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Is classical Hodgkin lymphoma a different disease in the elderly? A single-center retrospective cohort study

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Abstract. – OBJECTIVE: Although the clinical features and treatment results of Hodgkin lymphoma (HL) in young adults are well known, it is thought that the disease may have different characteristics in elderly patients with HL, which constitutes almost 25% of the group. In this study, our aim is to evaluate the clinicopathological features, treatment outcomes, and survival of elderly classical Hodgkin lymphoma (CHL) patients.

PATIENTS AND METHODS: Patients aged 60 and over who were treated with a diagnosis of CHL were included in our retrospective cohort study. Patients under the age of 60, those with a diagnosis of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) were excluded from the study.

RESULTS: The median age of 51 patients in the study was 66 (60-76). Forty (78.4%) patients had at least one comorbid disease. The most common histological subtype was mixed cellular HL (n = 23, 45%) and 23 (45%) patients had B-symptoms. Thirty-two (62.8%) patients were in the advanced stage. The most preferred regimen in first-line treatment was doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) combination chemotherapy (n: 45; 88.2%). Forty-three (84.3%) patients were able to complete the initially-planned treatment. Complete response was achieved in 34 (66.7%) patients. During the median follow-up period of 45.2 months, 23 (42.6%) patients had died. The 5-year OS was 57.4%.

CONCLUSIONS: In conclusion, it was observed that the distribution of histological subtypes was different in elderly patients with CHL, B-symptoms were more common in elderly patients, and OS decreased with increasing age.

Key Words:
ABVD, B-sypmtoms, Chemotherapy, Elderly patients, Hodgkin lymphoma.

Introduction

Lymphomas are among the top ten most common cancers, and approximately 85,000 people are diagnosed with lymphoma annually in the United States. Hodgkin lymphoma (HL) accounts for 10% of all lymphomas[1]. While 90% of HLs are in the classical HL (CHL) subtype, the remaining cases have nodular lymphocyte-predominant HL (NLPHL) histology[2]. Although it varies according to the subtype, HL has a bimodal age distribution, in general. While the first peak is seen between the ages of 15-35, the second peak is seen after the age of 60[3].

The clinical features and treatment results of HL in young adults are well known. However, it is thought that the disease may have different characteristics in elderly patients with HL, which constitutes almost 25% of the group[4-7]. While HL-related 10-year overall survival (OS) is close to 80% in patients between the ages of 19-35, this rate may drop below 20% in patients over 65 years of age[8,9].

Localized radiotherapy (RT) applied after two or four cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) combination chemotherapy in early stage HL is accepted to be the standard treatment for young patients[10,11]. However, intensive treatment in elderly patients may cause unacceptable toxicities. Second-line treatments, such as high-dose chemotherapy and stem cell transplantation may not be suitable for elderly patients. Therefore, first-line treatment should be tried in elderly HL patients[12,13]. In the treatment of advanced-stage HL, it is possible to obtain satisfactory results in young patients with dose-intensive regimens, such as bleomy-

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cin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone (BEACOPP). However, even the BEACOPP regimen administered at reduced doses in elderly patients causes a very high rate of treatment-related mortality[12,14].

We aim to evaluate the clinicopathological features, treatment outcomes, and survival of elderly CHL patients in this study.

Patients and Methods

Patients

This retrospective cohort study was conducted by examining the data of patients treated with a diagnosis of CHL between 2004 and 2020 in our clinic. Ethics Committee approval was obtained before the study. Patients under the age of 60, those with a diagnosis of NLPHL, and those with missing file records were excluded from the study.

Among the patients treated in our center with the diagnosis of HL between 2004 and 2020, 51 patients over 60 years old with a diagnosis of CHL were included in the study. Clinical information of the patients was obtained through manual file records and electronic medical record system. Patients' demographic characteristics, comorbidities, HL diagnosis date, HL subtype, disease stage at diagnosis, chemotherapy start and end dates, chemotherapy response, receiving RT, treatment-related side effects, last control date, and survival status of the patients were recorded.

Lugano classification system was used for staging. Patients in stages 1 and 2 were defined as early stage, and patients in stages 3 and 4 were defined as advanced stage[15].

