Paclitaxel plus ifosfamide and cisplatin in second-line treatment of germ cell tumors: a phase II study

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The aim of this study was to determine efficacy and toxicity of TIP combination (paclitaxel, ifosfamid, cisplatin) as first salvage treatment in patients with relapsed germ cell tumours (GCTs). Excellent results were achieved from TIP combination with a dose 250 mg/m^2 of paclitaxel [5]. Our hypothesis was that comparable efficacy with less toxicity could be achieved even with a lower dose of 175 mg/m^2 paclitaxel in TIP.

In 17 consecutive patients with failed standard 1st line treatment, we used four to six courses of paclitaxel 175mg/m^2 on day 1 and ifosfamide 1200 mg/m^2 plus cisplatin 20 mg/m^2, both on day 1 through 5, every 3 weeks.

Eleven patients achieved favorable response (65%; 95% confidence interval, 42 to 87%) with 7 complete responses (41%). Estimated 2-year disease free survival is 47% (95% CI, 23–71%). Treatment combination was well tolerated and myelosupression was major toxicity. Granulocytopenia Gr3-4 was observed in 8% and febrile neutropenia in 7% of the courses. No case of severe neurotoxicity or treatment-related death was observed.

In our study, TIP combination had good toxicity profile. The results however, did not show expected treatment efficacy and we raise the idea of paclitaxel dosage relevance in TIP.

Key words: germ cell tumors, cisplatin, ifosfamide, paclitaxel, salvage treatment

Germ cell tumors (GCT) belong to the most chemosensitive solid tumors and represent a model of curable cancer [7]. Cisplatin represents the mainstay in the treatment of GCTs and about 70%-80% of patients (pts) with disseminated testicular cancer can be cured with 1st line cisplatin-based chemotherapy [6, 15]. Salvage chemotherapy with standard dose cisplatin plus previously non-utilized drugs may cure about 20–25% of pts who were not initially cured with their induction chemotherapy [12, 18].

Because of insufficient results in the treatment of relapsed GCTs, evaluation of new treatment strategies and novel drugs with significant antitumor activity, as a single-agent or combination, remains a priority. Single agent paclitaxel was studied in the phase II studies of refractory GCTs at several centers with response rates ranging from 11 to 26% [1, 4, 14, 17]. High treatment efficacy with combination of paclitaxel, ifosfamide and cisplatin (TIP) was achieved in a phase I/II study. Twenty-three of 30 patients (70%) with relapsed GCT and good prognostic features (3 of 30 pt had seminoma) achieved complete response to chemotherapy alone, and 24 (80%) and 22 (73%) patients achieved favorable and durable favorable response, respectively, at a median follow-up of 33 months [16].

Complete remission was observed in 32 of 46 pts (70%) with relapsed GCT and favorable prognostic features (5 of 46 pt had seminoma) treated with paclitaxel (250 mg/m^2), ifosfamid (5 g/m^2), cisplatin (100 mg/m^2) and G-CSF support [5]. Additionally 2 pts achieved partial remission with negative tumor markers (4%) and 2-year relapse free survival rate was 91%.

As mentioned above, myelosupression was the main toxicity in the treatment with TIP. More than 50% of the pts (16 out of 30) were hospitalized because of nadir fever/sepsis. Neurotoxicity was observed in 4% [5] and or in 10% [16] of the patients.

The search for a more efficient and less toxic treatment combination in short, as well as in long-term view, belongs to the main goals of clinical studies. The excellent results achieved with TIP, where paclitaxel was used in higher than so-called “standard” dose suggest the important role of paclitaxel in the salvage treatment of GCTs [5]. However, it is not known whether it is possible to achieve the same efficacy

with a lower toxicity when so-called "standard" dose of paclitaxel is used.

The primary endpoints of this study were objective response rate (ORR) and duration of response of TIP combination using the dose of 175 mg/m^2 of paclitaxel in the salvage treatment of advanced nonseminoma GCT. Secondary endpoints were overall survival and toxicity of the treatment.

We hypothesized that the use of the "standard" dose of paclitaxel in TIP will maitain efficacy and lower toxicity in comparison with the results which were achieved with high dose of paclitaxel.

Patients and methods

Eligibility. Seventeen consecutive patients with advanced nonseminoma GCT were registered into this prospective, open-labeled, unicentric phase II study trial between May 1998 and October 2003.

All pts with recurrent nonseminoma GCT, after their treatment with cisplatin-based regimes, were approved for this study. Relapse was documented by rising serum concentrations of tumour markers (AFP and/or b-HCG) and/or radiographic findings.

