

## Nephroblastoma

# High-dose chemotherapy with autologous stem cell rescue in children with nephroblastoma

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### Summary:

Children with Wilms tumor who have a particular risk of failure at relapse or at primary diagnosis were treated with high-dose chemotherapy (HDC) and autologous peripheral blood stem cell rescue in order to improve their probability of survival. From April 1992 to December 1998, 23 evaluable patients received HDC within the German Cooperative Wilms Tumor Studies. Nineteen were given melphalan, etoposide and carboplatin (MEC); the others received different regimens. The dose of carboplatin was adjusted according to renal function. Indications for HDC were high-risk relapse in 20 patients, bone metastases in two patients and no response in one patient. Fourteen of 23 patients are alive after a median observation time of 41 months, 11 of 14 in continuous complete remission, three in CR after relapse post HDC. The estimated survival and event-free survival for these patients are 60.9% and 48.2%. Twelve children relapsed after HDC; nine of them died within 12 months and three are surviving from 20 to 33 months after relapse. The main toxicities were hematologic, mucositis and renal (tubular dysfunction; intermittent hemodialysis in one patient). There were no toxic deaths. About half of the children suffering from Wilms tumor with very unfavorable prognostic factors survive disease-free after HDC for over 3 years. Besides hematological toxicity, mucositis and infections, renal function is at risk during HDC. With dose adjustment on glomerular filtration rate, however, no permanent renal failure was observed.

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A child with newly diagnosed Wilms tumor (WT) has a probability of about 85% of being cured with multimodal treatment nowadays. Current treatment strategies stratify intensity and scheduling of the different treatment modalities – surgery, radiation and chemotherapy – according to biologic and prognostic features of the initial disease, most importantly, stage and histology. Three large multi-institutional study groups have contributed to this development: the National Wilms Tumor Study (NWTS), USA,<sup>1–3</sup> the United Kingdom Children's Cancer Study Group<sup>4,5</sup> and the International Society of Pediatric Oncology (SIOP).<sup>6–9</sup> For the 15% of patients with relapse or refractory disease, attempts have been made to use a similar risk-adapted strategy. These efforts were based upon the analysis of Grundy *et al*<sup>10</sup> demonstrating a 3-year survival of 30% in 367 patients who relapsed following treatment within studies NWTS-2 and -3. The authors identified prognostic factors with respect to time and site of relapse, histology and previous therapy, and used them to identify a good-risk group of relapsed patients who had a survival of >40% with conventional therapy.<sup>10</sup> For the complementary group of very high-risk patients, treatment alternatives were investigated. In phase II studies, single drugs or combinations gave the following results: single drug etoposide: 42% of response;<sup>11</sup> ifosfamide plus etoposide: overall response rate 39.5%;<sup>12</sup> etoposide and ifosfamide: 15% complete and 54% partial remission;<sup>13</sup> etoposide plus carboplatin: 70% response.<sup>14</sup> None of these approaches, however, could improve the long-term survival of these patients above 30%.<sup>14</sup> Consequently, dose-response strategies were investigated. Warkentin *et al*<sup>15</sup> who administered etoposide and thiopeta, reported eight out of 12 relapse-free survivors after 1 year. The Solid Tumor Registry of the EBMT reviewed 24

patients who had received different regimens, mostly containing melphalan, 34% of whom survived after a median of 14 months.<sup>16</sup> The French Society of Pediatric Oncology (SFOP) initiated a prospective study of HDC<sup>18</sup> in children with a high risk of failure as defined by the NWTs. Chemotherapy consisted of a combination of melphalan, etoposide and carboplatin (MEC), a regimen extensively applied in other solid tumors. Since the majority of patients underwent HDC after unilateral nephrectomy, the dose of carboplatin administered was adjusted to individual glomerular function using the formula defined by Calvert *et al.*<sup>17</sup> The estimated overall and disease-free survival in this study were 60% of 50%, respectively.<sup>18</sup> Here, we report the outcome of 23 children with Wilms tumor and very high risk features treated during a similar time period within the Wilms Tumor Study of the German 'Gesellschaft für pädiatrische Onkologie und Hämatologie' (GPOH, ie Society of Pediatric Oncology and Hematology). The outcome of eight of these patients was reported earlier.<sup>19</sup>

### Patients and methods

Between April 1992 and December 1998, 23 patients with Wilms tumor underwent high-dose chemotherapy (HDC) with autologous stem cell rescue in 12 pediatric oncology centers within the German Society of Pediatric Oncology and Hematology (GPOH). Two children with rhabdoid tumor of the kidney treated with HDC during the same period were excluded from this analysis.

