PERGAMON

European Journal of Cancer 36 (2000) 1343–1346

European Journal of Cancer

www.ejconline.com

Editorial Comment

Identification of risk groups in hepatoblastoma — another step in optimising therapy

D. von Schweinitz

Department of Paediatric Surgery, University Children's Hospital Basle, PO Box, CH-4005 Basle, Switzerland

Received and accepted 8 May 2000

As in the geriatric population, early childhood is the period of life with a high risk of suffering from malignant disease. However, in contrast to adults, in infants and young children so-called embryonal tumours predominantly occur, which display fundamental differences in their biology compared with adulthood cancers. These tumours, which are derived from undifferentiated embryonal tissue compartments, are characterised by extremely rapid growth and an often high sensitivity to cytotoxic drugs and also sometimes radiation. One of the rarer neoplasms of this group is hepatoblastoma, an embryonal liver tumour [1]. It occurs with an incidence of 0.7–1 case per million children under 15 years of age in Western countries [2], and still is the most common liver tumour during childhood in Europe and North America.

Hepatoblastoma particularily affects children between 6 months and 3 years of age. Because of missing clinical symptoms during early growth, these patients often present with locally extended tumours. Distant metastases, however, usually occur very late in advanced disease stages. Approximately 30% of patients have highly elevated serum levels of alpha-fetoprotein (αFP), which is a sensitive diagnostic marker and can be used to monitor therapy. Histologically, all hepatoblastomas are composed of epithelial tissue, but one-third of them contain additional mesenchymal tissue components with immature fibrous areas, spindle cells and cartilage-like osteoid and are then called mixed tumours. The epithelial components mostly display a high 'fetal' or a poor 'embryonal' differentiation. Rarely, other features such as macrotrabecular arrrangement, small undifferentiated cell areas, teratoid characteristics or a hepatocellular carcinoma-like histology are found [1].

The pathogenesis of hepatoblastoma is still unclear. Histological and immunohistochemical findings indicate that the tumour cells may be derived from early progenitor cells or stem cells of the liver and during tumorigenesis undergo variable differentiation [3,4]. One constant feature of hepatoblastomas is their ability to sustain extramedullary intratumoral erythro- and thrombopoiesis, thus imitating the prenatal liver [5]. As with other embryonal tumours, hepatoblastoma is associated with familial tumour syndromes, the most important of which are the Beckwith–Wiedemann syndrome and familial polyposis coli (FAP). Cytogenetic analysis has revealed the most typical chromosomal changes to be deletions on chromosome arms 1p and 11p, rearrangements on chromosome arm 2q and multisomy of chromosome 20 [6]. Recently, a variety of different chromosomal changes have been identified by application of the comparative genomic hybridisation (CGH) technique [6]. At this time, the most important molecular genetical abnormalities in hepatoblastoma seem to be loss of heterozygosity (LOH) at chromosome 11p15.5 [7], 1p and 1q [8], as well as activating mutations of the *β-catenin* gene in more than 50% of the tumours [9]. Since this is the central effector of the wingless/WNT developmental pathway, the latter seems to have an important role in the molecular pathogenesis of hepatoblastoma.

Thirty years ago, only children whose hepatoblastoma could be completely resected had a chance of survival [10]. In the early 1970s, evidence began to accumulate that hepatoblastomas usually respond to chemotherapy [11]. Thereafter, a dramatic improvement in response to therapy could be achieved by combining surgery with multi-agent chemotherapy in several multicentric cooperative trials [12]. Cisplatin and doxorubicin proved to be the most effective drugs and are now used in all study protocols. Treatment strategies still vary, with primary surgery generally being performed in the USA [13]. This contrasts with European groups, which increasingly use preoperative chemotherapy, as in the trial of the International Society of Paediatric Oncology (SIOPEL), which is described in

PII: S0959-8049(00)00138-6

the article by Brown and colleagues (pp. 1418–1425) in this issue of the *European Journal of Cancer* [14]. With these strategies, an overall tumour-free survival rate of 70–75% was achieved in the different recent trials [13,15–17].

