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REWIEV ARTICLE

Specific aspects of prognosis and treatment of elderly patients with large B-cell lymphoma

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Summary

Large B-cell lymphoma (LBCL) is the most common type of non-Hodgkin lymphoma in the general population, constituting 40-50% of all NHL cases, and over 60% of lymphoma cases in the population of patients over 65 years. Given their increasing life expectancy, the prevalence of this lymphoma type is expected to grow in the upcoming years. Treating these patients is a significant challenge due to numerous factors that complicate the treatment and worsen the outcome of the disease. Elderly patients often have comorbid conditions, weakened organ function, altered drug metabolism, and reduced hematopoietic capacity for bone marrow recovery, which makes them less tolerant to chemotherapy. A poorer prognosis is attributed to a higher frequency of the non-GCB subtype and histologically unfavorable types of LBCL, such as EBV-positive LBCL, High-grade B-cell lymphoma (HGBL), and plasmablastic lymphoma, as well as extranodal localizations associated with worse outcomes. Treating elderly patients is complex because they represent a highly heterogeneous population with significant variations in health status, comorbid conditions, and expected lifespans. Therefore, when it comes to elderly patients, a comprehensive geriatric assessment is necessary, including the determination of a comorbidity index to differentiate between those in good general condition (fit), those in poor general condition (frail), and those who are in between. The treatment can be aimed at recovery, life extension, or symptom control. The standard therapy for elderly patients with good general condition and advanced disease is R-CHOP, while for patients with comorbidities and poor general condition, reduced protocols with or without anthracyclines are considered. Previously, elderly patients with relapsed or refractory LBCL faced a very poor prognosis due to limited treatment options. However, the treatment of elderly patients with R/R LBCL has improved in recent years due to the introduction of new drugs (polatuzumab, tafasitamab, bispecific antibodies, and CAR-T cells) that can be used in older individuals.

Key words: large B cell lymphoma, elderly, prognosis, therapy

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INTRODUCTION

Non-Hodgkin lymphoma (NHL) is the eighth most common malignancy in both sexes (1). Large B-cell lymphoma (LBCL) is the most prevalent type of non-Hodgkin lymphoma (NHL), accounting for 40-50% of all NHL cases and over 60% of lymphoma cases in the population of patients over 65 years (1). Its incidence gradually increases with age, and one-third of patients are older than 75 years (2). The median age of patients at the time of diagnosis is 67 years (1). Considering the increasing life expectancy, it is expected that the number of elderly patients with NHL will continue to rise in the years to come. Although the population over 65 years constitutes 13% of the total population, this group sees 25% to 35% of new lymphoma cases (2). According to the data obtained from the Institute of Public Health of Serbia "Milan Jovanovic Batut", the incidence rate of LBCL in the Republic of Serbia in 2021 was 6.9 for males and 5.7 for females, showing an increasing trend among the elderly (3). In the population over 75 years, it was 20.1 for males and 13.4 for females (3). Lymphomas in the elderly deserve special attention, considering the numerous factors that complicate the treatment and affect the outcome of the disease.

SPECIFIC NATURE OF ELDERLY PATIENTS

Large B-cell lymphoma (LBCL) in elderly patients deserves special attention due to numerous factors that complicate the treatment and affect the outcome of the disease (Table 1). The outcome of LBCL in patients aged ≥65 years is significantly worse than in patients under the age of 55, with a 5-year relative survival rate of 55.1% and 79.7%, respectively (4). The aging process alters drug tolerance, absorption, diffusion, and metabolism, thus affecting the response to therapy (5). Most chemotherapy protocols lead to myelosuppression, and in elderly patients, the recovery of bone marrow function takes longer (2). Elderly patients often have heart conditions, necessitating an assessment of cardiac function, especially when anthracycline-based protocols are employed. Aging increases the likelihood of dysfunction in various organs, often contributed to by the frequent use of non-cytostatic medications for controlling chronic diseases.

