Treatment of Unresectable Hepatocellular Carcinoma with Intrahepatic Yttrium 90 Microspheres: A Risk-Stratification Analysis

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PURPOSE: To present the findings of a risk-stratification survival analysis with use of data collected on a heterogeneous group of patients with hepatocellular carcinoma (HCC) treated with TheraSphere.

MATERIALS AND METHODS: Baseline, treatment, and follow-up data were collected and analyzed from 121 TheraSphere-treated patients. Survival analyses were performed to identify those variables most strongly associated with 3-month mortality. The presence of any of the identified risk variables resulted in the assignment of a patient to the high-risk category.

RESULTS: Five liver reserve and two non–liver reserve variables were identified and used to stratify patients into low- or high-risk groups. Sixteen of the 33 patients assigned to the high-risk group (49%) did not survive the first 3 months after treatment, compared with six of the 88 patients assigned to the low-risk group (7%; Fisher exact test, $P < .0001$). Median survival for the low- and high-risk groups were 466 days and 108 days, respectively (hazard ratio, 6.0; $P < .0001$). Eleven of 12 patients who experienced a treatment-related major complication ending in death were included in the high-risk group. No single variable explained the major complication relationship to treatment.

CONCLUSION: Patients with HCC who are being considered for treatment with TheraSpheres should be evaluated for the presence of the risk variables described herein. The absence of these variables is predictive of improved survival (median of 466 days) compared with patients at high risk (median of 108 days).

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Abbreviations: CLIP = Cancer of the Liver Italian Program, HCC = hepatocellular carcinoma, HDE = Humanitarian Device Exemption, ULN = upper limit of normal

WORLDWIDE, hepatocellular carcinoma (HCC) is one of the most lethal malignancies and results in more than 1 million new cases annually. Although a relatively rare form of cancer in the United States, the number of deaths from the disease is almost equal to the number of new cases, and the number of new HCC cases diagnosed each year is increasing, primarily because of an increasing incidence of hepatitis C infection (1,2). Unfortunately, approximately 90% of HCC cases are diagnosed at a time when curative surgical resection or transplantation cannot be performed. Unresectable HCC is extremely difficult to treat because of the coexistence of cirrhosis and its sequelae, the associated decrease in liver function, and the chemotherapy resistance of the tumor (3). Currently, no standard treatment or generally accepted guidelines for the treatment of unresectable HCC exist in the United States; however, there is a growing reliance on the use of local and regional treatments such as radiofrequency ablation, transarterial embolization, and transarterial chemo-

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Table 1
Distribution of Treated Patients by Center

Center	Date of First Treatment	Time Frame	Patients Treated (n = 121)	Patients at High Risk	Median Liver Dose (Gy)
DR	7/24/86	Pre-HDE	13	5 (38)	74
TGH	4/3/92	Pre-HDE	22	5 (23)	104
UPMC	8/15/00	Post-HDE	65	14 (22)	130
HUP	8/21/01	Post-HDE	13	6 (46)	127
JHU	7/16/01	Post-HDE	8	3 (38)	135
All Patients					

Note.—Values in parentheses are percentages. Median live dose for all patients was 127 Gy. DR = Dose Ranging (Toronto General Hospital, n = 9; University of Michigan Hospital, n = 1; The Montreal General Hospital, n = 2; Ottawa Regional Cancer Centre, n = 1); HUP = Hospital of the University of Pennsylvania; JHU = Johns Hopkins University Hospital; TGH = Toronto General Hospital; UPMC = University of Pittsburgh Medical Center.

embolization (4–6). The use of these treatments is highly individualized, and these therapeutic modalities are often associated with mild to moderate toxicities such as abdominal pain, fever, nausea, and vomiting. In addition, these treatments can result (<2% risk) in cholecystitis, hepatic abscess, bleeding, seeding of the tract, hepatic decompensation, and fulminant liver failure resulting in death. Despite the introduction of these treatments, the observed survival rates for HCC in the United States have changed little during the past 25 years, with an estimated median survival time and 1-year survival rate of 8 months and 28%, respectively (7). Consequently, there continues to be a clinical need for new treatments that can increase survival while minimizing toxicity for patients with unresectable HCC.

TheraSphere (MDS Nordion, Ottawa, ON, Canada), a brachytherapy treatment for unresectable HCC, was approved for use as a medical device by the Food and Drug Administration in December of 1999 under the Humanitarian Use Device regulations, allowing TheraSphere to be exempt from strict efficacy requirements. This approval is known as a Humanitarian Device Exemption (HDE). Exemption was granted because no other medical device had been approved for this indication and because HCC is a relatively rare disease in the United States. The HDE approval was based primarily on data collected from 35 treated patients. Under the HDE, data have been collected from 86 additional patients treated in the United States. The purpose of this article is to present the findings of a risk-stratification analysis, in which data collected in a heterogeneous group of 121 TheraSphere-treated patients was used in the separation of patients into low and high mortality risk groups.

PATIENTS AND METHODS

Patients Treated

Prospective and retrospective data from 121 patients with unresectable HCC were included in this risk-stratification analysis. The distribution of treated patients by study center is provided in **Table 1**. The HCC study protocols were approved by each center's institutional review board or ethics committee, with all patients signing an informed consent form allowing use of their data. The first study, which began in July 1986, was a dose-ranging study with increasing liver doses targeted from 50 Gy to 100 Gy. The second study was a single-center fixed-dose (100 Gy) study that began in April 1992 (8). These two studies, plus data from a third study in which patients with liver metastases were treated, provided safety data for liver dosing as high as 150 Gy. Based on the combined results of these three studies, the FDA approved TheraSphere under the HDE regulations (Code of Federal Regulations; Title 21; Part 814; Section 100/21CFR814.100) for the treatment of patients with unresectable HCC. TheraSphere was approved for liver dosing from 80 Gy to 150 Gy.

Data after the HDE approval were collected on 86 patients treated at three centers (**Table 1**). The median liver doses at these centers were 127 Gy, 130 Gy, and 135 Gy. For patients with unilobar disease, the treatment approach was to treat the affected liver lobe. For patients presenting with bilobar disease, whole-liver treatment was the method of choice for the studies before HDE, whereas in the studies after HDE, the lobe with the dominant tumor burden was treated first. Then, if the patient tolerated the first treatment well and the tumor in the remaining lobe was believed to be the most immediate threat to survival, the remaining affected lobe was treated. Patients also received repeat treatment to the same lobe if needed. Data were collected until February 28, 2003.

TheraSphere Treatment

TheraSphere consists of nonbiodegradable glass microspheres in which yttrium 90 (^{90}Y) is an integral constituent of the glass and therefore cannot leach out. Among dose batches, 95% of the spheres have diameters ranging from 15 to 35 μm. ^{90}Y is a pure β-emitter and decays to stable zirconium 90 with a physical half-life of 64.1 hours. The average energy of β-emission is 0.9367 MeV, with a mean tissue penetration of 2.5 mm and a maximum of 10 mm. One gigabecquerel of ^{90}Y per kilogram of tissue provides a dose of 50 Gy (9). TheraSphere is supplied in 0.5 mL of sterile, pyrogen-free water contained in a 0.3 mL vee-bottom vial secured within a 12-mm clear acrylic vial shield. The method of calculating the required activity for injection, and for calculating the actual dose delivered to the liver and lungs, has been