XVIII IWCLL

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Clinical Assessment of CLL

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Disclosures

Advisor/ Consultant/Speaker: Janssen, Abbvie, Pharmacyclics, Gilead, Roche

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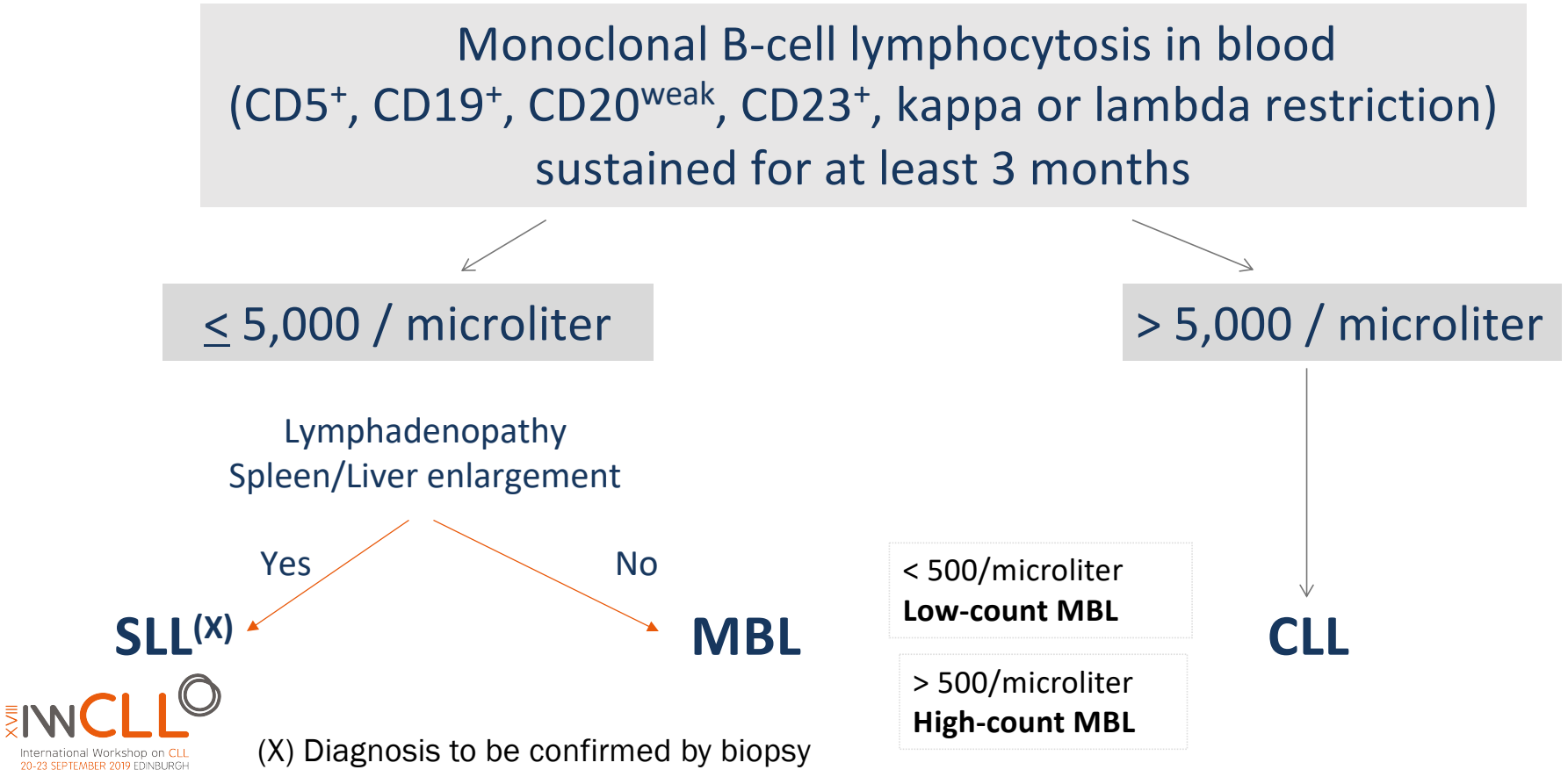
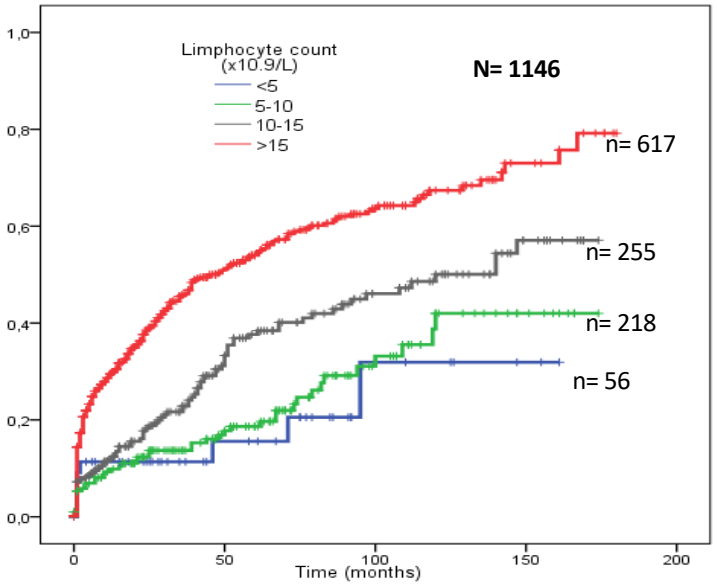
CLL, SLL, and MBL: Diagnosis