Table 1. Factors influencing the treatment of elderly lymphoma patients

Characteristics of elderly patients
Biological age diversity
Age-related stereotypes
Misconceptions among patients and healthcare professionals about the causes of the disease, disease progression, and treatment
A limited number of studies designed exclusively for elderly patients
Comorbid conditions in the elderly population
Decline in organ function
Age-related immune system weakening
Changes in drug pharmacokinetics associated with aging

Dysfunction pertains to the kidneys, liver, heart, and bone marrow (5). Changes in organ function affect treatment tolerance and the ability to apply protocols designed for lymphoma eradication, thus impacting the aim of the treatment (5). For example, in patients with renal insufficiency, cisplatin cannot be administered, adequate doses of doxorubicin cannot be given to patients with heart failure, and the presence of peripheral neuropathy prevents the use of vincristine at full doses. Age-related reduction in bone marrow reserves leads to marked myelosuppression and a higher incidence of infectious complications. Therefore, it is not surprising that advanced age is an independent prognostic factor for predicting the frequency of hospitalizations and febrile neutropenia.

Elderly patients may have poor general health, associated illnesses, and often take a large number of medications. The prevalence of severe comorbid conditions occurs in patients aged 60 to 69 and those over 70 years is 43% and 61%, respectively, and even more than 85% of patients over 80 years. In younger patients, comorbidity is present in only 20% of those affected (6). The most common comorbidities are other malignancies, diabetes, osteoporosis, arthritis, cardiovascular or pulmonary diseases, renal dysfunction, depression, Alzheimer's disease, and others. Patients with comorbidities are at a high risk of toxic treatment effects and a higher risk of mortality (6). Therefore, a comprehensive geriatric assessment (The Comprehensive Geriatric Assessment - CGA) is necessary for all elderly patients with lymphoma, along with an assessment of the comorbidity index (Charlson Index and Cumulative Illness Rating Scale - CIRS) (7). Geriatric assessment is a multidimensional diagnostic tool that evaluates nutritional status, cognitive abilities, and comorbidities, and its results help in defining the optimal therapeutic approach for elderly lymphoma patients (8).

Elderly patients may have misconceptions about the cause, progression, and treatment of the disease (2). On the other hand, diagnosing lymphoma in older individuals is associated with numerous end-of-life questions and a discussion about the necessity of curative treatment due to their age.

CLASSIFICATION OF LBCL AND THE FREQUENCY OF SUBTYPES AND ENTITIES IN OLDER PATIENTS

Based on the analysis of gene expression profiling (GEP), three types of LBCL have been identified. These include the germinal center B-cell (GCB)-like subtype, resembling the GEP of normal GCBs, the activated B-cell (ABC)-like subtype, resembling normal ABCs, and unclassifiable disease in the remaining 10-15% of samples (9). The distribution of these subtypes changes with age, with the highest frequency of the non-GCB subtype which has significantly poorer outcomes compared to GCB disease in the elderly patients (9). Patients with the GCB subtype

are, on average, 8 years younger than those with the non-GCB subtype (10).

LBCL is characterized by significant histological and clinical heterogeneity. According to the latest WHO-HEM5 classification in 2022, LBCL includes 18 different subtypes and entities. Some of them were categorized for the first time as separate entities in this classification (11). All subtypes of LBCL occur in older patients, but there is a higher incidence of histologically unfavorable types of LBCL, such as EBV-positive LBCL, high grade B cell lymphoma (HGBL), plasmablastic lymphoma, and extranodal localizations associated with a poorer prognosis, such as lymphomas of immune-privileged sites (brain, testes, vitreoretinal lymphomas), primary effusion lymphoma without HIV infection or adrenal lymphomas (12,13). One of the new LBCL subtypes added to the WHO-HAEM5 classification in 2022 is the so-called Fluid overload-associated large B-cell lymphoma. It most commonly occurs in elderly individuals who are not immunocompromised. Although it comes with exclusive localization in body cavities, it should be distinguished from primary effusion lymphoma which has a completely different genetic profile (11). It occurs in individuals with conditions characterized by fluid overload, such as heart and kidney failure, liver cirrhosis or protein-losing enteropathy. However, unlike PEL and most other lymphomas in older people, the prognosis of these lymphomas is quite favorable (11). EBV-positive LBCL is an aggressive lymphoma which occurs more frequently in the elderly and lacks distinctive morphology or immunophenotype. Diagnosis necessitates the demonstration of EBV-encoded small RNA through in situ hybridization (14). The median age at diagnosis is 71, with 70% of patients having extranodal disease. EBV-positive LBCL shows inferior survival across all IPI categories, with a median overall survival (OS) of 24 months (15).

