Review

Molecular Complexity of MDS and AML with Aberrations of Chromosome 7

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Molecular Complexity of MDS and AML with Aberrations of Chromosome 7

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Abstract: Complete or partial deletions of chromosome 7 (-7/del7q) represent the most frequent chromosomal abnormalities observed in myeloid neoplasms (MNs) and are associated with a poor prognosis. -7/del7q are observed in 10-15% of adult patients with myelodysplasia (MDS) or with acute myeloid leukemia (AML). The occurrence of -7/del7q is particularly frequent in pediatric MDS, often associated with germline mutations of *GATA2* or *SAMD9*/*SAMD9L* genes. The disease biology of -7/del7q and the genes driving leukemic development have not been completely elucidated, haploinsufficiency of tumor suppressor genes located in chromosome 7 deleted regions, seems to play a relevant role. The response to standard treatments based either on chemotherapy or to hypomethylating agents plus Venetoclax is limited. No approved targeted therapies exist for patients with -7/del7q; however, some recent studies have discovered some vulnerabilities of these myeloid neoplasms than can be efficiently targeted.

Keywords: leukemia; acute myeloid leukemia; myelodysplastic syndrome; chromosome abnormalities; chromosome 7; genomic instability

1. Introduction

Genetic alterations are responsible for the development of myeloid neoplasia (MN). Both recurrent gene mutation events and structural chromosomal alterations are observed in MN. The development of sensitive cytogenetic techniques allowed to detect frequent chromosomal aberrations in various types of MN, such as myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). Conventional karyotyping showed cytogenetic abnormalities in about 50% of MDS cases and in 50-60% of adult AML cases [1].

The chromosomal alterations observed in MN involve insertion, deletion, duplication, translocations and inversion events; the deletion events may involve whole chromosomes or chromosomal subregions. Aberrations of chromosome 7 [abn(7)] are recurrently observed in adult AML patients (about 10% of cases) and in adult MDS patients (about 13%) and particularly in pediatric MDS (30-40%) [2,3]. The most common abn(7) include complete loss of chromosome 7 (monosomy 7, -7) and deletions of the long arm of chromosome 7 [del(7q)]. Both these alterations may occur both in MDS and AML in the context of a complex karyotype (CK), defined as a condition in which at least three different chromosomal abnormalities coexist in the same leukemic cells.

Monosomy of chromosome 7 was initially reported in 1964 in the context of a study proposing the existence of a new clinical syndrome consisting in a refractory anemia lacking some chromosomes, including chromosome 7, in bone marrow cells [4]. This syndrome corresponds to what today is defined as myelodysplastic syndrome (MDS) carrying monosomy 7. Subsequent studies have shown that monosomy 7 is frequently observed in pediatric patients with preleukemic conditions, such as MDS and juvenile myelomonocytic leukemia (JMML) [5].

2. Techniques for Detecting Abnormalities of Chromosome 7 in MDS and AML

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Various abnormalities of chromosome 7 have been detected in MDS and AML and their characterization required multiple technique. The human chromosome 7 encompasses nearly 158 million nucleotides of DNA and 1917 gene structures; more than 360 disease-associated genes and loci on chromosome 7 have been discovered [6].

Different types of chromosome 7 abnormalities have been reported in myeloid neoplasms: i) full monosomy 7, corresponding to complete loss of one copy of chromosome 7; ii) deletions of the long-arm of chromosome 7, del(7q), with some minimal commonly deleted regions (CDR), defined as 7q22 (CDR1), 7q34 (CDR2) and 7q35-36 (CDR3); iii) der(1;7)(q10;p10), an imbalanced translocation leading to +1q and -7q; iv) uniparental disomy (UPD) 7q, also called copy-neutral loss of heterozygosity, an event of somatic loss of 7q with with duplication of the homologous 7q. (Figure 1)

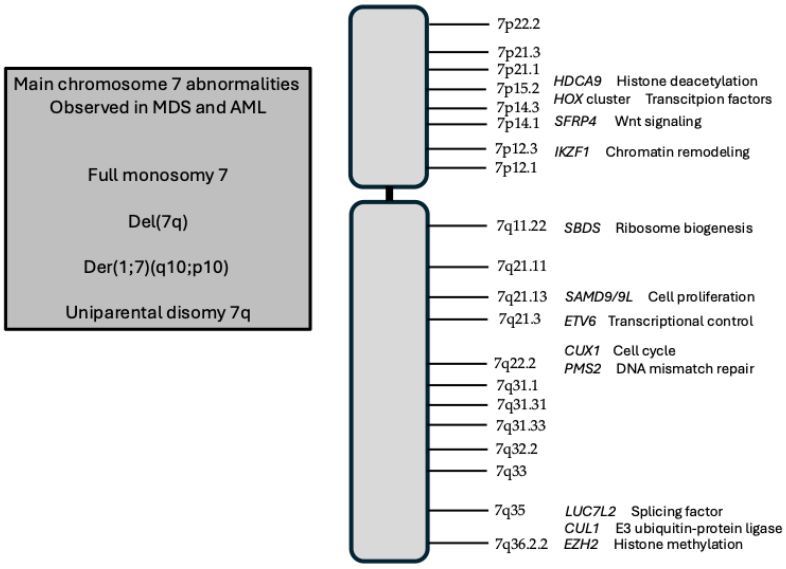

Figure 1. Schematic representation of human chromosome 2, with major chromosome bands and with the localization of genes relevant in pathological alterations of this chromosome. In the box at the left, the main structural abnormalities of chromosome 7 in MDS and AML are shown.

Various cytogenetic and molecular techniques are currently used for characterization of chromosome abnormalities.

Metaphase cytogenetics is based on Giemsa staining of metaphase chromosome alterations (such as trisomies or monosomies), unbalanced chromosomal defects, such as translocations and inversions, deletions and duplications. However, this technique cannot identify UDP and CN loss of heterozygosity (LOH) because the chromosome banding patterns remain unmodified.

Fluorescence in situ *hybridization (FISH)* in another important technique for molecular analysis of chromosomal alterations in MDS and AML and is based on the use of fluorescently labeled DNA probes to detect chromosomal sequences of interest and to detecteven small and hidden chromosomal alterations, such as gene fusions, deletions, or aneuploidies with high sensitivity. The FISH technique is very useful for the detection of hidden cases of monosomy 7 or del(7q).

The single nucleotide polymorphism array (SNP-A) technology is based on on the hybridization of fluorescently labeled fragmented single-stranded DNA to a microarray chip containing hundreds of thousands of unique nucleotide probes. This technique allows a high-resolution scanning of whole genome, detecting both copy number variation (CNV) and UDP.

Microarray-based comparative genome hybridization (Array-CGH) is an important technique allowing the detection and characterization of CNV and UDP together in a single analysis; this technique is based on competitive hybridization of differentially labeled fragmented sample DNA and control DNA to the genome at the microarray platform for the detection of chromosomal aberrations. The fluorescence ratio of sample vs control DNA hybridization signals is detected at the

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level of different positions at the genome and provides information about the relative DNA CN in the assayed genome in comparison with the normal diploid genome. The main advantage of Array-CGH over standard cytogenetic methods is that it can detect CNV simultaneously at the level of multiple genomic loci and can analyze a wide spectrum of genes on microarray in a single experiment.

*Next generation sequencing (NGS)*can provide valuable information for the detection of chromosomal aberrations; NGS can be used to decet CNV and structural variants in myeloid malignant genomes. The NGS technologies display some relevant advantages compared to standard cytogenetic methods, related to a higher capacity of detection of genome-wide chromosomal alterations; higher sensitivity in that alterations even present in 1% of cells can be detected; higher potential to longitudinally monitor alterations during treatment.

This technological armamentarium allows to detect and to characterize chromosome 7 alterations occurring in MDS and AML with a high specificity and sensitivity [7]

In a screening on 1131 myeloid neoplasms, Hosono et al. using metaphase cytogenetics and SNP-array-based karyotype analysis, detected LOH lesions affecting 7q in 14% of low-risk MDS, 34% of high-risk MDS, 8% of primary AML, 18% of secondary AML and 13% of MDS/myeloproliferative neoplasms [8].

Among the various chromosome 7 abnormalities, der(1;7)(q10;p10) displays some peculiarities. In fact, this unbalanced translocation, is much more frequent in Asian than in European patients with myeloid neoplasms (5.8% vs 0.4%, respectively) [9]. Der(1;7)(q10;p10) was more enriched in MDS (72.3% of total cases) than in AML (23.55) and MDS/myeloproliferative neoplasms (3.4%) [9]. In MDS, der(1;7)(q10;p10), as well as -7/del(7q) have a significantly shorter overall survival compared to the MDS without these abnormalities [9]. The co-mutational profile of der(1;7)(q10;p10) is significantly different from that observed in -7/del(7q) cases in that the frequency of *RUNX1, EZH2, ETNK1, ETV6* and *MYB* genes was markedly higher in the former than in the latter, while the opposite is true for *TP53* mutations [9]. Furthermore, del(5q) is absent in der(1;7)(q10;p10), while s frequent in -7/del(7q) cases [9].

