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Title: Comparison of Cisplatin monotherapy and PLADO in the management in children with standard-risk hepatoblastoma in a Resource Challenged Nation.

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Word counts

Abstract: 310

Main Text: 2785

Table: 1

Figures: 3

Running title: Chemotherapy for SR hepatoblastoma in RCN

Key words: Standard Risk Hepatoblastoma; cisplatin monotherapy; PLADO; Resource Challenged Nation

Abbreviation table:

Abbreviation	Full form
PLADO	Cisplatin and Doxorubic
SIOPEL	Société Internationale d'Oncologie Pédiatrique – Epithelial Liver Tumor Study Group / Childhood Liver Tumor Strategy Group of the International Society of Pediatric Oncology
SRHB	Standard-risk Heptoblastoma
RCN	Resource challenged nation
PRETEXT	Pretreatment extent of tumor
OS	Overall survival
EFS	Event free survival
SR	Standard-risk
HR	High-risk
CECT	Contrast enhance computed tomography
αFP/ AFP	Alpha-fetoprotein
IVC	Inferior vena cava
Echo	Echocardiography
CI	Confidence interval
SEER	Surveillance, Epidemiology and End Results

Abstract:

Background: Recent SIOPEL studies have shown cisplatin monotherapy to be equally effective in management of Standard risk Hepatoblastoma (SRHB) as compared to PLADO. **Aim**: To study the chemotherapy, response and outcomes in children with SRHB in a Resource Challenged Nation (RCN). **Material and Methods**: A retrospective study was conducted and all children with SRHB who were treated by us from June 2007 to December 2017 were included. All patients with standard risk hepatoblastoma who had received at least 2 courses of chemotherapy were included. Data regarding the demographics, PRETEXT stage, chemotherapy, response to chemotherapy and outcomes were recorded. Kaplan Meier survival analysis was performed to calculate 5-year overall survival (OS) and event free survival (EFS). **Results**: Thirty-two children were included in the study. Nineteen children (59.4%) received Cisplatin monotherapy and of these 6 patients (all PRETEXT III) had poor response and were upgraded to PLADO. The remaining 13 (40.6%) received upfront PLADO. The 5-year OS and EFS was 100% in the monotherapy group (n=13), 92% and 69% in the upfront PLADO group (n=13), and 62% and 22% in the upgraded to PLADO group (n=6). Patients in upgraded to PLADO group had significantly lower 5-year EFS (70% vs 22%; p= 0.036) compared to upfront PLADO group. **Conclusion:** Two thirds of SRHB patients with PRETEXT stage III who received cisplatin monotherapy showed poor response and were upgraded to PLADO chemotherapy. These patients had a significantly poorer outcome compared to the rest of the cohort. PRETEXT stage III standard-risk hepatoblastoma may benefit from PLADO chemotherapy instead of cisplatin monotherapy.

Introduction

Hepatoblastoma is the most common malignant liver tumor with an incidence of 1.5 cases per million children [1]. Hepatoblastoma accounts for 1% of all pediatric malignancies and is the fourth most common intra-abdominal neoplasm after neuroblastoma, Wilms tumor and rhabdomyosarcoma [2]. After institution of chemotherapy the survival of this tumor increased markedly from 30% to 60%-70% by the end of the last century [3,4]. With improved survival, the need arose to tailor the chemotherapy to patients to achieve better survival with minimal side effects. Hence, a need was felt to identify prognostic factors based on which chemotherapy can be tailored.

