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Efficacy of ifosfamide, carboplatin and etoposide chemotherapy protocol in relapsed refractory germ cell tumors

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ABSTRACT

Aims: This study aimed to evaluate the overall survival (OS) after the ifosfamide carboplatin plus etoposide (ICE) protocol for patients with relapsed refractory germ cell tumors (GCT). Differences in the contribution of the ICE protocol to patient survival according to the number of the treatment lines (four or more lines vs. three or fewer lines) were also evaluated.

Methods: This retrospective cross-sectional study included patients with relapsed refractory GCT who had previously received multiple-line chemotherapy. Gender, age, clinical stage at diagnosis, tumor marker levels, visceral metastasis status, previous treatment protocols, response rates to ICE, follow-up time, and hematologic side effects were recorded. The primary endpoint was OS after the ICE. The secondary endpoint was the difference in OS between patients who received the ICE on the fourth and subsequent lines vs. those who received the third and previous lines.

Results: The final sample included 15 patients (median age 26; males: 93.3%). At diagnosis, 80% of the patients had stage IIIC disease. The median OS in the whole group was 14.0 [interquartile range (IQR) 15.4] months. The median (IQR) OS after the ICE protocol in patients with three or fewer lines was significantly higher than in those who received four or more lines [21.6 (34.5) vs 10.8 (11.6), p=0.034]. Grade 3 neutropenia (46.6%), anemia (40%), and thrombocytopenia (40%) were frequently observed.

Conclusions: For heavily pretreated relapsed/refractory GCT, the ICE may show the potential to provide a significant survival. However, more severe hematological side effects may be encountered

Introduction

Germ cell tumors (GCT) are among the most common solid malignancies in the male population, especially in the second and third decades (1). Especially with the platinum-based treatment approach, a good response can be obtained even in advanced GCT patients. The 5-year overall survival (OS) for advanced disease is 80-90% (2).

There is an established systemic treatment approach in the first, second and third lines of advanced GCT. However, chemotherapy protocols that can be preferred in the fourth and next lines in patients with good performance status despite having a resistant disease are lacking (3-6). In this sense, it may be reasonable to evaluate potential treatment options in patients who are few but still need therapy.

The ifosfamide, carboplatin plus etoposide (ICE) protocol has been frequently preferred as a high-dose chemotherapy approach (7,8). However, this approach is usually used in the early lines (7). To the best of our knowledge, there is little information on the use of the ICE protocol in later lines and there is no recent up-to-date data. Considering the abovementioned information, we showed the patient characteristics, posttreatment survival time, and side effects of the ICE protocol in all relapsed refractory GCT patients. As a general oncological concept, the

survival benefit provided by the transition to each advanced line therapy is considered to decrease. Therefore, we also aimed in the current study to show whether the use of the ICE protocol in patients receiving four or more lines of chemotherapy shows the same impact on survival compared to those receiving three or fewer chemotherapy lines.

