Hepatocellular Carcinoma in Children and Adolescents: Results From the Pediatric Oncology Group and the Children's Cancer Group Intergroup Study


Purpose: To determine surgical resectability, event-free survival (EFS), and toxicity in children with hepatocellular carcinoma (HCC) randomized to treatment with either cisplatin (CDDP), vincristine, and fluorouracil (regimen A) or CDDP and continuous-infusion doxorubicin (regimen B).

Patients and Methods: Forty-six patients were enrolled onto Pediatric Intergroup Hepatoma Protocol INT-0098 (Pediatric Oncology Group [POG] 8945/Children's Cancer Group [CCG] 8881). After initial surgery or biopsy, children with stage I (n = 8), stage II (n = 25), and stage IV (n = 13) HCC were randomly assigned to receive regimen A (n = 20) or regimen B (n = 26).

Results: For the entire cohort, the 5-year EFS estimate was 19% (SD = 6%). Patients with stage I, II, and IV had 5-year EFS estimates of 88% (SD = 12%), 8% (SD = 5%), and 0%, respectively. Five-year EFS estimates were 20% (SD = 9%) and 19% (SD = 8%) for patients on regimens A and B, respectively (P = .78), with a relative risk of 1.2 (95% confidence interval, 0.60 to 2.3) for regimen B when compared with regimen A. Outcome was similar for either regimen within disease stages. Events occurred before postinduction surgery in 18 (47%) of 38 patients with stage III or IV disease, and tumor resection was possible in two (10%) of the remaining 20 children with advanced-stage disease after chemotherapy.

Conclusion: Children with initially resectable HCC have a good prognosis and may benefit from the use of adjuvant chemotherapy. Outcome was uniformly poor for children with advanced-stage disease treated with either regimen. New therapeutic strategies are needed for the treatment of advanced-stage pediatric HCC.


HEPATOBLASTOMA (HB) and hepatocellular carcinoma (HCC) are the most common liver tumors seen in children.1-2 Although these tumors have different epidemiologic and pathologic characteristics, children with primary liver malignancies have historically been treated similarly, and studies of the Pediatric Oncology Group (POG), the Children's Cancer Group (CCG), and others have typically used identical treatment for both HB and HCC.3-8 Children with HCC usually present at an older age with a heterogeneous group of tumors that often involve the liver multifocally and that may be associated with a number of different pre-existing liver diseases that may also influence surgical management.9 In contrast, the majority of children with HB are less than 3 years of age at diagnosis and more often have localized tumors without any underlying liver disease. Surgical resectability remains the foundation of curative therapy for both HB and HCC, but unfortunately, these tumors are typically resectable in at most one third (HCC) to one half (HB) of newly diagnosed cases.2,7,10 Chemotherapy has been shown to improve the survival of patients with HB tumors who have undergone an initial complete resection and may similarly benefit patients with HCC.7 In children with unresectable HB, chemotherapy has also been shown to be effective in enhancing the resectability of the primary lesion. Survival rates for children with HB who undergo a delayed complete resection are comparable with that of patients who have had a complete resection at diagnosis.4,10-14 However, unresected HCC remains largely unreponsive to chemotherapy and patients continue to have a very poor prognosis.

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Cisplatin (CDDP), doxorubicin (DOX), vincristine (VCR), and fluorouracil (5-FU) in different combinations have demonstrated clinical efficacy in the treatment of HB. In POG pilot study no. 8697 used CDDP, VCR, and 5-FU to treat children with HB and showed survival rates similar to that observed in a previous study from the CCG using CDDP and continuous-infusion DOX. In the Pediatric Intergroup Hepatoma Protocol INT-0098 (POG 8945/CCG 8881), patients with both HB and HCC were randomized to treatment regimens consisting of CDDP, VCR, and 5-FU (regimen A), or CDDP and continuous-infusion DOX (regimen B). The objectives of this study were to compare the surgical resectability, event-free survival (EFS), and toxicity for patients treated on the two different therapeutic regimens. The data on HB patients has recently been reported elsewhere. Herein, we report the clinical characteristics, prognostic factors, and outcome for a cohort of pediatric HCC patients treated with these regimens.

