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Introductory Chapter: Hematology in Times of Precision and Innovation

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1. Introduction

Hematological diseases are heterogeneous group of benign and malignant, inherited and acquired, acute and chronic disorders of different cell lineages that originate from a cell of the hematopoietic and lymphatic tissue with diverse incidence, etiology, pathogenesis, and prognosis.

During the past two decades, hematological disorders have been extensively studied by means of classical laboratory approaches, for example, microscopy, immunophenotyping, clinical chemistry, genetic diagnostic tests such as conventional cytogenetics, fluorescence in situ hybridization (FISH), and polymerase chain reaction (PCR), as well as by high-throughput technologies, including microarray-based platforms for the global analysis of DNA alterations (single nucleotide polymorphism (SNP); array, comparative genomic hybridization (CGH)), gene expression profiling (GEP), next-generation sequencing (NGS), digitalized imaging, and so on. Systemic application of these techniques has allowed for the refinement of the molecular mechanisms involved in the pathological transformation of hematopoietic stem/progenitor cells and disease progression in a number of hematological disorders. More importantly, they have permitted more precise and reproducible diagnoses of the different entities, risk stratification of patients, and treating them in the most appropriate manner with tailored therapeutic strategies.

2. Hematological malignancies

Hematological malignancies account for around 8–9% of all cancers, being the fourth to fifth most frequently diagnosed cancer in economically developed regions of the world [1]. The

estimated deaths from these tumors account for 7% of the cancer-related deaths [2]. The age-standardized incidence rates are 24.5 (per 100,000) for lymphoid malignancies and 7.55 for myeloid malignancies. The most common lymphoid malignancies are plasma cell neoplasms (4.62), small B-cell lymphocytic lymphoma/chronic lymphocytic leukemia (3.79), diffuse large B-cell lymphoma (3.13), and Hodgkin lymphoma (2.41). The commonest myeloid malignancies are acute myeloid leukemia (AML) (2.96), other myeloproliferative neoplasms (MPN) (1.76), and myelodysplastic syndromes (MDS) (1.24) [3].

Hematological malignancies arise through a multistep process of a sequential accumulation of a variety of chromosome aberrations and/or molecular abnormalities in a hematopoietic stem cell or a progenitor cell. These abnormalities affect the normal structure or the function of certain genes resulting in modifications in the genetic programs that control cellular proliferation, differentiation, programmed cellular death (apoptosis), relationships with neighboring cells, and the capacity to escape the immune system [4]. This process leads to the formation of a clone of deregulated cells, which escape the physiological control of normal cell growth and behavior [5].

The spectrum of genetic and epigenetic abnormalities that occur in hematological malignancies is extremely heterogeneous and ranges from single DNA nucleotide changes that affect the coding of a single amino acid to chromosomal gains and losses that disrupt the transcription of hundreds of genes. Frequently, the pattern of genetic defects is highly complex with multiple different abnormalities, such as structural and numerical chromosome aberrations, point mutations, gene amplifications, microdeletions, microinsertions, fusion genes, gene rearrangements, aberrant gene expression, and so on. The diversity in the form of a disease produced results from a combination of factors, particularly the type of cell affected, the nature of the genetic change that precipitates the malignancy, and the point in the cell's maturation process at which the malignant change occurs. Besides, most hematological malignancies are an oligoclonal disease even within a single patient, such that the predominant clone at the initial presentation is not necessarily identical to the clone ultimately responsible for clinical relapse and death. The progression to the overt clinical relapse may be associated (1) with the initial malignant clone that develops chemo-resistance after initial sensitivity to treatment, most frequently due to the acquisition of additional mutations; or (2) with a subclone, which initially presents at low frequency, but given a clonal advantage during treatment, replaces the founder clone and becomes the predominant clone. These add additional biological heterogeneity of the individual patients with one and same diseases.

On the other hand, it is important to specify that the presence of low levels of characteristic "initiating" leukemia- and/or lymphoma-associated molecular abnormalities do not lead directly to disease, even if these abnormalities confer advantages in self-renewal, proliferation or both, resulting in clonal expansion of the affected cells as a "pre-malignant" clone. Using highly sensitive (10^{-6}–10^{-8}) nested primer PCR approaches, a low level of various leukemia- and/or lymphoma-associated molecular abnormalities was detected in a significant proportion of healthy individuals.