The type of chromosome 7 abnormalities observed in various types of myeloid neoplasms was similar. Thus, Haferlach and coworkers reported the characterization of 81 cases with myeloid malignancies and del((7q); array-CGH showed and interstitial del(7q) in 67 cases and terminal in 14 cases [10]. FISH analysis showed unbalanced translocations in 10 of the 14 cases with terminal deletion; partner chromosomes of these translocations were heterogeneous the breakpoints on chromosome 7 were diverse ranging from 7q11 to 7q32 [10]. In the 67 cases with interstitial del(7q), the size of the del(7q) varied between 1.8 and 158.9 Mb [10]. Sizes and localizations of the del(7q) largely overlapped between MDS and AML [10]. 92% of all patients with del(7q) harbored at least 1 molecular mutation; *TET2 and ASXL1* were the most frequently mutated genes and were present at comparable frequencies in MDS and AML; AML with del(7q) is closely associated with *RUNX1* mutations [10].

3. Chromosome 7 Abnormalities in MDS

3.1. Germline genetic factors predisposing to pediatric MDS with monosomy 7 or del(7q)

Genomic sequencing of cohorts of pediatric MDS patients has supported the existence of monogenic disorders known as MDS predisposition syndromes. Particularly, gene sequencing studies have shown that a proportion ranging from 7% to 31% of pediatric MDS harbor germline variants, the two most frequent being *GATA2* deficiency and *SAMD9*/*SAMD9L* syndromes, which together account for about 15% of primary pediatric MDS [11]. Less frequently, germline predispositions are associated with germline variants of *RUNX1* and *ETV6* genes [11].

3.2. Germline GATA-2 Deficiency

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Germline *GATA-2* deficiency is an autosomal dominant disorder predisposing to myeloid malignancy and immunodeficiency [12]. (Figure 2) Germline GATA-2 mutations occur in about 15% of advanced and 7% of all primary pediatrics MDS but are absent in pediatric patients developing MDS secondary to therapy or to acquired aplastic anemia [12]. Monosomy 7 is the most frequent genetic alteration observed in *GATA-2* germline mutant patients: in 449 MDS pediatric patients, monosomy 7 was observed in 22.2% of cases and in 68% of patients with germline *GATA-2* mutations; within the group of pediatric MDS with monosomy 7, 37% displayed *GATA-2* mutations and the median age at diagnosis was significantly higher for *GATA-2* mutant than for *GATA-2*-WT patients (12.5 vs 4.5 years, respectively) [12].

Importantly, in addition to monosomy 7, 7% of germline GATA-2-mutant patients display an unbalanced aberration der(1;7), resulting in loss of the q-arm of chromosome 7 [13]. Der(1;7) was significantly enriched in GATA-2^{mut} compared with GATA-2^{WT} patients (9.2% vs 0.4%, respectively) [13]. 95% of these patients display co-occurrence of additional secondary mutations in leukemia driver genes, thus indicating a malignant phenotype [13]. The presence of additional secondary mutations in leukemia driver genes observed in 95% of these patients supports the need for bone marrow transplantation [13].

Recent studies have explored the role of somatic gene mutations and of monosomy 7 in the progression of germline GATA-2 mutations to malignancy. Thus, Largeaud et al., in the context of a study of the French GATA-2 study group, have reported clinical, biological and molecular features of 78 GATA-2 patients [14]. The comparison of the mutational profile of these patients with respect to AML patients showed: (i) a higher occurrence of monosomy 7 (29% vs 8%, respectively) and of der(1;7) (9% vs 1%, respectively); (ii) a higher frequency of the mutations of *STAG2* (33% vs 4%), *ASXL1* (22% vs 8%) and *EZH2* (8% vs 3%) compared to AML; (iii) a markedly lower frequency of *NPM1* (0% vs 37%), *FLT3* (0% vs 37%), *IDH2* (0% vs 10%), *IDH1* (0% vs 9%) or *SRSF2* (0% vs 6%) mutations [14]. According to their bone marrow morphology features, germline *GATA-2^{mut}* patients were subdivided into three different groups: spectrum 0 with no pathological features; spectrum 1 with hyperplastic and/or low-grade MDS morphological features; spectrum 2 with full MDS morphological features, with multilineage dysplasia [14]. In spectrum 0 patients, no somatic mutations a no monosomy 7 were observed; in spectrum1, there is a median of 1 mutation/patient, with enrichment of *STAG2* mutations and monosomy 7 in 28% of cases; in spectrum 2, there are a median of 3 mutations/patient, with enrichment of *SEPBP1, RAS* pathway, *ASXL1* and *RUNX1* mutations and monosomy 7 in 47% of cases [14]. These observations suggest that *SETBP1, RUNX1* and *RAS* pathway mutations and monosomy 7 and other chromosome alterations drive leukemic transformation of germline *GATA-2^{mut}* patients [14].

Another study reported that mutations in chromatin and cohesin-related genes, such as *STAF2, ASXL1* and *DNMT3A* are frequent in germline *GATA-2* deficiency [15]. Mutations of many genes involved in myeloid malignancies, such as *IDH1, IDH2, NPM1* and *TET2* are absent in germline GATA-2 deficiency [15]. The presence of *ASXL1* and *STAG2* conferred a lower survival probability to these patients [15].

A recent study reported the extensive characterization of 218 patients (90% pediatric and 10% adult) with germline heterozygous GATA-2 deficient variants [16]. It was explored the age-dependent phenotypic and molecular evolution of these patients: a pronounced age-dependent incidence in GATA-2-related MDS was observed, with MDS being absent in infants, rare before the age of 6 years, and markedly increasing in older children [16]. Among the various types of GATA-2 mutations, null mutations are those mostly associated with the risk of developing MDS. Monosomy 7 was the chromosomal abnormality most frequently observed in pediatric patients (about 55% of cases), while it was detected in a markedly lower proportion of adult patients (about 10% of cases). Somatic mutations were observed in 60% of the symptomatic pediatric patients and in 77% of adult patients, with *SETBP1* (26%), *ASXL1* (22%), *STAG2* (15%), *RUNX1* (8.4%) and *EZH2* (8%) being the most recurrent mutations [16]. All recurrent mutations, except for *STAG2*, co-occurred with monosomy 7; monosomy 7 was present in 74% of mutation-positive patients; patients with

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monosomy 7 had the highest mutation frequency (76.5%), compared to 31.6% in karyotype-normal patients [16]. Virtually all patients with *SETBP1* mutations had monosomy 7 clone [16]. All patients with *EZH2* mutations and almost all patients with *ASXL1* mutations harbored monosomy 7 [16].

The mechanisms through which *GATA2* germline mutations promote the development of myeloid neoplasia remain still unclear. GATA2 is a master regulator of hematopoiesis, required for the development and the function of the hematopoietic system. Mice with homozygous *GATA2* deletion die early during embryogenesis, due to the absent formation of the hematopoietic system, while conditional loss of *GATA2* in the bone marrow causes bone marrow failure [17].

As above discussed, individuals born with monoallelic mutations in *GATA2* gene or in *GATA2* gene enhancers regulating GATA2 expression, develop GATA2 deficiency syndrome, with a complex hematologic phenotype, encompassing bone marrow failure, cytopenias, MDS and AML. The mechanisms by which germline *GATA2* mutations promote leukemia development remain largely unresolved. A few observations suggest the complexity of these mechanisms.

The study of some families bearing germline *GATA2* variants showed variable penetrance of mutant *GATA2* alleles as supported by the observation that family members who carry an identical germline mutation yet display variable clinical manifestations; thus, reduced penetrance is a feature among certain *GATA2*-mutant MDS/AML families [18]. The analysis of five MDS/AML families harboring p.Thr354Met *GATA2* mutations, showed significant intrafamilial and interfamilial variations in disease latency and phenotype [19]. These observations suggest that additional cooperating events, in addition to germline *GATA2* mutations, are required for the development of hematological malignancy within the context of a shared germline mutation [19]. An additional element of complexity is given by the existence of epigenetic mechanisms regulating the level of expression of the mutant allele [19]. Similarly, it was impressive the variability in *GATA2* mutant allele penetrance in a family in which the father bearing a *GATA2c.1021_1031del* and remaining asymptomatic in his sixth decade, transmitted the germline *GATA2*-mutant allele to three sibling who displayed over an 18-year period MDS or AML, in all three cases associated with monosomy 7 and in one case also with trisomy 8 [20]. Extra-hematological manifestations were heterogeneous among these three siblings [20].

The need for additional mutational events for the development of MDS and AML is suggested also by the longitudinal analysis of individuals with germline *GATA2* variants [14–16]. More than 400 different *GATA2* germline mutations have been identified, but a clear genotype-phenotype correlation could not be established due to the high patient variability.

Studies in animal models have attempted to reproduce the main features associated with *GATA2* haploinsufficiency in humans. One model was based on the study of *GATA2* heterozygous mice (*GATA2*$^{+/-}$): ageing in these mice was associated with loss and functional defects at the level of HSC compartment; after transplantation of aged *GATA2*$^{+/-}$ bone marrow, B-lymphopenia and monocytopenia are generated; the transplantation of low number of GATA2 haploinsufficient bone marrow in irradiated WT recipients resulted in predisposition to develop BMF, preceding leukemia development [21].