Methods

Study design and population

This retrospective, single-center study was performed using the medical records of outpatients and inpatients with relapsed/refractory GCT from a tertiary clinic from January 2017 to June 2021. The inclusion criteria were age greater than or equal to 18 years, those with histologically confirmed advanced stage testicular cancer, imaging-proven metastases at diagnosis, or recurrent disease. The exclusion criteria were age <18 years and insufficient clinical data. This study was approved by the Gülhane Training and Research Hospital Local Ethics Committee (protocol number: 2021/58, date: 29.09.2021). Gender, age, localization, the histology of the primary malignancy, and stage at the time of diagnosis were recorded. Lung, liver, bone, and lymph node metastasis status before the ICE protocol, serum tumor marker status, and International Germ Cell Cancer Collaboration Group (IGCCCG) risk group and previous systemic treatments (BEP: Bleomycin, Cisplatin, Etoposide. TIP: Paclitaxel, Ifosfamide, and Cisplatin. HDC: High Dose Chemotherapy. GEMPOX: Gemcitabine, Paclitaxel, and Oxaliplatin) were evaluated within the scope of the study (9). Response to treatment and observed side effects were recorded after the ICE protocol. Survival after the ICE protocol, survival times from the first diagnosis, and survival status (alive/died) were evaluated. The patients were divided into two according to the systemic treatment lines they received before the ICE protocol (four or more lines vs. three or fewer lines). The interval between the first diagnosis and the ICE protocol is defined as the time between the first diagnosis of the patient and the date of starting the ICE protocol. OS after ICE protocol was calculated as the time from the start of the ICE protocol to the last seen date or the patient's death date. The interval between the first diagnosis and last visit is defined as the time elapsed from the diagnosis to the last follow-up visit or death. The ICE protocol was as follows: ifosfamide 1667 mg/m^2/day for 3 days, mesna 1667 mg/m^2/day for 3 days, carboplatin AUC 5 for a single day, etoposide 100 mg/m^2/day for 3 days. Granulocyte colony-stimulating factor (G-CSF) administration is recommended routinely after the ICE protocol.

Study endpoints

The primary endpoint of the study was to demonstrate OS in the entire group after the ICE protocol. Additionally, any difference between the survival times according to the systemic treatment lines they received before the ICE protocol (four or more lines vs. three or fewer lines) was also studied.

Definition of complete response, partial response, progressive disease, and stable disease

Complete remission was defined as the disappearance of all clinically and radiologically detectable lesions and the normalization of tumor markers. A More than 20% reduction in tumor burden was defined as partial response (PR). A tumor growth greater than 20% was defined as Progressive Disease. Any other response was classified as a stable disease (10).

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data are presented as a percentage of the total. The normality of the continuous variables was examined using the Kolmogorov-Smirnov test. Normally distributed continuous data were expressed as mean±standard deviation and non-normally distributed were expressed as median [interquartile range (IQR)]. Between-group differences were tested using the chi-square test, Student's t-test, or Mann-Whitney U test, as appropriate. A p-value less than 0.05 was considered statistically significant.

Results

Main characteristics

The final sample included 15 patients (median age 26; males: 93.3%). The median age was 26 (IQR: 14). Eighty percent of the sample had stage IIIC disease at the time of initial diagnosis. All GCTs were in the non-seminomatous histological type. In 73.3% of patients, the serum tumor marker levels were S3 [S3: lactate dehydrogenase (LDH) >10 × ULN or hCG (mIU/mL) >50,000 or AFP (ng/mL) >10,000]. According to the IGCCCG risk classification, 66.6% of the patients were in the poor risk category. In both groups, lung and liver metastases were frequently detected before the ICE protocol (53.3% for lung metastases and 80% for liver metastases, respectively). Patients who received ≥4 lines of treatment before the ICE protocol received the BEP, TIP, HDC, and GEMPOX protocols, respectively. The characteristics of the patients are presented in Table 1.

Response rates and side effects

The response rate to the ICE protocol (sum of complete response rate and PR rate) was 53.2%. The median OS in the general group after ICE was 13.9 (IQR: 15.3) months. The patients were divided into two groups according to the order in which they received the ICE protocol (four or more lines vs. three or fewer lines). The median OS (IQR) after the ICE protocol in patients with three or fewer lines was significantly higher than

