Fibrolamellar Hepatocellular Carcinoma in Children and Adolescents

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BACKGROUN. Children with hepatocellular carcinoma (HCC) were treated on a prospective, randomized trial and were then analyzed to determine whether children with the fibrolamellar (FL) histologic variant of HCC have a more favorable presentation, increased surgical resectability, greater response to therapy, and improved outcome compared with children who have typical HCC.

METHODS. Forty-six patients were enrolled on Pediatric Intergroup Hepatoma Protocol INT-0098 (Pediatric Oncology Group Study 8945/Children’s Cancer Group Study 8801) between August 1989 and December 1992. After undergoing initial surgery or biopsy, children with Stage I HCC (n = 8 patients), Stage III HCC (n = 25 patients), and Stage IV HCC (n = 13 patients) were assigned randomly, regardless of histology, to receive treatment either with cisplatin, vincristine, and fluorouracil (n = 20 patients) or with cisplatin and continuous-infusion doxorubicin (n = 26 patients).

RESULTS. Ten of 46 patients (22%) had the fibrolamellar variant of HCC (FL-HCC). For the entire cohort, the estimated 5-year event-free survival (EFS) rate (± standard deviation) was 17% ± 6%. There was no difference in outcome among patients who were treated with either regimen. The 5-year EFS rate for patients with FL-HCC was no different the rate for patients with typical HCC (30% ± 15% vs. 14% ± 6%, respectively; P = 0.16), although the median survival was longer in patients with FL-HCC. There was no difference in the number of patients with advanced-stage disease, the incidence of surgical resectability at diagnosis, or the response to treatment between patients with FL-HCC and patients with typical HCC.

CONCLUSIONS. Children with FL-HCC do not have a favorable prognosis and do not respond any differently to current therapeutic regimens than patients with typical HCC. Children with initially resectable HCC have a good prognosis irrespective of histologic subtype, whereas outcomes are poor uniformly for children with advanced-stage disease. The use of novel chemotherapeutic agents and the incorporation of other treatment modalities are indicated to improve the dismal survival of pediatric patients with all histologic variants of advanced-stage HCC. Cancer 2003;97:2006-12.

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KEYWORDS: hepatocellular carcinoma, pediatrics, liver, fibrolamellar.
Hepatocellular carcinoma (HCC) is a rare malignancy in children and commonly presents in older children with a history of underlying liver disease. Tumor resectability is the basis of curative therapy for patients with HCC; however, at most, these tumors are resectable in one-third of newly diagnosed patients. Pediatric patients with inoperable HCC remain largely unresponsive to chemotherapy, and these children have a very poor prognosis. The fibrolamellar (FL) variant of HCC (FL-HCC) was described originally in 1956 by Edmonson as a distinct pathologic variant that also has been referred to as eosinophilic HCC with lamellar fibrosis, polygonal cell with fibrous stroma, HCC with increased stromal fibrosis, eosinophilic glassy cell hepatoma, and fibrolamellar oncocytic hepatoma. In 1980, two simultaneous reports described the clinical entity of FL-HCC in association with patients who had a higher resection rate and better survival compared with patients who had the typical pathologic variant of HCC. Other small, retrospective series supported those findings and described FL-HCC as a favorable entity. However, some authors found no difference when comparing outcomes among children with different histologic subtypes of HCC.

Pediatric Oncology Group (POG) Study 8945/Children’s Cancer Group (CCG) Study 8881 was a prospective Intergroup trial in which children with both hepatoblastoma (HB) and HCC were assigned randomly to treatment regimens that consisted either of cisplatin, vincristine, and fluorouracil or of cisplatin and continuous-infusion doxorubicin. The results of that study were published recently. To determine whether FL-HCC is associated with a favorable prognosis, we compared clinical characteristics, surgical resectability, response to therapy, and outcomes of children who had FL-HCC with the same variables in children who had typical HCC.

MATERIALS AND METHODS

Patients
Pediatric Intergroup Hepatoma Study INT-0098 (POG-8945/CCG-8881) was open from August, 1989 to December, 1992. Eligible patients were age < 21 years at the time of diagnosis and had previously untreated HB or HCC. This report involves only patients who were diagnosed with HCC. All protocols were approved by the National Cancer Institute. Informed consent forms were signed and collected for all patients before entry, according to individual Institutional Review Board requirements of the participating POG-affiliated or CCG-affiliated institutions.

Disease stage was determined by surgical criteria after the assessment of initial resectability, as determined by the institutional surgeon in consultation with the treating oncologist, and after patients underwent either surgical resection or biopsy prior to the initiation of chemotherapy. Disease stage was defined as follows: Stage I, complete macroscopic resection with clear margins; Stage II, macroscopic total resection with microscopic residual disease at the margins of resection; Stage III, macroscopic total resection with lymph node involvement, or tumor spill, or incomplete resection with microscopic residual intrahepatic disease; and Stage IV, metastatic disease with either complete or incomplete resection or biopsy. Central pathologic review (M.J.F. for POG and J.E.H. for CCG) of representative tissue slides was required for study entry, and staging also was confirmed by review of institutional pathology and surgical reports.

