Acute Myeloid Leukemia

Telehematology: a pilot experience of cytological diagnosis of acute myeloid leukemia via the Internet. A GOELAMS study

Although modern communication technology is well developed, telehematology does not readily lend itself to practical laboratory use. Multicenter therapeutic protocols may offer preferential opportunities. The cytologists of the AML-2001 protocol established an innovative organization to demonstrate the reliability of the diagnostic assessment of acute myeloid leukemia through a rapid and decentralized exchange of information via the internet and to define the conditions optimizing expert diagnosis. Telediagnosis appears to be a powerful tool for cytological review and other issues.

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The AML-2001 is a multicenter study of adult patients with *de novo* acute myeloid leukemia (AML), excluding those with M3. Each participating center is equipped with a work station consisting of a personal computer, high grade microscope, charge-coupled device camera and Tribvn-ICS software® that allows for digitization and transmission of cell images and biological data via a standardized multimedia folder through the internet. In the pre-phase study, the participating cytologists defined working guidelines to standardize several factors (e.g. staining procedures, digitizing rules) which may influence the images and the experts' opinion. In order to sample representative images, each image collection contains at least several contiguous images: peripheral blood films (May-Grünwald-Giemsa (MGG) staining): 5 fields (×40), 5 (×100); bone marrow MGG-stained slides: 1 image (×10), 5 (×40) 15 (×100); cyto-chemical stained films (myeloperoxidase and α-naphthyl-butyrate-esterase stains): 5 fields (×100). A minimum of 30-50 blast cells and minimal cell numbers for evaluating persistent hematopoiesis are required. The patient's folder also contains biological data (cell counts, immunophenotype, etc.). For each newly included patient, a complete data folder is submitted to the server repository. Subsequently, the coordinating cytologists, informed by e-mail, select two review centers (R1 and R2) from among the participating institutions (n=28). These centers examine the data folder and, after review, submit back their own independent interpretation. All the proposed diagnoses follow the criteria of the WHO classification using an updated standardized α-numeric library codification.[1] There is a specific application to handle contradictory diagnoses.

Ten months after initiating the study, 84 multimedia folders (out of 100) had been fully reviewed (Table 1). These folders contained more images than anticipated at each of the magnifications used. The numerized cell numbers did not significantly vary from the AML subtypes or from the presence or lack of dysplasia (χ^2 Yates). Only nine of the 178 reviewers (R1 or R2) made minor critical observations about the quality of the data folders. The overall time from inclusion to expert review was about 65 days (±12). The organization, executed upstream, allowed for a rapid diagnostic assessment consistent with inclusion and constituted improved quality assurance more so than the classical slide review.

The morphological review system has been detailed for only one large series from among all the major cooperative AML studies.[2] In this work, each diagnosis was consensually re-considered by a centralized committee that re-examined the initial slides. The proportion of agreement was 77%. It should be noted that only two cytological opinions were compared in this study and that the major problem of assessing dysplasia was not taken into account. Our telediagnosis system resulted in absolute agreement between the assessment made by the initial diagnostic center (IDC), R1 and R2 for 56 folders (66.6%). There was total disagreement for only one folder (1.2%) (*not detailed*). Using the κ coefficient, the comparisons performed in pairs between the different proposed diagnoses always showed satisfactory agreement. A fourth independent review, based on examination of the initial slides by two external experts (termed the gold standard) did not reach better concordance versus IDC than the IDC versus R1 or R2 (Table 2).[3,4] This demonstrated reproducibility excludes any major problem of selection bias in the sampling of image files. Moreover,

Table 1. Cytological review: FAB/WHO subtypes in the 100 analyzed multimedia folders.