HGBL represents a newly defined category of aggressive lymphomas encompassing DHL, as well as various prior cases of Burkitt-like or aggressive immunoblastic variants. These lymphomas exhibit poorer outcomes with R-CHOP immunochemotherapy and an increased risk of central nervous system (CNS) invasion (16). Advanced age correlates with a higher prevalence of high-risk molecular LBCL subtypes and MYC rearrangement (17).

PROGNOSTIC PARAMETERS IN LBCL

The significance of age as a prognostic parameter was recognized very early, and it is not surprising that it is one of the parameters contained in all clinical scores currently used in clinical practice. The basic and oldest prognostic score for LBCL is the International Prognostic Index (IPI) (18). It served as the basis for defining aa-IPI, the revised International Prognostic Index (R-IPI), and the International Prognostic Index for the elderly (E-IPI). However, in recent years, the NCCN-IPI has been increasingly used, developed in the era of rituximab, which distinguishes four different prognostic groups with four-year survival ranging from 33% to 96%. (19). The prognostic power of NCCN-IPI increases when the CCI is added to the prognosis assessment, especially in the elderly population (20).

However, when it comes to age, it is essential to define the boundary for defining "old age." There are conflicting views on what age constitutes the threshold for defining "elderly" patients with DBKL. The International Prognostic Index (IPI) classifies patients above 60 years of age as elderly patients because it is based on the results of studies in which there were very few patients over 80 years of age (18). Given that the median age of newly diagnosed DBKL patients exceeds 65 years, the age limit of 60 years is certainly not adequate for defining elderly patients. The age limit of 75 years should be the threshold included in the definition of "elderly patients" because the outcome in the group over 75 years is significantly worse than in the group of patients under 75 years (21). The National Cancer Network (NCCN) classifies elderly patients into "young elderly" aged 65 to 75 years, "elderly" aged 76 to 85 years, and "very elderly" patients over 85 years (19).

In recent years, the prognostic significance of numerous clinical, laboratory, and histological parameters has been analyzed, and many novel markers with potential prognostic significance in the elderly patients with LBCL have been identified (22). Laboratory parameters, such as the ratio of absolute lymphocyte count (ALC), absolute monocyte count (AMC), and histopathological characteristics, i.e., BCL2, surviving, XIAP, MYC, and CD5 expression, showed a significant impact on clinical outcomes (23-25). They were used to develop new models with an improved ability to discriminate prognosis.

ASSESSMENT OF THE ELDERLY PATIENTS' SUITABILITY FOR THE TREATMENT

The population of elderly patients is a heterogeneous group, since the physiological age does not always correspond to the patient's condition. Traditional measures like the Karnofsky index or ECOG (Eastern Cooperative Oncology Group) performance status are not precise enough to determine the treatment goal according to them, i.e., to avoid the risk of under- or overtreatment. ESMO guidelines recommend the use of geriatric assessment in patients with lymphoma (26). Comprehensive geriatric assessment (CGA) in patients with DBCL enables the prediction of tolerance to chemotherapy and mortality, independent of the performance status (27). However, the implementation of CGA is sometimes hardly possible due to the time and resources required for its implementation. The Fondazione Italiana Lymphomi