SIOPEL 1, was the first prospective international clinical trial on childhood hepatoblastoma and conducted by the Childhood Liver Tumor Strategy Group of the International Society of Pediatric Oncology (SIOPEL)[5]. The SIOPEL group further conducted two trials (SIOPEL-2 (pilot) and SIOPEL-3) to treat patients according to risk stratification [6,7]. Under the SIOPEL-3 trial, patients with standard risk were randomized to receive less toxic cisplatin monotherapy or cisplatin and doxorubicin (PLADO) combination chemotherapy [7]. The study noted similar rates of complete resection and survival among children with standard-risk hepatoblastoma. However, the efficacy of cisplatin monotherapy has not been demonstrated in a resource challenge nation where patients often present late with larger tumors that are categorized as PRETEXT III often based on suboptimal cross sectional imaging, and with the availability of liver transplant being limited. Hence, we conducted this study to retrospectively evaluate the management and outcomes of standard-risk hepatoblastoma managed by us in the resource challenged settings.

Material and Methods

Prospectively maintained data set for all patients of hepatoblastoma, who had been treated by us form June 2007 to December 2017 were evaluated. All patients with standard risk hepatoblastoma who had received at least 2 courses of chemotherapy were included. The study had been approved by the Institute Ethics Committee.

Risk stratification into standard risk (SR) and high risk (HR) had been performed according to the SIOPEL-2 study i.e. PRETEXT I,II, and III without metastases, extrahepatic disease, portal or hepatic venous involvement [6]. Cisplatin monotherapy and PLADO regimen (cisplatin and doxorubicin) was administered in accordance with the national consensus, which had been adopted from the SIOPEL protocol [8]. In addition to the imaging findings, the surgeon's preference also affected the choice of chemotherapy. A total of 6 courses were administered, of which 4 courses were neoadjuvant and remaining 2 courses were administered after surgery. The response to chemotherapy was assessed with clinical examination, alpha-fetoprotein (αFP) values and radiological assessment which included a contrast-enhanced CT scan of the abdomen and chest (CECT) after every 2 courses. Surgery was performed after 4 courses of chemotherapy. Patients showing poor response after 2 courses of monotherapy were upgraded to receive PLADO subsequently.

Follow-up, after completion of chemotherapy, was performed with monthly αFP values for the first 6 months, 3 monthly until 12 months and after that 6 monthly. In addition to αFP, three monthly radiological assessments were performed (alternate ultrasonography and CECT) for the first year, followed by 6 monthly assessments for the next 2 years. Data regarding the demographics, PRETEXT stage, chemotherapy, response to chemotherapy and outcomes were recorded.

Demographic variables were described using median and range. Qualitative variables were analysed using chi-square test. Kaplan Meier survival analysis was performed for obtaining the 5-year overall (OS) and event-free survival (EFS). Events were defined as disease progression, recurrence or death. Statistical significance was considered p values <0.05. Statistical analysis was performed using the SPSS statistical package version (IBM inc.)

Results

General profile

During the study period, 62 children with hepatoblastoma were enrolled in our oncology clinic. Of these, 30 children (48.4%) were classified as high risk and the remaining 32 (51.6%) belonged to the standard risk group. The later cohort formed our study group. The median age at presentation for the SR patients was 12 months (range 4–72 months). Male to female ratio was 3:1. All patients received neoadjuvant chemotherapy. Before starting the chemotherapy the diagnosis of hepatoblastoma was confirmed on fine needle aspiration cytology in seven patients. Alpha-fetoprotein was raised in all children with a median value of 2,61,895 ng/ml (range 1999 to 14,49,190 ng/ml). Tumor extension was defined according to PRETEXT system (Table 1).

Chemotherapy

The chemotherapy administered to these patients as shown in Figure 1. Of the 32 children with SRHB, 13 (40.6%) received PLADO as neoadjuvant chemotherapy. The reason for the choice of PLADO in SRHB was surgeon's choice in 9 patients and the reasons attributed were large tumors making pre-treatment evaluation of tumor extension difficult. The vena cava or portal venous involvement was unclear due to poor imaging or distortion by the large mass. In 4

patients PLADO was administered upfront as the child had received 2 courses of PLADO elsewhere before being referred to us. The distribution of the PRETEXT stage among the two groups in shown in table 1.

