Gemcitabine plus cisplatine and paclitaxel (GCP) in second-line treatment of germ cell tumors (GCT): a phase II study

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The aim of the study was to determine the efficacy and toxicity of gemcitabine, cisplatin and paclitaxel (GCP) combination as a first salvage treatment of patients with relapsed GCT.

Four courses of paclitaxel 175 mg/m^2 and cisplatin 50 mg/m^2, both on day 1, and gemcitabine 1000 mg/m^2, on days 1 and 8, every 3 weeks, were given to 12 consecutive patients who had failed standard 1st line treatment.

Six patients (50%; 95% CI 21–79%) achieved favourable response and two of them are maintained 38+ and 29+ months. Median survival time was 16 months (range, 0.77–38+). All, but two patients had hematological toxicity Gr3–4 with infectious complication seen only in 6 courses of therapy. GCP is an active second-line combination regimen for relapsed GCTs with acceptable toxicity profile. However the results of this study did not show expected treatment efficacy and we raise the idea of cisplatin dosage relevance in this combination.

Key words: germ cell tumors, salvage chemotherapy, paclitaxel, gemcitabine, cisplatin

Germ cell tumors (GCT) are the most chemosensitive solid tumors and represent a model for a curable cancer [9]. Cisplatin represents the mainstay in the treatment of GCTs. Cisplatin-based 1st line chemotherapy can cure about 70–80% of patients with disseminated testicular cancer [7, 16]. Salvage chemotherapy with standard dose cisplatin plus previously not utilized drugs will cure 20–25% of patients who were not initially cured with their induction chemotherapy [12, 22].

Stratification according to prognostic factors plays an important role in the treatment strategy. Complete response to primary treatment, testicular primary and time to relapse after primary treatment are the strongest independent predictors of favorable outcome [10, 11, 16]. Patients with good prognostic factors are candidates to conventional dose second-line therapy with 2-year survival more than 50%, while patients with poor prognostic factors are candidates for high-dose therapy [10, 11, 17].

Because of insufficient results in the treatment of relapsed GCT, evaluation of new treatment strategies and new drugs with significant antitumor activity, as a single-agent or combination treatments, remains a priority. Single-agent paclitaxel has been studied in a phase II treatment studies of refractory germ cell tumors at several centers with response rate ranging from 11 to 26% [1, 3, 15, 20]. Gemcitabine was studied in heavily pretreated patients in phase II studies and response rates ranged from 15 to 20% [4, 8, 21]. Paclitaxel and gemcitabine are chemotherapeutic agents with different mechanisms of action and show synergistic activity in a wide range of malignancies. Response rate of 21% with 3 complete responses were observed in phase II study of gemcitabine and paclitaxel combination in 28 patients with relapsed GCT [12]. High treatment efficacy with major response of 50% was observed in the phase II study of PIZZOCARO et al who treated 22 consecutive patients with failed standard 1st and 2nd line or high dose chemotherapy with combination of paclitaxel, gemcitabine and cisplatin. No toxic death occurred, but toxicity was substantial [20].

According to results of previous studies we decided to evaluate the efficacy and toxicity of paclitaxel, gemcitabine and cisplatin combination as a second-line treatment for patients with relapsed GCT.

Material and methods

Eligibility. Twelve consecutive patients with advanced GCT were registered onto this prospective trial between September 2000 and August 2002. We conducted an open label, unicentric phase II study. The study protocol was reviewed and approved by Scientific Board and Ethical Committee at

the National Cancer Institute of Bratislava, Slovak Republic. The primary endpoint of the study was the objective response rate (ORR) of tested combination in the second-line treatment of advanced germ cell cancer. Secondary endpoints were duration of response, time to progression, overall survival and toxicity.

Patients with recurrent GCT after treatment with cisplatin-based regimen were approved. Relapse was documented by rising serum concentrations of tumor markers and/or radiographic findings.