Table 1. Demographic and clinical characteristics of the patients

	Total (n=15)	Before ≤3 lines of systemic therapy (n=6)	Before ≥4 lines of systemic therapy (n=9)
Gender, male, n (%)	14 (93.3)	6 (100)	8 (88.8)
Age, years, median (IQR)	26 (14)	23.5 (11.8)	31 (14)
Clinical stage (AJCC 8th), n (%)			
I	2 (13.3)	1 (16.6)	1 (11.1)
IIIB	1 (6.6)	-	1 (11.1)
IIIC	12 (80.0)	5 (83.3)	7 (77.7)
Serum tumor markers, n (%)			
S0	3 (20.0)	1 (16.6)	2 (22.2)
S1	1 (6.6)	-	1 (11.1)
S3	11 (73.3)	5 (83.3)	6 (66.6)
IGCCCG risk groups, n (%)			
Good risk	3 (20.0)	1 (16.6)	2 (22.2)
Intermediate risk	1 (13.3)	-	3 (22.2)
Poor risk	10 (66.6)	5 (83.3)	5 (55.5)
Visceral metastasis, n (%)			
Lung	8 (53.3)	3 (50.0)	5 (55.5)
Liver	12 (80.0)	5 (83.3)	7 (77.7)
Bone	3 (20.0)	2 (33.3)	1 (11.1)
Systemic treatments before ICE protocol, n (%)			
BEP+TIP+HDC+GEMPOX	9 (60.0)	-	9 (100)
BEP+TIP	4 (26.6)	4 (66.6)	-
BEP+TIP+VIP	2 (13.3)	2 (33.3)	-

AJCC 8th: The eighth edition American Joint Committee on Cancer, 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, IGCCCG: International Germ Cell Cancer Collaborative Group, ICE: Ifosfamide, carboplatin, etoposide chemotherapy protocol, BEP: Bleomycin, cisplatin, etoposide, TIP: Paclitaxel, ifosfamide and cisplatin, HDC: High dose chemotherapy, GEMPOX: Gemcitabine, paclitaxel and oxaliplatin, VIP: Ifosfamide, etoposide, cisplatin, RBPC: Red blood packed cells, PAS: Platelet additive solution, IQR: Interquartile range

in those who received four or more lines [21.6 (34.5) vs 10.8 (11.6), p=0.034]. Grade 3 neutropenia (46.6%), anemia (40%), and thrombocytopenia (40%) were frequently observed in all patients. Treatment side effects and responses to treatment are presented in Table 2.

Discussion

GCT is considered among the chemosensitive malignancies like lymphomas. However, the therapeutic management of patients with relapsed/refractory GCT is still challenging. Despite repeated chemotherapy lines and even HDC treatment, there are still patients with residual tumor burden and good performance status. Although the number of patients reaching this clinical condition is generally low, chemotherapy protocols that are expected to be effective in patients who are still relapsed or refractory despite receiving multi-line therapy are needed. The ICE protocol is an approach that comes to the fore at this point. In this study, the use of the ICE protocol was evaluated in patients with relapsed/refractory GCT who received multi-line therapy. There was a significant difference in the time to the last visit after ICE in patients who received ≤3 lines of treatment before compared to those who received ≥4 lines of treatment. The explanation for such a difference may be the higher fragility and lower performance of patients receiving more chemotherapy. Thanks to the use of chemotherapy protocols containing cisplatin, especially in patients with extensive visceral metastases and different negative prognostic features, advanced GCT can be successfully treated initially (5,6). All patients included in our study had been treated with combination chemotherapy protocols containing at least two lines of cisplatin in the past. The majority of the patients in the current study had liver metastases before the ICE protocol. The liver is the most common site of extrapulmonary organ metastases in patients with advanced GCT (11). In contrast to lung metastases, liver, brain, and bone metastases represent a poor prognostic feature in GCT (12-14). Given that the patients in the current analysis received multi-line therapy, a high frequency of liver metastases may be predictable. Lung metastases were also detected in more than half of our patients.

