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

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

METHODS: An observational retrospective study was performed containing seven patients with hepatoblastoma (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 the current literature related to 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 of seven patients received neoadjuvant chemotherapy according to SIOPEL-3 or SIOPEL-6 protocols. Tumor volume and alphafetoprotein 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 disease-free after a median follow-up period of 23 mo. With regards to the literature review, seventeen articles were found that were related to our search.

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

Key words: Liver tumors; 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 multimodal management therapy and a review of the 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 multimodal management of Hbl, exhaustive control and a meticulous surgical approach leads to almost 100% complete...
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INTRODUCTION

Hepatic neoplasms represent 1% of childhood malignant tumors[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 life[4].

Most children with Hbl present with an enlarging abdominal mass, and in 70% of cases are in an advanced stage at diagnosis[5]. Complete surgical resection is the cornerstone of treatment[6]; however less than 40% of patients have resectable disease at diagnosis due to local invasion, caval infiltration, or distant metastases[7]. In the early 1970s, some studies reported the response of Hbl to chemotherapy. The International Society of Pediatric Oncology (SIOP) was a pioneer in the concept of neoadjuvant chemotherapy for the management of hepatoblastoma[8,9]. Using neoadjuvant chemotherapy, 28% of patients may be down-staged, complete macroscopic resection may be achieved in 87%-91% of cases, and morbidity and mortality rates have decreased to 18% and 5%, respectively[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 transplantation (OLT) is an effective therapy for selected malignancies in childhood, such as multifocal Hbl without extrahepatic disease, type-2 hemangioendotheliomas, and hepatocellular carcinoma with tumors < 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 neoadjuvant chemotherapy and surgical resection for Hbl. We therefore report our experience with long-term outcomes of Hbl after multimodal management therapy.

MATERIALS AND METHODS

All patients diagnosed with Hbl and treated at our institution, a tertiary referral center, between 2003 and 2011 were included in this observational retrospective analysis. According to imaging techniques, such as computerized tomography (CT) scan or magnetic resonance imaging (MRI), all patients were assigned a PRETEXT (pretreatment extent of disease) stage, with four groups of patients identified as PRETEXT I - IV, both at diagnosis and after preoperative chemotherapy, according to the classification proposed by the Liver Tumors Strategy Group (SIOPEN) for their SIOPEN-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 protocol imaging technique for the immediate 5 years after surgery.

A review of the literature was carried out to identify all series that reported 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 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.

Statistical analysis

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.

RESULTS

Descriptive results

Seven children with Hbl were referred to our hospital between 2003 and 2012. The 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 cancer) 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 αFP level at diagnosis was 141.7 ng/mL, 1 patient. There were no metastases at diagnosis. An
additional criterion of PRETEXT staging, P1 (the involvement of either the left or the right branch of the portal vein), was suspected in three cases (two right branches and one left branch)\(^1\). Mean tumor volume at diagnosis was 735 cm\(^3\) (range, 150-1950 cm\(^3\)) (Table 1).

**Table 1 Patients features and outcomes**

| Age (yr) | PRE-TEXT pre-QT | Segments involved at diagnosis | AFP at diagnosis (ng/mL) | Histology | Chemotherapy (No. of cycles) | POST-TEXT at surgery (localization) | Surgery | Postoperative events | Follow-up (mo) | Current status |
|---------|-----------------|-------------------------------|--------------------------|-----------|-----------------------------|-------------------------------------|---------|----------------------|----------------|---------------|
| 3       | III, P1 (right branch) | I, V, VI, VII | 18597.37 | Embryonal | Neoadjuvant PLA (4 cycles) + adjuvant (2c) | II (V, VI, VII) | Right hepatectomy | Subphrenic abscess (drainage) | 18 | CR |
| 4       | II, P1 (left branch) | IVb, V, VII | 551.21 | Epithelial mesenchymal mixed | Neoadjuvant PLA (4c) + adjuvant (2c) | I (IVb) | Segmentectomy IVb | Uneventful | 19 | CR |
| 8       | I | II, III | 473856.00 | Epithelial fetal | Neoadjuvant PLADO (4c) + adjuvant (2c) | I (II, III) | Left hepatectomy | Uneventful | 56 | CR |
| 13      | I | VII | 1427.00 | Epithelial fetal | Neoadjuvant PLA (4c) + adjuvant (2c) | I (VII) | Right hepatectomy | Uneventful | 28 | CR |
| 15      | I | VI | 401800.00 | Epithelial mesenchymal mixed | Adjuvant PLADO (4c) | I (VI) | Tumorectomy | Uneventful | 106 | CR |
| 25      | II, P1 (right branch) | V, VI, VII | 83100.50 | Embryonal/fetal epithelial | Neoadjuvant PLA (4c) + adjuvant (2c) | II, VII | Bisectionectomy VII, VIII | Uneventful | 13 | Lung metastasis |
| 31      | I | VI | 379.00 | Epithelial | Adjuvant 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.

