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A Phase II Trial and Pharmacokinetic Study of Oxaliplatin in Children With Refractory Solid Tumors: A Children's Oncology Group Study

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Background. Platinating agents are used in the treatment of a spectrum of childhood cancers. Oxaliplatin, a third generation platinum compound, may provide less toxicity and be more effective. A phase 2 study was performed to estimate the response rate to single agent oxaliplatin in patients with refractory pediatric solid tumors, and to further describe the toxicities and pharmacokinetics of the drug in this population. ***Patients and Methods.*** Subjects, ≤21 years of age at original diagnosis, received oxaliplatin (130 mg/m^2) intravenously every 21 days. Prior platinum exposure was acceptable. Histologies included: Ewing sarcoma/peripheral PNET, osteosarcoma, rhabdomyosarcoma, neuroblastoma, high and low grade astrocytoma, brain stem glioma, ependymoma, hepatoblastoma and selected rare tumors. A two-stage design, enrolling 10 + 10 subjects, was used for each disease stratum. Limited sampling pharmacokinetic studies were performed. ***Results.*** Of 124 eligible subjects (75 males), 113 were evaluable for response and 69 (62%) had received platinum previously. Only one objective response was observed, a partial response in a 6-year-old child with ependymoma. An additional 13 subjects with various other solid tumors had stable disease, receiving a median (range) of 13.5 (2–17) cycles. Five subjects completed 17 treatment cycles. Thrombocytopenia was the most common toxicity observed. The median (range) terminal half-life and clearance for ultrafiltrable platinum were 293 (187–662 hr) and 14.0 (1.9–24.9 L/hr/m^2), respectively (n = 49). ***Conclusions.*** Although reasonably well tolerated, oxaliplatin administered as a single agent has limited activity in pediatric patients with relapsed or refractory solid tumors. Pediatr Blood Cancer. 2010;55:440–445. © 2010 Wiley-Liss, Inc.

Key words: oxaliplatin; pediatric; pharmacokinetics; phase II study; refractory solid tumor

INTRODUCTION

Platinating agents are useful in the treatment of many childhood cancers, including osteosarcoma, neuroblastoma, hepatoblastoma, germ cell tumors, and CNS malignancies. However, the use of cisplatin, the primary platinum agent utilized in childhood cancer, is limited by its high rate of ototoxicity and nephrotoxicity. Oxaliplatin, a third generation platinum agent containing a DACH (1, 2 diaminocyclohexane) carrier ligand [1–5], was developed to provide a less toxic and more effective platinum compound. DACH platinum-induced DNA adducts prevent binding of the mismatch repair (MMR) enzyme complex and interfere with replicative bypass [6,7]. In human tumor cell lines, oxaliplatin demonstrated activity against a wide variety of tumor types, including colon carcinoma [8], ovarian carcinoma [9], neuroblastoma [10], nonseminoma germ cell cancer [9], and breast cancer [8]. In preclinical models oxaliplatin retains activity against some cisplatin resistant cell lines, although cross resistance is demonstrated in other models [10–14].

In adult phase II studies, oxaliplatin appears to be more effective than cisplatin or carboplatin in patients with metastatic colon carcinoma [15–18] and is approved for use, in combination with 5 FU and leucovorin, in this population [19–22]. The most commonly observed toxicities include acute and chronic neurotoxicities, nausea, neutropenia, and thrombocytopenia. In a pediatric phase 1 trial, the maximum tolerated dose (MTD) of oxaliplatin administered as a 2-hr intravenous infusion every 21 days was 130 mg/m^2. The dose limiting toxicity was pharyngolaryngeal dysesthesia. Thrombocytopenia, myelosuppression, myalgia, and myositis occurred but were not dose limiting. No objective responses were observed [23].

