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Stem cell damage after chemotherapy- can we do better?

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ABSTRACT

Therapy-related myeloid neoplasms are unintended and unwanted complications of cytotoxic chemotherapy and radiation. Unlike other environmental toxin-induced malignancies, exposure to the inciting agent is required to eradicate a primary and life-threatening cancer. In this review, we will focus on the biochemical mechanisms that lead to therapy-induced myeloid malignancy. This includes discussion of known mechanisms by which cytotoxic chemotherapy and radiation induce genetic mutations and promote evolution and expansion of malignant hematopoietic clones. Mechanisms by which the hematopoietic stem and progenitor microenvironment may be injured during the course of chemotherapy and radiation therapy will also be presented. While prevention strategies have not yet been brought into clinical testing or practice, there is active basic research relevant to prevention of t-MNs which is also included in our attempt to answer the question of whether we can do better to prevent stem cell injury after chemotherapy and radiation.

1. Introduction

The treatment of any patient with cancer relies on a combination of surgery, medical therapy (chemotherapy, biological agents, immunotherapy), and radiation. Increasingly sophisticated combination of these modalities has significantly increased the overall survival for many individuals diagnosed with cancer. Unfortunately, between 5 and 10% of all cancer patients who are treated with either chemotherapy or radiation develop a therapy-related myeloid neoplasm (t-MN) [1–6], for which the prognosis is poor [7–9].

The designation 'therapy-related myeloid neoplasm' encompasses a broad range of myeloid malignancies that are induced by antecedent exposure to chemotherapy and/or radiation. The significance of this designation is highlighted in the 2016 classification strategy for myeloid malignancies which includes therapy-related MDS and AML (t-MDS/AML) as distinct sub-classifications of the primary disease [10]. 10–20% of all AML and MDS cases are therapy-related [11], and other myeloid neoplasms such as chronic myelomonocytic leukemia (CMMoL) and acute promyelocytic leukemia (APL) may be also be designated as therapy-related.

Some of the risk factors for later development of t-MDS/AML are non-modifiable by the time an oncologist meets a patient with newly diagnosed cancer. Patients may have an underlying clonal hematopoiesis of indeterminant potential (CHIP), which when exposed to cytotoxic therapy has an increased potential to transform into a t-MDS/AML [12]. Alternatively, patients may have a germline genetic mutation that predisposes them to myeloid malignancy, such as with *CEBPA*, *DDX41*, *RUNX1*, *ANKRD26*, *ETV6, SAMD9/SAMD9-L* or *GATA2* [13,14] mutations. Other inherited bone marrow failure syndromes including but not limited to Fanconi's anemia, Diamond-Blackfan anemia, Schwachman-Diamond syndrome, severe congenital neutropenia, and dyskeratosis

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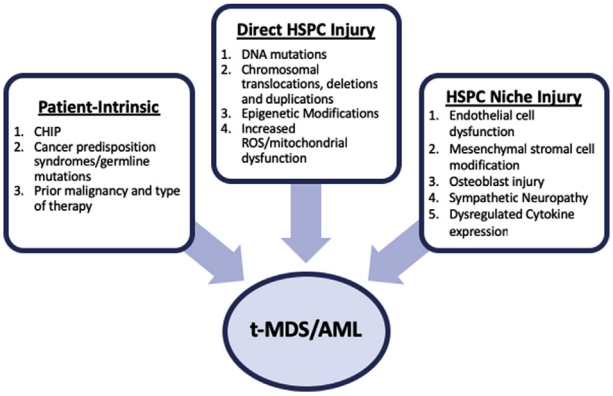

Fig. 1. Development of t-MDS/AML. Biological mechanisms of disease are divided into those that are intrinsic to the individual prior to chemotherapy or radiation exposure, the direct impact of chemotherapy and radiation on hematopoietic stem and progenitor cells (HSPCs) and those that indirectly impact HSPCs via modification of the HSPC microenvironment.

congenita can similarly predispose to MDS and AML. Between 16 and 21% of patients with t-MN are ultimately found to have a germline cancer predisposing mutation [15–18]. With an underlying predisposition towards development of a myeloid malignancy, exposure to cytotoxic chemotherapy and radiation may be the second-hit needed to accelerate development of MDS or AML.

