

Liquid Tumors at a Glance: Innovations, Challenges and Future Directions in Hematologic Oncology

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ABSTRACT

Hematologic malignancies, commonly referred to as liquid tumors, encompass a diverse group of cancers such as leukemias, lymphomas, and myelomas. Defined by unique genetic, molecular, and clinical characteristics, these diseases present significant challenges in diagnosis, treatment, and prognosis. Despite advances in therapeutic strategies-including immunotherapy, targeted therapies, and hematopoietic stem cell transplantation-patients with high-risk or relapsed disease often face poor outcomes. Notably, Multiple Myeloma (MM) remains an incurable plasma cell malignancy despite recent innovations, underscoring the need for more effective and durable treatment strategies. This article offers a comprehensive review of the classification, pathophysiology, and molecular features of liquid tumors, with a particular focus on emerging therapeutic approaches and unmet clinical needs. By addressing current challenges and future opportunities, this work seeks to contribute to the advancement of care for patients with these complex malignancies.

Keywords: Chronic Lymphocytic Leukemia (CLL); Acute Myeloid Leukemia (AML); Myelodysplastic Syndromes (MDS)

INTRODUCTION

Thomas Hodgkin described the first hematologic malignancy in 1832. The disease was called Hodgkin's disease until it was officially renamed Hodgkin lymphoma in the late 20th century. The published descriptions of other hematologic malignancies, such as leukemia and Multiple Myeloma (MM), soon followed. Hematologic malignancies have distinct genetic and epigenetic signatures and are traditionally categorised by site according to whether cancer is first detected in the blood (leukemias), lymph nodes (lymphomas-Hodgkin and non-Hodgkin) or bone marrow (myelomas) [1].

Despite its relatively lower frequency, tumor protein 53 (TP53) alterations including TP53 mutations or 17p deletions are closely linked with complex karyotype, poor prognosis, and chemotherapeutic response in hematologic malignancies [2]. Somatic TP53 alterations have been reported in Acute Lymphoblastic Leukemia (ALL) (16%), Acute Myeloid Leukemia (AML) (12%), Chronic Lymphocytic Leukemia (CLL) (7%) and Myelodysplastic Syndromes (MDS) (6%) [3-11]. As a matter of fact, the tumor suppressor gene TP53 is the most frequently

mutated gene in human cancers, with mutations occurring in more than 50% of human primary tumors [12,13]. Interestingly, the frequency of TP53 mutations is even higher in tumors that relapse after therapy. Noteworthy, the p53 protein (commonly referred to as the “guardian of the genome”), made by the TP53 gene, normally prevents the propagation of genetically defective cells by supervising the repair of damaged Deoxyribonucleic Acid (DNA). Consequently, defective p53 renders cells relatively resistant to chemo and radiotherapies and promotes a “mutator phenotype” prone to rapid accumulation of additional mutations [14]. Moreover, patients with germline TP53 mutations (the underlying cause of Li-Fraumeni and Li-Fraumeni-like syndromes) have a twenty-five fold greater risk of early-onset cancers (e.g., leukemia, sarcomas, breast cancer, and brain tumors) [15].

The mainstay treatment for high-risk or Relapsed/Refractory (R/R) hematologic malignancies (including leukemias) has historically revolved around allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT). Despite increasing survival rates, allo-HSCT is associated with long-term morbidity and mortality, mainly due to chronic Graft-versus-Host Disease (cGvHD) which remains a very challenging and serious complication of allo-

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HSCT. In this context, cGvHD is stigmatised by futile treatment options lying between the harmful corticosteroids as the standard first-line treatment and elusive second-line therapies [16]. In addition, given the poor prognosis of patients who relapse after allo-HSCT, targeted immunotherapies have emerged as a potential therapeutic option in hematologic oncology [17].

Leukemias

Leukemia is a blood cancer caused by the rapid production of abnormal white blood cells and is the most common cancer in children and adolescents. Despite advances made in therapeutic strategies, allo-HSCT remains a standard of care across various leukemia subtypes for curative intent [18]. Leukemia classification is based on the type of blood cell affected (includes both lymphoblastic and myeloid leukemias) and the rate of leukemia progression (includes an acute or chronic forms).

Acute leukemias represent a clonal expansion and arrest at a specific stage of myeloid or lymphoid hematopoiesis [19]. Acute leukemias are characterized by greater than 20% blast cells in the Bone Marrow (BM) or Peripheral Blood (PB) leading to a more rapid onset of symptoms. Nevertheless, the 20% blast cutoffs were eliminated for most Acute Myeloid Leukemia (AML) types with Defining Genetic Abnormalities (DGAs) [20-22]. Although allo-HSCT is an important therapeutic modality for acute leukemia, its outcomes remain unsatisfactory [23]. In contrast, chronic leukemia has less than 20% blasts with a relatively chronic onset of symptoms [24]. Unlike acute leukemias, blast cells in chronic leukemias are more mature and can carry out some of their normal functions [25].

Principally, leukemia is subdivided into four major subtypes: Acute Lymphocytic Leukemia (ALL), Chronic Lymphocytic Leukemia (CLL), Acute Myeloid Leukemia (AML), and Chronic Myeloid Leukemia (CML) [26]. However, this classification is an over-simplification. In the World Health Organization (WHO) classification, precursor B-lymphoblastic and T-lymphoblastic neoplasms overlap with their corresponding lymphoma i.e., B-cell lymphoblastic leukemia/lymphoma (B-ALL/B-LBL) and T-lymphoblastic leukemia/lymphoma (T-ALL/T-LBL) respectively [27]. It is important to note that mature B-ALL has been eliminated from the 2008 WHO classification of B-ALL as it is inseparable from Burkitt lymphoma (mature B-ALL is treated as stage IV Burkitt lymphoma) [28]. In addition, CML is classified as a Myeloproliferative Neoplasm (MPN). Importantly, CML is not to be confused with Chronic Myelomonocytic Leukemia (CMML). CMML is a hybrid or mixed myelodysplastic/myeloproliferative neoplasm characterized by a large heterogeneity of clinical features but allo-HSCT remains the only potentially curative option. However, the inherent toxicity of this procedure makes the decision to proceed to allo-HSCT challenging, particularly because patients with CMML are mostly older and comorbid [29].

Acute Lymphoblastic Leukemia (ALL)

ALL is still an important cause of morbidity and mortality in children and adults [30]. Accounting for 25% of all childhood cancers, ALL is the most common malignant neoplastic disease in children. 85% of the cases of childhood ALL are of the B-lineage (B-ALL) [31]. Despite cure rates exceeding 90% in children with B-ALL, outcomes of older adolescents and young adults with ALL still lag behind those of their younger

counterparts despite pediatric-inspired chemotherapy regimens and yet, childhood R/R ALL is associated with poor outcomes. Altogether, ALL still represents the leading causes of cancer-related death, underscoring a critical unmet need for effective new therapies [32,33].

