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Review Article

Therapy-Related Myeloid Neoplasms: Predisposition and Clonal Evolution

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Abstract. Therapy-related Myeloid Neoplasm (t-MN) represents one of the worst long-term consequences of cytotoxic therapy for primary tumors and autoimmune disease. Poor survival and refractoriness to current treatment strategies characterize affected patients from a clinical point of view. In our aging societies, where newer therapies and ameliorated cancer management protocols are improving the life expectancy of cancer patients, therapy-related Myeloid Neoplasms are an emerging problem. Although several research groups have contributed to characterizing the main risk factors in t-MN development, the multiplicity of primary tumors, in association with the different therapeutic strategies available and the new drugs in development, make interpreting the current data still complex. The main risk factors involved in t-MN pathogenesis can be subgrouped into patient-specific, inherited, and acquired predispositions.
Although t-MN can occur at any age, the risk tends to increase with advancing age, and older patients, characterized by a higher number of comorbidities, are more likely to develop the disease. Thanks to the availability of deep sequencing techniques, germline variants have been reported in 15-20% of t-MN patients, highlighting their role in cancer predisposition.
It is becoming increasingly evident that t-MN with driver gene mutations may arise in the background of Clonal Hematopoiesis of Indeterminate Potential (CHIP) under the positive selective pressure of chemo and/or radiation therapies. Although CHIP is generally considered benign, it has been associated with an increased risk of t-MN. In this context, the phenomenon of clonal evolution may be described as a dynamic process of expansion of preexisting clones, with or without acquisition of additional genetic alterations, that, by favoring the proliferation of more aggressive and/or resistant clones, may play a crucial role in the progression from preleukemic states to t-MN.

Keywords: t-MN, CHIP, Clonal Evolution.

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Introduction. Therapy-related Myeloid Neoplasms (t-MN) include Acute Myeloid Leukemia (AML), MyeloDysplastic Syndromes (MDS), and MyeloDysplastic/MyeloProliferative Neoplasm (MDS/MPN) arising in patients treated with chemo and/or radiation therapy for a previous cancer or an autoimmune disease.[1,2]

In the 5th edition of the WHO classification of

hematolymphoid tumors, t-MN have been included in a new segregated category of secondary myeloid neoplasm, encompassing diseases that arise in the setting of specific known predisposing factors such as Myeloid Neoplasms post Cytotoxic Therapy (MN-pCT). This term formally replaces "therapy-related".[3]

On the other hand, the term therapy-related has been retained by the "International Consensus Classification of myeloid neoplasms and acute leukemia" (ICC), but without differences in the concept that now both terms, "MN-pCT" and "therapy-related", are considered diagnostic qualifiers that should be added following the specific MDS or AML diagnosis.[4]

The 10-year cumulative incidence of t-MN ranges from 1–10% according to different cancers and different chemo and/or radiation regimens.[5,6] However, due to the steady improvement in the overall survival (OS) of cancer patients, an increase in the percentage of t-MN diagnoses has been shown in recent years.[7] Nowadays, t-MN represents one of the worst long-term side effects of cytotoxic therapy, since compared to *de novo* myeloid neoplasms, t-MN patients are characterized by a poor prognosis and refractoriness to current treatment strategies (about 5-year survival rate of 10%).[3,6]

In this line, in our aging societies, where newer therapies and ameliorated cancer management protocols are improving the life expectancy of cancer patients, t-MNs are an emerging problem.

Over the last few decades, according to the available screening technologies, factors predisposing the development of t-MN have been investigated in different directions.

