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Original Paper

Efficiency and Toxicity of Ifosfamide, Cisplatin and Doxorubicin in the Treatment of Childhood Hepatoblastoma

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For the Study Committee of the Cooperative Paediatric Liver Tumour Study HB89 of the German Society for Paediatric Oncology and Haematology

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The Cooperative German Paediatric Liver Tumour Study HB89 was conceived to evaluate the efficiency and toxicity of ifosfamide, cisplatin and doxorubicin (IPA) in children with resectable and non-resectable hepatoblastoma (HB) and to determine late sequelae including tubular nephropathy of tumour treatment. The study also assessed the results of a surgical strategy, which adapts the procedure at the initial operation to the tumour's extension in the liver. The relationship of the tumours' histological differentiation to response to chemotherapy was also examined. Patients with a HB restricted to one liver lobe underwent primary resection. Larger tumours were initially treated with IPA chemotherapy and resected at second-look surgery. All patients received IPA adjuvantly after tumour resection. The IPA regimen consisted of ifosfamide 3.5 g/m^2 (over 72 h days 1–3), cisplatin 100 mg/m^2 (over 5 days 4–8) and doxorubicin 60 mg/m^2 (over 48 h, days 9–10). Median follow-up of survivors was 64 months (range 28–82). Long-term disease-free survival (DFS) was for stage I: 21/21; stage II: 3/6; stage III: 28/38; and stage IV: 2/7 (overall 75%). Severe surgical complications occurred in 15% (4/27) of primary and 21% (8/38) of secondary resections with no lethality. 44/45 stage III/IV HB displayed PR after two IPA courses. Drug resistance developed in 8/12 tumours after four or five chemotherapy courses. Acute toxicity was observed in 34/242 (14%) IPA courses. Late sequelae were found in 7/54 (13%) of survivors, and subclinical renal tubulopathy occurred in 7/41 investigated patients (17%). Despite a more favourable prognosis in pure fetal and predominantly fetal histology, statistical analysis revealed no relationship between tumour differentiation and response to chemotherapy. In conclusion, IPA chemotherapy in combination with delayed surgery was highly effective in the treatment of HB. © **1997 Published by Elsevier Science Ltd.**

Key words: hepatoblastoma, surgery, chemotherapy, toxicity, late sequelae, histology

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INTRODUCTION

HEPATOBLASTOMA (HB) is the most common malignant epithelial liver neoplasm in infants and young children [1]. Until recently the prognosis of these patients was dismal, since the majority of HBs are non-resectable at the time of diagnosis [2]. However, during the last 15 years, increasing

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experience of chemotherapy has been gained, to which most HBs respond to some extent [3, 4]. This knowledge has been used in cooperative trials to reduce primarily non-resectable tumours to an operable size [4–6]. During the same period, it was observed in a few small series of patients that chemotherapy can be effectively administered prior to attempting tumour resection, thus increasing the proportion of resectable tumours [4, 6–10]. This strategy was also followed in the conception of the German Cooperative Pediatric Liver Tumour Study HB89 by treating all HB extending over the limits of one liver lobe with primary chemotherapy [11]. The intention of this strategy was to increase the resection rate of extended HBs and, at the same time, to avoid incomplete resections and surgical morbidity, where the majority of patients are operated on by surgeons who are not specialised in paediatric oncology. Primary resections of small tumours retained priority. Almost all chemotherapy regimens against HBs include cisplatin and many doxorubicin. To improve efficiency, we added ifosfamide as a third cytotoxic agent, an analogue of cyclophosphamide, which had been used before in different regimens in HBs [3, 4, 7, 9–11]. The study, which included a one year pilot phase, was conducted between 1988 and 1993. Recently, we identified complete resection before development of drug resistance as a crucial factor for short-term survival of children with advanced and metastatic HB [12]. Now, after a follow-up period of almost three years for all surviving patients, we report on our evaluation of the treatment concept concerning the surgical strategy and the efficiency, toxicity and long-term sequelae of the administered chemotherapy. Furthermore, we analysed the relationship between histological tumour differentiation, the tumours' response to chemotherapy and the patients' outcome.

