**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 5120**

**Columns: BRIEF ATICLE**

**Efficacy of neoadjuvant therapy and surgical rescue for locally advanced hepatoblastomas: 10 years single-center experience and literature review**

Ayllon Teran D *et al.* Neodjuvancy and surgery on locally advanced hepatoblastomas

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**Received:** August 16, 2013  **Revised:** October 18, 2013

**Accepted:** December 5, 2013

**Published online:**

**Abstract**

**AIM:** To report our experience with long-term outcomes after a multimodal management therapy.

**METHODS:** An observational retrospective study was performed, including seven patients with Hbl treated in our institution, a tertiary referral center, from 2003 to 2011. Demographic, preoperative, surgical and outcome variables were collected. A survival analysis and a review of current literature related to a combination neoadjuvant chemotherapy and surgical resection on Hbl were performed.

**RESULTS:** The median age at surgery was 14.4 mo, with a male to female ratio of 4:3. Pretext staging at diagnosis was as follows: stage I, 4 cases; stage II, 2 patients and stage III, 1 case. Mean pretreatment tumor volume was 735 cm3. Five out to seven patients received neoadjuvant chemotherapy according to SIOPEL-3 or SIOPEL-6 protocols. Tumor volume and alpha-fetoprotein levels significantly dropped after neoadjuvant therapy. Surgical procedures performed included hemihepatectomies, segmentectomies and atypical resection. All patients received chemotherapy after surgery. Median postoperative hospital stay was 8 d. All patients were alive and free-of-disease after a median follow-up period of 23 mo. Regarding the review, seventeen articles were found related to our search.

**CONCLUSION:** Our series shows how a multimodal management on Hbl, exhaustive control and meticulous surgical approach leads to almost 100% complete resection with optimal postoperative results.

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**Key words:** Liver tumours; Chemotherapy; Liver surgery; Multimodal Management

**Core tip:** Complete surgical resection is the cornerstone of treatment for hepatoblastoma (Hbl), but less than 40% of patients have resectable disease at diagnosis. Our experience with long-term outcomes after a multimodal management therapy and a review of literature are reported. An observational retrospective study was performed, including seven patients with Hbl treated in our institution, a tertiary referral center, from 2003 to 2011. Our series shows how a multimodal management on Hbl, exhaustive control and meticulous surgical approach leads to almost 100% complete resection with optimal postoperative results.

Ayllon Teran D, Gomez Beltran O, Ciria Bru R, Mateos Gonzalez E, Peña Rosa MJ, Luque Molina A, Lopez Cillero P, Briceño Delgado J. Efficacy of neoadjuvant therapy and surgical rescue for locally advanced hepatoblastomas: 10 years single-center experience and literature review.

*World J Gastroenterol 2013;*

Available from:

DOI:

**INTRODUCTION**

Hepatic neoplasms represent 1% of the malignant tumors in the childhood[1]. Hepatoblastoma (Hbl) is the most frequent tumor type, accounting for almost two-thirds of primary malignant liver tumors in children, with an overall incidence of 1.5 cases per million population[2,3]. Two thirds of these tumors occur in the first 2 years of age[4].

Most children with Hbl present with an enlarging abdominal mass and in 70% of cases are in an advanced stage at diagnosis[2]. Complete surgical resection is the cornerstone of treatment[5]; however less than 40% of the patients have resectable disease at diagnosis, because of local invasion, caval infiltration or distant metastases[6]. In the early 1970s, some studies reported the response of the Hbl to chemotherapy. The International Society of Pediatric Oncology (SIOP) was a pioneer in the concept of neoadjuvant chemotherapy for the management of hepatoblastoma[7,8]. Thereby, 28% of patients may be down staged, in 87%-91% of cases a complete macroscopic resection may be achieved and the morbidity and mortality rates have decreased to 18% and 5%, respectively, with the use of neoadjuvant chemotherapy[5,9]. Chemotherapy is used to reduce tumor size in lesions that appear unresectable at diagnosis and to control residual microscopic disease after definitive resection[9]. Orthotopic liver transpalantation (OLT) is an effective therapy for selected malignancies in the childhood, as multifocal Hbl without extrahepatic disease, type-2 hemangioendotheliomas and hepatocarcinoma with tumours < 5 cm without vascular invasion[10].

