MANAGEMENT OF HEPATOBLASTOMA

Christopher Lau
SUNY Downstate Medical Center
22 month old BB presented to KCHC in June 2010 when his mother felt a hard mass in his abdomen

Mother denied any other problems

Baby had normal eating and drinking, normal stool, normal activity

No other complaints
PAST MEDICAL HISTORY

- Negative
- Birth/Developmental History:
  + Uncomplicated NSVD
  + Mother unaware of pregnancy until she was in labor
  + First words 8 months
  + Walked 16 months
  + Drinks 8oz. Milk 3-4 times a day with occasional meat, fruits and vegetables
  + Immunizations up to date
PHYSICAL EXAM

- Well developing, well nourished, active
- Weight 12.8kg (84th percentile)
  - Was 13.5kg in April 2010
- Length 84cm (80th percentile)
- Chest: clear
- CVS: regular rate, no murmur
- Abdomen: large, hard mass occupying right side of abdomen and extending into LUQ
Clinical Impression: Hepatoblastoma metastatic to lungs

7/7: Open liver biopsy
  Pathology: undifferentiated hepatoblastoma

7/9: Chemoport placed

7/14: SIOPEL-3HR protocol initiated
### Chemotherapy

<table>
<thead>
<tr>
<th>Date</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/14/2010</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>7/22/2010</td>
<td>Carboplatin/Doxorubicin</td>
</tr>
<tr>
<td>8/12/2010</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>8/27/2010</td>
<td>Carboplatin/Doxorubicin</td>
</tr>
<tr>
<td>9/14/2010</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>10/3/2010</td>
<td>Carboplatin/Doxorubicin</td>
</tr>
<tr>
<td>10/19/2010</td>
<td>Cisplatin</td>
</tr>
</tbody>
</table>

### AFP

<table>
<thead>
<tr>
<th>Date</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/6/2010</td>
<td>60500</td>
</tr>
<tr>
<td>8/4/2010</td>
<td>72981</td>
</tr>
<tr>
<td>9/8/2010</td>
<td>10310</td>
</tr>
<tr>
<td>10/10/2010</td>
<td>3491</td>
</tr>
<tr>
<td>10/19/2010</td>
<td>2033</td>
</tr>
<tr>
<td>12/2/2010</td>
<td>4601</td>
</tr>
</tbody>
</table>
Presented to Downstate for hepatic resection on 12/3/2010

- Weight 13.5kg (50-75th percentile)
- Height 87cm (75th percentile)
- Abdomen: hard mass in RUQ extending 3cm below the costal margin and into the LUQ
LABS

- CBC: 3.6>9.5/30.1<304
- BMP: 137/4.3/107/19/19/0.38/90/9.5
- LFT: 7/4.4/26/16/271/0.1
- Coag: 15.7/36.6/1.3
OPERATION

- Bilateral subcostal incision with vertical extension
- Adhesions and falciform were taken down
- Divided right triangular ligament
- Ligated short hepatic veins, right and middle hepatic vein
- Cholecystectomy performed
- Isolated and ligated right hepatic artery, portal vein, and hepatic duct
- Liver parenchyma divided with electrocautery, blunt dissection and ligation of larger vessels and ducts
Right hepatic lobe
  + Hepatoblastoma
  + Mixed mesenchymal and epithelial cells
  + 12cm
  + Resection margins negative for tumor
  + Pathologic Stage I (pT1NxMx)
POST-OP COURSE

- Returned to PICU intubated
- POD#3 extubated
- POD#4 tolerating diet
- Drain output serosanguinuous
MANAGEMENT OF HEPATOBLASTOMA
HEPATOBLASTOMA

- Malignant liver tumors account for 1% of all pediatric malignancies
  + Hepatoblastoma
  + Hepatocellular carcinoma

- Liver tumors are the third most common intra-abdominal neoplasm after neuroblastoma and nephroblastoma
**Epidemiology**