PATIENTS AND METHODS

Patients

Pediatric Intergroup Hepatoma Study INT-0098 (POG 8945/CCG 8881) was open from August 1989 to December 1992. Patients were eligible for study entry if they were less than 21 years of age at diagnosis and had previously untreated HB or HCC. This report involves only patients diagnosed with HCC. All protocols were approved by the National Cancer Institute as well as the individual institutional review boards of the participating POG- or CCG-affiliated institutions, and written informed consent was obtained for all patients before study entry.

The following stages of disease were determined by surgical criteria after the assessment of initial resectability as determined by the institutional surgeon in consultation with the treating oncologist and after either a surgical resection or biopsy was performed before the initiation of chemotherapy: stage I, complete gross resection with pathologically negative margins; stage II, gross total resection with microscopic residual disease at the margins of resection; stage III, gross total resection with nodal involvement or tumor spill, or gross residual intrahepatic disease after either incomplete resection or biopsy; 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 all patients to be entered onto study, and staging was also confirmed by review of institutional pathology and surgical reports.

Treatment

Patients with all stages of HCC were randomized to receive chemotherapy on regimens A or B, described below and shown in Fig 1. Each course of regimen A consisted of intravenous (IV) CDDP (90 mg/m², for patients ≥ 1 year of age and 3 mg/kg for patients < 1 year of age) administered over 6 hours followed by IV hydration on day 1 and VCR (1.5 mg/m², IV push) and 5-FU (600 mg/m² IV push) on day 2. Each course of regimen B consisted of CDDP (dose as above) administered over 6 hours followed by IV hydration for 4 hours and then continuous-infusion DOX (20 mg/m²/d for patients ≥ 1 year of age and 0.60 mg/kg for patients < 1 year of age) given for 96 consecutive hours. Patients were re-evaluated at the end of the initial chemotherapy phase of four cycles, and the number of subsequent cycles was dependent on the response to therapy (see below). Each cycle was given ≥ 3 weeks apart, depending on the recovery of peripheral neutrophil and platelet counts to ≥ 1,000 cells/µL and ≥ 100,000 cells/µL, respectively. Initial chemotherapy was delayed for at least 2 weeks for any patient in whom ≥ 50% of the liver was resected.

Patients with stage I HCC who had no evidence of disease, including normal alpha-fetoprotein (AFP) levels, after four cycles of chemotherapy were considered to be in complete remission, and were to enter follow-up with no further treatment. All other randomized patients who did not have progressive disease were eligible for postinduction surgery I. If the tumor, including metastatic foci, was completely resected, or if there was no evidence of tumor at postinduction surgery I, the patient was to receive an additional two cycles of the same chemotherapy as was given for the first four cycles. If the surgery was not attempted or the tumor was not completely resected, but either a partial response or
stable disease was confirmed, patients were to receive an additional four cycles of the same chemotherapy. Patients who received eight cycles of chemotherapy were eligible for postinduction surgery II, if deemed feasible. If the tumor was completely resected after eight cycles of chemotherapy, no further therapy was administered. Otherwise, if complete resection was not possible or if gross residual disease persisted, protocol therapy was considered to have failed to control the patient’s disease and other therapeutic options were considered.

**Evaluation of Response**

Physical examination, blood counts, serum AFP levels, and appropriate imaging studies, including computed tomography of the chest and abdomen, were performed before therapy. Subsequent exams and AFP assays were performed before every additional cycle of chemotherapy. Imaging studies were repeated after cycles 1, 3, 4, and 8, and then at 2, 4, 6, 12, 18, and 24 months after the completion of therapy.

Complete response (no evidence of disease) was defined as no evidence of tumor by physical examination and computed tomography scans or magnetic resonance imaging of the liver, and a normal AFP level for ≥ 4 weeks. Partial response was defined as a decrease of ≥ 50% in the sum of the products of the maximum perpendicular diameters of all measurable lesions lasting for 6 or more weeks, with no evidence of new lesions or progression in any lesion. Stable disease was defined as any response less than a partial response, without an increase in tumor size and without appearance of new lesions. For purposes of this manuscript, residual disease was defined as either a partial response or stable disease. Progressive disease was defined as the unequivocal increase of at least 25% in the size of any lesion, the appearance of new lesions, or an increasing AFP level.

