Estudio del paciente recién diagnosticado

Francesc Bosch
Department of Hematology
Hospital Universitari Vall d'Hebron, Barcelona, Spain
fbosch@vhebron.net

Workshop Leucemia Linfática Crónica
Sociedad Chilena de Hematología
Santiago de Chile
Viernes 11 de Noviembre de 2016

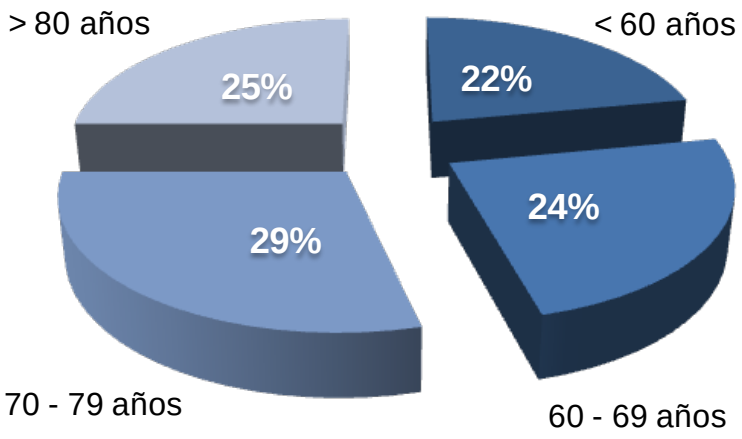
OUTLINE

1. LLC en 2016
2. Linfocitosis B monoclonal
3. LLC ”acelerada”

1. DIAGNOSTICO DE LA LLC

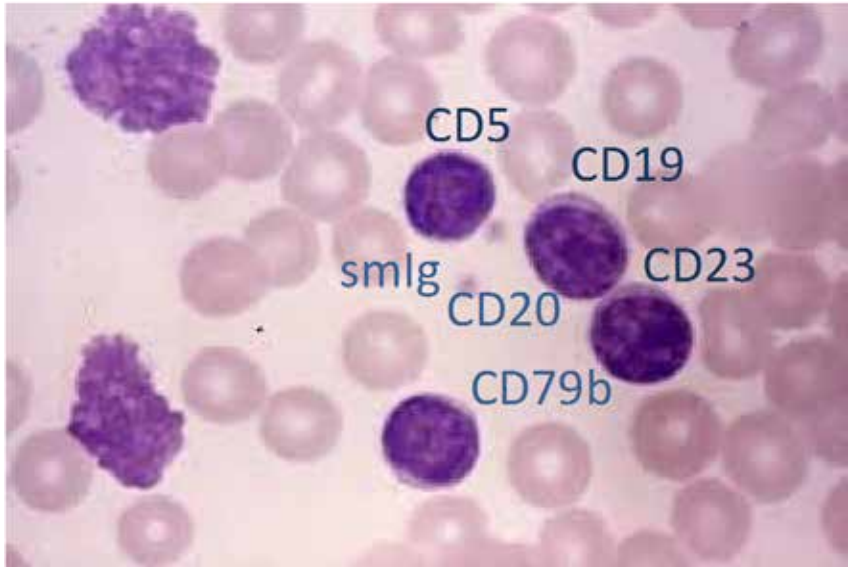
CLL: general overview

- Most frequent leukemia in adults in Western countries (5 new cases / 100,000 ih /year)
  - Median age at diagnosis 65 yrs
  - Male: female ratio 1.5:1
- Proliferation and accumulation of CD5+ B-lymphocytes in peripheral blood, bone marrow and lymphoid organs
- 80% à assymptomatic at diagnosis