We performed a phase II study of oxaliplatin in children with recurrent or refractory solid tumors. In addition to estimating the objective response rate to oxaliplatin, objectives included the determination of the cumulative toxicity, further characterization of pharmacokinetics, and an assessment of the relationship between oxaliplatin exposure and antitumor effects.

PATIENTS AND METHODS

Consent

Informed consent/assent was obtained from all participants according to federal and institutional guidelines.

Eligibility

Eligible subjects needed to be 21 years of age or less at original diagnosis and have recurrent or refractory measurable disease. There was no limitation to the number of prior chemotherapy regimens or prior platinum exposures. Subjects needed to have recovered from toxic effects of prior chemotherapy, immunotherapy

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or radiotherapy; have a Karnofsky or Lansky performance scores of at least 50%; have adequate renal function (a serum creatinine appropriate for age or creatinine clearance/radioisotope glomerular filtration rate of at least 20 ml/min); have adequate bone marrow function (absolute neutrophil count of at least 1,000/μl, a platelet count of at least 75,000/μl and a hemoglobin of at least 8 g/dl). Growth factor support was not acceptable within 1 week of entry. Subjects with bone marrow involvement were eligible if blood counts met the criteria but they were not considered evaluable for hematologic toxicity. Those with CNS tumors requiring steroids needed to be on a stable or decreasing dose schedule for a minimum of 1 week prior to entry. Neurologic toxicity needed to be no greater than grade 2. Verification of original tumor histology was required with the exception of brain stem and visual pathway gliomas.

Disease Strata

Eligible diagnoses included Ewing sarcoma/peripheral PNET, osteosarcoma, rhabdomyosarcoma, neuroblastoma, high grade astrocytoma, low grade astrocytoma, brain stem glioma, ependymoma, malignant germ cell tumor, hepatoblastoma, and selected rare tumors of interest (non-rhabdomyosarcoma soft tissue sarcoma, hepatocellular carcinoma, renal cell carcinoma, childhood and adolescent colorectal carcinoma, nasopharyngeal carcinoma and adrenocortical carcinoma).

Treatment

Oxaliplatin, provided by the Cancer Therapy Evaluation Program of the National Cancer Institute, was administered intravenously over 2 hr at a dose of 130 mg/m^2 (4.3 mg/kg in patients 12 months of age or younger) on day 1 of each 21-day course. Upon recovery to baseline laboratory eligibility requirements, subsequent doses could be administered in the absence of progressive disease, up to a total of 17 courses or 1 year of therapy, whichever came first.

Toxicity

All eligible subjects for whom an oxaliplatin infusion was started were considered evaluable for toxicity. The NCI Common Terminology Criteria for Adverse Events (CTCAE v3.0) was used to grade each toxicity. In addition, the following four targeted adverse experiences were evaluated with each treatment cycle: (1) paresthesia or dysesthesia; (2) cold related dysesthesia; (3) laryngeal dysethesia; and (4) muscle cramping, spasm, or jaw pain. A toxicity-evaluable cycle was considered to be one associated with an eligible patient where oxaliplatin was administered and the individual was followed according to protocol guidelines for more than 7 days.

Dose limiting hematologic toxicities were defined as grade 4 neutropenia or thrombocytopenia of >7 days duration; grade 3 or 4 thrombocytopenia requiring transfusion on greater than two occasions during a treatment cycle; or grade 4 myelosuppression causing a delay of greater than 14 days between treatment cycles. Dose-limiting non-hematologic toxicity included any grade 3 or 4 toxicity except grade 3 nausea and vomiting, transaminase elevation that returned to grade 1 prior to the subsequent course, fever, infection, alopecia or electrolyte abnormality.

Dose Modification for Toxicity

Filgrastim (G-CSF) 5 μg/kg/day was added if grade 4 neutropenia persisted for greater than 7 days after the first or subsequent treatment cycles without filgrastim support. Recurrence of grade 4 neutropenia with filgrastim support resulted in the reduction of oxaliplatin to 100 mg/m^2 (3.3 mg/kg for individuals 12 months of age or younger). Subjects were removed from study if grade 4 neutropenia recurred after dose reduction.