Several Authors have studied the impact of the host's genetic background on cancer predisposition. Polymorphisms in genes involved in detoxification, DNA repair, and apoptosis may modify the individual risk of developing a t-MN. In particular, when detoxification and/or DNA repair are ineffective, the DNA damage induced by therapy can cause chromosomal instability, leading to severe failure of cell functions and/or apoptosis. Moreover, these polymorphisms have been shown to influence the individual response to cancer treatment by increasing the concentration of active drug metabolites or impairing enzymatic pathways that rescue cancer cells from genotoxic damage and apoptosis.[8–13]

In the same line, germline variants typical of familial predisposition syndromes like Fanconi Anemia and Li-Fraumeni have been reported at higher frequencies in t-MN patients, and *TP53* uncommon germline variants may play a key role in t-MN pathogenesis.[14–16]

More recently, Clonal Hematopoiesis of Indeterminate Potential (CHIP) has been considered one of the main risk factors and has been identified at the time of the primary cancer diagnosis in 30%–70% of patients developing a t-MN, representing a pre-malignant state, which the exposure to cytotoxic agents[6,17,18] can further trigger.

Despite several research groups that have contributed to characterize the main risk factors in t-MN development, the multiplicity of primary tumors, in association with the different therapeutic strategies available and the new drugs in development, make interpreting the current data still complex. In addition, we also need to keep in mind that in 10-15% of cases, myeloid neoplasm occurs as a second neoplasm in patients who underwent surgery alone to treat the primary tumor, and a familial and/or personal history of multiple neoplasms is present in 5-10% of patients.[19]

Therefore, in order to better characterize the genotypic and phenotypic profiles of t-MN, the aim to be pursued in the early future should be to select a homogeneous study population consisting of patients affected by the same primary tumor, treated with similar treatment protocols before t-MN development, in order to limit the biases involved in the study of heterogeneous populations and treatments.

Risk Factors in t-MN Pathogenesis: Patient-Specific Predisposition. Due to the limited incidence of t-MN in treated patients, during past years, many researchers have tried to identify the main potential contributors involved in t-MN onset. Understanding the risk factors associated with t-MN development is crucial for identifying high-risk individuals and implementing preventive strategies to improve patient outcomes. To date, three main categories of risk factors have been identified: patient-specific, inherited, and acquired predisposition.

In the patient category, specific risk factors are included: age, previous cancer, autoimmune diseases (AD), and environmental exposure (smoking, benzene, irradiation, etc.).

Age is one of the most significant risk factors for t-MN development. Although t-MN can occur at any age, the risk tends to increase with advancing age. Older patients, characterized by a higher number of comorbidities and frequency of Clonal Hematopoiesis (CH), are more likely to develop the disease.[20,21]

Although the frequency of t-MN can be considered very low, some primary tumors have been associated with a higher risk of t-MN development. In particular, the most common primary malignancies are breast cancer and lymphoproliferative disorders such as Hodgkin's and non-Hodgkin's lymphoma, Multiple Myeloma (MM), and Chronic Lymphocytic Leukemia (CLL).[22–25]

The direct correlation between the type of primary tumor and the risk of developing a t-MN can be related to the specific type of treatment to which patients are subjected and to their survival duration.

Some chemotherapy drugs, alkylating agents, and

topoisomerase II inhibitors (cyclophosphamide, busulfan, and melphalan, as well as etoposide and doxorubicin), have been associated with an increased risk of t-MN. Alkylating agents damage DNA by adding alkyl groups to its structure. At the same time, topoisomerase II inhibitors interfere with the topoisomerase II enzyme's function, which helps manage DNA structure during cell division. As a result, DNA sequence and chromosomal structure would be altered, increasing the risk of t-MN.[26] Recently, PARP1 inhibitor therapy has been added in the 5th edition of WHO 2022 as a qualifying criterion for t-MN, while the treatment with methotrexate has been excluded.[3] The time of insurgence of t-MN is generally earlier (1-3 years) in patients treated with Topoisomerase inhibitors than Alkylating agents and/or radiation (7-10 years), even if the frequent contemporaneous administration of these drugs makes this difference not significant.[25]