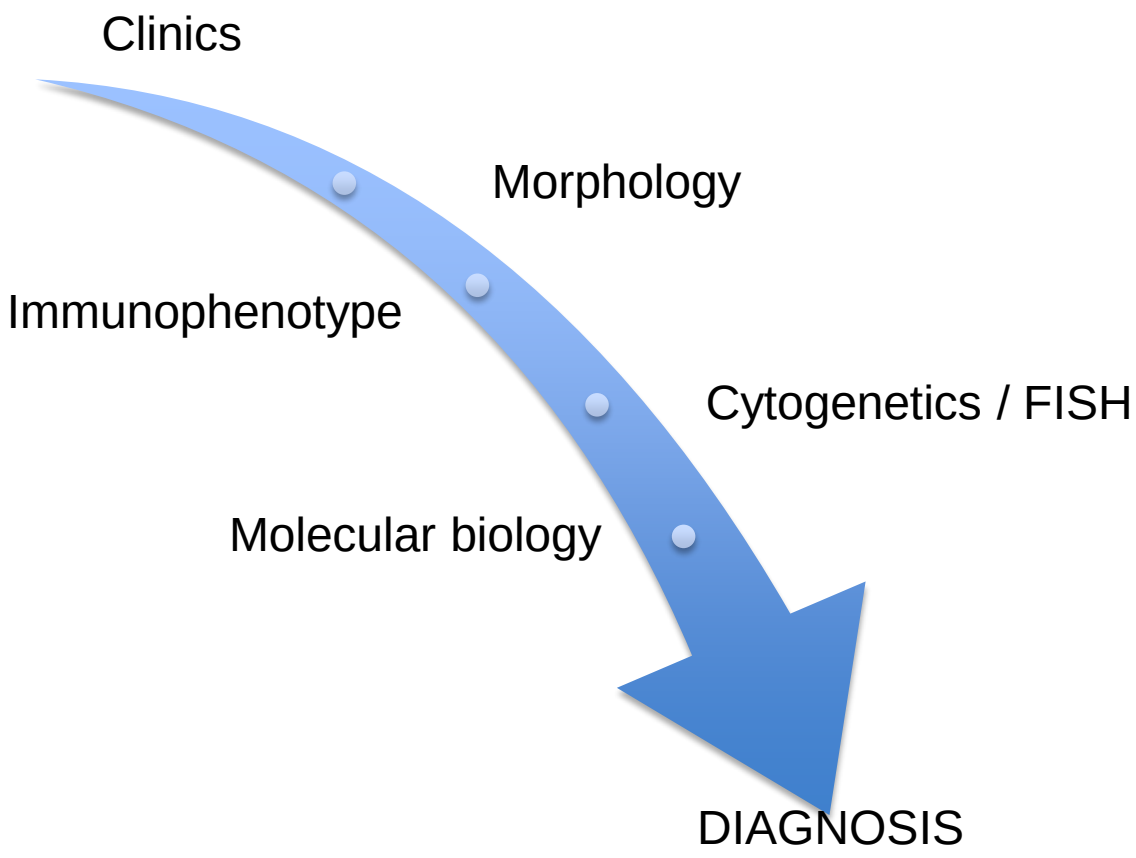


CLL: Definition

- WHO (2008)
  - Requires > 5,000 B-lymphocytes / µL for at least 3 months
  - Clonality confirmed by flow cytometry
  - Small, mature-appearing, lymphocytes (< 55% PL)
  - < 5,000 / µL, clonal
    à monoclonal B-lymphocytosis (MBL)
    (absence of lymphadenopaty, cytopenias, symptoms, …)



Clinico-biologic entities



Pruebas diagnósticas (I)

- Síntomas
  - Astenia (30%), a veces sin relación con la cantidad de enfermedad
  - Síntomas “B”
- Examen físico
  - Hepato-esplenomegalia 20%
  - Rara afectación del Waldeyer

Pruebas diagnósticas (II): Laboratorio

- Hemograma + fórmula leucocitaria manual
- Recuento reticulocitos + test de Coombs directo (10% LLC fenómenos autoinmunes)
- LDH sérica + beta2-microglobulina
- Proteinograma
- Serologías víricas (HBsAg, Anti-HBs + Anti-HBc, VHC, VIH)
- Examen médula ósea

Recordar: No toda anemia en LLC es debida a la enfermedad à Mayor riesgo de segundas neoplasias (3-4x)

Pruebas diagnósticas (III): Pruebas de imagen

- CT scan
  - No recomendado al diagnóstico
    - 20% estadios Rai 0 tienen adenopatías
    - Correlación con evolución adversa (Muntañola et al. JCO 2008)
  - Antes de empezar tratamiento
- Ecografia abdominal à adenopatías palpables
- PET/CT
  - No recomendado
  - Únicamente en sospecha de Sdr. de Richter