(FIL) has validated the simplified geriatric assessment (sGA) for people over 64 years old, whose score includes age (≥80/<80 age), CIRS-G (Cumulative Illness Rating Scale for Geriatrics), ADL (activities of daily living) and IADL (instrumental activities of daily living) (28). Based on the geriatric assessment, patients can be divided into three groups: patients in good general condition (fit), patients in poor general condition (frail) and those who are between these two groups (unfit) (28). One of the models for predicting the tolerability of therapy is a model developed by the Japanese group for the treatment of lymphoma that includes advanced age (>75 years), hypoalbuminemia (<3.7 g/dL), and a high Charlson Comorbidity Index score (≥3) (29). However, even simple gait speed tests can accurately identify frailty and predict the outcomes independent of the performance status as well as grip strength (every 5-kg decrease in grip strength was associated with worse survival) (30).

FIRST LINE THERAPY

Fit patients

The treatment goal for fit elderly patients <80 years is to cure them, using standard protocols, which has been the R-CHOP regimen for the last 20 years (31). In the population of elderly patients, complete remission in the era of rituximab is achieved in 60 to 80% of patients (31). However, the use of full doses of drugs within this protocol requires careful monitoring of the patient due to the possibility of side effects, primarily a regular check of cardiac function to minimize cardiotoxicity. A routine evaluation of the ejection fraction by echocardiography or by MUGA scan is suggested before therapy as well as after 4 cycles of anthracyclines with possibly more frequent monitoring if necessary (32). The International Society for Geriatric Oncology (SIOG) has given recommendations for the reduction of cardiotoxicity and the use of anthracyclines in the elderly in routine clinical practice (32).

The gold standard in the first line of treatment for fit elderly patients is 6 cycles of the R-CHOP protocol (33). Adding two more cycles or intense dose administration on 14 days did not improve treatment results but it increased toxicity (21.34). Shortening the treatment to 3 cycles of the R-CHOP protocol with consolidative radiation therapy (RT) in early stage DBCL showed identical survival outcome as full-course R-CHOP (≥6 cycles) and RT recipients experienced less acute toxicity (35.36). Also, a study of 592 patients showed the non-inferiority of the four-cycle regimen in comparison of six cycles of R-CHOP, but with relevant reduction of toxic effects (37).

The dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) combination has been employed in patients with high grade LBCL, even those over the age of 80. However, no advantage of using DA-EPOCH-R in >65 years has been shown (38) and the treatment in this group of patients remains a significant clinical challenge.

Attempts to improve the treatment outcome compared to the application of the R-CHOP protocol by using new biological agents, especially in non-GCB, did not show an advantage. Polatuzumab is the first drug that improved the results of the treatment of patients with DBKL in the first line of treatment compared to R-CHOP. In the POLARIX study, it was shown that patients treated with the pola-R-CHP protocol had a longer two-year PFS compared to the group of patients treated with the R-CHOP protocol (with equal OS), while patients over 60 years of age, those with non-GCB type, "double" expressors, and patients with high IPI had the greatest benefit (39). In a phase II study, it was shown that chemotherapy-free IR2 (ibrutinib+rituksimab+lenalidomid) regimen in patients 75 years or older with de novo diffuse large B-cell was clinically effective and safe (40). A phase 2 trial, known as REAL07, which evaluated the safety and effectiveness of lenalidomide in combination with standard doses of R-CHOP21 for elderly fit patients with untreated LBCL has been shown to be both effective and safe, with a high rate of overall response and manageable side effects (41). The ongoing front-MIND phase III trial aims to compare the efficacy and safety of tafasitamab-lenalidomide plus R-CHOP versus R-CHOP alone in newly diagnosed LBCL patients aged 18-80 years, with high-intermediate or high-risk disease (42).

A new direction in treatment is being introduced by a group from MD Anderson under the so-called smart start study principle, which is based on the initial application of 2 cycles of a biological agent (RLI: rituximab, lenalidomide, ibrutinib), followed by the application of standard chemotherapy (R-CHOP or REPOCH) in non-GCB DBCL aged 29-83 year (43). The results are promising with 100% ORR and a 2-year PFS of 91 % (43).

