Clinical heterogeneity of pediatric hepatocellular carcinoma

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Abstract

Background: Hepatocellular carcinoma (HCC) is often a chemoresistant neoplasm with a poor prognosis. Pediatric HCC may reflect unique biological and clinical heterogeneity.

Procedure: An IRB-approved retrospective institutional review of patients with HCC treated between 2004 and 2015 was undertaken. Clinical, radiographic, and histologic data were collected from all patients.

Results: Thirty-two patients with HCC, median age 11.5 years (range 1-20) were identified. Seventeen patients had a genetic or anatomic predisposition. Histology was conventional HCC (25) and fibrolamellar HCC (7). Evans staging was 1 (12); 2 (1); 3 (10); 4 (9). Sixteen patients underwent resection at diagnosis and five patients after neoadjuvant chemotherapy. Surgical procedures included liver transplantation (LT, 11), hemihepatectomy (9), and segmentectomy (1). Eighteen patients had medical therapy (13 neoadjuvant, 5 adjuvant). Most common initial medical therapy included sorafenib alone (7) and cisplatin/doxorubicin-based therapy (8). Overall, 14 (43.8%) patients survived with a median follow-up of 58.8 months (range 26.5-157.6). Cause of death was most often linked to lack of primary tumor surgery (11). Of the survivors, Evans stage was 1 (11), 2 (1), and 3 (2, both treated with LT). Four of 18 patients (22%) who received medical therapy, 8 of 17 patients with a predisposition (47%), and 14 of 21 patients (66%) who underwent surgery remain alive.

Conclusions: Genetic and anatomic predisposing conditions were seen in over half of this cohort. Evans stage 1 or 2 disease was linked to improved survival. LT trended toward improved survival. Use of known chemotherapy agents may benefit a smaller group of pediatric HCC and warrants formal prospective study through cooperative group trials.

KEYWORDS

chemotherapy, hepatocellular carcinoma, heterogeneity, liver transplantation, pediatric, sorafenib

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is an aggressive, chemoresistant neoplasm. HCC survival depends on surgical resection, although only 30% of pediatric patients are resectable at diagnosis.1,2 Adjuvant chemotherapy has been studied in various cooperative group trials, with minimal success.3,4 Response rates to chemotherapy are roughly 20% in adults and 40% in children, suggesting discrepant biologically driven chemoresistance.5 Biologically diverse molecular pathways drive carcinogenesis in HCC,6 the strongest example being...
fibrolamellar carcinoma that is associated with a specific molecular signature.\(^7\) Notable biological differences between pediatric and adult HCC include risk factors and presence of background liver disease.\(^5\)-\(^8\) Unfortunately, despite slightly better chemosensitivity, the 5-year overall survival in children remains low at 13\%-\(28\%\),\(^8\)-\(^10\).

No large series that define pediatric and adolescent HCC subtype and clinical heterogeneity exist in the literature. A recent publication did comment on the molecular heterogeneity of pediatric HCC by genetically profiling 15 pediatric tumors.\(^11\) Presence of background liver disease, surgical resectability, and response to medical therapy varies between patients. The purpose of this study was to retrospectively characterize HCC in children and adolescents treated at a single institution, to better characterize pediatric HCC heterogeneity.

2 | METHODS

Following institutional review board approval, a retrospective analysis was performed of patients with HCC \(< 21\) years of age treated at our institution between January 1, 2004 and December 31, 2015. Demographics, preexisting conditions, treatment, and outcomes were reviewed. Abernathy malformation was defined as a congenital portosystemic shunt with the absence of a portal vein. The histopathology, radiographic, and surgical data were reviewed by a pathologist (AG), radiologist (AJT), and surgeons (AB, JDN, MA, and GT).