Pruebas diagnósticas (IV): Citometria de flujo

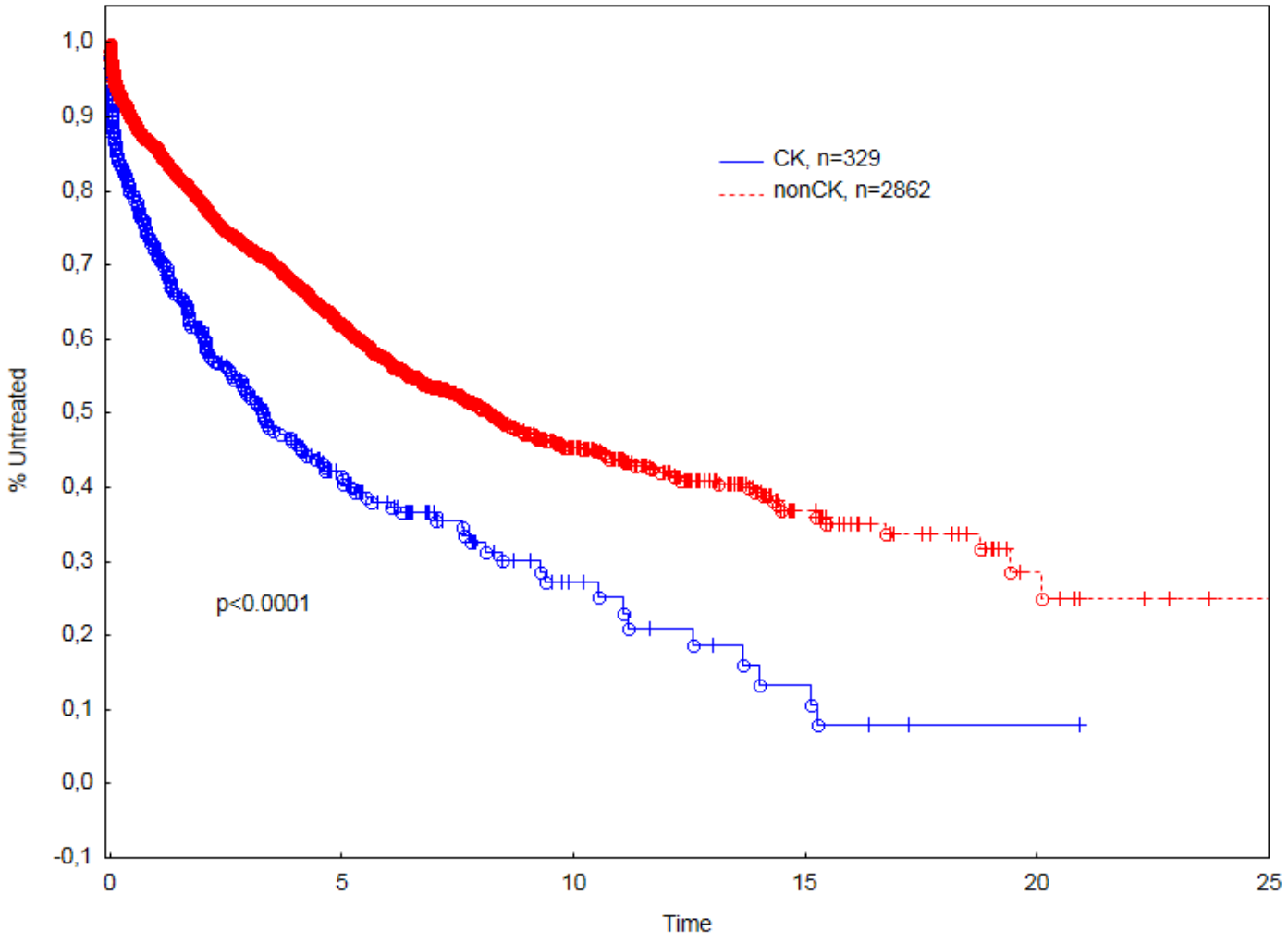
- Panel básico para diagnóstico
  - Determinación de clonalidad (kappa/lambda)
  - CD19, CD20, sIg, CD5, CD23, CD10, FMC7, CD200
  - ZAP-70/CD49d/CD38
    - Importante información pronóstica
    - No imprescindible al diagnóstico o antes de empezar el tratamiento