However, approximately one-quarter of the patients still die of their disease. Therefore, further attempts to improve treatment results have to be undertaken. One approach is to compare the results of treatment elements in the different trials, which recently have been undertaken in the USA, Germany, Japan and by the International SIOP-Group. One prerequisite for this is the application of uniform criteria for tumour staging and response. This has been achieved in a meeting of all groups in Berne, Switzerland in 1999, where it was decided that all groups would use the criteria of the SIOPEL-Group (publication in preparation) which are described by Brown and colleagues [14].

A second promising approach is the evaluation of prognostic factors. There have been several attempts to find such criteria on clinical and histopathological grounds (Table 1). Thus, histological features have been investigated several times without consistent results, with the exception of the identification of pure fetal histology in primarily resected tumours as a factor for favourable prognosis [18]. Only in one prospective study was there a correlation between epithelial differentiation and outcome [20]. In one previous study of the same group, histological proliferation markers, such as the expression of nucleolar organiser regions (NOR) seemed to indicate prognosis [21]. AFP serum levels [20], as well as the timing and magnitude of decline under chemotherapy [22] have also been found to indicate clinical outcome. In a prospective study, the German group identified other relevant prognostic factors, as tumour extension and growth pattern in the liver, lymph node and distant metastases, and vascular invasion. Multivariate analysis revealed tumour growth pattern, vascular invasion and serum-AFP levels as independent prognostic factors [20]. Brown and colleagues now performed a similar analysis in a large group of 154 hepatoblastoma patients. They found that intrahepatic extent of disease and distant metastases are predictors for event-free survival and 5-year overall survival. In addition, tumour focality was univariately associated with event-free survival [14]. This is a very important investigation, since only on a large group of uniformly treated patients is confirmation of these prognostic factors valid enough to be the basis for new clinical strategies. These results now enable the study groups to divide the patients into a low risk and a high risk group mainly according to the absence or presence of distant metastases and on the extension of primary tumour [14, 20] for further stratification of therapy. Now high risk, i.e. extended or metastasising hepatoblastomas are treated with intensified chemotherapy, either by addition of more courses and alternating drugs (SIOPEL, US-Intergroup Studies) or by application of megatherapy (German Study Group). It will be interesting to see whether one of these approches will result in better outcome of these high-risk hepatoblastoma patients.

Every one of these study groups has tested its own staging system and found it to be of significant prognostic relevance. This accounts for the postoperative staging in the USA studies [13] and the German studies [20, 21], the Japanese TNM-system for childhood liver malignancies [23], and now for the PreTreatment Extent of disease (PRETEXT) Grouping System introduced for the SIOPEL-studies [14]. Interestingly, the TNM-system of the Internationl Union against Cancer (UICC) for adult liver carcinoma was found to be highly predictive also for hepatoblastoma in the German analyses [20,21]. However, this system is relatively complicated and not accepted by the other groups. Now, since the study groups agreed to apply the PRETEXT-System, this can be tested prospectively under different treatment strategies.

Until now, the prognostic significance of DNA ploidy in hepatoblastomas of the different histological types is still controversial, since results of different studies have been inconsistent, (Table 1) [19,24,25]. In the future, it would be highly desirable to identify single molecular genetic alterations which are present only in one of the prognostic groups of hepatoblastoma. One could imagine that there exist single genomic aberrations, which occur only in poorly differentiated, aggressively growing hepatoblastoma cells, as is the case with the amplification of the *N-MYC* oncogene in neuroblastoma, which is strongly associated with poor outcome. It can be speculated, that specific mutations could initiate the growth of hepatoblastomas with a special differentiation, such as undifferentiated small cells, macrotrabecular type and hepatocellular-like transitional differentiation, which are associated with poor outcome. However, a comparison of the abovementioned molecular genetic aberrations found in hepatoblastomas with the stage and outcome of 56 tumours derived from the German studies HB89 and HB94 did not reveal any prognostic impact of these changes, besides loss of chromosomal regions on 4q, and gain of chromosomal regions on 8q and 20. These chromosomal inbalances were significantly correlated with outcome in this relatively small group of tumours [26]. It remains to be seen, whether these results are confirmed in larger prospective studies.