Rearrangements of the human Histone-lysine N-methyltransferase 2A (KMT2A) or Mixed Lineage Leukemia genes (MLL), detected in approximately 5% of childhood ALL, are most frequent in infants (< 12 months of age) and are associated with poor outcome [34,35]. Approximately 70% of infants with B-ALL have a KMT2A rearrangement (KMT2A-R), and their outcome is particularly unfavorable compared to infant ALL without KMT2A rearrangements (often referred to as KMT2A germline/KMT2A-G) [36]. In this context, infant ALL constitutes another rare ALL subtype for which innovative therapies are urgently needed, since their unfavorable outcome remains essentially unchanged over the past several decades [37]. Strikingly, even though noninfants with KMT2A-R ALL have a superior outcome to infants, their outcomes remain clearly inferior to those of childhood ALL and even allo-HSCT has failed to improve their outcome [38]. Moreover, there is an unmet need for developing immunotherapies for the large cohort of patients who are deemed unfit for post-remission intensive chemotherapy or HSCT in first remission because of toxicity to previous chemotherapy or significant co-morbidities [39]. In a similar vein, the poor outcome associated with Philadelphia chromosome (Ph)-like ALL (characterized by a gene expression profile similar to that of Ph⁺ ALL, but lacks the canonical BCR-ABL1 fusion) which has been improved significantly by the early addition of imatinib or related Tyrosine Kinase Inhibitors (TKIs) to intensive chemotherapy regimens with or without HSCT in Complete Remission1 (CR1) provided a compelling rationale to control targeted therapies or precision medicine approaches for ALL [40]. Nevertheless, most molecularly targeted approaches have thus far failed to improve long-term outcomes in relapsed ALL [41].

Remarkably, the emergence of immunotherapies has transformed therapy for relapsed ALL. As CD19 is expressed by essentially all B-cell malignancies at clinical presentation, the prototype Bi-specific T-cell Engager (BiTE) therapy (Blinatumomab) and Chimeric Antigen Receptor (CAR)-T cell therapy (Tisagenlecleucel) respectively, were granted approval by the United States Food and Drug Administration (FDA) as CD19-targeting B-cell malignancies. Nevertheless, relapses with loss or reduction in CD19 surface expression were increasingly recognized as a cause of treatment failure [42-44]. In the case with blinatumomab, the high initial overall response rate is frequently accompanied by subsequent relapse or refractoriness to treatment [45]. Relapses with loss or reduction in CD19 surface expression are being increasingly recognized as a cause of treatment failure of blinatumomab. Mechanistically, reduction in response may be due to low CD19 antigen expression or antigen loss from alternative splicing, non-functional membrane chaperone proteins, transformation to myeloid lineages, or CD19 mutations. Noteworthy, similar mechanisms of resistance develop in response to CD19-targeted CAR T-cell therapies. In addition, the increased expression level of Programmed Death-Ligand 1 (PD-L1) in blinatumomab-resistant patients is another explanation for tumor escape [46]. Remarkably, blinatumomab does not obviate the need for intrathecal therapy due to the lack of sufficient evidence to suggest that it crosses the blood-brain barrier (BBB) [47]. In this vein, despite that cranial irradiation

was omitted from treatment protocols for children with newly diagnosed ALL, intrathecal therapy alone was strongly associated with cognitive impairment [48].

Furthermore, T-ALL/T-LBL accounts for approximately 15% of pediatric and 25% of adult ALL [49]. Intriguingly, it is often debated whether T-LBL and T-ALL are different entities or represent manifestations of the same disease, owing to the great overlap in their morphological, clinical, and immune-phenotypic features [50-52]. T-LBL represents the second most frequent subtype of Non-Hodgkin Lymphoma (NHL) in children and adolescents [53]. While risk stratification is well-developed for patients with B-ALL, it remains challenging for those with T-ALL [54]. In tandem, outcomes for T-ALL are still lagging behind those for B-ALL by 5%-10% in most studies [55]. In particular, outcomes of relapsed T-ALL/T-LBL remain dismal (5-year overall survival (OS) <35%) [56]. In parallel, immunotherapeutic approaches for T-ALL has lagged significantly behind B-ALL [57]. Indeed, the search and identification of selective targets for T-ALL blasts not expressed by normal T-cells remains the main challenge [58].

Acute Myeloid Leukemia (AML)

AML is the most common acute leukemia in adults. AML is not just one disease, but rather a heterogeneous group of disorders caused by chromosomal translocations and rearrangements resulting in the uncontrolled proliferation of myeloid blast cells (myeloblasts) in the BM and impaired production of normal thrombocytes, erythrocytes, and leukocytes [59,60]. Strikingly, AML is an aggressive hematologic malignancy that has been suffering from stagnant survival curves for decades. More than 90% of patients with newly diagnosed AML fall into an intermediate or poor risk category per European Leukemia Network (ELN) criteria, and in this patient population, allo-HSCT in CR1 serve as the only chance for cure [61,62].

According to 5th edition of the World Health Organization (WHO) classification of Haematolymphoid Tumours (WHO-HEM5, also called WHO 2022), AML entities are now grouped into AML defined by differentiation, previously known as Acute Myeloid Leukemia Not Otherwise Specified (AML-NOS) and AML with Defining Genetic Abnormalities (DGAs) including PML::RARA, RUNX1::RUNX1T1, CBFβ::MYH11, RBM15::MRTFA and DEK::NUP214; rearrangements involving KMT2A, MECOM (EVI1) and NUP98; and NPM1 mutation. However, the biggest difference is the removal of the blast cutoff for all genetically defined AML cases except AML with BCR::ABL1 fusion, AML with CEBPA mutation and Myelodysplasia-Related AML (AML-MR). Notably, the presence of AML-DGA excludes a diagnosis of Myelodysplastic Syndrome (MDS), particularly in cases having >2% and >5% blasts in PB and BM respectively [63]. In addition, the remaining AML categories retain the 20% blast cutoff, discriminating it from MDS [64]. However, in parallel to the WHO-HEM5, an alternative International Consensus Classification (ICC) has been proposed. In contrast to the WHO-HEM5, ICC sets the blast cutoff for AML-DGA to 10%, assigning cases with 10-19% blasts without DGA to a new category MDS/AML [65]. In contrast to the WHO system which is established in 2008, the French-American-British (FAB) classification established in 1976 does not take into account chromosomal and molecular features but assigns AML into eight subtypes (M0-M7) based on the type of cells from which the leukemia developed and the maturity of cells (Table 1). Basically, subtypes M0 through

M5 all start in immature forms of white blood cells called myeloblasts. M6 AML starts in very immature forms of red blood cells, while M7 AML starts in immature forms of cells that make platelets (megakaryocytes) [66]. Despite that acute promyelocytic leukemia (APL or APML; AML-M3) is the most curable subtype of AML [67], it is considered a medical emergency with a very high pre-treatment mortality [68]. Approximately 10% of patients with AML-M3 still experience disease relapse following front-line therapy [69].

Table 1: The French-American-British (FAB) AML classification system.