Despite its effectiveness, isolated surgical resections may not be enough to control disease spread. Moreover, locally advanced Hbl may require extensive liver resections that may lead to increased postoperative morbidity and mortality. Few series have reported the efficacy of neoadyuvant chemotherapy and surgical resection for Hbl. Hereby we report our experience with long-term outcomes on Hbl after a multimodal management therapy.

**MATERIALS AND METHODS**

All the patients diagnosed of Hbl and treated at our institution, a tertiary referral center, between 2003 and 2011 were included in this observational retrospective analysis. According to image techniques such as computerized tomography (CT) scan or magnetic resonance imaging (MRI), all patients were assigned to PRETEXT (Pre-treatment extent of disease) stage and four groups of patients were identified as PRETEXT I-IV, both at diagnosis and after preoperative chemotherapy, according to the classification proposed by Liver Tumors Strategy Group (SIOPEL) for their SIOPEL-1 study[11]. Standard follow up was based on serial AFP levels every three months for the first year and every six months for the next ten years. MRI every six months was our protocolized imaging technique for the immediate 5 years after surgery.

Demographic (age, gender and weight); preoperative (initial presentation, alpha-fetoprotein (αFP) levels, location and volume of the tumor, method of diagnosis, tumor spread at diagnosis, preoperative chemotherapy; surgical procedure performed, tumor characteristics, histology, margins and vascular invasions and outcomes (complications of treatment, length of hospital stay, recurrence, overall and disease-free survival) variables were collected. Data were expressed as median and range. Independent and paired non-parametric tests were used for baseline comparisons. SPSS software 14.0 was used for statistical analysis.

A review of the literature was carried out to identify all series reported of hepatoblastomas treated with a combination of neoadjuvant chemotherapy and surgical resection. The Cochrane Database of systematic reviews, the Cochrane central register of controlled trials, and MEDLINE databases were searched using the keywords (preoperative chemotherapy OR neoadjuvant treatment OR locally advanced) AND (hepatoblastoma) to identify studies published up to September 2012. Free text words were used instead of MeSH terms to avoid missing recent articles that had not yet been given a MeSH label. Two investigators (MDA and OG) independently performed the literature search. Electronic links to related articles and references of selected articles were hand-searched as well. The search was not restricted to any language but only studies published in English were taken into account.

**RESULTS**

***Descriptive results***

Seven children with Hbl were referred to our hospital between 2003 and 2012. Male to female ratio was 4**:**3. The median age at surgery was 14.4 mo (range, 3-31 mo). Golabi-Behmel syndrome (congenital syndrome X-linked with an increased risk of embryonal cancers)[12] was associated in a male patient, but none of the patients were preterm. Median weight of the patients prior to the surgery was 9.26 kg (range, 4.8-13.5 kg). The most common symptom found was a palpable abdominal mass (85%). The median alpha-fetoprotein (αFP) level at diagnosis was 141.7 ng/mL (range, 379-483756 ng/mL). Thrombocytosis was found in 71.4% of cases. PRETEXT staging at diagnosis was as follows: Stage I 4 patients, Stage II 2 cases and Stage III 1 patient. There were not any metastases at diagnosis. P1, an additional criteria of PRETEXT staging (involvement of either the left or right branch of the portal vein) was suspected in three cases (two right branch, one left branch)[13]. Mean tumor volume at diagnosis was 735 cm3 (range, 150-1950 cm3) (Table 1).

***Therapeutic approach to locally advanced hepatoblastoma***

Chemotherapy was given to all patients. Five of seven patients received neoadjuvant chemotherapy, completing four cycles before surgery and two more after the surgery. The remaining two underwent primary surgery and received four cycles adjuvant chemotherapy. The pathological diagnosis of Hbl was confirmed by percutaneous biopsy previous to neoadyuvant chemotherapy in all cases. Chemotherapy regimens included the SIOPEL study protocols. PLADO regimen or SIOPEL-3 protocols (Platinum on day 1 at a dose of 2.7 mg/kg per day and Doxorubicin at a dose of 1 mg/kg per day on 2 d and 3 every 20 d) was used in four patients, and Cisplatin alone or SIOPEL-6 (at a dose of 2.7 mg/kg per day) was used in three patients. Neutropenia cases were treated with granulocyte stimulating grow factor and trimethopin/sulfamethoxazole was used for prophylaxis against Pneumocystis pneumonia. Neither mortality nor long-term toxicity related with chemotherapy was reported. The patients who underwent neoadjuvant chemotherapy were reassessed every two months and all of them received four cycles before surgery.

