Pergamon

European Journal of Cancer Vol. 30A, No. 8, pp. 1050–1051, 1994

0959-8049/94 $7.00+0.00

0959-8049(94)00210-X

Hepatoblastoma - a Bit of a Success Story?

E.A. Shafford and J. Pritchard

HEPATOBLASTOMA IS a rare malignant epithelial tumour of the liver, with a worldwide, relatively constant incidence of 0.5–1.5 cases per million children. Most cases occur in young children with a median age at diagnosis of 24 months. For unknown reasons boys are twice as commonly affected as girls. Presentation is usually with an abdominal mass. Over 90% of patients have a markedly elevated serum alpha-fetoprotein (AFP) level, which is a sensitive marker of disease and of treatment response. Thrombocytosis is also a common finding, shown to be caused by a circulating "thrombopoietin" secreted by the tumour. Hepatoblastoma can be divided into four histopathological subtypes, most frequently intermixed, and these are: fetal, embryonal, macrotrabecular and small cell undifferentiated. These subtypes may have prognostic significance [1]. Completely resected pure fetal tumours are thought to have a better prognosis [2]. Complete resection of the tumour is necessary for cure, but 60–70% of patients have unresectable disease at diagnosis, either because of an extensive primary tumour or the presence of pulmonary metastases (the most common site for metastatic disease). In the early 1970s, evidence began to accumulate that hepatoblastoma is a chemoresponsive tumour, with responses documented to combinations of cyclophosphamide, 5-fluorouracil, vincristine and actinomycin D, but overall survival was of the order of 20–30%.

Doxorubicin and cisplatin had a major impact on prognosis, especially for patients with initially unresectable disease (Table 1). The recent U.S.A. Intergroup (Children's Cancer Study Group/Paediatric Oncology Group CCSG/POG), German Paediatric Oncology Group (GPOG) and International Society of Paediatric Oncology (SIOPEL) studies have all used regimens containing cisplatin and doxorubicin given by continuous infusion [4, 7, 8, 9]. The American and German groups recommend primary surgery, but in the SIOPEL study, all patients receive four to six courses of chemotherapy prior to resection. The rationale for delayed surgery is 3-fold: first, children are cured of hepatoblastoma only if complete resection is achieved and preoperative chemotherapy increases the complete resection rate; second, the operation is almost always easier and safer after chemotherapy; third, there is no delay in treating metastases.

The early results of SIOPEL 1, as well as those of the Intergroup and GPOG studies, indicate a dramatic improvement in prognosis. Lung metastases usually disappear completely (Table 1) and the complete resection rate is 70–80%, with a correspondingly improved survival. Histopathological findings after chemotherapy are impressive. Most tumours show extensive necrosis and a few may be completely necrotic. There is also extensive osteoid present [10].

Despite the lower morbidity of continuous infusion chemotherapy compared with bolus administration, there is still concern about the late effects of these two drugs, particularly the potential cardiotoxicity of doxorubicin, since infants are known to be more susceptible than older patients [11], and the median age of hepatoblastoma patients is low. Although less toxic, epirubicin and carboplatin may not be as effective as doxorubicin and cisplatin in the management of hepatoblastoma. The time has now come to try and identify, from the current studies (pp. 1052–1058), prognostic variables (e.g. age, stage, histopathological subtype, AFP level at diagnosis and rate of fall of AFP on treatment) that will distinguish those patients with a good prognosis from those who still cannot be cured by doxorubicin and cisplatin chemotherapy and surgery. For the "good risk" patients, it may be possible to reduce the chemotherapy. There is already some evidence that cisplatin alone may be effective, although, if given in high doses, nephro- and ototoxicity is of concern [12]. A more dose-intensive regimen is needed for patients in the "poor risk" category. For patients with pulmonary metastases, which respond to but do not clear with chemotherapy, aggressive excision is justified [13]. Liver transplantation should now be considered a serious option for patients who have no evidence of metastatic disease, but whose primary tumour remains unresectable after chemotherapy [14]. External beam radiotherapy may have a limited role in the management of small volume residual disease [15]. Hepatic artery embolisation, intra-arterial chemotherapy or targeted therapy with ^{131}I-labelled Rose Bengal have been used in patients with resistant disease, but there is no evidence that they are sufficiently effective to be included in primary treatment.

In order to compare outcomes between studies using different treatment philosophies, common definitions are mandatory. To this end, the CELTIC Group (Childhood Epithelial Liver Tumours—International Criteria) was convened in 1990 [16] with the aim of establishing a consensus on three issues: histopathological definitions of childhood hepatocellular tumours, criteria for assigning pretreatment extent of disease and definitions of response to treatment.

Much progress has already been made, but the development of, and agreement on, a common pretreatment staging system is a priority.

Hepatoblastoma is a rare form of cancer, which means that few countries see sufficient patients to be able to run a randomised study on their own. The fact that the 232 patients registered in the SIOPEL study come from 32 countries indicates that international co-operation can be successful. There has also been close liaison between SIOP, GPOG, CCSG, POG and the Japanese liver study groups through the CELTIC meetings.

