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Perspective

2022: A big year for acute myeloid leukaemia

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Introduction

Acute myeloid leukaemia (AML) is the most common leukaemia in adults with a mean age at presentation between 65 to 72 years. During the first two decades of the 21st century we witnessed vast developments in the molecular pathogenesis of AML and the translation of these discoveries to clinical practice. The year 2022 saw the publication of three pivotal consensus papers on the classification and management of AML. Namely, International Consensus Classification (ICC) of Myeloid Neoplasms and Acute Leukemias[1], The 5th edition of the World Health Organization (WHO) Classification of Haematolymphoid Tumours: myeloid and histiocytic/dendritic neoplasms[2] and the European Leukemia Net (ELN) recommendations for diagnosis and management of acute myeloid leukaemia (AML) in adults[3]. In this article we will discuss these sentinel papers along with other communications from 2022 that made a significant impact on how we classify, diagnose, prognosticate, manage and follow up AML.

AML classification

Tumor classification not only forms the basis for diagnosis and treatment of cancer but also the foundation for research and education. In September 2022, ICC and the WHO independently published two special reports proposing a new classification for myeloid neoplasms. In the process both articles made subtle criticisms on each other's methodology of developing the new classification. Central to this debate was the role played by the clinical advisory committee which was omitted in the latest WHO update[4]. Nevertheless, both papers have provided very similar updates to the AML classification, and there is very little to debate between the two. A comparison of the major modifications to AML in the two classifications is shown in Table 1.

The blast threshold has been revisited for AML, with defining recurrent genetic abnormalities. A blast count of 10% has been deemed adequate for all AMLs with defining recurrent genetic abnormalities with the only exception of AML with BCR::ABL fusion and AML with CEBPA mutation. The previously defined bi allelic CEBPA mutation has been updated to include single mutations located in the basic leucine zipper (bZIP) region of the gene (smbZIP-CEBPA), after several studies demonstrated that mutations in the bZIP region define the prognostic significance of this category rather than the presence of bi allelic mutations[5]. The prior category of AML-MRC has also undergone significant changes. The AML-MRC entity identified purely based on morphological characteristics has been removed due to its overlap with good prognosis mutations such as NPM-1 and CEBPA. However, AML-MRC based on characteristic cytogenetic changes or characteristic gene mutations have been retained and the specific cytogenetic abnormalities or gene mutations refined. The WHO classification has coined this new group as AML – myelodysplasia related (AML-MR). When characteristic genetic abnormalities are present, either recurrent or MDS related and the blast count between 10-20%, they are known as AML/MDS.

Finally, both classifications have adopted the 2021 Human Genome Organization gene Nomenclature Committee recommendations in the use of double clone marks (::) to denote gene fusions[6].

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Table 1. Comparison of the 2022 ICC and WHO classification of acute myeloid leukaemia

Revision	**International Consensus Classification**	**World Health Organization Classification**
General classification structure	Genetically defined main category + diagnostic qualifiers	AML with defining genetic abnormalities vs AML defined by differentiation.
Blast threshold of <20% for diagnosis	More categories with recurring genetic included. A threshold of >10% specified	More categories with recurring genetic included. No lower limit specified
t-AML/MDS	Diagnostic qualifier	Included in a new segregated category termed secondary myeloid neoplasms
Antecedent MDS, MDS/MPN	Diagnostic qualifier	AML-MR
AML with germline predisposition	Diagnostic qualifier	Included in a new segregated category termed secondary myeloid neoplasms
AML - NOS	Retained	Removed
AML- MRC	Removed	Removed
AML with myelodysplasia-related cytogenetic abnormalities	New category replacing AML-MRC	New category replacing AML-MRC now referred as AML- MR
AML with myelodysplasia-related gene mutations	New category replacing AML-MRC	New category replacing AML-MRC now referred as AML-MR
TP 53 mutated AML	New category. Takes precedence over other subgroups except AML with recurrent genetic abnormalities	Not included as a separate category
AML with CEPBPA mutation	Replaced by in frame basic leucine zipper (bZIP) mutations	In frame basic leucine zipper (bZIP) mutations of the gene included with biallelic mutations
AML with other defined genetic alterations	Not addressed	A landing spot for new, often rare, emerging entities