PATIENTS AND METHODS

Principles of study protocol

A pilot phase for the study HB89 was conducted from March to December 1988. The main study with the original protocol was started thereafter in January 1989 and patient retrieval was closed at the end of 1993. All patients less than 21 years of age with a previously untreated HB were eligible. The study protocol was approved by the Ethical Committee of the Medical School Hannover and the Executive Board of the German Society for Paediatric Oncology and Haematology and written informed consent for data analysis was obtained from parents of all patients.

The protocol prescribed an initial laparotomy for all children with a primary liver tumour, except for infants with highly elevated serum α-fetoprotein (AFP) and distant metastases, in whom the diagnosis of an HB was clinically certain (Figure 1). At the initial operation, the surgeons were asked to resect only small tumours confined to one liver lobe. Larger tumours involving both lobes and those with metastases were only biopsied. These HB were treated for tumour reduction with chemotherapy consisting of ifosfamide (0.5 g/m^2 bolus and 3.0 g/m^2 over 72 h, days 1–3), cisplatin (20 mg/m^2 × 5 on days 4–8), and doxorubicin (60 mg/m^2 over 48 h, days 9 and 10) every 3 weeks (IPA). After two IPA cycles, tumours were re-evaluated for resectability using ultrasound and CT-scan and, if now feasible, a resection applying extended surgical procedures was attempted. If resection was still not possible, two more cycles of chemotherapy were given. In this case, the administration of cisplatin (90 mg/m^2 over 4 h, day 1) and continuous infusion of doxorubicin (80 mg/m^2 over 96 h, days 2–5) (PA-CI), similar to the regimen of the CCG study 823F [5], was recommended. However, patients who received additional IPA courses in this situation were not excluded from this study solely because of this fact. Thereafter, these tumours were resected whenever possible. After tumour resection the patients received two more cycles of IPA or PA-CI, respectively.

Staging and response criteria

The following staging criteria, according to the results of initial clinical evaluation and surgery, were applied: stage I, tumour completely resected; stage II, microscopic residual tumour; stage III, gross residual tumour; and stage IV, distant metastases. Response criteria were defined as follows: complete response (CR), absence of all tumour and normalised AFP; partial response (PR), regression of the tumour and reduction of AFP by at least 50%; stable disease (SD), tumour regression and/or AFP decrease of less than 50%; progressive disease (PD), growth of tumour mass or evidence of new metastases or increase of AFP.

Patients

All children with an HB, who were treated according to the study protocol, were included in this investigation. The initial tumour extension was evaluated using ultrasonography, thoracic X-ray and CT scan. Serum levels of AFP were measured prior to therapy and before each chemotherapy cycle or operation. During follow-up, these investigations except CT scans were performed monthly during the first year, every 3 months during the second year and every 6 months thereafter. Furthermore, we registered the outcome of primary and second-look surgery including perioperative complications, as well as efficiency, acute toxicity and late sequelae of the administered chemotherapy. Creatinine clearance was determined regularly during therapy and follow-up and renal tubular function was evaluated by examination of renal tubular reabsorption of amino acids and phosphate [13]. Response to chemotherapy of stage III and IV HB was evaluated with ultrasound and CT and by measuring the decrease of serum AFP. The rate of AFP decrease was calculated as the quotient of log-scale AFP by time. Toxicity of chemotherapy was graded according to the WHO toxicity score [14].

Histological investigation

All histological specimens were reviewed by one of us (D.H.) and classified according to the histological type as either pure epithelial or mixed epithelial and mesenchymal HB, and according to epithelial differentiation as fetal or embryonal HB [1]. The histological findings in stage III/IV tumours were correlated with the rate of AFP decrease during initial chemotherapy in order to evaluate a possible relationship of the tumours' histology with the response to chemotherapy.