FAB subtype	Name
M0	Undifferentiated acute myeloblastic leukemia
M1	Acute myeloblastic leukemia with minimal maturation
M2	Acute myeloblastic leukemia with maturation
M3	Acute promyelocytic leukemia (APL)
M4	Acute myelomonocytic leukemia
M4 eos	Acute myelomonocytic leukemia with eosinophilia
M5	Acute monocytic leukemia
M6	Acute erythroid leukemia
M7	Acute megakaryoblastic leukemia

Note: Society AC. Acute Myeloid Leukemia (AML) Subtypes and Prognostic Factors 2018.

The poor prognosis of AML is usually secondary to high-risk genetic features or due to antecedent hematologic disorders e.g., MDS. More than one-third of newly diagnosed children and adolescents with AML continue to relapse and experience suboptimal long-term outcomes [70]. On the other hand, AML is the most common acute leukemia affecting the elderly, with the average age of diagnosis being 70 years old, where it poses a great therapeutic challenge to the clinical hematologist [71,72]. The 5-year survival rate for adult patients with AML is at approximately 40% according to the WHO [73]. The nucleoside Analogue Cytarabine (Ara-C) combined with an anthracycline such as daunorubicin continues to be the backbone of therapy for AML. However, chemoresistance remains the main cause of poor long-term survival associated with high relapse rate in AML [74]. The occurrence of AML relapse is attributed to the persistence and clonal evolution of Leukemic Stem Cells (LSCs) that hijack stem cell programs (such as self-renewal capacity) to fuel leukemogenesis and progression [75,76]. Further, LSCs show different degrees of inherent treatment resistance and may acquire secondary resistance during treatment through genetic and non-genetic mechanisms [77]. On the other hand, despite that Hematopoietic Stem Cell Transplantation (HSCT) is an established curative treatment option for patients with AML, transplant recipients were at substantially higher risk of developing severe/life-threatening conditions and premature death [78].

The most frequent genetic alteration in AML is mutation of the FMS-like tyrosine kinase 3 (*FLT3*) gene which encodes the FLT3 receptor (CD135), emerging as a prognostic factor, a new marker for Measurable Residual Disease (MRD), and a potential novel

therapeutic target in AML [79,80]. By the way, FLT3 is a type III receptor tyrosine kinase that contributes to normal HSC survival. There are two major types of FLT3 mutations: Internal tandem duplication mutations in the juxtamembrane domain (FLT3-ITD) and point mutations or deletion in the tyrosine kinase domain (FLT3-TKD). FLT3-ITD is an independent poor prognostic factor that is strongly associated with high WBC and an increased blast percentage at diagnosis and frequently found in cytogenetically normal AML [81]. FLT3-ITD in the juxtamembrane region is thought to destroy the self-suppressing conformation of FLT3 receptor, thereby activating downstream pathways continuously, including Mitogen-Activated Protein Kinase (MAPK), Extra-cellular Signal Regulated Kinase (ERK), Signal Transducer And Activator Of Transcription 5 (STAT5) and Phosphoinositide 3-Kinase (PI3K) [82]. FMS-like tyrosine kinase-3 Internal Tandem Duplication (FLT3-ITD) is found in approximately 25% of adult patients but in more than 30% of patients over 55 years of age [83,84]. In contrast, FLT3-ITD occur in 10%-15% of pediatric *de novo* AML patients, and those with high FLT3-ITD AR (>0.4) have inferior outcomes with survival of approximately 50%-65% with HSCT [85-87]. The European LeukemiaNet (ELN) introduced the Allelic Ratio (AR) of FLT3-ITD for risk stratification. Several groups demonstrated that high FLT3-ITD AR (≥ 0.5) (FLT3-ITD_{high}) is associated with a poor prognosis but not the low FLT3-ITD AR (<0.5) (FLT3-ITD_{low}) [88]. Remarkably, the natural history of FLT3-mutated AML changed after the approval of the FLT3 inhibitors midostaurin for frontline therapy and gilteritinib for R/R patients [89]. Because FLT3 inhibitor-based therapy has improved survival, the new ELN classification (2022) categorized AMLs with FLT3-ITD in the intermediate-risk group, irrespective of the allelic ratio or concurrent presence of Nucleophosmin 1 (NPM1) mutation [90,91]. The reclassification of FLT3-ITD mutational status into the intermediate-risk group was one of most important changes provided by the ELN 2022 risk classification [92]. On the other hand, the clinical impact of FLT3-TKD, found in about 7% of patients at diagnosis, on the long-term outcome is controversial but in general is not considered a poor prognostic factor. Consequently, neither do the National Comprehensive Cancer Network (NCCN) or ELN consider the presence of FLT3-TKD mutations as a recommendation for allo-HSCT [93,94]. Nonetheless, the treatment of patients with FLT3-mutated AML remains challenging despite the approval of several FLT3 inhibitors over the last few years [95]. In this vein, Tarlock, et al., recently demonstrated that FLT3 inhibition is not an effective target for therapeutic intervention in ITD_{pos}/NUP98::NSD1 AML in a large cohort of patients with FLT3-ITD (included 3033 pediatric and young adult patients, aged 1 month-29 years); highlighting that further efforts to study the early intervention of novel and targeted therapies are urgently needed for those patients. This supports recent studies indicating that FLT3-ITD cooccurring with WT1, UBTF, or NUP98-NSD1 is associated with significantly inferior prognosis [96-101].

Myelodysplastic Syndromes (MDS)

Myelodysplastic Syndromes (MDS) are a heterogeneous clonal disease of myeloid neoplasms characterized by ineffective hematopoiesis, variable degree of cytopenias, and an increased risk of progression to AML. The threshold for defining dysplasia is recommended as 10% for all lineages; for megakaryocytes, micromegakaryocytes are the most specific indicator of MDS,

and a higher threshold of dysplasia may be warranted when other types of dysmegakaryopoiesis are included [102,103]. MDS entities are separated into two major groups: MDS with defining genetic abnormalities and MDS defined morphologically. MDS with defining genetic abnormalities includes the following entities: MDS with biallelic TP53 inactivation, MDS with low blasts and SF3B1 mutation (MDS-SF3B1) and MDS with low blasts and del(5q). MDS defined morphologically includes MDS with low blasts, hypoplastic MDS, MDS with increased blasts-1, MDS with increased blasts-2 and MDS with fibrosis. Although the 20% blast cutoffs were eliminated for most AML types with DGAs, this 20% blast cutoff was retained to delineate MDS from AML in order to avoid overtreatment of patients. In this context, the family of MDS with increased blasts (IBs) includes disease with $<20\%$ blasts [104].

Despite the approval of five MDS-specific therapies in the USA since 2004 and the increasing use of allo-HSCT, the prognosis remains dismal for most patients with Higher-Risk MDS (HR-MDS) [105]. Mutations in TP53, RUNX1, ASXL1, Janus kinase 2 (JAK2), and RAS pathway genes are associated with significantly shorter OS or Relapse-Free Survival (RFS) after allo-HSCT, with TP53 mutations being particularly adverse [106-108]. One potential mechanism underlying the poor prognosis associated with TP53 mutations is the induction of an immunosuppressive microenvironment that permits immune evasion of tumor cells [109-111]. Supporting this hypothesis, AM Zeidan, JP Bewersdorf, et al., recently found both a higher T-cell population and upregulation of inhibitory immune checkpoint proteins such as PD-L1 compared to TP53 wild-type in BM from TP53-mutated AML/HR-MDS [112]. Moreover, Ribonucleic Acid (RNA) sequencing analyses revealed higher expression of the myeloid immune checkpoint gene LILRB3 in TP53-mutant samples suggesting a novel therapeutic target.

