Oxaliplatin, Irinotecan, and Gemcitabine: A Novel Combination in the Therapy of Progressed, Relapsed, or Refractory Tumors in Children

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Summary: Therapeutic options for unresectable neuroendocrine carcinomas and relapsed or refractory solid tumors are still limited in pediatric patients. We present a retrospective review of 12 children (3 to 16 y) in a case series treated with a novel combination of oxaliplatin, irinotecan, and gemcitabine (triple therapy). We defined its feasibility in a mainly outpatient setting and assessed its toxicity and effectiveness. Three patients with unresectable neuroendocrine carcinomas received triple therapy as first-line treatment; 9 children with relapsed or refractory solid tumors of different entities were assigned after failure of standard treatment protocols. The treatment schedule comprised oxaliplatin (85 mg/m^2), irinotecan (175 mg/m^2), and gemcitabine (1,000 mg/m^2), the latter to be repeated on day 8. A median of 7 cycles was applied. Nine of 12 patients showed hematotoxicity 0-III degrees. Gastrointestinal toxicity I-II degrees were handled satisfactorily by supportive drugs. Tumor response was defined as partial response in 1 of 12 children, stable disease in 8 of 12 children, and progressive disease in 3 of 12 children with a median time of disease control of 7 months. We regard triple therapy as a well-tolerated outpatient treatment option offering children a high quality of life and showing considerable effectiveness in delaying tumor progress.

Key Words: combination chemotherapy, neuroendocrine carcinoma, children, solid tumors, triple therapy

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Despite multiagent chemotherapies and multidisciplinary approaches, unresectable or metastatic neuroendocrine carcinomas (NEC) and intraabdominal desmoplastic small round cell tumors still show a poor prognosis.[1–3] Standard treatment protocols (STP) are not yet available and extensive initial surgery can only be provided in $< 5\%$ of patients.[4] Similar conditions apply for the treatment of relapsed or refractory solid tumors in children. Besides STPs such as, CWS-96 ("Cooperative Weichteilsarkomstudie", cooperative soft tissue sarcoma study), COSS-96 ("Cooperative Osteosarkom Studie", cooperative osteosarcoma study) or HIT ("Hirntumorstudie", malignant brain tumor study), and protocols for relapsed disease, the remaining treatment options are often limited. Meanwhile, new chemotherapeutics such as irinotecan showed remarkable potential for different childhood cancers.[5–10]

Combinations of irinotecan, a platinum derivative and 5-fluorouracil have been used in adults as an accredited treatment in advanced colorectal cancer and served as a basis for our adopted schedule.[11–13] First pediatric trials of a combined treatment of irinotecan/cisplatin for refractory solid tumors showed evidence of disease stabilization.[14] In recent years, gemcitabine proved to be well tolerated with a modest antitumor activity[15,16] and showed some potential for a combined treatment in children suffering from refractory or relapsed solid tumors.[17,18]

We present a 7-year retrospective review of 12 children in a case series using a 4-week treatment schedule including irinotecan, oxaliplatin, and gemcitabine—referred to as "triple therapy"—for the treatment of progressed, relapsed, or refractory solid tumors. We determined its feasibility in a mainly outpatient setting and assessed dose-limiting toxicities and tumor response rates.

PATIENTS AND METHODS

Patients

Group "A" consisted of 3 patients (1 to 3), aged 12 to 14 years and diagnosed with an unresectable NEC. They received 4 to 6 cycles of first-line triple therapy before second-line treatments (Table 1).

Nine children in group "B" (4 to 12), aged 3 to 16 years at the beginning of triple therapy, reflected different entities of relapsed or refractory solid tumors and a heterogeneous background of pretreatment schedules (Table 1). Therefore, a varying number of 3 to 19 cycles (median of 8 cycles) of triple therapy were applied. In detail: 1 patient with relapsed medulloblastoma after initial STP, relapse protocol and autologous stem cell transplant (SCT) (4); 1 patient with III degrees neuroblastoma, relapsed after STP and autologous SCT (5); 1 patient with IV degrees neuroblastoma, progressed after 8 months of STP (6); 2 patients with pulmonary metastasized osteosarcomas (7 and 8) and 1 patient with pulmonary metastasized sarcoma of soft tissue, progressed after STP (9); 1 patient with refractory intraabdominal desmoplastic small round cell tumors, disseminated after STP (10); 1 patient with primitive neuroectodermal tumor, metastasized after STP (11); 1 patient with metastasized hepatocellular carcinoma after STP and relapse protocol (12). All except patient