**Therapeutic approach to locally advanced hepatoblastoma**

Chemotherapy was given to all patients. Five out of the seven patients received four cycles of pre-operative neoadjuvant chemotherapy, with additional two post-surgery. The remaining two patients underwent primary surgery and received four cycles of adjuvant chemotherapy. The pathological diagnosis of HBl was confirmed by percutaneous biopsy previous to neoadjuvant 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 day 2 and 3 mg/kg per day 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 trimethoprim/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 cm\(^3\); \(P = 0.02\)). The same happened to \(\alpha\)-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, bisectionectomy VII-VII in one, segmentectomy VI and IVb in two, and an atypical resection of a pediculated tumor arising from segment VI in one patient. The only postoperative complication was a subphrenic abscess that required percutaneous drainage. The median postoperative hospital stay was 8 d (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 that included case reports. We selected articles in which most of the study patients had been treated with...
ment strategy including only high-risk Hbl patients: tumor in all liver sections, vascular invasion, extrahepatic extension, metastatic disease or αFP less than 100 ng/mL at diagnosis.

In addition, the results of an English institution with 54 patients of all stages were reported by Towu et al [16] in 2004. Hishiki et al [17] published the results of 185 patients in a Japan centre in 2011, as well. Additionally, we have considered two studies that regard only patients with advanced stages: Katzenstein et al [18] include thirty three patients with stage III (unresectable or nodal involvement) and IV Hbl (metastatic disease), and Lautz et al [19] who include fourteen patients underwent resection for POST-Ⅳ or centrally located POST-Ⅲ after neoadjuvant chemotherapy.

Statistical analysis

All 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 distant metastases in the middle right lobe lung six months later that required a pulmonary atypical resection; after 18-mo follow-up the patient is free of disease. The remaining 6 cases have no evidence of recurrence or a
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, namely neoadjuvant chemotherapy followed by surgery. Complete tumor resection is essential for cure; therefore, any strategy that may reduce tumor volume, and thus lead to an increased resection rate, would provide a survival benefit. An initial surgical approach may be acceptable for resectable disease, but a combined approach may be preferable in advanced stages. Our series shows how multimodal management, exhaustive control, and a meticulous surgical approach led to almost 100% complete resection with optimal postoperative results. However, we are aware that our study is limited by its small sample size.

The prognosis for children with Hbl has improved over the last few decades; survival in the 1970s with surgical resection alone was about 10%-20%. After the routine use of preoperative cisplatin and doxorubicin (PLADO regimen), surgical resection was soon achieved in 87% of cases, whereas historically only 30% of cases were operable upfront. Liver transplantation later proved to be an effective treatment for certain children with Hbl. Criteria established by SIOPEL recommend that it should therefore 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). In our cohort, liver transplantation was not performed in any patient.