Abbreviations t-MDS – therapy related myelodysplastic syndrome, AML-MR – acute myeloid leukaemia myelodysplasia related, AML-MRC – acute myeloid leukaemia myelodysplasia related

The 2022 ELN genetic risk stratification

The 2017 ELN genetic risk stratification which was extremely useful in prognostication and choosing appropriate consolidation therapy has been updated. FLT3-ITD allelic ratio, and the concurrent presence of NPM 1 mutations are no longer considered in unison. The presence of FLT3-ITD mutation (without other adverse-risk genetic lesions) is now categorized in the intermediate risk group making its interpretation very straight-forward. The category AML with myelodysplasia-related gene mutations is now categorized in the adverse risk group. And as mentioned above this category is better defined with the inclusion of more genes.

In addition to baseline genetic characteristics, the importance of response assessment with MRD is emphasized. A patient with intermediate risk at diagnosis maybe re classified as favourable risk or vice versa depending on the absence or presence of MRD respectively.

The ELN guidelines recommend MRD assessment with multiparameter flow cytometry and molecular MRD using qPCR. Detailed recommendations on standardizing, testing and clinical application of MRD assessment was provided by the ELN network in 2021[7].

Treatment

Recommendations for intensive chemotherapy and consolidation remains largely unchanged. The concept of maintenance therapy for AML is fast gaining popularity despite limited amount of phase III trials. The FLT-3 inhibitor midostaurin, subcutaneous and oral azacitidine have shown modest improvements in OS with minimal toxicity when administered for definite periods as maintenance therapy[8].

Clinical trials

The results of the Dauno-Double trial were presented at the 64th American Society of Haematology, Annual Meeting and Exposition[9]. This trial was designed at answering two important questions related to intensive chemotherapy in AML. First, is 60mg/m^2 really sufficient for induction compared to 90mg/m^2? Second, can patients that show a good response following the first "7+3" induction safely be spared of the second induction? After recruiting an impressive 834 patients over an 8-year period this trial showed that the use of 90mg/m^2 of daunorubicin as part of a 7+3 induction over 60 mg/m^2 did not lead to higher remission rates of longer overall survival. It also showed that, in those who showed a good response on day+15 with less than 5% blasts in the bone marrow, an additional induction cycle did not lead to an overall survival benefit. These results were well received by clinicians who advocated a "less is more" strategy in haemato-oncology. The peer reviewed full paper of this important abstract is eagerly awaited.

The ideal post-remission therapy in intermediate risk AML at CR1 in those fit to undergo an allogeneic transplant has been a matter of debate. Another German AML trial, randomized intermediate-risk patients after first complete remission to receive allogeneic hematopoietic cell transplantation (HCT) or high-dose cytarabine for consolidation and offered salvage HCT only in case of relapse[10]. Primary allogeneic HCT at first remission was associated with a lower cumulative incidence of relapse and a higher disease-free survival at 2 years. However, this did not convert to an overall survival implying that HCT can be delayed in the subset of patients who relapse following HD cytarabine therapy. This study provides very useful information in the local context where MRD assessment and HSCT are both limited to a handful of patients who can afford it.

Conclusion

Important insights into the molecular biology of AML have resulted in refinement of the initial diagnosis and the availability of more effective and less toxic treatment modalities tailored to each patient's leukaemia. It is easy to ignore these changes as a great many of these developments may seem irrelevant to us practicing in a lower middle-income country grappling with a financial crisis. However, as shown in this brief review, careful selection of new evidence can help

clinicians actively involved in the treatment of AML make best use of limited resources and offer the best available therapies to our patients.

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