Pruebas diagnósticas (V)
Citogenètica / FISH

- FISH 4 sondas
  - No necesario al diagnóstico (información pronóstica)
  - **Esencial** antes de empezar tratamiento à Descartar deleción de 17p

- Cariotipo complejo à asociado a peor respuesta a ibrutinib en pacientes con del17p
  - Tecnología por estandarizar

CK and TTFT


1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
-0,1
% Untreated
0
5
10
15
20
25
Time
CK, n=329
nonCK, n=2862
p<0.0001

Pruebas diagnósticas (VI)
Biologia Molecular

- Estado mutacional IgHV
  - Mejor parámetro pronóstico
  - Requiere experiencia
  - No imprescindible al diagnóstico / tratamiento
- Estado mutacional TP53
  - Complementa al estudio por FISH
  - No imprescindible al diagnóstico
  - Esencial antes de empezar tratamiento
- Mutaciones NOTCH1, SF3B1, MYD88
  - Experimental

CLL: Essential tests

	Diagnosis	Pre-treatment
Physical examination	X	X
Virus (HVB, HVC, HIV)	X	X
DAT test	X	X
CT scan		X
BM examination		X#
Lymph node biopsy	Richter?	Richter?
Flow cytometry	X	
ZAP-70, CD49d	R	
FISH (4 probes)	R	X
IgHV mutational status	R	
TP53 mutational status		X

if cytopenias

International Prognostic Index
Another one…

- Age > 65 yo
- Beta2-microglobulin > 3.5 mg/L
- Clinical Stage Binet B-C
- TP53 abnormalities
- IgHV unmutated

But:
Requieres a complex formula
Applied for patients that did not recieve newer therapies

Lancet Oncol, 2016

2. LINFOCITOSIS B MONOCLONAL

MBL: definition

- MBL: monoclonal B-cell expansions in the peripheral blood of healty individuals
  - Not always correspond to an increase in the lymphocyte count

- Immunophenotype subgroups
  - 75%: CLL-like : $CD5^{+}$, $CD23^{+}$, $CD20^{dim}$, sIg^{dim}
  - 20%: Atypical CLL-like: $CD5^{+}$, $CD20^{bright}$
  - 5%: $CD5^{-}$ MBL

MBL prevalence (I)

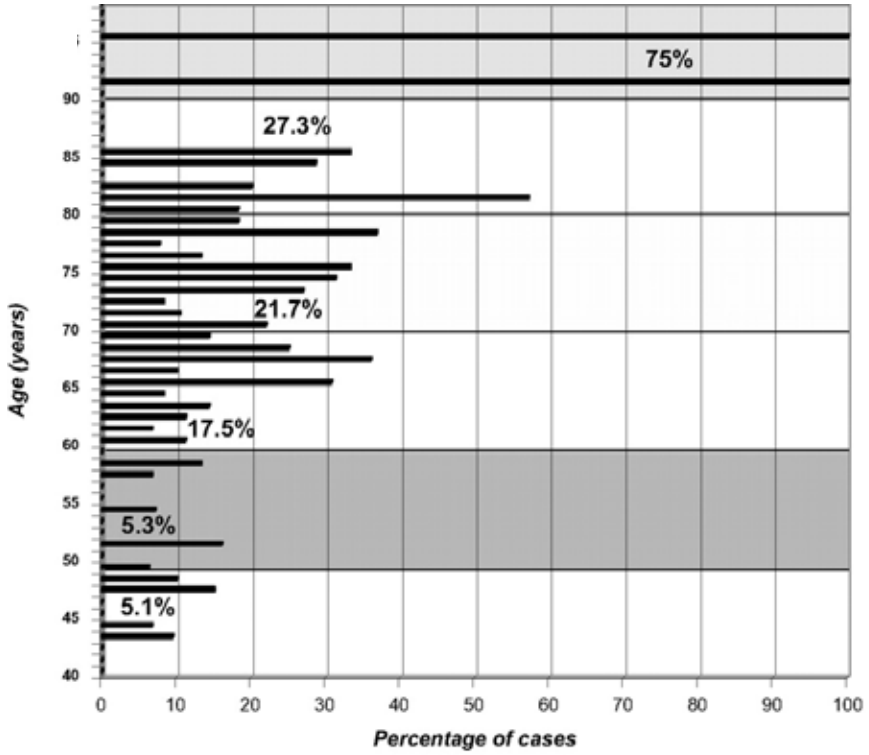
- Depends on the method of FC analysis
  - Number of colors
  - Number of events
- Depends on the age
- Normal population without lymphocytosis
- Appears in 13-18% of CLL families (*Goldin et al, BJH 2010*)