Eventually, it should be possible to stratify all patients with hepatoblastoma on the basis of such molecular findings. Then it might also become possible to use therapeutics, which are targeted to the specific biological properties of the tumours, such as specific antibodies, growth factors or gene–vector complexes in gene therapy.

Table 1
Significance of clinicopathological prognostic factors in hepatoblastoma, results of previous studies in univariate analysis

Author [Ref.]	Histology mixed/epithelial	Histological differentiation fetal-embryonic	Proliferative activity	Serum-αFP[b]	αFP decline under chemotherapy	Extension in liver	No. of hepatic segments	Focality in liver[a]	Vascular invasion	Lymph nodes	Metastases	DNA ploidy
Haas [18]	n.s.	n.s./s[a]										
Morita [23]							s					
Conran [19]	n.s.	n.s.										s
Von Schweinitz [21]	n.s.	n.s.	s	n.s.		s	n.s.	s	s		s	
Hata [24]												s
Schmidt [25]												n.s.
Ortega [13]				n.s.	s							
Van Tornout [22]				n.s.	s						n.s.	
Von Schweinitz [20]	n.s.	s		s	s	s	n.s.	s	s		s	
Brown [14]	n.s.			n.s.				s	n.s.	s	s	

[a] Significant for pure fetal histology, primary resection. s, Significant; n.s., not significant.
[b] Different categorisations of αFP-values. αFP, alpha fetoprotein.

