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Treatment of hepatoblastoma in the German cooperative pediatric liver tumor studies

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TABLE OF CONTENTS

1. ABSTRACT

Treatment with neoadjuvant and adjuvant chemotherapy together with tumor resection changed treatment strategies in hepatoblastoma and led to prospective cooperative studies. The treatment strategies and results of three German liver tumor studies HB89, HB94 and HB99 are reviewed. Here we provide an overview of the treatment of this tumor in the years 1989 to 2008 in Germany. The treatment protocols, aim of studies and results are outlined. The overall-survival (OS), response to chemotherapy and toxicity are followed over this period of different treatment. The overall-survival improved over the last years with 75% in HB89, 77% in HB94 and 89% in HB99. Patients with potentially resectable tumors have a good prognosis although the treatment was reduced over the last years. Patients with non resectable tumors or lung metastases have also a better but still bad prognosis. The intensified treatment for these patients in Germany in the last years showed comparable results to international studies but no advantage.

2. INTRODUCTION

The embryonic tumor hepatoblastoma is a rare tumor. The age standardized incidence in the German population is 1 per 1 million (1). The treatment with neoadjuvant and adjuvant chemotherapy together with tumor resection changed the treatment strategies in hepatoblastoma and led to prospective cooperative studies for treatment strategies in different countries (2). The first study in Germany started 1989 and was followed by another study 1994. The last German liver tumor study was then performed between 1999 and 2008. We will show an overview of the results in the treatment of Hepatoblastoma over the last 19 years in Germany.

3. GERMAN PEDIATRIC LIVER TUMOR STUDIES HB89 HB94 AND HB99

The results of the German liver tumor studies HB89, HB94 and HB99 are reviewed in the literature. The protocols and aims of the studies are outlined. The results,

Table 1. Overall Survival in the German liver tumor studies

	HB 89	HB94	HB99 (interim report)
Time	1989-1993	1994-1998	1999-2008
Number of patients	72	69	45
Chemotherapy	IPA, PA-Cont	IPA, Carbo/VP16	SR: IPA
			HR: Carbo/VP16, HD Carbo/VP16
3 –J –OS	75 %	77 %	89 %

Abbreviations: OS: Overall survival, IPA: ifosfamide – cisplatin - doxorubicin, Carbo/VP16: carboplatin and etoposide, PA Cont: continuous treatment with cisplatin and doxorubicin, SR: standard risk, HR: high risk, HD: high dose

overall survival, tumor resection, response to chemotherapy and resection rates are summarized.

3.1. German pediatric liver tumor study HB 89

Between 1989 and 1993 the German Society for Pediatric Oncology and Hematology conducted the first prospective cooperative pediatric liver tumor study. In the years before it was reported that the hepatoblastoma usually responded to chemotherapy and thereby can be reduced to an operable size (3).

3.1.1. Study protocol and aim of HB89

The aim of the first German liver tumor study was to evaluate the efficiency and toxicity of ifosfamide, cisplatin and doxorubicin (IPA) in the treatment of hepatoblastoma. The surgical strategy was evaluated and the resectability of the tumor after chemotherapy.

In the protocol of HB89 an initial laparotomy for all children with primary liver tumor was prescribed. Patients with hepatoblastoma restricted to one liver lobe underwent primary resection. In larger tumors only a biopsy was taken and then the patients were treated with IPA chemotherapy and the tumor was resected at second look surgery. The surgical strategy was to adapt the decision of a primary resection to the extension of the individual tumor and to avoid incomplete resections. All patients received IPA after tumor resection. The treatment regimen consisted of ifosfamide (0,5g/m^2 bolus and then 3,0 g/m^2 over 72h, day 1-3), cisplatin (5 x 20 mg/m^2, day 4-8) and doxorubicin (60 mg/m^2 over 48 h, day 9 and 10) every 3 weeks. After two cycles of IPA the tumor was reevaluated and if possible resected. If the tumor was still not resectable the administration of cisplatin and doxorubicin in a higher dosage was recommended (cisplatin 90 mg/m^2 over 4h, day 1 and doxorubicin 80 mg/m^2 over 96 h, day 2-5 (PA-cont)) (4, 5).

