Rationale and Results of the International Society of Pediatric Oncology (SIOP) Italian Pilot Study on Childhood Hepatoma: Surgical Resection *D'Emblée* or After Primary Chemotherapy?

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INTRODUCTION

Only complete resection can give hope for cure to children affected by hepatic malignancies. Historically, the survival rate of children with a completely resected hepatoblastoma (HPB) and hepatocellular carcinoma (HCC) is in the range of 60% and between 9 to 35%, respectively, according to the different series; few survivals are reported among patients with an unresectable tumor [1,2].

At diagnosis, the resectability rate of HPB is in general higher than that of HCC; as a whole a complete surgical excision is feasible in less than 50% of the cases. At the end of the 1970s, single institutional series and anecdotal case reports documented the chemosensitivity of HPB to agents such as doxorubicin (DOXO), vincristine (VCR), and cyclophosphamide (CYCLO) [3-5]. Significant tumor volume reduction was reported with the use of chemotherapy; tumors that were unresectable because of tumor volume were shown to have become resectable. In the 1980s, cisplatin (CPDD) was introduced into the chemotherapeutic armamentarium of childhood hepatoma. Dramatic tumor shrinkages were soon reported, indicating that CPDD is one of the most effective agents for HPB. The response rates of the largest series so far published of childhood HPB treated with regimens containing CPDD are reported in Table I [6-9]. Surgical excision after chemotherapy seems to give at least the same probability of long-term survival as primary surgery. It was also shown that chemotherapy makes the tumor more compact, less vascularized, and more resistant to surgical manipulation, and also allows a better demarcation be-

tween tumor and healthy tissue. Consequently, the surgical excision becomes easier and safer, and the risks of surgical bleeding and tumor rupture are reduced. For the reasons noted, some pediatric oncology centers now recommend the use of pre-operative chemotherapy (preop-CT) not only for those tumors that are clearly unresectable at presentation but also for those whose resection represents a surgical risk.

It has also been hypothesized that early chemotherapeutic treatment may be effective for the treatment of micrometastases. Furthermore, it may be important for minimizing the risk of local recurrence in case of microscopic tumor residuals; in fact, the same factors that stimulate hepatic regeneration after hepatic surgery could also play a proliferative role for the neoplastic cells.

This new trend toward prioritizing chemotherapy over surgery (regardless of the resectability of the tumor) is obviously open to criticism, mainly because the chemosensitivity of hepatic childhood tumors can vary. More clinical studies are needed. However, it is becoming more and more popular to perform tumor resection *d'emblée* only for those few tumors that are small, peripherally located, and for which the surgical risk is nil, while recommending preop-CT to all the others.

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TABLE I. Response Rates of Unresectable Hepatoblastoma to Cisplatin-Containing Regimens According to the Major Series so far Published*

Authors/ study groups	Regimen	No. of patients	No. of tumor responses	No. of delayed resections ^a
Douglass et al. [12]	CPDD/VCR	33	30	24
POG	5-FU	8 ^b	6	Not known
Ortega et al. [8]	CPDD/DOXO	33	28	16
CCSG				
Ninane et al. [7]	CPDD/DOXO	8	7	7
SIOP				
Filler et al. [6] ^c	CPDD/DOXO	15	15	13
Black et al. [9] ^d	High dose CPDD	7	7	6

*CPDD: cisplatin; VCR: vincristine; 5-FU: 5-fluorouracil; DOXO: doxorubicin; CCSG: Children's Cancer Study Group; POG: Pediatric Oncology Group; SIOP: International Society of Pediatric Oncology.

^aRefers to patients who had complete tumor resection after pre-operative chemotherapy.

^bRefers to patients with metastatic disease.

^cFrom the Hospital for Sick Children, Toronto, Canada.

^dFrom the M.D. Anderson Cancer Center, Houston, Texas.

SURGICAL CONSIDERATIONS

Diagnostic Biopsy

The use of preop-CT raises the problem of the histologic diagnosis. In some cases the clinical picture could be so suggestive of a malignant hepatoma (e.g., hepatic mass in a young child with elevated serum alpha-fetoprotein and perhaps thrombocytosis) as to make the histologic diagnosis unnecessary. However, if we want to evaluate tumor response to chemotherapy (and every other prognostic factor) in relation to the microscopic appearance of the tumor and to some other biological characteristics of the neoplasia, the histologic evaluation of the tumor becomes mandatory.

The risk of surgical biopsy (tumor bleeding or spreading) dictates the technique of tumor sampling. It is thought that transcutaneous fine needle biopsy is inadequate. Some investigators use transcutaneous ultrasound or computed tomography guided tru-cut (or with Minghini needle) biopsy; others prefer to perform a mini-laparotomy and to sample tumor tissue with a needle or with a wedge resection under "eye-control" and with the possibility of an immediate hemostasis.

