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Long term survival among patients with chronic lymphocytic leukemia (CLL) treated in Department of Hematology, Medical University of Lublin

Długoletnie przeżycie chorych na przewlekłą białaczkę limfatyczną (pbl)
w materiale własnym Kliniki Hematologii AM w Lublinie

A median survival in chronic lymphocytic leukemia (CLL) ranges widely from a few months to above 20 years. This fact has inspired clinical hematologists to search for parameters which predict survival in the moment of initial diagnosis. Among the patients with CLL treated in hematology out-patient clinic in Lublin between 1975 and 1998, 12 persons with survival from 10 to 23 years (median time 14.3 year) were observed. We evaluated: age and sex of the patients, performance status, stadium of disease according to Rai staging system, the blood lymphocyte count, lymphocyte doubling time, total tumor mass index (TTM), response to chemotherapy. The age of patients at the moment of initial diagnosis varied from 40 to 70 years (median 58 years of age). The group consisted of 6 males, 6 females. 8 patients were in the stage 0 and 4 patients - in the stage 1 according to Rai staging system. 6 out of 12 patients have stayed in the same stage of the disease during the whole time of the study. Among the rest of patients: 3 - have progressed from stage 0 to 1, 3 -

from stage 0 to 2. 5 persons did not receive any cytostatics, 6 received only chlorambucil, 1 received the multidrug therapy (CHOP). The last of the presented patients has been treated by polychemotherapy after 12-year observation because of progression from 0 to 2 stage of the disease.

Accordingly to basic clinical and morphological data we noticed that long term survivors presented the following features: 1) early (0-1) stage acc. to Rai staging system, 2) initial lymphocytosis not higher than 40.0 x 10^9/l, 3) lymphocyte doubling time longer than 12 months, 4) good response to chemiotherapy, 5) low Total Tumor Mass score (TTM), 6) female sex in the group above 50 years of age.

Chronic lymphocytic leukemia (CLL) is the most frequent type of adult leukemia. It occurs usually among older people with a median age of over 60 years, only 10% of patients with CLL are under 50 years of age. CLL is characterized by an uncontrolled proliferation and accumulation of lymphocytes usually of B-cell phenotype. A median survival in CLL ranges widely from a few months to above 20 years. This fact has inspired clinical hematologists to search for parameters which predict survival in the moment of initial diagnosis. The reliable prognostic factors acknowledged from many years are: clinical stage, bone marrow histology, blood lymphocyte count, lymphocyte doubling time.

The aim of this study was the retrospective analysis of prognostic factors conditioning long term survival (above 10 years) among patients with chronic lymphocytic leukemia treated in Department of Hematology, Medical University of Lublin.

MATERIAL AND RESULTS

Among the patients with CLL treated in hematology out-patient clinic in Lublin between 1975 and 1998 , 12 persons with survival from 10 to 23 years (median time 14.3 years) were observed. The analyzed patients were at the moment of initial diagnosis from 40 to 70 years old (median age 58 years). The group consisted of 6 females in the age of 52 to 70 years old (median age 61.3 years) and 6 males in the age of 40 to 68 (median age 54.7 years). 8 patients were in the stage 0 accordingly to Rai staging system, 4 patients in the stage 1. 6 out of 12 have stayed in the same stage of the disease during the whole time of the study. The rest of the group: 3 of them have progressed from stage 0 to 1, 3 - from stage 0 to 2.

Five persons did not receive any cytostatics, six received chlorambucil, one received the multidrug therapy (CHOP - cyclophosphamid, hydroxyrubicin, oncovin, prednison). One patient was receiving chlorambucil already in the year of initial diagnosis and received it during the 15 years time with pauses. Now he has been observed without any treatment for 6 years. In one female patient we have administered chlorambucil at the

end of the first year of observation because of elevation of leucocytosis which is continued to the present time in the sustaining dosis (1 tablet for 3 days). Five persons have been just observed during 5 to 7 years period and treated after it, mainly because of elevation of the leucocytosis. Four of them are not presently treated, two are given chlorambucil periodically. The last of the presented patients has been staying in the stage 0 for 12 years without treatment. In the 13th year of observation progression to stage 2 appeared and he took CHOP. The clinical characteristics of our patients was presented in Table 1.

Table 1. Clinical characteristics of patients in numbers

SEX AND AGE		AGE >50 YEARS		STADIUM OF DISEASE (acc. to Rai et al.)					TREATMENT		
Female	Male	Female	Male	Initially		Currently			Without	Chloram-bucil	CHOP
6	6	6	4	0	I	0	I	I I	5	6	1
52-70 yrs (61.3)	40-58 yrs (54.7)			8	4	3	6	3			

In the group of observed patients the median peripheral blood lymphocyte count in the moment of initial diagnosis was 28.29 x 10^9/l, currently it was 19.07 x 10^9/l. In the moment of initial diagnosis there was only one patient with lymphocyte count above 40.0 x 10^9/l. Total Tumor Mass score ranged in the moment of initial diagnosis from 2.9 to 8.6 (median score 5.2), currently it was from 2.1 to 8.9 (median score 5.96). Lymphocyte doubling time was shorter than 12 months only in one patient. These laboratory data were presented in Table 2.