Other studies have shown that germline *GATA2* variants alter the proliferation and differentiation of HSCs/HPCs. A recent study showed that pathogenic *GATA2* variants have both unique and GATA-like attributes and retain the capacity to activate an enhancer-dependent mechanism, which generates a fragmented, abnormal differentiation program [22]. This mechanism determines an elevation of C/EBPε levels which in part counterbalances hematopoietic defects of GATA2-deficient HPCs [22].

The elevated expression of the hematopoietic transcription factor Interferon Regulatory Factor 8 (IRF8) observed in granulocyte-macrophage HPCs from *GATA2*-mutant mice causes macrophage biased differentiation; genetic ablation of IRF8 in these mutant mice reverses the defective hematopoietic phenotype [23].

3.3. SAMD9 and SAMD9L Syndromes

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Sterile alpha motif domain-containing protein 9 (SAMD9) and its paralog SAMD9-like (SADMD9L) are two interferon response genes located on chromosome 7q21, encoding antiviral proteins exerting a negative regulation of cell proliferation. Heterozygous germline gain-of-function *SAMD9-SAMD9L* variants determine the development of multisystem syndromes with variable clinical features. Some features related to hematologic dysfunction unify all these syndromes, including pancytopenia, bone marrow failure, immunodeficiency, infections, monosomy 7 and increased risk of MDS [24]. Affected individuals display a variable clinical course, ranging from mild and transient alterations in the bone marrow to a rapid progression of MDS or AML with monosomy 7.

Schwartz reported the characterization of 46 pediatric primary MDS and showed the presence of germline variants in *SAMD9* and *SAMD9L* in 17% of cases; 42% of these patients bear monosomy 7 [25,26]. It is important to note that these SAMD9/SAMD9L variants were lost in the tumor cells by chromosomal deletions (monosomy 7) or copy number neutral loss of heterozygosity (CN-LOH) [20,21]. Pastor et al. described a familial syndrome in seven patients from unrelated pedigrees presenting with MDS and loss of chromosomes 7/7q; genome studies showed constitutional mutations in the *SAMD9L* gene. The non-random loss of the mutated allele was attained with monosomy 7, deletion 7q, UDP7q, or acquitted truncating variants [27]. Long-term outcomes showed either progression to leukemia and/or accumulation of driver mutations, persistent monosomy 7 and transient monosomy 7 [27].

In a large cohort of 669 pediatric MDS patients, germline *SAMD9*/*SAMD9L* mutations were observed in 8% of cases and were mutually exclusive with germline *GATA-2* mutations observed in 7% of cases [28]. Acquired monosomy 7 was observed in 32% of these patients [28]. In pediatric MDS with monosomy 7, corresponding to 21% of total MDS, 33% of refractory cytopenias of childhood, and 6% of MDS with excess blast subtypes are related ro SAMD9/SAMD9L syndromes [28].

In cohort of French patients with inherited bone marrow failure, Bluteau et al. reported the occurrence of *SAMD9* and *SAMD9L* mutations in 18.9% of cases; these patients often experienced transient aplasia and monosomy7/del(7q); monosomy 7 was observed in 73% of these patients [29].

The spectrum of most recurrent genetic abnormalities of SAMD9/SAMD9L pediatric MDS is predominantly defined by monosomy 7. In these patients, the genetic selection of the chromosome 7 deleted is nonrandom since the allele harboring the germline *SAMD9*/*SAMD9L* variant is lost, while the resulting monosomy 7 retains the WT *SAMD9*/*SAMD9L* allele [30]. Thus, gain-of-function mutations in *SAMD9*/*SAMD9L* predispose to malignancy through a mechanism of adaptation by aneuploidy; through this mechanism, hematopoietic stem cells that eliminate SAMD9 or SAMD9L gain a competitive advantage, but simultaneously predispose to the development of a malignant disease (MDS) [30].

Expression of gain of function *SAMD9*/*SAMD9L* mutations reduces cell cycle progression and favors the outgrowth of clones that have either lost the mutant clone or have acquired revertant mutations [31].

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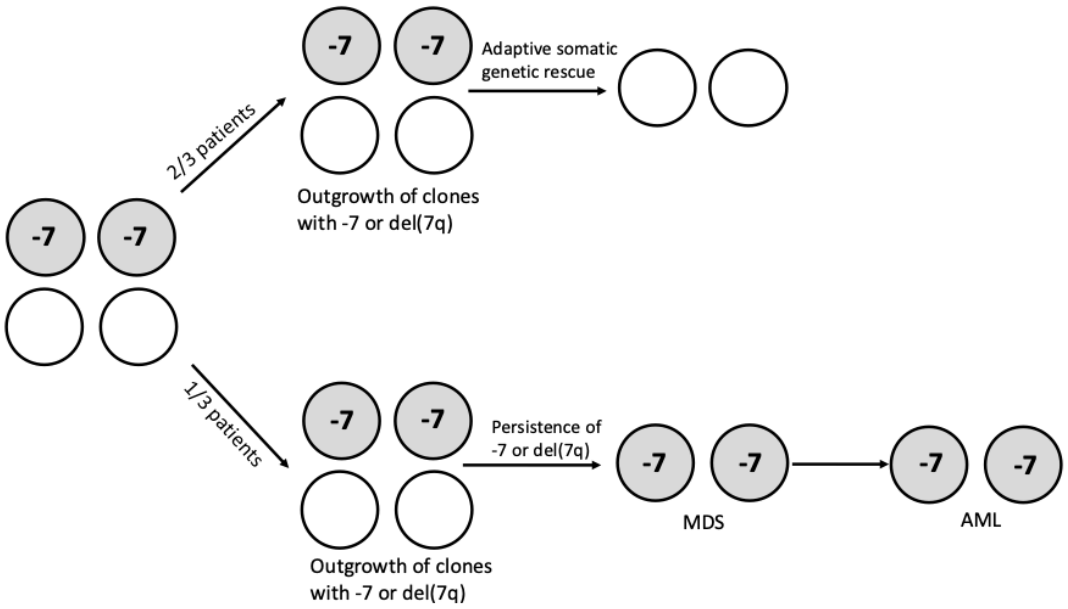

Figure 2. Clinical and clonal evolution of patients with germline SAMD9/SAMD9L gain-of-function mutations. Genetic instability mechanisms and microenvironmental conditions, such as inflammatory stress, favor the generation and outgrowth of clones bearing chromosome 7 abnormalities (-7 and del(7q)). About two-thirds of these patients undergo somatic genetic rescue (SGR), eliminating/inactivating the toxic mutant allele in hematopoietic compartment through acquisition of somatic SAMD9/SAMD9L mutations or UDP7q (duplication of the WT SAMD9/SAMD9L allele); the remaining one-third of patients display persistence of the clone with chromosome 7 abnormalities, with acquisition in the time of somatic mutations, driving together with chromosome 7 abnormalities, the development of MDS and AML.

The compensation of *SAMD9* or *SAMD9L* germline mutation by loss of the chromosome 7 bearing the mutant allele must be considered as a maladaptive compensation in that it eliminates the *SAMD9* or *SAMD9L* allele with gain-of-function mutations, but predisposes to the risk of developing a MDS. (Figure 2) The study by Tesi et al. showed that patients with germline gain-of-function *SAMD9*/*SAMD9L* mutations undergo primary somatic genetic reversion in vivo through different molecular mechanisms either uniparental disomy (UDP) of chromosome 7q, loss-of-function mutations in cis or adaptation by aneuploidy by monosomy 7 or der(1;7) [30].

The study of seven patients with familial MDS associated with germline *SAMD9L* mutations confirmed the existence of clonal escape mechanisms leading to loos of the mutant allele through monosomy 7, deletion 7q, UPD7q, or acquired truncating *SAMD9L* variants [27]. Long-term observations of these patients showed divergent outcomes, represented by persistence of monosomy 7 (most frequent), evolution to a leukemic condition or transient monosomy followed by spontaneous recovery with *SAMD9L-WT* UPD7q [27]. It is of interest to note that, using single-cell DNA sequencing, it was provided evidence that multiple adaptive clones and monosomy 7 arise independently and coexist within individual patients [27].

61% of SAMD9/SAMD9L patients underwent somatic genetic rescue, which resulted in clonal hematopoiesis, of which 95% was maladaptive (monosomy 7) and 51% had adaptive nature (revertant UDP7q, somatic *SAMD9*/*SAMD9L* mutations); single-cell studies showed the existence of multiple competing somatic genetic rescue mechanisms in the same individuals [28]. (Figure 2)

Longitudinal studies on young children with SAMD9/SAMD9L syndrome have shown that monosomy 7 can be transient, often associated with a hematological remission [25]. In fact, the longitudinal study of 7 SAMD9/SAMD9L patients showed that 3 of these patients exhibited

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spontaneous hematologic remissions within a median of 0.6 years (range 0.4-2.9), associated with disappearance of monosomy 7 and expansion of somatic SAMD9/SAMD9L mutations [25].