Of the 19 (59.4%) patients who received cisplatin monotherapy, chemotherapy was upgraded to PLADO in 6 (31.5%) patients [Table 1]. The reason for upgradation of chemotherapy was poor response after two courses of monotherapy. All these 6 patients had PRETEXT III tumors and had shown poor radiological response or progression with increase in αFP levels in 3 patients and modest decrease (approx. 30% decrease) in 3 patients. The histopathology of the tumor in these six patients (as reported after resection) did not reveal presence of small cell undifferentiated tumor. None of the patients with PRETEXT I or II needed upgradation of chemotherapy. The need for upgradation of chemotherapy in PRETEXT III tumors as compared to PRETEXT I/II tumors was statistically significant (66% vs 0; p= 0.003).

Surgery

Anatomic hepatic resection was performed in 31 children. One child abandoned treatment during neoadjuvant chemotherapy and died prior to surgical intervention. The surgical margins were free in 30 children. The patent with the microscopic positive margin had the tumor that was adherent at the junction of hepatic vein and IVC. This patient died in the immediate post-operative period.

Follow up and outcome

The median duration of follow-up of the cohort was 37 months (range 4- 131 months). At the time of last follow-up, 29 children (90.6%) were alive of which 28 were disease free while one had progressive local disease. Three children (9.4%) had died. The reason for death in these three

patients was the discontinuation of treatment during neoadjuvant chemotherapy, post-operative complication and recurrence with progressive disease in one patient each. There were no recurrences in the monotherapy group who did not need any upgradation of chemotherapy. There were five recurrences in the patients who received PLADO, either upfront (n = 2) or after upgradation from cisplatin monotherapy (n = 3). Both the patients with recurrence, who had received upfront PLADO chemotherapy, were salvaged with irinotecan-based chemotherapy and repeat resection of the recurrent tumor. Both these patients were in disease remission at last follow-up. Of the 3 recurrences in the patient who had been upgraded to PLADO chemotherapy, only one patient achieved remission with salvage chemotherapy and surgery. One child died and the remaining one had progressive disease. This difference in recurrence rates amongst patients who had upfront PLADO chemotherapy and those who were upgraded to PLADO chemotherapy was not statistically significant (15% vs 50%; p= 0.26). Four patients (2 each on cisplatin monotherapy and PLADO) developed febrile neutropenia for which chemotherapy was delayed for a week, and the child was managed on an outpatient basis. No inpatient admission was needed for any chemotherapy related adverse effect. All patients who received PLADO had an echocardiography (ECHO) immediately pre-operatively and all had normal ejection fraction with no myocardial dyskinesia. In addition, seven of these patients, who had received PLADO chemotherapy, had an another ECHO performed during the later follow-up period. All of these had normal ejection fraction with no myocardial dyskinesia.

5-year overall and event-free survival

The 5-year overall survival (OS) and event-free survival (EFS) of the cohort were 89% (95 CI71–96) and 80% (95CI 56-90). The 5-year OS and EFS of the monotherapy group who did not need any upgradation of chemotherapy (n = 13) was 100% (Figure 2). The 5-year OS and EFS in

the upfront PLADO group (n = 13) was 92% (95CI 56–99) and 69% (95CI 29–89), respectively. The 5-year OS and EFS in the upgraded PLADO group (n = 6) was 62% (95CI 14–89) and 22% (95CI 1–61) respectively (Fig 2). The difference in overall survival between these three groups was not statistically significant (p= 0.078), but the difference in event-free survival was significant (p= 0.001). The 5-year EFS of children who did not require the upgradation of chemotherapy (n = 26) was 85% and those who needed the upgradation of chemotherapy (n = 6) was 22% with a hazard ratio of 8.9 (p= 0.005).

On comparing the survival outcome in children with PRETEXT III disease who had received upfront PLADO with children who were upgraded to PLADO (Fig. 3), it was observed that the 5-year EFS was significantly lower in the latter group (70% vs 22%; p=0.036). However, the difference between the 5-year OS was not statistically significant (100% vs 62%; p= 0.07).