Grade 1 pharyngolaryngeal dysesthesia lasting greater than 7 days or persistent between treatment cycles was managed by increasing the infusion duration to 6 hr. No change in the infusion rate was recommended for grade 1 pharyngeal dysesthesia lasting less than 7 days. Grade 2 pharyngeal dysesthesia during oxaliplatin infusion resulted in the cessation of the infusion, and administration of benzodiazepines if necessary. At the discretion of the investigator, the infusion was continued at one-third of the original rate.

Grade 1 paresthesia/dysesthesia did not require modification of the oxaliplatin dose. Oxaliplatin was reduced to 100 mg/m^2 if grade 2 paresthesias/dysesthesias did not resolve prior to the next treatment cycle or if grade 3 paresthesias/dysesthesias lasted more than 1 day. If grade 3 paresthesias/dysesthesias recurred, the dose was reduced to 75 mg/m^2. Persistent grade 3 toxicity occurring between treatment cycles or grade 4 paresthesia/dysesthesia resulted in subject removal from the study.

Response

Subjects were evaluable for response if they received one complete infusion of oxaliplatin. Tumors were imaged after every other treatment cycle. Response assessment of extra-cranial tumors used the RECIST criteria [24] and CNS tumor response utilized the Children's Oncology Group tumor volume criteria [25,26]. The overall response rate was based on best response. Responses were required to be sustained for a minimum of two consecutive imaging evaluations. Responses and stable disease were confirmed by central radiographic review.

Pharmacokinetics

Subjects consenting to pharmacokinetic studies had 5 ml blood samples obtained prior to and at 2.5 hr, 6 hr, and 7 days after the oxaliplatin dose in cycle 1. The concentration of platinum in plasma ultrafiltrates (PUF) was measured according to a previously published method [27]. Pharmacokinetic analyses employed a non-linear mixed effects modeling with S-ADAPT [28]. A two-compartment pharmacokinetic model with first-order elimination was used to describe the data. The pharmacokinetic parameters included the elimination rate constant (k_e), volume of distribution of the central compartment (V), and intercompartmental rate constants (k_{12}, k_{21}). The area under the curve extrapolated to infinity ($AUC_{0\rightarrow\infty}$) was calculated by integration of the simulated concentrations obtained using the empirical Bayesian parameter estimates using ADAPT II [29] plus the area determined by the last measurable concentration divided by the elimination rate constant. The terminal half-life and clearance for ultrafiltrable platinum were calculated using accepted equations.

Statistics

A two-stage design was employed in each disease stratum. Ten evaluable subjects were to be enrolled to the first stage.

If no objective responses occurred, oxaliplatin was considered ineffective in that stratum and enrollment to the stratum would be closed. If six or more subjects responded, oxaliplatin would be considered effective and enrollment to that stratum would be closed. Observing one to six responses in the first stage resulted in adding 10 subjects as the second stage. If three or more subjects of the 20 responded, oxaliplatin was considered effective. Otherwise oxaliplatin would be considered ineffective. Confidence intervals for response rate were constructed according to the method of Chang and O'Brien [30,31]. This design had a type I error of 7% in each stratum if the true response rate was 5% and a type II error of 12% if the true response rate was 25%.

To assess the effect of prior treatment on the probability of disease progression, the proportions of patients who had prior platinum exposure and demonstrated PR or SD were compared with all other response-evaluable patients using the exact conditional test or proportions.

