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6th PCRDT

WorkPackage 10

CONSENSUAL EUROPEAN IMMUNOPHENOTYPING PANELS FOR LEUKEMIA

Introduction

This document is the result of an extensive consultation of European experts in the field of immunophenotyping in hematologic disorders. The work was based first, on a brainstorming meeting of the European Group for Immunophenotypic characterization of Leukemias (EGIL), which produced an initial matrix, second, on two half-day meetings of volunteer participants in the ELN WP10, and third, on a large e-mail consultation and circulation of the consecutive drafts.

It was made very clear by the participants that this should be a practical, but mostly *evidence-based panel*, produced as the initial key proposal before more elaborated recommendations dealing for instance with the use of marker combinations, fluorochromes or evaluation of minimal residual disease in flow cytometry.

The three latter topics are on the agenda of WP10 for the forthcoming months, but it was first necessary to obtain consensus on the immunophenotyping strategies. For this reason, some markers that may be considered useful by some groups were not initially included, although it is clearly stated in this document that any combination considered useful for patient's follow-up remains open. Likely, more tuned-up proposals will be elaborated in a near future through networking with the clinical groups of the European LeukemiaNet.
The following document comprises two parts.

The first provides recommendations as to the immunophenotyping of acute leukemias. One important feature to be stressed is the difference between the occasional aberrant expression on leukemic cells (2,21) of markers considered associated to another lineage (CD13, CD33) or known to display lineage promiscuity (CD7, CD4, CD19), and the clinically relevant identification of biphenotypic acute leukemias (BAL) as defined by scores higher than 2 in more than one lineage as proposed by EGIL (5). Another important characteristic of adequate immunophenotyping at diagnosis is that it should provide all relevant indications to the clinician, including classification of the disease, according to maturation arrest stages (6). For this reason, the first panel exposed is considered mandatory BUT not sufficient in most cases, a selection of markers from the second panel being necessary to strengthen the diagnosis. Indications as to the usefulness of the markers proposed have been provided and referenced. Also useful to read is the extensive review published in 2003 (33).

The second part of the document deals with chronic lymphoproliferative diseases, and again proposes a mandatory panel allowing the diagnosis and scoring (for B-CLL and lymphomas) of these disorders (18,23,35). It was unanimously proposed that the question to be answered was that of lymphocytosis and/or lymph node and/or skin involvement, notwithstanding potential clinical indices of a given type of proliferation. This part also includes recommendations for the immunophenotyping of myeloma. It is summarized, at the very end of the document, in a cartoon associating these disorders to the various types of mature B-cells that can be found during post-medullary differentiation, notably in lymph nodes.

Finally, a list of recent references supporting the statements expressed, but by now means exhaustive, is provided at the end of the document.

A diagnostic laboratory performing Acute Leukemia immunophenotyping should be able to recognize:

1. Biphenotypic Acute Leukemias: BAL (5,36)
2. Acute Lymphoblastic Leukemias: ALL (5)
    a) B lineage : B-I, B-II, B-III, B-IV (32)
    b) T lineage : T-I, T-II, T-III, T-IV (45)
3. Acute Myeloblastic Leukemias: AML (11,57)
    a) M0 (7)
    b) Granulocytic and monocytic differentiation (56)
    c) Acute promyelocytic leukemia : APL (42)
    d) Erythroid (15)
    e) Megakaryocytic (17)
4. Dendritic cell precursor neoplasms (8,24)
5. Basophil, Mast cell precursors neoplasms (16)

In addition, diagnosis of lymphoma, non haematological neoplasms and reactive cytopenias should be excluded.

Consensual Mandatory Acute Leukemia Diagnosis Panel (27)

For quick orientation or paucicellular samples

- cCD3, MPO, cCD79a, TdT (5)
- CD7, CD2, CD10, CD19, CD22 (s or c), sIg, CD13, CD33, CD34 (5)
- CD45 for gating purposes (28,47)

Sublineage classification and definition of clinical entities (also with adapted gating strategy)

- DR, CD1a, CD4, CD5, CD8, CD3 (m), IgM (c), CD14, CD117, CD56, CD65, CD41 or CD61, RBC marker such as CD238 (glycophorin A) or CD36.

Acute leukemia Diagnosis Panel
Other useful markers (≥20)

- MPO/LF (lactoferrin) (c): (i) Identification of late neutrophil granulocyte compartment (Lactoferrin positive) (25,52,54); (ii) for refined detection/quantification of MPO+ early myeloid cells in combination with CD14 (25,49)
- LZ (lysozyme) (c): (i) for myeloblastic leukaemia; (ii) to discriminate pDCs and myeloid cells (53); (iii) to positively identify early monocytic cells (48)
- K/L : (i) on surface for clonality, (ii) in the cytoplasm for rare B-IV cases
- CD11b, CD11c : negative in APL (14)
- CD15 : for myeloblastic leukemia (42)
- CD16 : to discriminate mature PMNs (9)
- CD35/36 : for GEIL´s AML classification (11), for RBC after excluding monocytes (10)
- CD58 : to distinguish between normal regenerating B cells and B-cell blasts (59)
- CD64 : for AML (9)
- CD68 (c): (i) for AML (bright) and subset of B-ALL (weak) (53); (ii) for positive identification of normal pDCs (bright) (55)
- CD71 : for cell proliferation/activation and/or RBC (22,41)
- CD86 : prognostic factor in AML (34)
- CD99 : to differentiate between blasts and non blastic T-cells (19)
- CD123 : IL-3 R, for pDC and AML, some NK (24)
- TCR chains for T-ALL, c and/or s (50)
- Therapeutic targets: CD20 (40), CD52 (40), CD45 (39), CD33 (31), CD123 (3), CD87 (46), CD44 (20), uPAR(CD87)/uPACD116 (1)