The type and stage of first malignancy has a profound impact on development of t-MDS/AML. This determines the specific chemotherapy and radiation protocols to which an individual is exposed. In addition, the original malignancy itself may predispose an individual to develop a myeloid malignancy. Plasma cell neoplasia-associated t-MDS and t-AML are one example of the complex interplay between these factors. Individuals with IgA or IgG monoclonal gammopathy of unknown significance (MGUS) as well as overt multiple myeloma carry a near 8-fold increased risk above that of the general population for developing a myeloid malignancy [19,20]. Unlike multiple myeloma, MGUS is not treated with chemotherapy or radiation. This increase may indicate a hematopoietic stem and progenitor cell (HSPC)-intrinsic predisposition towards malignancy or may be a consequence of the immune dysfunction secondary to the plasma cell dyscrasia. When chemotherapy is administered and autologous stem cell transplantation for multiple myeloma is performed, pre-malignant myeloid clones have the opportunity to acquire additional mutations and expand until overt t-MDS/t-AML develops [12,21].

Many of the patient-intrinsic factors detailed above are discussed with greater depth in other articles within this issue. In this review, we will focus on the biochemical mechanisms by which chemotherapy and radiation potentiate t-MDS/AML. Mechanisms of disease are divided into those that are the direct impact of chemotherapy and radiation on hematopoietic stem and progenitor cells (HSPCs) and those that indirectly impact HSPCs via modification of the HSPC microenvironment (Fig. 1).

2. Direct impact of chemotherapy and radiation on HSPCS

2.1. Genetic modification of HSPCs by chemotherapy and radiation

Traditional cytotoxic chemotherapy kills cells by chemical modification of individual nucleotides and induction of single- or double-strand DNA breaks. Ideally, these DNA changes are not corrected by DNA repair pathways and are sufficient activate cell death pathways leading to eradication of the neoplastic cells, but with minimal long-term consequences to off-target cells. However, these criteria are rarely fully met, and when HSPCs are the 'innocent bystander' of off-target cytotoxicity, the result may be evolution of t-MDS/AML.

DNA repair pathways are typically activated in an attempt to normalize DNA structure and content. Single-stranded break repair pathways (SSBR) correct inappropriate nucleotide methylation or alkylation, other single nucleotide chemical modification, and distortion of DNA helix conformation(1). SSBRs include O-6-alkylguanine DNA alkyl transferase (AGT) repair, base excision repair (BER) and nucleotide excision repair (NER) pathways(1). Double strand break repair pathways (DSBR) include homologous recombination repair (HRR) and non-homologous end joining repair (NHEJR) pathways, while a third mechanism, the mismatch repair (MMR) pathway, restores incorrect DNA base pairings. Cells undergo apoptotic cell death when these DNA-repair pathways cannot resolve chemical or radiation-induced DNA modification. Fidelity of DNA replication is absolutely dependent on these mechanisms.

If DNA repair is incomplete but sufficient to allow cell growth and replication to proceed, the residual DNA modifications may be carried forward into progeny cells. When this occurs in HSPCs, a pre-malignant clone may develop that evolves with time into t-MDS/AML [22,23]. This is often secondary to acquisition of an additional mutation in the *TP53* gene, which is another genetic hallmark of therapy-related malignancies, and the most frequently mutated gene in t-MDS/AML [23]. Mutations in *PPMD1* have also been identified in patients with therapy-related MDS [24,25]. The *PPMD1* gene product (protein phosphatase Mg^{2+}/Mn^{2+}-dependent 1D protein) works in concert with p53 to regulate DNA damage responses. In addition to *TP53* and associated pathway mutations, ABC transporter genes, *ASXL1, DNMT3A, FLT3-ITD, IDH1, IDH2, KRAS, NPM1, NRAS, PTPN11, RUNX1, STAG2*, and *TET2* genes are also frequently mutated in t-MDS/AML [3,21,23,26].