For men with good-risk advanced testicular GCTs, relapse-

Table 2. Treatment-related characteristics of the patients

	Total (n=15)	Prior to ≤3 lines of systemic therapy (n=6)	Prior to ≥4 lines of systemic therapy (n=9)	p
Best objective response after ICE protocol, n (%)				
Complete response	1 (6.6)	1 (16.6)	-	-
Partial response	7 (46.6)	2 (33.3)	5 (55.5)	-
Stable disease	3 (20.0)	1 (16.6)	2 (22.2)	-
Progressive disease	4 (26.6)	2 (33.3)	2 (22.2)	-
Interval between first diagnosis and ICE protocol, mean (SD), months	51.06 (35.04)	62.16 (41.61)	43.66 (30.20)	0.335
Overall survival after ICE protocol, median (IQR), months	13.95 (15.36)	21.62 (34.54)	10.80 (11.63)	0.034
Interval between first diagnosis and last visit, mean (SD), months	73.77 (43.21)	94.09 (37.25)	60.23 (43.41)	0.143
Haematologic side effects after ICE protocol				
Neutropenia, n (%)				
None	3 (20.0)	1 (16.6)	1 (22.2)	-
Grade 1	4 (26.6)	-	2 (44.4)	-
Grade 2	1 (6.6)	1 (16.6)	-	-
Grade 3	7 (46.6)	4 (66.6)	3 (33.3)	-
Anemia, n (%)				
None	3 (20.0)	1 (16.6)	1 (22.2)	-
Grade 1	2 (13.3)	-	1 (22.2)	-
Grade 2	4 (26.6)	2 (33.3)	2 (22.2)	-
Grade 3	6 (40.0)	3 (50.0)	3 (33.3)	-
Thrombocytopenia, n (%)				
None	3 (20.0)	1 (16.6)	2 (22.2)	-
Grade 1	3 (20.0)	1 (16.6)	2 (22.2)	-
Grade 2	3 (20.0)	1 (16.6)	2 (22.2)	-
Grade 3	6 (40.0)	3 (50.0)	3 (33.3)	-
Febrile neutropenia, n (%)	7 (46.6)	4 (66.6)	3 (33.3)	-
RBPC infusion counts, median (IQR)	2 (6)	3 (7.75)	2 (4)	-
PAS infusion counts, median (IQR)	1.5 (3)	2 (6)	2 (5.67)	-

ICE: Ifosfamide, carboplatin, etoposide chemotherapy protocol, SD: Standard deviation, IQR: Interquartile range, RBPC: Red blood packed cells, PAS: Platelet additive solution

free survival has been reported to be above 70% following first-line chemotherapy. Up to 50% of men with intermediate or poor-risk disease traits with the relapsed disease following first-line chemotherapy require additional treatment (15-18). In our study, most patients had IGCCCG moderate or poor-risk disease, most patients received ≥3 lines of chemotherapy before the ICE protocol. One of the important indicators of prognosis in GCT is the high course of serum tumor markers (12). In our study, serum tumor markers in were in the highest category in most patients, namely, S3 [S3: LDH >10 × ULN or hCG (mIU/mL) >50,000 or AFP (ng/mL) >10,000] before the ICE protocol. This finding may be explained by the resistant clinical course and poor prognosis characteristics of the patients in the current analysis. Patients who show relapse after the second-line chemotherapy and patients who progress within one month of completing the first cisplatin-based chemotherapy or during the treatment are considered platinum-resistant diseases. This group is often treated with HDC therapy. HDC achieves successful endpoints for treating patients with relapsed or treatment refractory GCT. HDC is also a treatment approach that achieves a favorable outcome when used after the second line (19-21). Erturk et al. (22) reported a 1-year progression-free survival (PFS) rate of 57.8% and a 1-year OS rate of 77.5% after a single course of HDC in patients with relapsed/refractory GCT. Additionally, median OS and PFS were 21.5±1.8 and 20±2 months, respectively. In our study, more than half of the patients