Histopathology was classified according to WHO Classification of Tumors of the Digestive System.\(^12\) Computed tomography scan and/or magnetic resonance imaging obtained at diagnosis were reviewed to determine the size and the number of liver lesions and the PRETEXT score, based on Children's Oncology Group (COG) modifications to the 2005 PRETEXT guidelines.\(^13\) Evans surgical staging\(^9\) and TNM staging (as per the American Joint Committee on Cancer) were obtained.\(^14\) The Child-Pugh,\(^15\) pediatric end-stage liver disease (PELD) (for children \(< 12\) years),\(^16\) and model for end-stage liver disease (MELD) scores (for children \(\geq 12\) years)\(^17\) were collected. Imaging response were classified as complete response (CR) (100\%), partial response (PR) (\(> 30\%\) but less than CR), progressive disease (PD) (\(\geq 20\%\) increase in tumor size), and stable disease (SD) (not qualifying for PR or PD). Second-line therapy and salvage therapy were defined as subsequent therapy for SD or PD or relapsed disease, respectively.

Kaplan-Meier curves were created using GraphPad Prism. A log-rank (Mantel-Cox) test was used to calculate P-values.

3 | RESULTS

3.1 | Patient characteristics

From 2004 to 2015, 32 patients with HCC were treated at our institution: median age was 11.5 years (range 1-20); 18 patients (56\%) were females; and 24 (75\%) were Caucasians (Table 1). Preexisting conditions were present in 53\%.

**TABLE 1** Demographics and presenting features

| Number of patients | 32 |
|--------------------|----|
| Age                |     |
| 1-6 y              | 6  |
| 6-12 y             | 10 |
| \(> 12\) y          | 16 |
| Gender             |     |
| Male               | 14 |
| Female             | 18 |
| Ethnicity          |     |
| Caucasian          | 24 |
| African American   | 3  |
| Middle Eastern     | 2  |
| Hispanic           | 1  |
| Unknown            | 2  |
| Evans stage        |     |
| 1                  | 12 |
| 2                  | 1  |
| 3                  | 10 |
| 4                  | 9  |
| Histology          |     |
| Conventional       | 25 |
| Fibrolamellar      | 7  |
| Cirrhosis present  | 10 |
| Preexisting conditions |   |
| Alagille           | 3  |
| PFIC-2             | 2  |
| A1AT               | 1  |
| Wilson disease     | 1  |
| Fanconi anemia     | 2  |
| Cryptogenic cirrhosis | 2  |
| Fatty liver disease| 1  |
| Fontan             | 1  |
| Abernethy malformation | 2  |
| Portal venous thrombosis | 2  |

Abbreviations: A1AT, alpha-1 antitrypsin; PFIC-2, progressive familial intrahepatic cholestasis type 2.

3.2 | Histopathology

The primary site of disease was the right lobe (17), left lobe (4), dome (1), and bilobar (10). Histology included early HCC (2), well-differentiated (Wd) HCC (15), moderately differentiated HCC (8), and fibrolamellar HCC (7). Cirrhosis was present in 10 patients, all of whom had prior liver disease, including one with fibrolamellar HCC secondary to a Fontan-related circulation/fibrosis. Of those that underwent primary tumor surgery (16), 6 patients had solitary tumors and 10 had multifocal disease. The largest tumor by pathology ranged from 0.5 to 15.2 cm (median 7 cm).

3.3 | Staging and risk factors

Evans stage was 1 (12), 2 (1), 3 (10), and 4 (9). PRETEXT stage was 1 (6), 2 (15), 3 (3), and 4 (8). Evans stage in those with versus without a predisposition were 1 (8 vs 4), 2 (0 vs 1), 3 (6 vs 4), and 4 (3 vs 6). All patients tested negative for Hepatitis B and C viruses. The Child-Pugh score was as follows: Class A (9), Class B (12), and Class C (1). MELD
TABLE 2  Characteristics of patients with HCC treated with liver transplantation

