Leukemia Research 57 (2017) 65–71

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Clinical relevance of hypogammaglobulinemia, clinical and biologic variables on the infection risk and outcome of patients with stage A chronic lymphocytic leukemia

Francesca R. Mauro[a,*], Fortunato Morabito[b], Iolanda D. Vincelli[c], Luigi Petrucci[a], Melissa Campanelli[a], Adriano Salaroli[a], Giuseppina Uccello[b], Annamaria Petrungaro[a], Francesca Ronco[c], Sara Raponi[a], Mauro Nanni[a], Antonino Neri[d], Manlio Ferrarini[e], Anna R. Guarini[a,f], Robin Foà[a], Massimo Gentile[b]

[a] Hematology, Department of Cellular Biotechnologies and Hematology, Policlinico Umberto I, Sapienza University, Rome, Italy
[b] Hematology Section, Cosenza Hospital, Cosenza, Italy
[c] Hematology, Azienda Ospedaliera Bianchi-Melacrino-Morelli, Reggio Calabria, Italy
[d] Department of Clinical Sciences and Community Health, University of Milano and Hematology CTMO, Foundation IRCCS Ca'Granda Ospedale Maggiore Policlinico, Milano, Italy
[e] San Martino IST, Direzione Scientifica IRCCS, Genova, Italy
[f] Department of Molecular Medicine, Sapienza University, Rome, Italy

ARTICLE INFO

Article history:
Received 13 November 2016
Received in revised form 6 February 2017
Accepted 26 February 2017
Available online 27 February 2017

Keywords:
Chronic lymphocytic leukemia
Immunoglobulins
Hypogammaglobulinemia
Infections
A stage

ABSTRACT

The prognostic effect of hypogammaglobulinemia (HGG), clinical and biologic characteristics on the infection risk and outcome has been retrospectively analyzed in 899 patients with stage A chronic lymphocytic leukemia (CLL). Low levels of IgG were recorded in 19.9% of patients at presentation, low levels of IgM and/or IgA in 10.4% and an additional 20% of patients developed HGG during the course of the disease. Before the start of any treatment, 160 (12.9%) patients experienced at least one grade ≥3 infection requiring a systemic anti-infective treatment and/or hospitalization. While IgG levels at diagnosis were not associated with an increased risk of grade ≥3 infection or with an adverse outcome, a significantly increased rate of grade ≥3 infections was recorded in patients with unmutated IGHV ($p = 0.011$) and unfavorable FISH aberrations ($p = 0.009$). Late onset HGG, more frequently recorded in patients with Rai stage I–II ($p = 0.001$) and unmutated *IGHV* ($p = 0.001$), was also associated with a higher rate of severe infections ($p = 0.002$).

These data indicate that, stage A patients with clinical and biologic characteristics of a more aggressive disease develop more frequently late onset HGG, grade ≥3 infections and require a closer clinical monitoring.

1. Introduction

Infections, the major cause of morbidity and mortality in patients with chronic lymphocytic leukemia (CLL) [1–3], represent the clinical manifestation of a multi-factorial immunodeficiency related to CLL itself, its treatment and other predisposing factors such as age and comorbidities [4]. A common abnormality is hypogammaglobulinemia (HGG) that has been ascribed to the inhibition of leukemic cells on the residual subset of normal B cells producing antibodies and frequently associated with other immune defects, such as impairments of T-cell number and function [5–8]. HGG is usually observed in patients with advanced and previously treated disease [1,9], but it is also recorded in patients with early stage of CLL. The rate of HGG is highly variable, ranging from 20% to 70% of cases in different studies [10–12] depending on the heterogeneous characteristics of the patient populations analyzed. The prognostic significance of HGG on survival and time to first treatment is also highly variable, with conflicting results [12–14]. Moreover, the clinical relevance of serum Ig levels in terms of infection risk in patients with early stage CLL is unclear [13,15,16].

In order to better define the prognostic effect and the infection risk of HGG in early stage CLL, we retrospectively analyzed the characteristics and outcome of a large series of patients with stage A CLL.

* Corresponding author at: Hematology, Department of Cellular Biotechnologies and Hematology, Sapienza University, Via Benevento 6, 00161 Rome, Italy.
E-mail address: mauro@bce.uniroma1.it (F.R. Mauro).

http://dx.doi.org/10.1016/j.leukres.2017.02.011
0145-2126/

Table 1
Characteristics of patients according to the baseline levels of serum Ig.