Frail and unfit patients

Frail/unfit patients show a very poor tolerance to therapy and therefore require protocols with reduced doses **(Table 2)** or the application of palliative non-anthracycline protocols which significantly affects the outcome of the treatment. However, it should be acknowledged that some elderly patients show a poor performance status due to lymphoma itself. In such situations, introductory therapy can be started to improve the patient's functional condition. The German lymphoma study group suggests that in patients with an ECOG score of 2 or more, prednisone should be administered for 7 days or 1 mg of vincristine before the first cycle of therapy (44). If the patient's condition improves, the goal of the therapy can be modified. According to the ASCO guidelines, prophylactic white blood cell growth factors can reduce the risk of potentially life-threatening neutropenic infections,

and should be considered for patients aged 65 and over who receive immunochemotherapy for LBCL, as the risk of febrile neutropenia in this group is up to 3% (45). In the prospectic B-R-ENDA clinical study it was shown that the results of treatment with BR in elderly or frail aggressive B-cell lymphoma patients are similar with results received after the treatment with R-CHOP. In this study progression-free survival (PFS) and overall survival (OS) at 2 years were 45% and 46% for the patients age >80, as well 32% (13%-51%) and 37% (17%-57%) for frail patients aged 64–80, respectively (46).

In the treatment of this group of patients, a "chemo-free" approach, based on new antibodies and small molecules has been analyzed. The combination Rituximab - Lenalidomide was tested in phase II of the ReRi study with promising results: the ORR is 41%, while the 11-year OS is 69% (47). In phase I/II, as the first line of therapy in those >80 years or >60 years of age with comorbidities, it is being tested bispecific antibody mosunetuzumab with an ORR of 56% (48). The phase II study with epcoritamab alone or in combination with lenalidomide as the first-line treatment in elderly LBCL patients who are considered anthracycline ineligible (ClinicalTrials.gov Identifier: NCT05660967) is announced.

Treatment of very elderly patients (over 80 years old)

The main cause of death in patients over 80 years of age was lymphoma, which shows that the main goal for them should also be reaching a cure (33). Considering results of clinical studies R-mini-CHOP represents a good balance between efficiency and safety in very elderly patients with DBKL (33, 49-50). In a study by the French lymphoma

Table 2. Studies with reduced chemotherapy protocols or protocols adapted for elderly patients with DBCL

Study	No of patients	Age (years)	Regimen	Relative dose intensity	CR(%)	OS(%)	EFS/PFS
Zinzani **(56)** (prospective)	350	69(60-87)	VNCOP-B	NA	60-69: 61 70-79: 59	5-god. 53% 51%	
Hainsworth 2010 (retrospective) **(57)**	51	78	R-CNOP/R-CVP	NA	NA	**5-year** 72%	**2-year PFS 71%**
Peyrade **(58)** (prospective)	149	83(80-95)	R-miniCHOP	Doxorubicine 50%, cycklophosphamide 53%	63%	2-god:59%	2-god:47%
Corazzelli, 2011 **(59)** (prospective)	41	73 (62-78)	R COMP/14 days	88,6%	68%	**67%**	4 year DFS 72%
Hasselblom (retrospective) **(49)**	70	>80	Pre-R: 40 Posle-R:30	86%		3-god:17% 3-god:41%	3-god:17% 3-god:41%
Spina,2012 **(60)** (prospective)	100	75 (70-89)	R-CHOP/ CHOP	Fit: 100% Frail: 75% Unfit: 50%	70-80: 83% >80:80%	5- year (70-80):54%	5- year (70-80):67%
Olivieri,2012 **(61)** (prospective)	91	74(65-92)	R-CHOP ili R-CDOP ili miniCHOP	Fit: R-CHOP 100% Frail: R-CDOP: NPLD 50%, doxorubicine 50%	81% 64% 50%	5 year:46%	5- year:31%
Gimeno, 2011 **(62)** (prospective)	35	76(61-88)	RCMyOP	NPLD: 50% Vincristine: 24% Th delay: 8%	69%	2- year:70%	2- year:58% PFS
Fields, 2014 (63) (prospective)	62	77 (52-90)	R GCVP	Gemcitabine/Cyclophosphamide/ vincristine (75% dose)	39%	2 years OS 55,8%	2 year PFS 49,8%
Peyrade, 2017 (64)	120	>80	O+miniCHOP	1000 mg ofatumumab, 25 mg/m2 s doxorubicin, 400 mg/m2 cyclophosphamide, and 1 mg of intravenous vincristine, on day 1 of each cycle; and 40 mg/m2 of prednisone on days 1–5.		2-year 64.7%	
Park et al 2019 Multicentre, single arm **(65)**	53	(≥75y: 21) Med age 73	Dose-reduced R-CHOP 21	cyclophosphamide 600 mg/m2, doxorubicin 30 mg/m2, vincristine 1 mg, prednisone 40 mg/day) 6–8 cycles	64.1 %	3y: 62.7 %	3y EFS: 45.7 % 7.5 %
Merli et al 2020 (multicentric single arm) **(51)**	33	82 (62-89)	O+ miniCHOP	IPI≥3: 64% Cardiac comorbidity grade 1-2:54%	CRR 42%	2-years 68%	2-years 49%