The DNA methyltransferase inhibitors azacitidine and decitabine, also known as Hypomethylating Agents (HMAs), have become standard of care for patients with HR-MDS [113]. Both HMAs are administered parenterally (requiring daily visits to a treatment centre for 5 consecutive days or 7 consecutive days of every 28-day treatment cycle) which represent a substantial burden for the older adult population with this disease (median age of 73 years at diagnosis) as well as is associated with so-called time toxicity [114]. Nonetheless, only half of the HR-MDS patients treated with HMAs achieves objective responses, and most responders (only 10%-20% of patients) eventually lose response within 1-2 years [115-119]. Unfortunately, there are no standard-of-care therapeutic options for patients after HMA failure [120]. Up to the present, the prognosis of patients with HMA failure remains bleak [121]. Moreover, outcomes with allo-HSCT in the context of TP53-mutated MDS/AML are quite poor [122]. Consequently, the most appropriate treatment recommendation for TP53-mutated MDS/AML is enrollment in a clinical trial [123].

Pediatric MDS

Childhood MDS (cMDS, defined as <18 years of age) is biologically distinct from adult MDS for example, MDS with del(5q) and MDS with mutated SF3B1 virtually never occur in children. Therefore, pediatric-type MDS classification criteria often do not fit into adult-type MDS classification criteria [124,125]. cMDS can either be primary ("*de novo*") or secondary, with secondary MDS being associated with antecedent or predisposing conditions such as certain genetic mutations, Inherited Bone Marrow Failure

Syndromes (IBMFSs), prior chemotherapy/radiation therapy (therapy-related MDS), or acquired Severe Aplastic Anemia (SAA). Notably, MDS in children often occur in the context of IBMFs and germ line syndromes (e.g., mutations in *GATA2*, *ETV6*, *SRP72*, and *SAMD9/SAMD9L*) [126-128]. Noteworthy, germline mutations in certain genes may confer substantially increased risk of MDS with an onset after age 18, such as *ATG2B/GSKIP*, *TET2* and *DDX41* [129-131].

Importantly, cMDS is divided into two main categories: (1) Refractory Cytopenia Of Childhood (RCC)/MDS with low blasts for cases with <2% PB and <5% BM blasts; (2) MDS-excess blasts/MDS-increased blasts for cases with 2% PB or 5% BM blasts. While the 5th edition of the WHO replaces RCC with “childhood MDS with low blasts” (cMDS-LB), the ICC retained the terminology of RCC for cases meeting defined morphologic criteria including <2% blasts in the PB and <5% blasts in the BM. WHO classifies pediatric MDS with 5% blasts in the BM and/or 2% blasts in the PB as “childhood MDS with increased blasts (cMDS-IB)”, while the ICC classifies pediatric MDS with PB blasts between 2% and 19% and/or BM blasts between 5% and 19% as MDS with excess blasts (MDS-EB) [132]. Strikingly, RCC is the most common subtype of MDS in children [133]. In this context, RCC must be distinguished from SAA and Inherited Bone Marrow Failure Syndromes (IBMFs) as clinical and histopathologic distinction between them is of important therapeutic value [134,135].

Notably, cMDS has a different biological signature. Monosomy 7 and del (7q) are the most common cytogenetic abnormalities in pediatric MDS. In contrast to adult MDS cases, the mutational landscape of cMDS often contains somatic RAS pathway or *SETBP1*, *ASXL1*, and/or *RUNX1* mutations (the frequently mutated genes in adult MDSs including *TET2*, *DNMT3A*, and *TP53* and the spliceosome complex are not involved in disease pathogenesis in cMDS) [136-138]. The treatment strategies for cMDS are context-dependent i.e., depends on the diagnosis (with or without excess blasts), clinical scenario, and cytogenetics. There are three main treatment strategies for cMDS: Watch-and-wait, Immunosuppressive Therapy (IST), and HSCT [139]. Patients with lower-risk disease may be managed conservatively while patients with higher-risk disease (particularly with excess blasts, therapy-related MDS, or complex karyotype) are optimally managed by allo-HSCT [140].

Myeloid leukemia associated with down syndrome: Constitutional trisomy 21 (T21), which results in the development of Down Syndrome (DS), is a state of aneuploidy associated with high incidence of childhood AML. Myeloid leukemia associated with DS (ML-DS) phenotypically reflects Acute Megakaryoblastic Leukemia (AMKL) observed in patients without DS. However, ML-DS has distinct clinical and biological features reflecting a model of step-wise leukemogenesis with perturbed hematopoiesis already presenting in utero [141]. ML-DS is preceded by a pre-leukemic state called Transient Abnormal Myelopoiesis (TAM). While TAM is triggered by truncating mutations in *GATA1* generating a short *GATA1* isoform (*GATA1s*), ML-DS emerges due to secondary mutations in hematopoietic clones bearing *GATA1s* [142]. Noteworthy, MDS almost always precedes AML in patients with DS [143,144]. However, it is well recognized that many children with ML-DS present with a low blast count and a more myelodysplastic picture. While in many cases progression from MDS to AML is slow, all cases with MDS will eventually progress to full-blown AML. Therefore, it is recommended

to commence treatment of MDS even with low blast counts. Unsurprisingly, ML-DS encompasses both MDS and AML occurring in DS under the WHO classification [145,146].

Chronic Myeloid Leukemia (CML)

CML is one of Myeloproliferative Neoplasms (MPN). CML is defined by the BCR::ABL1 fusion resulting from t(9;22)(q34;q11). The natural history of untreated CML before the introduction of targeted TKIs was biphasic or triphasic: An initial indolent chronic phase (CML-CP) followed by a blast crisis (CML-BC), with or without an intervening accelerated phase (CML-AP). CML treatment improved significantly following development of ABL TKIs, such as imatinib, dasatinib, nilotinib, bosutinib, and ponatinib. The incidence of progression to advanced phase disease has decreased, and the 10-year OS rate for CML is 80-90% [147]. However, development of drug resistance to TKIs due to BCR-ABL point mutations, such as the E255K, Y253F/H (P-loop), H396R (activation loop) or the T315I (gatekeeper), poses a major challenge in the clinical treatment of CML [148]. In particular, the gatekeeper mutation T315I confers resistance against all approved TKIs, with the only exception of ponatinib, a third-generation multi-target kinase inhibitor [149]. Despite that ponatinib exhibits good therapeutic activity against the T315I mutation, its clinical utility is somewhat limited due to its cardiovascular toxicity [150]. Consequently, it is vital to develop new therapeutic strategies that are effective against TKI-resistant CML cells.

