Retrospective analysis of long-term survival after combination treatment with gemcitabine, oxaliplatin and paclitaxel in patients with refractory or relapsed testicular cancers

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ABSTRACT

Aims: Testicular tumors are one of the most common malignancies in males, between 15 and 35 years of age. Testicular cancer patients are treated with the combination of gemcitabine, oxaliplatin and paclitaxel (GOP) in relapsed and refractory disease, but the literature about the GOP treatment is limited. We aimed to demonstrate the real-life data of progressive testicular cancer patients who received GOP treatment.

Methods: Medical records of 17 patients who received GOP treatment at the Gulhane Training and Research Hospital were reviewed retrospectively. Overall response rate (ORR), overall survival (OS) rate and progression-free survival (PFS) of the patients were evaluated.

Results: Overall response was obtained in 58.8% (n=10), and a complete response was achieved in 11.2% (n=2) of the cases. OS time was 14.2 months and the OS rate in the first year was 73.1%. The PFS time was 7.6 months. In most of the patients, thrombocytopenia, anemia and leukopenia were observed during GOP treatment.

Conclusions: GOP is a safe and effective treatment option for relapsed refractory testicular cancer patients with an acceptable ORR, OS and PFS time. Additionally, GOP treatment was associated with cognitive side effects in patients.

Introduction

Approximately 80% of patients with metastatic testicular cancers achieve long-term survival with cisplatin-based therapies (1,2). Patients with metastatic testicular tumors are curable in spite of the metastatic disease (3). The relapse after the first-line cisplatin-based chemotherapy may still be treated with salvage chemotherapy in up to 50% (1). However, after the tumor progression in spite of salvage chemotherapy rarely achieve long-term survival (4).

As single agents i.v. paclitaxel, gemcitabine, and, oxaliplatin have been demonstrated to be successful with testicular cancer patients with relapsed or refractory after the cisplatin-based chemotherapy (5–8).

After the positive effects of monotherapy demonstrated in the literature, a feasible and acceptable response rate of the combination therapy of oxaliplatin with gemcitabine was shown by Kollmannsberger et al. by GO study (9).

Additionally, Bokemeyer et al. reported that combination chemotherapy with gemcitabine, oxaliplatin, and paclitaxel (GOP) is feasible with acceptable toxicity treatment regimen in patients with refractory or relapsed germ-cell tumors (10). According to the literature, most of the patients had two or three lines of therapy before the GOP treatment regimen. Also, the presentations about relapsed or refractory testicular tumor patients who received GOP treatment are so limited.

We aimed to demonstrate the real-life data about relapsed or refractory testicular cancer patients who received GOP combination regimen and increase the awareness of this rare treatment choice.

Methods

A total of 17 patients who were diagnosed with testicular cancer were retrospectively collected from the database of oncology department, Gulhane Training and Research Hospital, Ankara, Turkey. Local ethics committee approved the study.

The laboratory findings including beta human chorionic gonadotropin (β HCG), lactate dehydrogenase (LDH), and alpha fetoprotein (AFP), histological types, characteristic features and toxicity profiles of the GOP treatment regimen were docu-

mented. All of the patients had relapsed or refractory testicular cancer after the cisplatin-based chemotherapy.

All the patients underwent chemotherapy regimen as BEP (bleomycin 30 mg/day at D1, 8, 15, etoposide 100 mg/m^2/day D1 D5, cisplatin 20 mg/m^2/day D1 D5, every 21 days) regimen as first-line therapy for at least three cycles before the GOP regimen (11).

The patients received gemcitabine at a dose of 800 mg/m² and paclitaxel at a dosage of 80 mg/m², both on days 1 and 8 and oxaliplatin was administered 130 mg/m² only on day 1 of a 3-week cycle.

Our aim is to asses the response rates, survival rates and side effect profile of GOP chemotherapy regimen retrospectively.

Statistical Analyses

The Statistical Package for Social Science SPSS for Window Version 22.00 (SPSS Inc., Chicago, IL., USA) was used to evaluate the statistical analyses. The Shapiro-Wilk test was used to examine the distribution of the continuous variables. For the descriptive statistics, non-normally distributed variables were demonstrated as median and IQR (interquartile range 25% and 75% interquartile range); continuous variables were shown as the mean ± standard deviation or median (minimum, maximum) as appropriate. Numbers and % were used in the presentation of categorical variables. Wilcoxon Signed Ranks Test was used for continuous variables that did not fit normal distribution independent groups. Spearman Correlation analysis was used to assess the relationship of the continuous variables between the groups. The Kaplan-Meier method was used for the survival curves. Statistical significance was accepted at 95% confidence interval, $p<0.05$ level.