All patients were required to give written informed consent before enrollment. Eligible patients were men aged 18 years or older with GCT confirmed by histology and measurable disease. Additional eligibility criteria included a WBC of 3000/μl or higher, hemoglobin level of 8 g/dl or higher, platelet count of 100,000/μl or higher, adequate liver function test and creatinine clearance rate of more than 50 ml/min. Patients were excluded if their prior treatment had included gemcitabine, paclitaxel or taxane analogs.

Pretreatment evaluation. Pretreatment evaluation included a medical history, physical examination, ECG, complete blood cell count (CBC), 12-hour urine collection for the determination of creatinine clearance rate, measurement of serum tumor markers (LDH, AFP, HCG), serum screening biochemistry panel, and computed tomography scan of the chest, abdomen, and/or pelvis.

Treatment program. Treatment consisted of four cycles of GCP given 21 days apart. Paclitaxel 175 mg/m^2 was administered on an inpatient basis by 3-hour infusion on day 1 after standard premedication that consisted of dexamethason, bisulepin-HCl, and ranitidine. Gemcitabine 1000 mg/m^2 was administered on day 1 and 8 over 30 minutes infusion and on day one cisplatin 50 mg/m^2 was administered after gemcitabine.

Standard antiemetic and hydration protocols were used. Dose adjustments for each subsequent cycle depended upon the worst toxicity demonstrated in the previous cycle. If febrile neutropenia and/or neutropenia Gr4 and/or trombocytopenia Gr4 and/or any non-hematological or renal toxicity Gr4 occurred, the doses of all three drugs were held. The treatment was discontinued in case of neurotoxicity Gr4. The dose of paclitaxel was reduced from 175 mg/m^2 to 135 mg/m^2 in case of neutropenia Gr3 and/or trombocytopenia Gr3 and/or any non-hematological toxicity Gr3 (except nausea/vomiting Gr3). The paclitaxel was omitted or reduced to 50% as well as cisplatin was reduced to 50% in case of neurotoxicity Gr3. The dose of cisplatin was reduced to 50% in case of creatinine clearence between 50–59 ml/min. Gemcitabine on day 8 was withheld in case of trombocytopenia and/or neutropenia Gr3/4. Doses held due to toxicity or missed were not given at the later time and patients to whom drug could not be administered for more than 6 weeks from the time of last treatment were discontinued from the study.

Supportive care. Management of complications included daily platelet transfusion for trombocyte count less than 10,000/μl and packed RBCs for hemoglobin levels less than 8 g/dl. Neutropenic fever was routinely treated with broad-spectrum antibiotics.

Evaluation of response and toxicity. Physical examination was performed and vital signs were taken before each cycle or as indicated. CBC count, serum screening biochemistry panel, serum tumor markers (LDH, AFP, HCG) were performed before each cycle and one month after the first day of the last cycle. After the completion of four cycles of chemotherapy, computed tomography scans of the chest, abdomen, and/or pelvis were performed for assessment of tumor response. Surgical resection of all residual masses was considered.

Responses were categorized as favorable or unfavorable. As favorable response was classified complete response or partial remission with negative serum tumor markers. Complete response to chemotherapy alone was defined as disappearance of all clinical, radiographic, and biochemical evidence of disease for at least 4 weeks; this included patients in whom surgical resection of residuum yielded necrotic debris, fibrosis, or mature teratoma but no evidence of viable malignant tumor. Complete response to chemotherapy plus surgery was defined as complete excision of all masses, at least one of which contained viable tumor other than mature teratoma. Unfavorable response was therefore observed in patients who did not achieve complete response to chemotherapy with or without surgery or who were observed to have failure of serum tumor marker normalization. In case of significant marker (more than 50%) and/or radiological progression (more than 25%) after one cycle, the treatment was stopped and the patient was classified as having progressive disease. Response duration and survival were measured from the initiation of therapy. Toxicity was graded according to NCI-CTC (version 2.0) criteria [14].