| Patient (n = 11) | Clinical and pathologic data | Milan criteria |
|-----------------|-----------------------------|---------------|
|                 | Clinical and pathologic data |               |
|                 | Evens stage | TMN stage | Preexisting liver disease | Cirrhosis | One lesion with diameter ≤ 5 cm | Up to three lesions each with diameter ≤ 3 cm | Vascular or extra-hepatic involvement | Exceeded Milan criteria | Reason for exceeding Milan criteria | Survival Outcome |
|                 |                    |             |                          |           |                            |                                  |                           |                         |                             |                   |
| 1               |                       |             | T2N0Mx                  | PFIC-2    | Y                           | +                                  | Absent                       | No                         | -                             | Alive             |
| 2               |                       |             | T1N0Mx                  | A1AT      | Y                           | –                                  | N/a                          | Absent                     | Yes                           | Solitary lesion > 5 cm   | Alive             |
| 3               |                       |             | T1N0Mx                  | PFIC-2    | Y                           | +                                  | N/a                          | Absent                     | No                            | Alive             |
| 4               |                       |             | T2N0Mx                  | Abernethy | N                           | –                                  | Absent                       | Yes                        | > 3 foci with largest focus > 3 cm | Alive             |
| 5               |                       |             | T2N0Mx                  | Alagille  | Y                           | –                                  | Absent                       | Yes                        | > 3 foci with largest focus > 3 cm | Alive             |
| 6               |                       |             | T3aN0Mx                 | Mesocaval shunt, PVT | N/a                                   | –                                  | Absent                       | Yes                        | > 3 foci with largest focus > 3 cm | Alive             |
| 7               |                       |             | T3aN0Mx                 | Mesocaval shunt, PVT | N/a                                   | –                                  | Absent                       | Yes                        | > 3 foci with largest focus > 3 cm | Alive             |
| 8               |                       |             | T2N0Mx                  | Alagille  | Y                           | +                                  | N/a                          | Absent                     | No                            | Dead               |
| 9               |                       |             | T3aN0Mx                 | –         | N                           | –                                  | Absent                       | Yes                        | > 3 foci with largest focus > 3 cm | Alive             |
| 10              |                       |             | T3aN0Mx                 | –         | N                           | –                                  | Absent                       | Yes                        | > 3 foci with largest focus > 3 cm | Alive             |
| 11              |                       |             | T2N0Mx                  | Alagille  | Y                           | +                                  | Absent                       | No                         | -                             | DOD               |

Abbreviations: A1AT, alpha-1 antitrypsin; DOD, died of disease; HCC, hepatocellular carcinoma; PFIC-2, progressive familial intrahepatic cholestasis type 2; PVT, portal vein thrombosis; Y, yes; N, no; N/a, not applicable; cm, centimeter.

a Patients diagnosed with HCC post-LT.
b Patient died of complications from dialysis.
c Patient relapsed in lung and abdomen.

score ranged from 6 to 15 (median 10); PELD score ranged from 0 to 47 (median 10).

3.4 Surgical treatment

Sixteen patients underwent primary surgical resection and five after neoadjuvant chemotherapy. Surgery included liver transplantation (LT, 11), hemihepatectomy (9), and segmentectomy (1). Nine had a conventional resection and were either PRETEXT I (4) or II (5). Eight had negative parenchymal margins, however three had either metastatic lung disease, regional lymph node disease, or intrabiliary tract and lymphovascular invasion. Other local control treatments included Yttrium-90 radioembolization (4), radiofrequency ablation (3), and abdominal radiation (1). Yttrium-90 radioembolization was utilized in patients with SD after chemotherapy prior to proceeding with additional chemotherapy. Radiofrequency ablation was performed at the time of biopsy in two patients and at the time of resection in another, due to concerns for margin status. One patient with multifocal disease received 50 Gy of palliative radiation as a bridge to phase I clinical trials. Five of nine patients did not receive postoperative adjuvant therapy (all Evans stage 1 cases) and are alive as previously reported.18

Five patients who underwent delayed surgery (conventional (1); LT (4)) had Evans stage 3 disease and were PRETEXT II (3) or IV (d2). Of the remaining 11 patients who did not have surgery performed, Evans stage was 3 (3) and 4 (8). Two patients with stage 4 disease had local control of their metastatic disease with thoracoscopic lung nodule resections; both progressed in the lung and liver and died of disease.