Adult T-cell Leukemia/Lymphoma (ATLL)

ATLL is a mature T-cell neoplasm most often composed of highly pleomorphic lymphoid cells. The Human Lymphotropic Virus Type 1 (HTLV-1) [151,152] causes the disease. In 2018 alone, HTLV-1 caused about 3600 cases of ATLL [153]. Most ATLL patients present with widespread lymph node involvement as well as involvement of PB. ATLL is endemic in several regions of the world, in particular southwestern Japan, the Caribbean basin, and parts of central Africa. ATLL is an aggressive malignancy associated with poor prognosis because of intrinsic chemoresistance and severe immunosuppression [154]. The treatment of ATLL is usually dependent on the ATLL subtype. Patients with aggressive forms (acute and lymphoma) have a very poor prognosis [155-158]. Patients with indolent ATLL (chronic or smoldering subtypes) have a better prognosis, but long-term survival is poor when these patients are managed with a watchful-waiting policy or with chemotherapy [159].

Multiple Myeloma (MM)

Plasma cell neoplasms including Multiple Myeloma (MM) and lymphoid leukemias are considered B-cell lymphoid malignancies in the WHO classification system [160]. MM is an incurable B-cell malignancy characterized by monoclonal proliferation of plasma cells within the BM. These malignant plasma cells produce and secrete a characteristic monoclonal immunoglobulin (M-protein) [161]. This M-protein is important for diagnosis and monitoring the disease status [162]. MM accounts for 1.8% of new cancer cases annually and about 10% of hematological malignancies [163]. Patients with MM usually suffer from hypercalcemia, renal damage, anemia, bone lesions and immunodeficiency [164]. In particular, bone disease is the main cause of MM morbidity.

Intriguingly, MM exists on a continuous disease spectrum

[165,166]. Almost all patients with MM begin with an asymptomatic pre-malignant stage termed Monoclonal Gammopathy of Undetermined Significance (MGUS) progressing to an intermediate asymptomatic but more advanced pre-malignant stage referred to as Smoldering Multiple Myeloma (SMM) which can be recognized clinically and lastly to MM [167,168]. Strikingly, genetic abnormalities, epigenetic alterations, and microenvironmental factors co-operate in the development of symptomatic MM [169]. Although MM is still considered a single disease, it is increasingly recognized as a collection of several different plasma cell malignancies characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness [170-173]. In this vein, the presence of del(17p), t(4;14), t(14;16), t(14;20), gain 1q, del 1p, or p53 mutation is considered high-risk MM. Presence of any two high risk factors is considered double-hit myeloma; three or more high risk factors is triple-hit myeloma [174].

Despite advances in treatment strategies, ranging from conventional chemotherapy with alkylating agents and HSCT, to the use of antiangiogenic or proteasome inhibiting drugs, MM is still an incurable disease, where almost all patients with MM eventually relapse or become refractory to treatment at some point in their lives [175-177]. As resistance to chemotherapy is one of the main challenges in MM management targeting tumor antigens with immunotherapy is rapidly emerging as a potential avenue for treatment of MM [178,179]. Nevertheless, around 40% of newly diagnosed MM patients treated with immunotherapy regimens containing daratumumab, a CD38-targeted monoclonal Antibody (mAb), progress prematurely [180]. In this line, the majority of patients treated with either daratumumab or isatuximab (both are mAbs that target CD38) will ultimately progress while on treatment or relapse after therapy. Strikingly, patients progressing after CD38 mAb-based therapies are also frequently resistant to other commonly used anti-myeloma agents such as lenalidomide and bortezomib [181]. In a similar vein, despite that the B-cell Maturation Antigen (BCMA) is preferentially expressed on mature B-cells [182], while > 70% of patients with R/R MM initially responded to anti-BCMA CAR T-cell therapy, clinical relapse and disease progression occur in most cases [183]. Intriguingly, Ledergor, et al., introduced the importance of cell states *in vivo* as possible predictors of outcome after CAR T-cell therapy [184,185]. By using single-cell transcriptomics to study changes in immune cells in patients with MM receiving anti-BCMA CAR T-cells, they found that patients with short-lived responses had increased frequencies of exhausted cytotoxic CD4⁺ CAR T-cells, whereas those with durable responses possessed a significantly higher proportion of CD8⁺ T-effector memory cells. In addition, the relevant exhaustion coexpressed markers are TIM-3 and TIGIT, rather than other canonical markers of exhaustion such as PD-1 or CTLA-4, which might inform future combination therapeutic approaches. Furthermore, severe (grade \geq 3) and persistent (40% at day *90) cytopenia (particularly thrombocytopenia) leading to severe (50%) bacterial (68%) infections occurring within 30 days (moderate viral infections were more prevalent later)-remains a challenge after anti-BCMA CAR T-cell therapy [186]. Not surprisingly, most physicians believed that post CAR T-cell prolonged cytopenia could be a potential barrier to the next-line relapse therapy, especially that nearly half of patients were offered a stem cell boost [187].

Strikingly, MM with Extramedullary Disease (EMD), defined as paraskeletal or organ involvement with high mortality and an average OS time of 36 months, is a well-established marker of inferior prognosis in MM, even in the era of novel therapies [180-192]. Based on current knowledge, extramedullary spread of MM may occur either at diagnosis (7%-18%), during the course of the disease (6%), or at relapse (up to 20%) [193,194]. Recently, Gagelmann, et al., showed that patients with organ involvement have significantly worse Progression-Free Survival (PFS) despite posttransplant maintenance, while patients with paraskeletal involvement appeared to be associated with similar outcomes in comparison with patients without EMD [195]. In a similar vein, the presence of EMD is an independent risk factor for inferior PFS despite CAR T-cell therapy. Among 351 patients with R/R MM from 11 US academic centers, who had EMD prior to Idecabtagene vicleucel (Ide-cel) infusion, have demonstrated significantly inferior Day 90 Objective Response Rates (ORR) [196,197].

Hodgkin lymphoma and Non-Hodgkin lymphoma

Hodgkin Lymphoma (HL): HL accounts for approximately 10% of lymphoma cases. It is developed in the lymphatic system and occurs mostly sporadically. It can also be associated with the Epstein-Barr Virus (EBV) or Human Immune Virus (HIV)/Acquired Immuno Deficiency Syndrome (AIDS) and originates from the lymph node [198]. Hodgkin/Reed-Sternberg (HRS) cells are the hallmark cells of HL [199]. HL is divided into two distinct categories that demonstrate different pathologic and clinical features: classical Hodgkin lymphoma (cHL) and nodular lymphocyte-predominant Hodgkin Lymphoma (NLP-HL). cHL accounts for approximately 95% of HL and is further subdivided into four subgroups: Nodular Sclerosis Hodgkin Lymphoma (NSHL), lymphocyte-Rich Hodgkin Lymphoma (LRHL), Mixed Cellularity Hodgkin Lymphoma (MCHL), and Lymphocyte-Depleted Hodgkin Lymphoma (LDHL) [200].

cHL is characterized by the recurrent genetic rearrangement 9p24.1 that shares the locus of PD-L1, PD-L2, and JAK2, leading to enhanced PD-L1/PD-L2 upregulation of HRS cells, which constitutes a mechanism to escape the immune-mediated anti-tumor response. Although PD-1/PD-L1 axis blockade has demonstrated efficacy in the treatment of R/R HL, many patients develop primary or secondary resistance to these agents, attributed, at least in part, to the expression of other immune checkpoints on HRS cells or in the Tumor Microenvironment (TME) such as Lymphocyte Activation Gene 3 (LAG-3/CD223) and T cell immunoglobulin and mucin-domain containing-3 (TIM-3).