Results

Patient's characteristics. The patient's characteristics are summarized in Table 1. All patients had nonseminoma histology. Seven patients achieved complete response to first line therapy, while 5 patients achieved PR with negative tumor markers. Eleven patients were treated as first relapse and one patient as second relapse. Eight patients relapsed very early after the 1st line therapy (median 4.1 months, range 2.5–6 months). Two patients were considered to have late relapse (69 months and 164 months), defined as recurrence of disease more than 2 years after the complete response to first-line chemotherapy [19]. All, but one had primary testicular cancer. One patient had primary retroperitoneal germ-cell tumor. Nine patients were pretreated with bleomycin, etoposid and cisplatin, three with etoposid, ifosfamid and cisplatin, and one with combination of vincristine, cisplatin and bleomycin. Ten patients had only one metastatic site at the beginning of the treatment.

Toxicity. The combination of gemcitabine, paclitaxel and

Table 1. Patients' characteristics (n=12)

	No.	%
Median of age (range)	31 (20 – 43)	
Primary tumor		
Gonadal	11	92
Retroperitoneal	1	8
Mediastinal	0	0
Histology		
Seminoma	0	0
Nonseminoma	12	100
Patients treated in		
1st relapse	11	92
2nd relapse	1	8
Late relapse	2	17
Favorable response after 1st line chemotherapy	12	100
Relapse after 1st line chemotherapy less than 6 months	8	67
Sites of metastases		
Lungs	8	67
Liver	2	17
Lymph nodes	6	50
Mediastinum	0	0
Retroperitoneum	5	42
Brain	0	0
No. of metastatic site		
1	10	83
2	1	8
More than 3	1	8
Prior chemotherapy regimen		
BEP	9	75
VIP	3	25
PVB	1	8
Elevation of tumor markers		
LDH	6	50
AFP	10	83
HCG	5	42
Median (range) of elevated pretreatments markers		
AFP mIU/ml	248 (23 – 5660)	
HCG IU/ml	141 (8 – 2105)	
LDH (μkat/l)	18 (11 – 62)	

HCG – human chorionic gonadotropin; AFP – alfa fetoprotein; LDH – lactate dehydrogenase; BEP – bleomycin, etoposid, cisplatin; VIP – etoposid, ifosphamide, cisplatin; PVB – bleomycin, vincristine, cisplatin.

Table 2. Main grade 3 or 4 toxicity per patient according to NCI-CTC (Version 2.0) classification (n=12)

Toxicity	No. of patients	%
Nonhematologic		
Nausea or vomiting	0	0
Neurotoxicity	0	0
Diarrhea	0	0
Mucositis	0	0
Liver	1	8
Hematologic		
Granulocytopenia	7	58
Thrombocytopenia	5	42
Anemia	3	25
Febrile neutropenia	2	17
Fever	5	42
Therapy-related deaths	0	0

NCI-CTC, National Cancer Institute Common Toxicity Criteria.

cisplatin was well tolerated (Tab. 2). A total of 41 courses of chemotherapy were administered to 12 patients, with a median of 4 cycles per patient (range 1 to 4). All, but two patients had hematological toxicity Gr3-4, however infectious complication was seen only in 6 courses of therapy and it was successfully treated with antibiotics. There was no treatment related death. Two patients needed G-CSF and one patient needed platelet transfusion. Non-hematological toxicity was mild, usually nausea and vomiting Gr1/2, and was successfully treated with antiemetics. One patient experienced Gr3/4 liver toxicity that was manifested by elevation of serum bilirubin. The toxicity disappeared after symptomatic therapy that was followed by dose reduction of paclitaxel in all subsequent cycles of therapy. Relative dose intensity (RDI) was 0.85 for gemcitabine (range, 0.46–1.00), and 0.98 for paclitaxel (0.7–1.00).