		FLOW CYTOMETRY			MBL PREVALENCE		
Source	N=	Colors	+ CD20	Events x 10^3	CLL-like	Atypical	$CD5^{neg}$
UK[1]	1520	4	No	200	5.1%		1.8%
USA[2]	2008	6	Yes	500	5.2%	1%	1%
Spain[3]	608	8	Yes	500	12%*	2.3%	
Italy[4]	500	4	Yes	200	5.5%		

*60% < 0.01%

[1]*Rawstrom et al, NEJM 2008*
[2]*Shim YK et al, Blood 2014*
[3]*Nieto et al, Blood 2009*
[4]*Ghia, Blood 2004*

MBL prevalence: influence of age



Age
45-54 y
55-64 y
65 y or older
All ages

[3]*Nieto et al, Blood 2009*

[2]*Shim YK et al, Blood 2014*

MBL and additional clones

- The presence of additional clones have been reported
  - 14/73 biclonal (Nieto et al, Blood)
  - 9/16 oligoclonal (Lanasa, Leukemia 2009)

- Suggest that concomitant clones can coexist in healthy individuals à one clone could be predominant by the time

Cell counts differentiate two types of MBL

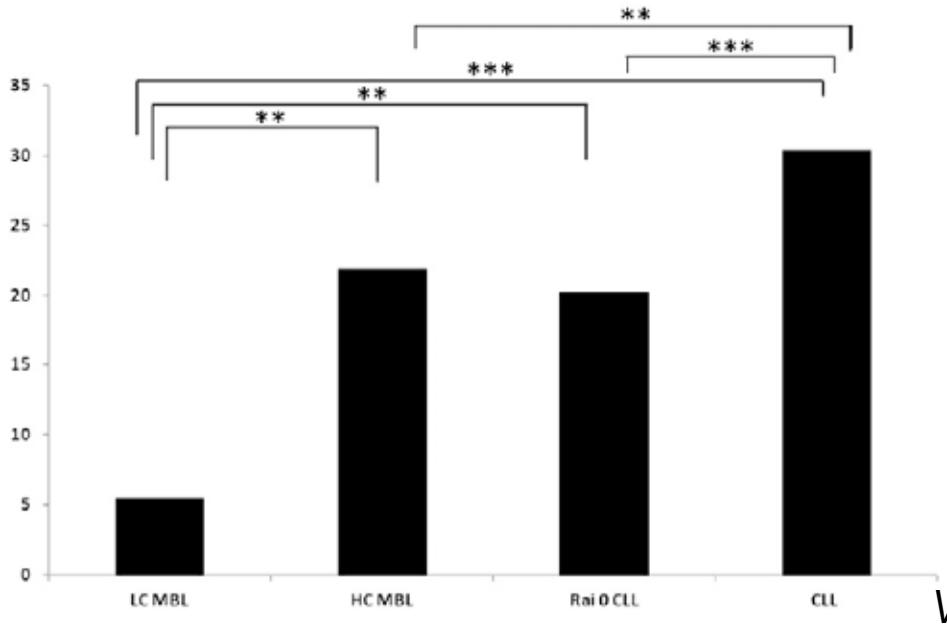
- Low-count MBL < 0.5 x 10^9/L
- High-count MBL 0.5 – 5 x 10^9/L (clinical MBL lymphocytosis < 5 x 10^9/L) à 30% CLL

MBL characteristics	LC-MBL	HC-MBL
MBL cell range	0 - 0.5 x 10^9/L	0.5 – 5.0 x 10^9/L
Median B-cell count	0.14 x 10^9/L	3.52 x 10^9/L
Median MBL count	0.008 x 10^9/L	3.38 x 10^9/L
Median absolute Lymphocyte count	2.17 x 10^9/L	6.0 x 10^9/L

