman MA. Clinical trials in primary hepatocellular carcinoma: current status and future direction. Cancer Treat Rev 1988; 15:1–31.
12. Bismuth H, Chiche L, Adam R, et al. Liver resection *versus* transplantation for hepatocellular carcinoma in cirrhotic patients. Ann Surg 1993; 218:145–151.
13. Kinami Y, Takashima S, Miyazaki I. Hepatic resection for hepatocellular carcinoma associated with liver cirrhosis. World J Surg 1986; 10:294–301.

14. Yokoyama I, Carr B, Saitsu H, et al. Accelerated growth rates of recurrent hepatocellular carcinoma after liver transplantation. Cancer 1991; 68:2095–100.
15. National Institutes of Health, Consensus conference statement on liver transplantation: June 20–23, 1983. Hepatology 1984; 4(suppl):107S–110S.
16. Haug CE, Jenkins RL, Rohrer RJ, et al. Liver transplantation for primary hepatic cancer. Transplantation 1992; 53:376–382.
17. Pichlmayr R, Weiman A, Ringe B. Indications for liver transplantation in hepatobiliary malignancy. Hepatology 1994; 20(suppl): 33S–40S.
18. Iwatsuki S, Starzl T, Sheahan D, et al. Hepatic resection *versus* transplantation for hepatocellular carcinoma. Ann Surg 1991; 214: 221–229.
19. Bismuth H, Morino M, Sherlock D, et al. Primary treatment of hepatocellular carcinoma by arterial chemoembolization. Am J Surg 1992; 163:387–394.
20. Jurim O, Martin P, Shaked A, et al. Liver transplantation for chronic hepatitis B in asians. Transplantation 1994; 57:1393–1395.
21. Sikic BI. Modulation of multidrug resistance: at the threshold. J Clin Oncol 1993; 11:1629–1635.
22. Bartlett NL, Lum BL, Fisher GA, et al. Phase I trial of doxorubicin with cyclosporine as a modulator of multidrug resistance. J Clin Oncol 1994; 12:835—842.
23. Colquhoun SD, Shaked A, Jurim O, et al. Reversal of neutropenia with granulocyte colony-stimulating factor without precipitating liver allograft rejection. Transplantation 1993; 56:755–758.

Discussion

DR. HENRY A. PITT (Baltimore, Maryland): I would like to thank the authors for the opportunity to review their manuscript. In the manuscript, they have made two statements that bear repeating at the outset.

First, they state that liver resection remains the mainstay for therapy for hepatocellular carcinoma.

Second, they state that to definitively answer the question of the benefit of adjuvant therapy after liver transplantation, a prospective randomized trial is necessary.

I agree completely with these statements. However, they also conclude that adjuvant chemotherapy after transplantation for hepatocellular carcinoma can provide long-term cure and improve survival. I am not so sure that this conclusion can be made from their present data.

They have compared a recent group of 25 patients with a 46% 3-year survival with an historical group of 17 patients with a 4% 3-year survival. The most important question is whether these two groups of patients are really comparable. For example, none of the recent patients had positive lymph nodes. Did you purposely exclude patients with positive nodes from the more recent patients, and was this policy also true when you staged the historical controls?

Similarly, was the TNM stage the same in the recent patients and in the historical patients? The historical group also had a very high 41% 6-month mortality. Whereas, only one of the 25 recent patients, or 4%, died at 6 months.

If the survival curves were begun at 6 months, they look very similar, with additional mortality being only 53% for the controls and 50% for the recent patients over the subsequent $2\frac{1}{2}$ years. Was the early mortality in the controls tumor related? If not, the difference between the old and the new patients may be related more to the multiple advancements that have occurred in transplantation rather than to the adjuvant therapies that were given to the more recent patients.

The second basic question that I have is your rationale for using only postoperative chemotherapy. The other five groups that have reported results have also given pretransplant therapy. Perhaps this is an issue of time on the transplant list. How long did it take you to find a liver for the 25 patients in this analysis? Were there other patients whose tumor progressed during the interval between being put on the list and transplantation and were not included in this report?

The third question that I have is related to the need for a backup recipient. Was this policy in effect for the historical as well as the recent patients? How often was a back-up recipient actually used? Or, to turn this question around, how many patients were explored and not transplanted?

My final question is what are you doing now? You have had some late deaths due to hepatitis. Are you still transplanting patients who are hepatitis B positive? You also had some problems with cardiac toxicity from doxorubicin. Are you still using doxorubicin, or would you switch to a regimen that did not include this particular agent?

And, finally, with the growing shortage of organs, and even with the better results with the most recent regimen, is transplantation for hepatocellular carcinoma justified? If so, would you still transplant stage four types of patients, none of whom were long-term survivors in this report?

DR. MICHAEL HENDERSON (Cleveland, Ohio): Dr. McDonald, Dr. Copeland, Members, and Guests. I rise to commend Dr. Busuttil for bringing this controversial area of liver transplant to this meeting. I think it is important that we do explore the new ways of managing these types of patients.

I'd like to briefly outline some of the data that we have had through the Ohio Transplant Consortium experience. This was recently reviewed and presented to the Consortium by Doug Hanto from Cincinnati.

In Ohio, you cannot transplant patients with hepatocellular carcinoma off protocol. The requirement for a known hepatocellular carcinoma to receive approval for transplant is that they must be on a pretransplant chemotherapy protocol. This outlines the patients with hepatocellular carcinoma who have been transplanted, represents less than 5% of the transplants performed in Ohio over this time interval.

Patients with preoperative diagnosis of hepatocellular carcinoma, a small number, 11 patients, are shown. A very similar profile to the profile Ron showed you, with more than half the tumors being greater than 5 cm in diameter. The outcome in this small group of patients, is a mean follow-up of just over 2 years. Fifty-four percent of these patients who have all received a single-agent pretransplant chemotherapy with doxorubicin have a 54% survival, which is exactly the same as the survival in those with undiagnosed, incidental hepatocellular carcinomas transplanted over the same time interval.

I have a couple of questions that really parallel some of the