Table 2. Laboratory parameters of patients

Median peripheral blood lymphocyte count		Number of patients with lymphocyte count initially		TTM		LDT	
Initially	Currently	< 40.0 x 10^9/l	> 40.0 x 10^9/l	Initially	Currently	<12 month	>12 month
28.30 x 10^9/l	19.07 x 10^9/l	11	1	2.9-8.6 (m. 5.2)	2.1-8.9 (m. 5.96)	1	11

DISCUSSION

The first modern classification of chronic lymphocytic leukemia was proposed by Rai and colleagues in 1975 (12). It distinguished five stages of disease from 0 to 4. In 0 group only changes in hematological parameters and bone marrow features are concerned. In stage 1 lymphadenopathy occurs, in stage 2 - splenomegaly, in stage 3 - anemia, in stage 4 - thrombocytopenia. 0 and 1 stages are treated as low-risk stages, stage 2 as an intermediate stage, stages 3 and 4 as high-risk stages. 30% of newly diagnosed patients are at low-risk stage which is associated with 10-year median survival. 60% of them are at intermediate-risk stage with 6-year median survival, 10% - at high-risk stage with 2-year median survival. All presented patients belonged in the moment of initial diagnosis to the low-risk stage group with predicted survival time above 10 years, which has really occurred.

Age and sex are independent prognostic factors in most investigators' opinion. Male CLL patients generally have a worse prognostic than female patients (Catovsky et al., 2). In the evaluated group we have the same number of males and females, although there were more females among patients with an age of over 50 years. Advanced age (over 60 years) was shown by Lee et al. (7) (study of 1987) to be an adverse prognostic factor. Adversely, the analysis by Montserrat et al. (10) indicated that the impact of CLL on survival (i.e. the disease-related mortality) is similar in patients under and above 50 years. Because of these differences age was not accepted as a disease - specific prognostic parameter. In our study most patients (10) was at the age of above 50 years in the moment of initial diagnosis, only 2 male patients were under 50 years.

Some investigators found the physicial performance status accordingly to Zubard's (7) or Karnovsky's (4) scale as an independent prognostic parameter. The physicial performance status of our patients was estimated as 80-100% accordingly to Karnovsky's scale.

Anemia and thrombocytopenia among hematological parameters indicating on the advanced stage of disease were adverse prognostic factors (13). Most investigators claimed that the presence of anemia predicted worse prognostics than the presence of thrombocytopenia. However thrombocytopenia more than anemia indicated an unfavorable outcome and was one of the most frequent causes of death (8). There were neither anemia nor thrombocytopenia among our patients in the moment of initial diagnosis and during the whole time of observation.

The blood cell count or the blood lymphocyte count both indicated the tumor mass, especially in early disease. The patients with 1 or 2 stage acc. to Rai were subclassified into two different groups. The group of good prognosis consisted of patients with lymphocyte count below 40.0 x 10^9/l – 50.0 x 10^9/l . The group of bad prognosis consisted of patients with lymphocyte count above 50.0 x 10^9/l [8,9]. Only one of analysed patients had lymphocyte count above 50.0 x 10^9/l, others - below 40.0 x 10^9/l .

In 1981 Jaksic and Vitale (6) proposed the new parameter to assess tumor mass - Total Tumor Mass score (TTM). To calculate TTM we use lymphocyte count, the

biggest diameter of lymph nodes and dimension of spleen. It is based on a fact that there are 3 compartments of lymphocytes: peripheral blood and bone marrow, lymph nodes, spleen and liver. As opposed to Rai staging system which is a quality classification, TTM is quantitative staging system. The quoted authors claimed that TTM score below 8.9 was connected with survival not shorter than 101 months, TTM score above 9.0 - with about 39 months survival. All analysed patients had TTM score below 8.9 with prognosis of survival above 10 years. In most of them TTM is still below 8.9. Only one person had just 8.9. He had progressed from 0 to 2 stadium acc. to Rai and took multidrug therapy.

Already in 1966 Galton et al. (5) as ones of the first suggested the prognostic relevance of lymphocyte kinetics. Lymphocyte doubling time (LDT) is a simple and valid parameter to assess the pace of the disease in particular in early disease. An LDT shorter than 12 months predicts an agresive course and short survival, while LDT longer than 12 months predicts an indolent course and long survival[3,11,15]. One of presented patients had LDT shorter than 12 months, but good response to therapy (he received chlorambucil) allowed them to attain longer than 10-years survival.