Vardi et al, Blood 2013

LC MBL & HC MBL biological characteristics

- 71% IgVH3 / 29% IgVH4 families
- HC MBL: ↑ IgHV1 ↓ IgVH4
- Underrepresentation of IgHV1-69 in LC MBL
- Unmutated IgHV
  - LC MBL: 26%
  - HC MBL: 24%
  - CLL Rai0: 25%



Stereotyped receptors

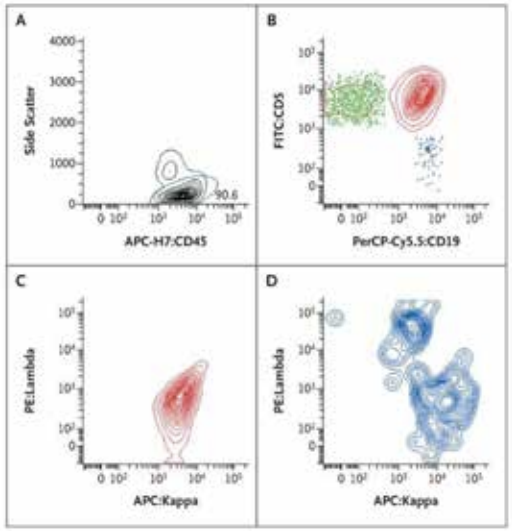
Vardi et al, Blood 2013

Biological characteristics depend on the presence of clinical MBL

Source	Median CLL cell count	B-cells with CLL-phenotype (median %)	Cases with <98% IGHV homology	Predominant CLL-phenotype cell IGHV gene	Similar to CLL?
CLL (23)	>5,000	>95%	534/927 (57.6%)	3-07, 1-69, 4-34, 3-23	–
Clinic MBL (Leeds) (7)	3,141	>95%	18/20 (90%)	3-07, 3-23, 4-34	Yes
Clinic MBL (Mayo) (11,12)	2,757	>95%	84/109 (77%)	3-07, 1-69, 4-34, 3-23	Yes
Familial MBL (Duke) (24)	26	25%	12/16 (75%)	3-07, 4-34	Yes
Population MBL (Leeds) (7)	9	80%	18/20 (90%)	3-07, 3-23, 4-34	Yes
Population MBL (Italy) (3)	1.0	7%	36/51 (70%)	4-59/61	No
Population MBL (Salamanca) (5)	0.5	0.4%	2/7 (29%)	No CLL-associated	No

All CLL are preceeded by MBL phase

- 45 pts diagnosed with CLL à blood collection as part of a cancer screening trial
- 44/45 à presence of a B-cell clone
- 46% IgHV3 + 25% IgHV4-subgroups
- Latency between 10-77 months



Landgren et al, NEJM 2009

MBL: Natural history and risk of progression

- UK 185 CLL-like MBL with lymphocytosis (median FU 7 years)
  - Progressive lymphocytosis in 28%
  - Progression to a CLL: 15%
  - Risk of progression estimated at 1.1%/year
- No differences in CD38, ZAP70, FISH between cMBL and CLL Rai0 < 10,000 ALC (Shanafelt et al, JCO 2009)

Risk of progression 1-2%
LC MBLs rarely progress
Need for prognostic parameters predicting not only progression to > 5 x 10^9/L but for treatment

Distinguishing MBL and CLL

	Clonal B-cells CLL phenotype	B-cell count < 5 x 10^9/L (PB)	Lymphadenopaties Hepatosplenomegaly	Bone marrow
MBL	Yes	Yes	No	Not required
SLL	Yes	Yes	Yes	
CLL	Yes	No	Yes or No	

MBL assesment and follow-up (I)

- Clinical MBL
  - Standard lymphocytosis evaluation, including physical examination
  - Anual follow-up: physical examination + PB test

- LC MBL à no formal evaluation, primare care physician (ethical issues?)