<table>
<thead>
<tr>
<th>Hepatoblastoma</th>
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</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
</tr>
<tr>
<td><strong>Age distribution</strong></td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td><strong>5-yr survival</strong></td>
</tr>
</tbody>
</table>
CLINICAL FEATURES

- Most present with an abdominal mass
- Most are asymptomatic
- Thrombocytosis is present in 60%
- Most sensitive lab test is serum AFP
  - Elevated in over 90% of hepatoblastomas
  - A nonspecific tumor marker
  - Can be used to monitor chemotherapeutic efficacy and tumor recurrence
DIAGNOSTIC AND TREATMENT ALGORITHM

Liver Mass

- Diagnostic Imaging (US and/or CT)
  - Solid
    - Staging Workgroup:
      - Labs (AFP, CBC, LFTs, PT/PTT, Chemistry)
      - CXR ± Chest CT
      - ± MRI
      - Surgery for Exploration
    - Resectable
      - Resection
      - Chemotherapy (± Chemotherapy for Stage I – Pure Fetal Histology)
      - Follow-up
      - OriginalAFP ↑
      - Serial AFP
    - Original AFP Normal
      - Serial Imaging
    - Not Resectable
      - Biopsy
      - Neoadjuvant Chemotherapy
      - Imaging
      - Not Resectable

- Vascular or Cystic
  - ± Angiography / Resection vs. Observation
  - (+) Metastasis
Ultrasound
- Well-defined hyperechoic solid lesion
- Color doppler can be used to assess vascular involvement

CT
- Usually reveals a low attenuation mass
- Can delineate tumor size, location, and regional adenopathy

MRI
- Useful for determining relationship to hepatic vasculature and biliary anatomy
- Homogenous hypointensity on T1-weighted and hyperintensity on T2-weighted images
Multiple staging systems

Current system used by Pediatric Oncology Group

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Complete resection</td>
</tr>
<tr>
<td>II</td>
<td>Microscopic residual tumor</td>
</tr>
<tr>
<td>III</td>
<td>Macroscopic residual tumor</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

PRETEXT staging system for neoadjuvant treatment

Describes liver segments involved, metastases, ingrowth of vena cava, ingrowth of portal vein, and extrahepatic extension
PRETEXT STAGING SYSTEM

I

- 3 adjoining sectors FREE

II

- 2 sectors in one lobe FREE

III

- L lat. sector FREE
- R post. sector FREE

IV

- L med. sector FREE
- R ant. sector FREE

- no FREE sector

(m) metastases
(v) ingrowth vena cava
(p) ingrowth vena portae
(e) extrahepatic extension
CHEMOTHERAPY

- Neoadjuvant therapy
  + Downstaging disease
  + Improves resectability
  + Improves long term survival
  + Non-responders can experience disease progression
    - AFP and imaging must be monitored for response
Several regimens are available

- **SIOP (Société Internationale d'Oncologie Pédiatrique)** advocates use of cisplatin/doxorubicin regimen

- Other regimens include:
  - Cisplatin, vincristine, 5-fluorouracil
  - Cisplatin, ifosfamide, doxorubicin

- Irinotecan may be considered for refractory or recurrent hepatoblastoma
Randomized prospective trial
- 182 patients with Stage I-unfavorable to Stage IV disease
- Randomized to receive (A)cisplatin/vincristine/fluorouracil or (B)cisplatin/doxorubicin after surgery
- 5 year event free survival was 57% and 69% (P=0.09)
- Overall toxicities, were significantly more frequent in patients who received regimen B
- Neutropenia (P <.001), thrombocytopenia (P <.0001), anemia (P <.001), stomatitis (P <.0001), adverse cardiac effects (P <.01), renal dysfunction (P =.02)
- However, there were no cures in Stage IV patients
Prospective clinical trial

Evaluates intensified regimen adding carboplatin to the cisplatin/doxorubicin regimen for high risk hepatoblastoma

