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Hepatoblastoma: 16-years' experience from a tertiary cancer centre in India

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ABSTRACT

Background: Hepatoblastoma is a rare pediatric tumor arising from the liver. The present study was conducted to ascertain the clinical profile and survival outcomes of patients with hepatoblastoma treated at our centre.

Methods: We collected the case records of patients with hepatoblastoma treated between January 2000 to December 2016 and analysed the baseline characteristics, treatment details and outcomes. Survival was analysed using Kaplan Meier method.

Results: Twenty-seven patients with hepatoblastoma received treatment at our centre during the study period. Median age of the patients was 12 months and 76% were males. The commonest presenting symptom was abdominal mass and the median Alpha Fetoprotein (AFP) level at the time of diagnosis was 40,000 ng/ml. PRETEXT stage II was documented in 11 and III in 11 patients. High risk disease (PRETEXT IV or metastatic disease or portal venous invasion or AFP < 100 ng/ml) was documented in 8/27 (30%) patients. Neoadjuvant chemotherapy (NACT) was given to 23/27 patients and complete surgical resection was possible in 15/23 (65%) after NACT. Infusional cisplatin and doxorubicin (PLADO) was given in 24/27 patients. Liver transplantation was done in 1 patient. The median follow-up was 51 months and the 5-year overall survival for standard risk and high-risk patients was 78.8% and 40% respectively.

Conclusion: Patients with standard risk hepatoblastoma have survival outcomes comparable to Western countries, however, outcomes in patients with high risk non-metastatic inoperable disease remains low due to financial constraints in performing liver transplantation. Multimodality treatment including NACT with PLADO based regimens followed by resection is a feasible strategy.

1. Introduction

Hepatoblastoma is a rare malignant embryonal tumor and accounts for about 1% of all pediatric cancers [1]. Hepatoblastoma commonly occurs in children less than 5-years of age and preterm delivery is a risk factor. Complete surgical resection of hepatoblastoma is essential for cure and chemotherapy is required for down-sizing the tumor for making it amenable for surgical resection and for preventing relapse [1]. Clinical trials on chemotherapy regimens by international cooperative groups, optimal supportive care, refined surgical techniques and emergence of liver transplantation has led to significant improvements in outcome in hepatoblastoma. Concomitantly, there has also been a reduction in treatment related morbidity [1]. Though studies from major international groups have contributed to better understanding of the disease and formulation of treatment strategies, data from India is limited [2]. The present study was performed to analyse the clinical and laboratory features, treatment and survival outcomes of patients with hepatoblastoma treated at our centre and to provide a better understanding of management of hepatoblastoma in a

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resource challenged setting.

1.1. Patients and methods

Case records of all patients diagnosed and treated for hepatoblastoma at our institute from January 2000 to December 2016 were analysed. Diagnosis of hepatoblastoma was based on clinical features, and elevated serum alpha-feto protein (AFP) levels. All the patients underwent contrast enhanced computed tomography (CT) scan of chest, abdomen and pelvis and PRETEXT (Pre-Treatment Extent) stage was assigned based on the CT findings [3]. Treatment decisions were taken by a multi-disciplinary team. High-risk (HR) was defined as follows: tumor in all liver sections (PRETEXT-IV), or vascular invasion (portal vein [P+], three hepatic veins [V+]), or intra-abdominal extrahepatic extension (E+), or metastatic disease, or alpha-fetoprotein less than 100 ng/ml at diagnosis [4]. During the year 2000, patients underwent surgery at presentation followed by adjuvant chemotherapy. From 2001 onwards all patients received neoadjuvant chemotherapy (NACT) followed by surgery. Serum AFP levels were monitored prior to each cycle and imaging was usually done after 3–4 cycles of chemotherapy. Those who had inoperable disease on reassessment, were given 2 more cycles of chemotherapy and reassessed. The timing of surgery was individualised and was decided by the surgical team. After surgery, adjuvant chemotherapy was delivered to complete a total of 6 cycles. Doxorubicin and cisplatin (PLADO) was the most commonly used chemotherapy regimen [5]. PLADO chemotherapy consisted of cisplatin on day 1 at a dose of 80 mg/m^2, administered in a continuous 24-h infusion and doxorubicin at a dose of 30 mg/m^2 per day, administered as a continuous 24-h intravenous infusion on days 2 and 3. The PLADO regimen was administered through a central venous catheter every 3 weeks. During follow-up serial AFP levels were done every 3 months for the first 3 years and every 6 months for the next 5 years and then annually. Ultrasound imaging of the abdomen was performed every 6 months for the first 3 years of follow-up.

