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POLYPHARMACY EXPERIENCE IN GERIATRIC HEMATOLOGY

GERİATRİK HEMATOLOJİDE POLİFARMASİ DENEYİMİ

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ABSTRACT

Background: Polypharmacy in hematological malignancies is also a research area with very little literature data. The development of personalized treatment approaches in this patient group is considerable for future needs. In this study, we aimed to examine the effects of polypharmacy on treatment response, and survival in elderly patients with different hematological malignancies.

Method: The data of 91 patients, who were ≥ 60 years old, with the diagnosis of a hematological malignancy was analyzed retrospectively. The data including gender, age, stage, treatment regimens, concomitant diseases, drugs used, history of radiotherapy, treatment response of the patients and treatment toxicity were examined.

Results: The overall survival was 36% in patients receiving ≤ 6 drugs, and 46% in patients receiving > 6 drugs (p=0.271). In subgroup analysis regarding the diagnosis of the patients, there was no difference between subgroups.

Conclusion: In our study, the response rates and overall survival was comparable in patients receiving polypharmacy or not. The polypharmacy is indispensable in a number of old patients with comorbidites, and this situation would not hinder the physicians from treating those patients with the diagnosis of hematological maligancies, at least the indolent types.

Keywords: Polypharmacy, treatment, response, survival, hematology

ÖZET

Giriş: Hematolojik malignitelerde polifarmasi, literatür verileri çok az olan bir araştırma alanıdır. Bu hasta grubunda kişiselleştirilmiş tedavi yaklaşımlarının geliştirilmesi gelecekteki ihtiyaçlar açısından dikkate değerdir. Çalışmamızda farklı hematolojik maligniteleri olan yaşlı hastalarda polifarmasinin tedaviye yanıt ve sağkalım üzerine etkilerinin araştırılması amaçlandı.

Gereç ve yöntemler: Hematolojik malignite tanısı alan 60 yaş ve üzeri 91 hastanın verileri retrospektif olarak incelendi. Cinsiyet, yaş, evre, tedavi rejimleri, eşlik eden hastalıklar, kullanılan ilaçlar, radyoterapi öyküsü, hastaların tedaviye yanıtı ve tedavi toksisitesini içeren veriler incelendi.

Bulgular: Genel sağkalım olasılığı ≤ 6 ilaç alan hastalarda %36, > 6 ilaç alan hastalarda %46 idi (p=0,271). Hastaların tanılarına ilişkin alt grup analizinde alt gruplar arasında fark yoktu.

Sonuç: Çalışmamızda, polifarmasi alan ve almayan hastalarda yanıt oranları ve genel sağkalım benzer bulunmuştur. Komorbiditesi olan birçok yaşlı hastada polifarmasi vazgeçilmezdir ve bu durum hekimlerin hematolojik malignite tanısı alan hastaları, en azından düşük dereceli tiplerini tedavi etmelerine engel olmayacaktır.

Anahtar Kelimeler: Polifarmasi, tedavi, yanıt, sağkalım, hematoloji

INTRODUCTION

Multimorbidity, which is generally described as the coexistence of two or more chronic diseases, is usually encountered in the elderly population (1). The therapeutic approach is complicated for the patients with more than one chronic condition for both healthcare professionals and patients, leading to unfavorable health outcomes. Also, management of the patients with these comorbidities, especially the ones with hematological malignancies and using chemo-immunotherapeutic agents, constitutes a very difficult clinical point (1, 2).

Due to the multimorbidity, the use of multiple drugs, defined as polypharmacy, is prevalant in the elderly population. Polypharmacy was found to be associated with adverse outcomes, adverse drug reactions, prolonged hospitalization, and readmission (1, 3). Patients carry high risk due to anormal kidney or liver functions or lower lean body mass (3, 4). Although a threshold value of 5 or

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more drugs has been used commonly, the definition of polypharmacy must be reassigned in the light of new data (5, 7).

Polypharmacy in hematological malignancies is also a research area with very little literature data. Although the median age of diagnosis of several hematological malignancies such as acute myeloid leukemia (AML), multiple myeloma (MM), chronic lymphocytic leukemia (CLL) and myelodysplastic syndrome is around 70 years (8), the elderly patients and those with comorbidities are frequently excluded in clinical trials (9). So the development of personalized treatment approaches in this patient group is considerable for future needs.

In this study, we aimed to examine the effects of polypharmacy on treatment response, and survival in elderly patients with different hematological malignancies.

MATERIAL AND METHOD

The data of 91 patients, who were ≥ 60 years old, diagnosed and followed at Istanbul Training and Research Hospital, Department of Hematology, between October 2012 - July 2017 with the diagnosis of a hematological malignancy of either MM or CLL or lymphoma was analyzed retrospectively. The patients who did not receive cytotoxic treatment due to the hematologic malignancy and whose drug history could not be found were excluded from the study.

