Efficacy of Gemcitabine, Paclitaxel, and Oxaliplatin Protocol in the Treatment of Relapsed or Refractory Germ Cell Tumours

Musa Baris Aykan, Gul Sema Yildiran, Ece Akcan, Ramazan Acar, Ismail Erturk and Nuri Karadurmus

Department of Medical Oncology, University of Health Sciences, Gulhane School of Medicine, Ankara, Turkey

ABSTRACT

Objective: To determine the survival endpoints and treatment-related adverse events after the use of the gemcitabine, paclitaxel, and oxaliplatin (GemPOx) protocol in relapsed/refractory germ cell tumours (GCTs) who had previously received multi-line systemic treatments including high-dose chemotherapy.

Study Design: Observational study.

Place and Duration of Study: Clinic of Medical Oncology, Gulhane School of Medicine, Ankara, Turkey, between January 2017 and August 2021.

Methodology: Clinical characteristics of adult patients with relapsed/refractory GCTs treated with the GemPOx protocol were recorded from the hospital's patient registry database. Patients without a medical record were not included in the study. Objective response rate (ORR), progression-free survival (PFS), overall survival (OS), one-year PFS rate, one-year OS rate, and treatment-related haematological side effects were determined after GemPOx.

Results: Fifty-three adult patients were included (47 of them were male). Seventy-eight percent had Stage 3 at initial diagnosis. Twenty-four percent of the patients received more than four lines of systemic chemotherapy. Ninety-six percent of the patients received high-dose chemotherapy prior to GemPOx. ORR, which is the sum of the complete and partial response rates, was 69.8%. PFS was determined as 8.5 ± 5.4 months. The one-year PFS rate was 30.3%. OS was 15.9 ± 10.6 months. The one-year OS rate was 72.6%. Febrile neutropenia was observed in 15.1% of the patients.

Conclusion: In patients with relapsed/refractory GCTs receiving multi-line systemic chemotherapy, significant PFS and OS are achievable, and a manageable spectrum of haematological side effects is observed with GemPOx.

Key Words: *Gemcitabine, Paclitaxel, Oxaliplatin, Germ cell tumour.*

How to cite this article: Aykan MB, Yildiran GS, Akcan E, Acar R, Erturk I, Karadurmus N. Efficacy of Gemcitabine, Paclitaxel, and Oxaliplatin Protocol in the Treatment of Relapsed or Refractory Germ Cell Tumours. *J Coll Physicians Surg Pak* 2022; **32(07)**:880-884.

INTRODUCTION

Germ cell tumours (GCTs) are one of the most common malignancies in males, especially in the second to fourth decades of life.[1] Successful response can be obtained with conventional cytotoxic chemotherapies, especially platinum-based treatment approaches, even in advanced GCTs. The overall survival (OS) rate at baseline for advanced-stage GCTs is 80% or more for five years.[2]

Correspondence to: Dr. Musa Baris Aykan, Department of Medical Oncology, University of Health Sciences, Gulhane School of Medicine, Etlik, Ankara, Turkey
E-mail: musabarisaykan@gmail.com

Received: January 26, 2022; Revised: April 02, 2022; Accepted: May 19, 2022
DOI: https://doi.org/10.29271/jcpsp.2022.07.880

There is an almost-established systemic treatment approach in the first, second and third lines of advanced GCTs. The use of second-line salvage regimens followed by high-dose chemotherapy in tertiary care after a failure of first-line therapy is now considered standard in the patients with appropriate performance.However, chemotherapy protocols that may be preferable for the patients in the fourth and subsequent lines with relapsed/refractory GCTs are still lacking.[3-6]

If these patients are considered appropriate, total surgical excision of residual masses or re-salvage autologous stem cell transplantation plus high-dose chemotherapy treatment can be tried.[7] The use of gemcitabine and platinum-based treatment protocols such as gemcitabine, oxaliplatin, and paclitaxel (GemPOx) may be considered.[8] However, there is no clearly defined optimal treatment recommendation for the patients who still need this effective treatment. The aim of this study was to determine the patient characteristics, post-treatment survival, and side effects of the GemPOx protocol in the patients with relapsed refractory GCTs.