Response and survival. One patient achieved complete response to chemotherapy and subsequent resection of residual masses from retroperitoneum, with finding of necrosis and fibrosis without any viable GCT cells. This patient was treated in second relapse of GCT and he was pretreated with BEP and VIP. He is free of disease 38+ months. One patient with late relapse in retroperitoneum achieved PR at the CT scan with slightly elevated AFP. There were not found any residual masses during the operation and he is alive 29+ months with inconstantly elevated AFP Additional four patients achieved partial remissions with negative tumor markers (PRnm neg). Thus, six patients (50%) achieved favorable response. (Tab. 3). All four patients with PRnm neg relapsed at 5, 5, 6 and 15 months. Two of them responded to dose-intensive salvage chemotherapy with PBSC rescue and achieved another PRnm neg for 24+ and 34+ months. Two of six pa-

Table 3. Response to Treatment

Relative dose intensity	Median	(Range)
Gemcitabine	0.85	(0.46 – 1.00)
Paclitaxel	0.98	(0.70 – 1.00)
Chemotherapy combination	0.85	(0.60 – 1.00)
	No. of Patients	%
Assessable	12	100
Response	6	50
Favorable response	2	17
Complete response	4	33
Partial response with normalized markers	3	25
Partial response with positive markers	3	25
Progression	10	83
Relapse		
Time to progression		
Median	5.5	
Range	3.9 – 15	
Survival (months)		
Median	16	
Range	1 – 38+	
Status		
Alive without disease	4	33
Death of disease	8	67

tients who achieved unfavorable response responded to second salvage therapy and achieved PRnm posit with duration of 3 and 6 months. Median time to progression was 5.5 months (range, 3.9 to 15), median time of survival was 16 months (range, 0.77–38+).

Four patients (33%) are currently alive. Eight patients (67%) died of disease. The proportion of patients alive at 2 years is 33%. The median follow-up period for the four survivors was 32 months (range, 24–38).

Discussion

Only 25% patients with relapsed GCT achieve durable response to combination chemotherapy of VIP or VeIP. Cisplatin maintains its important role in the treatment of relapsed GCT. The effectiveness of therapy strongly correlates with prognostic factors with 2-year survival of more than 50% or less than 10% in patients with good or poor prognostic factors, respectively [10, 11]. According to insufficient results in the treatment of relapsed GCT, evaluation of new treatment strategies and new drugs with significant antitumor activity remains a priority especially in the patient group with poor prognostic factors.

Recently two drugs, paclitaxel and gemcitabine, have been studied extensively in relapsed GCT and preliminary results were promising. In phase II studies single-agent paclitaxel achieved response rate ranging from 11 to 26% [1, 3, 15, 20]. In a phase I/II study MOTZER et al tested three different doses of paclitaxel (175 mg/m^2, 215 mg/m^2, 250 mg/m^2) in combination with ifosfamide and cis-platin and observed 73% of durable responses in good prognostic patients [17].

DONADIO et al observed high treatment efficacy with combination of paclitaxel (250 mg/m^2), ifosfamid (5 g/m^2) and cisplatin (100 mg/m^2) with G-CSF support in 46 patients with relapsed GCT and favorable prognostic factors, where 32 patients achieved complete remissions (70%) and additional 2 patients achieved PR with negative markers (4%). Relapse free survival at 2 years was 91%.

Gemcitabine was studied in heavily pretreated patients in phase II studies and response rates ranged from 15 to 20% [4, 8, 21]. Paclitaxel and gemcitabine are chemotherapeutic agents with different mechanisms of action and show synergistic activity in a wide range of malignancies. Response rate of 21% with 3 complete responses were observed in phase II study of gemcitabine and paclitaxel combination in 28 patients with relapsed GCT [12].

High treatment efficacy of three-drug combination of paclitaxel, gemcitabine and cisplatin was observed in the phase II study of PIZZOCARO et al who treated 22 consecutive patients after failure to standard 1st and 2nd line or high dose chemotherapy. No toxic death occurred, but toxicity was substantial [20]. Ten from 20 (50%) patients achieved major response (CR+PR) with 4 courses of paclitaxel 80 mg/m^2, cisplatin 50 mg/m^2, gemcitabine 800 mg/m^2 given on days 1 and 8 every 3 weeks. All 4 pathologically documented CR are being maintained for 3+, 10+, 18+ and 19+ months; 1 clinical CR relapsed after 6 months. The survival of responders and non-responders was 7–16 months and 2–9 months, respectively. All complete remissions occurred in patients in 3rd line therapy, with no difference in response between relapsing or progressive disease.