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TABLE 1. Patients and Treatment

Patient No.	Age (at Diagnosis)	Sex	Diagnosis	Primary. Tumor Size	Pretriple Treatment	Surgery yes/no	No. Cycles Triple Therapy	Posttriple Treatment	Outcome Pretreatment/ triple treatment/ posttreatment	Max. Hematotox. (CTC Grade)	Inpatient Days	Survival (Since Triple Therapy)
1	13.8	M	Metastatic NEC	5.5 × 2.4 × 3.7 cm	None	n	6 × triple 1-8-15	CWS 96 SCT gemcitabine temodal	Triple: SD 7 mo SCT: PD	III degrees	10	18 mo*
2	14.9	M	Metastatic NEC	1.3 × 1.6 cm	None	n	6 × triple 1-8	CWS 96 SCT	Triple: PR 8 mo SCT: SD	I degree	11	44 mo
3	12.1	F	Metastatic NEC	3.5 × 1.2 × 3.5 cm	None	n	4 × triple 1-8	PEI DOTATOC/ -TATE	Triple: SD 5 mo DOTATOC: PD	0 degree	15	36 mo
4	9.9	M	Relapsed medulloblastoma	n.e.	HIT-SKK 2000 HIT-Rez 97 auto SCT	y	8 × triple 1-8	None	HIT/SCT: PD triple: SD 6 mo	0 degree	7	9 mo*
5	11.9	F	Relapsed neuroblastoma III	n.e.	NB2004 auto SCT 19-cis-retinoic acid	y	5 × triple 1-8-15	J-131 MIBG Rx	NB 2004: PR t riple: SD 12 mo	III degrees	5	13 mo
6	3.2	F	Neuroblastoma IV	Diss.	NB2004	n	6 × triple 1-8-15 2 × triple 1-8	None	NB 2004: PD triple: SD 7 mo	0 degree	8	11 mo*
7	12	M	Metastatic osteosarcoma	315 mL	COSS 96	y	14 × triple 1-8	Surgery of mx trophosfamide; VP-16; Rx	COSS 96: PD triple: SD 15 mo	IV degrees	10	40 mo*
8	15.9	M	Metastatic/ relapsed osteosarcoma	n.e.	EURAMOS 1 iphosfamide/ etoposide	y	10 × triple 1-8	none	EURAMOS1: PD triple: SD 12 mo	IV degrees	18	13 mo
9	15.8	M	Metastatic soft tissue sarcoma	25 mL	CWS 96	y	3 × triple 1-8	Rx	CWS 96: PD triple: SD 2 mo	I degree	2	4 mo*
10	16.3	F	IDSRCT	n.e.	EURO-Ewing 99	y	4 × triple 1-8-15	None	Ewing99: PD triple: PD 4 months	IV degrees	4	7 mo*
11	15.7	M	Metastatic PNET	18 × 9 × 20 cm	CWS-IV 2002	y	15 × triple 1-8	None	CWS-IV: PD triple: PD 2 mo	III degrees	24	12 mo*
12	13.6	F	Metastatic HCC	8.5 × 9.5 × 11.7 cm	5-FU + IFN-α	y	19 × triple 1-8-15	None	5-FU + INF-α: PD triple: PD 3 mo	III degrees	20	17 mo*

*Patient died after denoted months of survival.

5-FU indicates 5-fluorouracil; auto SCT, autologous stem cell transplantation; COSS 96, trial protocol "Cooperative Osteosarcoma Study", till 12/2005; CTC, common toxicity criteria; CWS 96, trial protocol for soft tissue sarcoma; CWS IV 2002, trial protocol for soft tissue sarcoma stage IV; DOTATATE, ^{177}Lu-DOTA-Tyr^3-octreotate; DOTATOC, DOTA(0)-Phe(1)-Tyr(3))octreotide, edotreotide; EURAMOS 1, trial protocol for osteosarcoma, start 12/2004; EURO-Ewing 99, trial protocol for Ewing tumor; HCC, hepatocellular carcinoma; HIT-Rez 97, trial protocol for relapsed malignant brain tumors; HIT-SKK 2000, trial protocol for intracranial PNET/medulloblastoma and ependymoma; IDSRCT, intraabdominal desmoplastic small round cell tumor; IFN-α, interferon-alpha; J-131 MIBG, *m*-(I-131) iodobenzyl-guanidine; mx, metastases; n.e., not evaluated; NB2004, trial protocol for neuroblastoma; NEC, neuroendocrine carcinoma; PD, progressive disease; PEI, cisplatin, etoposide, ifosfamide; PNET, primitive neuroectodermal tumor; PR, partial response; Rx, radiotherapy; SD, stable disease; VP-16, etoposide phosphate.