3.1.2. Results of HB89

In HB89 72 patients with hepatoblastoma were evaluated. The median age at diagnosis was 12 month with a range from newborn to 11 years. The AFP level was elevated in 79 % of the patients. The OS for all patients with hepatoblastoma was 75 % (Table 1). The disease free survival (DFS) for patients with stage 1 was 100% (21/21). Out of the 6 patients with stage II tumor only 3 survived. One died due to a second malignancy. DFS in stage III patients was 74% (28/38) and in the stage IV group 2 out of 7 patients survived (29%) (Table2). A complete tumor resection was achieved in 54 patients (75%). Microscopic residuals occurred in 6 patients after primary resection and in 6 patients after second look surgery with chemotherapeutic pretreatment. The DFS for patients with complete resection was 89% whereas it was reduced to 50% for patients with microscopic residuals and dropped down to 0% for patients with incomplete resected tumors. The difference was significant (p less than 0,0001). Complete resection of the tumor is essential for final cure. The surgical experience was that larger tumors are easier to resect after chemotherapy because the tumors were more solid, smaller and had developed a pseudo capsule (5).

The response to the chemotherapy was excellent with 97% (44/45). The side effects of the chemotherapy with IPA were low and occurred in only 14% of the courses, mostly bone marrow depression. Drug resistance was observed in 8 out of 12 patients with stage III/IV hepatoblastoma with four or more cycles of chemotherapy. After an initial good response with decrease of the AFP level a renewed increase of the AFP level was observed after the fourth or fifth chemotherapy cycle. The PA cont treatment was given to 11 patients after initial therapy with IPA, but only 3 tumors became resectable. Acute grade 3 or 4 toxicity was observed in 21% of these cycles. The chemotherapy with IPA has proved to be effective with reasonably low toxicity, but the tumor develops resistance against chemotherapy after 4-5 cycles. The majority of patients could be treated with a maximum of 4 cycles IPA including pre- and postoperative treatment. The PA-cont therapy had no special benefit and showed more toxicity and was therefore not considered in further studies (5).

All patients had a primary laparotomy with tumor resection or at least a biopsy. Clinical criteria were evaluated according to diagnosis. A group of patients with special clinical criteria had in all cases the histological diagnosis of a hepatoblastoma. They all were at the age of 6 moths to 3 years, had an tumor located in the liver seen in MRI or CT and had an APP level elevated 3 times above normal. It was considered that patients with these clinical criteria can be treated without biopsy (6).

From the results and experiences of this study the next study was developed.

3.2. German pediatric liver tumor study HB94

The German Cooperative Pediatric Liver tumor study HB 94 was a prospective multicenter single arm study. The study ran from 1994 to 1998.

3.2.1. Study protocol and aim of HB94

The aim of the study was to evaluate the efficiency of the treatments with chemotherapy consisting of cisplatin, doxorubicin and ifosfamide without PA-cont and the efficiency of the therapy with carboplatin and etoposide. The surgical strategy was changed to more

Table 2. Complete remission in the HB89 and HB94 relating to stage

	HB89		HB94	
Stage	**total**	**CR**	**total**	**CR**
I	21	21 (100%)	27	26 (96%)
II	6	3 (50%)	3	3 (100%)
III	38	28 (74%)	25	19 (76%)
IV	7	2 (29%)	14	5 (36%)

Abbreviations: CR: complete remission

neoadjuvant treatment. The protocol prescribed a primary tumor resection only in patients with tumors that clearly were confined to only one liver lobe and the possibility of a microscopic complete resection was given. The prognostic significance of this strategy was to be evaluated together with prognostic factors in the tumor characteristics and pretreatment factors (7).

Patients with a not resectable liver tumor stage III and IV underwent a biopsy except for patients with significantly elevated AFP level (3 times above normal) and age between 6 months and 3 years. This group was treated without biopsy. The treatment started with neoadjuvant chemotherapy consisting of ifosfamide (0,5g/m^2 bolus and then 3,0 g/m^2 over 72h, day 1-3), cisplatin (5 x 20 mg/m^2, day 4-8) and doxorubicin (60 mg/m^2 over 48 h, day 9 and 10) They received two and, if still not resectable, 3 cycles of IPA and then the tumor was resected. The postoperative treatment was another cycle with IPA. If the tumor showed no response after 2 cycles or was still unresectable after 3 cycles the treatment was changed to two cycles of carboplatin (800 mg /m^2 over 96 h on day 1-4) and etoposide (400 mg/m^2 over 96 h on day 1-4). Then the tumor was reevaluated and if possible resected. The postoperative treatment was another two cycles with carboplatin and etoposide. Patients with primary resected tumor received postoperative two (stage I) or three (stage II) cycles IPA (7).