RESULTS

Subject Characteristics

A total of 126 subjects were enrolled on COG protocol ADVL 0421 from October 18, 2004 to September 1, 2006. Data current to March 2009 were used for this analysis. Two subjects were not eligible: the informed consent process for one patient was not appropriate and one patient did not have RECIST-measurable disease. Characteristics of the eligible subjects appear in Table I. Eleven of the 124 eligible subjects were not evaluable for response: three subjects had the first oxaliplatin infusion stopped prior to completion because of an allergic reaction; two subjects or their guardians refused protocol therapy before the administration of oxaliplatin; four were removed by the treating physician (family request, hospice transition, or non-medical issues), two died before best response could be assessed. Sixty-nine of 113 subjects (62%) evaluable for response had received prior platinum therapy. The number of subjects enrolled in each stratum and their responses appear in Table II.

TABLE I. Characteristics of Eligible Patients (n = 124)

Characteristics	Median (range)	
Age in years at diagnosis	9 (0–21)	
Age in years at study entry	11(1–22)	
Characteristics	**n (% of total)**	
Gender		
Male	75 (60)	
Female	49 (40)	
Race		
Caucasian	92 (74)	
African American	20 (165)	
Pacific Islander	1 (1)	
Other	5 (4)	
Not Reported	6 (5)	
	n (% of total)	**Median (range)**
Prior therapy regimens		
Chemotherapy	124 (100)	2 (1–6)
Surgery	41 (33)	1 (1–5)
Radiation	54 (44)	2 (1–8)
HSCT	13 (10)	2 (1–7)

Response

Of the 113 response evaluable subjects, only one PR was observed in a 6-year-old female with an ependymoma. This subject received oxaliplatin for the duration of protocol specified treatment (17 treatment cycles). Stable disease was observed in 13 subjects (3 neuroblastoma; 1 Ewing sarcoma; 3 low grade astrocytoma; 1 brain stem glioma; 2 hepatocellular carcinoma; and 1 each high grade astrocytoma, germ cell tumor, and a spindle cell sarcoma). A median of 13.5 treatment cycles (range 2–17) was administered to 14 subjects experiencing a PR or SD with five subjects completing 17 treatment cycles. There was not a significant difference in prior

TABLE II. Responses of Solid Tumors to Oxaliplatin

Stratum	Enrolled	Eligible	Response evaluable	Response		
				Partial response	Stable disease	Progressive disease/no response
Osteosarcoma	13	13	10	0	0	10
Neuroblastoma	14	13	10	0	3	7
Rhabdomyosarcoma	10	10	10	0	0	10
Ewing sarcoma/peripheral PNET	12	12	10	0	1	9
High grade astrocytoma or glioblastoma multiforme	10	10	10	0	1	9
Low grade astrocytoma	9	9	8	0	3	5
Brain stem glioma	10	10	9	0	1	8
Ependymoma	11	11	11	1	0	10
Hepatoblastoma	10	10	10	0	0	10
Malignant germ cell tumor	7	7	7	0	1[a]	6
Non-Rhabdo soft tissue sarcoma	10	10	10	0	1	9
Hepatocellular carcinoma	5	4	3	0	2	1
Nasopharyngeal carcinoma	4	4	4	0	0	4
Adrenocortical carcinoma	1	1	1	0	0	1

[a]Patient with a CNS-primary malignant germ cell tumor had a minor response according to COG tumor volume criteria.

TABLE III. Oxaliplatin Toxicity Attribution Profile (351 Toxicity-Evaluable Treatment Cycles; n = Toxicity Events)