Alkylating Agents kill cancer cells by transferring alkyl groups to DNA. These covalent DNA modifications cross-link nucleotides and induce double-stranded DNA breaks which in turn prevent cell division and induce cell death. In the case of alkylating-agent associated t-MNs, incomplete repair of double-strand DNA breaks promotes inappropriate DNA recombination and chromosomal translocations. Examples of alkylators that are associated with t-MNs are cyclophosphamide, melphalan, chlorambucil, bendamustine, busulfan, procarbazine, temozolomide, cisplatin, carboplatin and oxaliplatin [27]. The cumulative dose of alkylating agent exposure is positively correlated with development of t-MNs [16]. In these instances, t-MDS precedes the onset of t-AML- with the latency from time of drug exposure to onset of myeloid malignancy of 1–2 years, and peak incidence between 5 and 10 years [28]. Karyotypic abnormalities most often identified in alkylating agent-associated t-MNs include loss of part or all of chromosome 5 and/or 7 [29], and complex karyotypes [28,30]. TP53 mutations are also commonly identified in alkylator associated t-MNs [28,30].

Topoisomerase II (TopII) Inhibitors are chemotherapy agents that kill replicating cells via inhibition of topoisomerase II enzymes. These enzymes remove knots, tangles and relieve torsional stress from DNA by transient generation and repair of double strand DNA breaks [3,29]. Chemotherapy inhibitors of these enzymes prevent the re-ligation of DNA following introduction of double strand DNA breaks. Examples of topoisomerase II inhibitors that are associated with t-AML include etoposide, doxorubicin and mitoxantrone. As is the case for alkylating agents, TopII-inhibitor associated t-MNs are the consequence of inappropriate DNA recombination and chromosomal translocations resulting from double stranded DNA breaks [11,16,29,31]. There is a relatively short latency period to t-AML following Topo-II inhibitor exposure of approximately 12 months [28,32]. TopII-inhibitor induced t-MNs tend to have balanced chromosomal translocations such as *KMT2A* at 11q23.3 and *RUNX1* at 21q22.1 [16].

Antimetabolites, another major group of antineoplastic agents, are purine and pyrimidine analogs that are metabolized to form adducts which are then incorporated into DNA or RNA and inhibit DNA synthesis [11]. Examples of this drug class which are associated with increased risk of developing t-MDS/AML include fludarabine and 5-fluorouracil (5-FU) [33–35]. Fludarabine is a purine analog that is incorporated into DNA and leads to termination of DNA synthesis on the daughter strand [11], which increases the potential for double strand DNA breaks. The main metabolite of fludarabine, F-ara-ATP, can also inhibit ribonucleotide reductase which causes unbalanced deoxynucleotide pools. The pyrimidine analog 5-Fluorouracil (5-FU) induces DNA damage which necessitates activation of the BER and MMR pathways. Prolonged exposure to 5-FU adducts also leads to unbalanced nucleotide pools, impaired repair pathway activity, and ultimately increased regions of single-stranded DNA that are at risk for developing into double strand breaks.

Radiation Therapy: The risk of t-MDS/AML from radiation exposure is dose-proportionate [16]. Bone marrow injury occurs in part through induction of hematopoietic stem and progenitor cell (HSPC) senescence, i.e. loss of HSPC proliferative potential from a portion of the stem and progenitor cell pool [36,37]. High-energy photons cause double-stranded DNA breaks and increased oxidative stress which leads to increased reactive oxygen species (ROS). Ionizing radiation primarily kills cells within the high-energy field; however, cells on the periphery of the targeted zone may be damaged and then incorrectly repaired [30]. The radiation-induced injury that occurs in the bone marrow is part of this 'peripheral' field of damage. Approximately 60% of patients with radiation-induced t-MDS and t-AML have chromosome 5 and/or 7 abnormalities, which evolve over a longer period of latency from the time of radiation exposure [16], similar to that seen with alkylator-associated t-MNs.

