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Editorial

Cytogenetics in the management of hematological malignancies: Guidelines from the Groupe Francophone de Cytogénétique Hématologique

At present, hematological malignancies are classified according to the World Health Organization (WHO)'s classification (https://tumourclassification.iarc.who.int/chapters/63) and the International Consensus Classification ([1,2]). These diagnostic classifications are based on many clinical, cytological, histological, immunophenotypic, cytogenetic and molecular variables. This broad range of cytogenetic techniques (encompassing conventional karyotyping, chromosome banding analysis, fluorescence *in situ* hybridization (FISH), comparative genomic hybridization arrays, single nucleotide polymorphism arrays and, most recently, optical genomic mapping) is crucial for diagnosis, staging, prognosis, and measurement of the response to treatment.

The *Groupe Francophone de Cytogénétique Hématologique* (GFCH) has more than 100 active members throughout France and several French-speaking countries. It serves as the cytogenetics expert group of the French Society of Hematology (*Société Française d'Hématologie* (SFH)). The GFCH has extensive experience in national and international collaborative research projects (resulting in 79 peer-reviewed articles to date) and quality assessments of French-speaking laboratories. In 2004, the GFCH published their first guidelines on the cytogenetic management of hematological disorders [3]. The guidelines were updated in 2016 and have been of value in the GFCH laboratories' daily practice [4]. Thanks to the group's collective expertise and the involvement of disease experts with an international track record in their field, we have updated our guidelines with a view to helping cytogeneticists around the world.

In back-to-back articles, our new guidelines focus on cytogenetics. Conventional molecular tests are outside the scope of our work. However, given that the management of hematological disease requires a comprehensive understanding of several biological variables and the clinical setting, we provide these data whenever possible. We have also taken into account worldwide availability and applicability. An abbreviations appendix is available in a supplemental file.

The present guidelines were developed by a panel of 36 experts in cytogenetics, several of whom participate in national and international clinical trials. Each article was written by a subgroup of panel members, and then reviewed by two to four members from another subgroup. The general structure of all articles includes a mini-review of the literature, a description of the major chromosomal abnormalities (CAs) observed in each disease, technical guidelines, and guidance on FISH probe testing. Each article also contains a table summarizing the essential information in a nutshell.

We have tried to cover all hematological malignancies, including those with a germline predisposition, bone marrow failure syndromes, myelodysplastic neoplasms, myeloproliferative neoplasms, mastocytosis, myelodysplastic/myeloproliferative neoplasms, acute myeloid leukemia, histiocytic/dendritic cell neoplasms, B-cell acute lymphoblastic leukemia, T-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, mature B-cell lymphoma, plasma cell neoplasms, and mature NK/T-cell lymphoma. One article is dedicated to clonal chromosomal abnormalities of undetermined significance, which - to the best of our knowledge - have not yet been addressed in the literature. Lastly, we provide a mini-review of alternative technologies for the cytogenetic analysis of hematological malignancies.

Several of the GFCH guidelines apply to all the diseases covered, and so are summarized only once in this editorial:

Guidelines for the minimum number of cells required for conventional cytogenetic analysis

According to the International System of Human Cytogenomic Nomenclature (ISCN, 2020), a clone must have at least two cells with the same CA in the case of chromosome gain or structural rearrangement. For chromosome loss, the CA must be present in at least three cells. However, two cells with the loss of a chromosome and the same chromosome gain or structural aberration can be considered to be clonal. In order to detect clonal and subclonal abnormalities, we recommend analyzing a minimum of 20 metaphases using chromosome banding analysis. With regard to FISH, we recommend analyzing at least 10 metaphases and 100 interphase nuclei. This recommendation depends on the context (diagnosis, follow-up, or relapse) and the karyotype. For example, fewer than 10 metaphases may be sufficient if a CA is observed by karyotyping. Conversely, if the CA is rare (a subclonal CA or residual disease) or the sample is of poor quality, a greater number of metaphases and interphase nuclei should be analyzed.

Guidelines for counting chromosomal abnormalities by karyotype

We believe that the ISCN 2020 counting method needs to be improved and should be evaluated in trials [5]. Indeed, we believe strongly that all CAs are important in oncogenesis, and not only those (as recommended in the ISCN) present in the major clone [5]. We suggest counting one aberration for each position between commas, in all clones and subclones (i.e. in the whole sample, and not only in the clone with the highest number of CAs). This method has been validated in several hematological diseases [5]. We also suggest to distinguish between a low complex karyotype (CK) with 3 CAs, an intermediate CK with 4 CAs, and a high CK with 5 or more CAs [5]. All cytogenomic analyses must be

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performed under the supervision of a cytogeneticist. The report must be written by a skilled cytogeneticist and must give a clear conclusion for the clinicians. Close collaboration between clinicians, pathologists, and medical biologists is essential for accurate diagnosis and optimal patient follow-up.

Sensitivity of FISH

The sensitivity of FISH on metaphases depends on the number of metaphases analyzed (*e.g.* 1/20, 1/30, 1/50). Since more cells can be analyzed (usually 100 to 200), and the resolution could be better than on metaphases, FISH on interphase nuclei is a very sensitive technique, with a cut-off of 1 to 5 %, depending on the clinical situation -diagnosis, follow-up or relapse - and the abnormality detected - translocation, deletion, amplification, *etc*. In addition, FISH on interphase nuclei can be performed on uncultured cells, thereby eliminating a potential culture bias. FISH on formalin-fixed-paraffin-embedded (FFPE) sections is more delicate, requiring knowledge of localization and morphology of tumor cells (in collaboration with experienced pathologists), because of cutting-induced artifacts, without specification of the number of cells to be analyzed ([6,7]). It should be noted that the localization of the probes on the chromosomes can only be identified by FISH on metaphases.

Conclusion

The main goal of our previous guidelines was to enable application of the same decision trees, regardless of where a patient is diagnosed. Our harmonization of practice is primarily focused on analyses that are essential for diagnosis or treatment. We hope that the present guidelines will be as helpful and useful to the international cytogenetics community as the previous ones were.

Declaration of Competing Interest

The authors declare no competing financial interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.retram.2023.103411.

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