Currently, most hematological malignancies are treated with highly cytotoxic drugs, radiation, and/or hematopoietic stem cell transplantation (HSCT), and all these therapeutic approaches

are often toxic, elicit incomplete responses, and may have severe long-term negative effects. Besides, despite the improved response and survival rates, drug resistance and relapse remain major problems and several hematological malignancies remain incurable with standard treatments [6].

2.1. The effective implementation of rationally developed therapies requires rapid integration of new biological data

B-cell lymphomas comprise a rapidly developing field of remarkable transfer of knowledge and understanding into precise diagnosis and effective therapeutic approaches. The dissection of B-cell development has been in the focus of tremendous interest in the recent years. The understanding of normal B-cell biology versus B-cell lymphoma pathogenesis leads us inevitably to the B-cell receptor (BCR) signaling. The expression of a functional BCR retains a crucial role for B-cell survival and proliferation. In this regard, BCR activation and signaling pathways can support the growth and evolution of both normal and malignant B-lymphocytes, and as a result, from the functional perspective, it might act as a true oncogene [7]. Julieta Sepulveda et al. review the BCR as a driver of B-cell lymphoma development and evolution in Chapter 2 of this book and discuss the genetic mechanisms that create a functional antigen receptor and their errors leading to oncogenic events, the pathogenic activation of the B-cell receptor signaling cascade, and introduce some novel emerging therapies targeting the B-cell receptor at different levels.

The functional role of the BCR in the pathogenesis and lymphoma progression is particularly well characterized in diffuse large B-cell lymphomas (DLBCL). Gene expression profiling has separated DLBCL into two distinct sub-entities: the germinal center B-cell DLBCL (GCB) and the activated B-cell-like (ABC) DLBCL characterized by ongoing BCR signaling and substantially worse clinical outcomes when treated with standard immunochemotherapy. DLBCL is the most common type of non-Hodgkin lymphoma which accounts for approximately one-third cases of lymphoid malignancies in the Western world. There is a considerable variability in terms of clinical course and therapeutic outcomes due to the unique heterogeneity of biology that exists between and within lymphoma subtypes. In addition to GCB and ABC subtypes, double/triple-hit and double-expressor lymphomas with rearrangements and/or overexpression of MYC, BCL2, and/or BCL6 genes have also been associated with poor prognosis [8]. However, a number of clinical trials have demonstrated the feasibility of novel agents and combinations with encouraging efficacy [9]. The rapid pace in understanding biological mechanisms, recent molecular subclassification, and clinical developments has moved into the focus of personalization of therapy. The third chapter provides an overview of the recent advances in DLBCL presented by Kumar Vivek.

This is yet another demonstration of how hematology has advanced in parallel with technological developments that have expanded our understanding of the phenotypic, genetic, and molecular characteristics of the hematological neoplasms. Dissection of genetic abnormalities critical to leukemia, lymphoma, and myeloma initiation provided insights into the pathogenesis of hematological malignancies, but also identified distinct subsets of patient, predicted prognosis individually, and provided rational therapeutic targets for curative approaches [10].

The molecular characterization of malignant cells is currently regarded as being as important as the traditional morphological and immunological approaches to diagnosis. This trend is being additionally accelerated by the introduction of novel drugs designed to specifically target the molecular abnormalities responsible for the development of the tumor. Such developments are of fundamental clinical importance, as they increasingly define not just the diseases themselves but how an individual patient should be treated.

2.2. Information concerning the tumor genome into the routine clinical management is useful for better treatment strategy selection, delivering "the right treatment to the right patient at the right time"

The best efficacy would be achieved if treatment is directed toward specific genetic lesions within malignant cells, which have a key role in the pathogenesis of the respective disease, while minimizing damage to normal, healthy cells [11]. Unfortunately, several limitations still restrict the widespread application of this personalized approach, such as (1) various technological and methodological diagnostic problems; (2) insufficient level of our knowledge about the molecular mechanisms involved in the pathogenesis of different malignancies and the prognostic significance of individual molecular abnormalities; and (3) relatively low number of available targeted therapeutic agents approved for clinical use. Therefore, in practical terms, the personalized approach in hemato-oncology comprises a personalized risk stratification: refinement of clinical prognostic models for a better risk stratification and identification of biologic subtypes within pathologically similar diseases; identification of patients suitable for targeted treatment and "response-adapted" changes in therapy in individual patients [12].

