Hepatoblastoma in children: Management Strategies

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Introduction:

Hepatoblastoma (HB) which is embryonal in origin arising from hepatoblasts is the most common primary liver tumor in children. Hepatoblastoma usually occur before 3 years of age, and it contributes to approximately 90% of malignant liver tumors in children under the age of 4 years[1].

The incidence in western countries is 1.6 to 2 per million children.

Risk factors and associations:

Most hepatoblastomas are sporadic, while some are associated with genetic abnormalities like loss of heterozygosity at 11p15.5 locus, 17 q gain, Trisomies 20, 2, 3 and rarely 18. Beckwith Wiedmann Syndrome(BWS); familial adenomatous polyposis (FAP)/ Gardener syndrome; Li Fraumeni syndrome, NF type 1 and Sotos are some of the syndromes associated with increased risk of hepatoblastoma. Extremely premature infants have a higher incidence of hepatoblastoma. Very low birth weight (VLBW) and low birth weight (LBW) infants are known to have a 20 fold and 2 fold increase in risk for hepatoblastomas respectively[2].

Histological subtypes

There might be more than one cellular component in the tumor and based on major cellular component in the tumor and prognostic features on histology HB is classified into Major (common) and Minor (rare) categories (Table 1) About 67% of hepatoblastomas are of epithelial type, with a combination of mixed fetal and embryonal pattern and 21% display a mesenchymal component within them. Seven percent of tumors demonstrate a pure fetal histology (PFH) or a well differentiated fetal

Table 1 Histological types of Hepatoblastoma

Major categories	Minor categories
Epithelial	Cholangioblastic (ductal)
Foetal, well differentiated	Keratinizing squamous epithelium
Embryonal	Intestinal glandular epithelium
Macrotrabecular	Teratoid (neuroid-melanocytic)
Mixed	Rhabdomyoblastic
Small cell undifferentiated	Chondroid
Rhabdoid	Osteoid

histology (WDF) and 5 % are small cell undifferentiated tumors. None of the histological types except for the pure small undifferentiated (SCU) variety bear prognostic significance (Table 1)

Molecular genetics

Specific mutations of the APC gene are related to hepatoblastomas associated with FAP. Changes in the expression of *H19* and *IGF2* genes have also been implicated in the etiology of hepatoblastoma. Genetic aberrations invoving the *wnt* signaling pathway, hedgehog gene pathway, insulin like growth factor axis and hepatocyte growth factor/c-mert pathway are also noted. Telomerase activation, mutation of *CTNNB* or deletion of *CTNNB* exon 3 are found in a substantial proportion of hepatoblastomas. INI1 testing (absence) can help in differentiating rhabdoid tumors from hepatoblastomas.

Presenting signs and symptoms

Most hepablastomas present as a painless right upper quadrant abdominal mass. Children may have failure to thrive. Jaundice and other liver specific symptoms are extremely rare. Fever and anorexia may be the present in advanced disease. Hemihypertrophy and renal swelling may be present when it occurs as a part of BWS. Rare presentations of hepatoblastomas with midface hypoplasia and slit-like indentations of the earlobe have been described.There are cases reported with hypoglycemia at presentation. Severe osteopenia is seen in many patients. Symptoms suggestive of pulmonary metastasis or tumor thrombus extending into the IVC or right atrium can occur in tumors diagnosed late. Children with β-HCG secreting tumors can have isosexual precocity. Tumor rupture can present with anemia and acute abdomen.

Diagnosis liver function tests and Complete blood counts

Usually the liver function tests would be normal and Twenty to thirty percent can have transaminitis. Cholestasis in this condition is extremely rare and could be due to external tumor compression of the biliary system. Complete blood picture might reveal normocytic normochromic anemia and thrombocytosis. Thrombocytosis is because of thrombopoietin production by the liver.

Alpha Feto Protein (AFP) levels

AFP is an oncofetal glycoprotein secreted by the yolk sac, liver and gut during embryo and fetogenesis. As it is a foetal protein, new born babies have high levels which reach adult values by 10 months to 1 year of age. Term neonates have a median AFP of 41687 micrograms/l , while in pre-term the median levels are 158,125 micrograms/l. AFP levels are elevated in more than 90% of children with hepatoblastomas. Fetal tumors produce high AFP than embryonal tumors. Age specific AFP reference range should be compared with actual AFP levels before interpretation. AFP levels in hepatoblastomas can be as high as 1 to 3 million micrograms/l. Serial AFP levels are helpful in monitoring tumor response to chemotherapy. HB associated with low AFP of less than 100 mcg/L is associated with poor prognois. Raising AFP, after initial fall suggests development of tumor resistance to chemotherapeutic agents and is associated with bad prognois.