Lymphocyte count threshold for diagnosis

Time to treatment according to the lymphocyte count at diagnosis



Time to treatment based on lymphocyte count	
Lymphocyte count ($x10^9$/L)	**Median time to treatment (months)**
< 5	**Not reached**
5 -10	**Not reached**
10 -15	**120**
> 15	**45**

Courtesy of E. Montserrat – Hospital Clinic Barcelona (data on file)

See also Shanafelt et al. Blood 2009; Molica et al, Haematologica 2011; Scarfo et al, Leukemia 2012

Tests that may be useful for diagnosis

- Additional markers to refine diagnosis in difficult cases[1,2,3]
  - **CD200**
  - ROR-1, CD43, CD79b, CD81, CD10.

- In cases with atypical immunophenotype, cyclin D1 immunohistochemistry and FISH t(11;14) should be done.

  - The term “atypical CLL” should be avoided. “Atypical CLL” is not a diagnosis.

[1]Rawstron et al, Cytometry B Clin Cytom 2018; [2]Alba et al, Cytometry B Clin Cytom 2019; [3]Sorigue et al, Cytometry B Clin Cytom 2018

Key-elements of medical history and diagnosis

MEDICAL HISTORY	Co-morbidities (CIRS) Family history of CLL, lymphoma, autoimmunity or cancer
CLINICAL PRESENTATION	Past laboratory exams with neglected lymphocytosis General (“B”) symptoms
PHYSICAL EXAMINATION	Signs of anemia (pallor), thrombocytopenia (bruising, petechiae) or hemolysis (jaundice) Lymphadenopathy, splenomegaly, hepatomegaly Extranodal involvement, skin cancers?
LABORATORY	Complete blood cells counts Blood smear exam LDT (past lab exams; linear regression over 3 -6 m.) Flow-cytometry Reticulocytes DAT Biochemistry: basic, liver and renal function, LDH, B2M Protein electrophoresis HBV, HCV
LN, BONE MARROW B.	If clinically indicated, not essential for diagnosis
IMAGING STUDIES	As clinically indicated, not on a routine basis.

Other tests at diagnosis?

- *TP53* aberrations by FISH and molecular genetics
- IGHV mutational status

However

- In clinical practice, only patients with active disease should be treated.
- With the only exception of IGHV mutational status, outcome biomarkers may change during the course of the disease, before treatment is needed.

Are outcome predictors useful at diagnosis?