Tumor volume significantly dropped after neoadjuvant chemotherapy (from an initial median of 735-287 cm3; *P* = 0.02). The same happened to FP levels, although statistical significance was not reached (from pretreatment median of 141-7.9 ng/mL; *P* = 0.10) (Figure 1).

Surgical procedures performed included right hepatectomy in two patients, left hepatectomy in one, bisegmentectomy VII-VII in one, segmentectomy VI and IVb in two, and an atypical resection of pediculated tumor arising from segment VI in one patient. The only postoperative complication was a subphrenic abscess that required percutaneous drainage. Median postoperative hospital stay was 8 days (range, 5-26 d).

The histological types encountered were as follows: embryonal and mixed embryonal/fetal subtype in three patients, mixed epithelial and mesenchymal type in two patients and purely fetal type in two patients. All specimens had tumor-free margins.

***Review of current literature***

Using the aforementioned criteria, seventeen articles were found including case reports. We selected articles in which most of their patients had been treated with neoadjuvant chemotherapy and surgical resection and those reporting locally advanced hepatoblastomas (stage post-TEST III or IV). Seven studies were included (Table 2).

***Statistical analysis***

All the patients are alive after a median follow-up period of 23 mo (range, 18-111 mo). The median disease-free survival is 23 mo (range, 6-111 mo). One patient developed six months later distant metastases in the middle right lobe lung requiring a pulmonary atypical resection; after 18-mo follow up the patient is free of disease. The remaining 6 cases have not evidence of recurrence or rise in the AFP levels.

**DISCUSSION**

Management of Hbl has evolved from unresectable or extensive surgical resections with high rates of morbidity and mortality to the current standard of care of neoadjuvant chemotherapy followed by surgery[20]. Complete tumor resection is essential for cure; therefore, any strategy that may reduce tumor volume leading to an increased resection rate would provide survival benefit[21]. An initial surgical approach may be acceptable for resectable disease, but a combined approach may be preferable in advanced stages[18]. Our series shows how multimodal management, exhaustive control and meticulous surgical approach leads to almost 100% complete resection with optimal postoperative results. Otherwise, we are aware one limitation of our study is that we have few patients included.

The prognosis for children with Hbl has improved over last decades. The survival in 1970s with surgical resection alone was about 10%-20%[22]. After the routine use of preoperative cisplatin and doxorubicin (PLADO regimen), surgical resection was achieved in 87% of the cases whereas historically only 30% of the cases were operable upfront[23]. Later, Liver transplantation proved to be an effective treatment for certain children with Hbl. Criteria established by SIOPEL recommend that it should be considered in patients with neoplasm in all 4 liver sections, tumor extension into the vena cava or all 3 hepatic veins, invasion of the main and/or left and right portal veins, or recurrent disease after resection (rescue transplant)[24]. In our cohort, liver transplant was not performed in any patient.

Pritchard *et al*[8] published in 2000 the first international study (SIOPEL-1), applying preoperative chemotherapy (PLADO: cisplatin plus doxorubicin) and delayed surgery. However, the prognosis with advanced stages remained unsatisfactory. To improve the survival of these patients, the SIOPEL group intensified the chemotherapy in their subsequent studies. Thus, in the SIOPEL-2 study the patients were classified in two groups: one for patients with Hbl confined to the liver and involving no more than three hepatic sectors (standard-risk Hbl) treated with cisplatin alone every 14 d; and one for those with Hbl extending into all four sectors and/or with lung metastases or intra-abdominal extra hepatic spread (high-risk Hbl) treated with cisplatin alternating every 14 d with carboplatin and doxorubicin. In 2004, Perilongo *et al*[15] published their results in which, despite chemotherapy intensification, only half of the high-risk Hbl patients were long-term survivors. Later, the SIOPEL-3 study showed an improved survival in this group of patients. This study was designed to test the efficacy of this treatment strategy including only high-risk Hbl patients: tumor in all liver sections, vascular invasion, extrahepatic extension, metastatic disease or FP less than 100 ng/mL at diagnosis.

Some other series have reported their results with advanced Hbl, including specific surgical results[16,17]. Some other series have been published with a focus on advanced stage III-IV Hbl[18-19]. Unfortunately, although results have improved, complete resection rates are still between 60%-75% and free-of-disease survival rates between 65%-80%. In our series, surgical outcomes and hospital stay are in accordance with literature. The experience of an active paediatric liver transplant program surely is helpful for this multidisciplinary approach and for getting optimal surgical resections.