Surgery for Tumor Resection

Even after preop-CT, major surgical procedures are usually necessary to achieve complete excision of the tumor. Despite the refinements of surgical techniques and supportive measures, the perioperative mortality rate for childhood hepatic cancers is estimated to be in the range of 5-10% [10,11]. It is felt that hepatic surgery in childhood should be referred to specialized centers.

Hepatic resection is carried out in children using the same general techniques employed in adults. Uncontrolled bleeding is the most frequent complication of any hepatic surgery and the most common cause of intraoper-

ative mortality. Aggressive clinical monitoring of the patient during and after the surgical intervention is mandatory. In the immediate postoperative period particular attention should also be directed to acid-base imbalance, abnormalities of clotting factors, and infections.

Major procedures may be performed through a supraumbilical transverse incision. Some authors always prefer this approach. The toraco-phrenic laparotomy provides the best exposure and protects against embolism in the complicated cases. An accurate explanation of the peritoneal cavity is performed to evaluate the hepatic anatomy and the extension of the disease beyond the liver. When the tumor is resectable, the liver is mobilized from the diaphragmatic attachment and tapes are passed around the vena cava above (if possible) and below the liver for vascular control. The structures of the porta hepatitis are then dissected, and the vessels and the bile ducts are ligated, respecting the vessels supplying the healthy liver. The liver capsula is incised and the parenchyma dissected. The finger-fracture technique is the most practical procedure; nevertheless, other techniques such as laser ultrasonic dissection are employed. Hepatic veins, which are usually short in children, are isolated and ligated as the procedure continues. If the plane of resection is close to the edge of the tumor mass, liver biopsies should be taken along the margins of resection in order to discover microscopic residuals. Rarely, HPB has lymphatic metastases. Nevertheless, samples of the lymph nodes at the porta hepatitis should be always examined, regardless of their microscopic appearance. Any other suspicious extra-hepatic areas should be biopsied. In some centers profound hypothermia has been used as an adjuvant to resection in case of difficult hepatectomies, in order to prolong the safe interval for clamping the vascular inflow.

Fig. 1. Study design for the International Society of Pediatric Oncology (SIOP) Childhood Liver Tumor Study. PLADO, cisplatin 80 mg/m² 24 hours c.i. and doxorubicin 60 mg/m² 48 hours c.i.

Regeneration of the hepatic parenchyma is expected after any hepatic resection. It can be monitored by ultrasound or radionuclide scan: the regeneration of hepatic tissue is completed within approximately 3 months after surgery, but it may be prolonged by concurrent chemotherapy.

Surgery of Metastases

The surgical excision of pulmonary metastases can be considered if they persist after preop-CT, and also the primary can be resected.

CHEMOTHERAPEUTIC CONSIDERATIONS SIOP Study on Childhood Malignant Hepatoma

Based on all the considerations noted above, the International Society of Pediatric Oncology (SIOP) on January 1990 opened its first international cooperative childhood liver tumor study (for study design see Fig. 1). The study is based on the use of preop-CT, which is recommended for all HPB and HCC regardless of their initial resectability. Primary surgery is allowed only for those few tumors that are small and peripherally located. An initial diagnostic biopsy is strongly recommended for all cases and is made mandatory for tumors occurring in children less than 6 months of age. Preop-CT consists of four courses of CPDD (80 mg/m² over 24 hours continuous i.v. infusion) and DOXO (60 mg/mq in continuous i.v. infusion over 48 hours). This combination is called PLADO. After those four courses, tumor response and resectability are re-evaluated and then "delayed surgery" performed if feasible. After complete resection at "delayed surgery," two other courses of PLADO are planned and then therapy is stopped. Seventy-seven pediatric oncology centers worldwide are taking part in the study, representing 28 countries and all five continents. Eight nations joined as a national group. As of April 1992, 110 children younger than 16 years of age affected by a malignant hepatoma were registered; 73 HPB and 23 HCC

have been enrolled into the main trial (treated with preop-CT), while 9 HPB and 5 HCC are "on study" (treated with primary surgery despite protocol guidelines). The study core-committee elected not to publicize the preliminary data of the trial at this stage.

Italian Pilot Study on Childhood Malignant Hepatoma

The SIOP childhood liver tumor study has been anticipated by two pilot trials conducted in parallel in Belgium and Italy. The preliminary data from these studies have been published [7]. We report here the updated results of the pilot trial conducted in Italy.

Study design. The Italian pilot trial had the same study design and used the same chemotherapeutic agents as the SIOP trial (see Fig. 1). The only difference is that in the Italian study the final decision on tumor resection at diagnosis was left up to the single institution. Patients with a completely resected tumor (regardless of the presence of microscopic tumor residuals) were treated with four courses of PLADO after surgery.

