

Combination Chemotherapy With Gemcitabine Plus Oxaliplatin in Patients With Intensively Pretreated or Refractory Germ Cell Cancer: A Study of the German Testicular Cancer Study Group

C. Kollmannsberger, J. Beyer, R. Liersch, P. Schoeffski, B. Metzner, O. Rick, J.T. Hartmann, K. Stengele, K. Hohloch, C. Spott, L. Kanz, and C. Bokemeyer

From the Department of Hematology/Oncology, University of Tuebingen Medical Center, Tuebingen; Department of Hematology/Oncology, University of Marburg, Marburg; Department of Hematology/Oncology, University of Muenster, Muenster; Department of Hematology/Oncology, University of Hannover Medical School, Hannover; Department of Hematology/Oncology, Klinikum Oldenburg, Oldenburg; Department of Hematology/Oncology, Charite, University of Berlin, Berlin; Department of Hematology/Oncology, Hegau-Klinikum, Singen; and Department of Hematology/Oncology, University of Goettingen, Goettingen, Germany.

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Address reprint requests to C. Bokemeyer, MD, Department of Hematology/Oncology, University of Tuebingen Medical Center, Otfried-Mueller-Str 10, 72076 Tuebingen, Germany; e-mail: carsten.bokemeyer@med.uni-tuebingen.de.

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A B S T R A C T

Purpose

Long-term survival is rarely achieved in patients with cisplatin-refractory germ cell cancer (GCT). Both single-agent gemcitabine and oxaliplatin have shown activity in patients who experience relapse or are refractory to cisplatin treatment. This study investigates the activity of a gemcitabine plus oxaliplatin regimen in these patients.

Patients and Methods

Gemcitabine was administered at a dose of 1,000 mg/m² on days 1 and 8; oxaliplatin was administered at a dose of 130 mg/m² on day 1. Response was evaluated every 4 weeks.

Results

Thirty-five patients with a median age of 37 years (range, 21 to 54 years) were enrolled onto the study. Primary tumor localization was gonadal, retroperitoneal, or mediastinal in 30, one, and four patients, respectively. Patients had been pretreated with a median of six platinum-containing cycles (range, four to 13 cycles) and 89% of patients previously had experienced treatment failure after high-dose chemotherapy with peripheral-blood stem-cell transplantation. Sixty-three percent of patients were considered absolutely cisplatin-refractory or cisplatin-refractory. A median of two cycles (range, 1 to 6 cycles) per patient were applied. Toxicity consisted mainly of myelosuppression, with Common Toxicity Criteria grade 3 occurring in 54% of patients. Only 9% of patients developed neutropenic fever. Three patients attained a complete remission (CR), two patients attained a marker-negative partial remission, and 11 patients attained a marker-positive partial remission, resulting in an overall response rate of 46% (95% CI, 30% to 64%). All three patients with CR and one patient with a marker-negative partial remission remained disease free at 16+, 12+, 4+, and 2+ months of follow-up. Seven (44%) of these 16 responses, including one CR, occurred in cisplatin-refractory patients.

Conclusion

Gemcitabine plus oxaliplatin demonstrates antitumor activity with acceptable toxicity in heavily pretreated patients with relapsed or cisplatin-refractory GCT, and may offer a chance of long-term survival for selected patients.

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INTRODUCTION

The treatment of patients with intensively pretreated or cisplatin-refractory metastatic germ cell cancer remains a therapeutic challenge. Although 70% to 80% of patients with metastatic germ cell cancer will be cured with cisplatin-based combination chemotherapy, patients who experience disease progression during cisplatin-based chemo-

therapy or experience relapse after salvage treatment achieve long-term survival rates of less than 5% [1-3]. Therefore, the evaluation of new drugs with significant antitumor activity remains a priority in these heavily pretreated patients. Only four agents have thus far demonstrated single-agent activity in these patients; continuously applied low-dose oral etoposide, paclitaxel, gemcitabine, and, most recently, oxaliplatin, are active in

approximately 13% to 20% of patients with cisplatin-refractory germ cell cancer [4-9].