In 10-15 % of cases, myeloid neoplasms may occur as a second neoplasm in patients who underwent surgery alone to treat the primary tumor. Surgery is not typically associated with an increased risk of myeloid neoplasms; however, surgery can include adjuvant and neo-adjuvant therapies, such as chemotherapy or radiation, recommended to reduce the initial tumor mass or eradicate residual cancer cells to reduce the risk of new occurrence. The administration of these adjuvant treatments may also play a role in t-MN pathogenesis.[19]

Autoimmune diseases, such as Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), Multiple Sclerosis (MS), and Inflammatory Bowel Disease (IBD) have also been considered potential risk factors in t-MN development.[27] The involvement of the immune system and inflammation has been indicated as a possible driving factor contributing to myeloid neoplasm development and progression. Systemic-Inflammatory-Autoimmune-Diseases (SIAD) are increasingly considered in the hematological context.[28]

However, myeloid neoplasm development depends on several factors not yet fully elucidated, including the specific subtype of AD, the chronic immune stimulation, the duration and anti-rheumatic/anti-inflammatory treatment, and the genetic predisposition. The most well-documented leukemogenic potential is related to drugs such as azathioprine, cyclophosphamide, and mitoxantrone, which can impair the hematopoietic processes.[29–31]

Finally, environmental exposure to cigarette smoking, benzene, pesticides, chemicals including Formaldehyde, and ionizing radiation has been associated with myeloid neoplasm pathogenesis. So, it should be included in the category of patient-specific risk factors.[32,33]

Mutations in ASXL1 have been significantly associated with smoking history. Of note, current smokers showed a higher rate of ASXL1 mutations than former smokers.[33]

The higher incidence of myeloid neoplasms in survivors of the Nagasaki and Hiroshima atomic bombs reinforces the causal relationship between ionizing radiation and hematological disorders.[34,35]

In this context, the exposure of cells to ionizing radiation results in the increased formation of Reactive Oxygen Species (ROS), such as hydrogen peroxide, superoxide, and hydroxyl radicals. These molecules can oxidize and deaminate the nitrogenous bases of DNA, triggering damage to DNA structure. Cells with DNA damage are genomically unstable, cumulating somatic mutations and cytogenetic alterations, which are the basis for developing myeloid neoplasms.[36,37]

Similarly, Benzene exposure is now considered casually related to myeloid neoplasms. Benzene and its metabolites are found to be harmful to Hematopoietic Stem Cells (HSC), giving rise to a reduction in the number of HSC and impairing their maturation and differentiation in myeloid and lymphoid lineages. Although the majority of evidence comes from case-control studies and occupational studies with a relatively small number of cases, genotoxicity, immunotoxicity, altered gene expression, chronic inflammation, and induction of immunodepression are described as the main causes of benzene-induced damage.[38,39]

Risk Factors in t-MN Pathogenesis: Inherited Predisposition. Germline variants (mutations and polymorphisms) have also been reported as risk factors in t-MN development. Thanks to the availability of deep sequencing techniques, a germline cancer predisposition has been confirmed in 15-20% of t-MN patients.[14,40] These germline variants can affect genes involved in DNA repair, cell cycle regulation, genotoxic metabolism, and other biological pathways related to cancer development.[41–43]

Moreover, germline variants can make individuals more vulnerable to the harmful effects of chemo and/or radiation therapy. In this line, polymorphisms in genes belonging to the xenobiotic detoxification pathway, such as cytochrome p450, NADPH-quinone oxidoreductase 1 (NQO1), and glutathione S-transferase (GST), and DNA repair pathways like RAD51, XRCC1, XRCC2, XRCC3 and XPD, were among the first candidates to be studied for their possible involvement in t-MN development, since the ineffective repair of damaged cells, that survive to genotoxic stress, may be crucial for cancer genesis. Similarly, polymorphisms in apoptotic modulators could deregulate the apoptotic pathway, rescuing damaged cells from apoptosis and modifying the risk of t-MN (**Figure 1**).