Somatic leukemia driver gene mutations such as *SETBP1, ASXL1, STAG2, RUNX1, EZH2, ETV6* and *RAS* pathway members were observed in about 30% of germline *SAMD9/SAMD9L* mutant patients, and most of these occurred in patients with monosomy 7 [28].

Germline loss-of-function *SAMD9/SAMD9L* mutations were observed in 3% of adult MDS patients; recurrent somatic alterations observed in these patients were del(5q) and *TET2* mutations, while monosomy 7 or del(7q) were rare [33]. Genetic reversions via monosomy 7 or del(7q) or additional cis mutations are rare in adult MDS patients [33].

Few studies have explored the physiological role of SAMD9 and SAMD9L proteins. Initial studies have shown an antiproliferative effect in non-hematopoietic cells. The effect of WT and mutant *SAMD9/SAMD9L* overexpression in human $CD34^+$ HSCs/HPCs was evaluated, showing an effect on cell proliferation and differentiation with a decrease of erythroid (BFU-E) and multipotential colonies (CFU-GEMM) and with inhibition of cell proliferation, with accumulation of cells in G2/M phase [29]. The effect of mutant *SAMD9* and *SAMD9L* was more pronounced than the effect of the respective WT forms [29]. Interactome analysis showed a role of SAMD9/SAMD9L in ribosome assembly and in protein synthesis [34]. *SAMD9/SAMD9L* overexpression in human $CD34^+$ cells activates also DNA damage responses and apoptosis [34]. According to these observations, it was proposed that SAMD9 and SAMD9L regulate proteins involved in cell cycle, protein synthesis, DNA damage response and apoptosis, these responses being amplified by mutant *SAMD9* and *SAMD9L*. In the eventuality these events remain unchecked by cell response mechanisms, determine at the level of bone marrow cells a condition of hypocellularity. Alternatively, cells lacking the mutant SAMD9/SAMD9L proteins by monosomy 7 or somatic reversion, may acquire secondary cooperating mutations and develop a leukemic process [34].

3.4. Monosomy 7 and del(7q) in Pediatric Myelodysplastic Syndromes

The WHO classification (5th edition) subdivides pediatric mDS into two subgroups: pediatric MDS with low blasts (MDS-LB, <5% blasts in BM and <2% blasts in PB) and pediatric MDS with high blasts (MDS-HB, 5-19% blasts in BM and 2-19% blasts in PB) [35]. The International Consensus Classification (ICC) provides a more complete classification of pediatric MDS, with a Refractory Cytopenia of Childhood (RCC) including persistent cytopenia, BM dysplasia without blast cell increase; (ii) MDS not otherwise specified, including cases without morphological RCC features but with monosomy7; (iii) MDS with excess blasts including patients with 5-19% BM blasts and 2-19% PB blasts [36,37]. Most patients have as predominant presentation RCC/MDS-LB. (Figure 3)

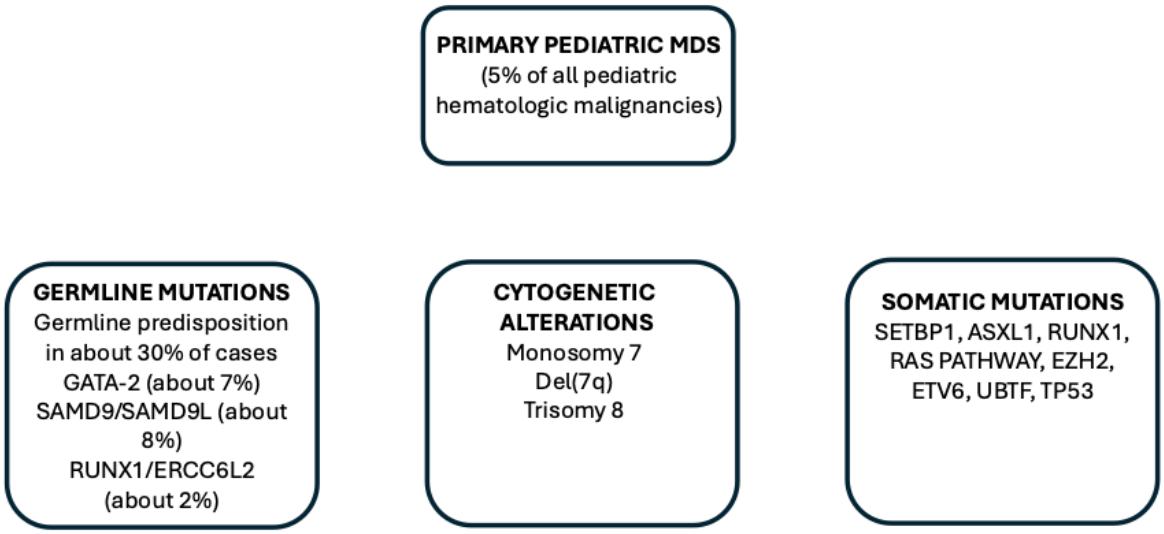

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Figure 3. Main genetic alterations observed in pediatric MDS, including germline mutations predisposing to MDS development, cytogenetic alterations and somatic mutations.

It was estimated that about 20-60% of pediatric MDS at diagnosis exhibit a cytogenetic abnormality. The most frequent chromosome abnormalities are represented by complete loss of chromosome 7 (monosomy 7) or partial [del(7q)] loss of chromosome 7 observed in 6-12% of RCC/MDS-LB and 27-32% of MDS-HB [11].

Somatic mutations are observed in a part of patients with pediatric primary MDS and their frequency is higher in MDS-HB than in RCC/MDS-LB. These studies have shown that the mutational landscape of pediatric-MDS is significantly different from that observed in adult-MDS: (i) *DNMT3A, TET2,* spliceosome genes *SF3B1, U2AF35* and *SRSF2* mutations, frequent in adult-MDS are virtually absent in pediatric MDS; (ii) *SETBP1, ASXL1* and *RAS* pathway genes (*PTPN11, NRAS* and *CBL*) mutations are frequent in pediatric-MDS [19,38].

Monosomy 7 strongly associated with *EZH2* (100%), *SETBP1* (90%), *RUNX1* (79%) and *ASXL1* (74%) mutations in children with MDS [39].

The studies carried out in pediatric MDS strongly support s major role for monosomy 7 as a major driver of malignant evolution of pediatric MDS; in fact, various somatic mutations such as *SETBP1, ASXL1, RUNX1* and RAS pathway mutations, are observed in the context of monosomy 7 background. According to these findings, it can be suggested that monosomy 7 arises as an ancestral clone, which rapidly and progressively acquires driver mutations, resulting in disease progression. In line with this hypothesis, a study by Kardos et al. showed that monosomy 7 is a main contributor to progression of RCC to advanced MDS or AML, as supported by the finding that the median time to progression among 20 children with RCC and monosomy 7 was 1.7 years, with a cumulative incidence of progression higher compared to patients with other chromosomal abnormalities or with normal karyotype [40].

3.5. Monosomy 7 and del(7q) in Adult MDS Patients

Monosomy 7 or del(7q) are observed in about 13% of adult MDS patients; chromosome 7 abnormalities often occur in the context of complex abnormalities, designed as complex karyotypes (CKs) [3].

Chromosome 7 abnormalities in adult MDS are frequently observed in the context of CKs; thus, in CK-MDS, with *TP53* mutations, monosomy 7 was observed in 39% of cases and del(7q) in 14% of cases; in CK-MDS, without *TP53* mutations, monosomy 7 was observed in 29% of cases and del(7q) in 7% of cases [41]. In these patients, the presence of *TP53* mutations and of monosomy 7 was associated with the greatest risk survival [28].

Crisà and coworkers reported the extensive characterization of 280 adult MDS patients with -7/del(7q) as isolated cytogenetic abnormality [42]. Somatic mutations were observed in 82% in -7 and 73% in del(7q) patients; mutation frequency was similar in these two groups of patients [42]. 54% had mutations in genes involved in epigenetic and chromatin modification, 33% in transcription factors, 30% in splicing factors and 20% in cell signaling; *ASXL1, DNMT3A, U2AF1, RUNX1, EZH2, NRAS* and *TET2* were the most frequently mutated genes [42]. Untreated del(7q) patients had better OS compared to -7 patients (34 vs 17 months, respectively) [42].

Bernard et al. in their extensive molecular characterization of 3233 adult MDS patients have reported that monosomy 7 cases were associated with *TP53* mutations, while del(7q) cases were associated with *EZH2* mutations [43]. Patients with cnLOH at 7/7q without CK display a markedly higher frequency of *EZH2, ASXL1, TET2, RUNX1* and *STAG2* co-mutations compared with LOH at at 7/7q; on the contrary, patients with LOH at 7/7q without CK display display a higher frequency of *U2AF1* and *DNMT3A* co-mutations than patients with cnLOH at 7/7q [43].

4. Monosomy 7 and del(7q) in AML Patients

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Genetic alterations are responsible for the development of myeloid neoplasia (MN). Both recurrent gene mutations events and structural chromosomal alterations are observed in MN. The development of sensitive cytogenetic techniques allowed to detect frequent chromosome aberrations in various types of MN, such as myelodysplastic syndromes and AML. Conventional karyotyping showed cytogenetic abnormalities in about 50% of MDS cases and in 50-60% of adult AML cases [44].

