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Original Article

What is the main reason of erectile dysfunction in lymphoma patients: Chemotherapy or Depression?

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ABSTRACT

Background Erectile dysfunction (ED) may be associated with chemotherapy and depression in lymphoma patients. The role of depression in developing ED in lymphoma patients may be more critical than chemotherapy. This study aimed to determine which plays a more important role in ED.

Material and Methods This study included 20 patients aged under 60 years who were admitted to the Hematology Outpatient Clinic between March 2015 and March 2016 and diagnosed with lymphoma. While the Beck Depression Inventory (BDI) was used to assess depression severity before (T1), during (T2) and after (T3) chemotherapy, the International Index of Erectile Function (IIEF) was used to assess sexual function. The Mann-Whitney U and Wilcoxon signed-rank tests were used for statistical analysis. A p-value of <0.05 was considered statistically significant.

Results Twenty male lymphoma patients (14 [70%] patients with non-Hodgkin lymphoma and 6 [30%] patients with Hodgkin lymphoma) were included in the study. The mean BDI score was 11.75±1.44 at T1, 6.60±3.61 at T2, and 3.25±2.12 at T3, respectively ($p<0.01$). The mean IIEF score was 15.25±6.12 at T1, 12.95±6.03 at T2, and 20.40±8.59 at T3, respectively ($p<0.01$). There was a significant decrease in the mean BDI and IIEF scores between T1 and T2. However, the mean BDI score decreased between T2 and T3, while the mean IIEF score tended to increase.

Conclusions It is impossible to suggest a single cause when considering the multifactorial aetiology of ED in lymphoma patients. However, our study showed that depression and related psychological factors are the leading cause of ED in lymphoma patients.

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INTRODUCTION

Erectile dysfunction (ED) is the persistent and/or recurrent inability to achieve and/or maintain an erection sufficient for satisfactory sexual activity.[1] Akkus *et al*.[2] reported that the prevalence of ED was 69.2% in 1,982 male individuals from Turkey (mild 33.2%, moderate 27.5%, severe 8.5%). They found that its prevalence was 7.6% in men aged 40-49 years, 33.3% in men aged 50-59 years, 70.2% in men aged 60-69 years, and 90.1% in men aged 70 years and older.[2]

ED is divided into organic and psychogenic impotence and usually has a multifactorial aetiology. While the prevalence of psychogenic ED is approximately 10% in men over 50 years, 45% of all patients with ED have psychogenic problems.[3] Psychogenic causes may include emotional problems (such as depression, anxiety, previous sexual traumatic experiences, low self-esteem, doubts in the sexual role), physical disabilities or loss of physical attraction to one's sexual partner, as well as socioeconomic factors (such as familial discordance or cultural differences, sexual myths or work-related stress).[3,4] The lifetime prevalence of major depression in the general population has been reported as 4.8-17.1%.[5] It is difficult to identify and distinguish the relationship between ED and depression. It is not clear whether depression leads to ED or vice versa. A Finnish study involving 1683 patients aged 50-70 years who were treated for depression and not treated found a strong relationship between depression and ED.[6]

Combining adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) is the most commonly used chemotherapy regime for Hodgkin lymphoma (HL). Neutropenia is the most common complication after the ABVD chemotherapy regimen.[7] Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP) chemotherapy regimens are first-line treatment for non-Hodgkin lymphoma (NHL). Complications of peripheral neuropathy/paresthesia occur in patients treated with vincristine.[8]

Drug-induced ED is very common. Several studies have reported its average incidence as 25%.[9] Chemotherapeutic drugs may cause a loss of sexual desire and a decline in the frequency of sexual intercourse.[10] Systemic side effects (such as fatigue, nausea, vomiting, taste and smell changes, diarrhoea, constipation, weight changes, insomnia, fear, anxiety, and stomatitis) after chemotherapy can lead to an individual to feel like asexual. Erectile dysfunction occurs predominantly in patients receiving chemotherapeutic agents (especially cyclophosphamide, chlorambucil, bleomycin and cisplatin).[11] This study aimed to determine which factor plays a more important role in ED in young lymphoma patients under 60 years.

MATERIAL AND METHODS

Study design and population

This study included 20 patients aged 25-60 admitted to the Haematology Outpatient Clinic of Dr Lütfi Kırdar Kartal Training and Research Hospital between March 2015 and March 2016 and diagnosed with lymphoma. ED was evaluated cross-sectionally. All patients enrolled in the study were married or had a regular sexual life, were at least primary school graduates, and could read and understand the survey questions. In addition, patients who had previously been diagnosed with ED had diseases leading to ED and had depression previously were excluded from the study. While the Beck Depression Inventory (BDI) was used to assess depression severity before (T1), during (T2) and after (T3) chemotherapy, the International Index of Erectile Function (IIEF) was used to assess sexual function. ED was evaluated by IIEF scores: 0-10 (severe), 11-16 (moderate), 17-21 (mild-to-moderate), 22-25 (mild) and 26-30 (none). Patients whose lymphomas did not improve or progress at T2 were excluded from the study. A physician recorded the answers during face-to-face interviews. A haematologist performed the medical follow-up of patients, and their information was recorded in the study file.