Imaging studies

Abdominal radiography may reveal a right upper quadrant mass with occasional calcifications. Hepatoblastomas are well defined and hyperechoic on ultrasound imaging. A triphasic computed tomography (CT) scan of abdomen with chest is usually done before initiating treatment. CT scan abdomen usually demonstrates a hypoattenuating well defined heterogenous mass sometimes large enough to displace vessels. Occasionally the tumor thrombus may be seen invading the IVC. MRI (Magnetic Resonance Imaging) is superior to CT in defining tumour margins, vessel involvement and adenopathy. On T1 weighted images they are generally hypo intense; gadolinium contrast can show heterogeneous enhancement and on T2 sequences they are generally hyper intense compared to liver. Areas of necrosis and haemorrhage are commonly noted in both CT and MRI (Magentic Resonance Imaging). Zhang et Al showed using 3D simulation software on CT image helps in looking at complex liver structure, and contributes to the optimal operation

planning[3]. PET-CT or Bone scan (Tc99m MDP) is usually not indicated in classical hepatoblastoma.

Biopsy and other tests

Children's Oncology Group (COG) surgical guidelines recommend resectable HB to be resected without preoperative chemotherapy and based on histology to give chemotherapy, if non-resectable then biopsy followed by chemotherapy. **S**ociété **I**nternationaled' **O**ncologie **P**édiatrique–**E**pithelial **L**iver (SIOPEL) Tumor Study Group guidelines suggest that biopsy may not be necessary between 6 months to 3 years of age if the liver tumor has in a classical presentation on radiological imaging with grossly elevated AFP[4]. Tissue diagnosis is essential before commencing therapy, if there is deviation from above mentioned criteria. Baseline echocardiogram, renal functions including Creatinine clearance and audiogram are essential before chemotherapy.

Hepatoblastoma staging:

Different staging systems like **C**hidrens **O**ncology **G**roup (COG) and SIOPEL exist. The PRE-Treatment EXTent of disease (PRETEXT) staging devised by the SIOPEL is widely accepted [5]. COG uses a postsurgical-based staging system. The SIOPEL presurgical staging system recommends neoadjuvant chemotherapy followed by definitive surgery, while the COG staging system is based on the findings at time of surgery, whenever possible.

Based on the Coinauds system, the liver can be divided into 4 sectors (Fig 1) - the anterior and posterior on the right side, and the medial and lateral sectors on the left. The right anterior consists of segments 5 and 8, and the right posterior consists of segments 6 and 7. The left lateral consists of segments 2 and 3, and left medial consists of segments 4a and 4b. The caudate lobe is categorized as segment 1 (Fig 1)

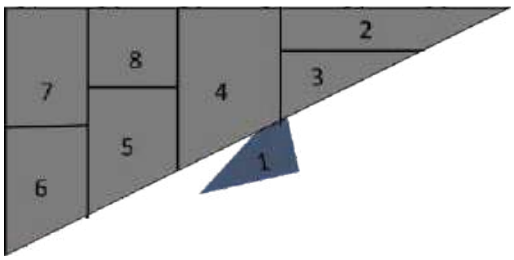

Fig. 1 : SEGMENTS OF LIVER

PRETEXT staging is based on these segments. Caudate lobe is given separate staging consideration, as are extrahepatic disease, tumor focus, tumor rupture, distant metastasis, lymph node involvement, portal, hepatic, and inferior vena cava (IVC) involvement (Table 1)

Treatment

The existing guidelines are based on the recommendations of one of the following cooperative groups: International Society of Pediatric Oncology – Liver Tumor Strategy Group (SIOPEL), Children's Oncology Group (COG), German Pediatric Hematology

Table 1 - PRETEXT Staging System	
PRETEXT 1	3 contiguous sectors are tumor free
PRETEXT 2	2 contiguous sectors are tumor free
PRETEXT 3	1 sector tumor free
PRETEXT 4	No sector tumor free
In addition any group may have V - ingrowth into the IVC or all three hepatic veins involved P - ingrowth into portal vein or involvement of portal bifurcation E - extrahepatic contiguous tumor C - involvement of caudate lobe M - distant metastases	

Oncology Group (GPOH) & Japanese Pediatric Liver Tumor Study Group (JPLT)

In the United States, the current COG study recommends a primary resection for HB limited to PRETEXT I and II tumors with at least 1 cm of clear margin, whereas those tumors with larger extension (PRETEXT III, IV), vascular invasion or distant metastases are treated with neo-adjuvant chemotherapy. The result of primary surgery determines the tumor stage. All patients are treated with adjuvant chemotherapy except patients with a completely resected (Stage I) HB with pure fetal histology.

In contrast, the SIOPEL and GPOH group do not recommend upfront surgery. They recommend neo-adjuvant therapy, which not only makes the tumor smaller and less risky to resect but potentially can also suppress, occult micro-metastases. Therefore, neo-adjuvant chemotherapy is recommended for more or less all HB [6]. When these tumors are managed by multidisciplinary team with expertise in pediatric oncology, liver resection, and liver transplantation, Improved outcomes can be achieved in children with HB even in countries with limited resources[7]

i. Medical management

Chemotherapy has been evolving as a treatment option since the early 1970s especially with the advent of effective chemotherapeutic agents like doxorubicin and cisplatin[8]. SIOPEL Group was formed under the auspices of International Society of Paediatric Oncology in 1987. SIOPEL has completed three major international collaborative studies in paediatric liver tumours (SIOPEL 1-3). SIOPEL recommendations shall be discussed subsequently.