The 5-year OS for PRETEXT I, II and III SRHB were 83%, 100%, and 86%, respectively. The 5-year EFS for PRETEXT I, II and III disease were 83%, 100%, and 54%, respectively.

Discussion

Hepatoblastoma is an extremely rare tumor in children. The exact incidence of this condition in India is difficult to determine due to the absence of population-based registry of hepatoblastoma. National centre for disease informatics and research compiled the hospital-based cancer registry data from 8 major hospitals under the National Cancer Registry Programme for 2012–2014. During these 3 years, only 43 patients with hepatoblastoma were seen in these 8 centres and comprised only 0.8%−4.2% of the childhood cancers presenting to the respective institute [9]. We noted a male to female ratio of 3:1 which is higher than that reported normally which can be due to a selection bias in favour of males due to prevailing gender bias in the society. The

Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute reports a male: female ratio of 1:2, however trials from United States and Europe report higher ratio ranging from 1.6 to3.3:1 [10]. Due to these small numbers, there is a lack of data regarding outcomes of chemotherapy in patients with hepatoblastoma from our country.

PLADO chemotherapy has proven efficacy in treatment of hepatoblastoma and is the most used chemotherapy in treatment of hepatoblastoma in India [11]. Due to potential toxicity of these agents, there is a constant effort to identify patients who could be treated with less toxic chemotherapy. SIOPEL −1 study could identify these risk factors and SIOPEL-3 study concluded that in children with standard-risk hepatoblastoma, cisplatin monotherapy achieved similar resection rates and survival compared to PLADO chemotherapy [5,7]. Before these recommendations are implemented in management of children in our practice, a deeper insight is needed in the SIOPEL-3 study. The study only mentions the resection rates in the groups and the resection in this study was achieved by hepatectomy or liver transplantation. Simultaneously, the liver transplantation rates have increased from 12% to 21% in the SIOPEL-2 and 3 studies, respectively [12]. Therefore, the use of cisplatin monotherapy in the resource challenge setting like ours can only be justified if the rates of hepatectomy are at par with those achieved with PLADO chemotherapy. The SIOPEL−3 study, however, did not provide data regarding the need for liver transplantation among both the groups. There is no data regarding the use of cisplatin monotherapy from India. Few recent studies with the inclusion of patients as late as 2015 or 2016 report use of PLADO chemotherapy irrespective of the risk stratification in all patients [13,14]. This observation highlights the importance of the findings of the index study. Hence, this study was conducted to evaluate the use of cisplatin monotherapy in children with standard-risk hepatoblastoma in a resource-challenged setting.

In the index study only 32/62 (51%) patients had standard risk disease. This in contrast with SIOPEL studies where children with standard risk disease constitute 70% of the patients [12]. Like our findings, other large studies from India report standard-risk disease in only 40%-50% of patients [14,15]. In this study, despite standard risk disease, 40% (13/32) of children received PLADO chemotherapy on the choice of the treating clinician even though 4 of these 13 patients (30.7%) had a PRETEXT I or II disease. Many patients present to us with a CECT done elsewhere, which was not optimal in quality and extent. These CECT often do not have a triple phase image acquisition. In resource challenged settings, like ours, magnetic resonance imaging (MRI) is usually not done due to the cost constraints and at times non-availability. Extremely poor imaging studies were repeated, however, in few cases, the decision was based on suboptimal imaging. Another reason for upfront PLADO chemotherapy in SRHB, could be the initial hesitation and gradual acceptance of cisplatin monotherapy. The acceptance of cisplatin monotherapy has increased with time in our study with none of the standard risk disease receiving PLADO chemotherapy in the later period of the study.