6 had undergone surgery during their first-line treatment strategies.

Triple therapy was initiated as a compassionate use in accordance with the Society for Pediatric Oncology and Hematology study centers if no other option of any standard treatment was available. Informed consent was obtained by the legal guardians.

Treatment Schedule (Fig. 1)

A 4-week treatment schedule consisted of intravenous administration of: oxaliplatin (85 mg/m^2/2 h) (in 250 mL glucose 5%), followed by irinotecan (175 mg/m^2/2 h), and gemcitabine (1,000 mg/m^2/0.5 h) on day 1. Sinlge intravenous gemcitabine (1,000 mg/m^2/0.5 h) was administered on day 8 and facultative on day 15, depending on a patient's individual clinical presentation at start of triple therapy (see below). NaCl 0.45% and glucose 5% at (3 L/m^2/d) were given continuously throughout application of triple therapy as prophylactic hydration.

Supportive Care

Ondansetron (5 mg/m^2), tropisetron hydrochloride (0.2 mg/kg), and/or dimenhydrinate (1 to 2 mg/kg/dose) were given intravenously for prevention of nausea and vomiting. Oral loperamide (2 mg) was administered to treat diarrhea and cholinergic syndrome. Trimethoprime and sulfonamide 5 mg/kg was given twice daily for 3d/wk to prevent *Pneumocystis carinii* pneumonia, completed by oral amphotericin B 4 × 2 mL/d for prevention of local fungal infection.

Toxicity and Tumor Response Criteria

Hematotoxicity was evaluated according to the National Cancer Institute's common toxicity criteria at least once a week and before the start of every new cycle. The 4-week treatment schedule was followed if granulocytes were > 1,000/μL and platelets were > 75,000/μL at day 1 of the following cycle. A dose reduction of 25% was considered whenever hematotoxicity reached IV degrees severity (leukocytes < 1,000/mm^3, platelets < 25,000/mm^3, hemoglobin < 6.5 g/dL) or other organ toxicity showed a ≥ III degrees toxicity.

Response rates for solid tumors were assessed according to Response Evaluation Criteria In Solid Tumors-criteria,[19] whereas tumors of the central nervous system were assessed according to the Neuro-Oncology Working Group criteria.[20]

As we present a retrospective review of cases, chronology and methods followed 2 different schedules: assessment for tumor response was either performed in a 3-month interval (2 to 3, 5, 9 to 10) or 6 months after initiating triple therapy (1, 4, 6 to 8, 11 to 12). Preferably corresponding diagnostics (magnetic resonance imaging, computed tomographic scan, or scintigram) were applied as for initial staging strategy.

RESULTS

Toxicity (Table 1)

Three of 12 (25%) patients did not experience any hematotoxicity. Six patients (50%) showed mild-to-moderate I-III degrees thrombocytopenia and/or leucopenia. One patient had a transfusion-dependent (IV degrees) thrombocytopenia more than 4 weeks (10). Two patients (7, 8) showed transfusion-requiring thrombocytopenia and anemia, and a IV degrees leucopenia more than 3 months besides dose reduction of all 3 substances: oxaliplatin was reduced to 65 mg/m^2 (76% of original dose), irinotecan to 130 mg/m^2 (74%), and gemcitabine was first reduced to 645 mg/m^2 (64%) later to 480 mg/m^2 (48%). However, only dropping the administration of gemcitabine at day 15 (7, 10) and irinotecan at day 1 (8), respectively, led to a sustained hematological stabilization in these patients without the need for any additional hospitalization.

After experiences in these patients, treatment schedules of 6 other patients were adjusted to a shortened cycle with gemcitabine given at days 1 and 8 only (2, 3, 4, 6, 9, 11). This adjustment depended either on the intensity of pretreatment chemotherapy (4, 6, 9, 11) or the severity of initial presentation of symptoms at diagnosis (2, 3).