Diagnosis and first-line treatment followed the SIOP 9 study and the SIOP 93-01/GPOH study. HDC was recommended for patients with high-risk criteria (cf. Table 1), but it was not a compulsory part of the protocol. Therefore, not all patients with such criteria received HDC, and it cannot be determined exactly how many may have died before they could have received it. The studies included 830 patients during the period mentioned above; 120 of them relapsed and 65/120 with one or more high-risk features. Of these 65, children, 43 have died (66%).

The 11 girls and 12 boys studied in this report had a median age of 74 months at diagnosis (range 11–210 months). Thirteen had stage IV disease, three stage III, four stage II and four stage I at the time of diagnosis. The chil-

dren received vincristine (VCR) and actinomycin D (ACT-D) (plus doxorubicin (DOX) if they had stage IV) preoperatively. Histology was intermediate-risk in 14, high-risk in five and completely necrotic in four tumors (Table 2). After surgery, patients with stage I disease were treated with VCR and ACT-D, stage II, III and responsive stage IV with additional DOX. Patients with unresponsive stage IV disease and unfavorable histology – except for stage I anaplasia – were given etoposide (E), carboplatin (C), ifosfamide (IFO) and DOX. Local radiotherapy was delivered according to the study protocol; in eight patients an abdominal site, in eight other patients a thoracic site and in one child both sites were irradiated (Table 3).

Four patients received HDC in first remission according to the high-risk criteria listed in Table 1 (incomplete response to chemotherapy, with initial stage IV in two and bone metastases in two children). After the first relapse, which occurred 9.5 months after diagnosis (median; range 2–24), 19 patients were treated with different drug combinations, all including C and E. The site of first relapse was the lung in 10, lymph node, primary site and liver in two each, skeletal in one and renal with an extrarenal primary tumor in one child. One patient had a combined local and pulmonary relapse. Second-line treatment consisted of various drug regimens and thoracotomy for resectable tumor lesions as well as local irradiation. Patients with chemosensitive tumors, ie in CR or PR after treatment of relapse, were considered for HDC according to the high-risk criteria given in Table 1. At the time of HDC, 13 patients were in complete remission (CR) and 10 in partial remission (PR, cf. Table 2). Autologous peripheral blood stem cells were harvested and cryopreserved according to the current practice of the participating institutions.

The conditioning regimen consisted of C, E and M in 20 patients. On days –7 to –3, 200 mg/m<sup>2</sup>/day of E were given i.v. over 4 h. For C, the total dose of a targeted area under the curve of 20 mg × min/ml using the formula defined by Calvert *et al.*<sup>17</sup> was administered in five doses on days –7 to –3 as a 1 h i.v. infusion. Glomerular filtration rate was estimated by the creatinine clearance in most children, since routine EDTA clearance was only available for a few. M was given as an i.v. bolus of 180 mg/m<sup>2</sup> on day –2, followed by reinfusion of the thawed peripheral hematopoietic stem cells on day 0. Five children were treated with alternative high-dose regimens: melphalan and ifosfamide (2), double melphalan (1), M and TBI 12 Gy (1) and E, thiotepa and cyclophosphamide (1). The autografts contained 3.1 CD34<sup>+</sup> cells/kg (median; range 0.4–43.1; an explanation other than coincidence for this low number could not be found).

Supportive care included hydration during chemotherapy, parenteral nutrition as necessary, prophylactic antimicrobial drugs and irradiated blood products. Recombinant human granulocyte colony-stimulating factor at a dose of 5 µg/kg/day was administered until neutrophil recovery.

Radiotherapy after HDC was given to six patients. One girl and one boy received consolidating irradiation to the lungs (15 Gy); the four other children were irradiated to palliate a recurrence after HDT.

Calculations of medians, means, standard errors and survival estimates according to the method of Kaplan and

**Table 1** High-risk criteria to select patients for high-dose chemotherapy

Criterion <sup>a</sup>	No. patients <sup>b</sup>
1. Relapse, progression or incomplete response of initial stage IV	12
2. Second or subsequent relapse	9
3. Relapse within radiation field	4
4. Bone or brain metastases	3
5. Relapse <6 months after nephrectomy (early relapse)	3
6. Relapse of tumor with unfavorable histology	1
7. Extraregional lymph node involvement	none
8. Clear cell sarcoma in first remission	none

<sup>a</sup>Numbers of criteria refer to patient characteristics in Table 2.