The data including gender, age, diagnosis, Eastern Cooperative Oncology Group (ECOG) score, stage, treatment regimens, concomitant diseases, drugs used, history of radiotherapy, treatment response of the patients and treatment toxicity were examined by obtaining the data of the relevant department. Laboratory tests were measurements of complete blood count, kidney and liver functions.

Lugano criteria for lymphoma (10), International Myeloma Working Group Uniform Response Criteria for multiple myeloma (11), International Workshop on Chronic Lymphocytic Leukemia for chronic lymphocytic leukemia (12) were utilized for response evaluation. The study protocol was approved by the local ethical committee.

Statistics

The SPSS 24 package program was utilized for statistical analysis. Data were described as numbers and percentages or median and range, when appropriate. x2 Fisher's exact test was used for analyzing categorical values, and Mann-Whitney U test for continuous values in patient groups. Kaplan-Meier test with log rank analysis was used for survival analysis. Statistical significance was accepted as $p < 0.05$ in all the analyses.

RESULTS

The median age of the patients was 70 (range, 60-85) years. Forty two (46%) patients were female and 49 (54%) were male. Table 1. shows the characteristics of the patients. Fourty (44%) patients were diagnosed with MM, 36 (40%) patients were diagnosed with lymphoma, and 15 (16%) patients were diagnosed with CLL. ECOG score was 0-1 in 84 (92%) patients, and 2-4 in 7 (8%) patients. Among the 91 patients, 19 patients (21%) had kidney failure, 2 patients (2%) had liver failure. The median number of drugs used by the patients was 6 (range, 1-14). The number

Table 1. Patients Characteristics.

Patients characteristics	N= 91	
Age, years, median (range)	70 (60-85)	
Gender, n (%)		
Female	42	46 %
Male	49	64 %
Diagnosis, n (%)		
Multiple myeloma	40	44 %
Lymphoma	36	40 %
Chronic Lymphocytic Leukemia	15	16 %
Treatment, n (%)		
Bortezomib-based	32	35.2 %
R-CHOP	22	24.2 %
R-CVP	5	5.5 %
ABVD	3	3.3 %
R-FC	3	3.3 %
Others	26	28.6 %
ECOG, n (%)		
0-2	84	92 %
2-4	7	8 %
Liver failure, n (%)		
Present	2	2.2 %
Absent	89	97.8 %
Kidney failure, n (%)		
Present	19	20.9 %
Absent	72	79.1 %
WBC, mm^3, median (range)	6925 (1.010-262.000)	
PLT, mm^3, median (range)	208.000 (8.000-635.000)	
HGB, gr/dl, median (range)	11.05 (5.7-16.7)	
Radiotherapy, n (%)		
Present	13	14.3 %
Absent	77	84.6 %
Number of drugs, median (range)	6 (1-14)	
Number of drugs, n (%)		
≤ 6	52	57.1 %
> 6	39	42.9 %
Drug toxicity, n (%)		
Present	23	25.3 %
Absent	66	72.5 %

ABVD: Bleomycin-Dacarbazine-Doxorubicin-Vinblastine; ECOG: Eastern Cooperative Oncology Group Performance Status; HGB: Hemoglobin; PLT: Platelets; R-CHOP: Rituximab-Cyclophosphamide-Doxorubicin-Vincristine-Prednisone; R-CVP: Rituximab-Cyclophosphamide-Vincristine-Prednisone; R-FC: Rituximab-Fludarabine-Cyclophosphamide.

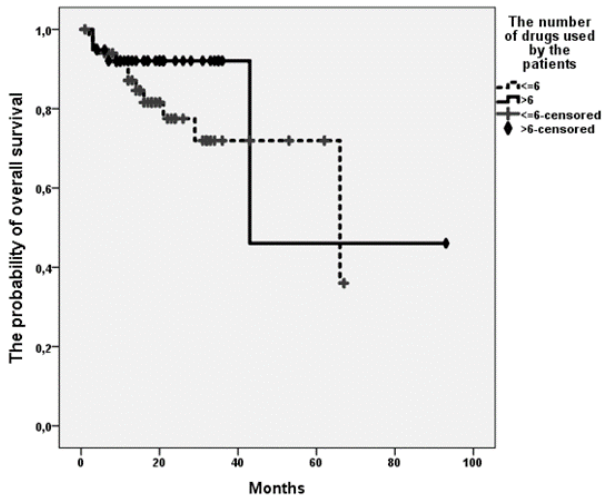

Figure 1: The probability of overall survival of at the end of follow-up in patients using concomitant drugs ≤ 6 and >6 (p=0.271).

of the patients using ≤ 6 drugs was 52 (57%), and the number of the patients using > 6 drugs was 39 (43%). The number of the patients treated with radiotherapy was 13 (14.3%). The drug-related signs of toxicity were detected in 23 (25.3%) patients. Fifteen (16.5%) patients died during follow-up period.