**Toxicity of Treatment**

The individual incidents of various toxicities were graded on a scale of 1 to 4, according to National Cancer Institute guidelines. Limits for toxicity grades were dependent on both patient age and the particular organ system involved; the specific toxicity scales used in this study are available from the Children’s Oncology Group Operations Office on request. For patients with liver toxicity, DOX dosage was modified as described by Powsis,20 using elevated bilirubin and liver enzymes as criteria. For patients with elevated serum creatinine, CDDP was modified as follows: age less than 5 years or ≥ 5 years with serum creatinine levels more than 1.0 mg/dl and more than 1.2 mg/dl, respectively, creatinine clearance was obtained; CDDP was omitted for one cycle if clearance rates were less than 50% of normal; and CDDP was discontinued if clearance rates were decreased during any subsequent chemotherapy cycles. In cases of delays in therapy because of neutropenia, dosing of DOX and 5-FU was reduced by 25% (> 1-week delay) or 50% (≥ 2-week delay). If subsequent cycles of chemotherapy could be administered in 3 weeks, full dosing was resumed; otherwise, the 25% reduction was maintained. Further delays (more than 1 week) in therapy resulted in further dose reductions. An amendment to the protocol was made in May 1992 to allow the use of filgrastim (granulocyte colony-stimulating factor [G-CSF], 10 μg/kg/d, subcutaneously) in place of drug-dose reductions for patients who developed grade 3 or 4 neutropenia (absolute neutrophil count < 1,000 cells/μl). G-CSF was discontinued when the absolute neutrophil count recovered to ≥ 1,000 cells/μl for 2 consecutive days. If there was no benefit from G-CSF, DOX and 5-FU doses were reduced as described above. For patients treated with DOX (regimen B), cardiac function was evaluated by multiple gated acquisition scan or echocardiogram before the initiation of chemotherapy, before cycles 2, 4, and 6, and at the end of therapy. Audiology was to be performed before the initiation of therapy and after the fourth and eighth cycles.

**Statistical Design and Analysis**

**Study Design.** Patients were randomized after initial surgical staging, and randomization was stratified according to stage of disease. The study was designed to have 48 eligible patients with HCC randomized over a 3-year accrual period, with the last patient observed for at least 1.5 years. The primary outcome comparison between the two treatment regimens was risk for an adverse event. The equality of risk was to be assessed with a log-rank statistic stratified by stage of disease. We projected this design would have 80% power to detect a 1.8-fold decrease in risk for adverse events across all stages when using a two-sided test of size 0.05 for patients with HB. Analysis for patients with HCC was to be performed at the same time the analysis for patients with HB was performed. Interim monitoring was performed once after 18 months of accrual. A P value of .005 for the stratified log-rank test was required to identify the study for possible termination of accrual.

**Outcome Definitions.** Event-free survival (EFS) was defined as the risk from the date chemotherapy was started until evidence of an event (progressive disease, death, or diagnosis of a second malignant neoplasm) or last contact, whichever occurred first. Survival time was defined as the period from the date chemotherapy was started until death or last contact. 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.

Outcome of patients with stage III and IV disease was also analyzed with respect to the results of postinduction surgery I. For this purpose, patients were categorized as having the following: (1) surgery resulting in complete resection; (2) residual disease with or without surgical intervention; (3) refused surgery; or (4) no surgery because of lack of radiographic evidence of tumor. EFS from postinduction surgery I was determined from the date of surgery for those who had surgery and from day 94 (the median time of postinduction surgery after four cycles of chemotherapy) for all others (relevant date). Patients experiencing an event before the relevant date were excluded from this analysis.