<sup>b</sup>More than one criterion/patient possible.

**Table 2** Patient characteristics

Patient No.	Sex	Age at diagnosis (months)	Stage (postop.)	Histology	High-risk criteria (see Table 1)	Localization 1. relapse	Time diagnosis to 1. relapse (months)	Irradiation before HDC: localization, dose [Gy]	Status at HDC	HDC regimen	EFS (months)	Relapse/progression after HDC	Survival status	Survival (months)
1	F	93	IV	N	1,5	Pulmonary	4	P 15	PR2	E-TT-CYC	3	P	CR2+	37+
2	M	105	IV	S	1,2	Pulmonary	14	Me 30	PR2+	MEC	5	Brain	CR2+	40+
3	F	129	IV	N	1,4				PR1	MEC	41+		CR1	41+
4	M	12	II	S	5	Pulmonary	8	A 25.5	CR2	MEC	44+		CR2	44+
5	F	84	III	Ana	5,6	Pulmonary	8	A 30	CR2	MEC	45+		CR2	45+
6	M	98	III	S	2,3	Abdominal	24	A 32	CR2	MEC	48+		CR2	48+
7	F	99	IV	S	1,3	Pulmonary	16	P 12–15	CR2	MEC	55+		CR2	55+
8	F	24	IV	S	1	Pulmonary	5	A 30	CR2	MEC	75+		CR2	75+
9	M	64	III	S	4	Bone	7	Me 30;A 30	CR2	MEC	77+		CR2	77+
10	M	142	IV	S	1,2	Pulmonary	16	P 15	CR2+	MEC	91+		CR2+	91+
11	M	11	II	S	2	Pulmonary	19	P 15	CR2+	MEC	92+		CR2+	92+
12	M	36	IV	S	1	Pulmonary	13		CR2	MEC	96+		CR2	96+
13	M	45	I	S	2	Pulmonary	10	P 15	CR2+	MEC	89	P	CR2+	109+
14	M	145	IV	Ana	1			Me 30;P 15	CR1	MEC	116+		CR2	116+
15	F	57	IV	N	1			P 15	PR2+	MEC	2	P	Died	4
16	M	74	IV	Ana	1,2	Abd. and pulm.	2		PR2+	2×M	3	P	Died	5
17	M	21	I	Ana	2,3	Abdominal	13	A 30	PR2+	MEC	3	A, L	Died	6
18	M	53	I	S	2	Abdominal	8		PR2+	ME-IFO	2	A, L	Died	7
19	F	100	IV	Sarc	4				PR1	MEC	4	B, L	Died	8
20	F	120	IV	S	1	Liver	21		CR2	MEC	7	L	Died	10
21	F	24	II	S	3	Abdominal	16	A 30	PR2	MEC	3	A	Died	10
22	F	75	IV	N	1	Liver	16	A 20	PR2	ME-IFO	2	A	Died	13
23	F	48	I	S	2	Abdominal	9	A 30	CR2+	MEC	8	P	Died	21

HDC = high-dose chemotherapy; EFS = event-free survival. Histology: N = necrotic (after chemotherapy); S = standard; Ana = anaplasia; Sarc = sarcomatous; CCSK = clear cell sarcoma of the kidney. Localizations: P = pulmonary; B = bone; A = abdominal; L = liver; Me = mediastinum. CR = complete remission; PR = partial remission; CR/PR2+ = third or subsequent CR/PR. Drugs: E = etoposide; TT = thiotepta; CYC = cyclophosphamide; M = melphalan; C = carboplatin; IFO = ifosfamide. TBI 12 = total body irradiation with 12 Gy.

High-risk criteria: numbers refer to the listing given in Table 1.

Explanatory notes concerning single patients: Patient No. 3: Status at HDC is summarized as PR resulting from partial regression of pulmonary and hepatic lesions. The skull lesion was not taken into account since it was expected to remain positive on bone scan at that time regardless of response. Patient No. 12: High-risk because of relapse after stage IV, according to our criteria. Extensive pleural effusion at relapse.