METHODOLOGY

Patients treated at the Clinic of Medical Oncology, Gulhane School of Medicine, Ankara, Turkey were included in this retrospective observational study. The study was conducted using medical records of relapsed/refractory GCTs between January 2017 and August 2021. Inclusion criteria were age ≥ 18 years, histologically and radiologically confirmed advanced GCTs at diagnosis or at recurrence, and receiving treatment with the GemPOx protocol. Patients who did not meet the inclusion criteria and those without follow-up data were excluded. The GemPOx protocol was administered: Gemcitabine was given at a dose of 800 mg/m^2 on the 1st and 8th day of a 21-day cycle. Paclitaxel was also administered at a dose of 80 mg/m^2 on the 1st and 8th days of the 21-day cycle. If oxaliplatin dose was 130 mg/m^2, it was administered only on the 1st day during the same period.[9] G-CSF was routinely given to all the patients. Age, gender, localisation, histology, and stage at the diagnosis of the primary malignancy were recorded. Within the scope of the study, lung, liver, bone, soft tissue, lymph node, and brain metastases status were evaluated before the GemPOx protocol. International Germ Cell Cancer Collaboration Group (IGCCCG) risk groups and the number of systemic chemotherapy lines before GemPOx and serum tumour marker levels were also evaluated.[10]

Progression-free survival (PFS) was defined as the time from the onset of GemPOx to local recurrence or distant metastatic disease to disease progression, death from cancer, or neither. Overall survival (OS) was calculated as the time from the first day of GemPOx to the date of the patient's last follow-up examination or the date of death due to cancer or non-cancer causes. The objective response rate (ORR) was determined as the sum of the complete and partial responses achieved. The one-year PFS rate and one-year OS rate were obtained from the survival analysis. The Ethics Committee of the study centre decided that the study protocol with approval number 2021/93 was appropriate.

SPSS 22.0 software (SPSS Inc., Chicago, Illinois) was preferred for statistical analysis. Descriptive data were expressed as the counts and percentages. The Kolmogorov-Smirnov test was used to evaluate the normality of continuous variables. The mean ± standard deviation (SD) was used for normally distributed continuous data. For continuous data that is not normally distributed, the median [interquartile range (IQR)] is preferred. Kaplan-Meier analysis was used for survival analysis (PFS, OS, one-year PFS rate, and one-year OS rate).

RESULTS

The final sample included 53 patients. The mean age was 30.6 years (SD:8.4 years). In 42 (79.2%) patients, the primary tumour site was the testes. Mixed GCT was found histopathologically in 28 (52.8%) patients. At the initial diagnosis, 41 (78%) patients had Stage 3 disease, and 60.4% of the patients had lung metastases. When evaluated according to IGCCCG, 38 (71.7%) of the patients were in the poor prognostic risk group. Of the patients, 12 (22.6%) had a serum tumour marker level S3 (S3 is the expression showing the highest serum tumour marker elevation). The number of patients, who received four or more lines of systemic chemotherapy before GemPOx, was 13 (24.5%) The median (IQR) number of cycles of the GemPOx protocol was determined as 4 (3). The characteristics of the patients are presented in Table I.

Table I: Demographic and clinical characteristics of the patients.

Features	n: 53
Age, in years, mean (±SD) (min-max)	30.6 (8.4) (18-52)
Gender	
Male, n (%)	47 (88.7)
Female, n (%)	6 (11.3)
Primary origin of tumor, n (%)	
Testes	42 (79.2)
Ovaries	7 (13.2)
Extragonadal	4 (7.5)
Histopathology, n (%)	
Mixt germ cell	28 (52.8)
Teratoma	6 (11.3)
Seminoma	5 (9.4)
Yolk Sac	5 (9.4)
Choriocarcinoma	5 (9.4)
Embryonal carcinoma	4 (7.5)
Stage at Diagnosis, AJCC, 8th,n (%)	
≤ Stage 2C	12 (22.6)
≥ Stage 3A	41 (77.4)
Site of Metastases, n (%)	
Lymph nodes	40 (75.5)
Lung	32 (60.4)
Liver	18 (34)
Bone	17 (32.1)
Soft tissue	13 (24.5)
Brain	5 (9.4)
IGCCCG Risk Groups, n (%)	
Good risk	11 (20.8)
Intermediate risk	4 (7.5)
Poor risk	38 (71.7)
Serum Tumor Markers before GemPOx, n (%)	
S0	17 (32.1)
S1	15 (28.3)
S2	9 (17)
S3	12 (22.6)
Number of systemic treatment lines before GemPOx, n (%)	
≤4 lines	40 (75.5)
>4 lines	13 (24.5)
HDC+AHSCT, n (%)	
Yes	51 (96.2)
Number of GemPOx cycles, median (IQR)	4 (3)