Patient characteristics. The study began in January 1988. As of December 1989, 23 evaluable HPB and 4 histologically proven HCC were registered, all affecting children aged less than 16 years. They were diagnosed and treated in nine Italian pediatric oncology centers (Ancona, Bologna, Cagliari, Genova, Padova, Palermo, Pisa, Roma, Torino). A male prevalence was documented in children with HPB (male:female ratio, 17:6), while the cases of HCC were equally distributed between the two sexes. Eighteen of the 23 HPB (68%) occurred in children less than 2 years of age, while all the 4 HCC children were older than 5 years at diagnosis. Three HPB patients (13%) had metastases at presentation—two lung, and one lung and bone. None of the HCC children had metastases at diagnosis. Twenty (87%) HPB and three HCC patients had an elevated serum alpha-fetoprotein (AFP) concentration at diagnosis. One child with HCC was suffering from post-neonatal hepatitis B virus cirrhosis.

RESULTS Hepatoblastoma

Primary surgery. Seven patients with HPB had complete tumor resection at presentation, one with microscopic tumor residuals. One child died at surgery with massive intraoperative bleeding. Five patients with a microscopic complete tumor resection are presently alive with no evidence of disease (NED) with a follow-up ranging from 19 to 36 months (median, 25.5 months). The patient with microscopic tumor residuals developed lung metastases at 12 months from diagnosis while off therapy and eventually died of disease 6 months after.

TABLE II. Follow-Up of Children Treated With Preoperative Chemotherapy for Hepatoblastoma*

Response to preop-CT	No. of patients	Radical resection	Non-tumor resection	Follow-up	
				Alive NED	DOD
Localized tumors	13				
Partial response	10	8 ^a	—	8	—
Mixed response	1	1	—	1	—
No response	2	—	2	—	2
Metastatic tumors	3				
Partial response	3	3	—	1	2 ^b

*CT, chemotherapy; NED, no evidence of disease; DOD, dead of disease.

^aTwo patients were lost to follow-up after preop-chemotherapy.

^bIncluding one patient alive with progressive disease.

Primary chemotherapy. Thirteen patients with a localized HPB were treated by preop-CT and are evaluable for treatment analysis (Table II). Ten of 13 (77%) had tumor shrinkage (= tumor response) after preop-CT. In one patient the AFP value decreased but the tumor volume changed minimally. We called this response a mixed one. Two unresectable tumors progressed during preop-CT, rapidly causing the death of the children (45 and 60 days after biopsy, respectively). By parental decision, two patients changed therapy after preop-CT. Nine patients had "delayed surgery." All nine had complete tumor resection at "delayed surgery" (including the child whose tumor had a mixed response), and all are presently alive NED, with a median follow-up of 24 months.

Three patients with metastatic HPB were also treated with preop-CT. All three had tumor response with complete clearing of lung metastases. Subsequently, all had complete tumor removal at delayed surgery. Of these three patients, one is alive NED at 24 months from diagnosis, while the other two suffered local recurrence and progressive lung disease at 1 and 7 months after surgery, respectively. Of these latter two patients, one died of disease 7 months from diagnosis while the other is presently alive with progressive disease at 11 months.

As a whole, children with HPB had a 3-year overall and disease-free survival of 61.0 and 69.2%, respectively. Patients treated with preop-CT had a 3-year overall and disease-free survival of 72.5 and 85.7%, respectively. (No reliable survival curves were feasible for the other patient categories.)

Hepatocellular Carcinoma

Among the four children with HCC, two had complete tumor resection at presentation, one with diaphragmatic microscopic tumor residuals. This latter child suffered lung metastases 22 months from surgery while off therapy and is presently alive without evidence of disease at 31 months from diagnosis. The former patient is alive

NED with a 21 month follow-up. Two children had primary chemotherapy. Both had only a minimal tumor shrinkage. Subsequently, one had complete tumor resection at delayed surgery and is now enjoying a 31-month disease-free status while the other, who never had the resection of his primary, died of disease 8 months from diagnosis.

Chemotherapy Toxicity

Therapy was well tolerated. Detailed data on chemotherapy tolerance were available from 82 courses of PLADO delivered to 20 children. The median interval between cycles was 22 days (mean, 23 days). Eighty-five percent of the dose of CPDD was delivered at full dose as well as 80% of the dosages of DOXO. Nausea and vomiting were frequent complications, but they were easily manageable with the appropriate anti-emetic treatment. One patient suffered sepsis from *Staphylococcus epidermidis*, while another was admitted for fever and neutropenia. Only one patient developed stomatitis. The audio-logical follow-up was often inadequate due to the young age of the vast majority of the patients. No overt cases of oto-, nephro-, or ototoxicity were reported.