Although several Authors have contributed to delineate the role of these polymorphisms, their association with t-MN development has not been confirmed in large and independent study cohorts, probably because of the lack of adequate controls not

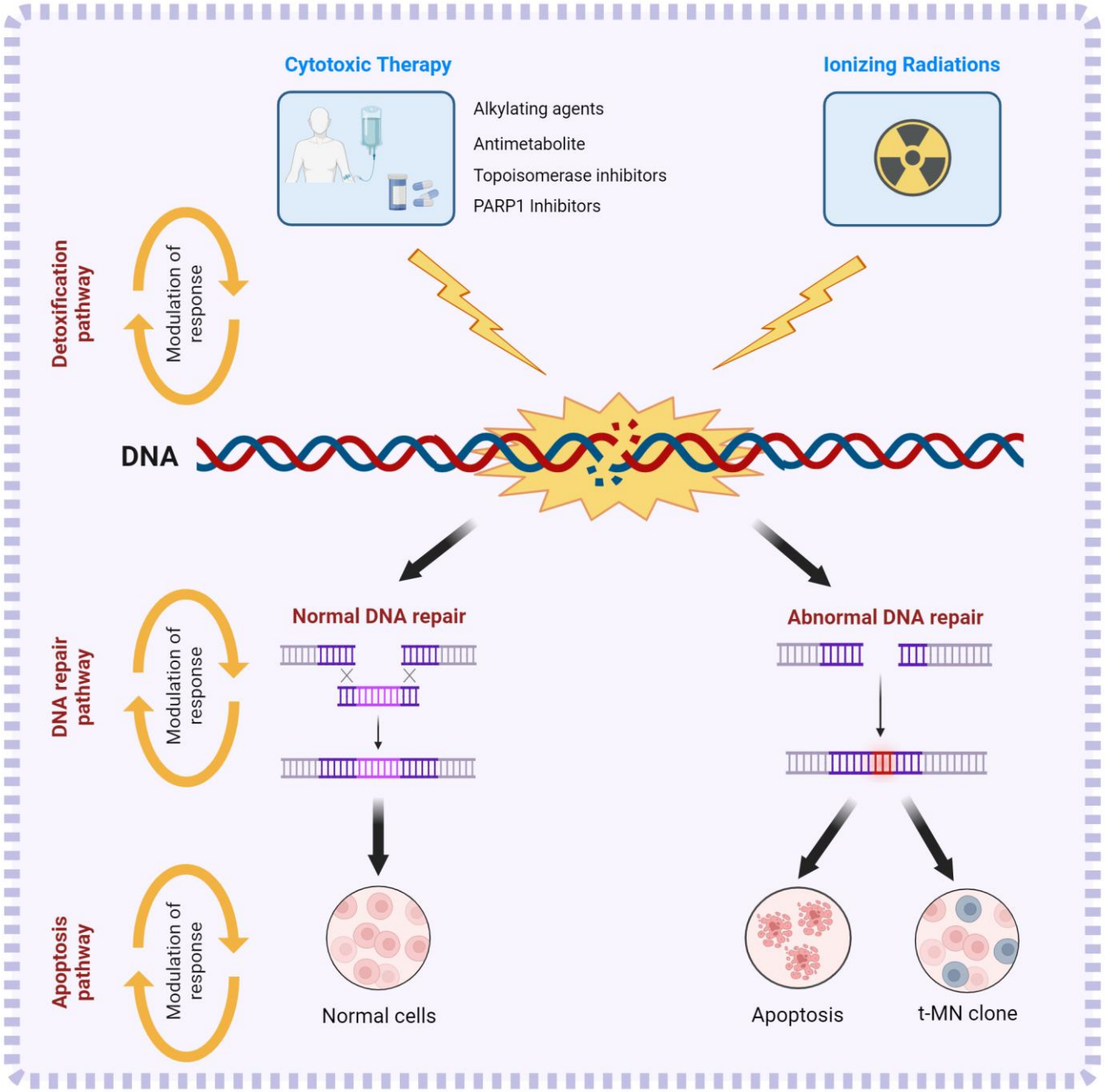

Figure 1. Modulation of response to cytotoxic therapy and ionizing radiation in patients with polymorphisms in detoxification, DNA repair and apoptosis pathways. A model of inherited predisposition. Created with BioRender.com.

only matched for sex, age, and primary disease but also for therapy and comparable follow-up.[11,44,45]

An increased susceptibility to t-MN development has also been described in individuals with inherited cancer predisposition syndromes such as Fanconi anemia (FA) and Li-Fraumeni syndrome.