- Tumor in all liver sectors (PRETEXT IV)
- Vascular invasion [+P] or 3 hepatic veins [+V]
- Intra-abdominal extrahepatic extension
- Metastatic disease [+M]
- AFP< 100ng/ml at diagnosis

151 enrolled, 118 achieved partial response to chemo, 115 had complete resection of tumor
3 year event free survival 65% (95% CI, 57% to 73%)
3 year overall survival 69% (95% CI, 62% to 77%)
EFS and OS for group with PRETEXT IV tumor as only high risk feature was 68% and 69%
Original SIOPEL study – 5 year EFS for PRETEXT IV tumor was 46% and metastases was 28%
Goal is complete anatomic resection

Non-anatomic resections associated with higher rate of incomplete resection

<table>
<thead>
<tr>
<th>Type of Resection</th>
<th>Liver Segments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left lobectomy</td>
<td>II and III</td>
</tr>
<tr>
<td>Left hepatectomy</td>
<td>II, III, and IV</td>
</tr>
<tr>
<td>Extended left hepatectomy</td>
<td>II, III, IV, V, and VIII</td>
</tr>
<tr>
<td>Right hepatectomy</td>
<td>V, VI, VII, and VIII</td>
</tr>
<tr>
<td>Extended right hepatectomy</td>
<td>IV, V, VI, VII, and VIII</td>
</tr>
<tr>
<td>Central hepatectomy</td>
<td>IV, V, and VIII</td>
</tr>
<tr>
<td>Segmentectomy</td>
<td></td>
</tr>
</tbody>
</table>
RIGHT HEPATECTOMY

- Cantlie’s line
RIGHT HEPATECTOMY
RIGHT HEPATECTOMY
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RIGHT HEPATECTOMY
6% with hepatoblastoma will require liver transplantation

Should be considered when:
- All four sectors are involved
- Complete tumor excision by partial hepatectomy is unlikely due to proximity to vessels

Contraindication is presence of extrahepatic disease after chemotherapy

Primary liver transplantation 10 year survival 85%

Rescue liver transplantation after primary partial hepatectomy 5 year survival 30-50%
SIOP-1 study evaluated use of preoperative chemotherapy for HB

- 138 received chemo, 115 underwent surgery
- 12 patients received liver transplants
  + 7 primary liver transplants
  + 5 rescue transplants
  - Overall survival 75% at 5 years, 66% at 10 years
    + For primary transplant 85%
    + For rescue transplant 40%

Meta-analysis of World data and later papers confirmed these findings
ABLATIVE THERAPIES

- For patient who cannot have anatomical resections and are not candidates for transplantation
- Types include:
  + Chemoembolization
  + Radiofrequency ablation
  + Percutaneous injection of ethanol
  + Cryoablation
- May offer palliation and improve survival but rarely leads to cure
PROGNOSIS

- 5 year event free survival

<table>
<thead>
<tr>
<th>Stage</th>
<th>Hepatoblastoma</th>
</tr>
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<tbody>
<tr>
<td>I (pure fetal histology)</td>
<td>100% (n = 9)</td>
</tr>
<tr>
<td>I (other histologic types)</td>
<td>91% (n = 43)</td>
</tr>
<tr>
<td>II</td>
<td>100% (n = 7)</td>
</tr>
<tr>
<td>III</td>
<td>64% (n = 83)</td>
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<tr>
<td>IV</td>
<td>25% (n = 40)</td>
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</tbody>
</table>

- Patients should be followed with AFP levels
- Those who had normal AFP levels should be followed with serial imaging

The goal is complete anatomic resection
Neoadjuvant chemotherapy for high risk tumors and unresectable tumors
Liver transplant is an option for tumor not amenable to partial hepatectomy
Intensified chemo regimen improves survival in high risk tumors
REFERENCES

- Grosfeld. Pediatric Surgery, 6th edition