Seventeen eligible pts were men aged 18 years or older with GCT confirmed by histology and with measurable expression of the disease. Additional eligibility criteria included 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 tests and creatinine clearance rate of more than 50 ml/min. Patients were excluded if their prior treatment had included ifosfamide or taxane analogs.

All pts were required to give written informed consent before enrolment. The study protocol was reviewed and approved by the Scientific Board and Ethical Committee at the National Cancer Institute in Bratislava, Slovakia.

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

Treatment program. Treatment consisted of four cycles of TIP given 21 days apart. Paclitaxel 175 mg/m^2 was administered on an inpatient basis by 3-hour infusion on day 1 after standard pre-medication that consisted of dexamethason, bisulepin-HCl, and ranitidine. Ifosfamide 1200 mg/m^2 and cisplatin 20 mg/m^2 were administered by infusion on an inpatient basis on day 1 through 5. Ifosfamide was administered after paclitaxel on day 1 and before cisplatin on day 1 through 5. Mesna was administered in three infusions with the first infusion administered together with ifosfamide and second and third infusions administered 4 and 8 hours thereafter, respectively. The total dose of mesna was 60% of ifosfamide dose. Urine was examined before each administration of ifosfamid, so early signs of hemorrhagic cystitis could be detected and appropriately treated.

Standard antiemetic and hydration protocols were used. Dose adjustments for each subsequent cycle were dependent upon the lowest toxicity level demonstrated in the previous cycle. Haemopoetic growth factors were not scheduled. 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 and in the case of febrile neutropenia in the previous treatment cycle, hemopoetic growth factor was used in the next cycle. 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 Gr3 nausea/vomiting). The paclitaxel was omitted or reduced to 50%, and cisplatin was reduced to 50% in the case of neurotoxicity Gr3. The dose of cisplatin was reduced to 50% in the case of a creatinine clearance rate of 50–59 ml/min. The doses held due to toxicity or missed were not given at a later time. The patients who could not received drugs for more than 6 weeks from the time of the last treatment were discontinued from the study.

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

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

Responses were categorized as favorable or unfavorable. Response duration and survival were measured from the initiation of therapy. A favorable response was classified as a complete response or a partial response, with negative serum tumor markers. A complete response to chemotherapy alone was defined as a disappearance of 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. A complete response to chemotherapy plus surgery was defined as a complete excision of all masses, at least one of which contained viable tumor other than mature teratoma. An 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. The treatment was stopped and the patient

was classified as having progressive disease in the case of significant marker (more than 50%) and/or radiological progression (more than 25%) after one cycle. Response duration and survival were measured from the initiation of therapy. Toxicity was graded according to NCI-CTC (version 2.0) criteria [13].

Results

Patient's characteristics. The patient's characteristics are summarized in the Table 1. All 17 pts had nonseminoma histology and were treated in their first relapse. The pts with good as well as poor prognostic factors were included in the study. Two pts (12%) had extragonadal GCT, one had retroperitoneal and one mediastinal primary tumor. All pts included in the study responded to the primary cisplatin-based chemotherapy. One patient achieved only partial remission with positive markers and relapsed within 2 months after the end of treatment. Thirteen pts (76%) achieved complete remission or partial remission with negative tumor markers that lasted more than 6 months and were classified as relapse with good prognostic features. Four patients who relapsed earlier than 6 months after the primary treatment were classified as relapse with poor prognostic features. Four pts (24%) were considered to have late relapse (41, 50, 105 and 256 months after the end of treatment), which is defined as a recurrence of disease more than 2 years after the complete response to the first line chemotherapy [2]. Most of the pts (11 of 17; 65%) had more than one metastatic tumor at the beginning of the treatment.

Response and survival. The patient's response to the treatment is summarized in the Table 2.

Two pts achieved complete remission with chemotherapy. Seven of nine pts that achieved partial remission, with negative tumor markers, underwent resection of postchemotherapy residua. Five of them achieved complete remission with surgery. The viable tumor cells were found only in one case. Two pts achieved only partial resection of postchemotherapy residua and, in both cases only necrotic tissue was found. These patient's results were classified as partial remission with negative tumor markers. In summary, the favorable response was achieved in 11 pts (65%; 95% confidence interval, 42 to 87%) including 7 pts with complete remission and 4 pts with partial remission with negative tumor markers. One patient had isolated CNS relapse and has been disease-free for 41 months after neuro-surgical treatment. Three pts had systemic relapse at 5, 6 and 12 months, respectively, after the end of treatment and they died of the disease. Eight of eleven pts with favorable response (73%), four with complete and four with partial response, with normalized tumor markers, are alive without systemic relapse.