Statistical analysis

The patients' disease-free survival (DFS) was analysed using the method of Kaplan and Meier [15] and survival curves were compared using the log-rank test [16]. For analysis of the relationship between the decrease of serum

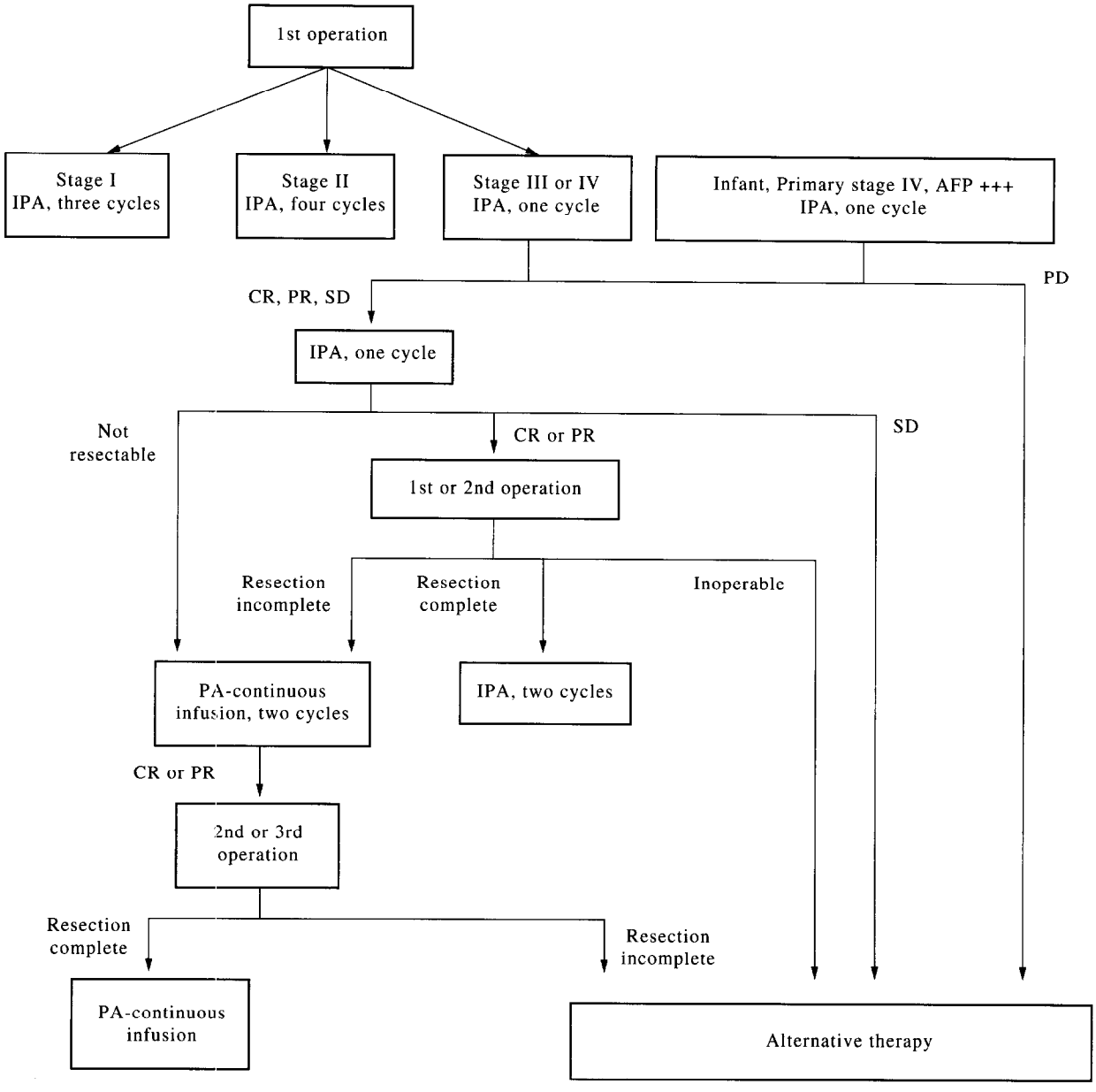

Figure 1. Strategy design for treatment in study HB89. AFP, alpha fetoprotein; IPA, ifosphamide, cisplatin, doxorubicin; PD, progressive disease; SD, disease; CR, complete response; PR, partial response.

AFP in stage III/IV tumours under chemotherapy and the patients' prognosis, we used the regression model of Cox [16]. Significance was assumed when $P \leq 0.05$.