**Analytic Methods.** Statistical analysis was conducted with data current to May 30, 1997. Life-table estimates were calculated using the Kaplan-Meier method, and the SD of the Kaplan-Meier estimate of the survivor function at selected points was calculated using Greenwood’s formula.17 Risk for adverse event and death was compared across therapies and groups of patients using the log-rank statistic. Estimates for relative risks and 95% confidence intervals (CIs) were calculated using a proportional hazards regression model with the relevant characteristic as the only variable.18 For treatment comparisons, outcome was assigned to the randomized treatment, regardless of the therapy received. Cumulative incidence was used to quantify the risk for failure for each of the individual types of adverse event. Estimates of the cumulative incidence were calculated as described by Gaynor et al.19 Qualitative patient characteristics, frequencies of various toxicities, and frequency of administration of total parental nutrition (TPN) were compared across regimens using Fisher’s exact test.20 Comparisons of the equality of median duration of hospitalization were performed using the Mann-Whitney test.21 Outcome across groups according to normal or elevated AFP at diagnosis was also compared. An initial AFP level was considered to be normal if it was less than 20 ng/mL.
Table 1. Clinical and Demographic Features at Diagnosis of Children With Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Regimen A [CCDP/5-FU/VOR] (n = 20)</th>
<th>Regimen B [CCDP/DOX] (n = 26)</th>
<th>Total (N = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>%</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>2</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>1-9 years</td>
<td>7</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td>≥ 10 years</td>
<td>11</td>
<td>55</td>
<td>15</td>
</tr>
<tr>
<td>Sex</td>
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<td></td>
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<td>11</td>
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</tr>
<tr>
<td>Female</td>
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<td>45</td>
<td>11</td>
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<td>Race</td>
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<td></td>
<td></td>
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<tr>
<td>White</td>
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<td>85</td>
<td>17</td>
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<tr>
<td>Hispanic</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Other*</td>
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<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>3</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Stage II</td>
<td>10</td>
<td>50</td>
<td>15</td>
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<tr>
<td>Stage IV</td>
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<td>35</td>
<td>6</td>
</tr>
<tr>
<td>AFP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20 ng/ml</td>
<td>6</td>
<td>32</td>
<td>8</td>
</tr>
<tr>
<td>≥ 20 ng/ml</td>
<td>13</td>
<td>68</td>
<td>16</td>
</tr>
<tr>
<td>Not assessable</td>
<td>1</td>
<td>-</td>
<td>2</td>
</tr>
</tbody>
</table>

* Two patients (4.3%) were Asian and three (6.5%) had unreported race.
† Three patients had their initial AFP level measured after surgical resection before the initiation of chemotherapy.

RESULTS

Patients

A total of 46 patients were diagnosed as having HCC and are the focus of this report. Among the 46 HCC patients, eight (17%) had stage I, zero (0%) had stage II, 25 (54%) had stage III, and 13 (28%) had stage IV disease. Twenty (43%) patients were randomized to regimen A, and 26 (57%) patients were randomized to regimen B.

The clinical and demographic characteristics, including age at diagnosis, sex, race, disease stage, and initial AFP level for HCC patients on regimens A and B are listed in Table 1. There were no statistical differences between regimens A and B in the distribution of any patient characteristics.

Pathology

Central histologic review resulted in some disagreement about the diagnosis in four patients (9%). One patient was diagnosed with HB by the institutional pathologist, but was subsequently agreed on to have HCC and was entered onto the study. In two cases, the distinction between HB and HCC carcinoma was difficult because of limited material for review after the initial biopsy. One additional case was diagnosed after central review with a malignant rhabdoid tumor. In all three of these cases, the final pathologic diagnosis of the treating institution was HCC, and the patients remained on study and are included in this analysis. Ten (22%) of the 46 cases were noted to have the fibrolamellar variant of HCC and will be the subject of a separate report.

Survival

For the entire cohort of 46 patients, EFS at 5 years was 19% (SD = 6%)(Fig 2). Patients with stage I disease experienced greater EFS compared with patients with stage III or stage IV disease (P < .0001, Fig 3). The 5-year EFS for patients with stages I, III, and IV disease were 88% (SD = 12%), 8% (SD = 5%), and 0%, respectively. One-year

![Fig 2. EFS for 46 children with hepatocellular carcinoma (inset: number of patients remaining in follow-up at indicated times).](image-url)
EFS for stage IV patients was 8% (SD = 7%). Only two of the 25 stage III patients have not experienced an event: one patient who had an orthotopic liver transplantation and one patient who had an initial complete resection with a pathologically involved lymph node. Overall survival was similar to EFS for each disease stage, with 5-year estimates of 88% (SD = 12%), 23% (SD = 9%), and 10% (SD = 9%), for stage I, stage III, and stage IV, respectively (P = .0053). The median follow-up time for event-free survivors (n = 9) was 4.3 years (range, 1.8 to 6.4 years). No events occurred more than 2 years after study entry.