Statistical analysis

Statistical analysis was performed with the Number Cruncher Statistical System (NCSS) 2007 statistical software program (NCSS, LLC, Kaysville, Utah, USA). Descriptive statistics (mean, standard deviation, median, frequency, rate) were used to summarize the data. When analyzing non-normally distributed variables, the Mann-Whitney U test was used for intergroup comparisons, whereas the Wilcoxon signed-rank test was used for intragroup comparisons. A p - value < 0.05 was considered statistically significant.

RESULTS

Twenty male lymphoma patients (14 [70%] patients with NHL and 6 [30%] patients with HL) were included in the study. The mean age was 46.90 ± 10.56 years. The number of patients aged under 50

Table 1. Sociodemographic and clinical data of patients.

	Mean ± SD/median (min:max)
Mean age (years)	46.90 ± 10.56/50.5 (26-59)
Disease duration (years)	1.60 ± 3.10/0 (0-10)
Smoking duration (years)	26.00 ± 16.43/25 (0-60)
Age groups (< 50/> 50 years) n (%)	10 (50)/10 (50)
Marital status (married) n (%)	20 (100)
Smoking (no/yes) n (%)	3 (15)/17 (85)
Alcohol consumption n (%)	20 (100)
Occupation n (%)	
Officer	3 (15)
Worker	12 (60)
Self-employed	5 (25)
Education n (%)	
Primary school	10 (50)
Secondary school	3 (15)
High school	6 (30)
University	1 (5)
Additional disease n (%)	6 (30)
Drug intake n (%)	6 (30)
Non-Hodgkin/Hodgkin lymphoma n (%)	14 (70)/6 (30)
Stage 1-2/Stage 3-4 n (%)	9 (45)/11 (55)

years was 10 (50%). NHL groups included eight diffuse large B-cell lymphomas, two T-cell-rich B-cell lymphomas, one mantle-cell lymphoma, one follicular lymphoma, one primary mediastinal large B-cell lymphoma, and one marginal zone lymphoma, respectively. ABVD chemotherapy regimens had been received with HL patients. R-CHOP, R-CVP, dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) chemotherapy regimens had received with NHL patients. The median number of chemotherapy cycles was 6 (range: 4-6) for HL groups and 6 (range: 2-8) for NHL groups. While 10 (50%) patients graduated from primary school, only 1 (5%) graduated from university. All the patients were married-smoking at diagnosis (85%). Abdominal bulky lesions and testicular mass were not observed in the pre-treatment evaluation. Grade 3 neutropenia was seen in 1 patient with HL groups. Vincristine was discontinued in 1 patient with peripheral neuropathy in NHL groups. Of them, 9

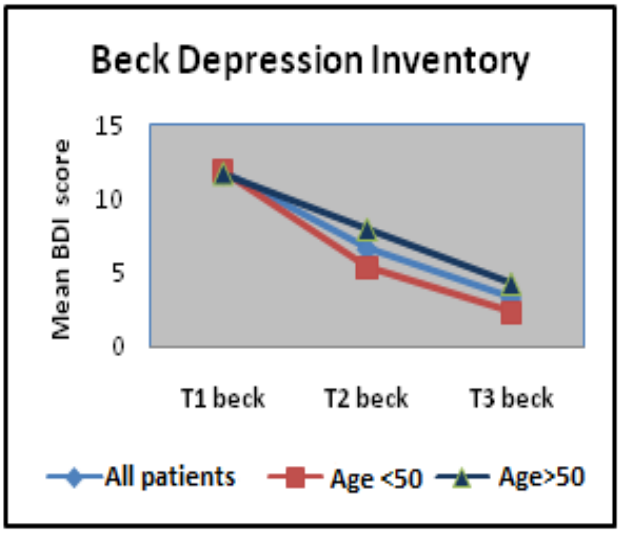

Figure 1. Evaluation of BDI scores according to follow-ups.