RESULTS

Patients characteristics

Seventy-seven children with a HB were registered between March 1988 and December 1993. Five of these were not further evaluated, as they were not treated according to the protocol ($n = 3$) or lost to follow-up ($n = 2$). The median age at diagnosis in the remaining 72 patients was 12 months (range 1 day to 11 years). Forty-five patients were male and 27 female (male:female = 1:7). In two of the children, HB was associated with a Beckwith–Wiedemann syndrome, in one with a Down's syndrome, and in one with a Klippel–Feil disorder. Other dysmorphisms were observed in three children. In two families, we observed siblings with HB. Three other patients had been delivered as premature neonates and received long-term parenteral nutrition thereafter. The serum AFP levels at diagnosis ranged from 5 to 10 200 000 ng/ml and were elevated above the normal range of age [17] in 57 (79%) patients. Median follow-up of the survivors was 64 months (range 28–82 months).

Table 1. Overall therapy results of hepatoblastoma in study HB89, n = 72 patients

Stage	Total	Disease-free	Dead
I	21	21	–
II	6	3	3
III	38	28	10
IV	7	2	5
Total	72	54	18

Overall therapy results (Table 1)

All 21 patients with a stage I tumour are alive and well, whereas three of the 6 with stage II disease encountered new tumour growth after termination of adjuvant chemotherapy. One of these achieved remission following additional chemotherapy, while the other 2 died. The third death in this group was due to acute myeloid leukaemia, which appeared 30 months after the end of adjuvant IPA chemotherapy. Twenty-eight of 38 (74%) patients with stage III HB are disease-free, 1 after a liver transplantation and 1 after repeated treatment of secondary lung metastases. The other 10 patients died, 3 from PD (one patient) or therapy side-effects (2 patients) while receiving therapy. The other 7 developed non-resectable recurrent tumour. Two of seven stage IV patients are in full remission after more than two years—both underwent chemotherapy and resection of the liver tumour and one also underwent resection of bilateral lung metastases. Two other stage IV patients displayed PD following primary chemotherapy, and the HB of another patient did not become resectable despite an initially good response. Finally, two stage IV tumours were resected following treatment with chemotherapy, but the patients died of recurrent lung metastases. DFS at the end of follow-up was 100% for stage I, 50% for stage II, 71% for stage III and 29% for stage IV patients, when calculated by the Kaplan–Meier method [15]; these differences were significant ($P = 0.0007$; Figure 2).

Surgery

Surgery was performed by paediatric surgeons in 36 different institutions. Three or more paediatric liver resections were performed during the study period in only four of these hospitals. The overall resection rate was 92% (66 of 72 HBs). A complete tumour resection was achieved in 54 patients. Microscopic residual tumour occurred after six primary and six second-look resections. Only half of these patients experienced a long-term remission. None of six other children with gross residual tumour after second-look surgery survived. The DFS for patients with a complete tumour resection was 89%, whereas it was reduced to 50% for patients with microscopic residual tumour and zero for patients with gross residual tumour ($P < 0.0001$). Peri-operative complications occurred in 3 of the 38 (8%) open tumour biopsies, 4 of the 27 (15%) primary (stage I/II) and 8 of the 38 (21%) secondary (stage III/IV) tumour resections. Major bleeding (seven operations) and postoperative bile leakage (four operations) were the main problems. There was no peri-operative death.

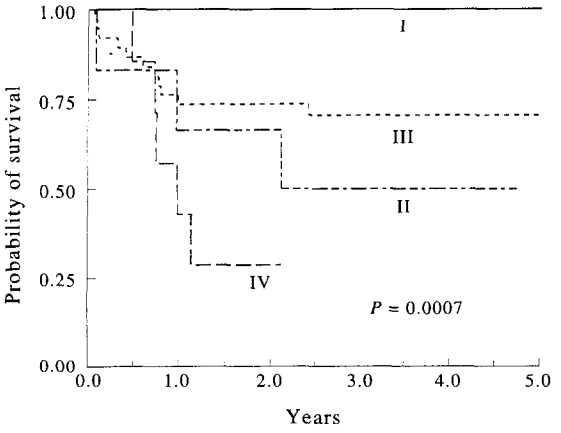

Figure 2. Kaplan–Meier disease-free survival of hepatoblastoma patients treated in study HB89 according to clinical stage, $n = 72$.