Of the 19 patients who were started on cisplatin monotherapy, chemotherapy was upgraded, to PLADO, in 6 (31.5%) due to poor response. This contrasts with the SIOPEL −3 study in which 10% patients showed poor response in the cisplatin monotherapy group compared to 5% in the PLADO group [7]. The remaining patients showed a partial response whose definition was not clear in the publication. There is a paucity of data regarding the response to cisplatin monotherapy in other studies. Interestingly, compared to SIOPEL −3, Sunil et al. reported that 4/14 patients (28%) of children with standard risk disease showed progressive disease on PLADO chemotherapy [14]. In our study, of the 13 patients who received upfront PLADO chemotherapy, one patient, who had abandoned chemotherapy, died pre-operatively of

progressive disease. The remaining 12 patients had a good response to PLADO chemotherapy, without any incidence of severe neutropenia/thrombocytopenia and could undergo resection.

The worst outcome in our study was in patients who were started on monotherapy and who, due to poor response, had been upgraded to PLADO chemotherapy. Disease-free survival (DFS) was achieved in only 3 patients (50%) in this subset of patients compared to 92.3% and 100% in patients who received upfront PLADO and cisplatin monotherapy alone, respectively. We also noted that two-thirds of the children PRETEXT III tumors on cisplatin monotherapy had to be upgraded to PLADO chemotherapy, whereas none of the patients with PRETEXT I or II disease needed an upgradation of chemotherapy. This difference was statistically significant and therefore in a resource challenged setting use of PLADO upfront in standard risk Pretext III tumors may be better option. Another aspect this study highlights is that SR HB patients who do not respond to cisplatin monotherapy, do not respond favourably to PLADO also. These patients may benefit by use of alternate drugs like irinotecan or a more intensive chemotherapy as compared to PLADO.

The 5-year OS and EFS of the cohort (n=32) were 89% and 80%, respectively, which is comparable to the 3-year OS and EFS of 95% and 83% reported in SIOPEL -3 [7]. The outcome of PRETEXT I disease appears to be inferior to PRETEXT II as one patient with PRETEXT I disease abandoned treatment after 2 courses and died. Ismail et al. [16] also reported a 76% survival in 38 standard-risk patients treated over a period of 20 years as compared to 90.6% survival noted in our series. The survival rates reported from India vary from 33%-100% from various reported series [10]. In our study, the 5-year EFS in children who were upgraded to PLADO was only 22% that was much lower than 69% in the upfront PLADO group. The reason for this difference could be development of tumor resistance to cisplatin that makes later

administration of PLADO chemotherapy less effective. Another interesting finding was that the 5-year EFS was 100% in the monotherapy group who did not need the upgradation of chemotherapy and was much higher than the upfront PLADO group. The reason can be the selection bias as the larger tumors with doubtful involvement of portal vein or hepatic vein were included in the upfront PLADO group.

Conclusion

Standard risk hepatoblastoma have good outcome with 5- year overall survival of 89%. Two thirds of patients with PRETEXT III tumors who received cisplatin monotherapy showed poor response and were upgraded to PLADO chemotherapy. These patients had a significantly ($p= 0.036$) poorer outcome compared to the rest of the cohort. In a resource-challenged setting, PRETEXT stage III standard-risk hepatoblastoma may benefit from PLADO chemotherapy instead of cisplatin monotherapy.

References

1. Mann JR, Kasthuri N, Raafat F, Pincott JR, Parkes SE, Muir KR, et al. Malignant hepatic tumours in children: incidence, clinical features and aetiology. Paediatr Perinat Epidemiol 1990;4:276–89.
2. Clatworthy HW, Schiller M, Grosfeld JL. Primary liver tumors in infancy and childhood. 41 cases variously treated. Arch Surg Chic Ill 1960 1974;109:143–7.
3. Douglass EC, Green AA, Wrenn E, Champion J, Shipp M, Pratt CB. Effective cisplatin (DDP) based chemotherapy in the treatment of hepatoblastoma. Med Pediatr Oncol. 1985;13:187-90.