Results

The mean age of the patients was 33.4±0.4 years. Histopathological examination revealed that more than half of the tumors (n=10, 58.8%) were mixed germ cell tumors. Nearly three-quarters of the patients had advanced cancer as stage 3A (n=12, 70.6%) at time of diagnosis. Approximately one-fourth of the patients (n=4, 23.5%) were found to have lymph node or metastasis to another vital organ (liver, lung or kidney). All cases before GOP treatment received at least 1 line chemotherapy. Two patients received four lines of chemotherapy before GOP treatment (n=2, 11.7 %). The risk classification of the majority of the cases according to International Germ Cell Cancer Collaboration Group (IGCCCG) was stage 3C (n=11, 64.7%). Autologous hematopoietic stem cell transplantation (AHSCT) was performed in 70.6% (n=12) of patients who were treated with GOP. Mean platinum-based treatment-refractory period was 9.60±3.4 weeks. The mean duration of relapse after platinum-based treatment until the AHSCT was calculated as 40.2±42.7 weeks (Table 1).

In our study, the median number of GOP treatment cycles was 4.0 (3-6). The median AFP, β HCG and LDH values before treatment were 433.0 (6.41-3803.0) mcg/L, 0.50 (0.13-204.0), and189.50 (182.0-430.0) mIU/ml, respectively. The median AFP, β HCG and LDH values after treatment were 52.0 (6.0-1398.0) mcg/L, 0.50 (0.13-296.0) mIU/ml, and 200.00 (190.00-350.00) IU/L, respectively. After GOP treatment the rate of complete response (CR) was 11.8% (n=2) and partial response was 23.5% (n=4). The overall response rate (ORR) was 58.8%. After the treatment 82.4 % (n=14) of cases did not undergo surgery. The best responding body region after the GOP treatment was lymph nodes (n=7, 41.2%).

When the side effects of the patients were examined during GOP treatment, more than half (64.7%, n=11) of patients had leukopenia, almost all of the patients had anemia (82.4%, n=14) and the majority of the patients had thrombocytopenia (82.4%, n=14). Neurotoxicity was found in 82.3% (n=14) of the cases

Table 1. The demographic and disease-related characteristics of the patients

Features	n (%)	Mean ± SD
Age (years)	17 (100)	33.4±0.5
Histopathology		
Mix germ cell tumor	10 (58.8)	
Yolk sac tumor	3 (17.6)	
Embrional carsinom	2 (11.8)	
Seminoma	1 (5.9)	
Choriocarcinoma	1 (5.9)	
Stage at the Time of Diagnosis		
≥ 3A	12 (70.6)	
≤ 2C	5 (29.4)	
Site of metastases		
No metastases	3 (17.6)	
Lymph Node and 1 other organ	4 (23.5)	
Lymph Node and 2 other organs	3 (17.6)	
Lymph Node and 3 other organs	1 (5.9)	
Lymph Node	3 (17.6)	
Lung	2 (11.8)	
Lung and Bone	1 (5.9)	
IGCCCG Risk Group		
1S	2 (11.8)	
2C	1 (5.9)	
3A	1 (5.9)	
3B	2 (11.8)	
3C	11 (64.7)	
AHSCT		
Yes	12 (70.6)	
No	5 (29.4)	
Number of lines before GOP treatment		
1 line	1 (5.8)	
2 lines	7 (41.1)	
3 lines	7 (41.1)	
4 lines	2 (11.7)	
Refractory period after platinum based treatment (weeks)	17 (100)	9.60±3.37
The duration of relapse before GOP treatment (months)	17 (100)	40.16±42.67

AHSCT: Autologous hematopoietic stem cell transplantation, GOP: Gemcitabine, oxaliplatin and paclitaxel, IGCCCG: International Germ Cell Cancer Collaboration Group,

Table 2. Descriptive characteristics of the patients during GOP treatment and follow-up.