The chromosomal alterations observed in MN involve insertion, deletion, duplication, translocation and inversion events; the deletion events may involve whole chromosomes or chromosome subregions. Aberrations of chromosome 7 [abn(7)] are recurrently observed in adult AML patients (about 10% of cases) [45]. The most common abn(7) include complete loss of chromosome 7 (monosomy 7, -7) and deletions of the long arm of chromosome 7 [del(7q)]. Both these alterations may occur both in MDS and AML in the context of a complex karyotype (CK), defined as a condition in which at least three different chromosomal abnormalities coexist in the same leukemic cells.

4.1. Monosomy 7 and del(7q) in Adult AML Patients

Mori reported a large screening of chromosome 7 abnormalities in a large cohort (8142 patients) of patients with myeloid neoplasia; 645 of these patients displayed chromosome 7 abnormalities: 501 with -7 and 144 with del(7q)([32]. -7/Del(7q) abnormalities were observed with different frequencies in the various MNs: 7% in primary AML, 12% in MDS/s-AML, 7% in MDS/MPN, 5% in MPN [46]. In patients with isolated -7 or del(7q) the survival was lower in -7 or del(7q) the survival was lower in -7 and del(7q) than in patients without chromosome 7 abnormalities and in -7 compared to del(7q) patients; in patients with chromosome 7 abnormalities associated with CK, the survival was equally lower in -7 and del(7q) patients than in CK patients without chromosome 7 abnormalities [46].

Initial studies on AMLs bearing chromosome 7 abnormalities were based on limited cohorts of patients and provided initial evidence about a molecular heterogeneity of these leukemias related to the presence of different chromosome abnormalities [-7 or del(7q)] or to the association or not with CKs or to the association with somatic mutations [47–50].

Only recent studies have reported the extensive characterization of large numbers of AML patients bearing chromosome 7 abnormalities. Halik and coworkers reported the detailed characterization of 519 AML patients with aberrations of chromosome 7, in the context of a multinational study [51]. According to the distribution of chromosome 7 abnormalities, various groups of AML patients were identified: (i) two large groups, one composed by 294 patients with chromosome 7 abnormalities, without CKs and the other composed by 225 patients with chromosome 7 abnormalities, with CKs; (ii) the CK group is subdivided into two subgroups, -7/CK (136 patients) and del(7q/CK (70 patients); (iii) the non-CK group is subdivided into two subgroups, -7/non-CK (192 patients) and del(7q)/non-CK (92 patients); (iv) the -7/non-CK group is subdivided into a subgroup without additional alterations (-7sole, 125 patients) and a subgroup with additional alterations (-7/non-CKns, 67 patients); (v) similarly, the del(7q(/non-CK is subdivided into two subgroups according to the absence (del(7q) sole, 69 patients) or presence of additional abnormalities (del(7q)/non-CKns, 23 patients) [51]. The analysis of the mutational profile showed that the most frequently mutated genes were: *TP53* (33%), *DNMT3A* (18%), *RUNX1* (16.7%), *KMT2C* (16.7%) *ASXL1* (16.3&), *NRAS* (14.2%), *TET2* (12.8%), *PTPN11* (11%), *EZH2* (10.3%) and *IDH2* (9.4%); *TP53* was mutated mostly in the CK group, while clonal hematopoiesis-associated mutations were mostly observed in non-CK group [51]. Analysis of variant allele frequency (VAF) and reconstruction of mutation acquisition suggested that *TP53* mutations are disease-initiating events, while -7 and del(7q) are subclonal events in one third of patients [51]. The groups without CKs had a better survival than those with CKs; the group with the poorest survival was the -7/CK group [51], Mutations in *TP53* and *PTPN11* showed the strongest association with worse overall survival; in contrast, patients with mutated *IDH2* exhibited prolonged OS and durable responses [51].

Mrozek and coworkers reported an extensive analysis of 160 CK-AML patients and proposed a classification of these AMLs into two groups: typical CK (corresponding to 70.5% of total) and

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atypical CK (corresponding to 29.5% of total) [52]. Typical CKs were characterized by the presence of abnormalities resulting in loss 5q, 7q and/or 17p; 65.5% of CK-AMLs displayed chromosome 7q loss [38]. Patients with atypical CKs differed from those with typical CKs for the lower frequency of *TP53* mutations and increased frequency of *PHF6, FLT3-TKD, MED12* and *NPM1* mutations; furthermore, atypical CKs involve younger patients, have higher bone marrow and peripheral blood blast counts and exhibit higher complete remission rates and longer OS [52]. Importantly, typical CKs with abnormalities of 7q, but not of 5q and 17p, differ from typical CKs with other combinations of 5q, 7q and 17p abnormalities in that they have more frequently *FLT3-ITD, BCOR, WT1, DNMT3A, NPM1* and *RUNX1* mutations and less frequently *TP53* mutations; furthermore, the OS of patients with only 7q abnormalities was longer than OS of the remaining patients with typical CK-AML [52]. *TP53* mutations are particularly frequent in AMLs bearing 5q, 7q and 17p abnormalities, or 5q, 17p without 7q abnormalities or 5q and 7q without 17p abnormalities or 7q and 17p without 5q abnormalities [52].

Kugler et al. reported the mutation dynamics of a group of 115 AML patients with chromosomal 7 deletions who achieved remission after induction treatments [38]. This group of patients was heterozygous with some showing -7/del(7q) as an isolated event or in association with other monosomies [53]. Importantly, in some of these patients, the -7/del(7q) alone may represent a founder clone or a late subclonal event. A significant proportion of these patients have *TP53* mutations, mostly associated with CKs, and display a shorter OS compared to those without *TP53* mutations (8.6 vs 13.04 months) [53]. Patients with *TP53* mutations, with co-mutations such as *NF1, GATA2* or *RUNX1* have a shorter OS than those with *TP53* mutations without these co-mutations [53].

Many studies suggest the existence of a link between abn(7) and *TP53* mutations. Most patients with *TP53* mutations have *de novo* AML, associated with chromosomal aneuploidies, including monosomy 7, monosomy 5/del(5q) or complex karyotype/monosomal karyotype. Rucher et al. in a group of 234 CK AML observed *TP53* alterations (mutations or deletions) in 70% of cases; among the patients with *TP53* alterations, 59% displayed -7/del(7q) and among those *TP53-WT*, 37% showed -7/del(7q) [54].

Abbas et al. reported the retrospective analysis of 243 treatment-naïve AML patients with chromosome 7 or 7q deletions; 69% of these patients had -7 and 31% del(7q) [55]. The composite CR+CRi in the whole population of leukemic patients was 49% and similar in the two groups of patients; RFS was significantly longer among AML patients with del(7q) compared to those with del(7) (6.0 months vs 2.7 months), but OS was similar (7.4 months vs 8.4 months) [55]. The frequency of *TP53* mutations was similar among del(7) and del(7q) (55% vs 54%, respectively); patients harboring *TP53* alterations had significantly shorter OS compared to those without *TP53* alterations (5.5 months vs 10.5 months) [55]. The presence of co-occurring del5/5q conferred worse outcomes in del(7) and del(7q) [55]. The profile of various somatic mutations was similar in del(7) and del(7q) AMLs [55].

Fleming et al. reported the study of 256 patients with *TP53*-mutant AML; among *de novo* AMLs, monosomy AML was observed in 36% and in secondary AMLs in 49.9% of cases [56]. The presence of *TP53* mutations concomitantly with monosomy 7 was associated with a significantly shortened OS compared to monosomy alone [56].

Single-cell transcriptomic studies have shown in -7 HSC/HPCs a downregulation of genes involved in maintenance of DNA, repair, cell cycle, apoptosis, immune response and hematopoietic differentiation [57]. According to these findings it was hypothesized that downregulation of genes required for maintenance of DNA stability and apoptosis may result in genomic instability, thus favoring the acquisition of a series of genetic alterations and ultimately inducing the development of a leukemic process [57].

Kaur et al. have reported the results of a real-world study on a cohort of patients with *TP53*-mutated myeloid neoplasms (mostly AML, 82.4% of cases) mostly treated using HMA+VEN (74% of cases) [58]. Some pre-therapy factors predicted an inferior response, including the presence of ≥2 autosomal monosomies, multihit *TP53* allelic state and *CUX1* co-alterations (either deletions or mutations) [58].

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Monosomal karyotype (MK) is defined as the presence of one autosomal and at least one structural aberration or two or more autosomal monosomies in the absence of recurrent AML genetic abnormalities including *t(8;21), inv(16), t(15;17)* [59]. Kayser et al. explored 1058 adult AML patients and observed that 11.9% of these patients display a MK; among MK^+ patients, 6% display -7 and 7% del(7q) [46]. Among AML patients with chromosome 7 abnormalities, MK^+ patients with -7 and del(7q) display a MK with a frequency of 52.8% and 18.4%, respectively, while MK^- patients with -7 and del(7q) exhibit a MK with a frequency of 14.4% and 18.4%, respectively [59]. MK may be observed alone or in association with CK: MK alone (7.5% of total AMLs, 74% with -7 and 9%with del(7q)), CK alone (9.2% of total AMLs, 1% with -7 and 14% with del(7q)) and MK/CK (24% of total AMLs, 35% with -7 and 19% with del(7q)) [60].