Gastrointestinal toxicity consisting of nausea, diarrhea, and vomiting I-II degrees was seen in most patients. All symptoms could be handled satisfactorily by the above mentioned supportive care drugs without any dose reductions.

An afebrile, minor increase of C-reactive protein was seen in patients 1, 2, 3, 8, 11 and prophylactically treated by intravenous antibiotics over a few days, whereas the treatment schedule was not affected. We did not experience any other toxicity in our cohort.

Tumor Response (Table 1)

Median time of disease control [partial response and stable disease (SD)] was 7 months (group A) and 9.5 months (2 to 15) (group B), respectively. Follow-up was

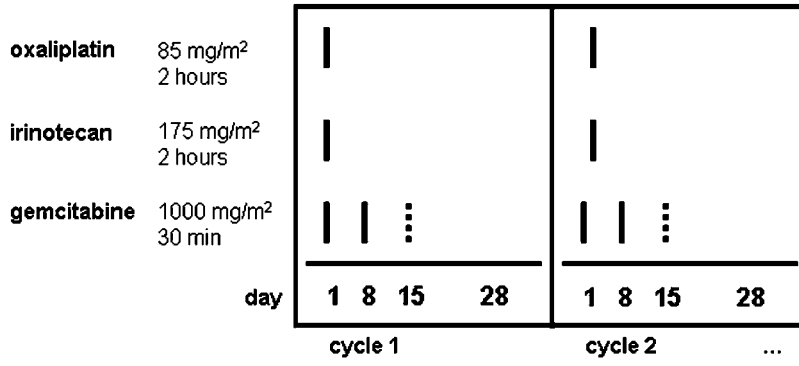
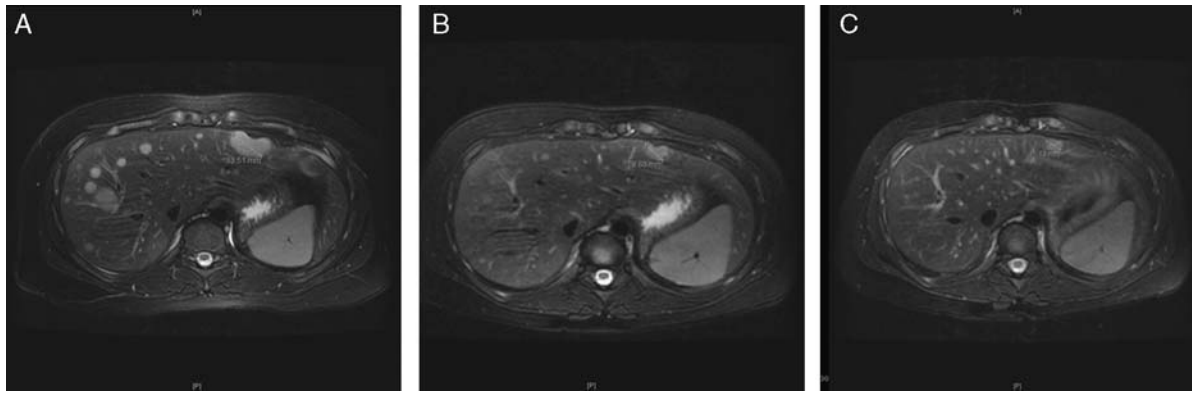


FIGURE 1. Triple therapy treatment schedule. Chemotherapeutics to be repeated on day 1 and 8. Five of 12 patients (1, 5, 6, 10, 12) also received gemcitabine at day 15 (dotted line).



FIGURES 2. A to C, Liver metastases in patient 2. A, Initial multiple liver metastases; after 2 cycles of triple therapy (B) and after 5 cycles of triple therapy (C) metastases are reduced in size and number >50% (partial response); computed tomographic scan abdomen and contrast medium. (With kind permission of Prof. Dr M. Galanski, Hannover Medical School, Institute for Radiology, Carl-Neuberg-Street 1, 30625 Hannover).