AJCC, 8th: The eighth edition American Joint Committee on Cancer; IGCCCG: International Germ Cell Cancer Collaborative Group; GemPOx: Gemcitabine, paclitaxel and oxaliplatin; S0: Marker's blood level within normal limits; S1: LDH <1.5 × ULN, hCG (mIU/mL) <5000 and AFP (ng/mL) <1000; S2: LDH 1.5 to 10 × ULN or hCG (mIU/mL) 5000 to 50,000 or AFP (ng/mL) 1000 to 10,000; S3: LDH >10 × ULN or hCG (mIU/mL) >50,000 or AFP (ng/mL) >10,000, HDC: High dose chemotherapy; AHSCT: Autologous Hematopoietic Stem Cell Transplantation.

The ORR to the GemPOx was 69.8% for all the patients. Median

PFS (IQR) was determined as 8.5 (5.4) months. The one-year PFS rate was 30.3%. Mean OS (SD) was 15.5 (6.7) months. The one-year OS rate was 72.6%. Although neutropenia, anaemia, and thrombocytopenia were frequently observed, they were usually found at the Grade 2 level. The frequency of febrile neutropenia during GemPOx was found to be 15.1%. Treatment side effects and responses to the treatment are presented in Table II, Figures 1 and 2.

Table II: Treatment-related characteristics of the patients.

Features	n:53
Best objective response, n (%)	
Complete response	13 (24.5)
Partial response	24 (45.3)
Stable disease	7 (13.2)
Progressive disease	9 (17)
PFS, median (IQR), months	8.5 (5.4)
OS, mean (SD), months	15.5 (6.7)
One-year- PFS rate, % (SE)	30.3 (7.1)
One-year- OS rate, % (SE)	72.6 (6.3)
Haematologic side effects	
Neutropenia, n (%)	
Grade 1	1 (1.9)
Grade 2	45 (84.9)
Grade 3	7 (13.2)
Anemia, n (%)	
Grade 1	10 (18.9)
Grade 2	28 (52.8)
Grade 3	15 (28.3)
Thrombocytopenia, n (%)	
Grade 1	11 (20.8)
Grade 2	33 (62.3)
Grade 3	9 (17)
Febrile Neutropenia, n (%)	8 (15.1)

PFS: Progression-free survival; OS: Overall survival; IQR: Interquartile range, SD: Standard deviation.

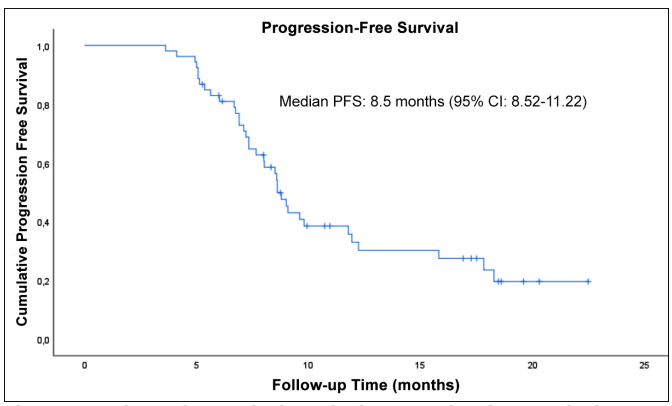

Figure 1: Kaplan Meier survival graph of progression-free survival.

DISCUSSION

Since GCTs are chemosensitive, they are considered to be malignancies with a long-term remission or cure, even if they are detected at an advanced stage.

Patients who have relapsed after first-line cisplatin-based chemotherapy still have a 20–45% chance of being cured with the salvage chemotherapy approach. However, continuing to have relapsed/refractory GCTs after salvage systemic therapy indicates poor prognosis and short survival.[11] Therefore, management of sequential systemic chemotherapies in the patients with relapsed/refractory GCTs remains challenging. Despite repeated chemotherapy lines and even high-dose chemotherapy treatment, there are still patients with a high tumour burden and good performance status. The number of these patients may be relatively small. However, in a malignancy that is expected to be chemosensitive, albeit relapsed/refractory, effective chemotherapy protocols are needed to prolong survival.