Of the 11 patients who underwent LT (Table 2), 4 had end-stage liver disease due to a preexisting condition, and 3 had anatomic predispositions (2 suffering from portal hypertension and variceal bleeding; 1 had previously undergone a right hemihepatectomy for an adenoma). These latter three patients had previous biopsies showing a WD hepatocellular neoplasm, confirmed to have HCC in the explants. Four patients with Evans stage 3 disease had a delayed LT, including two with the Alagille syndrome and two with de novo HCC. One patient with the Alagille syndrome received 2 weeks of oral chemotherapy, discontinued due to toxicity. The other patient with the Alagille syndrome had an SD with neoadjuvant chemotherapy. Both patients with de novo HCC had a PR with chemotherapy prior to LT and remain alive.
| Patient | Age | Stage | Preexisting disease | Histology | Neoadjuvant chemo | Upfront surgery | Parenchymal margins/LN status | Adjuvant chemo | Metastectomy | Salvage therapy | Outcome |
|---------|-----|-------|---------------------|-----------|------------------|----------------|-----------------------------|----------------|--------------|----------------|---------|
| 1       | 18  | 1     | No                  | WD        | N/a              | R hemi-hepatectomy | −/−                  | Cis/5-FU × 2 cycles | −             | No           | Alive         |
| 2       | 17  | 2     | No                  | FL        | N/a              | R hepatectomy      | −/−                  | Sorafenib × 6 cycles | −             | No           | Alive         |
| 3       | 15  | 3     | No                  | Md        | N/a              | L hemi-hepatectomy | +/−                  | Sorafenib¹      | −             | No           | Dead         |
| 4       | 5   | 4     | No                  | Md        | N/a              | R hepatectomy      | −/+                  | Cis/Dox + sorafenib ×ur 6 cycles | Yes          | Gem/Ox       | Dead         |
| 5       | 11  | 3     | No                  | FL        | N/a              | R hepatectomy      | −/+                  | Cis/Dox + sorafenib × 7 cycles; sorafenib alone × 4 cycles | −            | JX-594, IMC-A12 + temsirolimus, erlotinib + avastin, Gem/Ox | Dead       |
| 6       | 9   | 3     | Alagille            | WD        | Sorafenib × 2 weeks | SD                | LT                | No              | −            | No           | Dead¹        |
| 7       | 12  | 3     | No                  | WD        | C5V × 4 cycles   | PR                | LT                | C5D × 2 cycles, sorafenib¹ | −            | No           | Alive        |
| 8       | 6   | 4     | No                  | WD        | VI × 2 cycles, C5VD × 2 cycles | PD | No              | −            | Yes          | No           | DOD          |
| 9       | 15  | 4     | Fontan              | FL        | Sorafenib × 1 week | PD | No              | −            | No           | No           | DOD          |
| 10      | 11  | 4     | No                  | WD        | C5D × 2 cycles   | SD                | No              | −            | No           | ICE, Gem/Doce, sorafenib | DOD        |
| 11      | 17  | 4     | No                  | FL        | Cis/Dox × 2 cycles | SD | No              | −            | No           | Gem/Ox, Gem, sorafenib, Cyclo/Topo crizotinib, capecitabine, everolimus | DOD        |
| 12      | 7   | 3     | No                  | Md        | C5VD × 2 cycles  | PR                | LT                | C5VD × 2 cycles | −             | No           | Alive        |
| 13      | 3   | 3     | Alagille            | Md        | Cis/5-FU × 2 cycles | SD | LT                | −            | PIAF, Gem/Ox | DOD          |
| 14      | 11  | 3     | Fanconi Anemia      | WD¹        | Sorafenib²      | PD | No              | −            | No           | No           | DOD          |
| 15      | 13  | 4     | No                  | FL        | Sorafenib × 10 cycles | PD | No              | −            | No           | No           | DOD          |

(Continues)
TABLE 3 (Continued)

| Patient | Age | Stage | Preexisting disease | Histology | Neoadjuvant chemo | Upfront surgery | Parenchymal margins/LN status | Adjuvant chemo | Metastectomy | Salvage therapy | Outcome |
|---------|-----|-------|---------------------|-----------|------------------|----------------|-------------------------------|----------------|--------------|----------------|---------|
| 16      | 16  | 3     | No                  | FL        | PIAF × 3 cycles  | SD             | L hepatectomy                  | Sorafenib × 3 cycles | –            | c-Met/ALK inhibitor, VITAC | DOD     |
| 17      | 17  | 4     | No                  | Md        | Sorafenib × 8 cycles | PD             | No                            | –             | No           | JX-594, Gem/Ox | DOD     |

Note. Unresectable disease at diagnosis.