NSHL is the most frequently diagnosed subtype of HL and tends to occur in young adults, usually under age 50 years. Anterior mediastinal involvement is extremely common 90% of the cases in NSHL, with subsequent involvement of cervical and supraclavicular lymph nodes, upper abdominal lymph nodes, and spleen [201]. Histologically, NSHL is characterized by collagen bands that surround at least one nodule, and by HRS cells with lacunar-type morphology.

Non-Hodgkin Lymphoma (NHL): NHL includes all lymphomas except for Hodgkin lymphomas, which comprises more than 50 different neoplasms that arise from immature or mature B-cells, T-cells, or natural killer (NK) cells (effector lymphocytes of the innate immune system) [202]. The relative frequencies of various

subtypes of NHL vary significantly in different geographic regions of the world, and environmental and lifestyle factors, as well as host genetic makeup, appear to contribute to the development of NHL [203]. NHL is generally divided into 2 main types, based on whether it starts in B lymphocytes (B-NHL) or T lymphocytes (T-NHL). NHLs are also classified by whether it is aggressive (fast-growing) or indolent (slow-growing). There are huge differences between the fast-growing aggressive lymphomas (aNHLs; about 60% of all NHL cases) and the slow-growing indolent lymphomas. While DLBCL is the most common aggressive form of B-NHL, FL, and CLL are slow-growing lymphomas [204]. Notably, apart from cHL and primary mediastinal B-cell lymphoma (PMBL) combination therapies with PD-1/PD-L1 blockade have not resulted in obvious clinical responses in patients with other lymphomas [205,206]. Strikingly, PD-L1 has been reported expressed by tumor cells and PD-1 by tumor-associated T cells in DLBCL [207,208]. A multicenter cohort study of 288 DLBCL patients shows that high level of soluble PD-L1 (sPD-L1) in peripheral blood at the time of diagnosis is significantly associated with poorer OS for patients diagnosed with aggressive DLBCL, particularly for those treated with standard R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) [209].

Burkitt Lymphoma (BL): BL is an aggressive mature B-cell lymphoma derived from Germinal Center (GC) or post GC B-cells. BL is characterized by a very high proliferation rate and believed to be the fastest growing human tumor [210]. With a Ki67 (a cellular marker for proliferation) expression of nearly 100%, the clinical course of BL usually is highly aggressive requiring prompt institution of therapy [211]. In contrast to B-lymphomas with predominant lymph node involvement, BL most commonly involves extranodal sites such as the jaw, bones, gastrointestinal tract, gonads, or breasts.

There are three clinical variants of BL: Endemic (African-derived), sporadic (nonendemic), and Human Immunodeficiency Virus (HIV) associated BL. BLs occurring in each of these settings are histologically identical but differ in some clinical, genotypic, and virologic characteristics. Endemic BL is a pediatric cancer accounting for 30–50% of all childhood cancers in regions where malarial transmission is year-round [212-215]. Essentially all endemic BLs are latently infected with Epstein-Barr Virus (EBV), which is also present in about 25% of HIV associated tumors and 15% to 20% of sporadic cases. However, how EBV contributes to the BL lymphomagenesis is still to be defined [216]. All forms of BL are highly associated with translocations of the MYC gene (a potent oncogene located at chromosome locus 8q24.21) that lead to increased MYC protein levels. The translocation partner for MYC is usually the IgH locus [t(8;14)] but may also be the Ig κ [t(2;8)] or λ [t(8;22)] light chain loci. Rearrangement of MYC with immunoglobulin genes is a hallmark of Burkitt lymphoma [217]. In addition to BL, dysregulation of MYC has been shown to be an independent negative prognostic factor in other aNHLs [218-220].

Diffuse Large B Cell Lymphoma (DLBCL): DLBCL is the most common hematologic malignancy as well as the most common form of B-NHLs comprising 30%–40% of cases, with slight overrepresentation of the male gender [221-223]. DLBCL belongs to the family of Large B-cell Lymphomas (LBCL), a heterogeneous class of tumors characterized by large lymphoid cells of the B-cell lineage that by definition form sheets or clusters. “Large cell” cytology is usually defined as a lymphoid cell with a nucleus that

is larger than that of a macrophage or twice the size of a normal lymphocyte [224]. Notwithstanding the significantly improved outcomes of R/R LBCL induced by the autologous CD19-directed CAR T-cell therapy compared to standard of care salvage chemoimmunotherapy, most patients do not have durable benefit and post-CAR T-cell relapses are difficult to salvage [225,226].

DLBCL is characterized by a striking degree of genetic and clinical heterogeneity [227-231]. Based on gene expression profiling, three major molecular subtypes have been identified: GC B-cell-like (GCB-DLBCL), activated-B-cell-like (ABC-DLBCL) and PMBL [232]. However, around 10%-15% of cases are categorized as unclassifiable. The ABC-DLBCL and GCB-DLBCL subtypes show differences in chromosomal alterations, signaling pathway activation, and clinical outcome. The ABC-DLBCL has demonstrated inferior clinical outcome compared with the GCB-DLBCL. Although R-CHOP therapy remains the mainstay of treatment for DLBCL, this fails to achieve remission in about 40% of patients. In addition, despite the recent advances in management of DLBCL, outcomes for high-risk patients continue to remain suboptimal [233]. Hence, research is needed to discover novel therapeutic strategies [234]. Mechanistically, B-cell Antigen Receptor (BCR) signaling that activates downstream oncogenic pathways such as the nuclear factor kappa-light-chain-enhancer of activated B cell (NF- κ B) or phosphatidylinositol 3-kinase (PI3K) plays a critical role in pathogenesis of B cell malignancies, including DLBCL and CLL [235-239]. There are two fundamentally distinct mechanisms of BCR pathway activation in B cell lymphomas: Antigen-dependent and antigen-independent BCR signaling [240,241]. The hallmark of ABC-DLBCLs is chronic active antigen-dependent BCR signaling resulting in constitutive NF- κ B activity which blocks apoptosis [242]. In fact, ABC-DLBCL cells are highly dependent on NF- κ B for their viability [243,244]. Although chronic active BCR signaling in ABC DLBCL shares characteristics with antigen-dependent BCR signaling in normal B cells, intact BCR signal transduction pathway is tightly regulated and self-limited by the availability of antigen and other negative controls [245]. On the other hand, genomic data have shown that GCB-DLBCL lines exclusively use an antigen-independent signal, termed tonic BCR signaling [246]. Unlike chronic active BCR signaling, tonic BCR signaling is mediated by PI3K β and PI3K δ /AKT/mTOR (but not the NF- κ B pathway) to promote the proliferation and survival of malignant B cells [247]. In contrast to BL where MYC rearrangements are present in almost all of the cases, alterations in MYC have been detected in approximately 5% to 15% of DLBCL cases. However, MYC overexpression is one of the key prognostic and predictive biomarkers for survival in DLBCL, and some authors even showed that MYC overexpression is associated with the worst survival rates [248-252].