The most frequently used concomitant drugs were antihypertensive agents which were received by 46 patients (50%). Eighteen (19%) patients used diuretics, 75 (85.7%) patients used proton pump inhibitors (PPIs), 14 (15%) patients used angiotensin converting enzyme (ACE) inhibitors, 23 (25%) patients used beta-blockers, 18 (19%) patients used calcium channel blockers, 10 (11%) patients used angiotensin II receptor blockers, 28 (30.8%) patients used antiplatelet agents, 3 (3.3%) patients used statins, 23 (25.3%) patients used oral hypoglycemic drugs, 60 (65.9%) patients used allopurinol, 27 (29.7%) patients used bisphosphonates, 11 (12.1%) patients used selective serotonin reuptake inhibitor and 7 (7.7%) patients used alpha blockers (Table 2).

When the patients were divided into two groups according to the number of concomitant drugs as patients receiving ≤ 6 drugs and > 6 drugs, the groups were comparable in terms of the age and the gender. Although the diagnosis and the type of treatments differed in two patient groups, the response to the treatment was similar in two groups (Table 3).

Eleven of the patients receiving ≤ 6 drugs and 4 of the patients receiving >6 drugs died. The overall survival (OS) was 36% in patients receiving ≤ 6 drugs, and 46% in patients receiving > 6 drugs (p=0.271) (Figure 1). In subgroup analysis regarding the diagnosis of the patients, in MM patients; the probability of OS at the end of the follow-up was 37% in patients receiving ≤ 6 drugs and 97% in patients receiving > 6 drugs (p=0.08). In CLL patients; the probability of OS at the end of the follow-up was 77% in patients receiving ≤ 6 drugs and 100% in patients receiving > 6 drugs (p=0.325). In lymphoma patients; the probability of OS at the end of the follow-up was 61% in patients receiving ≤ 6 drugs and 81% in patients receiving > 6 drugs (p=0.964).

Table 2. The Concomitant Drugs Used by the Patients.

Concomitant drugs		
Antihypertensives, n (%)		
Present	46	50.5 %
absent	45	49.5 %
Diuretics, n (%)		
Present	18	19.8 %
Absent	73	80.2 %
ACE inhibitors, n (%)		
Present	14	15.4 %
Absent	77	84.6 %
Angiotensin II receptor blockers, n (%)		
Present	10	11 %
Absent	81	89 %
Beta-blockers, n (%)		
Present	23	25.3 %
Absent	68	74.7 %
Calcium channel blockers, n (%)		
Present	18	19.8 %
Absent	73	80.2 %
Alpha blockers, n (%)		
Present	7	7.7 %
Absent	84	92.3 %
Proton pump inhibitors, n (%)		
Present	78	85.7 %
Absent	13	14.3 %
Antiplatelet agents, n (%)		
Present	28	30.8 %
Absent	63	69.2 %
Statins, n (%)		
Present	3	3.3 %
Absent	88	96.7 %
Allopurinol, n (%)		
Present	60	65.9 %
Absent	31	34.1 %
Bisphosphonates, n (%)		
Present	27	29.7 %
Absent	64	70.3 %
Opioids, n (%)		
Present	1	1.1 %
Absent	90	98.9 %
Oral hypoglycemic drugs, n (%)		
Present	23 (25.3 %)	(25.3 %)
Absent	68 (74.7 %)	(74.7 %)
Serotonin selective reuptake inhibitors, n(%)		
Present	11	12.1 %
Absent	80	87.9 %

ACE: Angiotensin converting enzyme.

DISCUSSION

Due to the fact that polypharmacy is an important

Table 3. The Clinical Outcomes of the Patients According to the Number of Concomitant Drugs.

