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Review

The FAB classification for acute myeloid leukaemia—is it outdated?

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1. Introduction

The purpose of a classification is not only to group diseases with the same biological characteristics, but also to get insight into the pathogenesis and to define subgroups with different prognoses and different therapeutic approaches. In acute leukaemias the classification now most widely used is the French-American-British (FAB) classification as proposed in 1976, which was based on morphology and cytochemistry [1]. The FAB group felt that discrimination of myeloblasts from lymphoblasts on morphological characteristics only was insufficient. For this reason they proposed to define the difference between acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) by the positivity or negativity respectively of the blasts for the myeloperoxidase (MPO) or Sudan B Black reaction. Within acute myeloid leukaemia 6 categories were discriminated (M1-M6) by morphology and the use of α-naphthyl acetate esterase (ANAE) to discriminate monoblasts from myeloblasts [1,2].

Later, immunological markers were used to define two new subtypes in acute myeloid leukaemia, the acute leukaemia with minimal myeloid differentiation (AML-M0) and the megakaryoblastic leukaemia (AML-M7), both being Sudan B Black negative but not lymphoblastic (Table 1) [3–5]. Immunological marker analysis, however, was not introduced into the FAB classification for ALL, even when the subdivision of the acute lymphoblastic leukaemias into L1 and L2, merely based on the size of the blasts, showed very little relevance to their biological features and prognosis [1,7]. Immunological marker analysis is pivotal in the classification of ALL. In this way not only the distinction between T and B lineage ALL can be made, but also distinct subgroups within these categories can be defined which are of biological and prognostic relevance [8,9]. The definition of L3, morphologically distinct from L1 and L2, and also with a typical immunological phenotype is overruled by the presence of a translocation of the MYC oncogene located on the long arm of chromosome 8 to either the immunoglobulin heavy-chain gene on chromosome 14 (t(8;14)) or to one of the light-chain genes on chromosome 2 or 22 (t(2;8) or t(8;22)) in nearly 100% of cases [10–12].

The question then arises with respect to AML which on morphological and cytochemical grounds is much more differentiated than ALL, what im-

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Table 1
Summary of the FAB classification of AML

FAB subtype	Definition
M0	< 3% SBB + * blasts, My + **, Ly − ***
M1	> 90% blasts
M2	30–90% blasts > 10% myeloid cells < 20% monocytoid cells
M3	majority promyelocytes hypergranular
M3V	microgranular
M4	> 20% mature myeloid cells and > 20% ANAE + **** blasts $> 5 \times 10^9$/l monocytes in the blood
M5	> 80% monocytoid cells
M6	> 50% nucleated erythroid cells > 30% blasts of myeloid cells of the non erythroid population
M7	< 3% SBB + blasts > 30% megakaryoblasts defined by CD41/CD61 or electron microscopy with platelet peroxidase

* Sudan Black B.
** Myeloid markers positive (CD13, CD33, myeloperoxidase, CDw65).
*** Lymphoid markers negative (CD3, CD5, CD10, CD19).
**** α-Naphthyl acetate esterase.

munological markers and cytogenetic analysis may contribute to the characteristics of the different subtypes.

2. Concordance

Essential to any classification is an acceptable level of reproducibility between observers. In the FAB classification the introduction of cytochemistry contributed to concordance compared to morphology alone, as did the definition of quantitative criteria for acute leukaemias, for instance, to distinguish acute myeloid leukaemias from the myelodysplastic syndromes [1,2,13]. But even then the reproducibility between observers varies from 45.7 to 86.8% [14–18]. Review of AML bone marrow smears by the Dutch Slide Review Committee of Adult Leukaemias gives about 80% agreement. Most problems arise in discrimination between M1 and M2 and between M2 and M4 [19]. The addition of immunophenotyping to morphology and cytochemistry improves agreement between independent observers, although the estimation of Browman et al. who described an improvement to 99% seems fairly optimistic [14].

3. Correlation between FAB subtypes and immunological phenotype

Immunophenotyping can be helpful in confirming the diagnosis of AML and is indispensable in differentiating AML-M0 and AML-M7 from ALL (Table 1) [3–6]. For discrimination between myeloid leukaemias (M1-M3) and monocytic leukaemias (M4, M5) CD14 shows some correlation with monocytic leukaemias but is not very sensitive, being negative in the early monoblastic leukaemias [20,21]. Because distinct myeloid differentiation antigens are lacking, no further discrimination can be made immunologically between M1 and M2 than by the quantitative criteria of the FAB classification [19]. AML-M3, morphologically divided into two subtypes (hypergranular and hypogranular), both strongly positive for the myeloperoxidase reaction, shows a typical immunological pattern (CD13 +, CD33 +, CD9 +, CD68 +, CD34 −, HLA-DR −, CD15 −), but this pattern gives little additional information to a classification as the morphology itself is very characteristic and cytogenetic analysis is definite [22,23].