Our results support the key role for the neoadjuvant chemotherapy when the tumor appears in advanced stages and a complete resection at initial diagnosis is unlikely to happen. In addition, preoperative chemotherapy has led to an increase in surgical resection rates, allowing more limited hepatectomies and decreasing the rate of postoperative complications. Postoperative chemotherapy shows also good results, therefore avoids reoperation for positive resection margins. Multidisciplinary management of Hbl is mandatory, as children population is especially susceptible for complications in the surgical procedure. The combination of chemotherapeutic regimes and surgical techniques has shown to be the best option and has led to improve free-of-disease rates and long-term survival.

**COMMENTS**

***Background***

Hepatoblastoma (Hbl) is the most frequent malignant liver tumor in childhood. Complete surgical resection is the most important treatment, but a limited percentage of them have resectable disease at diagnosis. The International Society of Pediatric Oncology (SIOP) was a pioneer in the concept of neoadjuvant chemotherapy for the management of these neoplasms. Currently, a multimodal management is the best option for Hbl.

***Research frontiers***

The neoadjuvant chemotherapy is used in many tumours in order to reduce the tumour size and allow complete resection, and secondly to control residual microscopic disease. In the area of Hbl management, the research hotspot is how a multimodal therapy with several regimes of preoperativ chemotherapy may increase the rate of feasible surgical resection, improve the postoperative morbidity and consequently get better long-term survival outcomes, especially in advanced Hbl at diagnosis.

***Innovations and breakthroughs***

There are several studies in literature that report the benefit of a multidisciplinary treatment for Hbl in last decades, however in the case of advances stages, there are no so many papers and their prognosis remained unsatisfactory till recently. Three international studies conducted by the SIOP published their results applying preoperative chemotherapy in progressive stages. Their survival outcomes showed an improvement along the sequential studies, especially, in regard to high-risk Hbl. Unfortunately, although results have improved, complete resection rates cannot be always achieved. This report a series of cases, advanced stages Hbl included, with very good surgical and survival outcomes.

***Applications***

This results support the key role for the multidisciplinary therapy, such as neoadjuvant chemotherapy in unresectable tumors upfront, complete surgical resection and postoperative chemotherapy.

***Terminology***

Cisplatin is a chemotherapy drug. It was the first member of a class of platinum-containing anti-cancer drugs, which now also includes carboplatin and oxaliplatin. Doxorubicin is also an antineoplastic chemotherapy drug that is a standard component in treating many types of tumours.

***Peer review***

This is an interesting study in which the authors reported the experience of a single-center in the management of Hbl in last ten years, with a multimodal management therapy. The results are in accordance with literature and suggest that it has been the best way to improve the prognosis of Hbl.

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**P-Reviewers** Dziri C, Wang JG **S-Editor** Qi Y **L-Editor E-Editor**

**Table 1 Patients features and outcomes**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Age (yr)** | **PRETEXT** **pre-QT** | **Segments involved at diagnosis** | **AFP at diagnosis (ng/mL)** | **Histology** | **Chemotherapy (No. of cycles)** | **POSTEXT at surgery (localization)** | **Surgery** | **Postoperative events** | **Follow-up (mo)** | **Current status** |
| 3 | III, P1 (right branch) | I,V,VI,VII,VIII | 18597.37 | Embryonal | Neoadjuvant PLA (4 cycles)+ Adjuvant (2c) | II (V,VI,VII,VIII) | Right hepatectomy | Subphrenic abscess (drainage) | 18 | CR |
| 4 | II, P1 (left branch) | IVb,V,VIII | 551.21 | Epithelial mesenchymal mixed | Neoadjuvant PLA (4c) + Adjuvant (2c) | I (IVb) | Segmentectomy IVb | Uneventful | 19 | CR |
| 8 | I | II,III | 473856 | Epithelial fetal | Neoadjuvant PLADO (4c) + Adjuv (2c) | I (II,III) | Left hepatectomy | Uneventful | 56 | CR |
| 13 | I | VIII | 14277 | Epithelial fetal | Neoadjuvant PLA (4c) + Adjuv (2c) | I (VIII) | Right hepatectomy | Uneventful | 28 | CR |
| 15 | I | VI | 401800 | Epithelial mesenchymal mixed | Adyuvant PLADO (4c) | I (VI) | Tumorectomy | Uneventful | 106 | CR |
| 25 | II, P1 (right branch) | V,VI,VII,VIII | 83100.5 | Embryonal fetal epithelial | Neoadyuvant PLADO (4c) + Adjuv (2c) | II, P0 (VII, VIII) | Bisegmentectomy VII, VIII | Uneventful | 13 | Lung metastasis |
| 31 | I | VI | 379 | Epithelial | Adyuvant PLADO (4c) | I (VI) | Segmentectomy VI | Uneventful | 50 | CR |

