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Hepatoblastoma. Clinical experience at a single institution using the Siopel staging system

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ABSTRACT

Background. Staging in Hepatoblastoma has recently become controversial. In developing countries diagnosis occurs mostly in advanced stages under these circumstances, we propose another option that can be considered of prognostic value. **Method.** A retrospective analysis of cases diagnosed with Hepatoblastoma (HB), treated in a single Institution, in nine years was conducted. Chemotherapeutic regimens were analyzed, as well as the number of courses administered and response to treatment. **Results.** Thirty-two patients were studied. Patients had symptoms from 1 to 25 weeks before diagnosis. SIOP stratification was used, finding 12 cases in PRETEXT II, 6 cases in PRETEXT III, and 14 cases in PRETEXT IV. No single case was identified in PRETEXT I. **Conclusions.** When comparing survival using the PRETEXT system, SIOP and our study showed marked differences. These results may not be comparable due to differences in tumor volume among the same PRETEXT stratification. We believe that tumor volume is related to prognosis.

Key words. Hepatoblastoma. Tumor volume. Prognosis.

INTRODUCTION

Liver cancer is an infrequent neoplasm of childhood. It occurs approximately in 1% of all pediatric cancers with an annual incidence of 1.8 new cases per million each year in patients under 15 years of age. Among liver tumors, Hepatoblastoma (HB) represents 66% of cases, Hepatocarcinoma (HC) 20%, sarcomas 6%. Other histological types are very rare. Most cases appear before five years of age and half of them before the first year of life. It presents itself in a relation of 2:1 boys to girls.[1]

Hepatoblastoma has been associated with several genetic syndromes, including Beckwith-Wiedemann syndrome, familial adenomatous polyposis and hemihypertrophy. There are also reports that associate HB with prematurity, low birth weight and environmental factors like occupational exposure to welding fumes, petroleum and paint derivates.[2-6]

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The clinical presentation is characterized by an asymptomatic abdominal mass, in an apparently healthy child, younger than five years old. Asthenia, adynamia, pain, nausea, vomiting and jaundice indicate advanced disease.

Assessment of alpha-fetoprotein (AFP) is the most important laboratory test. AFP is a protein produced by the fetal liver. Its production starts during the 13th week of gestation and reaches its maximum levels by the first month of extra uterine life. Normal serum concentrations occur by the end of the first year of life. Ninety percent of patients with HB have elevated AFP, making it a useful marker for diagnosis, treatment response and follow up.[2]

Histologically, HB is an embryonic tumor that originates from hepatocyte precursor cells. Histological variants include pure epithelial, mixed epithelial and mesenchymal type, being the latter of dim prognosis.[2-8]

Diagnosis is clinically with AFP serum levels and image studies. Complete surgical resection remains the most important prognostic factor. Neoadjuvant chemotherapy using Cisplatin or its derivates has improved the chance of complete surgical resection in patients with advanced stage at presentation.[8,9]

When the tumor is completely resected, survival rates are optimistic. The International Society of Pe-

diatric Oncology (SIOP) reported an overall survival of 75% at 5 years when using the cisplatin/doxorubicin regimen.[9] The Pediatric Oncology Group (POG) published a study, PHIS (Pediatric Hepatoblastoma Intergroup Study), reporting a 77% rate of complete surgical resection in tumors not resectable at time of diagnosis after four courses of cisplatin/vincristine/5FU.[8]

The current method of stratification is the one proposed by SIOP by imaging and assessment of metastatic disease before treatment (PRETEXT). This system was created in 2000 and it is based in the number of hepatic segments involved shown by image, it also defines the probability for complete tumor resection, and has prognostic value.[9,10] The liver is divided in four segments: right anterior and posterior segments and left medial and lateral segments. It also evaluates the presence of disease in portal and hepatic veins, retro hepatic vena cava, hilar nodal extension and metastatic disease.

It is named PRETEXT I when three hepatic segments are free of tumor, PRETEXT II when only two adjoining hepatic segments are free of tumor, PRETEXT III if only one segment is free of tumor and PRETEXT IV when the four hepatic segments are involved by tumor.[9]

The purpose of this paper is to evaluate the PRETEXT SIOPEL staging system in a single Institution from a developing country.