4. Correlation between FAB subtypes and karyotype

Some chromosomal abnormalities are correlated to certain AML FAB subtypes and are of prognostic importance (Table 2). No specific chromosomal pattern was found in AML-M0 in different recent stud-

Table 2

Chromosomal translocations	FAB classification	Relative prognosis
t(8;21)(q22;q22)	M2	fair to good
t(15;17)(q22;q21)	M3	fair to good
inv(16)(p13;q22)/t(16;16)(p13;q22)	M4eo	good
t(9;11)(p21;q23)	M5	poor
t(11q23)	M4–M5	poor
t(6;9)(p23;q34)	M2, M4	poor
t(8;16)(p11;p13)	M5	undetermined
inv(3)(q21;q26)/t(3;33) t(1;3)(p36;q21)	M4	undetermined
t(1;22)(p13;q13)	M7	undetermined

ies [24–27]. In contrast, a higher frequency of abnormal karyotypes, complex karyotypes and unbalanced chromosomal changes (−5/5q− and/or −7/7q− and +13) compared with AML-M1 were observed by Cunea et al. in a large study of 26 patients, which may partly account for the very poor outcome in these patients [28]. Ninety percent of the patients whose leukaemia shows t(8;21)(q22;q22) have AML-M2. This subtype has a better prognosis than other subtypes [29]. In contrast, many leukaemias categorized as M2 have other or no cytogenetic abnormalities and may be derived from transformed myelodysplastic syndromes or early diagnosed AML-M1 having less than 30% blasts but with a maturing granulocytic component like AML-M2. As stated, virtually all promyelocytic leukaemias (M3) have t(15;17)(q22;q21). Hence one should reconsider the M3 classification if t(15;17) cannot be demonstrated. This subtype, clinically characterized by its bleeding tendency, needs special treatment with retinoid acid and has a better prognosis than the other subtypes [30]. The good prognostic inv(16)(p13q22) is associated with the diagnosis of M4 EO [31]. Common translocations such as t(6;11)(q26q23), t(9;11)(p21;q23) and t(11;19)(q23;p13) are found in monocytic leukaemias [29]. In acute myeloid leukaemia originating from myelodysplastic syndrome −5/5q− or −7/7q− is frequently found, and has a poor prognosis [32]. Complex karyotypic abnormalities are also associated with a poor prognosis [31]. Thus, to define the prognosis of certain AML subtypes, cytogenetic analysis is indispensable.

5. Differentiation between MDS and AML

The discrimination between AML and refractory anaemia with excess of blasts in transformation (RAEB-t) is based on the limit of 30% of nucleated bone marrow cells being blasts for the latter [1,2,13]. This 30% limit is arbitrary and with this limit not all cases of acute leukaemias will be recognized. For example, patients with *de novo* AML with a rapidly rising blast count but less than 30% blasts will not be regarded as having acute myeloid leukaemia. Immunophenotyping makes no contribution in distinguishing between AML and MDS, but cytogenetical analysis will add important information. In *de novo* AML translocations are often found; in the myelodysplastic syndromes, on the other hand, numeric chromosomal abnormalities such as −5/5q−, −7/7q− or +8 are more frequently observed [32–34].

6. Sudan B Black negative acute leukaemias

Following the FAB classification, Sudan B Black negative acute leukaemias are of myeloid (M0), megakaryocytic (M7) or lymphoblastic origin (ALL) [3–5]. However, there are some other Sudan B Black

Table 3
Definition of subtypes in Sudan B Black negative leukaemias

Subtypes	Immunophenotype	
ALL	Ly + ***	
AML M7	CD41 and/or CD42 and/or CD61	
AML M0	My + ****, Ly − *****,	CD34 +, HLA-DR +
AEL *	no lineage markers available	(CD34 +, HLA-DR +)
AUL **	My − ******, Ly −	(CD34 +, HLA-DR +)
SBB negative biphenotypic AL	My +, Ly +	(CD34 +, HLA-DR +)

* AEL = hypothetical acute erythroblastic leukaemia (less differentiated than AML-M6).
** AUL = acute undifferentiated leukaemia.
*** Lymphoid markers positive (CD3, CD22, CD79a).
**** Myeloid markers positive (CD13, CD33, myeloperoxidase, CDw65, CD117).
***** Lymphoid markers negative.
****** Myeloid markers negative.

negative acute leukaemias not described in the FAB classification such as acute undifferentiated leukaemia (AUL) and acute erythroblastic leukaemia (Table 3). Without immunophenotyping the classification of acute undifferentiated leukaemia is impossible [35,36]. For the hypothetical early erythroblastic leukaemias no early erythroid markers are available so far. Most often the undifferentiated or minimally differentiatied leukaemias are CD34 + [24–26,35,36]. It is not known if cytogenetical analysis adds more information in these subtypes.

