Cancer Therapy & Oncology
International Journal
ISSN: 2473-554X

Juniper Publishers
key to the Researchers

Editorial
Volume 16 Issue 2 - May 2020
DOI: 10.19080/CTOIJ.2020.16.555932

Cancer Ther Oncol Int J

Challenge of Personalizing therapy for Acute Myeloid Leukemia

Nahla A M Hamed*

Professor of Clinical Hematology, Faculty of Medicine, Alexandria University, Egypt

Submission: April 27, 2020; **Published:** May 07, 2020

***Corresponding author:** Nahla A M Hamed, Professor of Clinical Hematology, Faculty of Medicine, Alexandria University, Egypt

Abstract

the aim of precision medicine in AML is to understand the disease biology of each patient to improve patients' outcomes. This can be done by determining the subgroups of patients who have the greatest response to each therapy and identifying patients who are unlikely to respond to any therapy so drug toxicities can be spared. A number of new agents are studied with the goal of increasing response rates particularly in R/R AML patients or disease that is predicted to be resistant to chemotherapy.

Abbreviations: AML: Acute Myeloid Leukemia; NPM1: Nucleophosmin; MRD: Minimal Residual Disease; ELN: European Leukemia Network; IDH: Isocitrate Dehydrogenase; CHIP: Clonal Hematopoiesis of indeterminate Potential

Introduction

Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults. It accounts for ~1% of US cancer diagnoses and 2% of cancer deaths [1]. More than half of all new cases of AML are diagnosed among adults aged 65 or older (median age of onset between 68 and 72 years) [2]. AML is a heterogeneous and aggressive blood cancer. Diagnosis is based on morphology, immunophenotyping and genetics [3]. Genetics is increasingly guiding classification, risk stratification and selection of therapy in AML [1]. Optimal management of adults AML patients is complicated by the relatively recent recognition of molecular disease subsets with different responses to standard therapeutics [1].

Challenge of Personalizing therapies for Heterogeneous Genomic Data

The genetic profile of AML is notably heterogeneous [4]. The ELN 2017 prognostic model considers presence of just 1 mutation in the majority of patients and 2 in a minority of others [1]. A few mutations (e.g., Fms-related tyrosine kinase 3 [FLT3], nucleophosmin [NPM1], and DNA methyl transferase 3A [DNMT3A]) are present in more than a quarter of AML patients [4]. There are a large number of distinct genetic lesions and different mutation combinations in AML patients [5]. As many as 111 different mutations (median of 3 mutations per patient) in different possible combinations define the disease [5].

The revolution in molecular genetics and the use of next-generation sequencing (NGS) has defined the prognosis for approximately 50% of patients with a normal karyotype [6]. Many more genes are likely to contribute to leukemia pathogenesis as well as to potentially inform optimal therapeutic [1]. AML epigenome with its own heterogeneous subsets that function independently of AML genetic diversity adds an entirely new layer of complexity [1].

Challenge of personalizing therapies for heterogeneity of age

Decision-making, treatment tolerance/resilience, treatment responsiveness, and survival in older adults AML patients of the same chronologic age variably influenced by emotional health, cognitive performance, polypharmacy, social support, presence of geriatric syndromes, functional status and comorbidity [2]. These data are further confounded by the seemingly different contribution of select molecular events in older vs. younger patients [1]. Older patients have on average 1 more mutation than younger patients with associated worsening prognosis [1]. Many studies have shown a relationship between worse outcomes and increasing numbers of mutational events [1] and increased comorbidity burden [2].

There is currently no gold standard for assessment of fitness, unfitness, or frailty in AML. A phenotypically frail patient may

do well with a low-intensity therapy depending on the expected toxicity profile [2]. However, there is relatively limited data regarding response prediction for patients receiving non intensive therapy. Furthermore, many patients fall in a third category commonly referred to as "prefrail." This category of patients may be particularly target for supportive care interventions [2].

Can Precision Medicine change acute Myeloid Leukemia Therapy?

A fundamental shift is under way in the treatment of malignant blood diseases [7]. Classical cytotoxic therapies are targeted. Early chemotherapeutic agents were able to select and impair rapidly dividing cells rather than the relatively quiescent normal cells of the host organism [7]. Small molecule inhibitors of pathogenic mutant proteins have been studied in well-designed clinical trials and are now approved for the treatment of AML alone or in combination with chemotherapy [3]. It is a fallacy to draw too bright a line between targeted agents and cytotoxic therapy [7].

The clear responses to the genomic era are best articulated by attempts to targets FLT3 and isocitrate dehydrogenase (IDH) [6]. FLT3 inhibitors and IDH inhibitors are being studied in newly diagnosed adults AML in combination with standard intensive induction chemotherapy and hypomethylating agents. Hypomethylating agents or low dose cytarabine with venetoclax or low-dose cytarabine with glasdegib are studied in AML patients aged 75 or older and in patients with comorbidities precluding the use of intensive induction chemotherapy and Vyxeos (Jazz Pharmaceuticals, Dublin, Ireland) for the treatment of secondary AML or AML with myelodysplasia-related changes fit for intensive induction therapy [5].

Potential New Drugs inspired by Genomics

H3B-8800 is a splicesome inhibitor that directly target cells with recurrent mutations affecting genes encoding RNA splicing factors (NCT02841540). Pinometostat inhibits DOT1L histone methyl transferase activity by targeting partial tandem duplications involving KMT2A which occur in as many as 10% of AML patients. Poly ADP ribose polymerase inhibitors targets mutant genes responsible for the cohesion complex, like STAG2. Trametinib is the target of MEK in the RAS pathway. The BCL-2 inhibitor, venetoclax shows better response in patients with IDH mutations than patients without IDH mutations [6]. Specific pathway inhibitors and antibody-based therapies are studied particularly in patients with R/R AML or disease that is predicted to be resistant to chemotherapy. APR-246 induces apoptosis in cancer cells with mutated TP53 by reinstating the wild-type conformation of the protein [5]. Nearly all of the above genomically defined therapies are of relatively short response duration when response is achievable [6].