In 1995 Molica et al. (9) introduced criteria of special subtype of CLL - smouldering CLL, which is characterized by indolent course and good prognosis. These criteria are: low stage of disease, non-diffuse bone marrow histology, low lymphocyte count, high hemoglobin level, LDT longer than 12 months. The patients with smouldering CLL do not need treatment unless progression occurs. Nine out of twelve patients met with criteria of smouldering CLL. Five of them were not treated , four of them received chlorambucil after 5 to 7 years from diagnosis because of expressed features of progression. In the quoted paper Molica et al. (9) proved that in patients with smouldering CLL there were no survival advantages for immediate treatment administered in the moment of diagnosis versus delayed treatment administered because of progression. The same considerations apply when comparing combination versus single-drug regimens.

The good initial response to chemotherapy especially to alkylating agents is an important prognostic factor. It was investigated by Catowsky et al. in the study of 1989 (2). Dhodapkar et al. (3) in 1993 analysed the patients under 50 years old with early or intermediate B-CLL. The patients who did not respond to initial therapy with alkylating agents had worse prognosis with median survival of only 19 months. 2 of our patients had to be treated just in the year of initial diagnosis. There were good results of that treatment. One of them has not been treated for 8 years, the other - has been taking 1 tablet for 3 days, 4 others received chlorambucil patients had good response to chlorambucil, 2 of them have not been treated for 4 years, others take chlorambucil in the moment of leucocyte elevation only.

CONCLUSIONS

Accordingly to basic clinical and morphological data we noticed that long term survivors presented the following features: 1) early (0-1) stadium acc. to Rai staging systema, 2) initial limphocytosis not higher than 40.0 x 10^9/l, 3) lymphocyte doubling time longer than 12 months, 4) good response to chemiotherapy, 5) low Total Tumor Mass score (TTM), 5) low Total Tumor Mass score (TTM), 6) female sex in the group above 50 years of age.

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STRESZCZENIE

Czas przeżycia chorych z przewlekłą białaczką limfatyczną (pbl) waha się w bardzo szerokich granicach: od kilku miesięcy do ponad dwudziestu lat. Fakt ten skłania hematologów do poszukiwania czynników prognostycznych, dzięki którym już w momencie rozpoznania można byłoby ocenić szansę pacjentów na długoletnie przeżycie. Wśród chorych z pbl leczonych w Przyklinicznej Poradni Hematologicznej w Lublinie w okresie od r.1975 do r.1998 obserwowano 12 chorych z przeżyciem od 10 do 23 lat (średnio 14,3). W ocenie tych chorych braliśmy pod uwagę: ich wiek i płeć , stan ogólny, stadium choroby wg klasyfikacji Raia i wsp., limfocytozę we krwi obwodowej, czas podwojenia limfocytozy, wyliczaliśmy wskaźnik oceniający całkowitą masę guza (TTM), ocenialiśmy odpowiedź na chemioterapię. Analizowani przez nas pacjenci byli w chwili ustalenia rozpoznania w wieku od 40 do 70 lat (średnio 58). Było wśród nich 6 kobiet i 6 mężczyzn. 8 pacjentów w chwili rozpoznania było w stadium 0 wg klasyfikacji Rai i wsp., 4 – w stadium 1. Sześciu spośród 12 pacjentów pozostało w tym samym stadium choroby przez cały okres obserwacji. U pozostałych: u 3 nastąpiła progresja ze stadium 0 do stadium 1, u kolejnych trzech – również progresja ze stadium 0 do stadium 2. U pięciu chorych nie stosowano żadnego leczenia cytostatycznego, sześciu otrzymywało jedynie chlorambucil (leukeran), jeden pacjent otrzymał terapię wielolekową wg schematu CHOP. U ostatniego z przedstawianych pacjentów terapię wielolekową włączono po dwunastoletnim okresie obserwacji. Powodem leczenia była progresja choroby ze stadium 0 do stadium 2.

Na podstawie analizy podstawowych danych klinicznych i morfologicznych ustalono, iż chorzy z długoletnim przeżyciem wykazywali następujące wspólne cechy kliniczne: 1) wczesne tj. 0-2 stadium choroby wg klasyfikacji Raia 2) limfocytoza we krwi obwodowej w momencie rozpoznania nie była większa niż 40000 w mm^3; 3) czas podwojenia limfocytozy przekraczał 12 miesięcy; 4) dobrą odpowiedź na chemioterapię; 5) niski wskaźnik oceniający całkowitą masę guza (TTM-total tumor mass), 6) przewagę płci żeńskiej w grupie chorych poniżej 50 roku życia.