Diabetes mellitus, hypertension, coronary artery disease, chronic obstructive pulmonary disease, dementia, Parkinson's disease, rheumatological diseases requiring systemic treatment, and secondary malignancies were accepted as comorbid diseases.

The primary endpoint of the study was to demonstrate the treatment results of patients with advanced age CHL. The secondary endpoint was to demonstrate clinicopathological features and chemotherapy tolerance.

Statistical Analysis

The data were analyzed through SPSSS V23.0 (SPSS Inc., Armonk, NY, USA). The time from diagnosis of HL to death or last control date was defined as OS. Kaplan-Meier curve was used for survival analysis. The difference in survival between age groups and patients at different stages was compared using the log-rank test; p-value <0.05 was considered significant.

Results

The median age of the 51 patients included in the study was 66 (60-76). 29 (56.9%) of them were women. There were 39 (76.4%) patients between the ages of 60-69 and 22 (43.1%) patients over the age of 69. Forty (78.4%) patients had at least one comorbid disease.

When the histological subtypes were examined, it was seen that 23 (45.0%) patients were of the mixed cellular type, and 10 (19.6%) patients were in nodular sclerosing histology. While there were 19 (37.3%) patients with early-stage disease, 32 (62.8%) patients were in the advanced stage. Ten (19.6%) patients had extra-nodal involvement. There were 28 (54.9%) patients with HL without B-symptoms. All patient characteristics are shown in Table I.

Table I. Patient characteristics.

	N = 51	%
Medan age (year, min-max)	66 (60-76)	
Sex		
Male	29	56.9
Female	22	43.1
Histological subtype		
Mixed cellularity	23	45.0
Nodular sclerosis	10	19.6
Lymphocyte-rich	5	15.6
Lymphocyte-depleted Undefined	1	1.9
	12	23.5
Stage		
I	6	11.8
II	13	25.5
III	13	25.5
IV	19	37.3
B- symptoms		
Yes	23	45.0
No	28	54.9
Comorbidity		
Yes	40	78.4
No	11	21.6
Extranodal involvement		
Yes	10	19.6
No	41	80.3
Bulky mass (> 7 cm)		
Yes	7	13.8
No	44	86.2

All patients with early and advanced HL received at least one line of therapy. The most preferred regimen in the first-line treatment was ABVD combination chemotherapy (n: 45; 88.2%) and a median of four (1-8) cycles of ABVD was applied to these patients. Three (5.9%) patients could not receive bleomycin due to interstitial lung disease, therefore, doxorubicin, vinblastine, dacarbazine (AVD) combination was administered.

Bendamustine/brentuximab combination was given to one (2%) patient due to heart failure, one (2%) patient received doxorubicin, bleomycin, dacarbazine (ABD) due to neuropathy, and another patient received gemcitabine, cyclophosphamide, vincristine, dexamethasone (GCVP) for coronary artery disease. In the first-line treatment, 12 (23.6%) patients received RT in addition to chemotherapy. As a result of the first-line treatment; the complete response was achieved in 34 (66.7%) patients, partial response in 8 (15.6%) patients. 9 (17.6%) patients were resistant to treatment.

Treatment-related death occurred in one (2%) patient during first-line chemotherapy, and one (2%) patient refused treatment. Dose reduction was performed in 15 (29.4%) patients due to treatment-related toxicity and intolerance. Forty-three (84.3%) patients were able to complete the initially planned treatment.

During the median follow-up period of 45.2 months, 23 (42.6%) patients had died. The median estimated OS was 123.8 months (Std. Error: 56.145; 95% CI: 13.78-233.87), and the 5-year OS was 57.4%. While 5-year OS was 62.2% in the early stage patients, this rate was 54.4% in the advanced stage patients. This difference was not statistically significant (Figure 1; *p*: 0.242).

When OS is compared between age groups; 5-year OS was 60.8% in the patients between the ages of 60-69, this rate was 42.9% in patients 70 years and older (Figure 2; *p*: 0.44).

Five-year OS was 61.9% in those without B symptoms and 51.1% in those with B-symptoms (*p*: 0.451).