Fanconi anemia is associated with bi-allelic loss-of-function mutations in the FA pathway, including 21 FA or FA-like genes.

Voso *et al.* reported a high frequency of FA gene variants in t-MN patients (16%), with similar prevalence in t-MN secondary to lymphoproliferative diseases and breast cancer, indicating that heterozygous carriers of FA variants may have increased susceptibility to the DNA-damaging action of cytotoxic therapy.[15] Similarly, Schwartz *et al.* identified *TP53* germline variants in 15.5% of pediatric t-MN.[46]

Risk Factors in t-MN Pathogenesis: Acquired Predisposition. Clonal hematopoiesis (CH) can play a key role in the risk factors related to an acquired predisposition.

In two independent works, Jaiswal *et al.* and Genovese *et al.* reported the presence of somatic or acquired mutations in 1% of non-hematological patients. These studies also highlighted that mutations were very rare in patients under 40 (<1%) but progressively increased in older individuals, achieving the percentage

of about 20–30% in those aged 70 or older.[47,48] Since these mutations were present in patients without detectable hematologic disorders, this phenomenon has been defined as age-related clonal hematopoiesis (ARCH). In contrast, clonal hematopoiesis of indeterminate potential (CHIP) was defined by somatic mutations with Variant Allele Frequency (VAF) greater than 2%.

Notably, genes mutated at higher frequency were identified in myeloid neoplasms.[47,48]

It is becoming increasingly evident that t-MN with driver gene mutations may arise in the background of CHIP under the positive selective pressure of chemo and radiation therapies.

Hematopoietic stem cells accumulate somatic mutations during their biological life, most of which are nonpathogenic without functional consequences or potential for clonal expansion.

Some mutated clones might gain proliferation and survival advantages, triggering the clonal expansion of a specific myeloid cell subset characterized by genetic alterations such as cytogenetic abnormalities, somatic mutations, and/or copy number variations. These genomic alterations represent a heterogeneous condition that may promote the transition from a physiological state to myeloid malignancy.

Although ARCH and CHIP are mostly considered benign, they have been associated with an increased risk of t-MN. Their presence may create a preexisting pool of altered cells more prone to further genetic and malignant transformations and affect the hematopoietic microenvironment, driving bone marrow niche alterations.[49]

Genovese et al. showed that subjects with CHIP have a higher risk of progression to hematological malignancies than subjects without mutated clones, which appears proportional to the VAF of mutated genes. This risk is about 11 to 13 times higher in individuals with clonal hematopoiesis, and the overall transformation rate is about 1% per year.[48]

Gillis and Colleagues, in a proof-of-concept case-control study, identified a prevalence of CHIP in patients who developed therapy-related myeloid neoplasms (62%) than that of control patients (27%), showing that individuals carrying CHIP mutations were at increased risk of t-MN compared to individuals without detectable CHIP mutations.[50]

Similarly, our research group recently reported the high incidence of CHIP in Chronic Lymphocytic Leukemia (CLL) patients who developed a t-MN after treatment with chemo-(immuno)therapy, mostly Fludarabine, Cyclophosphamide, Rituximab (FCR). We detected 30 pathogenic/likely pathogenic variants in 10 of 13 patients with a t-MN (77%). In contrast, CHIP variants were present in only 34 of 285 patients (12%) from the CLL control cohort who received the same treatment. Of note, backtracking the prevalence of CHIP in paired samples collected at the time of CLL diagnosis, the same variants were identified in 62.5% of patients.[24]

These data highlight the potential role of CHIP as a risk factor for developing t-MN, suggesting the screening for myeloid clonal states, especially in older patients, before starting cytotoxic therapy.