- **Pro:** *advice patient* **Con**: *unnecessary worries*

Guidelines for CLL

- **International Workshop on Chronic Lymphocytic Leukemia** (iwCLL) (June 2018)
- **National Comprehensive Cancer Network** (NCCN) (Version 5.2019-May 23, 2019)
- **European Society of Medical Oncology** (ESMO) (submitted, September 2019)

- National Guidelines

Pretreatment evaluation (1)

	iwCLL 2018	NCCN 2019	ESMO 2019
History and physical examination (size of lymph nodes, spleen, liver) /PS	yes	yes	yes
CBC and differential count	yes	yes	yes
Marrow aspirate and biopsy	When clinically indicated	When clinically indicated	When clinically indicated
Serum chemistry, IgG levels, DAT	yes	yes	yes
Infectious disease status	yes (HBV, HCV, CMV, HIV)	yes (HBV, and e antigen, CMV)	yes (HBV, Hepatitis E HCV, CMV, HIV)

Pretreatment evaluation (and 2)

	iwCLL 2018	NCCN 2019	ESMO 2019
Molecular cytogenetics FISH for (del(13q), del(11q), del(17p), add(12)	yes	yes	yes
Stimulated metaphase karyotyping[1]	NGI	NGI	yes
TP53 mutation	yes	yes	yes
IGHV mutational status[2]	yes	NGI	yes
Imaging studies (CT, MRI, PET.CT)	NGI	NGI	NGI

NGI, not generally indicated; PET, positron emission tomography; MRI, magnetic resonance imaging

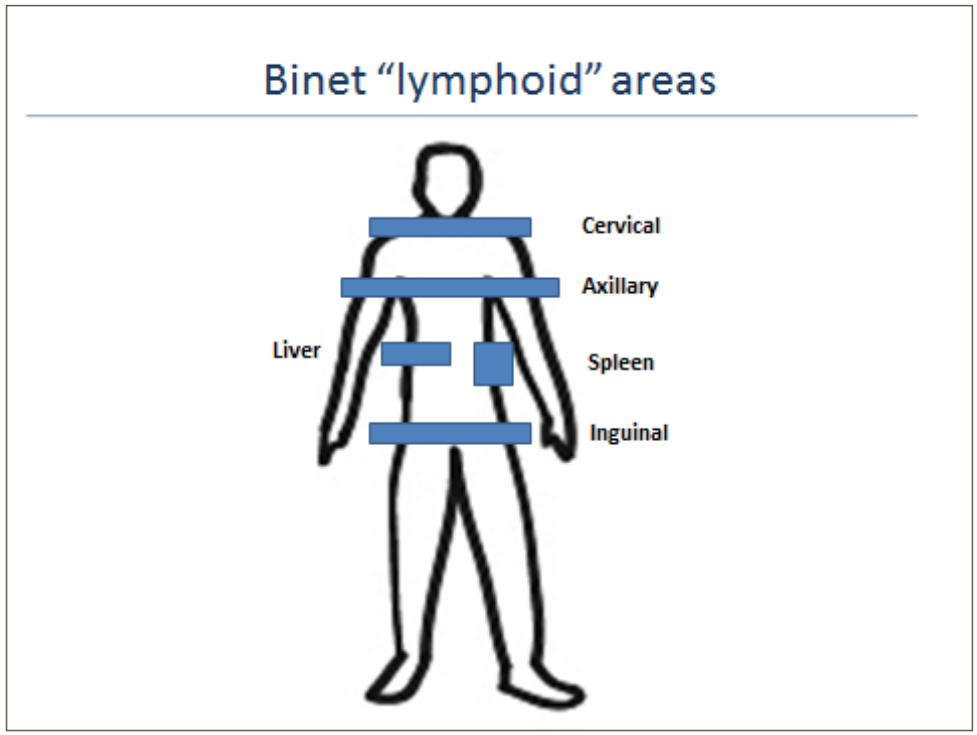
[1] Conventional karyotyping may be useful before therapy (i.e, complex karyotype)

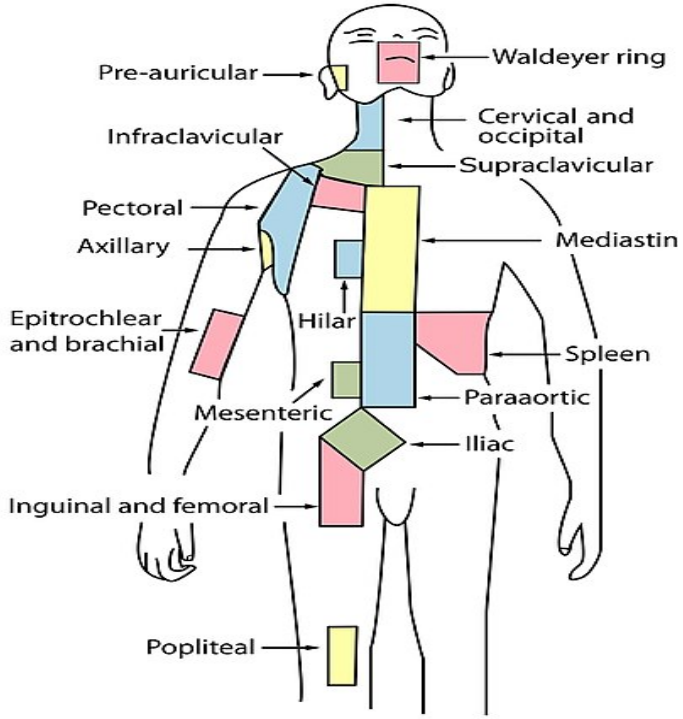
[2] IGHV rearrangements involving VH3-21 (sterotype subset 2) carry a poor prognosis even if mutated