group, which included 150 patients with DBKL over 80 years of age, it was shown that the reduced R-CHOP (R-miniCHOP) protocol has a 2-year PFS of 47% and 2-year OS of 59% (50). The only parameter that had a significant impact on survival in the multivariate analysis was the albumin level (≤35g/L), which indicates the great importance of nutritional status in these patients. In this study, lymphoma was the main cause of death, which shows that recovery should be the main goal. The results of the treatment of elderly patients using obinutozumab with mini CHOP in the LYSA study showed slightly better results than with R-miniCHOP as the 2-year OS is 64.7% (51). Considering the findings derived from the POLARIX research (39), a current study (ClinicalTrials.gov Identifier: NCT04332822.) conducted by the Nordic Group is in progress, wherein the integration of polatuzumab into the RminiCHOP protocol is being explored for patients aged 80 years and above or those who are above 75 and frail.

Treatment of patients when anthracyclines are contraindicated

According to ESMO recommendations, when the use of anthracyclines is contraindicated, it is suggested to replace doxorubicin with gemcitabine or etoposide (32). In a study by the British Columbia group, doxorubicin was replaced by etoposide, but the 5-year survival was 49%, which is shorter than the survival achieved with the R-CHOP protocol (52). The number of CRs was lower and involved less cardiotoxicity. An Italian phase II study evaluated the activity and safety of non-pegylated liposomal doxorubicin administered instead of doxorubicin within the R-CHOP protocol (R-COMP) (53). In this study, 3-year OS and PFS were 72% and 69%, respectively, with cardiotoxicity in 21% of patients. The results of a similar large and recently published Italian study showed that R-COMP had curative potential in elderly patients as three-year progression-free survival (PFS) was similar between R-CHOP and R-COMP (70% and 64%) and 3-year overall survival was 77%, and 71 (54). The risk of congestive heart failure associated with anthracyclines may also be reduced with the use of dexrazoxane, an iron chelator which is currently approved only for breast cancer (55).

TREATMENT OF ELDERLY PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B CELL LYMPHOMA

Despite new treatment strategies, a significant percentage of LBCL patients, around 30-40%, relapse or are refractory, i.e., they cannot achieve remission with the first-line treatment. The prognosis is particularly poor for primary and secondary refractory LBCL with an estimated median survival of only 5-7 months (66).