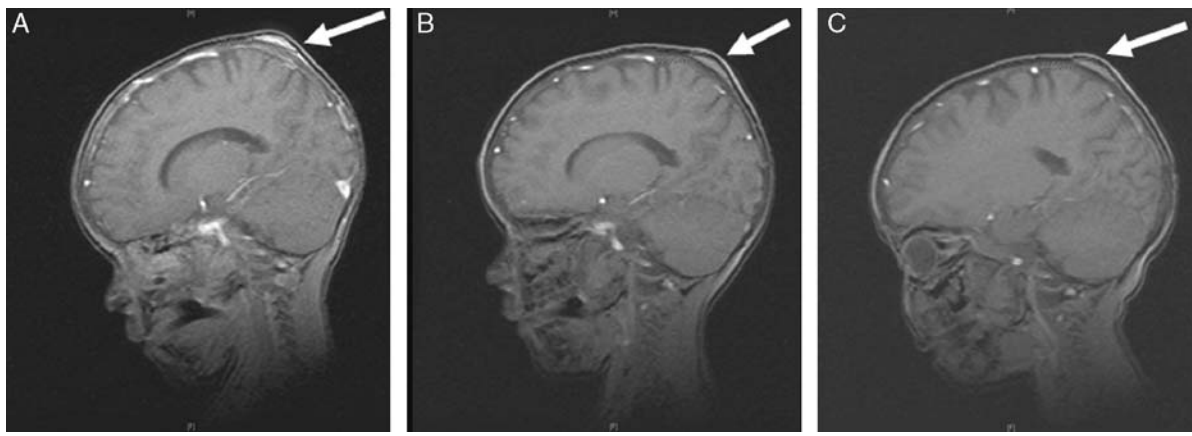
performed until death of patient or until triple therapy was replaced by another treatment protocol over a period of at least 6 months.

Group A: patients 1 and 3 showed SD after 7 months and 4 months of triple therapy, respectively, with identical extent of primary tumor site and a stable number of liver metastases, slightly decreasing in size. Patient 2, who additionally suffered from a Hyper-IgM-syndrome diagnosed before his NEC, showed a partial response during 8 months of triple therapy with a reduction in tumor size and metastatic extent > 50% (Figs. 2A–C).

After triple therapy, patients 1 and 2 received treatment according to CWS protocol before undergoing high-dose chemotherapy and SCT. At the time disease relapsed, patient 1 died after 6 months, whereas patient 2 to date shows SD. After 4 cycles of triple therapy, patient 3 received 3 cycles of PEI (cisplatin, etoposide, ifosfamide) treatment, still showing SD. Initial staging had shown a "somatostatine receptor positive" tumor entity, and radiotherapy with 90Y-DOTA-TOC (octreotide) was followed by 3 courses of 177Lu-DOTATATE (octreotate). The patient developed progressive disease (PD) 36 months after initial diagnosis.

Group B: 6 of 9 children showed SD more than 2 to 15 months (median of 9.5 mo) under triple therapy, of which 3 children (4, 6, 8) had no subsequent therapy. Among these, tumor responses lasted from 9 (4) to 11 (6), and 13 (8) months, respectively, since start of triple therapy. Three of 9 children showed PD under triple therapy for 6 to 17 months and died within 1 month after stop of triple therapy. To date 7 of 9 children have died 4 to 40 months after start of triple therapy.

In detail: patient 4 showed SD more than 6 months before progression and died 3 months thereafter. Patient 5 showed SD for 12 months, including 5 cycles of triple therapy followed by J-131-MIBG [*m*-(I-131) iodobenzylguanidine] treatment and radiotherapy before progression. Patient 6 showed SD of primary tumor site and skull metastases more than 7 months (Figs. 3A–C) until hepatic metastases progressed and died 11 months after initiation of triple therapy. Despite hematotoxicity and subsequent dose reductions patients 7 and 8 showed SD more than 15 (7) and 12 (8) months, respectively. Patient 7 then developed PD of his—earlier twice resected—lung metastases and underwent surgery, trophosphamide, etoposide



FIGURES 3. A to C, Scull metastasis in patient 5. A, At start of triple therapy; skull after 5 cycles of triple therapy (B) and 9 cycles of triple therapy (C) with metastasis stable in size (stable disease); progression of abdominal metastases after 9 months (progressive disease); magnetic resonance imaging head, T1 and contrast medium. (With kind permission of Prof. Dr H. Lanfermann, Hannover Medical School, Institute for Neuroradiology, Carl-Neuberg-Street 1, 30625 Hannover).

phosphate (VP-16) treatment and radiotherapy. He died 40 months after start of triple therapy because of ongoing PD. Pulmonary metastases of patient 8 to date still show SD without further treatment. Patient 9 received triple therapy to control his pulmonary metastases in a palliative situation. Although lung computed tomographic scan after 3 months showed SD, his clinical condition worsened and the patient died 5 weeks thereafter.