Features	n (%)	Median	Mean±SD
Number of GOP treatment cycles	17 (100)	4 (3-6)	
Pre-AHSCT AFP mcg/L	17 (100)	433.0 (6.41-3803.0)	
Post-AHSCT AFP mcg/L	17 (100)	52.00 (6.00-1398.0)	
Pre-AHSCT β-HCG mIU/ml	17 (100)	0.50 (0.13-204.0)	
Post-AHSCT β-HCG mIU/ml	17 (100)	0.50 (0.13-296.0)	
Pre-AHSCT LDH IU/L	17 (100)	189.50 (182.0-430.0)	
Post-AHSCT LDH IU/L	17 (100)	200.0 (190.0-350.0)	
The response of the patients after AHSCT			
Stable response	4 (23.5)		
Complete response	2 (11.8)		
Partial response	4 (23.5)		
Progressive disease	7 (41.2)		
Surgical resection after GOP treatment			
Yes	3 (17.6)		
No	14 (82.4)		
The best response site after GOP treatment			
Lung	1 (5.9)		
Liver, LN	1 (5.9)		
Lung, LN	2 (11.8)		
LN	7 (41.2)		
Leukopenia			
Yes	11 (64.7)		
No	6 (35.3)		
Hgb <10g/dl			
Yes	16 (94.1)		
No	1 (5.9)		
Thrombocyte <20000/mm^3			
Yes	14 (82.4)		
No	3 (17.6)		
Bleeding diatesis			
Yes	1 (625)		
No	16 (93.8)		
Neurotoxicity			
No	3 (11.2)		
Grade 1	4 (23.5)		
Grade 2	10 (58.8)		
Nausea,vomiting			
No	5 (29.4)		
Grade 1	11 (64.7)		
Grade 2	1 (5.9)		
Diarrhea			
No	15 (88.2)		
Grade 1	1 (5.9)		
Grade 2	1 (5.9)		
The final status of the patients			
Exitus	6 (35.3)		
Alive	11 (64.7)		
The duration of follow-up after GOP treatment (month)			7.7±5.8
The duration of follow-up after diagnosis /month			4.2±3.3

AFP: Alpha fetoprotein; β-HCG: Beta human chorionic gonadotropic hormone; GOP: Gemcitabine, oxaliplatin and paclitaxel, Hgb: Hemoglabin; IQR = interquartile range 25% and 75% interquartile range; LDH: Lactate dehydrogenase; LN: Lymph node

