

Original article

CIRS-G SCORE AS A RAPID WAY TO DETERMINE THE OVERALL MULTIMORBIDITY BURDEN AND TO SELECT OPTIMAL AND INDIVIDUALIZED THERAPY IN NEWLY DIAGNOSED ELDERLY CLL PATIENTS

CIRS-G СКОРОТ БРЗ НАЧИН ЗА ОДРЕДУВАЊЕ НА ВКУПНИОТ СТЕПЕН НА МУЛТИМОРБИДНОСТА И ЗА ИЗБОР НА ОПТИМАЛНА И ИНДИВИДУАЛИЗИРАНА ТЕРАПИЈА КАЈ НОВОДИЈАГНОСТИЦИРАНИ ПОСТАРИ ПАЦИЕНТИ СО ХЛЛ

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Abstract

Introduction. Chronic lymphocytic leukemia (CLL) is the most common lymphoproliferative disorder in the elderly population. Many of these patients have multiple comorbidities, which might influence the choice of an adequate upfront chemoimmunotherapy option. The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) score seems to be a reliable tool for assessment of the burden of comorbidity in elderly cancer patients.

Objectives. The primary objective of our study was to assess the distribution of CIRS score status in CLL patients in real clinical practice. The secondary objective was to analyze which treatment option was used, and the effects it produced in each patients' group, classified according to the CIRS score.

Methods. In our prospective, single-center study, we focused on CLL patients that were referred to the University Clinic for Hematology in Skopje between 2017 and 2019. Comorbidity was assessed by the CIRS-G score in all patients included in our study (n=56) prior to the process of deciding on the most adequate treatment option.

Results. The median age was 69 (±9.4) years. Comorbidities were identified in 80.4% of the study population, with an average CIRS score of 3.9. The three most common comorbidities were related to involvement of the vascular system (41.1%), endocrine-metabolic disorders (32.1%), and respiratory system disorders (17.9%). Only 16.1% of the patients had only 1 affected organ or system, other than hematological issues, while 64% of the patients had ≥2 affected systems. In 33.9% of the study patient cohort, the watch and wait initial approach was the standard of care. We considered 66.1% of patients to be requiring treatment, as follows:

chemotherapy (chlorambucil, fludarabine+cyclophosphamide, bendamustine) only (30.4%), rituximab-based therapy (33.9%), and 1.8% of patients, due to the high comorbidity burden, were eligible only for supportive care. There was a stable trend of correlation between the CIRS score assessment and the treatment option prescribed (rs=0.7188, p<0.000001).

Conclusions. The comorbidity status is a major consideration when treating elderly patients with CLL. Our study shows that comorbidity is quite a common feature in CLL patients and that it is increasing with age. CIRS is helpful in identifying the best treatment combination for the patients, that will enhance achieving long-term control of CLL, maintaining an optimal quality of life level.

Keyword: comorbidities, chronic lymphocytic leukemia, elderly, treatment

Апстракт

Вовед. Хронична лимфоцитна леукемија (ХЛЛ) е најчесто лимфопролиферативно заболување кај повозрасната популација. Многу од овие пациенти имаат повеќе коморбидитети, што може да влијае на изборот на соодветна иницијална опција за хемимунотерапија. Кумулативната скала за проценка на коморбидитетот во геријатрија (CIRS-G) се чини дека е сигурна алатка за проценка на коморбидитетното оптоварување кај повозрасни пациенти со карциноми.

Цели. Примарната цел на нашата студија беше да се процени дистрибуција на CIRS статусот кај пациенти со ХЛЛ во нашата клиничка пракса. Секундарната цел беше да се анализира ефектите на CIRS скорот во изборот на опциите на третман во секоја група на пациенти класифициран по CIRS.

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Методи. Во нашата проспективна, едноцентрична студија се фокусиравме на пациенти со ХЛЛ, упатени на ЈЗУ УК за Хематологија во Скопје во периодот од 2017 до 2019 година. Кај вкупно 56 пациенти вклучени во нашата студија, пред одлучување за најсоодветна опција за третман беше оценет степењот на коморбидитети со CIRS-G скорот.