3.2.2. Results of HB94

From 1994 until 1998 in total 69 patients with hepatoblastoma were registered (Table 1). The median age at diagnosis was 16 month. In the group who received primary chemotherapy without histological diagnosis, the diagnosis of hepatoblastoma was confirmed in all children after tumor resection. DFS for patients with stage I was 96% (26/27). All three children with stage II survived. The DFS for stage III patients was 76% (19/25) and 36% (5/14) for stage IV patients. The differences were significant (Table 2). A complete resection of the primary tumor was achieved in 54/69 (78%) patients. 22 patients had a primary tumor resection (32%). 48 patients received neoadjuvant chemotherapy with IPA. In 41/48 (85%) patients the tumor showed response to IPA. 7 tumors showed no response and all these patients died. Grade 3 and 4 toxicity was reported in 39/68 (57%) children. Two children died from sepsis due to severe aplasia of the bone marrow. 18 patients with advanced or recurrent hepatoblastoma were treated with carboplatin and etoposide. The response rate was 67% (12/18). A relevant pretreatment prognostic factor was the growth pattern of the tumor. 34 patients had one or two tumor nodes in the liver and 20 children had a multifocal disseminated tumor. They showed a significant worse outcome with DFS of 70% compared to 97% of the uni- or bifocal tumor. Vascular invasion, distant metastases and an initial AFP level below 100 ng/ml and the surgical radicalness were also significant prognostic factors (7).

3.3. German pediatric liver tumor study HB99

HB99 was the third German cooperative pediatric liver tumor study. The results of HB94 lead to the division into two risk groups with a standard risk group (SR) and a high risk (HR) group involving patients with non resectable tumor, multifocal tumor, vessel involvement, extra hepatic tumor and distant metastases. So HB99 was a prospective, not randomized, two armed multicenter study. The study ran from January 1999 to December 2008. The protocol and aims of the study are outlined according to the study protocol (8). The results reported are from interim reports of the German Liver Tumor study (8, 9). Final results are not published yet due to the short follow up after final closure of the study.

3.3.1. Study protocol and aim of HB99

The surgical strategy was restrictive. The protocol allowed the primary resection only in very small tumors confined to one liver segment on the liver margin. All other patients were treated with neoadjuvant chemotherapy. A biopsy was only performed in patients without the clinical criteria for a hepatoblastoma: age 6 months to 3 years, AFP level 3 times above the age corrected standard value. The chemotherapy for the SR-patients was reduced compared to the previous study. These patients were treated with two/three cycles IPA (ifosfamide: 3,0 g/m^2 over 72h, day 1-3, cisplatin: 5 x 20 mg/m^2, day 4-8, doxorubicin 60 mg /m^2 over 48 h, day 9 and 10) without the initial ifosfamide bolus, followed by tumor resection. The postoperative treatment was one/two cycles IPA. The high risk group was treated with two cycles carboplatin (800 mg/m^2 over 96h, day 1–4) and etoposide (400 mg/m^2 over 96 h, day 1–4). In between stem cell collection was performed. If the tumor showed response the treatment was continued with one/two cycles high dose carboplatin (500 mg/m^2/24h, day -8 to -5) and etoposide (500 mg/m^2/24h, day -8 to -5) until resection or liver transplantation was possible. If the tumor showed no response to carboplatin and etoposide the treatment was continued with IPA (8).

For the standard risk group the aim was to evaluate the efficiency and toxicity of treatment with IPA without the Ifosfamide bolus compared to the historical group of the HB 94. For the high risk group the aim was to evaluate the efficiency of high dose chemotherapy with carboplatin and etoposide. The overall survival, toxicity and response to chemotherapy were analyzed. The response to chemotherapy was evaluated according to the decrease of AFP after two cycles chemotherapy. A decrease of the AFP level of more than one log per cycle was defined as good partial response and a decrease of more than one log after two cycles was defined as partial response (8).