DISCUSSION

We present a novel combination of 3 chemotherapeutics—oxaliplatin, irinotecan, and gemcitabine, which had shown good clinical results in single or combined use, both in children and adults for the treatment of different entities of advanced solid tumors. Preclinical studies showed synergistic effects for gemcitabine/oxaliplatin[21] and oxaliplatin/irinotecan with reliable antitumor activity even in cisplatin-resistant cell lines.[22]

We created a mostly outpatient treatment schedule which allows these sometimes heavily pretreated children a good quality of life by staying in their familiar environment without severe side effects. Measurement of tumor response and the resulting potential of a novel triple agent chemotherapy in a variety of childhood cancers with limited treatment options was only a secondary aim.

Overnight hospitalization was necessary at day 1 of each cycle to ensure prehydration and consecutive application of all chemotherapeutics. The following applications of gemcitabine could be handled satisfactorily in an outpatient setting, resulting in very few nights inpatient (ie, patient 6 had only 8 nights inpatient during 6 months of treatment, Table 1).

As hematotoxicity was usually mild, additional hospitalization was a rare event. A transfusion-dependent anemia and thrombocytopenia IV degrees in 3 of 9 patients of pretreated group B (7, 8, 10) could be handled in an outpatient setting for weeks. Minimizing the applications of gemcitabine and irinotecan finally led to a significant decrease in hematotoxicity. No other dose-limiting toxicities were stated. Thus, triple therapy proved to be mildly toxic especially with gemcitabine administered on days 1 and 8 only (7 of 12 patients). In heavily pretreated patients one should therefore, consider the application of the latter regimen to avoid myelotoxic events or dose reductions. Our experiences correspond well with recent pediatric studies of protracted treatment schedules with up to 2 substances, which also describe high levels of tolerance.[5–7,17,23]

Authors are aware of the underlying limitations in this case series because of the limited number of patients, their heterogeneous background of diseases and the use of varying radiologic assessment techniques for tumor response at different times. Undoubtedly, these limitations and varying pretreatment strategies affect the comparability of patients. However, in a majority of patients (9 of 12) we found disease control (SD or PR) over a median period of 7 months (group A) and 9.5 months (group B), thus indicating a significantly higher response rate compared with single-drug or double-drug studies using irinotecan, gemcitabine, or oxaliplatin in children and adults so far.

Single irinotecan showed a 30% to 43% disease control rate (DCR) in different pediatric studies,[5–7,9] whereas gemcitabine had a DCR of 10% to 20%.[17,18] Adult trials of advanced pancreatic or biliary tract cancer stated a DCR of 42% to 57% when both substances were administered,[15,16,24] whereas time to progress and overall survival were not altered.[25] In 2002, Souglakos et al[13] used a combination of gemcitabine and a platinum derivative in the treatment of advanced solid tumors in adults with a reasonable result of 46% DCR, whereas Reid et al[17] and Wagner-Bohn et al[18] later adopted the latter for children. Souid et al[14] published a DCR of 63% using irinotecan/cisplatin for the treatment of refractory solid tumors in children. In adults, irinotecan/oxaliplatin as a first-line treatment in advanced colorectal cancer showed a DCR of 41% to 94% often in combination with 5-fluorouracil/leucovorin.[11–13,26,27]

Recently, 2 novel studies in adults dealt with a 3-drug therapy: Goel et al[28] combined irinotecan, gemcitabine, and cisplatin in the treatment of metastatic pancreatic cancer with a DCR of 87.5%, whereas de Lima Lopes et al[29] found a 68% DCR combining irinotecan, gemcitabine, and carboplatin in small cell and NEC. Both studies underlined an easy administration with tolerable side effects, which we confirmed in our evaluation.

In conclusion, we consider the triple therapy a mildly toxic, well-tolerated, mostly outpatient therapy regimen for children with relapsed or refractory solid tumors. It produced SD in the majority of patients ensuring a high quality of life. Further studies in larger number of patients will be necessary to determine tumor responsiveness.

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