Intensive salvage chemotherapy followed by autologous stem cell transplantation (ASCT) is the standard second-line approach with curative potential and durable response with a 3-year progression free survival (PFS) achieved in 30% to 40% of patients after transplantation (4). Although almost half of relapsed/refractory (R/R) LBCL patients respond to platinum-based regimens, only 13% of patients who are scheduled for and receive salvage treatment eventually undergo ASCT (67). The choice of optimal treatment in elderly patients with R/R LBCL is particularly challenging and delicate, as only a minority are suitable for this traditional approach. There is paucity of data on the efficacy and safety of ASCT in the elderly as there are no clinical trials in this setting. Retrospective analysis of 484 patients with R/R LBCL, aged 60 years or over, who received ASCT identified in the Japan Society for Hematopoietic Cell Transplantation database, found that overall non-relapse mortality did not significantly differ among the three age groups: ages 60 to 64, 65 to 69, and 70 years or over. They concluded that older age alone should not be a contraindication for ASCT (68). A careful assessment of frailty, functional status, and comorbidities using CGA may help in therapy choices (69, 70, 71).

With recent new drug approvals, treatment options for patients with R/R LBCL with potential to cure have expanded. Anti-CD19 chimeric antigen receptor (CAR) T-cells therapy emerged as the standard of care in primary refractory LBCL and its early relapse (<12 months) and is the treatment of choice in third line and subsequent therapy if not previously given (4). Axicabtagene clioleucel (axi-cel), tisagenlecleucel (tisa-cel) and lisocaptagene miraleucel (liso-cel) are currently approved with reported high rates of initial response (CRR 40-54% and ORR 52-82%) as well as durable (>18 months) complete remissions in about a third of patients enrolled in ZUMA-1, JULIET and TRANSCEND NHL 001 registration trials (72, 73, 74). Although there are no prospective studies that have directly compared different CAR-T cell products, reported outcomes as well as associated substantial toxicity including cytokine release syndrome (CRS) and immune effectors cell-associated neurotoxicity syndrome (ICANS) are similar. In a matched control multicenter cohort study comparing 41 elderly (≥70 years) R/R LBCL patients and 41 younger patients who underwent CAT-T cell therapy with similar ECOG performance status and serum lactate dehydrogenase level, no differences in the incidence of grade ≥3 CRS (P=0.29), grade ≥3 ICANS (P=0.54), and duration of hospitalization (P=0.55) were found. Furthermore, there was no difference in response rates (CRR 46% and PRR 17% in the elderly group, non-relapse mortality at 1 and 3 months (0 in both groups), and 6- and 12-months PFS and OS survival in elderly patients compared to younger patients were 39% and 32%, and 74% and 69%, respectively with a median follow-up of 7 months (75). Furthermore, real-world experience indicates that, in specialized centers

with certificated medical stuff trained and equipped to timely recognize and treat CRS (with corticosteroids and tocilizumab - a humanized monoclonal Ab against interleukin 6 receptor - IL-6R), ICANS and other adverse events, and with longer rehabilitation therapy aimed at improving disabilities and long-term symptoms, CAR-T cell therapy can be safely used even on elderly patients with comorbidities (75).

Bispecific T cell engager (BiTE) antibodies bind a CD3 molecule on a T cell and target a B cell molecule (CD20) thus redirecting patients' T cells to eliminate malignant B cells. Glofitamab and epcoritamab are recently approved CD20xCD3 BiTEs and are promising new agents for the treatment of R/R LBCL patients. They can be used as a bridging option until CAR-T cell product is available, in case of relapse or disease progression after ASCT or CAR-T cell therapy, and for the treatment of elderly and frail patients non eligible for ASCT or CAR-T cell therapy (4, 71). The advantages of BiTEs are rapid availability and modest toxicity (most of documented CRS are grades 1-2), but with reported high response rates in registration studies (Glofitamab: CRR 39% and ORR 52%: Epcoritamab: CRR 39%, ORR 63%) (76, 77).

Cell-directed therapy is highly expensive and is still not widely available. Therapeutic options effective for R/R LBCL patients ineligible for ASCT include moAbs directed against surface receptors expressed by LBCL cells (CD20, CD19, CD79b) which are applied as monotherapy or in combination with chemotherapy and immunomodulatory drugs **(Table 3)**.