METHODS AND MATERIALS

A retrospective analysis of cases diagnosed with Hepatoblastoma, treated at the "Instituto Nacional de Pediatría" (INP) in Mexico City from 1999 to 2008 was conducted.

Cases with an incomplete medical record, or having their diagnosis made elsewhere were excluded from the present study.

Alpha-fetoprotein serum levels were recorded in every case at the time of diagnosis and after each chemotherapy course; AFP was monitored on a monthly basis during surveillance for the first year, and thereafter, every three months for three years.

Chemotherapeutic agents were analyzed, as well as the number of courses administered and response to treatment by image and alpha-fetoprotein serum levels.

Time and type of surgery was also recorded.

Statistical analysis was performed with a SPSS software package™. The workshop included median, standard deviation, and Kaplan Meir curves analysis of all the variables mentioned above.

Outcome definitions

Complete Response: non-detectable disease by image or histopatologic study

Partial Response: Tumor reduction of 50% or more by any image method with histopatologic persistence.

Stable Disease: tumor reduction less than 50 % by any image method with histopatologic persistence.

EFS was defined as the period from the date chemotherapy was started until evidence of an EFS-event (progressive disease, death, diagnosis of a second malignant neoplasm) or last contact, whichever occurred first. Survival time (OS) 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 OS event, regardless of the cause of death.

RESULTS

Thirty two patients were studied between 1999 and 2008. The group included 21 males and 11 females, with a male: female ratio of 1.9:1. Age at diagnosis was 5 to 150 months with a median of 39.8 months, and a standard deviation of 30 (Table 1). Patients had symptoms during 1 to 25 weeks before the diagnosis of HB was made, with a median of 9.6 weeks. No patient was excluded from this series.

Twenty five cases were reported as pure epithelial (78%), whereas 7 patients showed mixed histology (22%).

AFP was elevated in 30/32 patients (93%), with a range of 103 to 3.409,000 IU/mL, a median of 450,000 IU/mL at diagnosis, and a standard deviation of 756,220 IU/mL (Table 1).

SIOP stratification was used, finding 12 cases in PRETEXT II (37.5%), 6 cases in PRETEXT III (18.9%), and 14 cases in PRETEXT IV (43.8%). In our series no single case was identified in PRETEXT I.

Five patients (15.62%) presented with metastatic disease at diagnosis, four of them had metastases to the lung, and one patient presented with central nervous system metastases, all of them had peri-hepatic positive lymphatic nodes.

Only three patients (9.37%), all PRETEXT II, were amenable to initial complete surgical resection, without neoadjuvant chemotherapy. No major surgical complications occurred in these patients.

Adjuvant chemotherapy was administered to twenty-nine patients (90.5%). Schemes used included:

Table I. Clinical, treatment and status of patients with Hepatoblastoma at our Institution