Gemcitabine and oxaliplatin were both investigated in refractory testis cancer patients by the German Testicular Cancer Study Group in sequential phase II studies [7,9]. Gemcitabine is a nucleoside analog that has been approved for the treatment of pancreatic and lung cancer. Its mechanism of action depends on phosphorylation and inhibition of the production of deoxynucleotide triphosphate required for normal DNA synthesis [10]. A response rate of 19% was observed for single-agent gemcitabine within the German Testicular Cancer Study Group trial, and this result was independently confirmed by a study of the Indiana University demonstrating a response rate of 15% [7,8]. Oxaliplatin is a third-generation platinum derivative, the activity of which is based on the formation of DNA adducts that inhibit replication and transcription. In comparison with cisplatin, oxaliplatin exhibits a favorable toxicity profile with a substantially lower rate of nephrotoxicity, ototoxicity, and myelosuppression. Oxaliplatin has shown activity in cisplatin-resistant cell lines *in vitro*, indicating incomplete cross-resistance between cisplatin and oxaliplatin. Subsequent functional studies suggested mechanisms of DNA damage other than those of cisplatin or carboplatin [11,12]. Oxaliplatin given at a dose of 130 mg/m² every 2 weeks induced a response rate of 19% in a group of heavily pretreated patients [9]. *In vitro*-studies suggest a supra-additive effect for the combination of oxaliplatin and gemcitabine, particularly for the sequence of gemcitabine followed by oxaliplatin [13]. Phase I/II trials have demonstrated the feasibility and acceptable toxicity of this combination in patients with solid tumors [14-16]. However, patients treated with this combination usually have not been intensively pretreated and certainly have not received previous high-dose chemotherapy plus autologous stem-cell transplantation. On the basis of the clinical activity of both drugs, this phase II study examined the activity and toxicity of a combination consisting of oxaliplatin and gemcitabine in refractory germ cell cancer patients.

PATIENTS AND METHODS

Eligibility criteria for this study included the diagnosis of metastatic germ cell cancer with evidence of tumor progression or relapse after at least two previous cisplatin-based chemotherapy regimens or after high-dose salvage chemotherapy with autologous stem-cell support. Patients who experienced disease progression during initial induction chemotherapy or during salvage therapy were also eligible as well as patients presenting with a late relapse, if they had experienced treatment failure after at least one cisplatin-based combination regimen for the treatment of late relapse. Patients also were required to be ≥ 18 years old, to have a Karnofsky performance status $\geq 60\%$, and to be at least 3 weeks past chemotherapy or major surgery and free of active infection. Additional inclusion criteria were the presence of bidimensionally measurable disease and/or elevated tumor markers as well as ade-

quate hematologic (WBC $> 2,500/\mu\text{L}$, platelets $> 75,000/\mu\text{L}$), renal (creatinine clearance > 50 mL/min), and liver function (bilirubin ≤ 1.5 -fold the upper limit of normal and liver enzymes < 3 -fold the upper limit of normal). No other concomitant chemotherapy, radiotherapy, or experimental medication was allowed. Patients pretreated with gemcitabine or oxaliplatin and patients with a preexisting neuropathy of greater than or equal to grade 2 using National Cancer Institute Common Toxicity Criteria (NCI-CTC) were excluded from the study. All patients gave their written informed consent. The study was approved by the University of Tuebingen (Tuebingen, Germany) Ethics Committee and also by the local committees of the participating centers.

Pretreatment evaluation included history and physical examination, documentation of all measurable disease by x-ray or computed tomography scan, assessment of performance status, serum tumor marker levels (alpha-fetoprotein [AFP], beta-human chorionic gonadotropin, and lactate dehydrogenase), liver function tests, creatinine levels, CBC with differential, and ECG.

Treatment

The treatment regimen consisted of gemcitabine 1,000 mg/m² given intravenously during 30 minutes on days 1 and 8 of a 3-week cycle. Oxaliplatin was administered as a 2-hour infusion immediately after gemcitabine at a dose of 130 mg/m² given intravenously on day 1 [17,18]. Concomitant antiemetic therapy included 5-hydroxytryptamine-3 antagonists and dexamethasone.

The next cycle was started only when the absolute neutrophil count was more than 1,500/ μL and the platelet count was $\geq 75,000/\mu\text{L}$ at day 21. If hematologic parameters had not recovered, treatment was delayed for 1 week. If a delay of more than 2 weeks was required, the patient was taken off study.