Treatment
Patients with all disease stages and histologic variants of HCC were assigned randomly to receive chemotherapy, which was comprised either of cisplatin, vinorelbine, and fluorouracil or of cisplatin and continuous-infusion doxorubicin, as detailed elsewhere and as shown in Figure 1. Patients were to receive four cycles of chemotherapy and were then reevaluated for resectability. After the four cycles of chemotherapy, patients who underwent primary resection and were in complete remission were to receive no additional therapy and were to be observed, whereas patients who were able to undergo a delayed resection were to receive two additional courses of the same chemotherapy. Children with tumors that remained unresectable after the initial four cycles of therapy were to receive four additional courses of the same chemotherapy. Patients with tumors that remained unresectable after eight cycles of chemotherapy were considered to have failed protocol therapy, and other therapeutic options were considered.

Statistical Design and Analysis

Study design
Patients were assigned after initial surgical staging and were stratified according to stage of disease. Event free survival (EFS) was defined as the period from the date chemotherapy was started until evidence of an event (progressive disease, secondary malignancy, or death) or last contact, whichever occurred first. Survival was defined as the period from the date chemotherapy was started until death or last contact, whichever occurred first. A patient who died was considered to have experienced an event, regardless of the cause of death. Patients who did not experience an event were censored on the date of last contact.
Analytic methods

Statistical analysis was conducted with data current as of January 17, 2002. Clinical and demographic characteristics were analyzed with chi-square statistics. Life table estimates were calculated by the method of Kaplan and Meier, and the standard deviation (SD) of the Kaplan–Meier estimate of the survivor function at selected points was calculated using the Greenwood formula. The risk of adverse events and death was compared across therapies and groups of patients using the log-rank statistic. Estimates for relative risks and 95% confidence intervals were calculated using a proportional hazards regression model with the relevant characteristic as the only variable. Qualitative patient characteristics were compared across regimens using a Fisher exact test. An initial AFP level was considered normal if it was < 20 ng/mL.

RESULTS

Patients

A total of 46 patients who were diagnosed with HCC were the focus of this report. Their clinical and demographic characteristics, including age at diagnosis, gender, disease stage, and α-fetoprotein (AFP) level at diagnosis, are shown in Table 1. Ten of 46 patients (22%) had FL-HCC (Table 2), and 36 patients (78%) had typical HCC. Eight of 46 patients (17%) with HCC had Stage I tumors, 25 patients (54%) had Stage III tumors, and 13 patients (28%) had Stage IV tumors. There was no difference in the distribution of tumor stages (P = 0.81) according to histologic variant: Eight of 10 patients (80%) with FL-HCC and 30 of 36 patients (83%) with typical HCC had advanced-stage disease (Stage III or Stage IV) at the time of diagnosis. Patients who had FL-HCC were more likely to be age > 10 years at the time of diagnosis compared with patients who had typical HCC (P < 0.01).

Forty-three of 46 patients had a serum AFP level measured at study entry, at the time they underwent either initial surgery or biopsy. Three patients had their initial AFP level measured at the initiation of chemotherapy, which may have occurred several weeks later, and were excluded from the analysis. Eight of 9 evaluable patients (89%) with FL-HCC had
low AFP levels at the time of diagnosis compared with 6 of 34 evaluable patients (18%) with typical HCC (P < 0.01).

Survival
The 5-year EFS rate (± SD) for the entire cohort of 46 patients was 17% ± 6% (Fig. 2). The 5-year EFS rate of patients who had lower stage disease was significantly longer compared with patients who had higher stage disease. The 5-year EFS rates for patients with Stages I disease, Stage III disease, and Stage IV disease were 75% ± 15%, 8% ± 5%, and 0%, respectively (P < 0.01).

There was no difference in the 5-year EFS for patients who had FL-HCC compared with patients who had typical HCC (30% ± 15% vs. 14% ± 6%, respectively; P = 0.18) (Fig. 3). No difference in survival between the HCC group and the FL-HCC group was seen within disease stages (P = 0.96 for Stage I, P = 0.31 for Stage III, and P = 0.10 for Stage IV). Only 2 of 25 patients with Stage III disease did not have events: 1 patient who underwent orthotopic liver transplant and 1 patient who underwent initial complete resection with a pathologically involved lymph node.

Overall survival was similar to EFS for histologic subtypes (30% ± 15% for the FL-HCC group and 18% ± 7% for the HCC group). The 5-year overall survival rate (± SD) also was similar to the EFS rate for each disease stage, with estimates of 75% ± 15%, 8% ± 5%, and 0% for patients with Stage I disease, Stage III disease, and Stage IV disease, respectively (P < 0.01). The median follow-up for patients who survived event free (n = 6 patients) was 7.2 years (range, 4.3–7.8 years). There was no statistically significant difference in the median survival for patients in the FL-HCC group (13.6 months) compared with patients in the typical HCC group (3.3 months; P = 0.16). Forty-one patients (89%) experienced disease progression as their first adverse event. No secondary malignancies have been reported.
Histology
Nine of ten patients (90%) with FL-HCC had the diagnosis made by the institutional pathologist in accordance with the central review (M.J.F. or J.E.H.). Only one patient with FL-HCC was diagnosed with typical HCC at the treating institution and was reclassified with FL-HCC by central review.