2.2. Non-genetic modification of HSPCs by chemotherapy and radiation

While genetic mutations are initiating events in the evolution of a myeloid malignancy, the consequences of these mutations include epigenetic modifications such as DNA hypermethylation, RNA transcriptome changes, and modifications in protein expression and function. These complex factors in turn drive the clonal expansion of dysplastic HSPCs and establishment of MDS/AML.

Radiation therapy can induce epigenetic changes including altered gene DNA methylation-which is another mechanism by which it induces tumor cell death [38]. DNA hypermethylation is well-described in *de novo* MDS and AML, and certainly many of the genes that are mutated in t-MDS/AML are epigenetic modifiers [24]. However, there is little data about whether the epigenetic modifications induced by radiation exposure are subsequently transmitted to t-MDS/AML initiating stem and progenitor cells, and if this is the case, whether such modifications would be exclusively derived from modification of epigenetic-regulatory genes or direct epigenetic modification from radiation.

Peripheral blood stem cell (PBSC) autografts have provided a wealth of information about gene transcriptional modifications that predict t-MDS/AML. Bhatia et al. compared PBSC gene expression patterns between patients treated for lymphoma who developed t-MDS/AML following autologous transplantation, and those who did not. They identified a 38-gene expression signature that was predictive of t-MDS/AML within the 6-years following transplantation. Transcription dysregulation occurred in pathways relevant to cell signaling, cell adhesion, cell cycle regulation, metabolism, mitochondrial and oxidative function and proteasome pathways [39].

In total, chemotherapy and radiation induce mutations, chromosomal translocations, deletions and duplications, epigenetic modifications, transcriptional dysregulation, and metabolic changes in HSPCs that ultimately lead to establishment of one or more pre-malignant hematopoietic stem cell clones. These clones may have an intrinsic growth advantage that facilitates their expansion into overt t-MDS/AML. Alternatively, chemotherapy and radiation induced modifications in their microenvironment may facilitate their clonal outgrowth.

3. Hematopoietic niche modifications from chemotherapy and radiation

Balanced production of blood cells depends on Hematopoietic Stem and Progenitor Cells (HSPCs) and their supportive niches [40]. HSPC function can either be regulated by cell autonomous mechanisms, or by their surrounding microenvironment [40,41],

both of which may be modified by exposure to chemotherapy and radiation. In order to understand how therapy-induced niche changes may impact development of t-MDS/AML, it is necessary to first understand the components of the hematopoietic niche, and how they may contribute to malignant hematopoiesis.

3.1. Major components of the bone marrow hematopoietic niche

Primary adult hematopoiesis occurs in the bone marrow. The cytoarchitecture of the bone marrow is complex—there is a well-organized vascular system including arteriolar vessels and a robust sinusoidal capillary network to allow nascent blood cells to be released into peripheral circulation. Sensory innervation provides circadian cues for proliferation and peripheral trafficking of HSPCs via indirectly signaling through arteriole-adjacent mesenchymal stromal cells [42–45]. Osteoblasts line the inner surfaces of trabecular bone and are adjacent to blood vessels and other hematopoietic cells. There are numerous subtypes of bone marrow-resident mesenchymal stromal cells, and with increasing age, the marrow cavity becomes progressively filled with adipocytes. Extracellular matrix proteins and glycosaminoglycans secreted by megakaryocytes, endothelial cells, stromal cells and adipocytes provide further structure, organization and biochemical cues to the marrow. Soluble cytokines, chemokines and growth factors including but not limited to CXCL12, kit-ligand/scf-1, TGF-β, and VEGF are also present, and subsets of mature lymphocytes recirculate back into the marrow.

HSPCs are not randomly distributed within the bone marrow niche, but rather localize and migrate between specific niche structures [46]. These hematopoietic niches provide specific cues that maintain normal HSPC number and function [40]. A majority of the data that has helped to elucidate mechanisms of hematopoietic regulation by the bone marrow niche is derived from mouse models-either all-murine or human HSPC xenografts. In these systems, expression of specific cytokines, growth factors and their receptors and localization of specific subsets of niche and hematopoietic cells can be highlighted using cell-specific conditional transgenic mouse lines.