Резултати. Средна возраст на нашите анализирани пациенти беше $69 \pm 9,4$ години. Коморбидитети се идентификувани кај 80,4% од популацијата, со просечен резултат на CIRS од 3,9. Трите најчести коморбидитети беа поврзани со васкуларниот систем (41,1%), ендокрино-метаболични нарушувања (32,1%) и нарушување на респираторниот систем (17,9%). Само 16,1% од пациентите имале 1 заболена органска систем надвор од хематолошкото основно заболување, додека 64% од пациентите имале ≥ 2 заболени системи. Кај 33,9% од нашите пациенти опсервација беше почетен пристап. Само 66,1% од пациентите имаа потреба од третман, и тоа: хемотерапија 30,4% (хлормабуцил, флударабин + циклофосфамид, бендамустин), терапија базирана на ритуксимаб (33,9%) и 1,8% од пациентите заради поголем број на коморбидитети беа поставени само на супертивна грижа. Постои стабилна корелација помеѓу резултатот од CIRS скорот и препишаната опција на третман ($r_s=0.7188$, $p<0.000001$).

Заклучок. Статусот на коморбидитети е од голем интерес при лекување на повозрасни пациенти со ХЛЛ. Нашата студија покажува дека коморбидитети се чести кај ХЛЛ и дека се зголемуваат со возраста. CIRS е корисен за идентификување на најдобриот третман што ќе овозможи постигнување на најдобра можна контрола на ХЛЛ а и истовремено одржување на оптималното ниво на квалитет на живот.

Клучни зборови: коморбидитети, хронична лимфоцитна леукемија, стари лица, третман

Introduction

Chronic lymphocytic leukemia (CLL) is a malignant lymphoproliferative disorder that accounts for approximately 30% of adult leukemias, characterized by the accumulation of small, mature-appearing B lymphocytes in the peripheral blood, bone marrow, lymph nodes, or other lymphoid tissue. CLL is the most common hematological malignancy in the Western world; the incidence is $\sim 5/100.0000$ [1]. The incidence increases to $>30:100.000$ /year at an age of >80 years [2]. The median age at diagnosis is 72 years. The disease typically occurs in elderly patients as clinically heterogeneous disease. The disease's clinical course varies. CLL prog-

resses rapidly in some patients but has an indolent course in others, not requiring therapy for many years. New data on combination therapies, and availability of new treatment options, are likely to change the clinical practice regarding treatment [3-5]. However, the options with chemoimmunotherapy are associated with significant toxicities and prolonged immunosuppression, and the rates of myelosuppression and infections are high. Such complications are more frequent and more severe in patients older than 65 years because of their reduced marrow reserve, and presence of comorbidities. Because CLL is a disease of the elderly, identifying effective therapies with lower toxicity profiles is thus a high priority. Selecting therapy for older patients with CLL requires a careful assessment that incorporates patient's frailty evaluation and state of comorbidities. It is known that chronic illness and age are surrogate markers for overall survival. One important prognostic factor in the elderly is the burden of comorbidity. Survival is significantly impaired in CLL patients with multiple comorbidities or with severe comorbidities. Therefore, not only age, but also the incidence and burden of comorbidity should influence the choice of treatment strategy for every patient individually.

Compiling and quantifying medical problems in the elderly population would allow meaningful comparison of medical burden and treatment outcomes in elderly patients with variable and complex medical problems. The fact that the majority of patients with chronic lymphocytic leukemia (CLL) present with comorbidities could shorten an individual's life, either directly or by enhancing CLL progression. It is a matter of necessity to distinguish patients that could undergo more aggressive treatment. The Cumulative Illness Rating Scale (CIRS), developed by Lin, Lin and Gurel, published in JAGS in 1968 is a reliable tool for the evaluation of the burden of comorbidity in elderly cancer patients. This scale was revised to reflect common problems of the elderly with an emphasis on morbidity, using specific examples and was renamed the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) [6-10]. CIRS labels the pathology and impairment of major organ systems and also psychological, metabolic, neurological and musculoskeletal aspects of the individual. The CIRS score is used to distinguish between fit and unfit CLL patients and influence therapy decision-making.