Four advanced-stage patients with progressive/recurrent disease demonstrated prolonged survival; one patient was alive 6 years after an orthotopic liver transplantation, one patient was alive 3.5 years after receiving chemotherapy (carboplatin, DOX, etoposide, and ifosfamide), and eventual complete tumor resection, one patient was alive 3.5 years after receiving additional chemotherapy after a recurrence after no evidence of disease had been found at second look surgery, and one patient was alive 5 years after complete resection of the primary tumor and resolution of metastatic pulmonary disease with multiple subsequent thoracotomies for recurrent pulmonary disease.

EFS according to treatment for all patients randomized to regimens A and B was not significantly different, with 5-year estimates of 20% (SD = 9%) and 19% (SD = 8%), respectively (P = .78; Fig 4) and a relative risk for regimen B versus regimen A of 1.2 (95% CI, 0.60 to 2.3). Similarly, overall 5-year survival was not significantly different for regimens A and B, with estimates of 38% (SD = 11%) and 25% (SD = 9%), respectively (P = .80), and a relative risk for regimen B versus regimen A of 1.10 (95% CI, 0.54 to 2.22).

There was no difference in EFS for patients with stage III and IV HCC combined on regimens A and B (P = .20; relative risk regimen B vs regimen A, 1.6; 95% CI, 0.81 to 3.2).

Thirty-five randomized patients (15 on regimen A and 20 on regimen B) experienced disease progression as their first adverse event. At 4 years of follow-up, the cumulative incidences for experiencing an event were 75% and 78% for regimens A and B, respectively (P = .86). The cumulative incidences for death as a first event after 4 years of follow-up were 5.0% and 3.9% for patients on regimens A and B, respectively (P = .86). There were no second malignancies diagnosed in this cohort of patients.

Outcomes were also examined for the combined group of stage III and IV patients with respect to results of postinduction surgery I. One-year EFS for the two patients who had complete resections at postinduction surgery I (50%, SD = 35%) was not statistically significantly better than that of the 12 patients who had residual disease (25%, SD = 13%), or the two patients who had no evidence of disease after four cycles of chemotherapy and did not undergo postinduction surgery I (50%, SD = 35%) (P = .71).

Forty-three of the 46 patients had a serum AFP level performed at study entry at the time that the initial surgery or biopsy was performed. The other three patients had their initial AFP level measured at the initiation of chemotherapy, which may have occurred several weeks after surgery, and so were excluded from the analysis. Elevated levels (≥ 20 ng/mL) were detected in 29 (67%) of the 43 assessable patients. Three (50%) of the six assessable patients with stage I disease had elevated AFP levels at diagnosis, whereas 26 (70%) of the 37 assessable patients with advanced disease had initially elevated AFP levels. A trend towards improved EFS was seen for the 14 children with a
normal AFP level at diagnosis compared with the 29 patients with elevated levels, with 5-year EFS estimates of 29% (SD = 12%) and 10% (SD = 6%), respectively ($P = .09$, Fig 5).

**Surgical Management**

All eight stage I patients had complete or gross total resections at the initial surgery. Therefore, these patients were not considered to be eligible for postinduction surgery I because there was no evidence of disease at that time. Surgical management for the 16 patients with stage III disease and the four patients with stage IV who were considered to be eligible for postinduction surgery I is shown in Table 2. Nine (36%) of 25 stage III patients and nine (69%) of 13 stage IV patients were considered ineligible for postinduction surgery I because they had experienced events. The majority of patients did not undergo postinduction surgery I because of the presence of unresectable residual disease. In addition, two stage III patients suspected to have residual disease were biopsied at postinduction surgery I, and no residual tumor was identified. Both of these patients have relapsed, one of whom remains alive after the administration of alternative chemotherapy (switched to regimen B).

Two stage III patients underwent postinduction surgery II after eight cycles of chemotherapy. One of these patients had a second partial resection after a partial resection at postinduction surgery I but ultimately did not survive. The other patient did not undergo the scheduled postinduction surgery I, but after eight cycles of chemotherapy, tumor resection and liver transplantation was attempted but not performed because of visible tumor on the exterior surface of the liver. Eleven eligible stage III and two eligible stage IV patients did not undergo surgery at any point in therapy.

**Toxicity**

Overall toxicities, including leukopenia ($P = .006$), neutropenia, ($P = .07$), thrombocytopenia ($P = .005$), and stomatitis ($P = .014$) were reported more frequently in patients receiving regimen B compared with regimen A (Table 3). The incidence of infection was similar for both regimens. Death without evidence of disease progression was reported as the first event for one patient on each regimen; the death on regimen A occurred 7 months after a liver transplantation was performed off-protocol, and the death on regimen B was a result of *Pseudomonas aeruginosa* sepsis.