Surgical Management
Three of 10 patients (30%) with FL-HCC had resectable disease at the time of diagnosis, including 1 patient who had a positive lymph node and disease that was considered Stage III. That was not statistically different from the 6 of 36 patients (17%) with typical HCC who had resectable tumors at the time of diagnosis ($P = 0.51$). There was no difference in response to treatment, because only 1 of 7 patients (14%) with FL-HCC became resectable after treatment, compared with 1 of 30 patients (3%) who had typical HCC ($P = 0.25$).

DISCUSSION
The POG and CCG Intergroup Hepatoma Study (INT-0098) was a prospective trial in which children with HCC were randomized to treatment regimens that consisted either of either cisplatin, vincristine, and fluorouracil, or of cisplatin and continuous-infusion doxorubicin. There was no difference in outcome for patients who were treated on either regimen. Ten of 46 patients (22%) were diagnosed with the histologic variant FL-HCC. However, the histologic subtype of HCC was not used to alter or determine therapy in this study. Children with localized, resectable HCC fared well regardless of histologic subtype, with a 5-year EFS rate of 88% ± 12%. Patients fared poorly who had typical HCC and FL-HCC that was unresectable or metastatic. Patients with FL-HCC did not have a greater likelihood of a favorable presentation, because advanced-stage disease was observed in 80% of patients with FL-HCC and in 83% of patients with typical HCC. There also was no difference in the rate of surgical resectability, in contrast to what has been reported previously in the literature.6,11 Ultimately, there was no statistically significant difference in outcome or median survival between patients with the two histologic subtypes of HCC.

This was the largest reported prospective trial of a uniform treatment approach for children with HCC. This report demonstrates that FL-HCC currently is not associated with a favorable prognosis, because the majority of children (60%) with FL-HCC did not survive. This is contrary to a widely held but erroneous belief: Much of the published literature that describes FL-HCC as a favorable entity is comprised of small, retrospective series of selected, nonuniformly treated patients, often with a relatively short period of follow-up.6,8,11 We reviewed the literature (Table 3), seeking pediatric patients age ≤ 18 years with FL-HCC to use as a comparison group for this study. Although it is believed that FL-HCC is a disease of adolescents and young adults, many published series have included a significant number of much older patients.8,9,11,12 We hope that our data can be combined with the previously reported experience in pediatric patients with FL-HCC to guide decisions for future pediatric cooperative group trials. Only 36% of previously reported, evaluable pediatric patients with FL-HCC have survived disease free (Table 3). Haas and colleagues reported the largest pediatric series, in which only 4 of 14 children with FL-HCC survived disease free.8 In one of the initial reports, Craig and coworkers described only 3 survivors among 10 pediatric patients with FL-HCC.13 Both of those reports described longer survival in children with FL-HCC, but most ultimately did not survive. Similarly, children with FL-HCC in the current series also had longer survival, although 4 of 10 children developed recurrent disease, and 2 children died within the first 4 months after the initiation of therapy.

Although pediatric HCC is relatively rare, institutional pathologists did not have trouble identifying the FL-HCC histologic subtype. Previous investigations have attempted to further explore pathologic characteristics of FL-HCC, such as vascular invasion, and have tried to correlate those features with tumor phenotype and outcome.8,9,11 Limited, centrally reviewed biopsy samples in our cohort precluded additional observations that associated pathologic features with outcome.

Because the overall survival of pediatric patients with HCC is poor, the true prognostic relevance of FL-HCC requires further evaluation and may not become apparent until a significant number of advanced-stage patients can be treated effectively. Certainly, the more indolent course of FL-HCC suggests that future therapeutic regimens should be designed in a manner that addresses more appropriately the treatment of patients who have tumors that may be less sensitive to traditional therapy.

This report demonstrates that pediatric patients with FL-HCC do not have a favorable prognosis, and it is important to note that they do not respond differently to current therapeutic regimens compared with pediatric patients with typical HCC. We caution against modifying therapy for children with FL-HCC because of prior study suggestions that this histologic variant of HCC is associated with a more favorable prognosis. The use of novel chemotherapeutic agents
TABLE 3
Pediatric Patients with Fibrolamellar Hepatocellular Carcinoma in the Literature

<table>
<thead>
<tr>
<th>Investigators</th>
<th>No. of patients</th>
<th>Localizeda</th>
<th>Alive (recurrence free)</th>
<th>Alive with diseaseb</th>
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a: Not available.
b: Patients age ≤3 years.
c: Tumor confined to liver.
d: Alive either after recurrence or with persistent disease.

and the incorporation of alternative treatment modalities is indicated to improve the dismal survival for pediatric patients with all histologic variants of advanced-stage HCC.

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