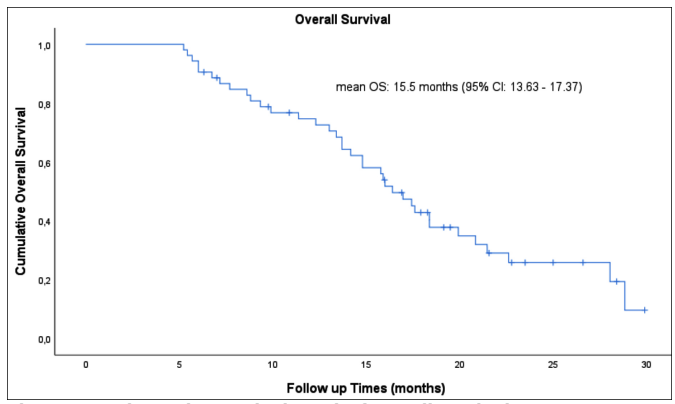

Figure 2: Kaplan Meier survival graph of overall survival.

The GemPOx protocol is an approach that finds its place in clinical practice at this point. This study evaluated the use of the GemPOx protocol in the patients with relapsed/refractory GCTs, most of them had previously received cisplatin-based triple combination chemotherapy protocols and nearly all of them had received high-dose chemotherapy. Significant survival data were observed in PFS and OS. This situation was also observed for the one-year PFS rate and one-year OS rate. In addition, a manageable haematological outcome profile was found. For the patients in this group, the GemPOx protocol should be evaluated for use in appropriate patients.

Bokemeyer and colleagues also reported data on the GemPOx protocol. In their study with 41 patients, 78% relapsed after high dose chemotherapy.[12] In this sample, 96% of the patients, who received high-dose chemotherapy, were treated with GemPOx. This is primarily considered to be a poor prognostic marker for the patients. However, in the patients who received multi-line systemic chemotherapy, including high-dose chemotherapy, the GemPOx protocol consisting of triple conventional chemotherapy agents may have successful survival results and response rates.

ORR, which provides important information about disease control in those who need treatment despite receiving multi line therapy, is one of the most important details showing the success of studied drugs. It is important to reveal protocols that provide as much meaningful radiological response as possible in cases of relapsed/refractory GCTs to pave the way for improved survival. Surgical resection of the remaining lesions can be achieved after a significant radiological response has been achieved, offering a long-term chance of complete remission.[13,14] Bokemeyer *et al.* reported that the ORR as 51% in their patients.[12] Einhorn *et al*. reported a 13% complete response

with dual conventional chemotherapy of gemcitabine and paclitaxel in the patients who relapsed after high-dose chemotherapy.[15] In this sample, the ORR was 69.8%. The significant benefit of adding the third chemotherapeutic agent to the treatment compared to the two-drug combination is now an accepted approach, especially for the selected fit patients. Significant response with GemPOx may allow for complete resection of residual masses after chemotherapy. Especially in the patients with high tumor burden, GemPOx is an important option to have the chance of surgery after the tumor has shrunk significantly.

GemPOx is considered to be a regimen that increases the haematological side effects but is not difficult to manage.[9] Seidel and colleagues reported grade 3 hematological side effects in almost half of their samples.[9] In this sample, the incidence of Grade 3 neutropenia was 13%. This can be attributed this situation to the routine and regular use of G-CSFs.

This study has some limitations. A cross-sectional analysis was made. Due to the nature of cross-sectional analysis, a causal link cannot be established for the results obtained. In addition, the number of the patients is relatively low, which limits the generalisability of the findings to the different populations. Since it is a retrospective study, the probability of error for data quality increases. Moreover, follow-up times and intervals cannot be controlled in retrospective analyses.

CONCLUSION

The GemPOx protocol may offer a successful contribution to PFS and OS in the patients with GCTs who continue to be relapsed/refractory despite receiving multi-line systemic chemotherapy. GemPOx also has a tolerable and manageable haematological side-effect profile.

ETHICAL APPROVAL:

Ethics Committee approval was received from the Ethics Committee of Gulhane Training and Research Hospital (No. 2021/93, dated December 15, 2021).

PATIENTS' CONSENT:

Because this study was retrospective, the condition of patients' consent was waived.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

MBA, NK: Carried out the conception and design of the research, drafted the manuscript, and carried out the analysis and interpretation of data.
GSY, EA, RA: Performed the statistical analysis.
EA, GSY, RA, IE: Participated in the acquisition of data.
All authors approved the final version of the manuscript to be published.