3.3.3. Staging systems

In HB99 two staging systems were used parallel. The first system was already used in the HB89 as originally

postoperative staging system. The categories were grouped according to the grade of resection. Stage I patients have completely resected tumors. Stage II patients have microscopic residuals, Stage III macroscopic residuals after tumor resection or biopsy and Stage IV patients have lung metastases irrespective of the extent of resection. In HB94 the stage III was adapted to all patients which were not resected primarily even if they had no biopsy (=macroscopic residuum) (7). In the HB99 study the patients were divided into two risk groups. High risk patients had a not resectable tumor, multifocal tumor, vessel involvement, positive lymph nodes, or distant metastases. Standard risk patients had a tumor considered as potentially resectable after chemotherapy. So the original stage III patients were divided into a stage III SR and a stage III HR group. The postoperative staging system changed to a preoperative assessment for resectability (8). For international comparability all patients were registered parallel with the grouping system PRETEXT (pretreatment extent of disease) of the SIOPEL Group (10). This system allows a grouping before treatment according to the size and localization of the tumor, and includes the registration of metastases, extra hepatic tumor and vessel involvement of the great vessels (V. cava or liver veins and V. portae). The high risk criteria in the PRETEXT staging system are the following: PRETEXT IV, vessel involvement, extra hepatic tumor, metastases and patients with an AFP level less than 100 ng/ml (10).

3.3.4. Interim results of HB99

Final results of HB99 are not published yet. The results for SR patients are reported for the first four years of the study (8). Results of the HR group are reported 2010, after closure of the study with a short follow up (9).

The interim report of HB99 in 2003 lists 53 patients with a hepatoblastoma who have entered the study until 2003. 8 patients were excluded from the evaluation because they were treated according to different protocols or lost to follow up. 10 patients with a small tumor underwent a primary complete (stage I, n = 8) or microscopically incomplete (stage II, n =2) resection. 26 patients with an extended but potentially resectable tumor (Stage III SR) were preoperatively treated with two to three courses of IPA, followed by a tumor resection and another course of IPA. 9 patients with a HR Hepatoblastoma were treated with two courses of carboplatin and etoposide and in case of response they received high dose chemotherapy with the same drugs, follow if possible by the tumor resection or liver transplantation. The age at diagnosis ranged from the newborn to 18 years. In the PRETEXT grouping system 4 patients had a PRETEXT I tumor, 16 patients a PRETEXT II tumor and 16 patients a PRETEXT III tumor. Out of the group with PRETEXT II/III 6 patients had high risk criteria as involvement of vessels, lung metastases of extra hepatic tumor. 3 patients had a PRETEXT IV tumor. 36 patients are in the standard risk group and 9 had to be considered as high risk patients (8).In the standard risk group (n = 36) more than 90 % of the patients showed a good response after the treatment with IPA. In the SR group two treatment related deaths occurred. 10 patients had a primary tumor resection (27%) and 25 had a delayed resection (69%). 1 patient in the SR group had no tumor resection because of an early death during therapy. The overall survival was 94% of the SR-patients (8). 40 of 45 (89%) of all patients with hepatoblastoma were in remission (8) (Table 1).

51 patients with high risk hepatoblastoma were reported in 2010. 6 out of these 51 high-risk patients had an AFP less than 100 ng/ml. All 6 patients died. All other subgroups were evaluated within the 45 patients with an AFP above 100 ng/ml. In 13/45 the large vessels were involved. In 9/13 patients the tumour could be resected. The 3-y-EFS was significantly lower with 35% (OS 35%) compared to 68% (OS 87%) in patients without vessel involvement but with other high risk criteria. Most of the patients with involvement of the vena cava also had lung metastases (6/7) and there was no significant difference in the OS in non-metastatic patients with or without vessel involvement. 26/45 patients had lung metastases, two died under therapy. In 21/24 patients the lung metastases showed good response to chemotherapy. The 3-y-EFS and OS was significantly lower with 44% (OS 58%) compared to 77% (OS 88%) in patients without metastases (9). The OS survival for all high risk patients was 62% (SE 7). Patients with metastatic disease and low AFP have an even worse prognosis within the high risk group and should be considered as an extra risk group (9).