IPA chemotherapy

Two hundred and forty-two cycles of IPA therapy were administered to the 72 patients. Ninety-six of these were given for tumour reduction before surgical resection in 45 stage III/IV patients; 44 (98%) of these tumours displayed a PR. Twenty-seven of these HB were resectable after two therapy cycles. Additional IPA brought further regression of the tumours in 7 patients. A rapid decrease of initially high AFP levels was usually associated with marked tumour shrinkage. Statistical analysis with the regression model of Cox [16] revealed a significant relationship between the rate of AFP decrease and the patients' DFS ($P = 0.0155$).

Acute grade III and IV toxicity was reported for 34 (14%) IPA-courses (Table 2). Severe neutropenia (6%), thrombocytopenia (4%) and generalised infections (2%) were the most common side-effects. Two children died during the first IPA cycle: one 2-month old infant with a large HB developed toxic liver failure and one 4-year old child with tumour involvement of the main portal vein died of sudden bleeding from oesophageal varices.

PA-CI chemotherapy

Thirty-eight courses of PA-CI were given to 13 patients. This regimen was applied to 11 patients, after previous IPA therapy, for further tumour reduction. Eight of the tumours showed a response, but only three became resectable thereafter and one was treated by a liver transplantation. PA-CI therapy was given to 6 patients adjuvantly after tumour resection. Three remained disease-free. Acute grade III/IV toxicity was observed in eight (21%) cycles, namely neutropenia, thrombocytopenia and septicaemia in 4 (11%), ANC and thrombocytopenia in 1, cardiac insufficiency in 2 (5%) and pneumonitis in 1 (3%) patient.

Drug resistance

Development of drug resistance was observed in 8 of 12 patients with a stage III/IV HB who were treated with four or more cycles of chemotherapy, 1 with four IPA courses and 11 with IPA and PA-CI. After an initial good response, a renewed increase of AFP was observed after the fourth (7×) or fifth (1×) chemotherapy course. Concurrently, further tumour regression could no longer be documented, and one child developed lymph node metastases. Only in 2

Table 2. Acute toxicity associated with IPA chemotherapy, $n = 242$ cycles

	Courses (%)
ANC < 1000/μl	15 (6)
Fever ≥39°C	10 (4)
Bacteraemia	5 (2)
Platelet count < 50 000/μl	10 (4)
Diarrhoea	2 (0.9)
Hepatic failure	1 (0.4)
Pneumonitis	1 (0.4)
Bleeding (oesophagus)	1 (0.4)
Total cases with grade III/IV toxicity	34 (14)

Table 3. Histological classification of 71 hepatoblastomas in study HB89

	Epithelial differentiation				
	Pure fetal	Predominantly fetal	Predominantly embryonal	Small undifferentiated	Total
Pure epithelial	17	23	13	–	53
Mixed epithelial mesenchymal	–	14	3	1	18
Total	17	37	16	1	71

of these 8 patients was a remission achieved by surgery. In 3 other patients with recurrent HB, IPA and PA-CI therapy were not effective, although the primary tumours had shown good response to these drugs.

Late sequelae

In 7 of the 54 (13%) survivors clinically detectable, late sequelae were observed. Three children suffered from a dilatation of the left heart ventricle and a decrease of the shortening fraction in echocardiography without other signs of cardiac insufficiency. In 3 patients, a high-frequency hearing deficiency was measured. One child had radiological signs of osteoporosis. In addition, the patient who died of acute myeloid leukaemia could also be included in this group, if this secondary malignancy is considered to have been caused by the carcinogenic effect of the chemotherapy. A temporary reduction in creatinine clearance was detected during chemotherapy in 8 children (8/72, 11%) but all had normal values during follow-up. A subclinical renal tubulopathy was detected in 7 of the 41 investigated patients (17%), in 5 cases a mild and in 2 a more severe form. In no case were relevant clinical symptoms such as rickets reported.