Clonal Evolution in Therapy-Related Myeloid Neoplasm. Clonal evolution is a dynamic process of expanding preexisting clones with or without acquiring additional genetic alterations that may be crucial in progressing from preleukemic states to t-MN. This process is directly shaped by therapy that may promote clonal competition, favoring the expansion of more aggressive and resistant clones, characterized by proliferative and survival advantages.

The first evidence of clonal evolution in t-MN comes from the studies conducted by Wong *et al.*, who described the role of *TP53* mutations in the origin and evolution of t-MN in 2015.[51]

Sequencing the genomes of 22 cases of t-MN, the Authors identified 7 carriers of specific *TP53* mutations. Backtracking these mutations in paired DNA samples collected at the time of primary malignancy (Hodgkin and non-Hodgkin lymphoma), they identified the same mutations at very low variant allele frequencies (0.003–0.7%) in 4 of the 7 patients, concluding that rare HSC carrying age-related *TP53* mutations may be resistant to chemotherapy and expand preferentially after treatment.[51] This paper was the first evidence that chemo and radiation therapy may promote the clonal selection and expansion of preexisting mutant HSC, favoring t-MN development in a sort of Darwinian selection.

Two years later, studying 14 t-MN patients with a primary hematologic malignancy using ultra-deep NGS, we identified two distinct clonal evolution models[17] (**Figure 2**).

Mutations identified at the time of t-MN were tracked backward in bone marrow samples preceding secondary leukemia occurrence in 8 paired DNA samples. Somatic mutations were detectable before any cytotoxic treatment in three patients, while the t-MN clone was acquired in the remaining five patients.

In our study, we confirmed the key role of somatic mutations of the *TP53* gene in the clonal evolution of t-MN and identified other genes, such as ASXL1, as pivotal players.

Of note, we also identified a t-MN patient with a particular pattern of clonal evolution characterized by *IDH1* and *SRSF2* somatic mutations. Both mutations were somatically acquired because they were not detectable in the CD3+ T-lymphocyte population, and the VAFs (38% and 35%, respectively) suggested their cohabitation in the same clone.