	No of drugs ≤ 6 (n= 52)	No of drugs >6 (n= 39)	p value
Age, years, median (min-max)	70 (60-84)	69 (60-85)	0.784*
Gender, n (%)			
Female	20 (38.5 %)	22 (56.4%)	0.096**
Male	32 (61.5 %	17 (43.6%)	
Diagnosis, n (%)			
MM	17 (32.7 %)	23 (59.1 %)	0.043**
CLL	10 (19.2 %)	5 (12.8 %)	
Lymphoma	25 (48.1 %)	11 (28.2 %)	
Treatment, n (%)			
Bortezomib-based	11 (21%)	21 (53.8%)	
R-CHOP	16 (30.7%)	6 (15.4%)	0.05**
R-CVP	4 (7.6%)	1 (2.5%)	
ABVD	2 (3.8%)	1 (2.5%)	
R-FC	0 (0%)	3(7.7%)	
Others	19 (36.9%)	7 (18.1%)	
Response to treatment, n (%)			
Present	36 (75 %)	27 (79.4 %)	0.792**
Absent	12 (25 %)	7 (20.6 %)	
OS, months, median, (min-max)	17 (1-67)	17 (3-93)	0.955*
The probability of OS at the end of follow-up, %	36 %	46 %	0.271**
The probability of OS at the end of follow-up, according to the diagnosis subtypes, %			
MM	37 %	95 %	0.080**
CLL	77 %	100 %	0.325**
Lymphoma	61 %	81 %	0.964**

MM: Multiple myeloma; CLL: Chronic lymhocytic leukemia; R-CHOP :Rituximab-Cyclophosphamide-Doxorubicin-Vincristine-Prednisone; ABVD :Bleomycin-Dacarbazine-Doxorubicin-Vinblastine; R-CVP: Rituximab-Cyclophosphamide-Vincristine-Prednisone; R-FC: Rituximab-Fludarabine-Cyclophosphamide; OS : Overall survival
* Mann-Whitney U test **x2 / Fisher's exact test

issue in old patients, studies evaluating the influence of polypharmacy in this patient group, especially the ones with the diagnosis of cancer and hematological malignancies, are substantially important. And the rate of polypharmacy is fairly high in elderly cancer patients (8, 13-15). In a study evaluating 117 elderly solid-cancer patients, the prevalence of polypharmacy (concurrent use of ≥5 medications) was found to be 80%. In addition, 41% of the patients used inappropriate medication which is also a common problem in elderly patients (13). In another study, where a comprehensive geriatric assessment was applied to elderly cancer patients for decision of treatment, the rate of polypharmacy (concurrent use of ≥5 mediactions) was nearly 66% (14). Similarly, in a study of 108 patients with hematological malignancies, 65% of patients were receiving ≥5 drugs (8). Differently, the use of polypharmacy (5 drugs of more) in chronic myeloid leukemia (CML) patients using imatinib was lower with a rate of 36.1% (15). As distinct from the previous studies, we employed concurrent use of > 6 medications as the polypharmacy which was determined according to the median number of drugs used by the patients in our study. This could be one of the the reasons of inferior prevalence of polypharmacy that was 42.8%, in our patient group.

The widespread use of polypharmacy in elderly patients brings into consideration the relationship of polypharmacy with response to the treatment and survival. In a study comprising old CML patients, response to treatment and survival did not differ whether the patients were exposed to polypharmacy or not (15). In contrast, it was found that increased number of medications at diagnosis (≥4 vs. ≤1) was associated with increased 30-day mortality and higher overall mortality in old AML patients (16). Similarly, in a study including relatively younger age patients who underwent allogeneic stem cell transplantation, polypharmacy was associated with inferior OS (17). In our study, the response rates and OS was comparable in patients receiving polypharmacy or not. Furthermore, OS was even higher in patients receiving >6 drugs. Our results can be explained by the inclusion of patients with the diagnosis of indolent nature of the types of the hematological diseases in this study. This is also encouraged by the similar results study

of containing patients with CML which is also an indolent type of hematological cancer.

Considering that, clinical studies based on hematological malignancies are carried out mostly on the young patients with a low comorbidity and old patients with comorbidities ages are excluded from clinical studies (18-20); this study contributes to the treatment approach of old patients who were diagnosed with hematological malignancies and treated with polypharmacy. However, the retrospective nature of the study and relatively small sample size were the limitations. The lack of data about the toxicity of the treatments was also a significant shortage of this study. Lastly, the subgroups of the hematological disease included in the study were limited.

CONCLUSION

Consequently, the polypharmacy is indispensable in a number of old patients with comorbidities, and this situation would not hinder the physicians from treating those patients with the diagnosis of hematological malignancies, at least the indolent types.

Additional information: This study was presented as a poster at the EHA 2023 congress.

Ethics Committee Approval: This study was approved by the Istanbul Research and Training Hospital Clinical Research Ethics Committee (Date:18/01/2019 and number: 1646). The experimental procedures were based on the Declaration of Helsinki and relevant institutional regulations.

Informed Consent: The study was conducted retrospectively.

Authorship Contributions: Idea/Concept: AK, İS, Design: -, Supervision: DK, ES, Data Collection or Processing: İS, CA, Analysis or Interpretation: DK, RE, Literature Search: AK, İS, Writing: AK, İS, Critical Review: RE, ES, References And Fundings: -, Materials: -.

Conflict of Interest: No conflict of interest was declared by the authors.

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