CONCLUSIONS

The data from this pilot study, which anticipates the present SIOP Childhood Liver Tumor Study indicate the following:

1. The feasibility of a therapeutic strategy for childhood HPB based on pre-operative chemotherapy with PLADO. In fact, for the HPB treated with preop-CT, the overall tumor response rate was 81% (13/16). Subsequently, 12 of 14 (86%—two children were lost to follow-up after preop-CT) had complete tumor resection at "delayed surgery." Delaying surgical resection does not seem to affect survival (Table III). In fact, all of the nine patients

TABLE III. Hepatoblastoma—Survival Rates by Time of Radical Surgery*

Time of surgery	No. of patients	Alive NED	Median follow-up (months)	Dead of disease	Dead at surgery
At diagnosis					
Without microscopic residuals	6	5	25.5	—	1
With microscopic residuals	1	—	—	1	—
After preop-CT					
Localized tumors	9	9	25	—	—
Metastatic tumors	3	1	24	2 ^a	—
Total	19	15		3 ^a	1

*NED, no evidence of disease; preop-CT, preoperative chemotherapy.

^aIncluding one patient alive with progressive disease.

with a localized HPB who were disease-free after "delayed surgery" are presently alive NED with a 25-month median follow-up, while only one of three children with a metastatic tumor is now alive NED (see below). No surgical deaths occurred in the patients who had tumor resection at "delayed surgery," while one was registered among the seven children who had radical surgery at presentation. Despite the small numbers, these data may indicate the safety of the hepatic resection after surgery.

2. The effectiveness and tolerability of the combination CPDD/DOXO. It must be said that because of the young age of the majority of the patients an accurate evaluation of ototoxicity and partially also of nephrotoxicity was not feasible. A more prolonged follow-up is needed to express a final comment on the actual toxicity of this combination.
3. The severe prognosis of children with a metastatic HPB. Larger numbers are needed to confirm what is just a trend now—only one long-term survival among the three evaluable metastatic HPB.
4. The poor sensitivity of childhood HCC to chemotherapy. We still think it is important to investigate the role of chemotherapy on the childhood "variant" of HCC, which potentially could have a different pattern of chemosensitivity than the adult counterpart. A different therapeutic philosophy from the one used for HPB may be adopted for childhood HCC, favoring, whenever possible, the surgical resection.
5. The need for large international cooperation on these rare tumors in order to conduct relevant clinical research.

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REFERENCES

1. Evans AE, Land VJ, Newton WA, et al.: Combination chemotherapy in the treatment of children with malignant hepatoma. *Cancer* 50:821-826, 1982.
2. Exelby PR, Filler RM, Grosfeld YL, et al.: Liver tumors in children in particular reference to hepatoblastoma and hepatocellular carcinoma. American Academy of Pediatrics Surgical Section Survey—1974. *J Pediatr Surg* 10:329, 1975.
3. Fegiz G, Rosati D, Tonelli F, et al.: A case report of hepatoblastoma treated by chemotherapy and hepatic lobectomy. *World J Surg* 1:407, 1977.
4. Shafer AD, Selinkoff PM: Pre-operative irradiation and chemotherapy for initially unresectable hepatoblastoma. *J Pediatr Surg* 12:1001, 1977.
5. Ikeda K, Suita S, Nakawara A, et al.: Preoperative chemotherapy for initially unresectable hepatoblastoma in children. *Arch Surg* 114:203, 1979.
6. Filler RM, Ehrlich PF, Greenberg ML, et al.: Preoperative chemotherapy for hepatoblastoma. *Surgery* 110:591-596, 1991.
7. Ninane J, Perilongo G, Staten JP, Guglielmi M, et al.: Effectiveness and toxicity of cisplatin and doxorubicin in childhood hepatoblastoma and hepatocellular carcinoma. *Med Pediatr Oncol* 19:199-203, 1991.
8. Ortega JA, Krailo MD, Haans JE, et al.: Effective treatment of unresectable or metastatic hepatoblastoma with cisplatin and doxorubicin chemotherapy. *J Clin Oncol* 9:2167-217, 1991.
9. Black CT, Cangir A, Choroszy M, et al.: Marked response to pre-operative high dose cis-platinum in children with unresectable hepatoblastoma. *J Pediatr Surg* 26:1070-1073, 1991.
10. Shafford EA, Pritchard J: Liver tumors. In Plowmann PNC, Pinkerton CR (eds): "Paediatric Oncology." London: Chapman & Hall Medical, 1992, pp 409-421.
11. Greenberg M, Filler RM: Hepatic tumors. In Pizzo PA, Poplack DG (eds): "Pediatric Oncology." Philadelphia: JB Lippincott Company, 1989, pp 569-571.
12. Douglass EC, Reynolds M, Finegold M, et al.: Cisplatin (CPDD)/vincristine (VCR)/5-fluorouracil (5-FU) therapy for hepatoblastoma: a Pediatric Oncology Group Study. *Proc Am Soc Clin Oncol* 10:307, 1991 (abstr).