MBL assesment and follow-up (II)

- Atypical phenotype
  - CT scan
  - Bone marrow biopsy
  - Serum/urine electrohporesis
  - If MCL à follow up every 3-6 months (including CT scan every 6 months)
  - If NHL NOS, follou-up every 6-12 monhts

MB: unanswered questions

- Insurance implications with the diagnosis of MBL
- Can MBL patients serve as organ donors?
  - Patients with malignancy cannot donate solid organs or blood-derived products
  - MBL can be identified up to 15% of normal individuals!
  - Not recommend to screen donors with normal lymphocyte counts
- Should relatives of CLL patients screened for MBL before being alloTPH donors?

MBL: Conclusions

- Appears in 5-12% healthy individuals
- 20% of CLL have criteria of MBL
- Risk of progression 1-2% / year
  - Patients with clinical MBL tend to progress more and are similar to CLL Rai0
- Caution with atypical or CD5neg MBL
- **Always send a positive message to the patients (not a pre-leukemia…)**

3. LLC ACELERADA

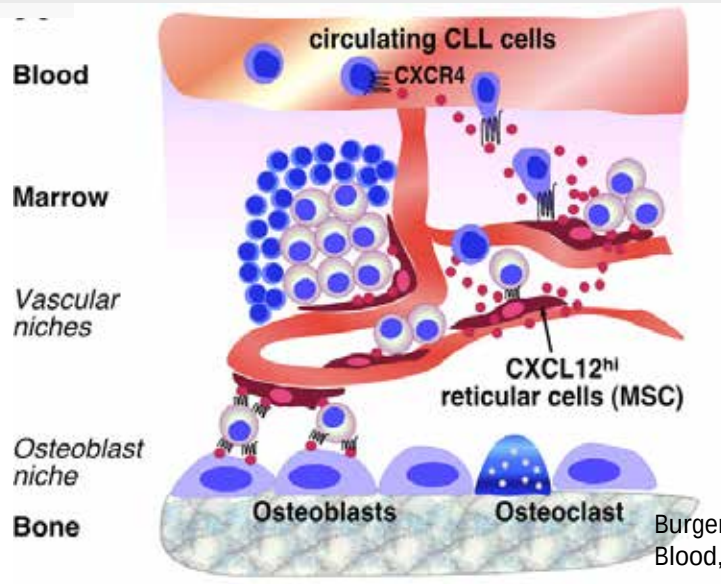
LLC y microambiente: compartimentos

Sangre periférica

- Células de LLC en fase G0 del ciclo celular
- Células accesorias:
  - Linfocitos T
  - Monocitos (CD14+)