These experimental modalities were critical to understanding the significance of the murine perivascular hematopoietic niches. In this model-the periarteriolar niche, including arteriolar endothelial cells, mesenchymal cells and the adjacent sympathetic nerve fibers contribute regulatory cues that maintain a long-lived and quiescent hematopoietic stem cell pool [46–48]. This fraction of hematopoietic stem cells divides infrequently, but when necessary, are able to fully reconstitute hematopoiesis [46,47]. In contrast, several reports suggest that proliferative hematopoietic stem cells are more often found in relative proximity to sinusoidal vessels [46,49]. Subsets of vessels are specifically proximal to the osteoblastic layer, and these as well as osteoblasts themselves contribute hematopoietic regulatory molecules into the niche [50].

A limited number of studies have looked at the structure of the human bone marrow niche [51,52]. In one instance, human HSPCs were identified immunofluorescently based on co-expression of huCD45$^+$ and huCD34$^+$, and subsequently localized to the bone marrow most proximal to trabecular as opposed to cortical bone [52]. Another earlier study looked at combinations of epitopes in bone marrow from healthy human bone marrow donors to visualize subsets of blood cells (i.e. B-cells, T-cells, myeloid progenitors and blood vessels) in 3-dimensions [53]. However, the localization of specific subsets of HSPCs (i.e. long-term quiescent HSCs, short-term HSCs) with respect to specific vessel subtypes or other structures within the human niche has not been determined.

In comparison to localization studies, there has been a significant amount of work done to detail neuronal-regulated circadian fluctuations in HSPC DNA synthesis and mobilization and from human bone marrow into the peripheral blood, including data to support optimized stem cell mobilization following GCSF and plerixafor administration in the afternoon as opposed to morning [54]. We point readers to a review by Mendez-Ferrer et al. for a more in depth discussion of data relevant to this topic [44].

3.2. Evidence that the bone marrow niche contributes to MDS/AML [55]

The available human data pertinent to mesenchymal stromal and osteoblast function in the evolution of MDS/AML is limited to case series of donor derived leukemia, where abnormalities in the recipient bone marrow niche may contribute to expansion of a pre-malignant clone in the donated cell product [56,57]. Much of what is known about niche-directed malignant transformation of myeloid progenitor cells is again derived from mouse studies. For instance, individuals with Shwachman-Diamond Syndrome (SDS) have skeletal defects and a high risk of developing MDS/AML (30% incidence by age 30) [58,59]. The genetic mutation that causes SDS is in the *SBDS* gene. Mice deficient for *sbds* expression in mesenchymal [50,59,60], but not hematopoietic [60,61] cells develop MDS, which is consistent with a niche-directed mechanism of disease initiation. Knock-out of Mind bomb-1 (*mib1*) in mice causes a myeloproliferative neoplasm secondary to Notch pathway inactivation [62] via a hematopoietic cell extrinsic (i.e. niche-dependent) mechanism. In other mouse models, induction of an activating beta-catenin mutation in osteoblasts precipitated development of AML [63], and dicer-1 deletion in osteoprogenitor cells induced a myeloproliferative neoplasm [64].

The potential for bone marrow endothelium to provide inductive signals to MDS and AML cells has been indirectly evaluated in clinical sample analysis and *ex vivo* cell culture systems. Bone marrow vessel morphology from clinical samples from patients with MDS and AML is consistent with altered vessel size distribution and progressive hypervascularity with the progression from MDS to AML [65,66]. A separate study imaged bone marrow from a patient who had been previously treated for AML found that AML cells (CD33$^+$, CD34$^+$) were predominantly adjacent to blood vessels(53). Serum levels of the angiocrine signals VEGF, HGF, and bFGF are also elevated in patients with MDS and AML [65–67]. In an *in vitro* serum-free cell culture system, E4-ORF-transformed endothelial cells facilitated MLL-AF9 leukemia cell expansion and resistance to cytarabine chemotherapy [68]. Collectively, these data point towards concurrent and interdependent processes of bone marrow vascular reorganization and progression from MDS to AML.