	Grade 3		Grade 4	
Toxicity	n	%	n	%
Hematologic				
Platelets	23	6.6	15	4.3
Neutrophils/granulocytes	10	2.8	3	0.9
Hemoglobin	7	2.0	4	1.1
Lymphopenia	7	2.0	1	0.3
Leukocytes (WBC)	6	1.7	0	
Non-hematologic				
Larynegopharyngeal dysesthesia	6	1.7	0	
Paresthesias/dysesthesia	6	1.7	0	
Cold related dysesthesia	4	1.1	0	
Muscle cramping/spasm jaw pain	1	0.3	0	
Decreased motor function	1	0.3	0	
Decreased sensory function	3	0.9	0	
Thoracic pain	1	0.3	0	
Extremity pain	1	0.3	0	
Decreased upper extremity function	1	0.3	0	
Allergic reaction/hypersensitivity	3	0.9	0	
Seizure	1	0.3	0	
Anorexia	2	0.6	0	
Dehydration	1	0.3	0	
Ileus	0		1	0.3
Nausea	3	0.9	1	0.3
Obstruction	1	0.3	0	
Vomiting	3	0.9	0	
Upper GI hemorrhage	1	0.3	0	
Elevated ALT	5	1.4	1	0.3
Elevated AST	3	0.9	0	
Hypercalcemia	0		1	0.3
Hypokalemia	3	0.9	1	0.3
Hyponatremia	1	0.3	1	0.3
Dyspnea	2	0.6	0	
Hypoxia	1	0.3	0	
Fatigue	1	0.3	0	
Bladder infection, normal ANC	1	0.3	0	
Lung infection, normal ANC	1	0.3	0	
Catheter-related infection	1	0.3	0	

platinum exposure or number of prior therapies in the 14 subjects with PR/SD compared with the 95 subjects who were considered non-responders ($P = 0.56$).

Toxicity

Three hundred fifty-one toxicity-evaluable cycles (Table III) were available from the 113 response evaluable patients. Eleven cycles were eliminated from consideration because the particular cycle was 7 days or less in length. Thrombocytopenia was the most common grade 3/4 hematologic toxicity occurring in 11% of treatment cycles (6.6% grade 3 and 4.3% grade 4). Other non-hematologic grade 3 toxicities included: laryngopharyngeal dysesthesia (1.7%), paresthesias/dysesthesia (1.7%), cold-related dysesthesia (1.1%), and muscle cramping/spasm-jaw pain (0.3%). Three grade 3 (0.9%) allergic reactions were observed. Two were classic immediate hypersensitivity reactions occurring during the first treatment cycle. The third was delayed, occurring after completion of the fourth treatment cycle.

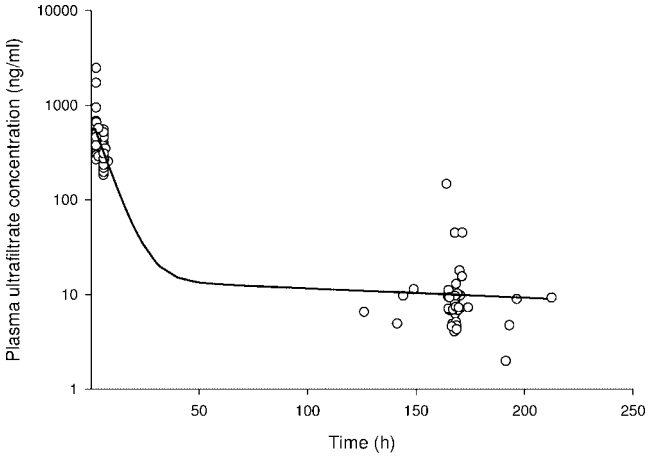

Fig. 1. PUF Pt (oxaliplatin) concentration verses time profile. Observed plasma concentrations are plotted (○) and the solid line represents the model predicted concentrations.

Ten children required dose reduction at a median (range) of the third cycle (2–17) primarily secondary to myelosuppression. No deaths attributed to oxaliplatin were observed.

Pharmacokinetics

Seventy subjects consented to pharmacokinetic studies. Samples from 21 subjects were not evaluable due to improper sample preparation (e.g., plasma, not PUF), inadequate samples for modeling (e.g., <3 samples), or subject logistical issues (e.g., did not receive drug). Population pharmacokinetics of platinum in plasma ultrafiltrates were described by a two-compartment model as depicted in Figure 1. The population pharmacokinetic parameters obtained were $k_e = 0.061\ h^{-1}$, volume of distribution 200.4 L/m^2, $k_{12} = 0.085\ h^{-1}$, and $k_{21} = 0.0055\ h^{-1}$. The median (range) $AUC_{0\to\infty}$ for the population was 5.7 μg h/ml (3.3–49.3 μg h/ml). The median (range) terminal half-life and clearance for ultrafiltrable platinum were 293 (187–662 hr) and 14.0 (1.9–24.9 L/hr/m^2), respectively (n = 49).