Patient	Age	Gender	Lag Time	Diagnosis AFP IU/ml	Histology	PRETEXT	Regimen	Second Look	Status
1	40.53	F	2.0	58,000	Epithelial	2	PLADO	NONE	NED
2	8.00	M	12.0	2,030,000	Epithelial	2	PLADO	NONE	NED
3	9.80	M	25.0	2,000,000	Epithelial	2	NONE	CR	NED
4	11.73	M	2.0	4,161	Epithelial	2	PHIS	CR	NED
5	29.23	F	3.0	141,793	Epithelial	3	PHIS	CR	NED
6	58.90	M	2.0	83,200	Mixed	3	PLADO	CR	NED
7	18.83	M	2.0	731,930	Mixed	2	PLADO	CR	NED
8	40.00	M	8.0	103	Epithelial	2	PLADO	CR	NED
9	39.77	F	8.0	2,176	Epithelial	3	PLADO	CR	NED
10	14.73	F	5.0	2,217	Epithelial	2	PLADO	CR	NED
11	18.13	F	20.0	6,594	Epithelial	2	PLADO	CR	NED
12	41.03	F	12.0	38,273	Epithelial	3	PLADO	CR	NED
13	18.97	M	2.0	87,800	Epithelial	2	PLADO	CR	NED
14	18.13	M	20.0	165,941	Epithelial	2	PLADO	CR	NED
15	44.17	M	3.0	548,920	Mixed	2	PLADO	IR	NED
16	110.47	M	24.0	1,070,000	Epithelial	4	PLADO	NONE	AAD
17	62.63	M	2.0	182	Epithelial	2	PHIS	CR	AAD
18	52.00	F	8.0	260,936	Epithelial	3	NONE	NONE	DAD
19	5.33	M	16.0	600,000	Epithelial	4	NONE	NONE	DAD
20	54.40	M	12.0	126,900	Mixed	4	PHIS	NONE	DAD
21	37.90	M	17.0	300,000	Mixed	4	PHIS	NONE	DAD
22	41.63	M	2.0	5,179	Mixed	4	PHIS	CR	DAD
23	150.17	F	10.0	0	Epithelial	4	PLADO	CR	DAD
24	52.63	F	16.0	522,238	Epithelial	4	PLADO	CR	DAD
25	41.40	M	1.0	900,000	Epithelial	4	ICE	IR	DAD
26	41.40	M	10.0	900,000	Epithelial	4	ICE	IR	DAD
27	38.47	M	4.0	2,600	Epithelial	4	PHIS	IR	DAD
28	5.73	F	18.0	162,337	Mixed	4	PLADO	IR	DAD
29	72.63	M	25.0	0	Epithelial	4	PLADO	IR	DAD
30	17.23	F	5.0	90,000	Epithelial	3	PLADO	IR	DAD
31	26.50	M	3.0	300,000	Epithelial	4	PLADO	IR	DAD
32	52.23	M	10.0	3,409,310	Epithelial	4	PLADO	IR	DAD

M: Male. **F:** Female. Lag Time before diagnosis in weeks. **PLADO:** Cisplatin+doxorubicin+vincristine. **PHIS:** Cisplatin+5FU+Vincristine. **ICE:** Ifosfamide +carboplatin+etoposide. **CR:** Complete response. **IR:** Incomplete response. **NED:** Non evidence of disease. **AAD:** Alive with active disease. **DAD:** Dead with active disease.

a) Cisplatin or carboplatin + doxorubicin + vincristine (PLADO) in 20 cases (62.5%), including nine patients in PRETEXT II, four in PRETEXT III, and seven in PRETEXT IV.
b) Cisplatin + 5FU + vincristine (PHIS) in seven cases (21.8%), including two patients with PRETEXT II, one in PRETEXT III, and four patients with PRETEXT IV.
c) Ifosfamide + carboplatin + VP16 (ICE) in two patients (6.2%) with metastatic disease.

Twenty nine patients underwent a second look surgery, achieving complete resection in 17 of them (58.6%), incomplete resection in seven (24.13%), and only biopsy in five (17.24%) cases.

A total of 172 chemotherapy courses were administered with moderate toxicity. No patient presented with OMS III and /or IV toxicity.

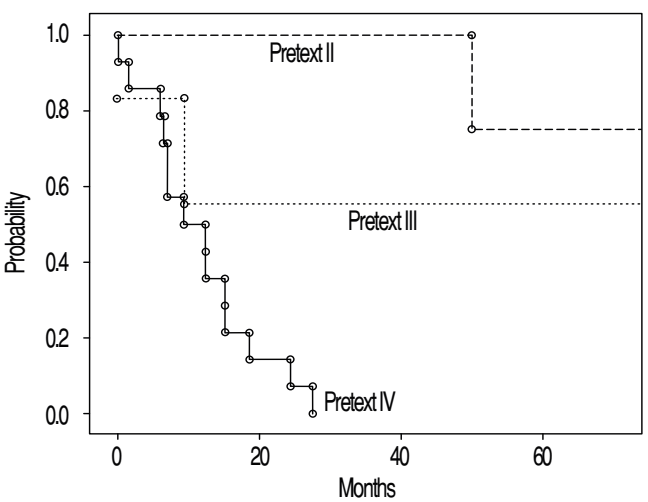

Figure 1. *DFS by PRETEXT.*

One patient died during the immediate post operatory period due to a fatal hemorrhagic event.