Abbreviations: Cis/5-FU, cisplatin and 5-flourouracil; Cis/Dox, cisplatin and doxorubicin; C5V, cisplatin, 5-flurouracil, and vincristine; C5VD, cisplatin, 5-FU, vincristine, and doxorubicin; Cyclo/Topo, cyclophosphamide and topotecan; DOD, died of disease; FL, fibrolamellar; Gem/Doce, gemcitabine and docetaxel; Gem/Ox, gemcitabine and oxaliplatin; ICE, ifosfamide, carboplatin, and etoposide; IMC-A12, anti-insulin-like growth factor-I receptor monoclonal antibody; JX-594, Pexa-Vec (oncolytic virus); LN, lymph node; LVI, lymphovascular invasion; Md, moderately differentiated; PD, progressive disease; PIAF, cisplatin, interferon α-2b, doxorubicin, and fluorouracil; SD, stable disease; VI, vincristine and irinotecan; VITAC, vincristine, irinotecan, temozolomide, bevacizumab; Wd, well differentiated.

*Patient also had chronic GVHD of the liver.
*Duration of sorafenib treatment unknown.
*Cisplatin was discontinued after the first two cycles due to ototoxicity.
*Died from dialysis complication.

Seven of the 11 patients who underwent LT exceeded Milan criteria (MC) (Table 2). One patient had a solitary lesion >5 cm and six had more than three foci with the largest being >3 cm. The rationale to transplant outside of MC was due to concern for impending liver failure or complications from preexisting liver disease as detailed above.

3.5 | Medical treatment

Five patients received adjuvant chemotherapy and 13 received neoadjuvant chemotherapy or chemotherapy alone (Table 3). Common upfront medical therapy was sorafenib alone (7) and a cisplatin/doxorubicin-based regimen (8; 3 with concurrent sorafenib). Three patients discontinued sorafenib due to rash (3) and pancreatitis (1). Other platinum-based regimens used upfront included cisplatin and 5-fluorouracil (Cis/5-FU; 2), cisplatin, 5-FU, and vincristine (C5V; 1), gemcitabine/oxaliplatin (Gem/Ox; 1) and cisplatin, interferon, doxorubicin, and fluorouracil (PIAF; 1). Of note, one patient with Fanconi anemia required reduced-intensity conditioning allogeneic stem cell transplantation for myelodysplastic syndrome 2 months after upfront HCC tumor resection and subsequently died of transplant-related complications. This patient did not receive HCC-directed medical therapy.

Four patients received second- and subsequent-line chemotherapy, most commonly a gemcitabine-based regimen (4) or sorafenib (2). One patient received ifosfamide, carboplatin, and etoposide (ICE; 1) and one patient was treated on a phase I trial with intratumoral injection of the oncolytic virus JX-594. Three patients received salvage therapy after relapse, including Gem/Ox (2), temsirolimus (1), VITAC (vincristine, irinotecan, temsirolimus, bevazcumab; 1). Two of these patients were also treated on phase I trials including crizotinib (1); JX-594 (1); IMC-A12, a human IgG1 monoclonal antibody to the insulin-like growth factor receptor (1). Two patients with HCC in the setting of cryptogenic cirrhosis did not receive any therapy due to poor clinical status and died of disease.