DISCUSSION

As a single agent, oxaliplatin appears to have limited activity for a broad range of refractory or recurrent solid or CNS tumors in a heavily pretreated pediatric population. One partial response occurred in a subject with an ependymoma. Thirteen subjects had stable disease, including one with high grade astrocytoma who completed 17 courses. This subject experienced disease progression 4 months after stopping protocol therapy. Two of three subjects with hepatocellular carcinoma exhibited stable disease for 10 and 14 treatment cycles, respectively. A subject with neuroblastoma exhibited stable disease as well as clearing of tumor from the bone marrow after 6 treatment cycles. That subject was removed from the study and underwent resection of the residual tumor. The resected mass showed near complete maturation of metastatic neuroblastoma to residual ganglioneuroblastoma. Of the 14 subjects with PR/SD, 9 (64%) had received prior therapy with a platinum agent.

Hematologic toxicity was generally tolerable in this population. Four subjects met criteria to receive filgrastim. No infections during neutropenia were reported. Thrombocytopenia was the most common grade 3 and 4 toxicity (Table III). It has been suggested

that thrombocytopenia from oxaliplatin may be a consequence of an oxaliplatin-induced immune-mediated mechanism resulting in antibodies directed towards the platelet glycoprotein IIb/IIIa complex in the presence of normal megakaryocyte numbers, rather than true myelosuppression [32].

The prominent toxicity in adult studies using oxaliplatin as a single agent in similar doses (130 mg/m^2 i.v. every 21 days and 85 mg/m^2 i.v. every 14 days) was neurosensory [33,34]. In the current pediatric trial, the most common non-hematologic grade 3 toxicity was laryngopharyngeal dysesthesia (1.7%). Grade 3 paresthesia/dysesthesia and cold-related dysesthesia occurred during 1.7% and 1.1% of the 351 total toxicity evaluable cycles. This extends the experience observed in the pediatric phase 1 trial of oxaliplatin study in children [23] in which pharyngolaryngeal dysesthesia was dose limiting at 160 mg/m^2. Although cumulative neurotoxicity is relatively common in adults [35,36] there was no evidence of cumulative neurotoxicity in the 14 pediatric/adolescent subjects with stable disease and partial response.

Pharmacokinetic studies were conducted to relate platinum exposure to pharmacologic effect and to describe oxaliplatin disposition in this patient population. A pharmacokinetic limited sampling model was used to obtain samples at time points most informative of oxaliplatin disposition [37]. The estimates of platinum ultrafiltrate clearance and half-life were similar to that published for children and adults [23,37–40]. We were unable to find a relationship between exposure and either toxicity or disease stabilization and the platinum ultrafiltrate exposures determined from the model.

In summary, oxaliplatin was reasonably well tolerated by children, adolescents, and young adults on this phase 2 study. However, in a broad range of pediatric solid tumors, oxaliplatin had limited activity as a single agent. Although combinations of oxaliplatin with other cytotoxic agents may prove efficacious, enthusiasm for studying such combinations is tempered by the results of this single agent trial.