Currently fifteen patients (46.8%) are alive with no evidence of disease, two patients (6.2%) are alive with active disease, and 15 patients (46.9%) died with active disease.

Event free survival was of 39% at 89 months with a median of 40 months (IC 95% of 25-54 months). Follow-up was 0-90 months with a median of 23 months. Overall survival was 40.58% at 89 months with a median of 44 months (IC 95% of 28.5-59.5). Follow up was 0-90 months with a median of 23 months (Figure 1).

DISCUSSION

Although HB is a relatively infrequent disease, about 5 new cases are seen at the "Instituto Nacional de Pediatria" each year, an interesting number for only one institution. Our series reports an age at diagnosis three times older than those reported in other American collaborative groups[1,11] presumably due to a delayed diagnosis. This correlates perfectly with advanced PRETEXT cases shown in this report. When comparing Aronson's series[10] with ours, the PRETEXT distribution differs importantly. Our institution reports 2/3 of patients in stages III and IV, while Aronson reports advanced stages in only 1/3 of cases (Figure 2). Our Institution is a national referral center, therefore we believe that patents at early stages are treated at their local Hospitals, and we only receive patients with inoperable tumors. Additionally patients in our country take a lot of time to reach prompt medical attention.

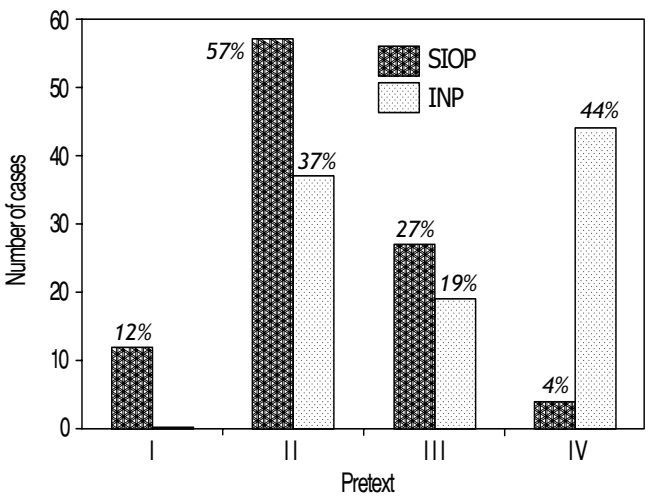

Figure 2. *Comparative SIOP vs. INP cases by PRETEXT.*

The primary chemotherapeutic agent is cisplatin. We used carboplatin in some patients to minimize cisplatin related ototoxicity.[12] SIOP has also used carboplatin in some protocols with good results.[13] The chemotherapeutic scheme with cisplatin/5FU/VCR was published by the PHIS group reporting good efficacy with this combination of drugs, especially in early stages.[8,11]

Our series didn't show a difference in survival when comparing it with serum AFP levels, though the two patients without elevation of this protein at diagnosis died with disease. We couldn't obtain a significant difference when comparing chemotherapeutic schemes and histology,[11] probably because of the number of patients in the series.

It would be important to analyze the total tumor volume, or the volume/weight relation because it is probable that patients in PRETEXT III may present with different tumor volumes, and therefore have different therapeutic and prognostic factors. Such a study is being designed, with tumor volume as one factor of poor prognosis.

CONCLUSION

These series represents an important number of patients for a single institution. The age of presentation differs three fold that reported in developed countries. A small percentage of patients are diagnosed at early PRETEXT. When comparing survival using the PRETEXT system, SIOP and our study showed differences. These results may not be comparable due to tumor volume. Serum levels of alpha-fetoprotein don't always correlate to tumor burden, we therefore propose to initiate a study using image methods to measure tumor volume and correlate them with serum AFP levels to elucidate this new possibility, specifically in non resectable disease.

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