AML with Myelodysplasia-Related Changes

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Acute myeloid leukemia (AML) with myelodysplasia-related changes (AML-MRC) is a distinct biologic subtype of AML that represents 25–34% of all AML diagnoses and associates with especially inferior outcomes compared to non-MRC AML. Typically, patients with AML-MRC experience low remission rates following intensive chemotherapy and a median overall survival of merely 9–12 months. In light of these discouraging outcomes, it has become evident that more effective therapies are needed for patients with AML-MRC. Liposomal daunorubicin–cytarabine (CPX-351) was approved in 2017 for adults with newly diagnosed AML-MRC and those with therapy-related AML (t-AML), and remains the only therapy specifically approved for this patient population.

Keywords: Acute myeloid leukemia ; Myelodysplasia-related changes ; AML-MRC

1. Introduction

Acute myeloid leukemia (AML) is a disease of the myeloid lineage of blood cells that results in a block in differentiation of myeloid cells and uninhibited growth of leukemic blasts that constrain the growth of normal blood cells [1] Clinical sequelae often include malaise and fatigue, infections, bleeding and/or bruising, and possibly bone pain [1]. AML is the most common acute leukemia in adult patients, with nearly 20,000 estimated new cases in the year 2020 and a median age at diagnosis of 68 years [2]. The disease is classified into multiple biologic subtypes according to genetic abnormalities, including both cytogenetic and molecular changes, degree of differentiation, myeloid lineage involved, and dysplastic changes [3]. Notably, these classifications associate with disease prognosis and predict outcomes for patients [3].

AML with myelodysplasia-related changes (AML-MRC) is one such subtype of AML that is estimated to represent a sizeable 25–34% of all AML cases and is more commonly seen in older AML patients, with a median age of 73 years [4][5]. AML-MRC portends a worse prognosis than non-MRC AML with both decreased complete remission rate and overall survival [6]. Furthermore, it is often less responsive to standard intensive induction chemotherapy regimens, likely due to both disease biology and clinical characteristics of the patient population that it affects [6].

2. Definition and Diagnostic Features of AML-MRC

AML-MRC was first introduced in the 2008 World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia and expanded on the prior category of AML with multilineage dysplasia [5]. The 2008 WHO defined AML-MRC as ≥20% myeloid blasts in the bone marrow or peripheral blood and one or more of the following features: a prior history of myelodysplastic syndrome (MDS) or an MDS/myeloproliferative neoplasm (MPN) overlap syndrome, dysplasia in 50% or more of the cells in two or more myeloid lineages, or myelodysplasia-related cytogenetic abnormalities (Table 1) [5]. In the most recent 2016 WHO classification, the definition of AML-MRC was further revised to exclude patients who had *NPM1* or biallelic *CEBPA* mutations, even in the presence of bone marrow findings demonstrating multilineage dysplasia [3]. This change was based on emerging data showing that multilineage dysplasia in the absence of myelodysplasia-related cytogenetic changes did not appear to associate with poor prognosis in the presence of an *NPM1* mutation or biallelic *CEBPA* mutation [7][8][9]. As such, the presence of del(9q) was also removed as a defining myelodysplasia-related cytogenetic abnormality because its association with *NPM1* and biallelic *CEBPA* mutations [10][11].

Table 1. Myelodysplasia-related cytogenetic abnormalities (adapted from Arber, D.A., et al. *Blood* 2016.).

Complex Karyotype-3 or More Abnormalities Balanced Translocations
t(5; 10)(q32; q21.2)
t(3; 5)(q25.3; q35.1)
t(5; 17)(q32; p13.2)

Complex Karyotype-3 or More Abnormalities Balanced Translocations
t(5; 7)(q32; q11.2)
t(5; 12)(q32; p13.2)
t(2; 11)(p21; q23.3)
t(1; 3)(p36.3; q21.2)
t(3; 21)(q26.2; q22.1)
t(11; 16)(q23.3; p13.3)
Unbalanced Translocations
del(12p)/t(12p)
idic(X)(q13)
del(11q)
−13/del(13q)
i(17q)/t(17p)
del(5q)/t(5q)
−7/del(7q)

With the introduction of next generation sequencing (NGS), our understanding of AML-MRC is again evolving with the discovery of the emerging role that common molecular mutations play in AML-MRC and their impact on prognosis. An analysis by Baer and colleagues sought to classify AML-MRC on the basis of molecular aberrations and were able to detect 96–99% of patients with AML-MRC per WHO definition criteria [12]. Mutations that were highly predictive of AML-MRC were *RUNX1*, *TP53*, *SETBP1*, epigenetic regulators, and splicing factors. Furthermore, the molecular MRC-like pattern was identified in over 10% of patients not classified as MRC per WHO criteria but who experienced a similarly poor overall survival (OS), suggesting the definition of AML-MRC may need expanded to include this molecularly-determined subset as well.

3. Leukemic Transformation of MDS to AML

The precise mechanism through which MDS progresses to AML remains unclear. However, several factors have been implicated in this phenomenon [13]. Epigenetic changes including abnormal methylation patterns are seen in all MDS bone marrow samples, with a higher amount of methylated CpG sites in high-risk MDS and MDS transforming to AML; it is thought that methylation at CpG sites gives survival advantage to transformed cells [14]. The bone marrow microenvironment has also been proposed to foster MDS progression to AML through increased angiogenesis, development of marrow fibrosis, and promotion of a pro-inflammatory environment [13]. Imbalance between apoptosis and proliferation can heed AML development, as it has been shown that, at the time of MDS progression to AML, there are increased antiapoptotic and pro-proliferative signals as well as increased expression of bcl-2 (b-cell lymphoma 2; an antiapoptotic protein) [15]. The most predominant molecular theory is the so-called “two-hit” model of MDS progression to AML in which sequential genetic alterations in genes altering cellular differentiation (e.g., *TET2* or *RUNX1*) followed by a second “hit” in a gene impacting cellular proliferation and survival (e.g., *FLT3*, *NPM1*, *IDH1*) eventually result in leukemic transformation from antecedent MDS [16][17].

Recently, newer platforms such as targeted deep sequencing and single-cell sequencing have led to an updated non-linear theory of MDS to AML progression. A compelling study by Chen and colleagues proposes that MDS does not directly evolve into AML, but rather parallel clonal evolutionary changes occur in which pre-MDS stem cells and/or MDS stem cells concurrently develop into two separate cell populations: an MDS population and a separate population of pre-AML/AML-stem cells [18]. The latter, through acquisition of additional molecular mutations, is what eventually progresses to AML. Thus, MDS and AML both arise from the stem cell level. MDS stem cells acquire early initiating mutations (such as in *TET2*, *U2AF1*, and *TP53*) then accumulate additional mutations (such as in *NOTCH2* and *KMT2C*), resulting in subclones that can develop into both MDS blasts and pre-AML/AML stem cells. However, pre-MDS/MDS stem cells require other additional mutations in order to develop into AML blasts (such as mutations in *RUNX1*, *NRAS*, and *NTRK3)*.

Chen et al. also show that stem cells harbor a higher complexity of subclonal mutations than blasts cells, and the size of different clones varies from MDS blasts to AML blasts. Therefore, dominant and passenger mutations cannot be determined only on the basis of the size of the clone.

In current practice, targeted NGS studies of the blood or bone marrow blasts is performed in order to determine disease mutations in AML but lacks specificity for being able to differentiate between AML and MDS blast populations. Further work is needed to determine how new models of MDS leukemic transformation will be translated into the clinic.

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