	All patients N [%]	IgG levels		*P* value	IgM levels		*P* value	IgA levels		*P* value
		Normal N [%]	Reduced N [%]		Normal N [%]	Reduced N [%]		Normal N [%]	Reduced N [%]	
No of patients	899 [100]	**720**	**179**	–	**669**	**116**	–	**682**	**108**	–
IgG [mg/dL] mean ± SD	1011 ± 326	1105 ± 293	634 ± 106	–	1059 ± 327	865 ± 290	–	1062 ± 333	836 ± 233	–
IgM [mg/dL] mean ± SD	124 ± 103	134 ± 102	74 ± 90	–	141 ± 102	25 ± 8		125 ± 100	120 ± 120	–
IgA [mg/dL] mean ± SD	155 ± 101	165 ± 103	106 ± 71	–	160 ± 104	128 ± 78		174 ± 97	38 ± 13	–
IgG [mg/dL] [n = 899] > 760/ ≤ 760	720/179 [80.1/19.9]	–	–	–	580/89 [86.7/13.3]	70/46 [60.3/39.7]	<0.0001	586/96 [85.9/14.1]	67/41 [62/38]	<0.0001
IgM [mg/dL] [n = 785] > 40/ ≤ 40	669/116 [85.2/14.8]	581/70 [89.2/10.8]	89/46 [69.1/30.9]	<0.0001	–	–	–	580/98 [85.5/14.5]	89/18 [83.2/16.8]	ns
IgA [mg/dL] [n = 790] > 70/ ≤ 70	682/108 [86.3/13.7]	587/67 [89.8/10.2]	96/41 [70.1/29.9]	<0.0001	580/89 [86.7/13.3]	98/18 [84.5/15.5]	ns	–	–	–
No of reduced Ig classes [n = 785] <2/ ≥ 2	703/82 [89.6/10.4]	643/7 [98.9/1.1]	60/75 [44.4/55.6]	<0.0001	640/29 [95.7/4.3]	63/53 [54.3/45.7]	<0.0001	643/35 [94.8/5.2]	60/47 [56.1/43.9]	<0.0001
Median age	65	65.1	66.1	ns	65.8	64.8	ns	65.1	67.5	ns
Age [years] < 65/ ≥ 65	439/460 [48.8/51.2]	356/364 [49.4/50.6]	83/96 [46.4/53.6]	ns	321/348 [48/52]	58/58 [50/50]	ns	336/346 [49.3/50.7]	45/63 [41.7/58.3]	ns
Gender, female/male	399/500 [54.1/45.9]	312/408 [43.3/56.7]	87/92 [48.6/51.4]	ns	302/367 [45.1/54.9]	50/66 [43.1/56.9]	ns	306/376 [44.9/55.1]	48/60 [44.4/55.6]	ns
ALC [10^9/L] < 10/ ≥ 10	370/529 [41.2/58.8]	302/418 [41.9/58.1]	68/111 [38/62]	ns	294/375 [43.9/56.1]	41/75 [35.3/64.7]	0.05	295/387 [43.3/56.7]	40/68 [37/63]	ns
Rai stage, 0/I-II	566/333 [63/37]	461/259 [64/36]	105/74 [58.7/41.3]	ns	443/226 [66.2/33.8]	58/58 [50/50]	0.001	437/245 [64.1/35.9]	65/43 [60.2/39.8]	ns
Splenomegaly[a] absent/present	799/100 [88.9/11.1]	644/76 [89.4/10.6]	76/24 [86.6/13.4]	ns	593/76 [88.6/11.4]	102/14 [87.9/12.1]	ns	613/69 [89.9/10.1]	86/22 [79.6/20.4]	0.003
β2-microglobulin [n = 725] normal/increased	432/293 [59.6/40.4]	347/224 [60.8/39.2]	85/69 [55.2/44.8]	ns	320/210 [60.4/39.6]	52/47 [52.5/47.5]	ns	324/219 [59.7/40.3]	49/39 [55.7/44.3]	ns
CD38 [n = 481] negative/positive[b]	404/77 [84/16]	319/57 [84.8/15.2]	85/20 [81/19]	ns	279/48 [85.3/14.7]	66/15 [81.5/18.5]	ns	319/53 [85.8/14.2]	28/10 [73.7/26.3]	0.05
ZAP-70 [n = 222] negative/positive[c]	152/70 [68.5/31.5]	129/58 [69/31]	23/12 [65.7/34.3]	ns	125/53 [70.2/29.8]	20/10 [66.7/33.3]	ns	130/54 [70.7/29.3]	15/9 [62.5/37.5]	ns
IGHV [n = 282] mutated/unmutated	206/76 [73/27]	169/62 [73.2/26.8]	37/14 [72.5/27.5]	ns	162/56 [74.3/25.7]	29/14 [67.4/32.6]	ns	173/59 [74.6/25.4]	19/11 [63.3/36.7]	ns
FISH analysis [n = 265]	94 [35.5]	81 [37.4]	13 [27.1]	ns	75 [37.1]	10 [23.8]	ns	71 [32.7]	14 [50]	ns
no aberrations	125 [47.2]	98 [45.2]	27 [56.3]		92 [45.5]	24 [57.1]		106 [48.8]	11 [39.3]	
del 13q	19 [7.2]	16 [7.4]	3 [6.3] 2 [4.2]		15 [7.4]	3 [7.1] 2 [4.8]		16 [7.4]	2 [7.1] 0 [0]	
+12	9 [3.4]	7 [3.2]	3 [6.3]		7 [3.5]	3 [7.1]		9 [4.1]	1 [3.6]	
del11q	18 [6.8]	15 [6.9]			13 [6.4]			15 [6.9]		
del17p										

[a] Splenomegaly, longitudinal diameter of the spleen assessed by ultrasound ≥14 cm.
[b] Positive CD38, ≥30% expression.
[c] Positive ZAP-70, ≥20% expression.