These panels are intended for diagnostic purposes of acute leukemia. They may need to be completed using markers that will prove later useful for MRD

A Laboratory doing lymphoproliferative diseases immunophenotyping should be able to recognize features compatible with:

Clinical question arising from lymphocytosis and LN or skin involvement

- CLL (35)
- HCL (13)
- B-Cell lymphomas (27)
  - Burkitt
  - Follicular lymphoma (compatible with..)
  - Mantle cell lymphoma
  - Marginal zone lymphoma (37)
  - And others…*
- T- cell proliferative disorders, Sezary (38)
- LGL (29,51)
- NK proliferative disorders (51)

*for some diseases there are no clear correlations between the immunophenotype and the pathological findings

Chronic lymphoproliferative diseases.
Mandatory panel (22 Abs)

Samples : peripheral blood, bone marrow, LN suspensions… (Fine needle aspiration for primary screening to avoid unnecessary biopsies) (26,27,58)

- *Gating markers*

CD19, CD3, CD56*

- *B oriented panel gated on CD19*

CD5, CD20, CD22, CD23, CD103, FMC7, CD10, K, L, Ig, CD25, CD79b, CD38

- *T oriented panel gated on CD3 or other T-lineage marker*

CD2, CD3, CD4, CD5, CD8, CD7

**Caution : CD56 has a broader specificity than just NK lineage*

**Aberrant panels are useful for post-therapy follow-up*

Lymphoproliferative diseases: additional useful markers (≤ 15)

- *B lineage*

  CD2, CD7, CD123, CD138, DR, CD24*, CD43

  (G, A, M, D), CD81*

  Cytoplasmic : Bcl2, Zap70 (relative to internal control) (12)

- *T lineage(4,30)*

  TCRs*, CD30, CD10

  NK panel excluding CD19 and CD3 cells/ CD56

  CD57, CD16, CD94, perforin, granzyme B

** Absence of CD24 on marginal zone and HCL*

**CD81/CD22 useful for CLL follow-up based on dim co-expression level*

**V-beta panel and immunophenotype*

Particular case of Multiple Myeloma (44)

- CD38, CD19, CD138, CD56, CD45
- Cytoplasmic light chains

- Other interesting markers

  Cytoplasmic heavy chains

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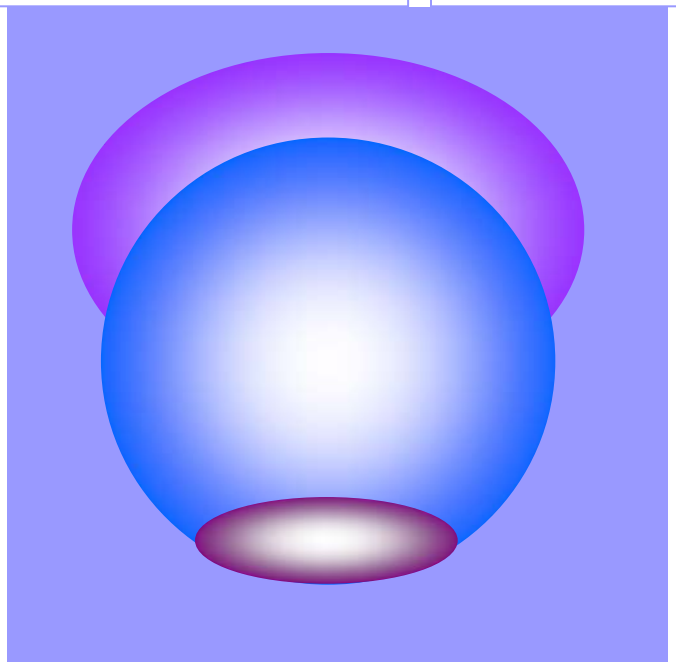
MARGINAL ZONE CD19, CD20, CD22, CD79, sIg, FMC7, bcl-2 (CD5, CD10, CD23, CD24, bcl-6 neg)
NODAL MALT
CLL *CD19, CD20, CD23, sIg+/-, CD5 (CD79, CD10, CD22, FMC7 neg)*
HCL *CD19, CD20, CD22, sIg++, CD11c, CD25, CD103 (CD5, CD10, CD23, CD24 neg)*

T LYMPHOMAS
SEZARY CD3, CD2, CD5, CD4, CD7+/- (CD8 neg)
LARGE CELLS ANAPLASTIC CD2, CD4, CD3+/-, CD30
PERIPHERAL CD2, CD3, CD5, CD4
ANGIOCENTRIC CD2, CD5, CD4 ou CD8, CD56
INTESTINAL CD3, CD7, CD103



MANTLE ZONE CD19, CD20, CD22, CD79, CD5, CD43, bcl-1 (CD10, CD23 neg)

BURKITT CD19, CD20, CD22, CD79, sIg, CD10, DR, bcl-6 (CD5, CD23, Tdt neg)

FOLLICULAR CD19, CD20, CD22, CD79, sIg, CD10 (CD5, CD23, CD43 neg)

INTESTINAL OR LUNG MALT
Follicular, mantle zone, marginal zone

WALDENSTROM CD19, CD20, CD22, CD79 cIg, FMC7 (CD5, CD10, CD23 neg)

CENTROBLASTIC or IMMUNOBLASTIC
Large cell Lymphomas CD19, CD20,CD79, CD22++, CD79, CD10+/- (CD5 neg)

SLVL
Circulating marginal zone

MYELOMA cIg, CD56, CD45, CD38, CD138 (CD19, CD20, CD22 neg)

Compiled by A Kennel & MC Béné, 2005