Meier were performed using with Excel (Microsoft) and Prism (GraphPad Software, San Diego, CA, USA) software programs.

**Table 3** Radiotherapy applied before high-dose chemotherapy

Patient No.	Thoracic site (Gy)	Abdominal site (Gy)
17		left abdominal & paraortic 30
2	mediastinum and hili 30	
6		left abdominal 32
14	mediastinum 30	
1	lungs 15	
11	lungs 15	
10	left lung 15	
19	thoracic spine 30	left abdominal/tumor region 15/30
4		right abdominal 25.5
15	lungs 15	
13	lungs 15	
7	lungs 15	
8		abdominal bath 20
22		right abdominal 20
5		left abdominal 30
23		right abdominal 30

## Results

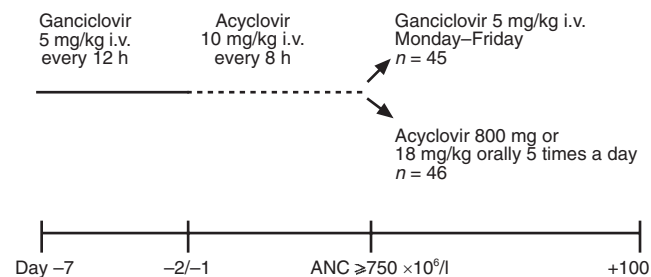
### Efficacy

At the time of analysis, 23 patients had been observed for a median of 41 months (range 4–116). Ten patients were transplanted in partial remission (PR) at HDC. Two achieved a complete remission (CR) post HDC; both are alive. A third child reached CR after HDC plus oral etoposide/trofosfamide for progression of a small lung lesion and has been alive as well for 33+ months. The other seven of these children died of recurrent or progressive disease within 2–12 months. HDC was followed by relapse in three of the 13 patients transplanted in CR. One of them is alive after excision of a solitary lung lesion 89+ months after HDC. The other two children died after pulmonary and hepatic relapses which occurred 2 and 7 months after HDC, respectively. Relapse or progression occurred in 12 patients. Eleven of these events happened early, ie between

2 and 8 months after HDC. Of the 12 patients, nine died within 2 to 12 months after the relapse. Three patients are survivors of a recurrence or progression after HDC. One boy developed an isolated intracerebral metastasis 5 months after HDC which was irradiated; he has been in second CR for 20+ months. The other two survivors had solitary pulmonary recurrences, one of them found 3 months after HDC, treated with oral etoposide/trofosfamide for 12 months (CR 33+ months after the relapse), and the other excised 7 years after HDC (CR since 20+ months). The survival of all 23 patients, estimated by the Kaplan–Meier method, is 60.9% ( $\pm 10.2\%$ ) after a median follow-up of 58 months (range 37–116; Figure 1). The event-free survival (EFS) estimate is 48.2% ( $\pm 13.6\%$ ; Figure 1). For the subgroup of 19 patients all treated with the identical MEC consolidation regimen, these estimates are 63.2% ( $\pm 11.0\%$ ) for survival and 54.1% ( $\pm 14.9\%$ ) for EFS.

### Toxicity

Toxic side-effects involved mainly hematopoiesis, gastrointestinal mucosa and kidneys. As expected, all patients developed pancytopenia. Recovery of leukocytes to  $>1.0/\text{nl}$  and of granulocytes to  $>0.5/\text{nl}$  occurred on day 11 (median; range 8–21). Platelets rose to unsupported values of  $>50/\text{nl}$  on day 37 (median; range 10–153;  $n = 20$ ). Thus, the low median number of transplanted CD34<sup>+</sup> cells did not translate into delayed hematopoietic recovery. The majority of patients developed mucositis and diarrhea, mostly requiring analgesia with opiates. WHO grading of gastrointestinal toxicity was available in 20 patients: grade III or IV was observed for stomatitis in 10/20, for nausea and vomiting in 9/20 and for diarrhea in 6/20 children. One episode of acute gastric bleeding occurred which required a blood transfusion. All patients had febrile episodes and septicemia was documented in two children. Pulmonary toxicity was mild; mechanical ventilation was necessary in one child with acute renal failure (see below). Liver toxicity included transient elevation of liver enzymes and one episode of VOD which resolved. Before HDC, the evaluable creatinine clearances of 21 children at the time of HDC were 102.2 ml/min/1.73 m<sup>2</sup> in mean (s.e.  $\pm 43.0$ ). Eight children had a clearance of less than 80 ml/min/1.73 m<sup>2</sup>. Five of those had MEC as a consolidation regimen and none developed renal failure. The only patient who developed renal failure had a normal glomerular filtration rate (GFR) at HDC. He needed hemodialysis from day +7 to day +29 after reinfusion of stem cells. Tubular dysfunction was



