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Chapter 1

# Introductory Chapter: Myeloid Leukemia

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Additional information is available at the end of the chapter

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## 1. Introduction

Myeloid leukemia regroups a variety of myeloid disorders. Some are more frequent and well characterized such as acute myeloid leukemia (AML) or chronic myeloid leukemia (CML). However, other clonal myeloid disorders, designed myelodysplastic/myeloproliferative neoplasms (MDS/MPN), are still subjected to diagnosis and therapeutic challenges. MDS/MPN might possess both dysplastic and proliferative features and cannot simply be listed in myelodysplastic syndrome (MDS) and chronic myeloproliferative disorder (CMPD) categories. Currently, three distinct groups are well classified: chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), and atypical chronic myeloid leukemia (aCML). An additional group called myelodysplastic/myeloproliferative neoplasm-unclassifiable (MDS/MPN-UC) has also been included. Apparently, MDS/MPN-UC shows both MDS and CMPD characteristics but differs at some extent from the other three MDS/MPN groups. MDS/MPN implicates defects in the modulation of myeloid pathways leading to cell survival and proliferation. However, the etiology of the defects remains elusive.

In this introductory chapter, we have succinctly described each of the myeloid disorders and provided some highlights on diagnosis and available therapies.

## 2. Acute myeloid leukemia (AML)

AML is a complex malignancy characterized by a high heterogeneity of aberrant myeloid precursors. In addition to family history of hematologic disorders and exposure to environmental factors, aging increases the incidence of AML. Although AML arises from transformed hematopoietic stem cells, the etiology of this form of leukemia remains mostly

unidentified. However, we know that consecutive genomic mutations and epigenetic modifications lead to the progression of the disease. Alterations in important genes have been characterized leading to the development of novel targeted therapeutic strategies. However, significant variations in the genetic and the epigenetic of AML are found among patients. Thus, development of efficient treatment of AML remains a significant clinical challenge.

Current AML treatment is generally based on classical chemotherapy, targeted therapy, and stem cell transplantation. The emergence of personalized medicine is still underway. Optimal biological information leading to patient selection and individual therapy are uncommon.

In addition to the age of AML patients, cytogenetics of the tumor and clinical appreciations are fundamental for the prognosis and the success of the treatment. Promyelocytic leukemia is the subset of AML with the highest proportion of cure rate. Patients are benefiting from targeted therapy such as all-transretinoic acid treatment. Currently, several other targeted therapies are available.

The limiting parameters for AML targeted therapy are the tumor heterogeneity and its variability during the course of disease and therapy, resulting in unpredictable response, and constitute the current challenge for establishing successful personalized therapeutic regimens.

## 3. Chronic myeloid leukemia (CML)

CML is a myeloproliferative disorder characterized by the presence of the BCR-ABL oncogene fusion protein, resulting from reciprocal translocation between chromosomes 9 and 22 [t(9;22)], commonly designed by Philadelphia chromosome (Ph chromosome) (Ref). As a result, Bcr-Abl tyrosine kinase becomes constitutively activated and triggers apoptosis resistance and other biological alterations responsible for CML pathogenesis. With the introduction of tyrosine kinase inhibitors (TKIs), significant benefits for CML patients are currently achieved. Nilotinib, dasatinib, and imatinib are the commonly TKIs small molecules used in the clinic for the treatment of CML. These inhibitors are designed to block the adenosine triphosphate-binding site of the Bcr-Abl tyrosine kinase and inhibit the activation of downstream effector proteins, responsible for CML exacerbations.

The success of TKI therapy is associated with the reduction of BCR-ABL1 transcript levels in the CML patients. Current guidelines refer to major molecular response (MMR) for the BCR-ABL1 level not exceeding 0.1% or deep molecular response (DMR) for the BCR-ABL1 level not exceeding 0.01%. DMR can be achieved in almost 50% of CML patients who stopped TKI treatments. However, important questions remain regarding the mechanisms leading to CML remission and lack of relapse. Addressing such questions will help identify biomarkers that could predict which patient could discontinue TKI therapy without relapse and also determine the long-term success of the treatment.

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## 4. Chronic myelomonocytic leukemia (CMML)

CMML displays irregular features, varying from myelodysplastic to myeloproliferative. The majority of CMML patients show persistent somatic mutations. Around 15% of CMML can evolve to AML, and when this transition occurs, a poor prognosis is predicted. Many chemotherapy regimens for CMML have been used with only limited success. Bone marrow transplantation or stem cell transplantation appears to be more effective.

## 5. Juvenile myelomonocytic leukemia (JMML)

JMML is a rare myeloid disorder of childhood. Although the etiology of JMML is not known, children with neurofibromatosis type 1 (NF1) have high risk for developing JMML. Children diagnostic at 2 years old and up have a poorer prognosis. Thrombopenia and a high HbF level have also been associated with a poor prognosis. Currently, BMT appears to be the best therapy for JMML.

## 6. Atypical chronic myeloid leukemia (aCML)

aCML is a very rare myeloid leukemia, mainly occurring in elderly people. This disorder displays both MDS and CMPD features. aCML seems to respond poorly to interferon alpha therapy. However, treatment with hydroxyurea may lead to a limited remission.

## 7. Myelodysplastic/myeloproliferative neoplasm-unclassifiable (MDS/MPN-UC)

MDS/MPN-UC is also called mixed myeloproliferative/myelodysplastic syndrome. Since it shows both MDS/MPN features and not meeting the criteria of the described MDS/MPN categories, this disorder is unclassifiable. A mutation on Jak2 kinase causing its constitutive activation might be involved in the disease at least in some MDS/MPN-UC patients. Adult patients with platelet-derived growth factor receptor gene rearrangements might be treated with imatinib mesylate.

## 8. Conclusion

Important progress in both the diagnosis and the treatment of myeloid leukemia has been realized. Currently, many treatments are proposed. In CML tremendous success has been achieved with TKI therapy. However, important challenges remain for establishing more focused therapies and determining useful biomarkers associated with the resistance or the success to therapy.

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