The burden of therapy, as measured by the cumulative duration of hospitalization and the frequency of administration of TPN during the initial four cycles of chemotherapy, was greater for regimen B compared with regimen A. The median cumulative duration of hospitalization during the first four cycles of therapy was longer for patients on regimen B (median, 27 days; range, 3 to 75 days) compared with regimen A (median, 18 days; range, 2 to 86 days), respectively ($P = .06$). Among patients with available data, a total of 16 (64%) of 25 patients on regimen B, compared with

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**Table 2. Outcome of Planned Postinduction Surgery I for Eligible Patients With Stage III and IV Disease**

<table>
<thead>
<tr>
<th></th>
<th>Stage III (n = 16)</th>
<th>Stage IV (n = 4)</th>
<th>Total (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery with complete resection</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Residual disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery with partial resection</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Biopsy only</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>No surgery because of presence of residual disease</td>
<td>7</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Refused surgery</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>No surgery because of lack of evidence of disease</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>4</td>
<td>20</td>
</tr>
</tbody>
</table>
Table 3. Toxicities Resulting From Treatment of Children With Hepatocellular Carcinoma According to Randomized Chemotherapy Regimen

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Regimen A (CDDP/5-FU/VCR) [n = 20]</th>
<th>Regimen B (CDDP/DOX) [n = 26]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>%</td>
</tr>
<tr>
<td>Neutropenia†</td>
<td>7</td>
<td>35</td>
</tr>
<tr>
<td>Thrombocytopenia†</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Anemia†</td>
<td>3</td>
<td>15</td>
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<tr>
<td>Stomatitis</td>
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<td>0</td>
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<tr>
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<tr>
<td>Arhythmia</td>
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<tr>
<td>Hypotension</td>
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<td></td>
</tr>
<tr>
<td>Renal†</td>
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<tr>
<td>Blood urea nitrogen</td>
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<tr>
<td>Creatinine clearance</td>
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<td>Hematuria</td>
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<td></td>
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<tr>
<td>Proteinuria</td>
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<td>Diastolic blood pressure</td>
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<tr>
<td>Sepsis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Central venous catheter infection</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>

*Fisher's exact test.
†Neutropenia, absolute neutrophil count < 1,000 cells/µl; thrombocytopenia, platelet count < 50,000 cells/µl; anemia, < 8 g/dl.
‡Blood urea nitrogen ≥ 60 mg/dl; creatinine clearance ≤ 49% of normal; gross hematuria with clots or requiring transfusion. Some patients exhibited multiple symptoms.

nine (47%) of 19 patients on regimen A received TPN at least once during the first four cycles of chemotherapy (P = .36).

**DISCUSSION**

This report demonstrates that chemotherapeutic regimens containing either CDDP, VCR, and 5-FU or CDDP and continuous-infusion DOX were not effective as given in this study in controlling residual or metastatic disease in pediatric patients with HCC. A total of 46 patients with HCC accrued over a 3-year period had 5-year EFS of 19% (SD = 6%). Similar to previous studies, only eight (17%) of the 46 patients were initially amenable to surgical resection. These stage I patients demonstrated excellent survival after postoperative chemotherapy with either regimen, but the DOX-containing regimen was associated with a greater degree of toxicity. Whether or not there is a true advantage to the use of adjuvant chemotherapy in those children who present with stage I disease is unclear. This question needs to be addressed in a randomized prospective trial because a review of the literature reveals that some of these initially resectable patients have fared well without any additional therapy after surgical resection.

In contrast, 18 (47%) of 38 patients with advanced-stage disease had an event before postinduction surgery I, and tumor resection was only possible in two (10%) of the remaining 20 children after the administration of chemotherapy. Overall survival for the group of patients with unresectable disease was extremely poor. Importantly, however, the two patients who did undergo delayed complete resection experienced prolonged survival, although both ultimately relapsed and died 20 and 63 months from diagnosis. In addition, four other advanced-stage patients with progressive/recurrent disease demonstrated prolonged survival after alternative therapies. These data further demonstrate the importance of surgical resection for this disease and suggests that novel strategies that render HCC tumors resectable need to be thoughtfully investigated.