REFERENCES

1. Siegel R, Miller K, Fuchs H, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin* 2021; **71(1)**:7-33. doi: 10.3322/caac.21654.
2. Carver B, Serio A, Bajorin D, Motzer R, Stasi J, Bosl G, *et al*. Improved clinical outcome in recent years for men with metastatic nonseminomatous germ cell tumors. *J Clin Oncol* 2007; **25(35)**:5603-5608. doi: 10.1200/JCO.2007.13.6283.
3. Feldman D. Medical treatment of advanced testicular cancer. *JAMA* 2008; **299(6)**:672. doi: 10.1001/jama.299.6.672.
4. Einhorn L, Williams S, Loehrer P, Birch R, Drasga R, Omura G, *et al*. Evaluation of optimal duration of chemotherapy in favorable-prognosis disseminated germ cell tumors: A southeastern cancer study group protocol. *J Clin Oncol* 1989; **7(3)**:387-391. doi: 10.1200/JCO.1989.7.3.387.
5. Sattar A, Masood M, Nisar H, Fatima I, Baker Shahid A. Disease characteristics and treatment outcome of testicular germ cell tumors treated with platinum-based regimens. *J Coll Phys Surg Pak* 2018; **27(4)**:292-6. doi: 10.29271/jcpsp.2018.04.292.
6. Mego M, Rejlekova K, Svetlovska D, Miskovska V, Gillis A, De Angelis V, *et al.* Paclitaxel, ıfosfamide, and cisplatin in patients with poor-prognosis disseminated nonseminomatous germ cell tumors with unfavorable serum tumor marker decline after first cycle of chemotherapy. The GCT-SK-003 phase II trial. *Eur Urol Open Sci* 2021; **33**:19-27. doi: 10.1016/j.euros.2021.09.002.
7. Ertürk İ, Yıldız B, Karadurmuş N, Tosun B, Esen R, Acar R, *et al*. Retrospective analysis of long-term survival after combination treatment with gemcitabine, oxaliplatin and paclitaxel in patients with refractory or relapsed testicular cancers. *GUL MED J* 2018; **60(4)**:145. doi: 10.26657 / gulhane.00040.
8. Acar R. Gemcitabine, oxaliplatin and paclitaxel (GemPOx) in patients with relapsed or refractory germ cell tumors after high dose chemotherapy, a retrospective single-center experience. *Int J Hematol Oncol* 2020; **30(4)**: 191-196. doi: 10.4999/uhod.204657.
9. Seidel C, Oechsle K, Lorch A, Dieing A, Hentrich M, Hornig M, *et al*. Efficacy and safety of gemcitabine, oxaliplatin, and paclitaxel in cisplatin-refractory germ cell cancer in routine care — registry data from an outcomes research project of the German testicular cancer study group. Urol Oncol 2016; **34(4)**:168.e21-168.e28. doi: 10.1016/j.urolonc.2015.11.007.
10. International germ cell consensus classification: A prognostic factor-based staging system for metastatic germ cell cancers. International germ cell cancer collaborative group. *J Clin Oncol* 1997; **15(2)**:594-603. doi: 10.1200/JCO.1997.15.2.594.
11. Oing C, Seidel C, Bokemeyer C. Therapeutic approaches for refractory germ cell cancer. *Expert Rev Anticancer Therapy* 2018; **18(4)**:389-397. doi: 10.1080/14737140.2018.1450630.
12. Bokemeyer C, Oechsle K, Honecker F, Mayer F, Hartmann J, Waller C, *et al*. Combination chemotherapy with gemcitabine, oxaliplatin, and paclitaxel in patients with cisplatin-refractory or multiply relapsed germ-cell tumors: A study of the german testicular cancer study group. *Ann Oncol* 2008; **19(3)**:448-53. doi: 10.1093/annonc/mdm526.
13. Woldu S, Meng X, Wong D, Baky F, Margulis V, Xi Y, *et al*.

Performance characteristics of 18F-fluciclovine positron emission tomography/computed tomography prior to retroperitoneal lymph node dissection. *Canadian Urological Assoc J* 2021; **16(3)**. doi: 10.5489/cuaj.7317.

14. Zor M, Yilmaz S, Topuz B, Kaya E, Yalcin S, Coguplugil A, *et al*. Post-chemotherapy modified template retroperitoneal lymph node dissection in patients with nonseminomatous germ cell tumours. *Aktuelle Urol* 2021. doi: 10.1055/a-1469-6892.
15. Einhorn L, Brames M, Juliar B, Williams S. Phase II Study of paclitaxel plus gemcitabine salvage chemotherapy for germ cell tumors after progression following high-dose chemotherapy with tandem transplant. *J Clin Oncol* 2007; **25(5)**:513-6. doi: 10.1200/JCO.2006.07.7271.