4. Ortega JA, Krailo MD, Haas JE, King DR, Ablin AR, Quinn JJ, et al. Effective treatment of unresectable or metastatic hepatoblastoma with cisplatin and continuous infusion doxorubicin chemotherapy: a report from the Childrens Cancer Study Group. J Clin Oncol. 1991;9:2167-76

5. Brown J, Perilongo G, Shafford E, Keeling J, Pritchard J, Brock P, et al. Pretreatment prognostic factors for children with hepatoblastoma — results from the International Society of Paediatric Oncology (SIOP) Study SIOPEL 1. Eur J Cancer 2000;36:1418–25.
6. Perilongo G, Shafford E, Maibach R, Aronson D, Brugières L, Brock P, et al. Risk-adapted treatment for childhood hepatoblastoma. Eur J Cancer 2004;40:411–21.
7. Perilongo G, Maibach R, Shafford E, Brugieres L, Brock P, Morland B, et al. Cisplatin versus cisplatin plus doxorubicin for standard-risk hepatoblastoma. N Engl J Med 2009;361:1662–1670.
8. Agarwala S, Gupta A, Bansal D, Vora T, Prasad M, Arora B, et al. Management of Hepatoblastoma: ICMR Consensus Document. Indian J Pediatr 2017;84:456–64.
9. "HOSPITAL BASED CANCER REGISTRY - ncdirindia.org." [Online]. Available: https://www.ncdirindia.org/NCRP/ALL_NCRP_REPORTS/HBCR_REPORT_2012_2014/ALL_CONTENT/PDF_Printed_Version/TVM__HBCR_2012_2014.pdf. [Accessed: 04-Nov-2020]
10. Herzog CE, Andrassy RJ, Eftekhari F. Childhood cancers: hepatoblastoma. Oncologist 2000;5:445-53.
11. Arora RS. Outcomes of hepatoblastoma in the Indian context. Indian Pediatr 2012;49:307–9.

12. Aronson DC, Czauderna P, Maibach R, Perilongo G, Morland B. The treatment of hepatoblastoma: Its evolution and the current status as per the SIOPEL trials. J Indian Assoc PediatrSurg 2014;19:201–7.
13. Shanmugam N, Scott JX, Kumar V, Vij M, Ramachandran P, Narasimhan G, et al. Multidisciplinary management of hepatoblastoma in children: Experience from a developing country: Shanmugam et al. Pediatr Blood Cancer 2017;64:e26249.
14. Sunil BJ, Palaniappan R, Venkitaraman B, Ranganathan R. Surgical Resection for Hepatoblastoma—Updated Survival Outcomes. J Gastrointest Cancer 2018;49:493–6.
15. Qureshi SS. PRETEXT II–III multifocal hepatoblastoma: significance of resection of satellite lesions irrespective of their disappearance after chemotherapy. Pediatr Surg Int 2015;37:573-9
16. Ismail H, Broniszczak D, Kaliciński P, Dembowska-Bagińska B, Perek D, Teisseyre J, et al. Changing treatment and outcome of children with hepatoblastoma: analysis of a single center experience over the last 20 years. J Pediatr Surg 2012;47:1331-9.

Figure Legends

Figure 1. Chemotherapy administered to the cohort. (HB: Hepatoblastoma; PLADO: Cisplatin and Doxorubicin)

Figure 2 A. Kaplan Meir curve showing 5-year overall survival of the three chemotherapy groups. The difference was not statistically significant (p=0.078). B. Kaplan Meir curve showing 5-year event free survival of the three chemotherapy groups. The difference was statistically significant (p=0.001).

Figure 3 A. Kaplan Meir curve showing 5-year overall survival of the children with PRETEXT III disease who had received PLADO (upfront or after upgradation). The difference was not statistically significant (p=0.07). B. Kaplan Meir curve showing 5-year event free survival of the children with PRETEXT III disease who had received PLADO (upfront or after upgradation). The difference was statistically significant (p=0.036).