In several hematological malignancies, such as acute leukemias, MDS, chronic lymphocytic leukemia (CLL), and so on, cytogenetics remains the most important disease-related prognostic factor for predicting remission rate, relapse, and overall survival (OS) [13–15]. In addition, recent genetic studies identified a large number of mutations in most of the hematological malignancies that point to novel pathways involved in the pathogenesis of the respective disease, and some of these molecular abnormalities have allowed substantial improvements in clinical decision making. As a result, the current prognostic models based on genetic abnormalities are nowadays subject to change as new cytogenetic and mutational findings are revealed, contributing to refine better and better these approaches.

Multiple myeloma (MM) is an incurable malignancy characterized by the clonal proliferation of neoplastic plasma cells in the bone marrow that produce monoclonal protein that can be detected in the serum or urine. MM is a highly heterogeneous disease composed of multiple molecularly defined subtypes, each with varying clinico-pathological features and disease outcomes. Cytogenetically, there are two main subtypes: (1) hyperdiploid myeloma—characterized by trisomies of certain odd-numbered chromosomes and generally associated with a better survival; and (2) nonhyperdiploid myeloma—characterized by translocations of the immunoglobulin heavy chain alleles at chromosome 14q32 with various partner chromosomes, the most important of which are 4, 6, 11, 16, and 20. Several abnormalities have been reported to be associated with poor prognosis, such as t(4;14)(p16;q32)/IGH-MMSET, t(14;16)(p32;q23)/

IGG-MAF, t(14;20)(q32;q11)/IGG-MAFB, del(17p), and gains of 1q, despite that the adverse effect of t(4,14) can be partially abrogated by bortezomib-based treatment [16]. Technological development provides various opportunities to evaluate the tumor genome. In this regard, Sridurga Mithraprabhu and Andrew Spencer provide a comprehensive chapter on the possible role of liquid biopsies in multiple myeloma as an innovative methodology for diagnostics and disease monitoring, implementing the analysis of circulating cell-free nucleic acids (CFNAs) and circulating tumor cells (CTCs) as representative of the underlying mutational profile of a cancer as well as of extracellular RNA (exRNA) that can be utilized as a prognostic biomarker. The authors discuss the potential of these noninvasive, repeatable biomarkers to provide additional information as an adjunct to bone marrow biopsies and conventional disease variables in multiple myeloma.

2.3. "Acute leukemia: the challenge of capturing disease variety"

The many levels of morphological, immunophenotypic, clinical, genetic, and epigenetic heterogeneity of acute leukemias represent an extraordinary challenge to our capability to understand and to beat these diseases (Löwenberg modified [17]). Acute leukemias were incurable 50 years ago. Significant progress has been achieved by applying intensive regimes and transplantation programs. The 5-year survival rate of people of all ages with acute lymphoblastic leukemia (ALL) increased from 41% for those diagnosed from 1975 to 1977 to 71% for those diagnosed from 2006 to 2012; however, with considerable variations depending on several factors, including biologic features of the disease and a person's age, the 5-year survival rate for people with acute myeloid leukemia (AML) is still approximately 27% which is fairly unsatisfactory [www.cancer.net]. Many recent biologic insights have shed light on these challenging nosological categories, and attempts have been devoted to develop strategies for improved outcomes.

According to the European LeukemiaNet (ELN) recommendations for the diagnosis and management of acute myeloid leukemia in adults (2017), several genetic abnormalities are associated with the response to therapy and survival, allowing to stratify patients into three genetic risk groups [18]:

Favorable: t(8;21)(q22;q22.1)/*RUNX1-RUNX1T1;* inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB-MYH11*; Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}, Biallelic mutated *CEBPA;*

Intermediate: Mutated *NPM1* and *FLT3*-ITD^{high}, wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} (without adverse-risk genetic lesions); t(9;11)(p21.3;q23.3)/*MLLT3-KMT2A*, cytogenetic abnormalities not classified as favorable or adverse;

Adverse: t(6;9)(p23;q34.1)/*DEK-NUP214;* t(v;11q23.3)/*KMT2A* rearranged; t(9;22)(q34.1; q11.2) /*BCR-ABL1;* inv(3)(q21.3q26.2) or t(3,3)(q21.3;q26.2)/*GATA2,MECOM (EVI1);* −5/del(5q); −7; −17/abn(17p); complex karyotype, monosomal karyotype; wild-type *NPM1* and *FLT3*-ITD^{high}, mutated *RUNX1,* mutated *ASXL1,* and mutated *TP53.*