i. Surgery

Complete surgical resection of the primary tumor is the mainstay of treatment, often combined with chemotherapy. The timing of the surgical approach is critical. For this reason, surgeons who have experience performing pediatric liver resections and transplants are involved early in the decision-making process for determining optimal timing and extent of resection. Heroic resections are better avoided as salvage transplantation after unsuccessful resecton has poor outcome when compared to primary liver transplantation after chemotherapy [9]. The various surgical options are:

SIOPEL 1
All tumors were subjected to pre operative chemotherapy (neoadjuvant) with cisplatin and doxorubicin – termed **PLADO**. Cisplatin (80mg/m^2) was used as a 24 hours IV continuous infusion along with Doxorubicin (60mg/m^2) as a continuous 48 hours IV continuous infusion. Overall survival rates were as follows 100% for PRETEXT 1. 91% for PRETEXT 2. 68% for PRETEXT 3. 57% for PRETEXT 4 and 25% for patients with metastasis.
SIOPEL 2
Categorised tumors into “standard risk” and “high risk tumors” at diagnosis. 'Standard risk' patients were those whose tumor was confined to part of the liver and ‘high risk patients were those with tumor involving the whole of the liver or had spread beyond the liver. Standard risk patients were treated with cisplatin alone and high risk patients were put on an intensive chemotherapy with Carboplatin in addition to PLADO in an alternating myelotoxic/non-myelotoxic sequence referred to as **"Super PLADO”**regimen.

SIOPEL 3HR
Cisplatin alternating with carboplatin/doxorubicin (Super PLADO) was administered in a dose-intensive fashion to high-risk patients with hepatoblastoma. This rendered a great proportion of tumors resectable, and, in comparison with previously published results, led to an improved survival in patients with high-risk hepatoblastoma.
SIOPEL 4
Multinational trial of dose-dense cisplatin/doxorubicin chemotherapy and radical surgery for children with high-risk hepatoblastoma. Patients whose tumors were resected or whose livers were transplanted after three cycles of chemotherapy subsequently received two postoperative cycles of carboplatin and doxorubicin. Patients whose tumors remained unresectable after three cycles of chemotherapy received two cycles of very intensive carboplatin and doxorubicin before surgery. 97% of children had partial response to chemotherapy; 85% underwent complete macroscopic resection. 3 year overall survival 83% and disease-free survival 76%
SIOPEL 5
A new protocol for the management of the HCC family of tumours in children/adolescents and young adults – closed due to insufficient recruitment
SIOPEL 6
A multicenter open-label randomized phase III trial of the efficacy of sodium thiosulphate (STS) in reducing ototoxicity in patients receiving cisplatin (Cis) monotherapy for standard-risk hepatoblastoma (SR-HB) – currently on

- Segmentectomy – single involved segment is removed
- Hemi hepatectomy(either right or left)
- Extended right hepatectomy – only segment 2,3 and caudate lobe are left behind.
- Extended left hepatectomy–most of segments 5 and 8 are removed along with the left lobe.
- Liver transplantation

Outcomes of Liver transplantation, either cadaveric or living donor are the same in children with hepatoblastomas. Patient and graft survival is reported to be greater than 80% at 10 yrs after transplantation [9, 10]. Pulmonary metastasis at the time of diagnosis is not a contraindication resection/ liver transplantation provided the lung lesion disappear after neo-adjuvant chemotherapy.

Indications of liver transplantation are:

1. Multifocal HB in all 4 liver sectors (PRETEXT IV)
2. Patients with solitary PRETEXT IV HB that are not clearly down staged to PRETEXT III
3. HB with portal vein involvement
4. HB with involvement of all 3 hepatic veins (V3)
5. Central HB (if a conventional resection does not seem feasible)

Treatment options for relapsed/refractory Hepatoblastoma:

Treatment at relapse depends on the site of relapse and type of chemotherapy received. Outcomes are better if the tumor is amenable to surgery. Children treated with cisplatin/ vincristine/fluorouracil could be salvaged with doxorubicin-containing regimens and vice-versa. Combined vincristine/irinotecan and single-agent irinotecan have been used with some success. SIOPEL recommends 4 cycles of Irinotecan in relapsed hepatoblastoma. Sorafenib has been successfully used a child with post liver transplant relapse of refractory hepatoblastoma.[11]

ii. Newer agents

Hepatic artery chemoembolization (HACE, also called transarterial chemoembolization-TACE) has been tried with success in limited situations to increase resectability in tumors

which remain unresectable even after neo-adjuvant chemotherapy and as a bridge to liver transplantation [12, 13]. Other chemotherapeutic agents like Topotecan, Ifosfamide, Etoposide and certain newer drugs like Gemcitabine and Bevacizumab are being tried in relapsing or recurrent tumors [14, 15]. Pediatric MATCH study is currently on studying targeted agents against specific molecular antigens on relapsed tumors–[16].

Conclusion:

Atypical presentation, raising AFP while on treatment etc. is associated with bad prognosis. Hepatoblastoma when managed by a multidisciplinary team that includes liver transplantation as an option is associated with good prognosis. The optimal treatment HB based on tumor genome profiling is still evolving.

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