Discussion

The primary endpoint of our study was to demonstrate the treatment results of elderly patients with CHL. It was observed that the most preferred first-line treatment in our patients was ABVD regimen. Approximately 30% of them had dose reduction and 84% completed the planned treatment. With the treatments, 5-year OS was 57.4% in all cohort, 62% in the early stage and 54% in the advanced stage.

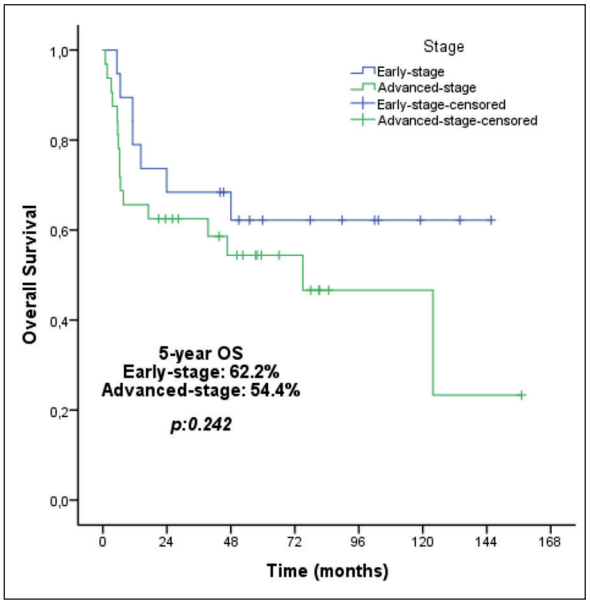

Figure 1. Comparison of overall survival according to the stages.

In previous studies evaluating the clinical characteristics of elderly CHL patients, the histological subtype distribution shows differenc-

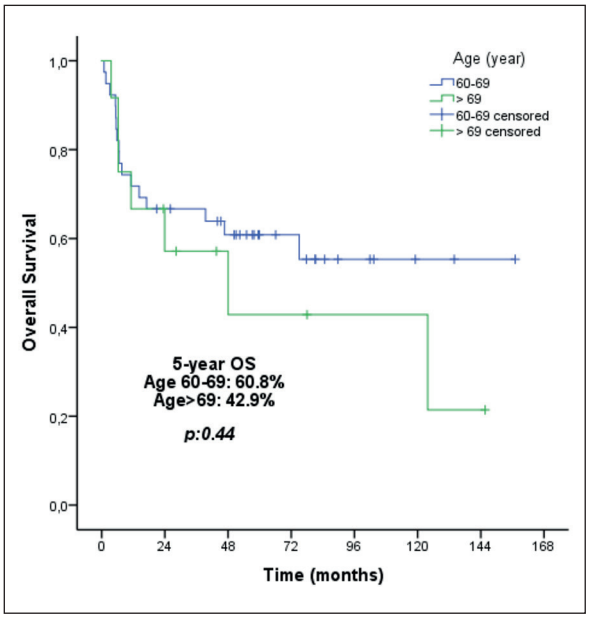

Figure 2. Comparison of overall survival according to the age groups.

es. Polish Lymphoma Group, German Hodgkin Study Group[6,7], and Evens et al[8] from the US reported that nodular sclerosing HL (NSHL) was the most common type of CHL. On the other hand, in a study conducted in the Netherlands[16], and in the Swedish Group's trial[17], it was reported that mixed cellular HL (MCHL) was seen most frequently. Although it is known that MCHL is more common in developing countries, different results can be seen even in studies conducted in the same population[7,16,18,19]. In our study, 45% of our patients had MC histology. The common point in all studies is: the rate of MC subtype is higher in patients with advanced age CHL when compared to younger patients[6-8, 16-17].

Although it has historical importance in HL, one of the parameters is still valid in determining prognosis is B-symptoms. In patients with HL in the geriatric population, B-symptoms are observed at rates varying between 32% and 54%[7,8,16,18]. In almost all previous studies, it is mentioned that there is a higher rate of B-symptoms in elderly patients compared to young HL patients[7,8,17,18].This is seen as one of the reasons why OS is worse in elderly patients compared to young patients. In our study, 45% of our patients had B-symptoms, while 5-year OS was found as 51% in patients with B-symptoms and 61.9% in those without B-symptoms. Although this difference did not appear to be statistically significant due to the small number of patients, it suggested that the B-symptoms still may have prognostic significance.