AML with t(8;21) or inv(16)/t(16;16) is commonly referred to as core-binding factor (CBF) AML, because in both, the heterodimeric protein complex CBF is affected, which is involved in the transcriptional regulation of normal hematopoiesis. CBF-AMLs in patients treated

with cytarabine-anthracycline-based induction and high-dose consolidation are considered to have relatively good prognosis compared to other leukemia subtypes, with 10-year OS, disease-free survival (DFS), and event-free survival (EFS) of 63.9, 54.8, and 49.9%, respectively [19]. Nevertheless, 40–45% of these patients eventually relapse and die of their disease. Integration of cytogenetic results with molecular genetics and epigenetic data refines the risk stratification of CBF AML. Several variables might worse prognosis of these patients, such as the level of the respective fusion transcripts *RUNX1-RUNX1T1* and *CBFB-MYH11* [20]. Some authors even suggested that *FLT3*-ITDs carriers constitute a biologically distinct group of APL patients [21].

Almost half of AML is normal cytogenetically, and this subgroup shows a remarkable heterogeneity in terms of genetic mutations and response to therapy. In patients with normal karyotype, as well as in cases with chromosome abnormalities with intermediate prognosis, the intensity of therapy is driven by the prognostic subgroup. Therefore, the current standard of care combines cytogenetic results with testing for mutations in *FLT3, NPM1, CEBPA,* and *KIT* to precise the risk. The presence of *NPM1* and *CEBPA* gene mutations is associated with a favorable prognosis, however, only in the absence of *FLT3*-ITD [22].

Several other gene alterations (mutations in *WT1*, *RUNX1*, *ASXL1*, *TP53*, *IDH1*, *IDH2*, *DNMT3A* genes, partial tandem duplication of *MLL* gene, overexpression of *BAALC*, *MN1*, *EVI1*, *ERG*, *WT1*) have also been demonstrated to predict prognosis and probably will play a role in future risk stratification, although some of these have not been confirmed in multiple studies or established as the standard of care [23].

About 30% of AML have an unfavorable karyotype, and if treated with conventional chemotherapy, a complete response rate of about 50% and a 5-year OS of 10–20% are expected. The best chance for patients with an unfavorable karyotype who achieve a complete response is the allogeneic HSCT [24].

A major achievement is the incorporation of genetic and molecular data in the current classification systems. However, the major principle of the World Health Organization (WHO) Classification of tumors of hematopoietic and lymphoid tissues (2016) is to integrate these data with essential clinical features, morphology, and immunophenotyping in order to define distinct disease entities of clinical significance [25]. Morphology is the gold standard, and though it has been the classical tool for diagnosis and classification, it is routinely performed by subjective microscopic evaluation and is strongly dependent on the morphologist's expertise. To extract more accurate and detailed information from patient tissue samples, digital pathology integrated with advances in machine learning is emerging as a powerful tool to enhance morphology-based decisions. In the fifth chapter in this book, Cecilia Lantos et al. provide up to date information about the possibilities that computational histology can provide to improve leukemia diagnosis with an automated biologically meaningful pattern recognition, as well as the additional contribution of deep-learning approach for a higher accuracy. The authors claim that if mathematical pattern recognition methods that recognize cellular phenotypes from microscopic slides and define how morphological features relate to clinical genetic data and protein signatures, this could significantly speed up leukemia

diagnosis, reduce the cost of the diagnostic workup, and optimize the assignment of patients to a particular therapy.

Rare conditions pose a number of problems in both theoretical and practical terms. Myeloid sarcoma has been recognized for more than a century; however, owing to the rarity of the entity, most of the study comprises small retrospective studies and case reports. Myeloid sarcoma can occur under different clinical scenarios including an extramedullary leukemic tumor with concurrent AML, preceding the blood and bone marrow involvement or without any history of myeloid neoplasia, as well as an extramedullary AML relapse. These phenomena may not share common mechanisms and outcomes and may need to be treated differently [26]. Kahali Bhaskar presents a review of current published data regarding the incidence, clinical presentation, morphological, cytogenetic and immunophenotypic features, prognosis, and treatment of this rare neoplastic myeloid entity.