Methods

We analyzed data from 56 CLL patients diagnosed at the University Clinic for Hematology in Skopje from March 20th, 2017 to January 22nd, 2019. Comorbidities existing simultaneously with the CLL diagnosis were recorded at the time of first CLL evaluation. The Cumu-

Table 1. Scoring Sheet for Cumulative Illness Rating Scale for Geriatrics (CIRS-G)

ORGAN SPECIFIC CATEGORIES	Level of severity*				
HEART (angina pectoris, myocardial infarction, arrhythmias, congestive heart failure and valvular disease; requiring daily medications; invasive heart procedures in the past)	0	1	2	3	4
VASCULAR (peripheral atherosclerotic disease, aortic aneurysm, hypertension, requiring daily antihypertensive drugs; serum cholesterol, previous surgery for vascular problem)	0	1	2	3	4
HEMATOPOIETIC (anemia, leucopenia, any hematological malignancy, hypercoagulability, other disorders of blood, spleen and lymphatic system; if yes, what drugs are taken for these problems)	0	1	2	3	4
RESPIRATORY (bronchitis, pneumonia, asthma, emphysema, pulmonary embolism; requiring daily medications; smoking status)	0	1	2	3	4
EYES, EARS, NOSE AND THROAT AND LARYNX (impaired vision, hearing impairment, sinusitis, vertigo, lightheadedness, dizziness, medications are required for control those disorders and if surgical intervention in the past)	0	1	2	3	4
UPPER GI (esophagus, stomach, and duodenum; pancreas; does not include diabetes)	0	1	2	3	4
LOWER GI (intestines, hernias)	0	1	2	3	4
HEPATIC (liver and biliary tree)	0	1	2	3	4
RENAL (kidneys only)	0	1	2	3	4
OTHER GU (ureters, bladder, urethra, prostate, genitals)	0	1	2	3	4
MUSCOLO-SKELETAL-INTEGUMENTARY (muscle, bone, skin)	0	1	2	3	4
NEUROLOGICAL (brain, spinal cord, nerves, does not include dementia)	0	1	2	3	4
ENDOCRINE-METABOLIC (includes diabetes, thyroid; breast; systemic infections; toxicity)	0	1	2	3	4
PSYCHIATRIC/BEHAVIORAL (includes dementia, depression, anxiety, agitation/delirium, psychosis)	0	1	2	3	4

0-No Problem; 1-Current mild problem or past significant problem; 2-Moderate disability or morbidity/ requires "first line" therapy; 3-Severe/constant significant disability/"uncontrollable" chronic problems; 4-Extremely severe/immediate treatment required/end organ failure/severe impairment in function

lative Illness Rating Scale (CIRS) score was calculated for each patient, based on comorbid health conditions present at the time of diagnosis of CLL, in 14 disease categories using the 14-system version of Miller *et al.* [7] (Table 1).

Careful examination on each aspect of health was done and everybody received a score on the level of impairment. The ratings of severity for each aspect is assigned based on guidelines and questions specific to each section. It consists of 14 aspects of health. The final CIRS score is the sum of each of the 14 individual system ratings. Assessment is performed using a 5-level "degree of severity" scale, ranging from "none" (0 points-if no problem is detected) to "extremely severe" (4 points-if serious condition is present). The CIRS Comorbidity Score was calculated for each patient at the time of admission to our hospital and recorded in clinical records. The scoring may theoretically vary from 0 to 56.

Results

The characteristics of our patients are shown in Table 2. Median age at diagnosis was 69 years. Sixty percenta-

Table 2. Clinical features of patients

	Patients (N=56)	Number (%)
<i>Age ad diagnosis</i>		
Age <60		22
Age 60-69		20
Age >70		14
Median age (range). y		69(38-85)
<i>Gender</i>		
Male		30 (53.6%)
Female		26 (46.4%)
<i>RAI</i>		
0		35 (62.5%)
I		9 (16.1%)
II		7 (12.5%)
III		2 (3.6%)
IV		3 (5.4%)
<i>Binet stage</i>		
A		39 (69.9%)
B		12 (21.4%)
C		5 (8.9%)

ge of patients were 60 years old or above. Most of the patients had been diagnosed at early clinical stages, Binet's A 69.9%, and Rai's 0, I, II 91.1% of patients. The majority of them (80.4%) had at least one comorbidity

at diagnosis. In terms of the types of comorbidity, the proportion of patients who suffered from cardiovascular disorders was the highest (69.7%). Other comorbidities according to their prevalence at the time of CLL diagnosis are shown in Table 3.