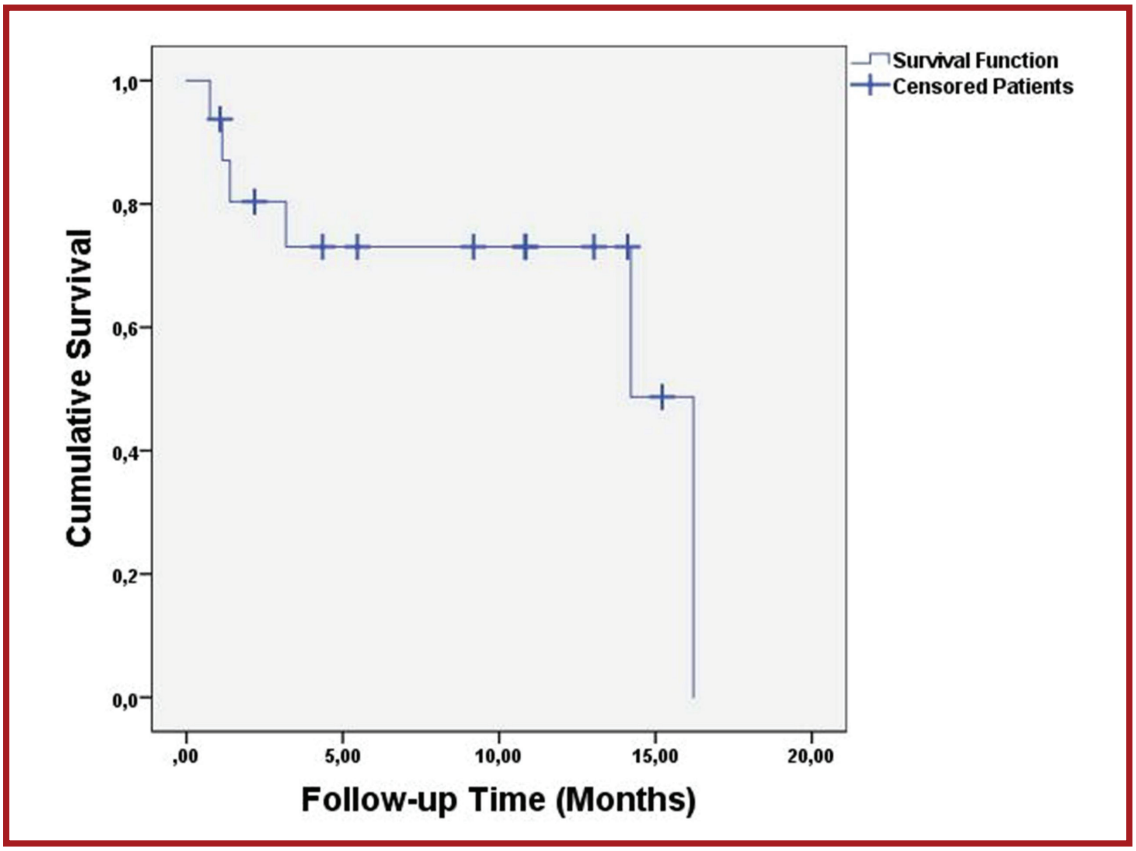

Figure 1. Survival of patients underwent GOP treatment (Kaplan-Meier Curve)

and 58.8% (n=10) was grade 2. In our study, bleeding occurred in 1 patient (5.9%). In addition, nearly four-thirds of patients (70.6%, n=12) had first- and second-degree nausea and vomiting and 11.8% (n=2) of patients had diarrhea (Table 2).

The mean follow-up time after the GOP treatment was 7.69±5.80 months. Furthermore, the mean follow-up time of the patients after the diagnosis was calculated as 4.15±3.31 years. In our study, a strong correlation between AFP, β-HCG and LDH values before and after treatment was determined (r=0.771, p<0.001, r=0.977, p<0.001, r=0.949, p<0.001, respectively) (Table 3). When the relationships among the AFP, β-HCG, LDH values of the patients before and after GOP treatment and the relapse duration of the disease (month) were examined, there was no statistically significant correlation (p>0.05).

The median OS time of patients after GOP treatment was 14.2 months (95% CI: 6.75-21.67) and the survival rate was 73.1% in the first year (Figure 1). One patient's treatment was not included in the calculation because the end date was uncertain and the follow-up period could not be calculated (n = 16). The median PFS time was 7.6 months (95% CI: 6.60-8.54) (Figure 2). PFS was 43.9% in the first year after starting GOP treatment.

Discussion

In this single-center real-life experience, we evaluated the efficacy of clinical findings of relapsed or refractory testicular cancer patients. Several prospective studies have investigated gemcitabine, paclitaxel, and platinum-compounds in patients with progressive testicular cancers (12–13). Some studies evaluating double combination chemotherapy regimens in refractory germ cell tumors also showed ORRs in the range of 20% to 40% (14–16). In these prospective studies, the percentages of ORR were 20–40%, and the median OS times were in the range of 7–9 mo (12,13). Currently, there is no standard salvage chemotherapy for these patients. The treatment options are so limited (17). Shiraishi et al. presented a triple-combination regimen using nedaplatin with gemcitabine and paclitaxel (18). They observed ORR in 47% of patients in a small group of patients as 15. The majority of our patients had progressive testicular cancer after cisplatin-based therapy (100) or even AHSCT (70.6%), indicating an especially poor prognosis of these testicular cancer patients. In spite of these unfavorable cases, a promising response rate of 58.8% was observed including 11.2% complete response. These results were compatible with the previous reports (10). In the literature mostly all of the patients received one or two cycles of chemotherapy. More than half of our patients received 3 or 4 lines of chemotherapy (52.8%). Two patients had CR and received three lines of chemotherapy, and both of them underwent AHSCT. Both of the patients still have CR. It brings to mind before AHSCT, GOP treatment may be a reasonable salvage treatment option. Further analyses are needed in this respect. Two patients underwent surgery after GOP treatment. One of them relapsed after the 12th week, and one of the patients had a partial response and still have partial response almost near CR.

Nicolai et al. demonstrated the results of a phase 2 study consists of GOP treatment in progressive testicular cancers. They reported a rate of 20% of patients who had achieved long-term survival for seven years (19).