Molecular testing for MRD assessment

FDA views MRD as a reliable biomarker for quantitation of tumor burden, independent of the assay [5]. The sensitivity of the MRD assay should be at least 10-fold below the technical cutoff of the MRD test [1]. Patients must be investigated at diagnosis or at least a diagnostic specimen of viable cells should be stored for later analysis [5]. MRD monitoring during follow-up is currently only recommended if the patient is monitored by a molecular technique [5]. BM is most likely to be representative of residual AML for the majority of patients without extramedullary disease. PB provides lower sensitivity than BM (1 log less for mutated NPM1) [8].

At which time points MRD should be tested?

After standard induction and consolidation chemotherapy, MRD assessment is recommended after two chemotherapy cycles, at the end of consolidation and within 4 weeks before alloHCT. Bone marrow and peripheral blood should be monitored every 3 months for the first 2 years during follow-up. After 2 years, the decision to continue MRD monitoring should be assessed on an individual basis. Alternatively, MRD may be monitored in peripheral blood every 4 to 6 weeks for 2 years, with the monitoring interval informed by the relapse kinetics of the underlying disease and/or MRD marker. For example, the median time from molecular to clinical relapse is 1month in MLL-translocated AML, 2 to 3 months in RUNX1-RUNX1T1-, NPM1-mutated/FLT3-ITD– positive and in DEK-NUP214-mutated AML, and 4 to 6 months in CBFB-MYH11 and NPM1-mutated/FLT3-ITD–negative AML [5].

The challenges of using molecular testing for MRD assessment in AML patients

i. AML patients have an average of 3 acquired mutations (range, 0-9) at the time of diagnosis [1]. Additional complexity is the presence of mutations associated with CHIP, including DNMT3A, TET2, ASXL1, or germ line events, which can persist in the context of disease clearance. Their presence is not prognostic at MRD assessment [3].

ii. Proteins and genes associated with chemotherapy resistance and cell survival are modulated hours after start of induction therapy in AML [3]. Mutations in genes involved in signal transduction (e.g., FLT3, NRAS) often disappear at relapse which may limit their use for MRD analysis [3].

Conclusion

Precision medicine enables the selection of the right individualized treatment for patients based on disease and patient characteristics. This can be achieved by developing more new agents in the future and learning their sequence in treatment. Furthermore, understanding the relevance of MRD and how to assess in AML, make our assessment of treatment response better.

References

1. Roloff GW, Griffiths EA (2018) When to obtain genomic data in acute myeloid leukemia (AML) and which mutations matter. Hematology Am Soc Hematol Educ Program 2(21): 3070-3080.

How to cite this article: Nahla A M H. Challenge of Personalizing therapy for Acute Myeloid Leukemia. Canc Therapy & Oncol Int J. 2020; 16(2): 555932. DOI: 10.19080/CTOIJ.2020.16.555932

2. Klepin HD, Estey E, Kadia T (2019) More versus less therapy for older adults with acute myeloid leukemia: new perspectives on an old debate. Am Soc Clin Oncol Educ Book 39(1): 421-432.

3. Gjertsen BT, Tislevoll BS, Fagerholt OHD, Hellesoy M. Early response evaluation in AML using mass cytometry. HemaSphere Educational Updates in Hematology Book 3(S2): 3-5.

4. Di Nardo CD, Cortes JE (2016) Mutations in AML: prognostic and therapeutic implications. Hematology Am Soc Hematol Educ Program 2016(1): 348-355.

5. Heuser M, Mina A, Stein EM, Altman JK. How precision medicine is changing acute myeloid leukemia therapy. Am Soc Clin Oncol Educ Book 39(1): 411-420.

6. Pollyea DA (2018) New drugs for acute myeloid leukemia inspired by genomics and when to use them. Hematology Am Soc Hematol Educ Program 2018(1): 45-50.

7. Michaelis LC (2018) Cytotoxic therapy in acute myeloid leukemia: not quite dead yet. Hematology Am Soc Hematol Educ Program 2018(1): 51-62.

8. Freeman SD, Hourigan CS (2019) MRD evaluation of AML in clinical practice: are we there yet? Hematology Am Soc Hematol Educ Program 2019(1): 557- 569.

DOI:10.19080/CTOIJ.2020.16.555932

How to cite this article: Nahla A M H. Challenge of Personalizing therapy for Acute Myeloid Leukemia. Canc Therapy & Oncol Int J. 2020; 16(2): 555932. DOI: 10.19080/CTOIJ.2020.16.555932

How to cite this article: Nahla A M H. Challenge of Personalizing therapy for Acute Myeloid Leukemia. Canc Therapy & Oncol Int J. 2020; 16(2): 555932. DOI: 10.19080/CTOIJ.2020.16.555932

How to cite this article: Nahla A M H. Challenge of Personalizing therapy for Acute Myeloid Leukemia. Canc Therapy & Oncol Int J. 2020; 16(2): 555932. DOI: 10.19080/CTOIJ.2020.16.555932

How to cite this article: Nahla A M H. Challenge of Personalizing therapy for Acute Myeloid Leukemia. Canc Therapy & Oncol Int J. 2020; 16(2): 555932. DOI: 10.19080/CTOIJ.2020.16.555932