The *IDH1* mutation was originally present at similar

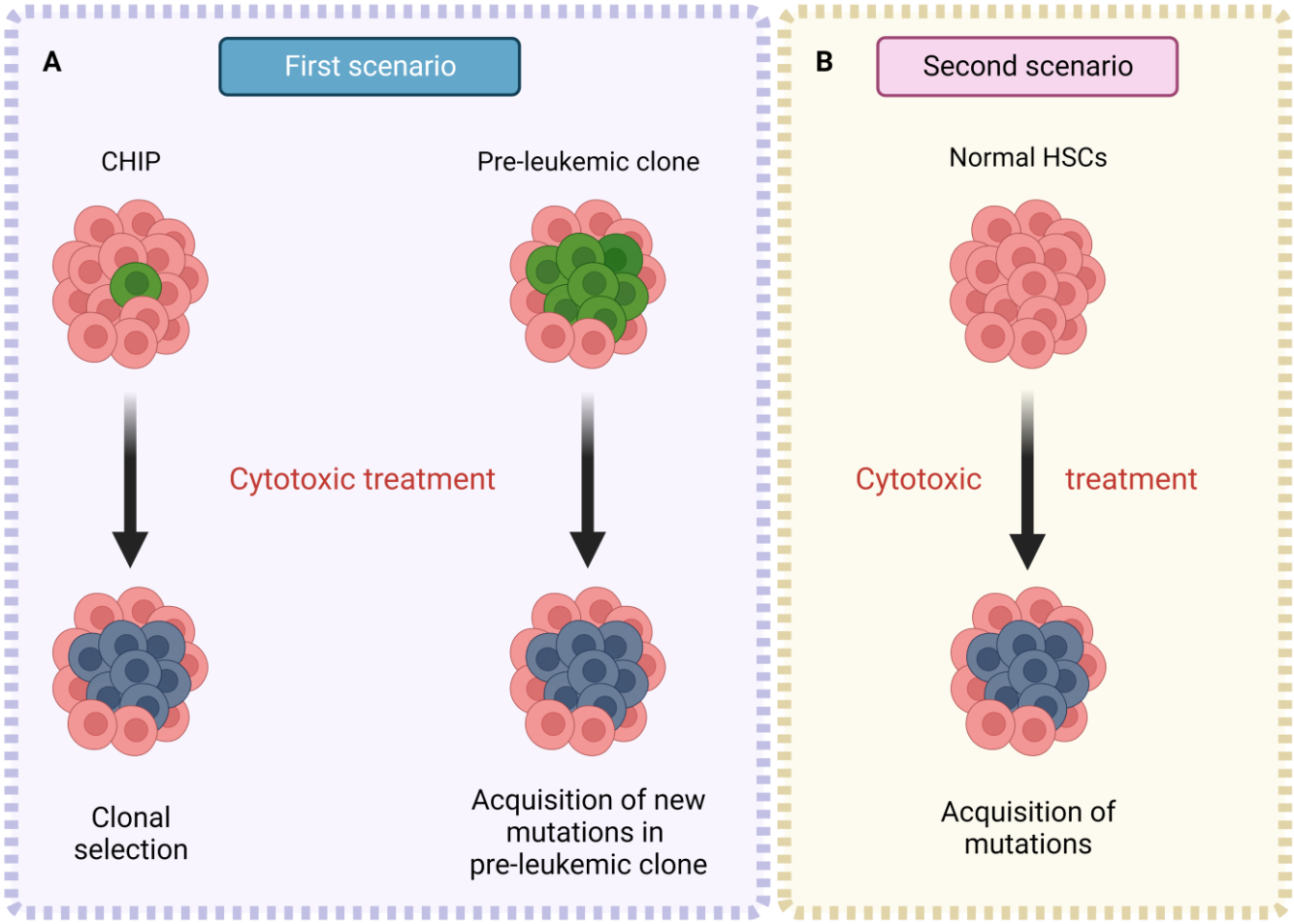

Figure 2. Patterns of clonal evolution. A) In response to cytotoxic therapy, mutated clones might gain proliferation and survival advantages triggering the clonal expansion (left side) or the acquisition of new pathogenic mutations (right side) driving t-MN onset. B) Acquisition of novel mutations as a direct effect of cytotoxic treatment. Created with BioRender.com.

VAF (35%) 9 years before t-MN onset. In contrast, the *SRSF2* mutation was undetectable, suggesting a pre-leukemic role for *IDH1* mutation and a pathogenic role for *SRSF2* mutation in a susceptible individual (**Figure 2A**).

In the second scenario, somatic mutations characterizing the t-MN clone, 5 out of 8 patients were not present at primary cancer diagnosis. They appeared only after chemo and/or radiation therapy as a direct effect of treatment, suggesting the dual role of cytotoxic therapy in t-MN pathogenesis (**Figure 2B**).

To date, NGS technology has become commonly used in research and diagnostics too; thanks to it, the number of patients affected by t-MN who have been mutationally screened has increased enormously.

Although many authors have demonstrated that the mutational burden of *de novo* myeloid neoplasm and t-MN are similar, all agree in identifying a higher incidence of *TP53* mutations in t-MN patients.