Event was defined as death due to any cause or relapse or progression of disease. Patients were censored on the date of last follow up. Event-free survival (EFS) was calculated from date of initiation of treatment to date of relapse or progression or death. EFS and Overall survival (OS) was estimated using Kaplan–Meier method. Statistical analysis was performed using SPSS software version 20.0.

2. Results

During the study period, 27 patients diagnosed with hepatoblastoma received treatment at our Institute. Median age of presentation was 12 months (range 3–72 months) and 20 (74%) were males. Commonest presenting symptom was abdominal mass (85%, n = 23) followed by fever (15%, n = 4). One patient had history of prematurity and none of the patients had documented congenital anomalies. Median platelet count was 5,98,000/mm^3 (100,00–840,00). Median AFP level was 40,000 ng/ml (150-2,08,000 ng/ml). PRETEXT was Stage I in 3/27 (12%), Stage II in 11/27 (40%), stage III in 11/27 (40%) and stage IV in 2/27 (8%) patients. HR disease was observed in 8/27 (30%) patients, among them 4/8 had metastatic disease at presentation, 2/8 had PRETEXT IV (1 patient also had metastatic disease) and 4/8 had portal vein involvement (1 patient had also had metastatic disease). All the patients had normal liver function tests at the time of presentation. Upfront liver biopsy/cytology was performed in 37% of patients (n = 10). The decision to perform liver biopsy was not uniform and was based on physician preference.

2.1. Treatment details

Twenty-three of 27 patients (85%) received NACT and 4/27 (15%) had upfront surgery followed by adjuvant chemotherapy (Fig. 1). Fifteen of 23 patients (65%) responded to NACT and underwent resection of the involved segments, 1/23 had response to NACT but remained unresectable and required liver transplantation, 5/23 had refractory/progressive disease on NACT and did not undergo surgery and 2/23 died while receiving NACT. Overall 19/27 (70%) patients could undergo surgical resection of the tumor (4 upfront and 15 after NACT) and 1 patient underwent liver transplantation after NACT. Surgical resection could not be done in the remaining 7 patients because of disease progression on NACT in 5/7 patients (3 patients eligible for liver transplant) and treatment related mortality in 2/7 patients. Mixed histology was seen in 16/20 patients who underwent surgery, rhabdoid/teratoid differentiation in 2/20 and epithelial in 2/20. All the patients who had tumor resection had negative margins.

Among the 3 patients with PRETEXT stage I, 2/3 responded to NACT and underwent surgery and one patient underwent upfront surgery. Among the 11 patients with PRETEXT STAGE II, 2/11 underwent upfront surgery, and of 9 patients who received NACT, 7/9 (78%) could undergo surgery. Among the 11 patients with PRETEXT STAGE III, 1/11 underwent upfront surgery, and 7/10 (70%) patients who received NACT could undergo resection (including one patient who underwent liver transplantation). Two patients had PRETEXT IV disease both received NACT and one underwent surgery (50%) and the other had progressive disease.

Surgery could not be performed in 4/19 patients with standard risk (SR), among whom two patients had inoperable disease due to progression on NACT and 2 patients died due to chemotherapy toxicity. HR disease was seen in 8 patients and surgery could not be performed in 4/8 patients (2 patients with metastatic disease and 2 patients with portal vein involvement) as they had progressive disease while receiving NACT. Liver transplantation as a curative option was indicated in 4 patients who had disease progression in the liver without distant metastasis, however, only 1/4 could undergo the procedure and the rest 3/4 could not afford the cost of liver transplantation.

The most common chemotherapy regimen used was PLADO (25 patients, 92%). One patient with standard risk disease received single agent (SA) cisplatin as NACT and another patient with high-risk disease received intensification of chemotherapy with cisplatin alternating carboplatin and doxorubicin given every 2 weeks rather than 3 weeks (SUPERPLADO) prior to surgery. Median number of NACT cycles were 4 (range: 2–6).

2.2. Toxicity

Commonest grade 3 or 4 toxicity was neutropenia (n = 5, 20%) followed by anemia, thrombocytopenia and vomiting (1 patient each). Febrile neutropenia was seen in 4 (16%) patients and 6 patients (24%) required dose reductions during some point of treatment. Two patients died during NACT due to pneumonia and unexplained sudden death. None of the patients had any significant surgical complications. One patient had major morbidity post-surgery in the form of hepatic insufficiency due to Budd-Chiari syndrome. The patient was managed with supportive measure and had complete recovery.

2.3. Relapse and mortality

Six patients had disease progression or relapse, 5/6 patients (2 metastatic and 3 non-metastatic) had progressive disease while receiving neoadjuvant chemotherapy and could not undergo

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