Other human bone marrow niche cells have also been examined. Sympathetic nerve fiber degeneration is described in the bone

marrow of individuals with both AML [69] and myeloproliferative neoplasms [70]. Mouse studies suggest that these two hematopoietic disorders derive instructive and sympathetic neuron-derived β2 and β3 adrenergic signals [51], respectively. Again-these studies suggest concurrent and interdependent processes of evolving sympathetic neuropathy and myeloid malignancy.

3.3. Therapy-induced bone marrow microenvironment dysregulation

Both radiation and 5-FU modify the murine hematopoietic niche and its ability to support hematopoiesis. Following radiation or 5-FU administration, murine bone marrow sinusoidal and arteriolar endothelial cells degenerate and then normalize during the subsequent 1–2 weeks [48,71,72]. Endothelial cell expression of kit ligand/scf-1 [48], VEGFR2 [72], DLL4 and Jagged1 [71,73] are required for bone marrow microvascular repair and re-establishment of hematopoiesis. Additional studies have looked at requirements for plasminogen [74–76] and thrombomodulin [77] expression, both of which are required for recovery of the bone marrow vascular niche following radiation and/or 5-FU injury. In each instance, hematopoietic recovery is dependent on endothelial cell recovery. A more agnostic evaluation of bone marrow endothelial cell-derived transcripts following radiation highlights differential transcription of genes that encode extracellular matrix, proteases, notch ligands, Wnt and VEGF-associated factors [78].

The potential to separate bone marrow arteriolar from sinusoidal endothelial cells is increasingly refined and facilitated comparison of transcripts between the two vascular compartments during hematopoietic recovery. Both sets of endothelial cells play significant but non-overlapping roles in maintaining hematopoiesis. However, arteriolar endothelial cells have significantly higher transcript levels for the canonical stem cell support molecules than do sinusoidal cells (i.e. Kit ligand, CXCL12, Jag1, Jag1, Tgfb2 and Il6) [48], and reduction of arteriolar kit ligand expression profoundly reduced HSPC numbers and ability to reconstitute hematopoiesis following radiation-conditioned bone marrow transplantation. Importantly, for both endothelial cell subsets, genetic modification as evidenced by fluorescent transgene expression prior to 5-FU or radiation exposure was transmitted to progeny endothelium post-bone marrow recovery. This raises the question of whether less-specific genetic modification to endothelial progenitor cells as may occur following chemotherapy and radiation therapy could be similarly transmitted through multiple generations of bone marrow endothelium and potentially impact the clonal expansion of pre-malignant hematopoietic stem and progenitor populations.

Chemotherapy toxicity may also modify the bone marrow niche and attendant hematopoiesis by injuring sympathetic neurons. Vincristine and cisplatin are both neurotoxic chemotherapies that can cause sympathetic neuropathy. Following their administration to mice, the number of catecholaminergic thymidine hydroxylase (Th+) neurons in the bone marrow is reduced [79]. When vincristine or cisplatin pre-treated mice then underwent radiation-conditioned bone marrow transplantation, hematopoietic recovery was reduced, as was survival in comparison to mice treated only with saline or the less-neurotoxic chemotherapy, carboplatin [79]. While the sympathetic neuropathy did not induce MDS/AML, one may postulate that this sort of niche injury could alter clonal dynamics and potential for pre-malignant clones that lack normal proliferation and apoptosis cues to expand.

4. Prevention of t-MDS/AML

Once an individual has developed a t-MDS/AML, their ability to tolerate the potential complications of myeloid malignancy treatment is limited, and their potential for long-term disease-free survival is low [7–9]. However, there are multiple potential points of early intervention that are worth consideration in designing future pre-clinical research studies and clinical trials (Fig. 2).

The first point of intervention is prior to initiation of therapy for the original non-myeloid malignancy. Pre-screening for CHIP or germline cancer-predisposition syndromes prior to initiation of chemotherapy or radiation may one day allow selection of a regimen to minimize cumulative exposure to genotoxic regimens. However, the link between ChiPs and myeloid malignancies in general is tenuous and not yet causally linked. For now, there is no indication for pre-chemotherapy CHIP or cancer predisposition syndrome screening unless there is a family history suggestive of heritable hematopoietic malignancy risk such as with Fanconi's Anemias, and optimal management of the original malignancy takes precedence.