A recent study reported the analysis of 156 adult AML patients with MK; in these patients the most common monosomies were -17 (41%) and -7 (37%), with 88% having; the most frequent mutations were *TP53* (69%), *DNMT3A* (19%), *TET2* (13%) and *IDH1* (7%) [61]. The OS of these patients was affected by the presence of *TP53* mutations (reduced in patients with *TP53* mutations compared to those without *TP53* mutations), but was not affected by the presence or absence of CK [46]. Among the various monosomies, only monosomy 17 affected outcomes [61].

MK is associated with a dismal prognosis in AML patients. In a South Korean Registry, MK was observed in 5.7% of adult AM patients [62]. In these patients, the presence of single monosomy and absence of abn(17p) was associated with a better prognosis following aloo-HSCT [62].

4.2. Monosomy 7 and del(7q) in Pediatric AML Patients

Chromosome 7 abnormalities are observed in a minority of pediatric AML patients, with 2-3% of monosomy 7 and of del(7q). A retrospective analysis on 258 children with AML or refractory anemia with excess of blasts in transformation (RAEB-T) allowed a characterization of these patients [63]. A part of these patients exhibited -7 or del(7q) as isolated abnormalities or in association with other cytogenetic abnormalities. Overall survival was superior for patients with del(7q) compared to those with monosomy 7 [63]. Cytogenetic aberrations associated with favorable prognosis, such as *t(8;21), inv(16), t(15;17), t(9;11)* were strongly associated with del(7q) and displayed a higher 5-year survival rate compared with del(7q) without favorable cytogenetics [63]. On the contrary, patients with -7 in association with *inv(3), 5del/del(5q)* or *+21* had a markedly reduced survival rate [63].

Ries et al. have reported a genomic and transcriptomic analysis of 45 pediatric AML patients with monosomy 7: 22 of these patients had additional karyotypic alterations, such as CNAs or translocations [64]. The patients were subdivided into two groups according to MECOM expression: MECOM high with a poor prognosis and MECOM low, with a better prognosis [64]. In a part of these patients, MECOM high expression was associated with 3q26 variants [64].

Westover et al. have explored a group of 108 pediatric and young patients with myeloid neoplasms, including 48% of AML patients, showing in these patients, frequent mutations involving Ras/MAPK pathway [65]. Clonal analysis showed that chromosome 7 alterations are early-initiating events in these pediatric patients; it was hypothesized that chromosome 7 deletions could cooperate with secondary mutations and inflammatory stress in the development of a leukemic process [65].

Poor-risk cytogenetic abnormalities at diagnosis predict survival after allo-HSCT in pediatric AML patients; an analysis carried out in 845 patients with these features (36% with 11q23 abnormality, 24% with monosomy7/del(7q) or monosomy5/del(5q), 24% with a MK or CK and 16% with other poor-risk cytogenetic abnormalities) showed that patients with monosomy 5/del(5q) and monosomy7/del(7q) had a higher risk of disease relapse compared to 11q23 and other poor-risk cytogenetic abnormalities [66].

4.3. Chromosome 7 Abnormalities in Therapy-Related Myeloid Neoplasms

Therapy-related myeloid neoplasms (t-MNs) include a group of myeloid neoplasms comprising AML, MDS and MDS/myeloproliferative neoplasms (MDS/MPN). Occurring as a late complication of cytotoxic therapy-chemotherapy, and/or radiation therapy used for the treatment of malignant

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disorders or immunosuppressive therapy for autoimmune diseases [53–55]. It was estimated that the risk of developing a MN is about 4.7-fold higher among cancer survivors compared to the general population of an equivalent age [67]. The risk of developing a t-MN is influenced both by the type of primary cancer, by the type of primary cancer, by the type and dose of cytotoxic factors and by individual, patients specific-factors, genetic factors, comorbidities and age of the patient. Currently, it is estimated that t-MNs correspond to 5-15% of newly diagnosed MDS, AML and MDS/MPN [67].

T_MNs are characterized by the presence of genetic alterations similar to those observed in the primary tumors, with an accentuation of the frequency of high-risk genetic alterations. Particularly, chromosomal alterations are observed in >90% of t-MNs; the most frequent karyotype alterations observed in tMNs are represented by a decreased prevalence of normal karyotype and by the predominance of complex and unbalanced karyotypes with frequent chromosomal deletions, compared to *de novo* MDS and AML [68]. Complete or partial deletions of chromosome 5 and 7 and CKs have been observed in the large majority of t-MNs occurring after CT with alkylating agents or with radiotherapy [67–69]. Smith et al. reported the analysis of 306 patients with t-MDS or t-AML: 40% of these patients had undergone CT alone (alkylating agents, 78% and topoisomerase 2 inhibitors, 39%), 14% RT alone and 45% both CT and RT [70]. At diagnosis, 92% of these patients had karyotypic clonal abnormalities involving chromosome 5 (20.5%), chromosome 7 (27.7%), both chromosome 5 and 7 (21.5%), balanced rearrangements (10%) and other clonal abnormalities (12.7%) or normal karyotype (7.8%). Importantly, abnormalities of chromosome 5,7, or both accounted for 76% of all cases with an abnormal karyotype [70].

A recent analysis on most of the available studies on the characterization of t-MN in comparison with p-MN showed a marked increase of del7/7q (26% vs 8%, respectively), del5/5q (24% vs 5%, respectively), of MK (26% vs 12%, respectively) and of CK (36% vs 10%, respectively) [67].

TP53 mutations are more frequent in t-MN than in p-MN (30.9% vs 7.9%, respectively), t-MDS vs p-MDS (35.1% vs 11.3%, respectively) and t-AML vs p-AML (26.2% vs 11.3%) [67].

Chromosome 7 abnormalities, as well as chromosome 5 abnormalities are enriched in *TP53*-mutated t-MDS and t-AML, in association with CK [57,58]. The association between del(7q), CK and *TP53* mutations was particularly evident for t-MN with *TP53*-mutated with a viant allele frequency of ≥10% [71]. Chromosome 7 abnormalities were significantly more frequent in *TP53*-mutated t-MN compared to *TP53*-WT t-MN [71,72].

5. Pathogenesis of Myeloid Neoplasia with Chromosome 7 Abnormalities

Chromosome 7 alterations in hematologic malignancies are almost always deletion events or copy neutral losses of heterozygosity (LOH), in contrast to solid tumors where amplifications are frequently observed [73]. Loss of all or of a part of chromosome 7 del(7) or del(7q) is one of the most common chromosomal abnormalities observed in myeloid neoplasms [74]. The high frequency of chromosome 7 loss observed in high-risk myeloid neoplasia supports the hypothesis that chromosome 7 harbors tumor suppressor genes (TSGs), whose loss could contribute to the development of MN. This tumor suppressor seems to act in part in a haploinsufficiency manner since the other allele present on the other intact chromo some 7 is seemingly functional. The study of the regions deleted at the level of 7q has led to identify the *CUX1* as a potential TSG. *CUX1* is a gene encoding a homeodomain-containing transcription factor. *CUX1* is the most significantly differentially expressed gene within the commonly deleted region of 7q and is expressed at haploinsufficiency level in -7/del(7q) MNs [75]. Importantly, haploinsufficiency of *CUX1* confers to human HSCs a significant engraftment advantage on transplantation into immunodeficient mice [75].

Several experimental studies support a functional role of *CUX1* haploinsufficiency in MN development. Thus, Aly et al. showed that the introduction of *CUX1* mutations or the experimental decrease of *CUX1* expression in bone marrow cells induces a defective base repair, thus favoring the accumulation of genetic alterations [76]. Furthermore, these authors showed also that *CUX1* is mutated in 2.4% of MNs [76].

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CUX1 knockdown in human CD34+ HSCs/HPCs induced a gene signature similar to that observed in leukemic cells of patients with -7/del (7q) [77]. *CUX1*$^{-/+}$ mice develop mild anemia and bone marrow dysplasia; furthermore, *CUX1* haploinsufficiency induces apoptosis evasion and favors leukemia development [78].

KMT2C, KMT2E and *EZH2* genes are collectively lost together with *CUX1* in 70% of patients with del(7q). *EZH2* deficiency synergizes with *CUX1* deficiency in promoting hematopoietic expansion after exposure to alkylating agents [65]. Multiple 7q gene knockout experiments in HSCs provided evidence that combined *CUX1* and *EZH2* deficiency promotes cell expansion after chemotherapy exposure and thus drive chemoresistance [79]. Furthermore, combined *CUX1* and *EZH2* deficiency induces the abrogation of DNA damage response after genotoxic stress [79].

CUX1 mutations are frequently associated with RAS pathway mutations; the association of activating *NRAS* mutation with *CUX1* deficiency causes AML generation in mice, not seen with either mutation alone [80].

The generation of mice with heterozygous deletions of different chromosome bands systemic to commonly deleted segments of human 7q22 d determines different phenotypes and cooperation when associated expression of genes commonly mutated in -7/del(7q) leukemias [81,82].