**Figure 1** (a) Survival and (b) event-free survival estimates for 23 children with bad-risk nephroblastoma after high-dose chemotherapy.

observed in six children after HDC which was reversible in five of them. While acute cardiac side-effects were rare and only noted as a pericardial effusion in the child with acute renal failure, two cases of cardiomyopathy were observed. One already existed before HDC after doxorubicin treatment (300 mg/m<sup>2</sup>) and one occurred after consolidative mediastinal irradiation of 1440 cGy post HDC. Both children are free of symptoms on treatment. The latter patient also suffered from esophageal stenosis after esophagitis and irradiation; he has no functional deficit now after mechanical dilatation of the esophagus. Hypergonadotropic hypogonadism is being treated by hormone replacement in one boy and one girl. One case of focal nodal hyperplasia of the liver was found.

### Discussion

Nowadays, recurrence of a Wilms tumor is quite a rare event. With modern multimodal treatment strategies it occurs in only 10–15% of patients. Prognostic factors for cure after a recurrence have been described by Grundy *et al*<sup>10</sup> for NWTS patients: children with early relapse, unfavorable histology or relapse from stage IV (no matter which histology) had a likelihood of 15–20% of being alive after 3 years; of the complementary group, 30% survived relapse-free after 3 years. From an analysis of response to second-line chemotherapy in 49 evaluable patients with nephroblastoma, Pinkerton and colleagues<sup>20</sup> derived a salvage rate of little more than 50% for patients with localized disease and favorable histology, while all other patients only had a remote likelihood of surviving. Ifosfamide, etoposide and mesna were found to be effective in 69% of children with relapsed Wilms tumors (CCSG Study<sup>13</sup>). The French study group (SFOP) identified ifosfamide, etoposide and etoposide+carboplatin as active second-line agents.<sup>11,14,21</sup> Since these drugs could be used in a dose-response strategy with autologous bone marrow or hematopoietic stem cell rescue and since clinical experience existed from other solid tumors with high-dose regimens including melphalan, etoposide and carboplatin (MEC), this combination of drugs was also studied as consolidation therapy for nephroblastoma. A survey from the EBMT Solid Tumor Registry including 25 children and six different regimens yielded short-term results which justified further evaluation of the high-dose chemotherapy concept in these patients.<sup>16</sup> The prospective study of the French Study Group published in 1998 included 28 assessable patients with high-risk recurrent Wilms tumor as defined by Miser and Tournade.<sup>22</sup> Disease-free survival and overall survival at 3 years (Kaplan–Meier estimates) were 50% and 60%. The toxic morbidity was considerable, but no child died because of the treatment.

Our group of patients, even if analyzed retrospectively, is comparable to the cohort of the French group in that it included 23 patients of the same poor prognostic risk profile and 19 of them received the identical MEC consolidation regimen. We can confirm the observations described by Pein and colleagues (SFOP<sup>18</sup>). First of all, the regimen is effective in increasing survival of these poor-prognosis patients from 30% at 3 years to 60% at 3 years (SFOP

and 63% at 4.5 years (this report). The estimated relapse-free survival is 50% and 43%, respectively. Of the 10 patients transplanted while not in CR, eight progressed and seven died. This observation demonstrates that patients must have chemosensitive disease in order to profit from HDC. Two patients received consolidative pulmonary irradiation after HDC. The role of this part of the treatment in the setting of HDC is not well defined. Remarkably, all relapses after HDC in our patients occurred within 1 year except for one single lung relapse after more than 7 years, whereas the cohort of recurrences in the French study levels off at 2.5 years with two relapses later. Taken together, most treatment failures occur within 2 years post HDC. Furthermore, most of the patients grafted in second or subsequent CR who survived had had consecutive single pulmonary recurrences and had attained a further CR after thoracotomy with or even without chemotherapy before HDC. The detailed results of the French group and the observations of our own patients show that, within this adverse prognostic group, the children with only pulmonary locations of relapse – even after multiple recurrence – fared best. They account for 64% (SFOP) and 83% (this report) of the survivors. The feasibility of complete surgical excision of lung lesions, repeatedly if necessary, certainly contributes to these results. Besides the smallest amount of residual disease, the other important factor for success of HDC is that the tumor is responsive to chemotherapy. In our cohort, only two patients out of 10 grafted in PR are surviving; the other 14 survivors were grafted in CR 1 or CR2 ( $n = 11$ ) or subsequent CR. In the French study, a significantly higher disease-free survival was seen in children consolidated in second remission (CR or PR) as opposed to subsequent remissions.<sup>18</sup>