De-escalation of cytotoxic therapy for all individuals, regardless of antecedent CHIP or cancer-predisposition syndrome, has

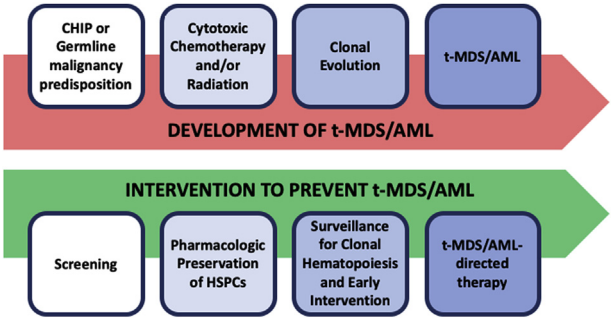

Fig. 2. Timeline for evolution of t-MDS/AML and potential points of intervention. Along the trajectory from pre-existing CHIP or germline malignancy predisposition, exposure to cytotoxic chemotherapy or radiation and clonal evolution to t-MDS/AML, there are potential points of intervention that should be evaluated within the context of prospective clinical trials.

already occurred for some lower-risk malignancies. For instance, specific lower-risk breast cancers are optimally treated by surgical resection followed by hormonal therapy, completely eliminating the need for cytotoxic chemotherapy or radiation in their front-line treatment [80,81]. Similarly, the treatment of adults with low-risk acute promyelocytic leukemia (APL) has evolved in the past 10-years to combination therapy with all-trans-retinoic acid and arsenic trioxide, again, completely excluding standard cytotoxic chemotherapy [82,83]. For chronic lymphocytic leukemia, use of the Bruton's Tyrosine Kinase inhibitor, Ibrutinib, may fully eclipse fludarabine-containing regimens as the optimal up-front treatment strategy [84,85]. However, de-escalation or modification of chemotherapy and radiation treatment protocols for curable malignancies should only be done within the context of well-monitored clinical trials, as the peril is insufficient treatment of the original cancer. While the hope is that newer biological and immunomodulatory drugs and treatment protocols will take the place of cytotoxic chemotherapy and radiation and reduce the incidence of t-MNs, careful longitudinal study of the rate and pattern of therapy-induced myeloid malignancies will be necessary to discern whether this is in fact the case. Certainly, investigation of the impact of these newer therapies on the incidence of t-MNs in individuals with pre-treatment CHIPs or germline cancer predisposition syndromes is worth careful attention, as it is not clear whether immune modulation will positively or negatively impact these individuals.

Another strategy to reduce the incidence of t-MDS/AML may be longitudinal screening for hematopoietic clonal expansion via next generation sequencing throughout the months and years following cytotoxic chemotherapy and radiation. If clones develop that either contain targetable mutations, such as in the genes encoding for FLT-3, IDH1 and IDH2, or a signature of aberrant hypermethylation, FLT-3, IDH1 and IDH2 inhibitors and hypomethylating drugs could be considered to pre-emptively eradicate the pre-malignant clones before overt t-MDS/AML develops. While appealing, there is no data to support such strategies, and the financial and physical cost to serial NGS screening of bone marrow or peripheral blood mononuclear cell screening is high.

Finally, it will be worth investigating strategies to prevent the genetic injury that occurs from cytotoxic chemotherapy and radiation all together. While there are no clinically validated pharmacologic strategies to prevent the development of therapy-related myeloid malignancies, there is precedent for pharmacologic prevention of other chemotherapy toxicities. Leucovorin [86] and MESNA [87] are incorporated into lymphoid malignancy treatment regimens to reduce methotrexate-induced cytopenias and gastrointestinal toxicity, and cyclophosphamide-induced hemorrhagic cystitis, respectively. Dexrazoxane, an oxygen free radical chelator, is approved for prevention of cumulative anthracycline-induced cardiotoxicity in patients with metastatic breast cancer [88]. G-CSF and erythropoietin mimetics are administered to shorten the duration hematologic toxicity from some cytotoxic chemotherapies by augmenting the rate of neutrophil and red cell production.