Two of six pts, who did not achieve favorable response, has lived with active disease for more than 2 years.

In the group of pts with relapse with good prognostic features (13 pts), a favorable response was obtained in 62% of the pts. Three of five (60%) pts in the group with relapse with poor prognosis features achieved favorable response and they have lived without relapse at the median follow-up of 24 months.

One patient with primary mediastinal tumor progressed during the treatment and died because of disease progression. The patient with primary retroperitoneal tumor achieved partial remission with negative markers

There were four pts treated with late relapse; two pts achieved complete response, one partial response with negative and one with positive tumor markers. One complete response was achieved with chemotherapy alone. A second complete response was achieved with chemotherapy and subsequent retroperitoneal lymphadenectomy followed with two additional cycles of chemotherapy because of the viable cells found in retroperitoneal residua. The patient however relapsed 6 months after the completion of treatment and died of disease. The remaining three pts treated with late relapse

Table 1. Patient's characteristics (n=17)

	No.	%
Median of age (range)	31 (19 – 51)	
Primary tumor		
Gonadal	15	88
Retroperitoneal	1	6
Mediastinal	1	6
Late relapse	4	24
Favorable response after 1st line chemotherapy	16	94
Relapse after 1st line chemotherapy less than 6 months	4	24
Sites of metastases		
Lungs	9	53
Liver	3	18
Lymph nodes	17	100
Mediastinum	5	29
Retroperitoneum	13	76
Brain	1	6
No. of metastatic site		
1	6	35
2	7	41
More than 3	4	24
Prior chemotherapy regimen		
BEP	15	88
T-BEP	1	6
PVB	1	6
Elevation of tumor markers		
LDH	5	29
AFP	11	68
HCG	8	47
Median (range) of elevated pretreatments markers		
AFP mIU/ml	164 (31 – 8250)	
HCG IU/ml	1 493 (80 – 14 320)	
LDH (kat/l)	12 (9 – 121)	

HCG – human chorionic gonadotropin; AFP – alfa fetoprotein; LDH – lactate dehydrogenase; BEP – bleomycin, etoposid, cisplatin; PVB – bleomycin, vincristine, cisplatin; T-BEP – paclitaxel, bleomycin, etoposid, cisplatin; HD-CT – high dose chemotherapy

Table 2. Response to treatment

	No. of Patients	%
Assessable	17	100
Favorable response	11	65
Complete response	7	41
Partial response with normalized markers (PRnm-)	4	24
Incomplete response	4	24
Progression	4	24
Relapse	4	36
– systemic	3	27
– central nervous system	1	9

Table 3. Main grade 3 or 4 toxicity per patient according to NCI-CTC (version 2.0) classification (n=17)

Toxicity	No. of Patient´s	%
Nonhematologic		
Nausea or vomiting	1	6
Neurotoxicity	0	0
Diarrhea	0	0
Mucositis	0	0
Liver	0	0
Hematologic		
Granulocytopenia	7	41
Thrombocytopenia	1	6
Anemia	4	24
Febrile neutropenia	5	29
Therapy-related deaths	0	0

NCI-CTC – National Cancer Institute Common Toxicity Criteria

are alive for 24+, 29+ and 57+ months after the end of TIP treatment. Among the surviving patients with late relapse belongs one patient who achieved only partial remission with positive tumor markers and his disease was inoperable due to bulky masses. He has been surviving for 2 years without the signs of disease progression.

Ten of 17 (60%) pts have lived at the median follow-up of 24 months (4–78 months). Two-year Kaplan-Meier estimated relapse-free survival is 47% (95% CI 23–71% while 2-year overall survival is 64% (95% CI; 37–91%).

Toxicity. The combination of paclitaxel, ifosfamide and cisplatin was well tolerated as is shown in the Table 3. A total of 73 courses of chemotherapy were administered in 17 pts with a median of 4 cycles per patient (range 4 to 6). Myelosupression with granulocytopenia was the major toxicity. Febrile neutropenia was observed in 29% of patients and was successfully treated with antibiotics. Three pts needed G-CSF and one patient needed platelet transfusion. Non-hematological toxicity was mild with only nausea and vomiting Gr1/2 observed and successfully treated with antiemetics. There was no dose reduction of chemotherapy needed. Median dose intensity of paclitaxel was 62 mg/m^2/week (range; 36 to 68 mg/m^2/week).