Besides efficacy, toxicities are also comparable between the French cohort of patients and ours. Bone marrow depression was profound in all patients, but could be reversed by autologous hematopoietic stem cell transfusion with comparable recovery dates: leucocytes  $>1.0/\text{nl}$  and PMN  $>0.5/\text{nl}$  on day 11 and 14, platelets  $>50/\text{nl}$  after day 37 and 36 in our patients and those of the French study, respectively.<sup>18</sup> Severe gastrointestinal mucositis was common, leading to life-threatening hemorrhages in two children of the French group and to stenosing esophagitis in one of our patients. Of most concern is renal function, since virtually all children receive high-dose carboplatin with a single kidney which has not yet completed its compensatory hyperplasia. Therefore, carboplatin was dosed according to glomerular function<sup>17</sup> in both patient cohorts. We treated eight children with a subnormal creatinine clearance at time of HDC, five of them with MEC including carboplatin with a dose mentioned above. None of these children developed renal failure. Three of the five children treated with MEC are survivors. Thus, the carboplatin dose adapted to a reduced glomerular function does not usually seem to lead to treatment failure, while further renal damage during conditioning is prevented. However, there are exceptions to this. We observed transient renal failure requiring hemodialysis in one patient with nephroblastoma<sup>23</sup> (plus one boy with rhabdoid tumor of the kidney who was not included in this analysis) after HDC with MEC, both with a normal creatinine clearance at the time of HDC. Our French col-

leagues did not need dialysis for any one of their patients. Tubular damage occurred in 7/21 evaluable children of our group and in 7/28 patients treated by the French group.<sup>18</sup> In spite of the encouraging absence of glomerular toxicity in the French patients, our experience calls for caution in treating these uninephric patients with a high-dose regimen such as MEC. Further escalation of doses would, in our opinion, carry the risk of increasing renal toxicity.

Toxic side-effects to other organ systems appear to be rare. Transient heart failure has been noted in three patients of the French cohort. However, an analysis of congestive heart failure after treatment for Wilms tumor – without HDC – has documented a rate of 4.4% after 20 years of follow-up.<sup>24</sup> Thus, the frequency of this complication after HDC in these patients must be expected to rise with further observation. The paucity of pulmonary problems is remarkable, many of these patients having received radiation therapy to the lungs and/or mediastinum before the HDC (cf. Table 3).

With this analysis, we confirm the conclusion of Pein and colleagues<sup>18</sup> that high-dose consolidation treatment with MEC is of long-term benefit for children with high-risk relapse of Wilms tumor. Intensive conventional chemotherapy in comparison to HDC has not yet been studied in such high-risk patients. Because these patients are rare, this may require a multinational study, but it should be undertaken because the toxicity of HDC, although not lethal, is considerable. Kidney function of these uninephric children is at risk with high-dose carboplatin, and a GFR-adapted dose must be recommended. Dosing and scheduling of the drugs within the MEC regimen should be discussed with respect to the pharmacokinetics of high-dose melphalan in uninephric children.<sup>25</sup> As to drugs other than M, E and C which may be suitable for a dose-response strategy in Wilms tumor, experiences with larger patient numbers are awaited for thiotepa and cyclophosphamide.<sup>15</sup> HDC with MEC has no curative potential for children whose tumors do not respond well and who do not achieve a state of minimal residual malignant disease. The search for active agents to treat these patients must continue.

The bad-risk profile of these patients has been defined by histology and clinical criteria of response and relapse pattern. Further understanding of the biology of the different renal tumors of children may enable us to use genetic factors such as loss of 16q<sup>26</sup> or biologic features of the tumor such as the expression of a functional receptor of the neurotrophin receptor TrkB<sup>27</sup> to discriminate patients at high risk of failure.

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