Correspondence to E.A. Shafford at the Clinical Dept. of Paediatric Oncology, First Floor, Lucas Block, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE, U.K.
J. Pritchard is as the Dept. of Haematology and Oncology, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH, U.K.
Received 5 May 1994; accepted 17 May 1994.

Table 1. Response of incompletely resected or unresectable hepatoblastoma to doxorubicin and cisplatin

Reference	No. of patients Stage II	III	IV	Complete surgical resection	Metastases cleared	Outcome
Pritchard *et al.* 1989 [3]	—	9	5	10	4/5	8 alive NED 2+ years
Ortega *et al.* 1991 [4]	8	15	10	23	No details	Estimated survival at 2 years 66.6%
Ninane *et al.* 1991 [5]	7*		1	7‡	1/1	All alive NED median 12 months (4–32 months)
Filler *et al.* 1991 [6]	5†	4	6	15	6/6	12 alive NED median 21 months (3–54 months) of treatment

Stage II, microscopic residual; stage III, macroscopic residual/unresectable; stage IV, metastatic disease. *All patients given pre-operative chemotherapy; extent of tumour not defined. †All patients given pre-operative chemotherapy; for 5 patients tumour was confined to one lobe or R lobe + medial segment L lobe. ‡Eighth patient survives after successful orthotopic liver transplant. NED, no evidence of disease.

Continued international co-operation is essential if the remarkable progress made over the past 10 years is to be sustained.

1. Conran RM, Hitchcock CL, Waclawiw MA, *et al.* Hepatoblastoma: the prognostic significance of histologic subtype. *Pediatr Path* 1992, **12**, 167–183.
2. Haas JE, Muczinsky KA, Krailo M, *et al.* Histopathology and prognosis in childhood hepatoblastoma and hepatocarcinoma. *Cancer* 1989, **64**, 1082–1095.
3. Pritchard J, Shafford EA, Spitz L, *et al.* Cisplatin doxorubicin and surgery for advanced hepatoblastoma: a real chance of cure? *Am Soc Clin Oncol* 1989, **298**, abstract.
4. Ortega JA, Krailo MD, Haas JE, *et al.* Effective treatment of unresectable or metastatic hepatoblastoma with cisplatin and continuous infusion doxorubicin chemotherapy: a report from the Children's Cancer Study Group. *J Clin Oncol* 1991, **9**, 2167–2176.
5. Ninane J, Perilongo G, Stalens JP, *et al.* Effectiveness and toxicity of cisplatin and doxorubicin (Plado) in childhood hepatoblastoma and hepatocellular carcinoma. A SIOP pilot study. *Med Pediatr Oncol* 1991, **19**, 199–203.
6. Filler RM, Ehrlich PF, Greenberg ML, Babyn PS. Preoperative chemotherapy in hepatoblastoma. *Surgery* 1991, **110**, 591–597.
7. Ortega JA, Douglass E, Feusner J, *et al.* A randomised trial of cisplatin, vincristine, 5-fluorouracil vs cisplatin/doxorubicin IV, continuous infusion for the treatment of hepatoblastoma. Results from the Pediatric Intergroup Hepatoma Study. *Am Soc Clin Oncol* 1994, abstract.
8. Von Schweinitz D, Bürger D, Weinel P, Mildenberger H. The treatment of malignant liver tumours in childhood. An interim report of the multicentre study HB-89 of the GPOH. *Klin Pädiatr* 1992, **204**, 214–220.
9. Plaschkes J, Perilongo G, Shafford EA, *et al.* SIOPEL - 1. The first SIOP hepatoblastoma and hepatocellular carcinoma study. *Med Pediatr Oncol* 1993, **21**, 554 abstract.
10. Saxena R, Leake JL, Shafford EA. Chemotherapy effects on hepatoblastoma, a histological study. *Am J Surg Pathol* 1993, **17**, 1266–1271.
11. Lipshultz SE, Colan SD, Gelber RD, *et al.* Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukaemia in childhood. *N Engl J Med* 1991, **324**, 808–815.
12. Black CT, Cangir A, Choroszy M, Androssy RJ. Marked response to preoperative high dose cisplatinum in children with unresectable hepatoblastoma. *J Pediatr Surg* 1991, **26**, 1070–1073.
13. Black CT, Luck SR, Musemeche CA, Androssy RJ. Aggressive excision of pulmonary metastases is warranted in the management of childhood hepatic tumours. *J Pediatr Surg* 1991, **26**, 1082–1086.
14. Konera B, Flye MW, Basattil RW, *et al.* Liver transplantation for hepatoblastoma: the American experience. *Ann Surg* 1991, **213**, 118–121.
15. Habrand JL, Nehme D, Kalifa C, *et al.* Is there a place for radiation therapy in the management of hepatoblastomas and hepatocellular carcinomas in children? *Int J Radiat Oncol Biol Phys* 1992, **23**, 525–531.
16. MacKinlay GA, Pritchard J. A common language for childhood liver tumours. *Paediatr Surg Int* 1992, **7**, 325–326.