Patients were also analyzed to investigate whether initial serum AFP levels were predictive of outcome. A trend towards improved EFS was observed in children who had normal AFP levels at diagnosis. This finding may be related to the higher proportion of children with localized disease who had normal AFP levels at diagnosis. Multivariate analysis could not be meaningfully performed because of small patient numbers. Whether or not initial AFP levels or the rate of decline can predict outcome in HCC similarly to what has been observed in HB remains to be seen. The prognostic relevance of AFP levels will need to be further evaluated and may not become apparent until a significant number of advanced-stage patients can be effectively treated.

Outcomes for these HCC patients contrast sharply with that seen in the children with HB who were treated on the same intergroup study. Five-year EFS for patients with stage I, III, and IV HB were 91% (SD = 4), 64% (SD = 5),
and 25% (SD = 7), respectively, compared with 88% (SD = 12), 8% (SD = 5), and 0% for patients with stage I, III, and IV HCC. The majority of children (forty of 79) with stage III HB responded to therapy and were rendered surgically resectable after treatment with either of the regimens compared with only one of 16 eligible stage III HCC patients. Unfortunately, patients with metastatic disease at diagnosis fared poorly regardless of histology.

This report is the largest reported prospective trial using a uniform treatment approach for children with HCC. Previous anecdotal reports in children had suggested that some HCC patients could be successfully treated with chemotherapy. Several studies from the International Society of Pediatric Oncology (SIOP) have treated children with HCC preoperatively with CDDP and continuous-infusion DOX similar to regimen B. Ninane et al published their results of a pilot SIOP study that treated three HCC patients, without staging information available, with one patient demonstrating a very good partial response and one patient having a partial response. All three patients subsequently underwent complete excision and were alive with short follow-up. Guglielmi et al also published a pilot study with slightly lower doses of CDDP and DOX and observed minimal response to preoperative chemotherapy in two HCC patients. More recently, Plaschkes et al presented preliminary data using the same chemotherapeutic approach with a larger group of forty HCC patients and observed any tumor shrinkage in 43% of 30 assessable patients with a 2-year overall survival of 40%. Although the use of a different surgical approach in the above studies limits the ability to compare the results with those reported here, the results from the SIOP studies are equally disappointing.

Alternative local ablative approaches including chemoembolization, intra-arterial chemotherapy, radiofrequency ablation, percutaneous ethanol injection, and cryosurgery have demonstrated some benefit in appropriately selected adult patients with HCC. Reports of these techniques applied to children are somewhat more limited. A recent report from Malagolowkin et al described their single-institution experience with arterial chemoembolization. A total of 11 patients, including three with HCC and six with HB, were treated over approximately a 7-year period. Two of the three HCC patients were rendered resectable, including one patient that had a complete resection and has been disease-free for over 6 years. The second patient had microscopic residual disease after a delayed resection that prompted two more courses of therapy. This patient survived in remission for 3.5 years but succumbed to progression of the underlying liver disease with no clinical evidence of tumor. Ultimately, however, the rarity of HCC in the pediatric population suggests that the application in national cooperative group trials of novel, local ablative techniques would be performed so infrequently on an institutional basis that it would make it difficult to assess their actual therapeutic efficacy and could result in significant treatment-associated morbidity and mortality.

The use of orthotopic liver transplantation as another therapeutic option in HCC remains controversial. Mixed results have been observed in adult patients, which may be partially attributable to poor patient selection criteria. Reports of transplantation in primary pediatric hepatic malignancies are much more limited but have been performed with some measure of success. In this series, 18 (47%) of 38 patients with advanced disease progressed before postinduction surgery I. Therefore, it would seem most appropriate to consider liver transplantation in unresectable cases as soon as possible after diagnosis, before the dissemination of disease during ineffective chemotherapy administration.

The use of novel chemotherapeutic agents as well as other classes of drugs appears indicated to improve the dismal survival of this cohort of patients. Finally, this intergroup study definitively demonstrates the dramatic difference in clinical behavior between HCC and HB and strongly indicates that further therapeutic studies for children with HCC with the incorporation of alternative treatment modalities need to be formulated independently of HB.

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APPENDIX

The appendix of participating investigators is available online at www.jco.org.

REFERENCES

PEDIATRIC HEPATOCELLULAR CARCINOMA