PLA: Cisplatin; DO: Doxorubicin; P1: Involvement of either the left or the right branch of the portal vein; CR: Complete remission.

**Table 2 Review of current literature**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **N NACH/****N** | **Gender (M/F)** | **Age (mo)** | **CH Regimen** | **CH Morbidity** | **PR CH** | **Complete resection** | **Postoperative events** | **OS** | **FDS** |
| Pritchard *et al*[8] 2000 SIOPEL-1 | 138/154 | 97/ 57 | 16.5 | PLADO (cis+dox) | 2% death 6% myelotoxicity < 2% others  | 82 % | 92% | 5 deaths 8% infections 3% bleeding 9% others | 75% | 66% |
| Katzenstein *et al*[18] 2002 | 33/33 | 21/12 | 22 | Car-vin-5FU | 60% myelotoxicity  | 82% | 58% | - | 57% | 48% |
| Perilongo *et al*[15] 2004 SIOPEL-2 | 135/135 | 81 / 54 | 16-25 | Cis Carb-Dox-Cis | Neutropenia 43-81% Infections 40-76% Transfusion 19-76% | 90% (SR HB) 78% (HR HB) 90% (SR-HR) | 97 % (SR HB) 67% (HR HB) 100% (SR-HR) | - | 91% (SR HB) 53% (HR HB) 86% (SR-HR) (\*) | 89% (SR HB) 48% (HR HB) 89% (SR-HR) |
| Towu *et al*[9] 2004 | 54 / 56 | 34 / 22 | 12 | 22 PLADO 14 SIOPEL-2 17 SIOPEL-3 | - | 92% | 74% | 1 death 22% (bile leakage, collections, others) | 75% | - |
| Zsíros *et al*[16] 2010 SIOPEL-3 | 150 / 151 | 90 / 61 | 21 | Cis / Car-dox | 1 death 76% neutropenia 51% infections 33% renal toxicity | 78.7% | 76.2% | 4 deaths | 69%1 | 65% |
| Lautz *et al*[19] 2010 | 14 / 14 | 7 / 7 | 8 | Cis-vin-5FU Others | - | 61% | 85% | 1 Iscq Colangiop 1 portal thrombosis | 88% | 77% |
| Hishiki *et al*[17] 2011 | 185 / 212 | 132 / 80 | 17 | Cis-Pir Iof-car-pir-eto | 90% neutropenia 10% infections < 10% others | 65% | 63 % | - | 81 % | 62.4% |
|  |  |  |  |  |  |  |  |  |  |  |

13-years overall survival. NACH: Number of pacients with neoadjuvant chemotherapy; N: Total number of patients; CH: Chemotherapy; PR: Partial response; OS: 5-years overall Survival; FDS: Free disease survival; cis: cisplatin; dox: Doxorubicin; carb: carboplatin; pir: Pirarubicin; iof: Iofosfamide; eto: Etopoxido; vin: Vincristine; 5FU: 5-fluoracilo. SR HB: Standard risk hepatoblastoma; HR HB: High risk hepatoblastoma; SR-HR: Standard risk hepatoblastoma treated as high risk hepatoblastoma.

**Figure 1 Changes after neoadjuvant chemotherapy.** A: CT- Down-staging effect of neoadjuvant chemotherapy; B: Tumor volume at diagnosis and before surgery; C: AFP level at diagnosis and before surgery.



A



|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| At diagnosis | 712 | 150 | 378 | 486 | 1950 | 840 | 631 |
| Pre-Qx | 140 | 150 | 172 | 486 | 86 | 86 | 135 |

B



|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| AFP at diagnosis | 401800 | 379 | 551.21 | 83100.5 | 18597.37 | 14277 | 473856 |
| AFP Pre-Qx | 23 | 3.7 | 298.5 | 30126.6 | 2461.2 | 125 | 1078.8 |

C