If the absolute neutrophil count was 1,000 to 1,500/ μL or the platelet count was 50,000 to 100,000/ μL , the gemcitabine dose at day 8 was reduced by 25%. If a platelet count was less than 50,000/ μL or an absolute neutrophil count was less than 1,000/ μL , gemcitabine on day 8 was omitted. If gemcitabine therapy on day 8 was omitted, treatment was restarted on day 15 with application of both drugs. A patient who required a dose adjustment for neutropenic fever or thrombocytopenia less than 50,000/ μL was scheduled to start the next cycle at a 25% dose reduction of gemcitabine. The use of granulocyte colony-stimulating factor was allowed for treatment of prolonged neutropenia (absolute neutrophil count $< 500/\mu\text{L}$ for > 5 days) or neutropenic fever.

If NCI-CTC grade 3 or 4 neurotoxicity occurred, administration of oxaliplatin was stopped. For other nonhematologic NCI-CTC grade 3 toxicities (except alopecia, nausea, and vomiting), 25% dose reductions were suggested; if NCI-CTC grade 4 toxicity occurred, the decision about continuation of treatment was at the discretion of the treating physician. All patients were treated on an outpatient basis.

Definitions

Disease was considered cisplatin refractory when at least tumor stabilization or a remission had been achieved, but tumor progression occurred again within 4 weeks of the last cisplatin-based chemotherapy. Disease was considered absolutely cisplatin refractory when tumor progression had occurred while patients were receiving cisplatin-based therapy [19,20].

Response and Toxicity

Patients were assessed for response at every cycle for disease measurable by physical examination, serum tumor markers, and standard radiologic means. More extensive diagnostic procedures

(eg, computed tomography scan or magnetic resonance imaging) were performed every other cycle. Toxicity was assessed after every cycle. Response and toxicity were graded according to WHO and NCI-CTC (version 2.0) criteria, respectively [21]. In addition, reduction of the size of a tumor lesion and normalization of previously elevated tumor markers were considered partial remission with tumor marker normalization (PR-negative), whereas a reduction $\geq 50\%$ in the sum of the perpendicular diameters of measurable disease plus a tumor marker decrease for at least 1 month, but without complete normalization, was considered marker-positive partial remission (PR-positive). If elevated marker(s) were the only evidence of progressive disease, a decrease of at least 90% was required for a PR. Levels of serum tumor markers were measured every 2 to 3 weeks. All responses as well as the diagnosis of stable disease had to be reconfirmed after a 4-week interval. All patients were scheduled to receive at least two cycles of treatment. However, if a significant marker ($\geq 50\%$) and/or radiologic progression ($\geq 25\%$) occurred after one cycle, the treatment was stopped and the patient was classified as having progressive disease. In patients with tumor responses or disease stabilization, therapy was continued for at least two more cycles after achievement of the best response unless severe toxicity occurred.

Statistical Considerations

A two-stage design according to Simon was used to determine the number of patients required [22]. The study was built to distinguish a true response rate of 20% from a response rate of clinical interest of 40%. On the basis of a probability of 12% for the acceptance of an inactive drug combination (type I error) and a probability of 5% for rejecting an active drug combination (type II error), 22 patients had to be enrolled onto the first cohort. If more than four objective remissions occurred within these first 22 patients, patient accrual continued up to a maximum of 47 patients. If 12 or fewer responses were observed by the end of the trial, the combination would be considered inactive according to the study design. This design had a power of 95% to detect a true response rate of at least 40%. Response rate was calculated on an intention-to-treat basis.

Survival and follow-up time were calculated from the beginning of gemcitabine plus oxaliplatin therapy until the date of death or the date of last follow-up, respectively, using the Kaplan-Meier test [23].

RESULTS

Thirty-five patients with heavily pretreated or cisplatin-refractory nonseminomatous germ cell cancer were entered onto the study between August 2001 and March 2003. Patient characteristics at the time of inclusion onto this study are listed in Table 1; 13 patients (37%) had liver metastases and five patients (14%) had brain involvement. All patients were heavily pretreated with a median number of six (range, four to 13) cisplatin-containing chemotherapy cycles before gemcitabine plus oxaliplatin therapy, and 31 patients (89%) had previously received carboplatin plus etoposide-based high-dose chemotherapy with autologous stem-cell support. Nineteen of 31 patients (61%) had undergone at least two high-dose chemotherapy cycles. Twenty-two