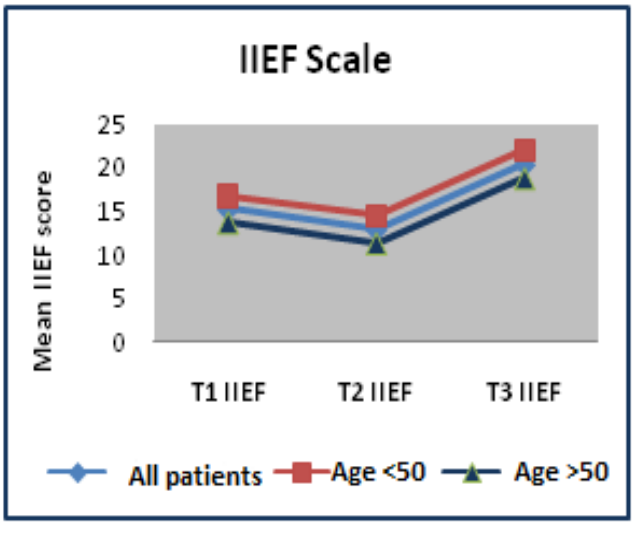

Figure 2. Evaluation of IIEF scores according to follow-ups.

(45%) had early-stage cancer (Stage 1-2), and 11 (55%) had advanced-stage cancer (Stage 3-4) (Table 1).

Comorbidities were three patients with essential hypertension, two patients with diabetes mellitus, and one patient with asthma. Only one of the patients with hypertension used a selective beta-1-blocker (atenolol). Patients with diabetes mellitus were used metformin. Age, diabetes mellitus, hypertension, smoking history, and disease stage distribution were similar in both groups.

The mean BDI score was 11.75 ± 1.44 at T1, 6.60 ± 3.61 at T2, and 3.25 ± 2.12 at T3, respectively ($p < 0.01$). The mean BDI score significantly decreased from T1 to T2 ($p = 0.001$; $p < 0.01$) and from T2 to T3 ($p = 0.001$; $p < 0.01$) (Figure 1). The mean IIEF score was 15.25 ± 6.12 at T1, 12.95 ± 6.03 at T2, and 20.40 ± 8.59 at T3, respectively ($p < 0.01$). The mean IIEF score significantly decreased from T1 to T2 ($p = 0.009$; $p < 0.01$). However, the mean IIEF score significantly increased from T1 to T3 ($p = 0.002$; $p < 0.01$) and from T2 to T3 ($p = 0.001$; $p < 0.01$) (Figure 2).

IIEF measurements at T1 ($p = 0.191$), T2 ($p = 0.256$) and T3 ($p = 0.161$) did not show statistically significant differences according to age groups. In cases under 50, the mean decrease of 2.20 ± 3.26 in IIEF measurements from T1 to T2 was statistically significant ($p = 0.042$; $p < 0.05$). The mean increase of 5.20 ± 4.02 in IIEF measurements from T1 to T3 was statistically significant ($p = 0.009$; $p < 0.01$). The mean increase of 7.40 ± 5.46 in IIEF measurements from T2 to T3 was found to be statistically significant ($p = 0.007$; $p < 0.01$) (Table 2). In cases over 50 years of age, the mean decrease of 2.40 ± 4.09 in IIEF measurements from T1 to T2 was not found to be statistically significant ($p = 0.068$; $p > 0.05$). The mean increase of 5.10 ± 6.77 in IIEF measurements from T1 to T3 was statistically significant at borderline ($p = 0.050$; $p < 0.05$). The mean increase of 7.50 ± 8.24 in IIEF measurements from T2 to T3 was found to be statistically significant ($p = 0.022$; $p < 0.05$) (Table 2).

DISCUSSION

Although ED is not life-threatening, it negatively affects the quality of life. The survival of HL and NHL is significantly prolonged by current treatments.[12,13] Mental disorders such as anxiety and depression caused by lymphoma and chemotherapy are frequently seen in lymphoma patients, similar to all cancer patients.[14] Kornblith *et al*.[15] reported that male patients with HL had more frequent and longer-lasting sexual problems than leukaemia patients of similar age. However, it should be noted that approximately half of the patients in this study received radiotherapy and that radiotherapy was one of the reasons. In our study, patients were newly diagnosed and did not receive radiotherapy since it is less frequently indicated in current treatment guidelines.

Predictably, lymphoma patients have increased rates of psychological problems (especially depression).[15,16] It is usual to experience anxiety in this period when negative emotions such as stressful thoughts of everyday life and fear of death are predominant. Our study found that patients had higher depression scores at the first assessment. There was a significant decrease in depression scores at the mid-term evaluation (usually after 3 or 4 cycles of chemotherapy) in patients receiving treatment. This can be explained by the fact that 17 of 20 patients in our study were informed that lymphoma responds well to treatment and is likely to improve. It was observed that depression scores continued to decrease during follow-up and reached their lowest value at the end of the treat-

Table 2. Evaluation of IIEF measurements according to age groups.