Many studies have shown that the prognosis of HL is worse in the geriatric population. In studies conducted so far, 5-year OS has been reported to be between 38% and 90% in elderly patients with HL. The presence of OS in such a wide range is due to the heterogenity of patient characteristics and the difference in the treatments applied.

One of the oldest studies conducted on elderly patients with HL is the study of Guinee et al[16]. Similar to our study, half of 136 patients over the age of 60 in this study had MC histology, while fewer patients had comorbidity (24%). The 5-year OS rates obtained in this study were very similar to our results in both patient groups aged 60-70 years (60%) and those aged 70-80 years (40%).

In the study of Evens et al[8] including 95 patients with CHL, over the age of 60 in the US, 5-year OS was found to be 58% in the whole geriatric population, in which 79% in the early stage and 46% in the advanced stage[8]. Unlike our patient group, the predominantly nodular sclerosing histology of the patients in that study provided better OS results in the early stage.

In a study of 182 patients in Sweden, 5-year OS was reported to be significantly lower in patients over 60 years old (33%) compared to those under 60 years old (86%)[18]. While RT was given to only 20% of the elderly patients in this study, chemotherapy was administered less than 40% of the planned dose in 54% of the patients. At the same time, the regimens which are not used in daily practice such as 'vincristine, procarbazine, prednisolone (OPP)', 'mechlorethamine, vincristine, procarbazine, prednisolone (MOPP)', 'chlorambucil, vinblastine, procarbazine, prednisolone (ChlVPP)' and, 'vincristine, prednisolone, etoposide (OPEC)' were preferred by clinicians in the study. Compared to this study, the higher rate of patients in our study who can receive planned treatment enabled us to obtain better OS results.

One of the comprehensive studies conducted with elderly patients with HL was published by the Polish Lymphoma Group in 2018[6]. Although 350 patients over the age of 50 were included in this study, 57% of the patients were younger than 60 years old. RT could be applied to 90% of the patients. All patients between the ages of 50-60 in the early-stage and 85% of the advanced-stage patients were able to complete the planned treatment including chemotherapy. Thus, the 3-year OS was achieved as 90% in the early stage and 81% in the advanced stage. The lower median age of the patients in this study compared to the patients in our study enabled more patients to receive RT. Therefore, a higher proportion of patients completed the planned chemotherapy. This caused OS to be better in both early and advanced stage patients in this study when compared to our study.

In the highly comprehensive series of the German Hodgkin Study Group, which included 4251 patients, 372 (8.2%) of the patients were reported to be over the age of 60[7]. In this study, the rate of completing the treatment at the planned dose in the geriatric patient group was reported as 75%, and the 5-year OS was 65%. In another German study[19] involving 117 patients with early stage HL, the tolerance of the ABVD regimen was evaluated. The four cycles ABVD combination regimen planned in this study could not be completed in 14% of the patients due to toxicity and, 5-year OS has been reported as 75%[19]. While the clinical features of the patients in these two German studies, histological subtypes of HL, and the

rate of B symptoms were similar to our study, the OS obtained appears to be slightly better compared to our study. It was thought that the reason for this difference in OS was that patients in the German population could complete the targeted treatment at a higher rate.

Limitations

The limitations of our study were the small number of patients and its retrospective nature. One of the most important limitations of retrospective studies is that they allow access to a limited number of data. This prevented us from revealing the treatment-related toxicities in detail and the performance scoring that would enable us to predict the treatment tolerance of patients, especially in the geriatric group. However, our study is one of the rare studies investigating the clinical features and treatment results of patients with CHL in the geriatric population outside of Europe and the US.

Conclusions

In summary, it was observed that the distribution of histological subtypes was different in elderly patients with CHL compared to the younger age group, B-symptoms were more common in elderly patients, and OS decreased with increasing age in our study. The use of fragility indices that will evaluate the performance status of geriatric patients in detail before treatment will allow us to predict treatment tolerance, and more patients can complete the planned treatment and increase the survival.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

HSU Dr. A.Y. Ankara Oncology Training and Research Hospital Ethics Committee Approval was obtained before the study.

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