Table 1. Patient Characteristics at Study Entry (N = 35)		
Characteristic	No. of Patients	%
Included and assessable patients	35	
Age, years		
Median	37	
Range	21-54	
Primary tumor		
Gonadal	30	
Retroperitoneal	1	
Mediastinal	4	
Sites of metastases		
Lungs	25	71
Liver	13	37
CNS	5	14
Bone	5	14
Lymph nodes	21	60
Elevation of tumor markers		
AFP	13	37
β -HCG	19	54
LDH	20	57
No elevated markers	1	3
No. of standard-dose platinum-containing cycles during previous therapy		
Median	6	
Range	4-13	
Pretreated with HD chemotherapy with autologous stem-cell support	31	89
Prior paclitaxel therapy	17	49
Late relapse > 2 years*	10	29
Platinum-refractory disease†	13	37
Absolutely platinum-refractory disease‡	9	26

Abbreviations: AFP, alpha-fetoprotein; β -HCG, beta-human chorionic gonadotropin; LDH, lactate dehydrogenase; HD, high dose.
 *All patients received at least one cisplatin-based chemotherapy regimen for late relapse and experienced disease progression prior to study entry.
 †Achievement of at least stable disease or better but evidence of tumor progression within 4 weeks of the last cisplatin-based chemotherapy.
 ‡Experienced disease progression while receiving cisplatin-based chemotherapy.

patients (63%) were considered to have platinum-refractory or absolutely platinum-refractory disease and 10 patients (29%) had experienced relapse later than 2 years after initial therapy.

A total of 102 cycles of gemcitabine plus oxaliplatin were applied with a median of two cycles (range, one to six cycles) per patient. Gemcitabine and/or oxaliplatin doses were reduced because of toxicity in 29 cycles (28%). Therapy had to be delayed for a maximum of 2 weeks in 39 cycles (39%).

The combination of gemcitabine and oxaliplatin was associated with an acceptable toxicity profile in this patient population (Table 2). Ten patients (29%) developed CTC grade 3 or 4 nonhematologic side effects: diarrhea in two patients, nausea and vomiting in five patients, and grade 3 polyneuropathy in three patients (all three patients had pre-existing polyneuropathy grade 1). Polyneuropathy improved to grade 2 in one of these patients and completely

Table 2. Main Grade 3 or 4 Toxicity per Patient According to NCI-CTC (version 2.0) Classification (N = 35)

Toxicity	No. of Patients	%
Nonhematologic		
Nausea or vomiting	5	16
Neurotoxicity*	3	9
Diarrhea	2	6
Hematologic		
Leukocytopenia	19	54
Thrombocytopenia	17	48
Anemia	4	11
Fever	3	9
Therapy-related death (sepsis)	1	3

Abbreviation: NCI-CTC, National Cancer Institute Common Toxicity Criteria.
*Newly developed neuropathy or worsening of pre-existing neuropathy.

resolved in another after the end of chemotherapy. Hematologic toxicity was acceptable despite the previous use of high-dose chemotherapy plus autologous stem-cell support in almost all patients. Seventeen patients (48%) developed a CTC grade 3 or 4 thrombocytopenia and four patients (11%) developed CTC grade 3 anemia. Thirty-four percent of patients developed a CTC grade 1 or 2 leukocytopenia, 49% of patients developed a grade 3 leukocytopenia, and 6% of patients developed a grade 4 leukocytopenia. There were three patient cases of granulocytopenic fever. One (3%) of these patients died as a result of therapy-related septic shock caused by pneumonia and neutropenia.

Overall, 16 responses (46%; 95% CI, 30% to 64%) were observed in these 35 patients (Table 3). Two patients achieved a complete remission; another patient with a marker-negative remission after chemotherapy attained a surgical complete remission after resection of residual masses. The first patient was pretreated with 10 cycles of cisplatin-based combination chemotherapy and was considered absolutely cisplatin refractory because of disease progression during salvage high-dose chemotherapy. This patient showed lung and abdominal lymph node metastases as well as an AFP elevation of 4,483 ng/mL before treatment with gemcitabine plus oxaliplatin. After six cycles of gemcitabine plus oxaliplatin, metastases had resolved and the AFP normalized. The second patient had experienced relapse after extensive chemotherapy including 10 standard cisplatin-based and one high-dose chemotherapy cycle. After four cycles of gemcitabine plus oxaliplatin, the lymph node metastases had completely disappeared and the AFP had decreased from 1,543 ng/mL to normal values. The third patient had experienced relapse with unresectable liver and supraclavicular lymph node metastases after first-line high-dose chemotherapy with autologous stem-cell support for poor-prognosis disease according to the International Germ Cell Cancer Collaborative Group criteria.