There was achieved response rate of 50% with two durable responses (38+, 29+ months) in our study group with combination of gemcitabine, paclitaxel and cisplatin. However, median time to progression of all responders lasted only 11 months. This result is worse in comparison with above-mentioned studies of DONADIO and PIZZOCARO [5, 20].

We suppose that results may depend not only on the therapeutic agents used in treatment combination but also on the number of patients studied and their prognostic factors. All patients in DONADIO study had favorable prognostic factors: primary testis tumor and favorable response for more than 6 months achieved by first line chemotherapy. On the other hand, 70% of our patients had poor prognostic factor: shorter time to relapse after primary treatment (median: 4.7 months).

In comparison with PIZZOCARO et al, we used the lower dose of cisplatin and higher doses of paclitaxel and gemcitabine. We observed that, although none of our patients was cisplatin resistant, 3 of 12 studied patients progressed during the treatment. It is interesting, that 2 of these patients achieved PR by 3rd line VIP chemotherapy. We thus suppose that dose of cisplatin in GCP may play an important role in treatment efficacy. In comparison with VIP or VeIP, we used only 50% of cisplatin dose, used in VIP or VeIP combination. The idea of cisplatin dosage importance in the treatment efficacy may be supported by the fact, that 2 other patients achieved PR with negative markers by 3rd line high-dose chemotherapy with PBSCT and are disease-free at 24+ and 34+ month.

In the view of cisplatin dosage importance, notable is complete remission of one patient treated just recently with GCP combination with 100 mg/m^2 of cisplatin used when comparing with 50 mg/m^2 used in our study. The dosage and timing of paclitaxel and gemcitabine was used at the same treatment schedule as in here-presented study.

In contrast with the above-mentioned study of PIZZOCARO et al, in our study gemcitabine and paclitaxel were used at higher dose and only on day one. It is known that paclitaxel and gemcitabine have synergistic activity when used in combination. We do not suppose that lower dose that was used by PIZZOCARO et al could be responsible for better results when compared with our results.

Leading toxicity of the treatment combination used in our study was myelosupression that was of short duration and that did not lead to higher incidence of infectious complications, bleeding or prolongation of treatment cycle. We observed neurotoxicity that was of lesser intensity, mostly of Gr 1, even when using higher RDI of paclitaxel when compared with other studies [6, 15, 19].

We thus suppose that the combination treatment of

paclitaxel, gemcitabine and cisplatin that we used in our study is efficient in the treatment of patients with relapsed GCT and is comparable with VIP and VeIP treatments. We suppose that higher effficacy could be achieved by higher dose of cisplatin.

References

[1] AMATO RJ, PROW DM. Paclitaxel-based chemotherapy for patients with refractory or relapsed nonseminomatous germ cell tumors. Urol Oncol 2000; 1: 134–138.

[2] BANIEL J, FOSTER RS, GONIN R, MESSEMER JE, DONOHUE JP et al. Late relapse of testicular cancer J Clin Oncol 1995; 13: 1170–1176.

[3] BOKEMEYER C, BEYER J, METZNER B, RUTHER U, HARSTRICK A et al. Phase II study of paclitaxel in patients with relapsed or cisplatin-refractory testicular cancer. Ann Oncol 1996; 7: 31–34.

[4] BOKEMEYER C, GERL A, SCHOFFSKI P, HARSTRICK A, NIEDERLE N et al. Gemcitabine in patients with relapsed or cisplatin-refractory testicular cancer. J Clin Oncol 1999; 17: 512–516.

[5] DONADIO AC, SHEINFELD J, BACIK J, MAZUMDAR M, MARION S et al. Paclitaxel, ifosfamid, and cisplatin (TIP): An effective second-line therapy for patients (pts) with relapsed germ cell tumors (GCT). Proc Amer Soc Clin Oncol 2001; 22: 382.