	Age <50 (n: 10) Mean ± SD (median)		Age >50 (n: 10) Mean ± SD (median)	*P* value
T1 IIEF	16.80 ± 6.94 (19.5)		13.70 ± 5.05 (15.5)	0.197[a]
T2 IIEF	14.60 ± 6.20 (15.0)		11.30 ± 5.68 (11.0)	0.256[a]
T3 IIEF	22.00 ± 9.26 (26.0)		18.80 ± 8.02 (21.0)	0.161[a]
Pairwise comparisons	Difference mean ± SD	P value	Difference mean ± SD	
T1-T2	2.20 ± 3.26	0.042*[b]	2.40 ± 4.09	0.068[b]
T1-T3	-5.20 ± 4.02	0.009**[b]	-5.10 ± 6.77	0.050*[b]
T2-T3	-7.40 ± 5.46	0.007**[b]	-7.50 ± 8.24	0.022*[b]

IIEF T1: before chemotherapy, T2: during chemotherapy, T3: after chemotherapy.
[a]Mann-Whitney U test, [b] Wilcoxon signed-rank test (adjustment for Bonferroni).

ment. The fact that psychological fear and anxiety experienced by patients at the time of initial diagnosis significantly decreased and partially disappeared is mainly responsible for this. Previous studies demonstrated that psychological problems improved during long-term follow-up after treatment and that chronic fatigue and aesthetic concerns/social issues related to physical changes continued.[17,18] No such evaluation was performed in our study. Long-term follow-up was not planned because our study was a cross-sectional study.

Alkylating drugs are known to cause germ cell damage with the dose increase. Cyclophosphamide (total dose > 6-10 g), chlorambucil, procarbazine, busulfan, nitrogen mustard, and nitrosoureas have been shown to cause azoospermia. Testicular atrophy occurs in 80% of HL patients receiving the MOPP (nitrogen mustard, vincristine, procarbazine, and prednisone) treatment regimen. Reversible azoospermia was reported in 35% of HL patients receiving the ABVD treatment regimen.[19]

Considering the pathogenesis and aetiology of ED, the frequency of ED is expected to increase over time because the negative effects of the disease and treatment would occur over time. The leading causes are the accumulation of chemotherapeutic drugs (such as anthracycline and bleomycin) in the body over time, increased side effects, and treatment-related fatigue and strength loss. In our study, ED scores decreased at the mid-term assessment (indicating that the frequency and severity of ED were increased). This increase was in contrast with the improvement in depression. However, depression scores continued to decrease after the mid-term assessment, while ED scores tended to increase (indicating that the frequency and severity of ED decreased). This decrease was found to be higher than expected. Our results showed that ED seen during treatment often have a psychological origin and are not organic. Long-term follow-up studies revealed that sexual disorders (particularly chronic fatigue) increased over time.[16-18]

Depression decreases significantly during treatment in lymphoma patients, whereas ED shows a slight increase in the early stage of treatment. However, depression decreased after the mid-term assessment while ED improved. The most important reason for this is that patients were informed about the improvement in lymphoma at the mid-term evaluation, and the psychological effects of this situation appeared immediately. It is known that there are organic and psychogenic causes in the aetiology of ED and that psychogenic ED may occur acutely and improve in a short time.[20]

The frequency of ED increases with age. This is explained by decreased testosterone levels, increased frequency of chronic diseases, and atherosclerosis.[21] Because our patients were generally concentrated within a certain age range, a statistical analysis was performed as under and over 50. As a result, it was observed that the age range did not reveal a significant difference for both depression and ED.

CONCLUSIONS

Maintaining the quality of life during treatment in male lymphoma patients is very important. Sexual life is considerable, especially in young patients and is one of the main factors determining the quality of life. Therefore, it is necessary to provide support and treatment for these patients to have a healthy sex life during the treatment period. Erectile function is essential for a healthy sexual life. The correct identification of ED causes is the basis of the treatment in these patients. It is impossible to suggest a single cause when considering the multifactorial aetiology of ED in lymphoma patients. However, our study showed that depression and related psychological factors are the leading cause of ED in lymphoma patients. Organic causes are often put forward in the long-term follow. These patients should be closely monitored psychologically during treatment and evaluated in detail for anxiety and depression. Starting pharmacological or psychological treatment based on this evaluation and maintaining the chemotherapy process with this support would significantly improve quality of life.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical Approval

This study was approved by Dr Lütfi Kırdar Kartal Training and Research Hospital ethics committee (Decision number: 514/87/11 dated 29.06.2019). All male patients who participated in the study signed a

consent form.

Authors' Contribution

Study Conception: GY, CY,; Study Design: GY, CY,; Literature Review: CY,; Critical Review: GY, CY,; Data Collection and/or Processing: CY, AE,; Analysis and/or Data Interpretation: CY, AE,; Manuscript preparing: CY.

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