After three cycles of gemcitabine plus oxaliplatin, the liver metastases had resolved and the supraclavicular lymph node metastases were resectable. Histologic work-up revealed still vital carcinoma in the resected specimen. All three patients are disease free at 16+, 4+, and 12+ months of follow-up. Two additional patients attained a marker-negative PR, but could not be completely resected because of extensive and inoperable disease. One of these patients is disease free at 3+ months of follow-up, whereas the second patient subsequently experienced relapse after 4 months and is currently alive with disease at 9 months of follow-up. Eleven patients showed a marker-positive PR lasting for 2 to 6 months.

All other patients experienced disease progression during treatment with gemcitabine plus oxaliplatin. In one patient without marker increase, who was included into the study after biopsy-proven embryonal carcinoma and who had progressed at all metastatic sites during gemcitabine plus oxaliplatin therapy, only mature teratoma was found at the time of salvage surgery. On the basis of the intention-to-treat principle, this patient was included in the calculation for response and rated as having progressive disease. Median overall survival time for all patients was 6 months (95% CI, 3.4 to 7.7 months). Median overall survival for responding patients only was 13 months (95% CI, 10 to 16 months).

After a median follow-up of 6 months (range, 0.5 to 18 months), 22 patients (63%) have died and seven patients (26%) are alive with disease. Four patients are still free of disease progression after treatment with gemcitabine plus oxaliplatin. Two additional patients are currently free of disease after salvage treatment for relapse after gemcitabine plus oxaliplatin therapy.

DISCUSSION

Despite the overall success of cisplatin-based chemotherapy in patients with metastatic germ cell cancer, the prognosis of cisplatin-refractory patients remains poor. Currently, no standard salvage chemotherapy exists for these patients and only a few agents have been determined to be active in this therapeutic situation. Chemotherapy with single-agent paclitaxel, gemcitabine, oxaliplatin, or orally administered etoposide induces remissions in only approximately 15% to 20% of these patients [4,5-9]. Complete remissions, marker-negative remissions, or even long-term freedom of disease rarely have been achieved [3]. On the basis of the single-agent activity of the above-mentioned drugs, it was a logical step to combine two of these agents to improve the results. Hinton et al [24] were among the first to demonstrate the feasibility of a combination regimen consisting of gemcitabine and paclitaxel in relapsed or cisplatin refractory germ cell cancer. A 21% response rate was observed among 28 patients, which seems not substantially different

Table 3. Characteristics of Patients Responding to the Combination of Gemcitabine Plus Oxalipatin