[6] DU BOIS HJ, LUECK W, MEIER V et al. Cisplatin/Paclitaxel vs Carboplatin/Paclitaxel in ovarian cancer. Proc Amer Soc Clin Oncol 1999; 18: 356a.

[7] EINHORN LH. Clinical trials in testicular cancer. Cancer 1993; 71: 3182–3184.

[8] EINHORN LH, STENDER MJ, WILLIAMS SD. Phase II trials of gemcitabine in refractory germ cell tumors. J Clin Oncol 1999; 17: 509–511.

[9] EINHORN LH. Treatment of testicular cancer: A new and improved model. J Clin Oncol 1990; 8: 1777–1781.

[10] FOSSA SD, OLIVER RT, STENNING SP, HORWICH A, WILKINSON P. Prognostic factors for patients with advanced seminoma treated with platinum-based chemotherapy. Eur J Cancer 1997; 33: 1380–1387.

[11] GERL A, CLEMM C, SCHNELLER N, HARTENSTEIN R, LAMERZ R, WILMANNS W. Prognosis after salvage treatment for unselected male patients with germ cell tumours. Br J Cancer 1995; 72: 1026–1032.

[12] HINTON S, CATALANO P, EINHORN LH, LOEHRER PJ, KUZEL T et al. Phase II study of paclitaxel plus gemcitabine in refractory germ cell tumors (E9897): A trial of the eastern cooperative oncology group. J Clin Oncol 2002; 20: 1859–1863.

[13] LOEHRER PJ, WILLIAMS SD, NICHOLS CR, EINHORN LH. Clinical trials with ifosfamide: The indiana university experience. Semin Oncol 1992; 19: 35–39.

[14] MILLER AB, HOODGSTATEN B, STAQUET M, WINKLER A. Reporting results of cancer traetment. Cancer 1981; 47: 207–211.

[15] MC GUIRE WP, HOSKINS WJ, BRADY MF, KUCERA PR, PARTRIDGE EE et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and IV ovarian cancer. N Engl J Med 1996; 334: 1–6.

[16] MOTZER RJ, BAJORIN DF, SCHWARTZ LH, HUTTER HS, BOSL GJ et al. Phase II trial of paclitaxel shows antitumor activity in patients with previously treated germ cell tumors. J Clin Oncol 1994; 12: 2277–2283.

[17] MOTZER RJ, GELLER NL, TAN CC, HERR H, MORSE M et al. Salvage chemotherapy for patients with germ cell tumors. The Memorial Sloan-Kettering Cancer Center experience (1979–1989). Cancer 1991; 67: 1305–1310.

[18] MOTZER RJ, SHEIFELD J, MAZUMDAR M, BAINS M, MARIANI T et al. Paclitaxel, ifosfamide, and cisplatin second-line therapy for patients with relapsed testicular germ cell cancer. J Clin Oncol 2000; 18: 2413–2418.

[19] OZOLS RF, BUNDY BN, GREER BE, FOWLER JM, CLARKE-PEARSON D et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer. J Clin Oncol 2003; 21: 3194–3200.

[20] PIZZOCARO G, NICOLAI N, SALVIONI, R, GIANNI L. Paclitaxel, cisplatin, gemcitabine (TGP) third line therapy in metastatic germ cell tumors of the testis. Proc Amer Soc Clin Oncol 2001; 20: 194a.

[21] SANDLER AB, CHRISTOU A, FOX S, WILLIAMS SD, NICHOLS CR et al. A phase II trial of paclitaxel in refractory germ cell tumors. Cancer 1998; 82: 1381–1386.

[22] STENDER M, LOEHRER PJ, EINHORN LH. Phase II trial of gemcitabine in refractory germ cell tumors. Proc Amer Soc Clin Oncol 1998; 17: 321.

[23] WILLIAMS SD, EINHORN LH, GRECO FA, OLDHAM R, FLETCHER R. VP-16-213 salvage therapy for refractory germinal neoplasm. Cancer 1980; 46: 2154–2158.