3.6 | Outcomes

Overall, 14 patients (43.8%) survived (Figure 1; median follow-up of 58.8 months (range 26.5–157.6)). Cause of death for the other 18 patients were PD (12—primary surgery not performed (11), subtotal resection (1)), relapse (4), Fanconi bone marrow transplant complication (1), and dialysis complication (1). Of the survivors, Evans stage was 1 (11), 2 (1), and 3 (2), with a statistically significant difference in overall survival in Evans stage 1 to 2 disease compared to Evans stage 3 or 4 (Figure 2A; P < 0.0001). There was no difference in median survival between those with PRETEXT I/II disease (35.9 months) versus PRETEXT III/IV disease (20.3 months) (Figure 2B; P > 0.43). There was also no difference in median survival based on age <15 years (35.9 months) compared to ≥15 years (20.1 months) (Figure 2C; P > 0.22). Of the 17 patients with preexisting liver disease, 8 (47%) are alive (Figure 2D). Causes of death for the remaining nine patients were nononcologic issues (2), progression without any therapy (2), progression despite therapy (4), and relapse after medical therapy.
FIGURE 2  Other Outcome measures in HCC cohort. (A) Overall survival based on Evans stage. Evans stage 1 and 2 patients had significantly improved survival compared to stages 3 and 4 (P < 0.0001). (B) Overall survival based on PRETEXT. There was no difference in survival between PRETEXT I/II and III/IV (P > 0.43). (C) Overall survival based on age. Patients 15+ years of age had slightly worse outcomes compared to younger patients, although this was not statistically significant (P > 0.25). (D) Overall survival based on genetic predisposition. Patients with preexisting liver disease had no difference in outcome compared to those with no genetic or anatomic predisposition (P > 0.98). (E) Overall survival based on histology. There was no difference between outcomes for conventional versus fibrolamellar HCC (P > 0.41). (F) Overall survival based on surgical therapy. There was a trend to improved survival for patients treated with liver transplantation compared to conventional resection (P > 0.08). (G) Overall survival based on Evans stage and surgical modality. Stage was the most prognostic factor, however in patients with higher stage disease (Evans stages 3 and 4), liver transplantation lead to better survival compared to conventional resection (P < 0.0012).
and LT (1). Two of 7 patients (28%) with fibrolamellar HCC and 12 of 25 patients (48%) with conventional HCC remain alive (Figure 2E; $P > 0.41$).

Only 4 of 18 patients (22%) who received medical therapy survived. There was a trend to improved survival in patients who underwent LT (9/11; 82%) versus conventional resection (5/10; 50%), although not statistically significant (Figure 2F; $P > 0.08$). Patients with advanced stage disease who underwent LT did better than those treated with conventional resection (Figure 1G; $P < 0.0012$).

### 4 DISCUSSION

HCC is an aggressive neoplasm with age-dependent differences in epidemiology, baseline liver function, histology, and response to therapy, suggesting biological differences. A recent publication on the genomic heterogeneity of pediatric HCC did note a molecularly distinct pattern of 15 sequenced tumors. $^{11}$ Moreover, there is clinical heterogeneity of HCC comparing younger children to adolescents and young adults, thus far not well described.

Both genetic and anatomic predispositions to HCC are seen in pediatric patients, especially younger children. $^{19-22}$ While previous data suggested that 30% of pediatric HCC in the Western world is associated with a predisposition, $^{19}$ 53% of our cohort had a genetic or anatomic predisposition, reflective of data from a large, tertiary care center. There was no difference in survival between patients with a predisposition versus those without.

The cornerstone for HCC-directed therapy is a complete surgical resection, however two-thirds of pediatric patients with HCC present with unresectable disease. In our cohort, patients with complete surgical resectability and no evidence of regional or distant disease had a favorable outcome, as evidenced by survival based on Evans stage, consistent with prior reports. $^{7,18}$

Given frequent chemoresistance and challenges with conventional resection, the role of LT in pediatric HCC continues to evolve. Some studies have shown improved disease-free survival (range 63-89%) with LT, especially in children with background cirrhosis due to an underlying predisposition. $^{23-29}$ The Pediatric Liver Unresectable Tumor Observatory Registry presented interim data in 2015, examining 53 patients <18 years of age with HCC treated with LT, including 29 with underlying liver disease. Long-term survival was excellent in all patients with chronic liver disease, and cure was still demonstrated in two-thirds of patients with unresectable HCC and no background liver disease. $^{30}$ In our cohort, there was a trend toward improved survival with LT, but not significant (Figure 1E). It is important to note that both patients who relapsed after LT did so outside of the liver (lung and abdominal cavity) and both who relapsed after conventional resection had local relapses in the liver in the setting of narrow negative margins (0.2-0.3 mm). While the issue of adequate margins remains debatable, $^{31-34}$ these data support LT being a practical method to control local disease in the absence of metastatic disease and in settings where a conventional surgery is challenging.