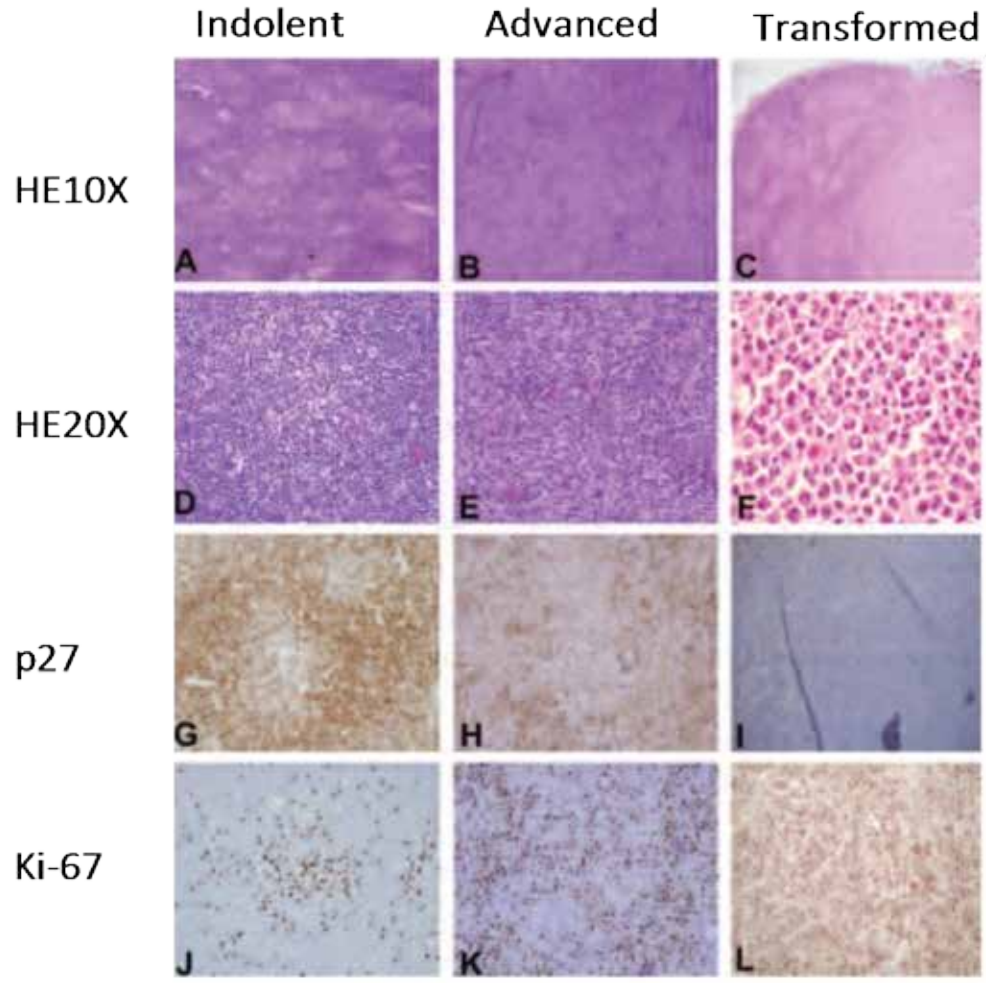
Médula ósea

- Incremento proporción de células proliferantes
- Células accesorias :
  - BMSC: quimioatracción, supervivencia, proliferación y quimioresistencia

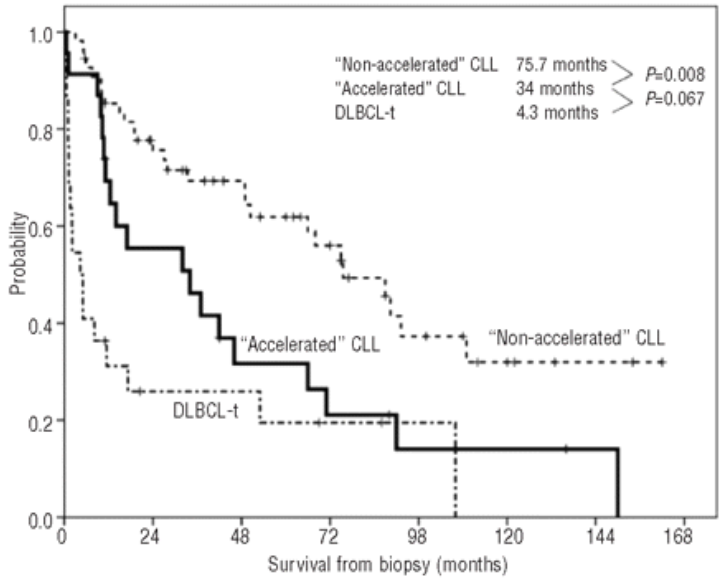


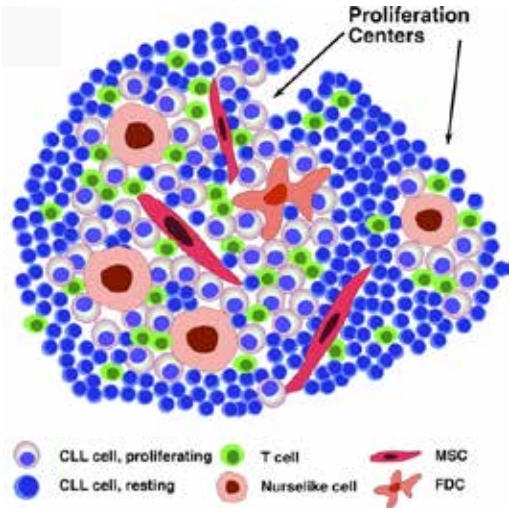
Burger et al, Blood, 2009

“Accelerated CLL”: cell proliferation as prognostic marker



Giné et al, Haematologica, 2010





Diagnóstico Hematológico Integrado

Curso on-line DIH

e.alonso@vhebron.net

mjmontoro@vhebron.net

Gracias!