Several bone marrow preservation strategies have been evaluated in mice. In one instance, low-dose arsenic was used as a protective agent against 5-FU-induced toxicity in a colon cancer xenograft model [89]. While tumor regression was indistinguishable between both groups, the mice pretreated with the low-dose arsenic better maintained their body weight, had less gastrointestinal injury, and higher bone marrow cellularity compared to the group that was not pre-treated with sodium arsenite [89]. This study concluded that the bone marrow protection was secondary to differential regulation of the p53/NFκB axis by arsenic. In another study, metformin was evaluated in the setting of radiation-induced bone marrow suppression [36]. Metformin is a biguanide derivate that is commonly used to treat type II diabetes mellitus. It regulates cellular metabolism and ROS production by activating AMP-activated protein kinase (AMPK) [36], and is hypothesized to have a role in chemoprevention as well based on its ability to directly scavenge ROS [90,91]. Xu et al. evaluated the impact of metformin on total body irradiation (TBI) – induced long-term bone marrow suppression in mice, and found that mice pre-treated with metformin had significantly decreased levels of ROS, DNA double strand breaks and NOX4 expression in HSCs following radiation [36]. The authors concluded that metformin may decrease radiation-induced HSC senescence and has the potential to decrease radiation-induced bone marrow injury. Using a similar strategy, Weiler et al. found that either soluble thrombomodulin or activated protein C could improve hematopoietic recovery from radiation. The mechanisms of hematologic preservation were primarily via protection of the bone marrow vascular niche, with some evidence of a direct HSPC effect as well [77].

While promising, each of these chemoprevention studies have focused in mouse models of chemotherapy and radiation toxicity, and only the arsenic study examined the differential effect of the protective strategy on treatment efficacy against a target malignancy. In each instance bone marrow cellularity or peripheral blood cell enumeration and recovery were used as metrics for efficacy of the interventions, and none of these studies were designed to look at the impact of the intervention on mitigation of DNA mutations or epigenetic changes within the HSPC compartment.

5. Summary

Therapy related MDS/AML remains a significant therapeutic challenge in the field of hematologic oncology. Patients who develop t-MDS/AML have already been through the rigors of cytotoxic chemotherapy and radiation, only to find themselves with a secondary cancer for which treatment options are difficult, and the long-term prognosis is poor. Standard therapies for MDS and AML are not as well tolerated in t-MDS/AML patients, nor are they as effective at providing long-term disease-free survival. While the majority of individuals exposed to cytotoxic chemotherapy and radiation do not develop t-MDS/AML, the incidence is still startlingly high. In order to improve the outcome for these patients, basic research will need to answer questions specifically related to mechanisms of HSPC and niche injury from cytotoxic therapy and radiation therapy. Clinical trials will need to be developed that look not only at treating t-MDS/AML when they develop, but also at the multiple points of earlier intervention surrounding the initial cytotoxic chemotherapy and radiation exposure.

6. Research agenda

a. Attention should be given to identification of the optimal timing and patient selection for post-chemotherapy and radiation screening for clonal hematopoietic expansion prior to development of t-MDS/AML. This is especially relevant in the era of targeted therapies (such as those for IDH1, IDH2 and FLT3-mutated AML). Screening studies may be paired with clinical intervention trials using these agents with the goal of reducing the clonal expansion of mutated HSPCs prior to establishment of overt t-MDS/AML.
b. There is significant room for basic research aimed at understanding whether chemotherapy and radiation induce epigenetic modifications in HSPCs and hematopoietic nice cells to potentiate t-MDS/AML. There is also a great need for development of pharmacologic strategies to prevent chemotherapy and radiation-induced HSPC and hematopoietic mutagenesis and epigenetic dysregulation.

Conflicts of interest

The authors have no conflicts of interest to declare.

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