Table 3. Monoclonal antibodies in the treatment of R/R LBCL

R-GemOx (rituximab/ gemcitabine/oxaliplatin) (78)	CRR 44% Median OS of 10 months
Tafasitamab + lenalidomide (79)	CRR 43%, ORR 57.5% 22-month duration of response
Polatuzumab vedotine + bendamustine + rituximab (80)	CRR 38.7%, ORR 41.5%
Loncastuximab tesiren (71)	CRR 24% and ORR 48.3%

Responses to monotherapy with the immunomodulatory drug lenalidomide, Bruton-tyrosin kinase inhibitor Ibrutinib, and Selinexor, an oral selective inhibitor of nuclear export that functionally inactivates p53 and other tumor suppressor proteins, are modest. For very frail R/R LBCL patients, supportive and palliative end-of-life care is the only option.

CONCLUSION

Elderly patients with LBCL have a worse prognosis than patients who are 65 years old and younger. The elderly have a higher incidence of histologically unfavorable types of LBCL, comorbidities, they are generally in a worse condition and have poor tolerance to therapy. Due to these factors treating these patients represents a significant challenge. Treatment should be individualized according to clinical condition and present comorbidities. In the past few years, new therapeutic option cells have emerged and improved the course of disease and prognosis of LBCL in the elderly.

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POSEBNI ASPEKTI PROGNOZE I LEČENJA STARIJIH PACIJENATA SA KRUPNOĆELIJSKIM B-LIMFOMOM

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Sažetak

Krupnoćelijski B-limfom (KBL) najčešći je tip nehočkinskog limfoma (NHL) u opštoj populaciji, čineći 40-50% svih slučajeva NHL i preko 60% NHL u populaciji starijih od 65 godina. S obzirom na sve dužu očekivanu dužinu života, očekuje se da će prevalencija ovog tipa limfoma biti u porastu u narednim godinama. Lečenje ovih pacijenata predstavlja značajan izazov zbog brojnih faktora koji komplikuju lečenje i pogoršavaju ishod bolesti. Stariji pacijenti često imaju prateće bolesti, oslabljenu funkciju organa, izmenjen metabolizam lekova i smanjenu hematopoetsku sposobnost oporavka koštane srži, što ih čini manje tolerantnim na hemioterapiju. Lošija prognoza povezana je sa većom učestalošću non-GCB podtipa i histološki nepovoljnih tipova KBL, poput EBV-pozitivnog KBL, "high grade" B-ćelijskog limfoma (HGBL) i plazmablastnog limfoma, kao i ekstranodalnim lokalizacijama koje su povezane sa lošijim ishodom. Lečenje starijih pacijenata je kompleksno jer predstavljaju visoko heterogenu populaciju sa značajnim varijacijama u zdravstvenom statusu, pratećim bolestima i očekivanim životnim vekom. Stoga je potrebna sveobuhvatna gerijatrijska procena za starije pacijente, uključujući određivanje komorbiditetnog skora radi kategorizacije pacijenata na one dobrog opšteg stanja (fit), one lošeg opšteg stanja (fragilne) i one između. Zavisno od stanja bolesnika cilj lečenja može biti izlečenje, produženje života ili kontrola simptoma. Standardna terapija za starije pacijente dobrog opšteg stanja i uznapredovalu bolest je R-CHOP, dok se kod bolesnika sa pratećim bolestima i lošim opštim stanjem primenjuju redukovani protokoli sa ili bez antraciklina. U prethodnim godinama, stariji pacijenti sa recidivantnim ili KBL otpornim na lečenje imali su vrlo lošu prognozu zbog ograničenih mogućnosti lečenja. Međutim, uspeh lečenja starijih pacijenata sa R/R KBL značajno se poboljšao poslednjih godina zahvaljujući uvođenju novih lekova (polatuzumab, tafasitamab, bispecifična antitela i CAR-T ćelije) koje se mogu koristiti kod starijih osoba.

Ključne reči: krupnoćelijski B-limfom, starija populacija, prognoza, terapija

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