As above mentioned, *CUX1* mutations are observed in 4% of AML patients; interestingly, the most frequent cytogenetic abnormality observed in *CUX1*^{mut} AMLs is monosomy 7 (20% of cases) [83]. The study of clonal hierarchies in MDS and AML suggests that chromosome 7 abnormalities are early events. This conclusion is supported also by the studies of clonal hematopoiesis, defined as a clonal hematopoiesis (CH), defined as a clonal hematopoietic population carrying somatic mutations in one of the leukemia-associated genes. In CH, healthy individuals harbor alterations of genes involved in myeloid malignancy (such as *DNMT3A, ASXL1* or *TET2*), at low frequency; these individuals have an increased risk of developing a hematologic malignancy. The study of large cohorts of normal individuals showed the existence in CH not only of somatic mutational variants, but also of copy number alterations [84,85]. These studies identified among these copy number alterations, also chromosome 7 deletions and LOH [84,85]. Importantly, one of these studies showed that individuals with del(7q) and 7qLOH display a significantly increased risk of developing a hematologic malignancy, particularly pronounced for the development of myeloid malignancies [85]. It is important to note that, according to this study, the risk of developing a hematologic malignancy is equally pronounced for CH bearing chromosome 7 abnormalities and 17p deletions (the chromosome arm encoding *TP53*) [86]. In addition to CNAs involving chromosome 7, also *CUX1* gene mutations have been identified in some individuals with CH [86–88].

In addition to *CUX1* and *EZH2, MLL3, SAMD9*/*SAMD9L* and *LUC7L2* represent additional TSGs present in chromosome 7 regions commonly deleted in del(7q). AS such, myeloid cancers driven by loss of chromosome 7 seen to be consistent with contiguous gene syndrome in which combined loss of multiple neighboring TSGs drives to malignant transformation [89].

Chromosome 7 abnormalities often occur in the context of CK, a condition characterized by complex chromosomal rearrangements, intratumor heterogeneity, therapy resistance and poor overall survival. The characterization of molecular abnormalities occurring in CK AML is complex and requires adequate molecular techniques. In fact, copy-number analyses failed to capture the full karyotypic heterogeneity occurring in CK-AML because copy-balanced and complex rearrangement structures remain unresolved in these malignancies [84]. To obviate to this limitation, Leppa and coworkers have developed a single-cell multiomics analysis, based on structural variant discovery, nucleosome occupancy, transcriptomic and immunophenotypic changes in single cells [76]. Individual leukemic cells of patients with CK-AML were characterized by linear and circular breakage-fusion-bridge cycles and chromotripsis. Three different patterns of clonal evolution were observed in these patients: monoclonal, linear and branched polyclonal, with 75% of cases displaying multiple clones, often exhibiting karyotype remodeling [90]. Patient-derived xenograft models provided evidence about a consistent heterogeneity of clonal evolution of leukemic stem cells, showing subclone-specific drug responses [90]. Finally, longitudinal studies in some patients further

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supported the heterogeneity of genetic evolution and showed the existence of a consistent cell-type plasticity as mechanisms of disease progression [90]. In conclusion, this study provided strong evidence about the dynamic genomic, phenotypic and functional heterogeneity of CK-AML.

Chromoangiogenesis (CAG) events, represented by a spectrum of catastrophic events such as chromotripsis, chromoanasynthesis and chromoplexy are very frequent in CK-AML (92% of cases) [91]. Among patients with MK, those with CAG have a strongly higher frequency of chromosome 7 abnormalities compared to those without CAG (88% vs 12%, respectively) [91]. Patients with CAG have a clearly shorter mOS compared to those without CAG [91].

As above discussed, a significant proportion (43%) of AML patients with -7/del(7q) exhibit a CK; the group with CK was strongly associated with *TP53* mutations, while those without CK were rarely *TP53*-mutated [51]. These observations suggest two main pathogenetic pathways in which are involved AMLs with chromosome 7 alterations: one related to AMLs with CK and *TP53* mutations with chromosome 7 alterations as subclonal events and associated with high genomic instability; another related to AMLs without CK, where predominantly clonal chromosome 7 alterations cooperate with co-mutational events at the level of some genes to drive leukemic development. Chromosome alterations, such as chromosome 5 and 7 alterations significantly contribute to the malignant development of *TP53*-mutant AMLs, as supported by the observation that *TP53*-mutant AMLs with low *TP53* VAF (variant allele frequency) without chromosome 5/7 alterations have a clearly better OS than those with low *TP53* VAF associated with chromosome 5/7 abnormalities [92].

In addition to CNAs, structural variants can generate fusion proteins or remove or create new enhancer-promoter interactions. Examples of these events are given by 5% of AML cases harboring *inv(3)(q21q26.2)* or a *t(3;3)(q21q26.2),* which reposition the *GATA2* enhancer in close vicinity of MECOM, leading to aberrant MECOM expression and haploinsufficiency of *GATA2* [93]. Other examples of genes activated by enhancer hijacking in AML are given by *BCL11B* in AML with a mixed phenotype and *MNX1* in pediatric AML with *t(7;12)(q36;p13).* The development of Pyjacker, a computational tool, showed the existence of enhancer hijacking events in AML patient samples with CK, including aberrant expression of *MNX1*, which can result from del*(7q)(q22p36)* and is associated with hijacking of a *CDK6* enhancer [93]. MNX1 activation occurs in 1.4% of patients with AML (8.7% of AMLs with *del(7q))* and co-occurred with *BCOR* mutations [93]. Xenograft mouse models showed that MNX1 activation is required for leukemia cell fitness. Thus, the discovery of MNX1 overexpression showed that deletions on chromosome 7q can not only lead to haploinsufficiency but also the activation of oncogenes by enhancer hijacking.

6. Therapy of Myeloid Neoplasms with Chromosome 7 Abnormalities

Deletions in chromosome 7 are associated with poor outcomes and allogeneic hematopoietic stem cell transplantation (HSCT) is recommended for patients who achieve post-induction complete remission. Two induction therapies were available for these patients; one based on intensive chemotherapy (IC) and the other on hypomethylating agent (HMA) plus venetoclax (VEN). It is unclear in these patients whether IC is superior to HMA+VEN. A recent retrospective study reported the results of the analysis of 228 AML patients treated with induction therapy based on IC (38% of patients) or HMA+VEN (62% of patients) [94]. Patients treated with HMA+VEN were older than those treated with IC (/72 years vs 61 years) [94]. TP53 mutations and cK were more frequent among patients treated with HMA+VEN than among patients treated with IC (for *TP53* mutations 70% vs 37% and for CK 84% vs 63%, respectively) [94]. In the entire cohort of patients, including also 897 AML patients without chromosome 5 or 7 abnormalities, median OS was shorter in patients with deletions in chromosomes 5 or 7 than in those without these alterations (7.4 months vs 27 months) [94]. Overall survival for patients with chromosome 5 or 7 deletions was improved by allo-HSCT (24 months for those undergoing allo-HSCT compared to 5.5 months without allo-HSCT) [94]. There was no difference in induction with IC vs HMA+VEN in patients with age comprised between 60-75 years and in patients who received allo-HSCT after induction therapy [94]. Patients with chromosome abnormalities treated with IC had longer OS compared to those treated with HMA+VEN (10 months

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vs 6.1 months, respectively). As HMA+VEN-treated patients were older, OS comparison was made on patients with age comprised between 60 and 65 years. There was no difference in mOS following induction with IC vs HMA+VEN in patients with concomitant *TP53* mutations [94].

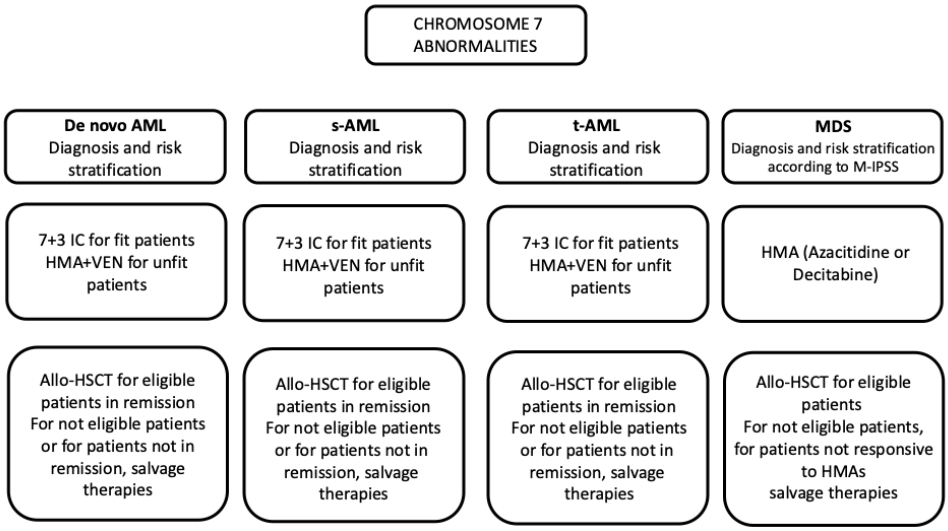

Figure 4. Outline of treatment of MDS and AML patients with chromosome 7 abnormalities.