References

1. Weinberg AG, Finegold MG. Primary hepatic tumours of childhood. *Hum Pathol* 1983, **14**, 512–532.
2. Mann JR, Katshuri N, Raafat F, *et al*. Malignant hepatic tumours in children: incidence, clinical features and aetiology. *Pediatr Perinatal Epidemiol* 1990, **4**, 276–289.
3. Abenoza P, Manivel JC, Wick MR, *et al*. Hepatoblastoma: an immunohistochemical and ultrastructural study. *Hum Pathol* 1987, **18**, 1025–1035.
4. Ruck P, Xiao JC, Pietsch T, *et al*. Hepatic stem-like cells in hepatoblastoma. Immunohistochemical and immuno-electronmicroscopic investigations with OV-1 and AV-6, and antibodies against cytokeratin 7 and albumin. *Histopathology* 1997, **3**, 324–329.
5. Von Schweinitz D, Schmidt D, Fuchs J, *et al*. Extramedullary hematopoiesis and intratumoral production of cytokines in childhood hepatoblastoma. *Pediatr Res* 1995, **38**, 555–563.
6. Hu J, Wills M, Baker BB, *et al*. Comparative genomic hybridization analysis of hepatoblastoma. *Genes Chromosomes Cancer* 2000, **27**, 196–201.
7. Albrecht S, von Schweinitz D, Waha A, *et al*. Loss of maternal alleles on chromosome arm 11p in hepatoblastoma. *Cancer Res* 1994, **54**, 5041–5044.
8. Kraus JA, Albrecht S, Wieslter OD, *et al*. Loss of heterozygosity on chromosome 1 in human hepatoblastoma. *Int J Cancer* 1996, **67**, 467–471.
9. Koch A, Denkhaus D, Albrecht S, *et al*. Childhood hepatoblastomas frequently carry a mutated degradation targeting box of the β-catenin gene. *Cancer Res* 1999, **59**, 269–273.
10. Exelby PR, Filler RM, Grosfeld JL. Liver tumours in children in the particular reference to hepatoblastoma and hepatocellular carcinoma: American Academy of Pediatric Surgical Section Survey — 1974. *J Pediatr Surg* 1978, **10**, 329–337.
11. Evans AE, Land VJ, Newton WA, *et al*. Combination chemotherapy (vincristine, adriamycin, cyclophosphamide and 5-fluorouracil) in the treatment of children with malignant hepatoma. *Cancer* 1982, **50**, 821–826.
12. Shafford EA, Pritchard J. Hepatoblastoma — a bit of a success story? *Eur J Cancer* 1994, **30A**, 1050–1051.
13. Ortega JA, Douglass E, Feusner J, *et al*. A randomised trial of cisplatin/vincristine/5-fluorouracil vx cisplatin/doxorubicin i.v. continuous infusion for the treatment of hepatoblastoma. Results from the Pediatric Intergroup Study (CCG-8881/POG-8945), ASCO Abstracts. *J Clin Oncol* 1994, **13**, 416.
14. Brown J, Perilongo G, Shafford E, *et al*. Pretreatment prognostic factors for children with hepatoblastoma — results from the International Society of Pediatric Oncology (SIOP) Study SIOPEL 1. *Eur J Cancer* 2000, **36**, 1418–1425.
15. Plaschkes J, Perilongo G, Shafford E, *et al*. Pre-operative chemotherapy — cisplatin (PLA) and doxorubicin (DO) PLADO for the treatment of hepatoblastoma and hepatocellular carcinoma — results after 2 years' follow-up. *Med Ped Oncol* 1996, **27**, 256.
16. Von Schweinitz D, Byrd DH, Hecker H, *et al*. Efficiency and toxicity of ifosfamide, cisplatin and doxorubicin in the treatment of childhood hepatoblastoma. *Eur J Cancer* 1997, **33**, 1243–1249.
17. Sasaki F, Ohmuma N, Iwafuchi M, *et al*. Outcome of hepatoblastoma in children treated with the JPLT protocol. *Med Pediatr Oncol* 1998, **32**, 308.
18. Haas JD, Muczinsky KA, Krailo M, *et al*. Histopathology and prognosis in childhood hepatoblastoma and hepatocarcinoma. *Cancer* 1989, **64**, 1082–1095.
19. Conran RM, Hitchcrock CL, Waclariw MA, *et al*. Hepatoblastoma: the prognostic significance of histologic types. *Pediatr Pathol* 1992, **12**, 167–183.
20. Von Schweinitz D, Hecker H, Schmidt-von Arndt G, *et al*. Prognostic factors and staging systems in childhood hepatoblastoma. *Int J Cancer* 1997, **74**, 593–599.
21. Von Schweinitz D, Wischmeyer D, Leuschner J, *et al*. Clinicopathological criteria with prognostic relevance in hepatoblastoma. *Eur J Cancer* 1994, **30A**, 1052–1058.
22. Van Tornout JM, Buckley JD, Quinn JJ, *et al*. Timing and magnitude of decline of alpha-fetoprotein levels in treated children with unresectable or metastatic hepatoblastoma are predictors of outcome: a report from the Childrens Cancer Group. *J Clin Oncol* 1997, **15**, 1190–1197.
23. Morita K, Okake J, Uchino J, *et al*. The proposed Japanese TNM classification of primary liver carcinoma in infants and children. *Jpn J Clin Oncol* 1983, **13**, 361–370.
24. Hata Y, Ishizu H, Okmani K, *et al*. Flow cytometric analysis of the nuclear DNA content of hepatoblastoma. *Cancer* 1991, **68**, 2560–2570.
25. Schmidt D, Wischmeyer P, Leuschner J, *et al*. DNA analysis in hepatoblastoma by flow and image cytometry. *Cancer* 1993, **72**, 2914–2919.
26. Weber RG, Pietsch T, von Schweinitz D, *et al*. A role for gains on chromozone 8q, 20 and loss on 4q as predictors of outcome in hepatoblastoma. *Am J Pathol* 2000, in press.