FAB/WHO subtypes	*IDC (initial slide examination)*	*R1 (electronic review)*	*R2 (electronic review)*	*GS (slide review)*
AML with t(8;21)	4	5	6	5
AML with inv16	5	6	6	8
AML with multilineage dysplasia	18	19	15	9
AML M0	3	4	5	5
AML M1/M2	31	28	33	33
AML M4	7	7	7	10
AML M5	15	13	10	13
AML M6	1	1	1	1
AML M7	1	1	1	1
AML unclassified	0	0	1	5
Missing folders	15	16	15	10
	100	100	100	100

One hundred consecutive patients are prospectively were analyzed. Each diagnosis was evaluated four times: first by the initial diagnostic center (IDC) on the initial blood and bone marrow slides by two independent reviewers on the electronically transmitted folders (R1 and R2) and, finally, to fully evaluate the reproducibility of the telediagnosis, a direct slide review termed the gold standard (GS) was also performed by two other independent experts who were unaware of the initial diagnosis (IDC) and the review assessments (R1 and R2). The GS was established in 85 cases. For 10 patients, the slides were not transmitted and for 5 others the external experts declined to give their opinion because of the poor quality of the transmitted smears. The distributions of the diagnoses are summarized here. AML with multilineage dysplasia is the category showing the greatest dispersion. The global concordance between the different assessments was evaluated by the κ coefficient.

Table 2. κ coefficient (κ): diagnosis agreement analysis.

κ	*Gold standard (GS)*	*Initial diagnostic center (IDC)*	*Reviewer 1 (R1)*
Initial Diagnostic centre (IDC)	0.65	–	–
Reviewer 1 (R1)	0.59	0.71	–
Reviewer 2 (R2)	0.58	0.66	0.71

The comparisons performed in pairs between the four independently proposed morphological diagnoses always showed satisfactory agreement. All the calculations were performed with S.A.S 8.0 software (SAS institute, Cary, NC, USA). κ values and concordance rates: > 0.81 excellent; 0.80-0.61 good; 0.60-0.41 acceptable; 0.40-0.21 bad; 0.20-0 very bad and <0 unacceptable.

the global distribution of diagnoses shows that the most important factor of dispersion may be the evaluation of dysplasia. The WHO classification considers AML with multilineage dysplasia as a fully-qualified category.[5] Nevertheless, original tools are still required to standardize the assessment of the degree of dysplasia. Telehematology may provide an interesting and worthwhile contribution. With this in mind, the AML-2001 review was also set up to validate a new scoring system: a semi-quantitative evaluation grid comprising 25 individual items. Using this diagnostic scoring system via the internet will allow interclass correlations (per lineage and per item) to be tested between a large number of observers and will also enable evaluation of the prognostic impact in a large homogeneous series (study in progress). It was first necessary to standardize and validate the multimedia system on the basis of the diagnoses and to check the absence of major biases in respect to all the WHO classification subtypes. Our system has also demonstrated that cytological diagnostics can be an active process involving all the participating cytologists as both data suppliers and reviewers.

Telehematology has so far been used only by a small band of enthusiasts,[6-9] although its use in clinical protocols is now showing more promise. Progress in hematology is not only related to the application of new biological techniques but also to the exploitation of new electronic media which may enable the transfer of images and information between centers, allowing for a rapid increase in the knowledge of the community as a whole.

Vincent Leymarie, Georges Flandrin, Maria Elena Noguera, Florence Leymarie, Bruno Lioure, Sylvie Daliphard and the GOELAMS cytologists (Groupe Ouest-Est des Leucémies Aiguës et Autres Maladies du Sang)

Department of Hematology, Hautepierre University Hospital, Strasbourg, (VL, BL), Necker Enfants Malades University Hospital, Paris (GF), Saint-Louis University Hospital, Paris (MEN), Department of Medical Information and Laboratory of Hematology, Debre University Hospital, Reims (FL, SD), France

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Key words: telehematology, acute myeloid leukemia, AML, cytological review.

Correspondence: Vincent Leymarie, Centre Hospitalo-Universitaire Hautepierre, Laboratoire d'Hematologie, 67098 Strasbourg Cedex, France. Phone: international +33.3.88127527.
Fax: international +33.3.88127551.
E-mail: vincent.leymarie@libertysurf.fr/sdaliphard@chu-reims.fr

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