Patient	Prior Therapy	Late Relapse (> 2 years)	Response to Last Cisplatin-Based Chemotherapy	Site of Metastases at Study Entry	Marker at Study Entry (U/L)	Response	Time to Progression (months)	Overall Survival (months)	Status
1	1 × VIP, 1 × Tax/HD-VIP, 3 × HD-VIP 2 × irinotecan	No	PR+ Refractory	Lungs Lymph nodes	AFP, 875	PR+ AFP, 96	2.1	11.0	DOD
5	3 × VIP 3 × VIP + 2 × HD-CC 2 + 1 × irinotecan Irinotecan	No	PR- Sensitive	Lungs Bones	β-HCG, 129,450	PR+ β-HCG, 689	2.7	5.8	DOD
8	3 × PEB 3 × VIP + HD-CEC	No	PR Refractory	Lungs, liver CNS, bones	AFP, 149	PR+ AFP, 67	5.3	16.5	DOD
10	4 × PEB 2 × VIP	Yes	PD Absolute refractory	Liver Lymph nodes	AFP, 59,238	PR+ AFP, 6421	2.7	11.2	DOD
11	2 × VIP 2 × HD-VIP	No	PR- Sensitive	Liver Lymph nodes	AFP, 2.5 β-HCG, 2.0	PR/SCR	8.8	16.1	SCR
12	1 × VIP, 4 × Tax/HD-VIP	No	PR+ Refractory	Lungs, liver	β-HCG, 111	PR- β-HCG, 12	1.6	17.8	AWD
17	3 × PEB 1 × VIP 1 × VIP + 3 × HD-CE 4 × TIP	No	PR- Sensitive	Lymph nodes	β-HCG, elevated (> 29)	PR+ β-HCG, 8.4	3.8	4.9	DOD
19	5 × PIVB 2 × PB-epirubicin 8 × epirubicin 3 × TIP + HD-TEC	Yes	PD	Lungs Lymph nodes	AFP, 4483	CR AFP, 5.3	11.9	11.9	CR
20	1 × PE, 3 × PEB 3 × VIP + HD-CEC	No	PR- Sensitive	Lungs	β-HCG, 560	PR- β-HCG, 43	2.4	7.7	AWD
23	3 × VIP, 3 × Tax/HD-VIP Etoposide	No	PR+ Refractory	Lungs, liver Lymph nodes	β-HCG, 440	PR+ β-HCG, 141	6.0	13.1	DOD
24	5 × PEB PVI 2 × VIP, 2 × HD-CE 4 × TIP 3 × Etoposide	Yes	PR- Sensitive	Lungs, liver lymph nodes	AFP, 73.3 β-HCG, 12.8	PR- AFP, 4.3 β-HCG, < 2	4.0	9.1	AWD
26	2 × PEB 2 × PVB	No	PD Absolute refractory	Lungs, CNS Lymph nodes	β-HCG, 21,700	PR+ β-HCG, 2.6	2.4	5.2	DOD
32	3 × PEB 3 × VIP + HD-CEC	No	CR Sensitive	Liver Lymph nodes	AFP, 436	PR+ AFP, 16 β-HCG, 4	3.1	4.3	AWD
33	4 × PEB 3 × VIP 1 × VIP + 3 × HD-CE	Yes	PR+ Refractory	Lymph nodes	AFP, 80,000 β-HCG, 900,000	PR+ AFP, 15,000 β-HCG, 7,000	3.0	3.7	AWD
34	3 × VIP 2 × POMB 1 × ECE 2 × VIP + 1 × PVI 3 × TIP + HD-TEC	Yes	PR Sensitive	Lymph nodes	AFP, 1,543	CR AFP, 2	4	4	CR
35	6 × VIP 1 × VIP + 3 × HD-CE	No	PR- Sensitive	Lungs	β-HCG, 2,373	PR- β-HCG, 3.6	2	2	PR-

Abbreviations: Tax/HD-VIP, paclitaxel plus high-dose etoposide, ifosfamide, and cisplatin; HD-VIP, high-dose etoposide, ifosfamide, and cisplatin plus autologous stem-cell support; TAX, paclitaxel; PR+, marker-positive partial remission; AFP, alpha-fetoprotein; DOD, dead as a result of disease; VIP, etoposide, ifosfamide, and cisplatin; HD-CC, high-dose carboplatin; PR-, marker-negative partial remission; β-HCG, beta-human chorionic gonadotropin; PEB, cisplatin, etoposide, and bleomycin; PD, progressive disease; HD-CEC, high-dose cyclophosphamide, carboplatin, and etoposide; PE, cisplatin and etoposide; SCR, surgical complete remission; AWD, alive with disease; HD-CE, high-dose carboplatin and etoposide plus autologous stem-cell support; TIP, paclitaxel, ifosfamide, and cisplatin; PIVB, cisplatin, ifosfamide, vinblastine, bleomycin; PB, cisplatin, bleomycin; HD-TEC, high-dose thiotepa, etoposide, carboplatin; CR, complete remission; PVB, cisplatin, vinblastine, and bleomycin; PR, partial remission; POMB, cisplatin, vinoristine, methotrexate, bleomycin; ECE, etoposide, carboplatin, epirubicin; PVI, cisplatin, vinblastine, and ifosfamide.