There is currently no distinct pediatric criteria to determine the best candidate for transplant. The MC is widely used in adult HCC management algorithms, which prognosticates transplant outcomes based on the number and size of tumors, as well as the presence of extrahepatic disease or vascular extension. While these criteria have significantly improved recurrence-free survival in adult HCC, $^{35-37}$ they have not been validated in pediatrics. In fact, several papers have shown good outcomes in patients exceeding MC, supporting the need for specific pediatric criteria. $^{24,26,28,29,38}$ In our cohort, 11 patients underwent LT, and 7 of 11 (63%) patients exceeded the original MC, all of whom remain alive and disease free (Table 2).

Despite increasing experience with medical management of HCC, there is no convincing evidence to suggest that chemotherapy improves survival. The North American Intergroup Hepatoma study (INT-0098) studied the role of chemotherapy by postoperatively randomizing pediatric patients with HCC to receive a combination of C5V (Regimen A) or cisplatin and continuous-infusion doxorubicin (Regimen B). $^{9}$ There was no difference in response or survival rates between the two treatment regimens, with the best outcome in patients with complete tumor excision at the time of diagnosis (stage 1, 5-year event-free survival (EFS) = 88%) and uniformly poor outcomes in patients with advanced-stage disease (stage 3, 5-year EFS = 23%; stage 4, 5-year EFS = 10%). The International Childhood Liver Tumor Study (SIOPEN 1) also studied the role of chemotherapy by administering a combination of cisplatin and doxorubicin (PLADO) in the neoadjuvant setting and showed similarly discouraging results with a 5-year EFS of 17%. $^{8}$ Eighteen of 37 patients (49%) had a PR to chemotherapy. Complete tumor resection was achieved in 36% of patients (a minority of which became resectable as a result of neoadjuvant chemotherapy); 51% never became operable. Long-term survival was only seen in patients with complete surgical excision. Subsequently, SIOPEN 2 and 3 investigated the concept of a dose-intensified platinum- and doxorubicin-based regimen and showed no improvement in survival. $^{39}$

Sorafenib, a receptor tyrosine kinase inhibitor, is one of the few FDA-approved drugs for pediatric HCC, $^{40}$ and the most commonly utilized in our cohort, both as a single agent and in combination with PLADO (Table 3). The next most common upfront regimen was PLADO-based therapy without sorafenib. Of the 13 patients with unresectable disease at diagnosis who received medical therapy, only two had a PR to chemotherapy and subsequently underwent LT. All other patients who had neoadjuvant chemotherapy had SD or PD. Alternate treatment regimens utilized predominately as second/subsequent-line or salvage therapy included vincristine and irinotecan, Gem/Ox, PIAF, ICE, and Cyclo/Topo. While these drugs have been described in the adult literature, pediatric data regarding response rates remain scarce.

There are several limitations of this retrospective review. As a single institutional study from a large tertiary care center, our epidemiological data may not be generalizable to other centers. Additionally, surgical guidelines vary between institutions and may lead to differing outcomes. Our cohort, while the largest single institutional study in the literature to date, remains small and as such, limits extensive analytics.
In summary, pediatric HCC is often a chemoresistant neoplasm in which complete surgical resection by either conventional methods or LT remains the best chance for cure. There is significant heterogeneity in pediatric HCC in regard to risk factors, background liver disease, and resectability, suggesting the need for tailored therapy, rather than a uniform treatment approach to all pediatric and adolescent HCC. The Pediatric Hepatic International Tumor Trial (PHITT), (COG AHEP1531; JCCG - JPLT4; SIOPEL - PHITT), is the first prospective, multicohort group international trial studying outcomes in patients with HCC using standardized therapy arms based on having resectable or unresectable and/or metastatic disease, as well as the presence or absence of preexisting conditions. Importantly, a major aim of the study will be to analyze the biology of HCC in order to develop biomarkers of clinical heterogeneity in effort to optimize individualized treatment, as well as to advance novel therapeutics.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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