Discussion

The results of salvage treatment in the pts with relapsed GCT are unsatisfactory. Currently, only 25–30% of the pts with relapsed GCT achieve durable response with VIP/VeIP. In our study, the favorable response was achieved in 65% of the pts and 73% of the responses have lasted until the median follow-up of 24 months. The results are better when compared with VIP/VeIP, however worse than the results achieved with TIP in the study of DONADIO et al [5]. There are two main differences between the designs of our study and above-mentioned study with TIP [5, 16]: 1. different inclusion criteria and 2. different dose of paclitaxel.

Treatment efficacy strongly correlates with prognostic factors. The first and most important prognostic factor is complete remission that is achieved either with primary cisplatin-based chemotherapy only or with cisplatin-based chemotherapy (partial remission), followed with surgical complete removal of all residual masses. The pts that achieve partial remission with negative tumor markers (PRnm-) comprise a non-homogenous group and their residual tumor may contain viable malignant cells, teratoma, necrosis or fibrosis. It is believed that durable PRnm- to cisplatin-based chemotherapy is an indicator of favourable response to cisplatin. These pts are usually included in a prognosis-favorable group [5]. The second most important prognostic factor is the duration of interval from primary therapy to relapse. It is generally accepted that the longer the time to relapse, the better the prognosis. However a different observation exists regarding the length of this time interval. Significantly different 2-year survival rates were observed between the pts who relapsed within 24 months (less than 33%) and after 24 months from the end of the primary treatment (more than 73%). Univariate analysis and predictive value of prognosis with time to relapse were confirmed by multivariate analysis [8]. In other studies, the significant differences in 5-year survival rates were found between time to relapse ≤3 and >3 months (7% and 72%, respectively) [6], or <6 and ≥6 months (12% and 45%, respectively) [10]. MOTZER et al included only pts with relapse after complete remission, independently on the duration of response [16] and all but one patient in the study of DONADIO et al [5] relapsed after complete remission that lasted more than six months. In addition, only one patient included in the study had PRnm+ after primary treatment.

On the other hand, 6 of 17 patients achieved PRnm- after primary treatment and 10 pts achieved CR in our study. Four pts had response that lasted less than 6 months. In comparison with previous studies, the pts included in our study had worse prognostic features; however we did not consider our different inclusion criteria to influence substantially the study results. In a small subset of our pts with good prognos-

tic features, similar to the pts included in other studies [5, 16], we did not achieve such good results. On the contrary, 3 of 4 patients with relapse after attainment of PRnm-, that lasted less than 6 months, achieved durable favourable response.

We used paclitaxel at a dose of 175 mg/m^2, which is considered the standard dose in the treatment of other malignancies. The optimal dose of paclitaxel in the treatment of testicular cancer has not been uniformly accepted. In other studies, a substantially higher dose of paclitaxel (250 mg/m^2) was used [5, 16]. The efficacy and safety of the higher doses of paclitaxel (175, 215, and 250 mg/m^2) in TIP regimen was confirmed in the phase I/II study.

It is believed that the effect of cytostatics is dependent on the dose. However, data from the clinical trials trying to confirm this idea are contradictory. Better results were not obtained with the maximal tolerable doses of cytostatics in comparison with their standard dose in the studies of different malignancies. Different doses of paclitaxel were tested in phase III studies of the breast, ovarian, and lung cancer treatment [3, 11, 19]. In the studies of the treatment of more chemosensitive cancers (breast and ovarian), the dose of paclitaxel higher than 175 mg/m^2, did not improve the results significantly. However, in the studies with a less chemosensitive lung cancer, the use of a higher dose of paclitaxel led in increased time to progression. The higher dose of paclitaxel was accompanied with increased toxicity in all the studies.

We suppose, that better results in the study of DONADIO et al [5] were achieved because a higher dose of paclitaxel was used. We also conclude that higher than so called standard dose of paclitaxel plays an important role in TIP salvage treatment of GCTs. Another explanation for different results in these two studies, may arise from the small number of pts that makes generalization of the results for whole group of the patients difficult.

We believe a broader phase III clinical study is needed and propose to use a higher than "standard" dose of paclitaxel in TIP salvage treatment.

The results of this study were presented in part (poster session) at the 40th Annual Meeting of the American Society of Clinical Oncology, June 5–8, 2004, New Orleans, LA.

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