Table 4. Comparison of Patient Characteristics in Recent Trials of New Agents for the Treatment of Refractory Germ Cell Cancer

Author, Year [Reference]	Treatment	No. of Patients	% of Patients Treated for Late Relapse (> 2 years)	% of Patients Pretreated With HD Chemotherapy	% of Patients With Cisplatin-Refractory Disease	Response Rate (%)	95% CI (%)
Motzer, 1994 [5]	Paclitaxel	31	NS	16	76	26	3 to 29
Bokemeyer, 1996 [6]	Paclitaxel	24	NS	50	75	25	10 to 47
Bokemeyer, 1999 [7]	Gemcitabine	31	13	71	55	19	13 to 45
Einhorn, 1999 [9]	Gemcitabine	20	10	55	65	15	3 to 38
Kollmannsberger, 2002 [24]	Oxaliplatin	32	34	78	85	13	1 to 24
Hinton, 2002 [24]	Paclitaxel and gemcitabine	28	NS	36	36	21	12 to 49
Current series	Gemcitabine and oxaliplatin	35	29	89	63	46	30 to 64

Abbreviations: HD, high dose; NS, not stated.

from the single-agent response rates reported for each of these drugs. However, three complete remissions were observed, two of which were still ongoing at 15+ and 25+ months, and thus may offer a chance of cure. Pizzocaro et al [25] investigated the combination of paclitaxel, gemcitabine, and cisplatin as third-line treatment in 20 patients. A 50% major response rate was achieved, including four complete remissions, but toxicity was substantial. This study has thus far only been published in abstract form and no information on prognostically important patient characteristics or on the definition of refractory disease is available, which makes the interpretation of these results difficult.

The response rate of 46% and a median overall survival time of 13 months for responding patients for the combination of gemcitabine plus oxaliplatin in patients with multiply relapsed or cisplatin-refractory germ cell cancer as demonstrated in this study seems encouraging. This response rate is considerably higher than the response rates of 15% to 25% reported for single-agent therapy with one of four active agents. In addition, the three patients who are continuously disease free in complete remission may have a reasonable chance of cure. Durable remissions have thus far been extremely rare in these patients receiving single-agent therapy. In this study, approximately 50% of remissions (including one complete remission) occurred in cisplatin-refractory patients; 14 patients had experienced treatment failure after previous high-dose chemotherapy and five patients presented with late relapse. This study was conducted in a prognostically comparable group of patients to those treated within the trials evaluating the role of paclitaxel, gemcitabine, and oxaliplatin and the combination of gemcitabine plus paclitaxel in relapsed germ cell cancer (Table 4). Twenty-nine percent of our patients presented with a late relapse, 89% were pretreated with high-dose chemotherapy plus peripheral stem-cell support, and 63% had to be classified as cisplatin refractory (Table 1).

The toxicity of the gemcitabine plus oxaliplatin regimen was generally acceptable. Similar to other studies in heavily pretreated patients, myelosuppression was the major toxicity and consisted mainly of leukocytopenia and thrombocytopenia [8,7]. However, no episodes of severe bleeding occurred. Mild neurotoxicity was seen in 40% of patients, but three patients developed grade 3 neurotoxicity. Patients with mild (grade 1) pre-existing neurotoxicity from previous cisplatin treatment also had been included in this study. However, the potential of oxaliplatin to induce neurotoxicity might be underestimated because of the limited number of cycles delivered per patient, with a median cumulative dose of 260 mg/m² reached in these patients. The peripheral sensory neurotoxicity with functional impairment affects more than 10% of patients when cumulative doses of more than 600 mg/m² are applied [26]. In both patients, polyneuropathy improved after the end of therapy. One therapy-related death occurred as a result of pneumonia and subsequent septic shock in a heavily pretreated patient who rapidly developed grade 4 neutropenia after three chemotherapy applications. This is known to be a serious complication in heavily pretreated patients.

The achievement of a high response rate in refractory patients, as in our study with the combination of gemcitabine and oxaliplatin, is important because the induction of a remission may subsequently allow the resection of residual masses and may thus offer an opportunity for some patients to achieve long-term survival. The complete resection of residual masses after a chemotherapy-induced remission seems to be an important step in the treatment of these patients to achieve cure, as demonstrated by a retrospective analysis from Indiana University [3]. In this specific analysis of 101 patients with relapsed and/or cisplatin-refractory disease, only 5% of patients achieved long-term survival and all of these had had surgery of metastatic disease as an important component of their salvage treatment.

In conclusion, the combination of gemcitabine and oxaliplatin demonstrated antitumor activity in patients with heavily pretreated or cisplatin-refractory germ cell cancer. A study investigating the three-drug combination of gemcitabine, oxaliplatin, and paclitaxel has been initiated.

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