TP53 mutations have been reported in 30-47% of t-MN cases, more frequently associated with complex karyotype (80%).[52] In t-MN, these mutations may also occur associated with TP53 deletion, copy-neutral loss of heterozygosity, and in a multihit state.[53–56]

The *TP53* gene encodes for the p53 tumor suppressor protein, which is activated in response to cellular stress. Subsequently, it activates the mechanisms of cell cycle arrest, senescence, and apoptosis, playing an essential role in controlling cell proliferation and differentiation.

Many studies have shown the negative prognostic role of *TP53* mutations in myeloid neoplasms, demonstrating poor response to standard cytotoxic therapy and lower median overall survival and disease-free survival compared to unmutated patients.[57–59]

Although revised diagnostic criteria for myeloid neoplasms (WHO and ICC) recommend major changes concerning *TP53* mutations in relationship with their prognostic role, at least 2 mutations or 1 mutation with loss of *TP53* wild-type or VAF≥ 50% as evidence of biallelic/multihit *TP53* mutation, Shah *et al.* recently hypothesized a different prognostic role for *TP53* mutations in the context of t-MN.[57] Analyzing 488 t-MN patients found that $TP53^{mut}$ t-MN with VAF≥ 10% had significantly shorter survival than wild-type patients, while $TP53^{mut}$ with VAF < 10% was comparable to wild types.

We now know that not only the presence of clonal hematopoiesis may play a role in the development of t-

MNs but also that this role may be directly related to the specific treatment patients undergo. In this line, the direct link between clonal hematopoiesis, as a risk factor, and the specific treatment, as a selective agent, in clonal evolution and t-MN development is becoming evident.

For this reason, several Authors are trying to focus on the study of a selected cohort of patients affected by the same primary tumor and homogeneously treated, comparing them with similar control cohorts.

Sperling *et al*. recently reported the landscape of 416 t-MN diagnosed and treated at MD Anderson Cancer Center[60] to uncover the exposure relationships that provide selective advantage to specific CH mutations. As expected, the Authors found a predominance of *TP53* and *PPM1D* mutations and mutations in DTA genes (*DNMT3A*, *TET2*, and *ASXL1*). Complex karyotypes were enriched in patients treated with platinum agents, while chromosome 5 and 7 abnormalities were more frequent in patients treated with alkylating agents.

They also identified an enrichment of *TP53* mutations in patients with a previous history of multiple myeloma (MM) treated with thalidomide analogs and proteasome inhibitors.

Since *TP53* mutations have been associated with resistance to lenalidomide therapy in del(5q) MDS patients and secondary AML, the Authors tested, using long-term in vitro competition assays, on HSPC from mice engineered by CRISPR-Cas9 system, the effect of Thalidomide analogs on *TP53* mutated cells.[61,62] They found that lenalidomide, but not pomalidomide, can induce the clonal selection of *TP53* mutated HSPCs, while none of the other cells, *PPM1D*, *TET2*, and *DNMT3A* mutated, showed the same positive selection under treatment pressure. These data were also reproduced in "*in vivo*" mouse models, highlighting the potential role of lenalidomide treatment in t-MN development and suggesting the usefulness of CHIP screening in the context of personalized therapies.

Summary and Future Prospective. Although the main risk factors involved in therapy-related leukemogenesis seem to be identified, their specific weight about the whole panoply of the current cytotoxic therapies still needs to be well understood.

In the near future, a comprehensive understanding of these heterogeneous interactions can be achieved by studying homogeneous cohorts of patients affected by the same primary disorder undergoing similar treatment strategies.

In these rare and precious study cohorts, it will be our task to use all the available tools to identify patients at major risk of t-MN for whom certain cytotoxic treatments should be avoided and replaced with less leukemogenic approaches.

In this line, high-throughput sequencing technologies, able to trace clonal evolution in single cells, are the most promising tool to achieve our goals.

In the meantime, however, since CHIP has been recognized as a novel predisposing factor in the pathogenesis of t-MN, somatic mutation screening through NGS technologies should be carried out from the early diagnostic stage of primary cancers to guide the choice of treatment and minimize the risk of developing t-MN.

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