7. Biphenotypic and bilineage acute leukaemias

In the FAB classification there is a strict discrimination between acute myeloid leukaemia and acute lymphoblastic leukaemia. However, a small subset of leukaemias (less than 5%) consist of leukaemic cells expressing markers of both myeloid and lymphoid lineage (biphenotypic leukaemias) or consist of two different populations of cells each expressing different markers (bilineage acute leukaemias) [3,38]. Markers expressed on more than 20% of the blasts are considered positive, except for TdT (more than 10% expression). Here, the FAB classification is lacking and immunophenotyping is essential for the recognition of these types of leukaemias. Catovsky et al. proposed a scoring system to distinguish biphenotyping acute leukaemias from acute leukaemias with aberrant expression, using immunophenotyping and rearrangement of the B or T-cell receptor [3,37]. This scoring system has recently been updated by the European Group for Immunophenotyping of Leukaemias (EGIL) [38]. Prognosis and choice of treatment are difficult to determine since larger studies are never published, but the prognosis seems very poor.

8. Prognostic value of the FAB classification

In AML, some differences in prognosis are seen between the different AML FAB subtypes. AML-M0 has a worse outcome than all other subtypes of AML [24,26–28]. M1 shows a lower remission rate than M2 and M4. M3 has a much better prognosis than the other subtypes. M5, M6 and M7 show a lower remission rate [19,39]. Immunophenotyping is of no prognostic value. Studies on the prognostic value of CD34 expression are inconclusive, as is CD7 expression [40–43]. The prognosis for the different FAB subtypes is best correlated with characteristic cytogenetic abnormalities—e.g., t(15;17), t(8;21), inv(16) or del(16) (Table 2) [29–31].

9. Conclusions

The FAB classification is a good guide to classifying AML, on the basis of morphologically recognizable criteria, but is insufficient for the recognition of undifferentiated leukaemias, Sudan B Black negative non-lymphoblastic leukaemias, biphenotypic and bilineage leukaemias, and certain important subgroups like t(8;21) in AML-M2. Immunophenotyping and cytogenetics are therefore indispensable. An attempt to integrate morphological, immunological and cytogenetic methods into a new classification was made by the MIC Cooperative Study Group (Table 4), but so far only 10 categories have been defined, which means that not all acute myeloid leukaemias can be categorised in this classification [44].

In addition, several new techniques can make important contributions to the diagnosis and monitoring of acute leukaemias. Fluorescent in situ hybridization (FISH) can be routinely used to identify specific chromosomes involved in chromosome

Table 4
The MIC classification of AML

Karyotypic change	Morphology (FAB)	Suggested MIC nomenclature
t(8;21)(q22;q22)	M2	M2/t(8;21)
t(15;17)(q22;q12)	M3, M3v	M3/t(15;17)
t/del/(11)(q23)	M5a(M5b, M4)	M5a/t(11q)
inv/del(16)(q22)	M4Eo	M4Eo/inv(16)
t(9;22)(q34;q11)	M1(M2)	M1/t(9;22)
t(6;9)(p21–22;q34)	M2 or M4 with basophilia	M2/t(6;9)
inv(3)(q21q26)	M1(M2, M4, M7) with thrombocytosis	M1/inv(3)
t(8;16)(p11;p13)	M5b with phagocytosis	M5b/t(8;16)
t/del(12)(p11–13)	M2 with basophilia	M2 Baso/t(12p)
+4	M4(M2)	M4/+4

translocations [45,46]. More cells can be observed than with cytogenetic analysis and it is not restricted to cells in metaphasis. Direct correlation of chromosomal abnormalities with morphology or immunological markers is possible by this technique [47,48]. The polymerase chain reaction (PCR) is used as a fast and reliable technique to detect chromosomal re-arrangements, e.g., t(8;21) and t(15;17), at diagnosis and can be used for the detection of minimal residual disease after treatment due to its high sensitivity [49–51].

Expression of P-glycoprotein, a protein associated with multidrug resistance and treatment failure, may be of prognostic significance [52,53].

Thus, the FAB classification is not outdated for the diagnosis of AML, but it does require other procedures for refinement of the diagnosis and determination of the prognosis. This classification remains an important cornerstone of a 'combined modality' classification of the acute myeloid leukaemias.

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