Oechsle K et al. reported that after a median follow-up of

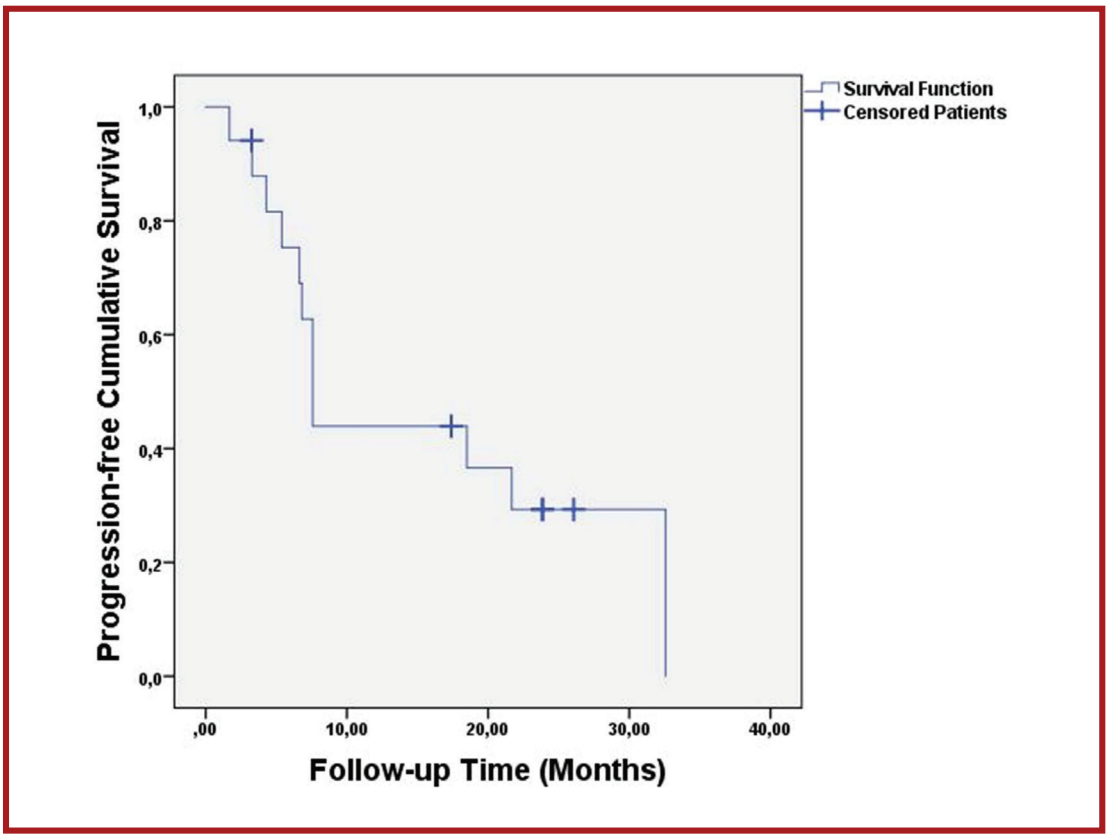

Figure 2. Progression-free survival of patients underwent GOP treatment (Kaplan-Meier Curve)

19 months, median OS was eight months for relapsed and refractory germ cell tumor patients (11). Christoph Seidel et al. demonstrated in a cisplatin-resistant germ cell cancer group the median PFS and OS were 4.0 months and 13.3 months, respectively (20). In our study, we found the median OS and PFS of 14.2 and 7.6 months, respectively. These results were similar to the literature reported before. Thus, GOP remains one of the best determined systemic treatment options for progressive testicular cancer patients even after AHSCT. In the current study, 70.6% of, patients underwent AHSCT.

Toxicity analysis of this report affirms the feasibility of the GOP regimen in patients with heavily pretreated testicular cancer. The most common hematologic toxicities were anemia and thrombocytopenia. These results were similar to the literature (10). Grade 3 and four thrombocytopenia occurred in 82.4% of patients. In one case bleeding was reported, and none of the was life-threatening. In spite of the combination of two potentially neurotoxic drugs, no excess neurotoxicity was observed as grade 3 and 4. None of the patients died due to treatment toxicities. Additionally, no patients quitted the treatment due to the toxicity.

There are some limitations to the study. The sample size of patients was small. Also, the follow-up time was short. Additionally, it was a retrospective study, and the control group was absent. Strengths of the study include new findings as CR achieved by GOP treatment followed by AHSCT as consolidation treatment. Additionally, the study consists of a report of a rare case series who relapsed or refractory testicular cancers.

In conclusion, the GOP treatment is a safe and effective treatment option for relapsed refractory testicular cancer patients with an acceptable OS, PFS and ORR. Also, the GOP treatment was associated with low treatment-related mortality and cognitive side effects in patients with poor prognosis.

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Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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