Retrospective studies on AML patients undergoing allo-HSCT in first CR showed that monosomal kayotypes negatively affect outcomes of transplantation: the adverse prognostic impact of MK tended to be more prominent in the younger age group (<40 years) than in the older age (>40 years) [95]. A recent study reported the results of a large retrospective analysis on a group of 1735 adult AML patients with adverse ELN2022 cytogenetics allografted in first remission, showing that monosomy 7 or monosomy 7 or del(5q) in the presence of CK or monosomy 17 or 17p abnormalities are associated with poor leukemia-free survival and overall survival; patients with monosomy 7 or monosomy 5 or del(5q) without CK or monosomy 17 or 17p abnormalities had significantly better survival compared to those with CK and/or 17 abnormalities [96].

A second recent study confirmed these findings in a group of 240 patients with *TP53*-mutated MDS or AML with a median age of 72 years who underwent allo-HSCT. Variant allele frequency (VAF) of *TP53* mutations and cytogenetics (5q deletions/7q deletions) were identified as the two most important prognostic factors [92]. Patients with *TP53* mutant >50% had a 2-year PFS of 3%; patients with *TP53*-mutant VAF<50% and chromosome 5/7 abnormalities had a 2-year PFS of 22% and patients with *TP53*-mutant VAF <50% without chromosome 5/7 deletions had a 2-year PFS of 60% [92].

No specific targeted therapies for chromosome 7 abnormalities have been developed. Monosomy 7 and del(7q) determine the haploinsufficiency of many genes, some of which contribute to the development of myeloid malignancies, such as *SAMD9, SAMD9L, KMT2C, EZH2* and *CUX1*. A recent study showed that the haploinsufficiency of *NAMPT* (nicotinamide phosphoribosyltransferase) determines a vulnerability that can be exploited at therapeutic level [97]. Thus, in vitro studies using primary AML cells showed that -7/del(7q) leukemic blasts are particularly sensitive to the cytotoxic effects of Daprinad and of other NAMPT inhibitors [82]. Biochemical studies confirmed that AML blasts with -7/del(7q) have low NAMPT levels. The combination of Daprinad with Venetoclax (a BCL-2 inhibitor) efficiently eradicated AML blasts with -7/del(7q) [97].

Another recent study confirmed these findings, showing that -7/del(7q) AML cells are sensitive to the cytotoxicity induced by the NAMPT inhibitor KPT-9274; interestingly, both -7/del(7q)(cells without or with *TP53* abnormalities are equally sensitive to KPT-9274 [83]. Interestingly, KPT-9274 synergistically interacts with PARP inhibitors to target NAMPT-deficient AML cells [98].

AML and MDS patients with *inv(397t(3;3)* have an aggressive myeloid neoplasia, associated with short survival. 70% of these patients harbor additional monosomy 7. 3q-rearranged myeloid cancers

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drive leukemic transformation through expression of EVI that acts as an oncoprotein with multiple activities. A recent study showed the existence of specific vulnerabilities that could be targeted in these leukemias. Thus, high throughput drug screens and functional assays have shown that EZH2 inhibitors induce apoptosis preferentially in MDS/AML cells with *inv(3)/t(3;3)* and monosomy 7 through the activation of GADD45γ-p38-p53 axis [84]. EVI 1 activated in 3q-rearranged MDS/AML was responsible for GADD45γ silencing by direct binding to its consensus sequence present at the level of the GADD45γ promoter and recruitment of PCR2 complex through interaction with EXH2, which can be therapeutically targeted by EZH2 inhibition [99]. Thus, MDS/AML cells with *inv(3)/t(3;3)* and -7 display preferential sensitivity to EZH2 inhibition.

A comprehensive analysis of bone marrow including evaluation of cytomorphology, cytogenetic analysis with chromosome banding, and gene sequencing is essential to establishing the diagnosis and classification of patients with MDS. The Revised International Prognostic Scoring System (IPSS-R) distinguish MDS into two groups: low-risk MDS (including those classified as lo, very-low and intermediate-risk) and high-risk (including those classified as high and very high-risk) [100]. According to the MDS Cytogenetic Scoring System contained in IPSS-R, del(7q) pertains to the intermediate-risk group, -7 and double chromosomal abnormalities including -7/del(7q) as poor-risk and -7/del(7q) in the context of CK as very poor-risk [100]. The Molecular International Prognostic Scoring System (IPSS-M) risk stratification system introduced additional criteria based on molecular genetics and allowed a more accurate risk stratification [101]. The International Working Group for Prognosis in MDS had defined disease subtypes according to genetic lesions; this analysis enabled the formulation of a molecular taxonomy comprising 18 distinct groups [43]. Monosomy 7 pertains to a group characterized by aggressive disease with poor survival and high risk of leukemic transformation [43]. MDS patients with monosomy 7 are considered as potential transplant candidates [102]. In these patients, allo-HSCT should be considered at the time of diagnosis in all eligible patients [102].

Outcome of MDS patients is mainly related to the biology and molecular genetic of the disease and by its general status prior to allo-HSCT, which remains the only curative option in suitable patients. Early in the management of a a MDS patients it is fundamental to provide a general prognostication in terms of HSCT planning [103]. It was estimated that only 15% of all MDS patients are generally eligible for allo-HSCT [103]. HSCT in MDS patients is potentially associated with a high rate of complications and a significant risk of associated mortality [103].

No randomized clinical trial directly compared allo-HSCT and conventional therapy in MDS. However, a number of studies have indirectly compared these two therapeutic approaches and have shown the significant improvement in long-term outcomes with HSCT, thus supporting the superiority of allo-HSCT over non-HSCT therapy [104]. Few studies have specifically analyzed the outcome of MDS with chromosome 7 abnormalities after allo-HSCT. Thus, van Gelder et al. have analyzed 277 adult MDS patients with a chromosomal 7 abnormality undergoing allo-HSCT, present in the European Group for Blood and Marrow Transplantation (EGBMT) database [105]. These patients were classified according to the presence of monosomy 7 (-7) or of other chromosome 7 abnormalities (no-7); particularly, among -7 MDS, 77% had a MK but not CK, while no-7 MDS do not display these features; furthermore, among -7 MDS 24% had MK and CK, while only 7% of no-7 MDS exhibited these features [105]. In the whole MDS population, 5-year PFS and OS were 22% and 28%, respectively; in multivariate analysis, the presence of CK or MK were predictors of worse outcome [105].

In a study by Versluis et al. 309 adult MDS patients characterized at genomic level by targeted sequencing and undergoing allo-HSCT, observed that 22$% of these patients were classified as very high-risk (VHR) patients according to IPSS-M; 57% of these VHR MDS displayed *TP53* mutation and 43% were without *TP53* mutations [106]. 27% of VHR patients displayed chromosome 7 abnormalities: 38% in the *TP53*-mutated group and 13% in the no-*TP53*-mutated group [106]. In the *TP53*-mutated group, 94% of chromosome 7 alterations occurred in the context of CK; in the *TP53*-WT group, most of MDS with chromosome 7 alterations co-occurred with *ASXL1* mutations [106].

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Importantly, allo-HSCT improved OS compared with no transplantation in both subgroups of VHR patients, *TP53*-mutated and *TP53*-WT; VHR *TP53*-WT patients allo-transplanted displayed a better OS compared to VHR *TP53*-mutated patients [106].

The majority of MDS patients with chromosome 7 abnormalities are considered as high-risk patients and hypomethylating agents currently are the only approved non-transplant therapy for these patients and the standard of care for patients not eligible for allo-HSCT [107].

7. Conclusions

Myeloid neoplasms bearing chromosomal abnormalities of chromosome 7, complete or partial deletions, sre characterized by a high genomic instability and are associated with poor outcomes. Chromosome 7 abnormalities are frequent in MDS and AML and only recently these tumors have been extensively characterized at molecular level, showing their heterogeneity and their association with other cytogenetic abnormalities and with some somatic mutations.

Chromosome 7 abnormalities are particularly frequent in pediatric MDS associated with germline mutations of *GATA-2* and *SAMD9*/*SAMD9L* genes; these germline variants represent genes predisposing to MDS development and contribute to define a peculiar and separate group of myeloid neoplasms.

The pathogenic mechanisms underlying the development of myeloid neoplasms with chromosome 7 abnormalities have been only in part elucidated, but it appears now evident that chromosome 7 deletions usually repsresent an early key event whose leukemogenic potential is mediated through the deletion of tumor suppressor genes and cooperate with other cytogenetic abnormalities and with some gene mutations.

Alterations of chromosome 7 in MDS and AML patients are frequently associated with other chromosomal abnormalities in the context of MK or CK and with *TP53* mutations. MNs with deletions of whole chromosome 7 or del(7q) present great challenges due to inherent chemoresistance and poor outcomes and only a part of these patients benefit induction therapies and allo-HSCT (basically those without other concomitant chromosomal abnormalities and *TP53* mutations).

To date no targeted specific treatment for chromosome 7-deleted MDS and AML was approved. However, recent studies have led to the identification of some vulnerabilities that could be specifically targeted by a pharmacologic approach.

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