PEDIARTIC HEPATOBLASTOMA: A BRIEF REVIEW

Running title: Pediatric hepatoblastoma.....

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ABSTRACT

Hepatoblastoma is a rare pediatric liver tumor. The management has evolved in last three decades with involvement of multimodality approach. This review aims to highlight the pathology, diagnosis, management and prognosis of hepatoblastoma.

Key words: Hepatoblastoma, chemotherapy, rare

INTRODUCTION

Hepatoblastoma (HB) is the most common primary pediatric liver tumor, diagnosed during the first 3 years of life.[1] Most of the cases are sporadic, however, some are associated with constitutional genetic abnormalities, malformations, and familial cancer syndromes, such as Beckwith – Wiedemann syndrome (BWS) and familial adenomatous polyposis (FAP).[2]

There is an increase in the incidence of HB during the last 30 years. Premature birth and very low birth weight have been found to be associated with the later appearance of HB. Oxygen therapy, medications such as furosemide, Total Parenteral Nutrition (TPN), radiation, plasticizers, and other toxins are postulated to perhaps play a role, but the exact mechanisms are not yet understood.[3]

PATHOLOGY

HB is an embryonal tumor thought to originate from a hepatocyte precursor cell (hepatoblast). Weinberg in 1983 reviewed that two-third of HBs were epithelial, with a combination of mixed

embryonal and fetal patterns. 21% of HBs showed mesenchymal component while 5% had primitive appearing or small cell undifferentiated (SCU) tumor cells. Most HBs are extremely heterogeneous, often with mixed histological components. The SCU subtype is associated with low serum AFP levels and poor response to chemotherapy (CCT).[4]

GENETICS

Several genetic syndromes such as Trisomy 18/Edward's syndrome, BWS, and FAP have been reported in association with HB.[5] There are a few published cases of HB in children with trisomy 18/Edward's syndrome. BWS is associated with embryonal tumors in 7.5 – 13.5% of cases, with the most frequent tumors being Wilms' tumor and HB. In FAP, there may be genotype – phenotype links between specific mutations to the APC gene, which is mutated in FAP. The most frequent genetic aberrations (70 – 90%) in HB occur in genes involved in the Wnt signaling pathway.[6] MYC signaling plays a role in the more aggressive phenotypes of hepatoblastoma.

PROGNOSTIC FACTORS

There are several study groups evaluating the management of childhood tumors. Important prognostic factors have been identified. Good prognosis has been shown for Stage I tumors resected at diagnosis and tumors with pure fetal histology. Poor prognostic factors identified include metastatic disease, AFP less than 100, and SCU histology. Other poor prognostic factors are tumor rupture prior to diagnosis, tumor multifocality, macrovascular tumor invasion, extra hepatic tumor extension, age at diagnosis and very high (> 1.2 million) or borderline low (100 – 1000) AFP.[7]

Factors in response to treatment that had been hypothesized as poor prognostic factors include poor response or progressive disease on chemotherapy, gross positive surgical margins, surgically unresectable tumor, and tumor relapse.[8]

MANAGEMENT

Treatment of hepatoblastoma in children represents a true success story of pediatric oncology in the last 25 years. From prechemotherapy survival rates in the 1970 s of 30%, the use of adjuvant

and neoadjuvant chemotherapy brought the survival to 70 – 80%.[9] This progress was possible because of the introduction of new chemotherapeutic drugs improvement in surgical approaches (i.e. hepatic exclusion, Pringle, ultrasonic dissection, liver transplantation) and, perhaps most importantly, because of multicenter cooperative efforts of the major international study groups.[10] One fundamental controversy between various study groups has been the sequence of primary hepatic resection and chemotherapy. The current COG trial, AHEP- 0731, has moved away from putting surgical decisions arbitrarily in the hands of an individual surgeon. This study's surgical guidelines recommend upfront resection only for early stage tumors, when the diagnostic imaging shows clear radiographic margins on the contralateral portal vein, the middle hepatic vein, and the retrohepatic inferior vena cava.

Chemotherapy protocols from the four major study groups have used a different combination and schedule of drugs. Cisplatin is the most widely used chemotherapeutic agent in HB. Other agents commonly used are vincristine, 5FU, doxorubicin and irinotecan. However, fever and neutropenia are common adverse effects of chemotherapy, occurring in two-third of patients. The number of patients with significant hearing loss was greater than 50%.[11]

Novel strategies have been investigated by different study groups. The use of high dose chemotherapy with autologous stem cell /bone marrow transplant rescue was used in the highest risk patients, but was not found to improve survival.

PROGRESSIVE DISEASE AND TUMOR RELAPSE

Doxorubicin, carboplatin, etoposide, and ifosfamide have been used for patients with progressive disease and relapse. Approximately one-third of the patients whose disease progressed or recurred after initial treatment without anthracyclines could be successfully rescued with a doxorubicin containing regimen and surgery.[12] Irinotecan has been used experimentally as a maintenance therapy in a few patients suspected of being at high risk for relapse. High dose chemotherapy with stem cell rescue has been used in the setting of progressive or relapsed HB. Hepatic intra-arterial chemoembolization has been shown to be efficacious in shrinking these

tumors and allowing complete surgical resection after initial systemic chemotherapy. Surgical resection of relapse nodules in the lungs can be curative, but has a high failure rate.

CONCLUSION

The management of HB is a paradigm of cooperation between clinicians, surgeons and pathologists from establishing diagnosis to organizing the therapeutic strategy. With new techniques and drugs, there is a significant improvement of therapeutic standard and HB represents a model of therapeutic implementation and achievement in oncology.

Source of Support: None **Conflict of Interest:** None

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