had received HDC treatment before. Patients who still require treatment despite receiving this dose-dense treatment are one of the main groups for which survival outcomes are to be evaluated in this study. The treatments available for cases with relapsed or still a residual disease, even after dose-dense therapy such as HDC, are very limited. In these difficult-to-manage clinical situations, gemcitabine-based therapies such as gemcitabine plus oxaliplatin, gemcitabine, oxaliplatin, and paclitaxel (GEMPOX) can be used. Surgery may be recommended if the patient has a residual tumor suitable for surgery. A second HDC treatment may also be recommended if the patient's performance and tumor burden are suitable. GEMPOX therapy has shown a positive impact on PFS and OS endpoints in cases of testicular cancer that relapsed or remained refractory after cisplatin-based chemotherapy (23-25). In a previous study, successful real-life data of the combination of GEMPOX in patients with relapsed or refractory GCTs were reported (26). One-year OS, PFS, and overall response rate were reported to be significantly higher in favor of the clinical benefit. In our study, many patients received the GEMPOX protocol before the ICE protocol. In these patients, we can state that there was a significant median time from ICE to the last visit. This gives us an idea that the ICE protocol is useful in the post-GEMPOX period. Hematological side effects were frequently observed after the ICE protocol in the current analysis, which may be considered acceptable as most patients received multiple-line chemotherapy, including HDC. Although G-CSF was used routinely in our cases, neutropenia was frequently observed (27). However, the frequency of febrile neutropenia did not differ between those who received three or fewer systemic treatments and those who received four or more systemic treatments. Also, the frequency of anemia and thrombocytopenia were similar between the groups. Hence, hematological side effects of the ICE chemotherapy protocol are prominent features beyond the past chemotherapy regimens and bone marrow reserve.

This paper has several limitations. First, the number of patients was low, limiting the generalizability of the findings to different populations. Second, the retrospective design of the study raises the possibility of errors in data quality. Third, since the analysis was cross-sectional, the results cannot be assumed to be causal. Finally, follow-up times and intervals cannot be controlled in retrospective analyses.

Conclusion

In conclusion, the current study that was conducted on a less common, chemotherapy-resistant malignancy with residual tumor requiring advanced-line chemotherapy despite initial multiple-line chemotherapy showed that the ICE protocol was associated with a favorable outcome profile including OS. Nevertheless, hematological side-effects were quite common.

Ethics

Ethics Committee Approval: This study was approved by the Gülhane Training and Research Hospital Local Ethics Committee (protocol number: 2021/58, date: 29.09.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.B.A., İ.E., R.A., G.S.K., N.K., Concept: M.B.A., İ.E., N.K., Design: M.B.A., R.A., N.K., Data Collection or Processing: M.B.A., E.Ö., G.S.K., Analysis or Interpretation: M.B.A., İ.E., N.K., Literature Search: M.B.A., G.S.K., Writing: M.B.A., E.Ö.

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References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021;71:7-33.
2. Carver BS, Serio AM, Bajorin D, et al. Improved clinical outcome in recent years for men with metastatic nonseminomatous germ cell tumors. J Clin Oncol. 2007;25:5603-5608.
3. Feldman DR, Bosl GJ, Sheinfeld J, Motzer RJ. Medical treatment of advanced testicular cancer. JAMA. 2008;299:672-684.
4. Einhorn LH, Williams SD, Loehrer PJ, 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;7:387-391.
5. Massard C, Plantade A, Gross-Goupil M, et al. Poor prognosis nonseminomatous germ-cell tumours (NSGCTs): should chemotherapy doses be reduced at first cycle to prevent acute respiratory distress syndrome in patients with multiple lung metastases? Ann Oncol. 2010;21:1585-1588.
6. Kondagunta GV, Bacik J, Donadio A, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. J Clin Oncol. 2005;23:6549-6555.
7. Yildiz B, Pinar Aral I, Balyemez U, et al. What is the optimal high-dose treatment following autologous stem cell transplantation in relapsed or refractory germ cell cancer: a retrospective comparison of high-dose ICE and high-dose CE. J BUON. 2020;25:1136-1140.
8. Simonelli M, Rosti G, Banna GL, et al. Intensified chemotherapy with stem-cell rescue in germ-cell tumors. Ann Oncol. 2012;23:815-822.
9. No authors listed. 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;15:594-603.

10. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92:205-216.
11. Wood MJ, Thomas R, Howard SA, Braschi-Amirfarzan M. Imaging of metastatic germ cell tumors in Male patients from initial diagnosis to treatment-related toxicities: A primer for radiologists. Am J Roentgenol. 2020;214:24-33.
12. International Prognostic Factors Study Group; Lorch A, Beyer J, et al. Prognostic factors in patients with metastatic germ cell tumors who experienced treatment failure with cisplatin-based first-line chemotherapy. J Clin Oncol. 2010;28:4906-4911.
13. Pico JL, Rosti G, Kramar A, et al. A randomised trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours. Ann Oncol. 2005;16:1152-1159.
14. McCaffrey JA, Mazumdar M, Bajorin DF, Bosl GJ, Vlamis V, Motzer RJ. Ifosfamide-and cisplatin-containing chemotherapy as first-line salvage therapy in germ cell tumors: response and survival. J Clin Oncol. 1997;15:2559-2563.
15. Culine S, Kramar A, Théodore C, et al. Randomized trial comparing bleomycin/etoposide/cisplatin with alternating cisplatin/cyclophosphamide/doxorubicin and vinblastine/bleomycin regimens of chemotherapy for patients with intermediate- and poor-risk metastatic nonseminomatous germ cell tumors: Genito-Urinary Group of the French Federation of Cancer Centers Trial T93MP. J Clin Oncol. 2008;26:421-427.
16. Motzer RJ, Nichols CJ, Margolin KA, et al. Phase III randomized trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. J Clin Oncol. 2007;25:247-256.
17. Hinton S, Catalano PJ, Einhorn LH, et al. Cisplatin, etoposide and either bleomycin or ifosfamide in the treatment of disseminated germ cell tumors: final analysis of an intergroup trial. Cancer. 2003;97:1869-1875.
18. de Wit R, Stoter G, Sleijfer DT, et al. Four cycles of BEP vs four cycles of VIP in patients with intermediate-prognosis metastatic testicular non-seminoma: a randomized study of the EORTC Genitourinary Tract Cancer Cooperative Group. European Organization for Research and Treatment of Cancer. Br J Cancer. 1998;78:828-832.
19. Nichols CR, Tricot G, Williams SD, et al. Dose-intensive chemotherapy in refractory germ cell cancer--a phase I/II trial of high-dose carboplatin and etoposide with autologous bone marrow transplantation. J Clin Oncol. 1989;7:932-939.
20. Einhorn LH, Williams SD, Chamness A, Brames MJ, Perkins SM, Abonour R. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. N Engl J Med. 2007;357:340-348.
21. Beyer J, Kingreen D, Krause M, et al. Long-term survival of patients with recurrent or refractory germ cell tumors after high dose chemotherapy. Cancer. 1997;79:161-168.
22. Erturk I, Karadurmus N, Kızıloz H, et al. Treating relapsed and refractory metastatic germ cell tumours with high-dose chemotherapy with carboplatin and etoposide and autologous haematopoietic stem cell transplantation. J Oncol Pharm Pract. 2021;27:1657-1664.
23. Kollmannsberger C, Rick O, Derigs HG, et al. Activity of oxaliplatin in patients with relapsed or cisplatin-refractory germ cell cancer: a study of the German Testicular Cancer Study Group. J Clin Oncol. 2002;20:2031-2037.
24. Ertürk İ, Yıldız B, Karadurmuş N, et al. Retrospective analysis of long-term survival after combination treatment with gemcitabine, oxaliplatin and paclitaxel in patients with refractory or relapsed testicular cancers. Gulhane Med J. 2018;60:145-150.
25. Bokemeyer C, Oechsle K, Honecker F, 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;19:448-453.
26. Acar R, Ertürk I, Kızıloz H, et al. Gemcitabine, oxaliplatin and paclitaxel (Gempox) in patients with relapsed or refractory germ cell tumors after high dose chemotherapy, a retrospective single-center experience. International Journal of Hematology and Oncology. 2020;30:191-196.
27. Pérez-Ruixo JJ. Hematopoietic growth factors. Pharm Biotechnol Fundam Appl. 2019:521-535.