Table 3. Comorbidities in different organ systems

Organ system	N #	%
Cardiac	16	28.6%
Vascular	23	41.1%
Hematological	/	/
Respiratory	10	17.9%
EENT (eye. ear. nose. throat. larynx)	4	7.1%
Upper GI	6	10.7%
Lower GI	5	8.9%
Hepatic and Pancreatic	4	7.1%
Renal	3	5.4%
Genitourinary	6	10.7%
Musculoskeletal	5	8.9%
Neurological	5	8.9%
Endocrine-Metabolic	18	32.1%
Physiatric/Behavioral	4	7.1%

The CIRS-G score was calculated to be <6 in 38 patients (67.9%), subgroup of patients in good overall condition ('GO-GO' patients), 6-12 in 16 patients (28.6%), with significant comorbidities or 'Slow GO' patients, not fit for intensive treatments and >12 in 2 patients (3.6%), considered suitable for supportive care ('NO

Table 5. CIRS score and the treatment options

CIRS classification	#	%	R based	%	ww	%	chemo	%	Supportive care
CIRS <6	GO	38	67.9%	14	36.8%	13	34.2%	11	28.9%
CIRS 6-12	SLOW GO	16	28.6%	5	31.3%	6	37.5%	5	31.3%
CIRS >12	NO GO	2	3.6%					1	50.0%

Discussion

Since we are the only hematology center in our country, our data match the overall statistics regarding chronic lymphocytic leukemia (CLL). Generally, comorbidity is an important consideration in oncology practice, particularly among older patients, because elderly patients are an extremely heterogeneous population with regard to comorbidity. In a variety of common cancers, an increased comorbidity level was associated with poorer overall survival. Treatment of elderly CLL patients with comorbidities represents a challenging task. In addition, the complexity of the hematological disorder itself as well as considerations regarding individual patient attributes, such as age and comorbidities, require that treatment decisions be specifically tailored to the overall situation. There is a growing number of therapeutic options for elderly patients with previously untreated chronic lymphocytic leukemia and comorbidities, thus making clinical aids necessary for choosing between the available modalities.

GO' patients) [11]. There was a positive correlation between the CIRS score and the age ($rs=0.2276$, $p=0.04$). In 33.9% of the study patient cohort, the watch and wait initial approach was the standard of care. We considered 66.1% of patients to be requiring treatment as the Table 4 shows.

There was a stable trend of correlation between the CIRS score assessment and the treatment option prescribed ($rs=0.7188$, $p<0.000001$) (Table 5).

Table 4. Treatment of our CLL patients after initial assessment

Treatment option	#	%
WW	19	33.9%
R-Chl (Rituximab+chlorambucil)	3	5.4%
G-Chl (Gazyva+Chlormabucil)	0	0.0%
FCR (Fludarabine+cyclophosphamide+rituximab)	11	19.6%
R-CVP (Rituximab+cyclophosphamide+vincristine+prednisone)	2	3.6%
Supportive care	1	1.8%
Chlorambucile	13	23.2%
Bendamustine	1	1.8%
Ibrutinib	0	0.0%
R-CHOP	1	1.8%
CHOP	1	1.8%
FC	2	3.6%
RC	2	3.6%

We analyzed the spectrum and frequency of comorbidities in our patients with chronic lymphocytic leukemia. The aim of our study was to evaluate the role of Cumulative Illness Rating Scale for Geriatrics (CIRS-G) in fitting therapy to CLL patients and we have confirmed that CIRS-G is a reliable tool for evaluation of the burden of comorbidity in elderly CLL patients.

The CIRS score may provide assistance to physicians in choosing between a wider range of therapeutic options now available. The treatment decision in elderly CLL patients is to be made carefully in each individual, considering not only the stage and risk factors of the disease, but also the patients' physical condition and social environment. In our group of CLL patients, CIRS-G represents a reliable and rapid comorbidity risk adjustment model for pretreatment stratification.

We did not evaluate the associations between the burden of comorbidities and overall survival. Further studies are warranted to assess the powerful prognostic role of CIRS score regarding overall survival in our group of patients with CLL.

Conflict of interest statement. None declared.

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