Table 2  Review of current literature

| Study          | NACH/N (n) | Gender (M/F) | Age  (mo) | CH regimen | CH morbidity | PR CH | Complete resection | Postoperative events | OS   | DFS |
|---------------|------------|--------------|-----------|------------|--------------|-------|--------------------|---------------------|------|-----|
| Pritchard et al, 2000 | 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, 2002 | 33/33      | 21/ 12       | 22        | Car-vin-5FU | 60% myelotoxicity Neutropenia 43%-81% Infections 40%-76% Transfusion 19%-76% | 82% | 58% | - | - | 57% | 48% |
| Perilongo et al, 2004 | 135/135    | 81/ 54       | 16-25     | Cis Car-dox-cis | Neutropenia 90% (SR HB) Infections 78% (HR HB) Transfusion 90% (SR-HR) | 90% | 75% | - | - | 91% (SR HB) | 89% (SR HB) |
| Towne et al, 2004 | 54/56      | 34/ 22       | 12        | 22 PLADO 14 SIOPEL-2 17 SIOPEL-3 22 PLADO | 1 death 76% neutropenia 51% infections 33% renal toxicity | 78.70% | 76.20% | - | 1 death 22% (bile leakage, collocations, others) | 69% | 65% |
| Zsíros et al, 2010 | 150/151    | 90/ 61       | 21        | Cis/car-dox 150/151 14 SIOPEL-2 17 SIOPEL-3 | 1 death 76% neutropenia 51% infections 33% renal toxicity | 76.20% | 73.70% | - | 4 deaths | 69% | 65% |
| Lautz et al, 2010 | 14/14      | 7/ 7         | 8         | Cis-vin-5FU | 1 death 76% neutropenia 51% infections 33% renal toxicity | - | 61% | 85% | 1 Isq cholangio 1 portal thrombosis | 88% | 77% |
| Hishiki et al, 2011 | 185/212    | 132/ 80      | 17        | Cis-pir iof-car-pir-eto | 90% neutropenia 10% infections < 10 % others | 65% | 63% | - | 81% | 62.4% |

3-year overall survival. NACH: Number of patients with neoadjuvant chemotherapy; N: Total number of patients; CH: Chemotherapy; PR: Partial response; OS: 5-year overall survival; DFS: Disease-free survival; cis: Cisplatin; dox: Doxorubicin; car: Carboplatin; pir: Piranubicin; iof: Iofosfamide; eto: Etoposide; vin: Vincristine; 5FU: 5-fluorouracil; SR HB: Standard risk hepatoblastoma; HR HB: High risk hepatoblastoma; SR-HR: Standard risk hepatoblastoma treated as high risk hepatoblastoma.
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 the literature. The experience of an active pediatric liver transplant program would surely be helpful for this multidisciplinary approach and for getting optimal surgical resections.

Our results support the key role of neoadjuvant chemotherapy when the tumor appears in advanced stages and a complete resection at initial diagnosis is unlikely to occur. In addition, preoperative chemotherapy has led to an increase in surgical resection rates, allowing more limited hepatatectomies and decreasing the rate of postoperative complications. Postoperative chemotherapy shows also good results, thereby avoiding reoperation for positive resection margins. Multidisciplinary management of Hbl is mandatory, as the childhood population is especially susceptible for complications during surgical procedure. The combination of chemotherapeutic regimes and surgical techniques has shown to be the best treatment option, and has led to improved 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 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. Multimodal management is currently the best treatment option for Hbl.

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

Innovations and breakthroughs
Although there are several studies in the literature that report the benefit of a multidisciplinary treatment for Hbl in the last few decades, there are fewer studies concerning Hbl in its advanced stages and the prognosis for such cases remained unsatisfactory until 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 with regards to high-risk Hbl. Unfortunately, despite improving results, complete resection rates cannot be always achieved. The current report contains a series of cases, including advanced stages of Hbl, with very good surgical and survival outcomes.

Applications
The results support the key role of multidisciplinary therapy, such as neoadjuvant chemotherapy in resectable 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 an antineoplastic chemotherapy drug that is a standard component in treating many types of tumors.

Peers review
This is an interesting study in which the authors reported the experience of a single center in the management of Hbl over ten years with a multimodal management therapy. The results are in accordance with the literature and suggest that it is the best option for improving the prognosis of Hbl.

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