Follicular Lymphoma (FL): FL is a CD5⁻ and CD10⁺ indolent lymphoma representing approximately 40% of all NHLs. The genetic hallmark of FL is the t(14;18) translocation resulting in B cell lymphoma-2 (Bcl-2) oncoprotein overexpression (found in up to ~85% of patients) [253]. Bcl-2 is a prototypic anti-apoptotic protein (promotes tumor cell survival) and its overexpression in FL is the classic example of its anti-apoptotic mechanism (prevents programmed cell death by limiting the exit of cytochrome c from mitochondria). The pathobiology of FL is complex and involves alterations within the FL microenvironment in addition to the cell-intrinsic genetic changes, frequently including (in addition to the hallmark t(14;18) translocation) mutations in histone-

encoding genes (in ~ 40% of cases), the Susceptibility weighted imaging (SWI)/(Sucrose Non-Fermentable) SNF complex or the interconnected BCR and CXCR4 chemokine receptor signaling pathways [254].

Chronic Lymphocytic Leukemia (CLL): CLL is a disease of the elderly population. Although it is the most common adult leukemia in western countries, it is less common in Asia and relatively rare in Japan and Korea, even among Japanese people who immigrate to western countries [255]. CLL is a malignancy of mature, antigen-experienced B lymphocytes that is characterized by the accumulation of mature circulating IgM^{low} CD5⁺ B cells [256]. In simple words, CLL is a cancer of CD19⁺ B cells that co-express the T cell marker CD5. CLL cells proliferate in distinct microanatomical tissue sites called proliferation centers or pseudofollicles, a hallmark finding in CLL histopathology [257]. Despite a common CD5⁺CD19⁺ phenotype, CLL is marked by a heterogeneous clinical course ranging from a benign disease to one that can be fatal within a few years of diagnosis [258]. As a disorder of B-lymphocytes, CLL is intrinsically characterized by adaptive immune response dysfunction, but alterations of multiple elements and effectors of the innate immune response are also found in CLL patients [259]. Interestingly, CLL and Small Lymphocytic Lymphoma (SLL) are morphologically, phenotypically, and genotypically indistinguishable, differing only in the degree of peripheral lymphocytosis [260].

Despite being a slow-proliferating disease and the great progress recently achieved in the management of CLL, the disease remains potentially incurable [261]. Prognostic biomarkers and risk scoring systems play important roles in guiding CLL treatment decisions [262]. In this context, several genetic aberrations with prognostic value and impact on treatment decisions in CLL have been described. These include deletions of the chromosomal regions 17p13 (containing the TP53 tumor suppressor gene), 11q23 (containing DNA damage checkpoint protein Ataxia Telangiectasia Mutated ATM), or 13q14 (miR-15a, miR-16-1), and trisomy of chromosome 12 [263,264]. Patients with TP53 alterations including TP53 mutations or 17p deletions are classified as high-risk and usually associated with an unfavorable prognosis and poor response to chemotherapy and immunotherapy [265,266]. On the basis of somatic hypermutation status of the Immunoglobulin Heavy-Chain Variable Region Gene (IGHV), CLL can be grouped into mutated CLL (M-CLL) and unmutated CLL (UM-CLL). M-CLL (derived from post-GC B cells) has a more favourable prognosis than those with UM-CLL (derived from CD5⁺ mature B cells) [267]. Numerous genes like ZAP-70 (zeta-associated protein 70), CD38 and LPL (lipoprotein 73 lipase), whose expression was associated with an unmutated status of IGHV genes and poor outcome, were proposed as surrogate markers [268-272]. Although the expression of these markers was found to correlate with the expression of unmutated IGHV genes, this correlation is not absolute [273].

Strikingly, novel immunotherapies showed disappointing results in CLL, in contrast to several B-cell lymphomas where responses were impressive. Mechanistically, the strong immunomodulatory effect of CLL causes low response rates to immunotherapy strategies [274]. For instance, CLL cells have the ability to transform the effector functions of the bystander T cells in the Tumor Microenvironment (TME), thus rendering them a source of trophic signals for the survival and proliferation of the malignant clone. Indeed, substantial evidence implicates T cells present in the TME in the natural history of the CLL as well

as in the establishment of certain CLL hallmarks such as tumor evasion and immune suppression. Although CLL cells are able to manipulate T-cell functionality, T cell abnormalities in CLL appear to be reversible, which is why therapies targeting the T cell compartment, including CAR-T cells, immune checkpoint blockade and immunomodulation, represent a reasonable therapeutic option in CLL [275]. Nevertheless, novel targeted therapies demonstrated improved PFS and OS that were superior to chemoimmunotherapy. Nowadays, Bruton's Tyrosine Kinase (BTK) inhibitors, Bcl-2 inhibitors, and CD20 mAbs are established treatments for CLL, both in frontline and R/R settings [276]. In this context, substantial evidence have established the central role of chronic BCR-mediated signaling in CLL pathogenesis [277]. It is worth noting that BTK, a signal transduction pathway located downstream to the BCR, is essential for constitutively active pathways implicated in CLL cell survival [278-281]. On the other hand, metabolic reprogramming is a hallmark of CLL and underlies disease progression and relapse but the exploitation of metabolic dependencies in clinical settings is still minimal [282].

Noteworthy, Richter transformation (RT), also known as Richter's syndrome, the progression of CLL into an aggressive lymphoproliferative disorder, primarily DLBCL-although HL, plasmablastic lymphoma, or other rare lymphomas have been also reported occurs in approximately 2-10% of patients with CLL [283,284]. Intriguingly, RT is associated with poor response to chemotherapy and short survival e.g., the overall response rates for patients treated with chemoimmunotherapy such as R-CHOP are <40% with a median OS of 6-8 months [285,286]. Since RT remains a therapeutic challenge, innovative management of this grave complication is warranted [287]. Interestingly, MYC aberrations were found in most RT cases [288]. The association of MYC translocation with an unfavorable prognosis of CLL/RT patients was confirmed in several studies [289-291].

Mantle Cell Lymphoma (MCL): MCL results from malignant transformation of B lymphocytes in the mantle zones surrounding GCs [292]. MCL is a very rare form of aggressive B-NHL with a dismal prognosis. Similar to CLL and ABC-DLBCL, MCL also show activation of the BCR pathway and constitutive NF- κ B signaling [293,294]. On the other hand, primary resistance curbed the initial effectiveness of several inhibitors targeting BCR-associated Kinases Bruton Tyrosine Kinase (BTK), Spleen Tyrosine Kinase (SYK), or Phosphatidylinositol 3 Kinase (PI3K), in DLBCL and MCL, especially in the case of first generation BTK inhibitors (e.g. ibrutinib) [295].