3.4. Summary and international comparison

The staging systems changed over the years from a postoperative staging system to a system that can be used before treatment. But for comparison of study results is it very important to use identical staging systems as for example the PRETEXT system of the SIOPEL group. This staging system has proven to be prognostically relevant (11). It is possible to use it upfront without resection or biopsy only by imaging of the tumor. The additional criteria as the involvement of the great vessels, distant metastases or extra hepatic tumor are relevant for risk stratification. The PRETEXT staging system was used in parallel in the HB99 and therefore a comparison with the SIOPEL studies is possible.

An important problem in the treatment of hepatoblastoma is the development of drug resistance already observed in the first German liver tumor study (12). The tumor showed a good response to treatment with cisplatin containing therapy, but after 4 to 5 cycles the AFP level raised again which shows indirect the development of drug resistance (HB89). Later research for drug resistance factors confirmed this observance (13, 14). For the treatment it is important to condense the treatment in the beginning and perform the tumor resection not too late, because of the risk of development of drug resistance (12). It is especially important for non resectable tumors to develop new therapies targeted to drug resistance capability of the tumors (15).

The results for patients with standard risk hepatoblastoma are good. The results in the treatment of the standard risk patients stayed the same over the years although the therapy was reduced by reducing the total

dose of ifosfamide and the number of cycles. So this treatment is effective to allow in most of the SR patients a complete resection of the tumor, before development of drug resistance (12). The IPA regime has proven to be effective against hepatoblastoma, as have other drug combinations containing cisplatin (16). The response rate in the German studies was altogether about 90% or above. Also in other international studies from the SIOPEL group cisplatin is the most valuable treatment for hepatoblastoma (16, 17). It is possible to use it as a single drug in 6 cycles with equivalent results, which was shown by the SIOP group (18). But it is important to follow the possible long term side effects like hearing loss or nephro-toxicity.

The prognosis for patients with high risk hepatoblastoma is still not very good. A slight improvement was achieved over the last years by preoperative treatment but it is still not satisfying. What possibilities do we have for patients with metastasized hepatoblastoma or for patients with vessel involvement of the tumor? It is possible to resolve the lung metastases with chemotherapy only, but it might also be important to resect them if they do not disappear with chemotherapy (19). Also the patients with vessel involvement show shrinkage of the tumor thrombus but they mostly do not disappear completely. These patients have a chance to survive by aggressive surgery (20). The aim of the HB99, to improve the outcome with aggressive chemotherapy regime showed an international comparable result but no advantage (9, 21).

The complete resection of the hepatoblastoma is still the mainstay of treatment and is the only chance of cure (12, 22). The primary resection of the tumor was performed in the first two studies for tumors restricted to one liver lobe and in the HB99 the primary resection was only recommended in very small tumors. And this condenses in the lower numbers for stage I and II tumors in the later study HB99, with only 27% primary resected tumors compared to 38%/32% in the HB 89/94. In not resectable tumors the transplantation of the liver can cure these children. In the German studies the transplantation rate is low. In SIOPEL 3 for example altogether 34 liver transplantations out of 158 (22%) high risk patients were performed (21). It is important to plan the transplantation in potentially not resectable tumors from the beginning on. The primary transplantation shows a better prognosis compared to rescue-transplantation (23). So patients with non resectable tumors and no metastases after treatment have a prognosis nearly as good as standard risk patients (85%) with a primary liver transplantation (24).

For the future it is very important to treat these patients with such a rare disease in international studies. New strategies for the high risk patients and especially for those within the high risk group who have even a worse outcome have to be found. So the basic research for new targeted drugs can hopefully improve the prognosis in this rare tumor.

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Abbreviations: IPA: ifosfamide – cisplatin - doxorubicin, Carbo/VP16: carboplatin and etoposide, PA Cont: continuous treatment with cisplatin and doxorubicin, SR: standard risk, HR: high risk, HD: high dose, CR: complete remission, PD: progressive disease, DOD: dead of disease, OS: Overall survival, DFS: disease free survival, GPR: good partial response, PR: partial response, V: involvement of all liver veins or v. cava, P: involvement of the portal vein, E: extrahepatic tumor, M: distant metastases, PRETEXT: pretreatment extend of disease, AFP: alpha fetoprotein, SE: standard error

Key Words: Hepatoblastoma, Childhood Liver Tumor, Cisplatin, HB 89, HB94

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