CLL: Clinical Stages

RAI			
Low-risk	Stage 0	lymphocytosis	> 15 yrs
Intermediate-risk	Stage I	lymphadenopathy	7-8 yrs
	Stage II	Spleen/Liver enlarged	
High-risk	Stage III	Hb < 11	5-6 yrs
	Stage IV	Platelets < 100,000	
BINET			
Low-risk	Stage A	< 3 lymphoid areas enlarged	> 15 yrs
Intermediate-risk	Stage B	≥ 3 lymphoid areas enlarged	7-8 yrs
High-risk	Stage C	Hb < 10 Platelets < 100,000	5-6 yrs

Open issues in clinical staging





Areas of involvement considered for staging include: 1) Head and neck, including the Waldeyer ring (this counts as 1 area even if more than 1 group is enlarged; 2) Axillae (involvement of both axillae counts as just 1 area); 3) Groins, including superficial femorals (involvement of both groins counts as just 1 area); 4) palpable spleen; 5) palpable liver

Imaging studies

	N	Aim	Conclusions
CT			
Muntañola et al[1]	140	Px value in early stage	Association with adverse Px factors and disease progression
Gentile et al[2]	240 (69)	Px value in early stage/MBL	Association with adverse Px factors and disease progression
Eichhorst et al[3]	1372	Px value in the follow up pts with advanced stage	No impact on Px value of bulky disease, detection of clinical relapse and response assessment after CIT
PET/CT			
Falchi et al[4]	332	Correlation PET (SUV > 10) with RS	Strong correlation between histological features and PET CT Maximum SUV > 10 associated with short OS
Bruzzi et al[5]	37	Correlation of PET (SUV >5) with RS	High sensitivity and high negative predictive value
Michallet et al[6]	240	Correlation with RS and determine SUV > 10 as marker for RS	Good correlation between RS and PET CT and SUV max 10 better than 5 to distinguish RS
Mato et al[7]	167	Predictive value of PET CT after BCRi failure	Low specificity to detect RS after BCRi failure SUV max cut off of 10 did not predict RS development on venetoclax

Px, prognostic; CIT, chemoimmunotherapy; PET, positron emission tomography; SUV, standardized uptake value; RS, Richter syndrome; OS, overall survival

[1]Muntañola et al 2007; [2]Gentile et al Am J of Hematol 2013; [3]Eichhorst et al, Blood 2011; [4]Facci et al, Blood 2014; [5]Bruzzi et al, J Nucl Med 2006; [6] Michallet et al Leukemia and Lymphoma 2016; [7]Mato et al, Haematologica 2018

Imaging studies

Although CT scans/PET CT may be helpful to predict progression/or detection of RS and identify sites to target for biopsy (in the context of chemoimmunotherapy)

General recommendation in all guidelines is that *"outside clinical trials imaging studies are not necessary for diagnosis, surveillance, routine monitoring of treatment response or progression"*

Identifying a reliable surrogate for lymph node involvement and bulky disease could be useful

Conclusions

- Current guidelines ensure a uniform diagnosis and management of patients with CLL.
- iwCLL, NCCN, and ESMO guidelines show a high degree of agreement.
- Because most patients with CLL are not treated in academic centers, guidelines must be as simple as possible, but at the same time should identify areas deserving research.
- Guidelines must be adapted to new treatment agents and management tools, regular updates being necessary.
- Modifications in guidelines should be based on robust practice-changing data.

Thank you!

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