The pathognomic feature of MCL is the chromosomal translocation t(11;14) (q13;q32) (IGH/CCND1), which is observed in >95% of cases, resulting in the constitutive overexpression of G1-phase cell cycle protein cyclin D1 (CCND1) [296,297]. MCL usually overexpress IgM as compared to normal B cells, which likely contribute to the pathogenesis of this lymphoma type [298]. TP53 mutations have been associated with an inferior prognosis in MCL and patients usually have a poor response to standard chemotherapy [299]. Therefore, patients with TP53 mutations should be considered for alternative frontline treatment [300].

Myeloproliferative Neoplasms (MPNs)

MPNs are clonal hematopoietic stem cell disorders with overproduction of mature myeloid blood cells. MPNs include CML, Polycythemia Vera (PV), Essential Thrombocythemia (ET), Primary Myelofibrosis (PMF), Chronic Neutrophilic Leukemia (CNL), Chronic Eosinophilic Leukemia (CEL), Juvenile

Myelomonocytic Leukemia (JMML) and Myeloproliferative Neoplasms-Not Otherwise Specified (MPN-NOS). The WHO classifies CML, PV, ET, and PMF as classic MPNs.

The classic MPNs are further classified as Philadelphia chromosome-positive (or BCR-ABL-positive) (CML) and Philadelphia chromosome-negative (BCR-ABL-negative) (PV, ET, and PMF) [301]. Whereas ET and PV are characterized by platelet and erythrocyte overproduction, respectively, PMF is marked by aberrant proliferation of cells of the megakaryocytic lineage and progressive BM fibrosis [302]. However, PMF, ET and PV share common MPN-initiating somatic mutations in the genes that encode for JAK2, Thrombopoietin Receptor (TPO-R) also known as myeloproliferative leukemia protein or MPL and Calreticulin (CALR) leading to the activation of the MPL and downstream signaling pathways (MPL-JAK-STAT signaling) in MPN stem cells [303]. Of these, the *JAK2 V617F* mutation was the first identified, and, is present in 95% of PV, and about 55% and 60% of ET and PMF patients, respectively. *CALR* and *MPL* mutations are almost always associated with an ET or MF phenotype, but not a PV phenotype. *MPL* mutations are present in about 3% ET patients and about 7% of PMF patients [304]. *CALR* is mutated in the majority of *JAK2/MPL* mutation-negative patients, which corresponds to about a quarter of all ET and PMF patients [305-307].

ET has the most favorable prognosis among MPNs but a minority of patients who develop progression to MF or AML, referred to as Blast-Phase (BP) MPN, have a much poorer outcome [308]. In a large cohort of patients with ET (1000 patients), major thromboses at the time of diagnosis were documented in 19%, with a predominance of arterial (13%) *versus* venous (6%) events [309]. On the other hand, PMF is the most aggressive subtype among classical BCR-ABL1 negative MPNs. Approximately 1 of 3 responds to currently approved JAK inhibitor treatment; however, hematotoxicity especially in patients with cytopenic MF which results in treatment discontinuation for many patients. PMF results when cytokines produced by the MPN clone stimulate Bone Marrow Stromal Cells (BMSCs) to deposit an excess of collagens and other Extracellular Matrix (ECM) proteins, consequently destroying the hematopoietic microenvironment [310-312].

PMF is morphologically characterized by abnormal megakaryocyte proliferation that is often accompanied by reticulin fibrosis [313]. The fibrotic BM remodeling and pronounced systemic inflammation cause BM failure, extramedullary hematopoiesis, splenomegaly, profound constitutional symptoms and a median survival of around 5 years [314]. However, the mechanisms by which the hematopoietic tissue in the BM is replaced by a fibrotic scar tissue are not yet fully understood [315]. Common fatal complications of PMF include transformation to acute leukemia, thrombohemorrhagic events, organ failure, and infections [316]. Patients who develop acute leukemia typically involves the myeloid lineages secondary AML (sAML) but rarely, lymphoid transformation (secondary ALL) may also occur, have a median survival time of less than 3 months [317]. Approximately 90% of patients harbor a mutation affecting JAK2, MPL, or CALR. As mutations in these genes all converge on JAK/STAT signaling, the JAK1/2 inhibitor ruxolitinib is currently front-line therapy for MF [318]. In contrast, PMF that lacks these canonical alterations, termed triple-negative PMF (TN-PMF), is associated with poor prognosis [319,320]. In addition to PMF, PV and ET can also progress to post-PV (PPV) MF and post-ET (PET) MF, also known

as Secondary Myelofibrosis (SMF) [321].

• Despite approval of JAK inhibitors and novel agents, allo-HSCT remains the only potentially curative treatment for for both PMF and SMF [322]. Nonetheless, HSCT is limited by its highly concerning risks of Treatment Related Mortality (TRM) and therapy-related complications [323]. Increased risk of post-transplantation relapse was observed for accelerated phase MF compared with chronic phase MF and patients with splenomegaly prior to transplantation [324]. Recently, Gagelmann, et al., identified a novel very high-risk group in patients with MF undergoing HSCT [325]. Compared to patients with monoallelic *TP53* mutated (*TP53mut*) MF, patients with *TP53* multi-hit, MF following HSCT had an increased relapse risk. In a similar vein, this study has also shown that AML transformation was a more frequent relapse presentation in patients with *TP53MH*, compared with patients with monoallelic *TP53mut/TP53WT* which highlights a need for an alternative approach to allo-HSCT in this subgroup [326]. In this regard, clonal evolution to secondary (sAML) is one of the most feared complications of MPN. A significant proportion of patients with MPN (10%-20%) transform to devastating and rapidly fatal sAML, characterized by cytopenias, increased myeloid blasts, acquisition of aberrant LSC properties by Hematopoietic Stem/Progenitor Cells (HSPCs) and median survival of less than one year [327,328]. Notably, the risk of AML transformation was highest for patients with MF (occurring in up to 20% of patients) [329]. Collectively, *TP53* mutations are detected in approximately 20-35% of post-MPN sAML (known as *TP53-sAML*) [330-332]. Recently, Rodriguez-Meira et al., has disentangled the mechanistic basis for this phenomenon by implicating inflammation in *TP53*-driven clonal evolution [333].

CONCLUSION

Hematologic malignancies, encompassing leukemias, lymphomas, and myelomas, represent a diverse and complex group of cancers that continue to challenge modern oncology. Since the first documented case of Hodgkin lymphoma in 1832, advances in understanding their genetic and molecular basis have prepared for targeted therapies and innovative treatment strategies. However, high rates of relapse, resistance to therapy, and significant treatment-related complications underscore the need for further advancements. This article delves into the classification, pathophysiology, and clinical features of liquid tumors, highlighting current therapeutic approaches and emerging frontiers in treatment. By addressing these challenges, it aims to equip researchers and clinicians with the knowledge needed to improve outcomes for patients with these devastating diseases.

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