3. Benign hematological disorders

"Benign hematology isn't so benign" if we use the words of Prof. Alice Ma in ASH Clinical News (2015). Clotting disorders, anemias, thrombocytopenias, and so on may present as serious as malignant disorders and are a field of significant progress too.

3.1. New therapies improve the outlook of bleeding and clotting disorders

Coagulation is a dynamic process, and the understanding of blood coagulation system and the ways to modulate the process have been evolving significantly. The concept of coagulation originates back to the 1960s when Davie, Ratnoff, and Macfarlane described their cascade theories [27]. Hemostasis is a complex physiological process that maintains the blood flow and is regulated by a delicate balance between procoagulants supporting the formation of hemostatic plugs to prevent the leakage or blood loss and anticoagulants, preventing the formation of unwanted clots. The imbalance between the two components may cause either bleeding or thrombosis. The seventh chapter comprises a review of the defects in the coagulation system and the recent clinical modulators of the coagulation system by Pilli Vijaya.

The different hereditary and acquired defects of the finely regulated coagulation systems might result in severe of even life-threatening bleeding complications or thrombotic events. The recent advances in the knowledge about the structure, function, and regulation of the coagulation system, as well as in the hereditary genetic abnormalities leading to qualitative and/or quantitative defects of the multiple elements of clothing cascade, and acquired disorders of coagulation as a consequence of other underlying conditions, were an important prerequisite of the development of new diagnostic tools and therapeutic strategies based on the product of recombinant technology. The understanding of the physiology of these processes is crucial to identify the pathological scenarios and to predict clinical consequences in order to implement the relevant therapeutic interventions. In combination with the classical

laboratory tests and therapeutic blood components, the current management of patients with disorders of hemostasis and thrombosis is based on the individual approach according to the individual patient.

3.2. New sickle cell disease research shows improved patient outcomes

Sickle cell disease (SCD) is one of the most frequent inherited genetic disorders in the world. It predominantly affects people of African descent as well as individuals from the Middle East, India, and Mediterranean regions [28]. It is an autosomal-recessive disease caused by a point mutation in the hemoglobin beta gene found on chromosome 11p15.5, Hb S (HBB: c.20A>T) along with or without any other abnormal Hb gene, and results in a number of health problems, for example, anemia, acute and chronic pain, infection, acute chest syndrome, pulmonary hypertension, cardiac, CNS, gastrointestinal involvement, and so on, leading to significant morbidity and mortality. Significant advances in prophylactics and therapy achieved improved survival among children with sickle cell disease, with the majority of children attaining adulthood [29]. However, the median age at death of 39 years with only 35.0% surviving beyond age 35 years was reported by the Centers for Disease Control (CDC). Sickle cell disease substantially alters renal structure and function leading to nephropathy which is not only a chronic comorbidity but is also one of the leading causes of mortality in patients with sickle cell disease [30]. Knowledge of the natural progression of the disease, as well as identification of persons at risk, allows for timely intervention and improved outcomes. The search for biomarkers for the early diagnosis of the disorder and its outcomes is an area of intense contemporary research [31]. The current understanding of the presentation, diagnostic, and therapeutic challenges in sickle cell nephropathy is presented in detail by Inusa Baba et al. in the chapter 8. Risk factors for renal impairment and acute kidney injury are reviewed in detail. In addition, data coming from established mouse models are invaluable to elucidate the pathogenesis of SCD-associated multiple organ complications and to identify targets for prevention and therapy.

The continuous and rather extensive influx of new information regarding the key features and underlying mechanisms as well as treatment options of blood disorders requires a frequent updating of this topic. The primary objective of this book is to provide the specialists involved in the clinical management and experimental research in hematological diseases with comprehensive and concise information on some important theoretical and practical developments in the biology, clinical assessment, and treatment of patients, as well as on some molecular and pathogenetic mechanisms and the respective translation into novel therapies. Specific clinical scenarios such as myeloid sarcoma or sickle cell nephropathy are also within the scope of this book. An international panel of experts provides novel insights of various aspects of hematology and contributes their experience to an update of the field.

Each chapter is a separate publication that reflects each author's views and concepts. However, this book presents an update and introduces novel insights in our current understanding of the biology and clinical presentation, the risk assessment, and therapeutic challenges in patients with hematological diseases.

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