Histology

Tumour samples were available for histological examination from 71 HBs (Table 3). Fifty-three (75%) of these were pure epithelial and 18 (25%) mixed epithelial and mesenchymal HBs. Seventeen (24%) of the tumours displayed a pure fetal histology. The majority were predominantly fetal (23 pure epithelial and 14 mixed HBs, 52%), while 16 (23%) showed a predominantly embryonal differentiation (13 epithelial and 3 mixed HBs). Three of the latter tumours also contained small undifferentiated (anaplastic) cells and one rhabdoid features. The epithelial component of one (1%) mixed HB consisted exclusively of small undifferentiated cells. Kaplan–Meier analysis revealed no difference in survival between patients with an epithelial or a mixed HB ($P = 0.2756$). In contrast, pure fetal and predominantly fetal HB were associated with an significantly better outcome than the predominantly embryonal tumours ($P = 0.0093$). However, there was no statistical relationship between the tumour differentiation and size at diagnosis ($P = 0.1011$), extension in the liver ($P = 0.3990$), or the occurrence of metastases ($P = 0.2915$). In the histological specimens taken from stage III/IV HBs after chemotherapy, necrosis and scars were seen. In mixed HBs, fibrous and osteoid tissue were increased after chemotherapy. In epithelial HB, the fetal tissue became more predominant. However, in none of the tumours was an alteration of the basic histological type found. Furthermore, it was not possible to identify histological characteristics associated with sensitivity to chemotherapy, as in the stage III/IV HBs, there was no statistical difference between the epithelial and the mixed type as to the rate of decrease in the patients' serum AFP ($P = 0.7009$). Similarly, there was no significant correlation between fetal and embryonal histology with AFP reduction ($P = 0.9386$).

DISCUSSION

Twenty years ago surgery was the only means of treating children with HB [2], but in the last two decades, chemotherapy has been successfully applied to reduce the size of this tumour [3, 4, 7–10]. This has improved surgical resectability, which is still essential for a final cure [11, 12, 18]. These facts were considered in the conception of the HB89 study, which was based on two principles. (1) A surgical strategy was used in which the first operation was adapted to the extension of the individual HB. With this strategy, we wanted to achieve a high resection rate while, concurrently, reducing surgical morbidity and mortality. Furthermore, the aim was to avoid incomplete resections which, in our experience, resulted in rapid growth of residual tumour [11]. The option of primary resection of small tumours was preserved in order to reduce chemotherapy in these children. (2) A chemotherapy regimen was tested, which potentially combined high efficiency with reasonably low toxicity. Therefore, the IPA combination was chosen, with cisplatin and doxorubicin, both effective against HB [4, 10, 20] and ifosfamide, an analogue of cyclophosphamide, which had also been used against this tumour in combination with other drugs [3, 7, 9–11].

With our strategy, a resection rate of 92% was achieved, which is similar to that obtained in other studies [4, 20–22]. The high resection rate was not bought at the cost of high operative risks. On the contrary, surgical complications were rare and no peri-operative death was registered, despite the fact that most of the operations were performed by non-specialised surgeons. It was the experience of most of them that large HBs were easier to resect after chemotherapy, because then the tumours were more solid and had developed a pseudocapsule. Therefore, the concept of limiting the initial operation to a resection of small tumours or a biopsy seems appropriate in order to achieve a high resection rate and, at the same time, reduce surgical morbidity.

The high resection rate in this study was an important factor for good results, with an overall DFS of 75%. Notably, all children with a primary complete resection are in remission, and the majority of those with a completely resected stage III HB remain tumour-free. However, in stage II patients the course was not so favourable. This contrasts with results from other studies, with survival rates near 100% [5, 6, 25]. Our results may be due to the small number of stage II patients, a category which ideally should not occur according to the protocol. However, in 2 of the stage II patients of this study and in former patients [11],

we noted that microscopic residual HBs without prior chemotherapy can undergo rapid proliferation during the first four postoperative weeks after resection, which is the period of liver regeneration. This suggests that a causal relationship may exist between liver regeneration and tumour growth [11].