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REFERENCES

1. Gibbons GR, Page JD, Mauldin SK, et al. Role of carrier ligand in platinum resistance in L1210 cells. Cancer Res 1990;50:6497–6501.
2. Mamenta EL, Poma EE, Kaufmann WK, et al. Enhanced replicative bypass of platinum-DNA adducts in cisplatin-resistant human ovarian carcinoma cell lines. Cancer Res 1994;54:3500–3505.
3. Page JD, Husain I, Sancar A, et al. Effect of the diaminocyclohexane carrier ligand on platinum adduct formation, repair, and lethality. Biochemistry 1990;29:1016–1024.
4. Raymond E, Faivre S, Woynarowski JM, et al. Oxaliplatin: Mechanism of action and antineoplastic activity. Semin Oncol 1998;25:4–12.
5. Woynarowski JM, Chapman WG, Napier C, et al. Sequence- and region-specificity of oxaliplatin adducts in naked and cellular DNA. Mol Pharmacol 1998;54:770–777.
6. Rixe O, Ortuzar W, Alvarez M, et al. Oxaliplatin, tetraplatin, cisplatin, and carboplatin: Spectrum of activity in drug-resistant cell lines and in the cell lines of the National Cancer Institute's Anticancer Drug Screen panel. Biochem Pharmacol 1996;52:1855–1865.
7. Scheeff ED, Briggs JM, Howell SB. Molecular modeling of the intrastrand guanine-guanine DNA adducts produced by cisplatin and oxaliplatin. Mol Pharmacol 1999;56:633–643.
8. Schmidt W, Chaney SG. Role of carrier ligand in platinum resistance of human carcinoma cell lines. Cancer Res 1993;53:799–805.
9. Dunn TA, Schmoll HJ, Grunwald V, et al. Comparative cytotoxicity of oxaliplatin and cisplatin in non-seminomatous germ cell cancer cell lines. Invest New Drugs 1997;15:109–114.
10. Riccardi A, Ferlini C, Meco D, et al. Antitumour activity of oxaliplatin in neuroblastoma cell lines. Eur J Cancer 1999;35:86–90.
11. Mathe G, Kidani Y, Noji M, et al. Antitumor activity of l-OHP in mice. Cancer Lett 1985;27:135–143.
12. Pendyala L, Creaven PJ. In vitro cytotoxicity, protein binding, red blood cell partitioning, and biotransformation of oxaliplatin. Cancer Res 1993;53:5970–5976.
13. Pendyala L, Creaven PJ, Perez R, et al. Intracellular glutathione and cytotoxicity of platinum complexes. Cancer Chemother Pharmacol 1995;36:271–278.
14. Tashiro T, Kawada Y, Sakurai Y, et al. Antitumor activity of a new platinum complex, oxalato (trans-l-1,2-diaminocyclohexane)platinum (II): New experimental data. Biomed Pharmacother 1989;43:251–260.
15. Becouarn Y, Rougier P. Clinical efficacy of oxaliplatin monotherapy: Phase II trials in advanced colorectal cancer. Semin Oncol 1998;25:23–31.
16. Diaz-Rubio E, Sastre J, Zaniboni A, et al. Oxaliplatin as single agent in previously untreated colorectal carcinoma patients: A phase II multicentric study. Ann Oncol 1998;9:105–108.
17. Levi F, Perpoint B, Garufi C, et al. Oxaliplatin activity against metastatic colorectal cancer. A phase II study of 5-day continuous venous infusion at circadian rhythm modulated rate. Eur J Cancer 1993;29A:1280–1284.
18. Machover D, Diaz-Rubio E, de Gramont A, et al. Two consecutive phase II studies of oxaliplatin (L-OHP) for treatment of patients with advanced colorectal carcinoma who were resistant to previous treatment with fluoropyrimidines. Ann Oncol 1996;7:95–98.
19. Giacchetti S, Perpoint B, Zidani R, et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol 2000;18:136–147.
20. Levi F, Misset JL, Brienza S, et al. A chronopharmacologic phase II clinical trial with 5-fluorouracil, folinic acid, and oxaliplatin using an ambulatory multichannel programmable pump. High antitumor effectiveness against metastatic colorectal cancer. Cancer 1992;69:893–900.
21. Levi F, Zidani R, Misset JL. Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer. International Organization for Cancer Chronotherapy. Lancet 1997;350:681–686.
22. Levi FA, Zidani R, Vannetzel JM, et al. Chronomodulated versus fixed-infusion-rate delivery of ambulatory chemotherapy with oxaliplatin, fluorouracil, and folinic acid (leucovorin) in patients with colorectal cancer metastases: A randomized multi-institutional trial. J Natl Cancer Inst 1994;86:1608–1617.
23. Spunt SL, Freeman BB III, Billups CA, et al. Phase I clinical trial of oxaliplatin in children and adolescents with refractory solid tumors. J Clin Oncol 2007;25:2274–2280.

24. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–216.
25. Bagley CM, Jr. Measurement of brain tumor volumes by the perimeter method. J Clin Oncol 2001;19:3159–3160.
26. Sorensen AG, Patel S, Harmath C, et al. Comparison of diameter and perimeter methods for tumor volume calculation. J Clin Oncol 2001;19:551–557.
27. Morrison JG, White P, McDougall S, et al. Validation of a highly sensitive ICP-MS method for the determination of platinum in biofluids: Application to clinical pharmacokinetic studies with oxaliplatin. J Pharm Biomed Anal 2000;24:1–10.
28. Bauer RJ, Guzy S. Monte Carlo parametric expectation maximization (MC-PEM) method for analyzing population pharmacokinetic/pharmacodynamic data. In: D'Argenio DZ, (Ed.), Advanced methods of pharmacokinetic and pharmacodynamic systems analysis, Vol. 3. Netherlands: Springer; 2004. pp 135–163.
29. D'Argenio DZ, Schumitzky A. Adapt II user's guide. Los Angeles: Biomedical Simulations Resource, University of Southern California: 1990.
30. Chang MN, O'Brien PC. Confidence intervals following group sequential tests. Control Clin Trials 1986;7:18–26.
31. Chang MN, Therneau TM, Wieand HS, et al. Designs for group sequential phase II clinical trials. Biometrics 1987;43:865–874.
32. Kaliszewski J, Marques MB, Saif MW. Immune-mediated thrombocytopenia resulting from sensitivity to Oxaliplatin. Am J Hematol 2006;81:193–198.
33. Becouarn Y, Ychou M, Ducreux M, et al. Phase II trial of oxaliplatin as first-line chemotherapy in metastatic colorectal cancer patients. Digestive Group of French Federation of Cancer Centers. J Clin Oncol 1998;16:2739–2744.
34. Rothenberg ML, Oza AM, Bigelow RH. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin interim results of a phase III trial. J Clin Oncol 2003;21:2059–2069.
35. Pasetto LM, D'Andrea MR, Rossi E, et al. Oxaliplatin-related neurotoxicity: How and why? Crit Rev Oncol/Hematolgy 2006;59:159–168.
36. Wilson RH, Lehky T, Thomas RR. Acute oxaliplatin-induced peripheral nerve hyperexcitability. J Clin Oncol 2002;20:1767–1774.
37. Graham MA, Lockwood GF, Greenslade D, et al. Clinical pharmacokinetics of oxaliplatin: A critical review. Clin Cancer Res 2000;6:1205–1218.
38. Bastian G, Barrail A, Urien S. Population pharmacokinetics of oxaliplatin in patients with metastatic cancer. Anticancer Drugs 2003;14:817–824.
39. Delord JP, Umlil A, Guimbaud R, et al. Population pharmacokinetics of oxaliplatin. Cancer Chemother Pharmacol 2003;51:127–131.
40. Fouladi M, Blaney SM, Poussaint TY, et al. Phase II study of oxaliplatin in children with recurrent or refractory medulloblastoma, supratentorial primitive neuroectodermal tumors, and atypical teratoid rhabdoid tumors: A pediatric brain tumor consortium study. Cancer 2006;107:2291–2297.