The IPA regime has proved to be as effective against HBs as have other drug combinations which usually contain cisplatin [4–6, 22]. In our study, 44 of 45 advanced tumours initially responded to this therapy. It has to be pointed out that the majority of the patients, even those with large tumours, did not need more than a total of four chemotherapy courses. The acute toxicity of the IPA therapy was low in comparison to that of the chemotherapy administered in other trials [5, 6, 22, 23]. Only 14% of the courses had severe side-effects, mostly bone marrow depression. However, it should be noted that one very young infant with a large HB died of rapidly progressive toxic liver failure. The massive bleeding from oesophageal varices with lethal outcome in another patient was considered to be a side-effect of chemotherapy, as it occurred during drug-induced thrombocytopenia.

The PA-CI therapy was applied in patients with advanced HB in order to achieve additional tumour shrinkage. Its efficiency in HB had been shown previously [5] and an additional effect was observed in 8 of 11 tumours in our study. However, the benefit was not greater than that of additional IPA and gained at the cost of more severe toxic side-effects. This is consistent with the observation of an increased toxicity of this regimen in comparison to other combinations [23]. Therefore, the PA-CI therapy was not included in the protocol of our new therapeutic trial HB94 [24].

Late sequelae were observed only in a small number of our patients. These included minor cardiac disorders and high-frequency hearing losses. It is not clear whether the osteoporosis of one patient resulted from chemotherapy, as it may also be a paraneoplastic symptom [25].

In a number of recent studies, it has been shown that ifosfamide, especially in combination with cisplatin, can induce renal dysfunction [13, 26]. We found no cases of permanent reduction of glomerular filtration, and defects of renal tubular reabsorption without clinical or radiological symptoms of a Fanconi syndrome were seen in fewer than 20% of the patients. The relatively low incidence of late renal tubular defects [26] seems to allow the further application of ifosfamide in patients with HB. However, it may be that chemotherapy without this drug or with cyclophosphamide in its place might achieve equal treatment results without the risk of renal tubular damage.

It is important to note that HB can develop resistance against cytotoxic drugs [12], occurring after the fourth or fifth chemotherapy cycle in our study. To date, this has not been investigated systematically. Since HB cells are derived from hepatocytes, which constitutively express the P170-glycoprotein, the multiple drug resistance (MDR) mechanism can be expected, at least in part, to be responsible for the development of resistance. Preliminary results of our own investigations do not confirm an enhanced expression of the MDR1 gene and the P170 glycoprotein in comparison to normal liver [27]. However, there exist other molecular mechanisms of drug resistance, which have to be considered in HB.

Recurrent HB usually does not respond to the combination of ifosfamide and etoposide [28], but the alternative regimen of carboplatin and etoposide can be of benefit in otherwise resistant tumours [29]. We observed that the latter combination given as a continuous infusion was effective against six of eight recurrent or progressive HBs, which had developed resistance against the IPA combination. Therefore, we have proposed the application of carboplatin and etoposide for this group of patients in the new German Cooperative Study HB94 [24].

It has been reported that undifferentiated small cell (anaplastic) HBs and tumours with rhabdoid features are associated with a poor prognosis, since these often do not respond to cytotoxic drugs [31]. In our series, we encountered three HBs with this type of histology, which were essentially resistant to chemotherapy. The results of the HB89 study show a significantly better outcome of patients with a pure fetal or predominantly fetal HB in comparison to those with a predominantly embryonal histology. This is in contrast to former studies which found no such correlation at all [18, 31] or only for stage I tumours [30]. Despite the relationship between histology and the patients' prognosis, we could not identify histological subtypes with a specific response to chemotherapy when analysing the rate of AFP decrease. Therefore, a relatively mature histology of HB is not necessarily associated with a good response to cytotoxic drugs. Specimens taken from tumours after chemotherapy display a more differentiated histology [32]. Further studies are necessary to distinguish whether mature tumour cells are selected or whether immature tumour cells differentiate under chemotherapy.

In conclusion, IPA chemotherapy is highly effective in HBs and is associated with low acute toxicity and acceptable late sequelae. When combined with delayed surgery in advanced tumours, a cure rate of 75% was achieved. Marginal resections without prior chemotherapy may result in rapid growth of recurrent tumour. An alternative chemotherapy regime should be considered for tumours resistant to IPA.

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