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Senescence in the bone marrow microenvironment: A driver in development of therapy-related myeloid neoplasms

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HIGHLIGHTS

- Cytotoxic therapy increases the risk for therapy-related myeloid neoplasms (t-MN).
- While HSC-intrinsic effects are crucial, t-MN is also dependent on extrinsic factors.
- Cytotoxic therapy drives senescence in the bone marrow microenvironment (BMME).
- Current studies support a role for BMME senescence in the development of t-MN.
- Targeting of senescent BMSCs may alleviate BM dysfunction and mitigate t-MN.

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ABSTRACT

Therapy-related myeloid neoplasms (t-MN) are a growing concern due to the continued use of cytotoxic therapies to treat malignancies. Cytotoxic therapies have been shown to drive therapy-induced senescence in normal tissues, including in the bone marrow microenvironment (BMME), which plays a crucial role in supporting normal hematopoiesis. This review examines recent work that focuses on the contribution of BMME senescence to t-MN pathogenesis, as well as offers a perspective on potential opportunities for therapeutic intervention.

1. Introduction

The last two decades have seen a remarkable expansion of novel, anti-neoplastic agents, including immunomodulators and targeted therapies, that have helped to reduce cancer mortality rates. However, for many malignant conditions, standard of care continues to involve the administration of cytotoxic chemotherapies (e.g., alkylating agents, platinum agents, antimetabolites, topoisomerase inhibitors, *Vinca* alkaloids, and other antineoplastics) and/or radiotherapy which induce cell death in tumor cells by exploiting their accelerated replication and metabolic differences compared to normal cells. Despite their ability to slow or ablate cancer progression, these agents lack complete selectivity for tumor cells, and their non-specific toxicity invariably affects healthy cells and disrupts normal tissue homeostasis, increasing the risk for morbidities and secondary malignancies [1,2]. For certain early-stage, non-metastatic cancers, off-target cytotoxicity can be prevented by local or targeted delivery. Unfortunately, this is often not possible for advanced, metastatic disease or systemic hematologic malignancies. Furthermore, the use of high-dose cytotoxic drugs (e.g., melphalan, cyclophosphamide) or radiotherapy as conditioning agents prior to autologous/allogeneic bone marrow transplant or chimeric antigen receptor (CAR)T-cell therapy in cancer patients requires these cytotoxic effects within normal cells in the bone marrow microenvironment (BMME) for successful engraftment; this profound impact on the BMME, the primary site of hematopoiesis, puts these patients at risk for secondary, therapy-related myeloid neoplasms (t-MNs) [3].

Myeloid neoplasms are clonal hematopoietic stem cell (HSC) disorders characterized by the expansion of abnormal hematopoietic cells and a paucity of normal hematopoiesis. While myeloid neoplasms can arise *de novo*, t-MNs arising following therapy (i.e., exposure to chemotherapy or radiotherapy for an antecedent condition [4]) represent a significant portion of newly diagnosed myeloid neoplasms. The incidence of t-MNs is rising and expected to continue to grow due to the increasing aging population, the increased use of DNA-damaging

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therapies in the treatment of other malignancies, and the overall improved survival following primary cancer diagnoses, which widens the window for development of secondary t-MNs [4–6]. Although much of the early t-MN research focused on HSC-intrinsic factors, recent studies have demonstrated that alterations in the BMME inflicted by cytotoxic therapies can play a crucial role in driving disease pathogenesis [7,8]. In this review, we will introduce myeloid neoplasms vs. t-MNs, examine recent findings as to how cellular senescence within the BMME can drive the initiation and progression of t-MNs, as well as discuss opportunities for therapeutic intervention by targeting senescent cells.

2. Myeloid neoplasms

Myeloid neoplasms are a spectrum of diseases including myelodysplastic syndrome (MDS) which may progress to acute myeloid leukemia (AML). MDS is characterized by dysfunctional and dysplastic hematopoiesis of one or more myeloid lineages resulting in abnormal myeloid maturation in the presence of less than 20 % bone marrow blasts. AML is characterized by expansion of bone marrow blasts (≥20 %) and an aggressive clinical course. Clinically, dysplasia and defective maturation manifest as cytopenia—low hemoglobin (anemia), low white blood cell count (leukopenia), and/or low platelet counts (thrombocytopenia)—imparting substantial morbidity and mortality. Despite tremendous research and progress over the last decade, virtually all MDS and a majority of AML remain uncured [9–12].

Overall, MDS and AML are rare diseases with reported incidence of 3–4 per 100,000 per year. The risk of MDS and AML increase substantially with age with the median age at diagnosis being 65–72 years. MDS and AML, therefore, are rare before the age of 40, with less than 5 % of newly diagnosed AML cases in patients younger than 40 years [13–16]. In addition, older age is associated with more aggressive disease and refractoriness to therapy. For example, in AML, response to chemotherapy is achieved in 60–85 % of patients younger than 60 years of age, translating to a cure rate of 35–40 %. In contrast, in patients 60 years or older, the response (40–60 %) and cure (5–15 %) rates are dramatically lower, culminating in extremely poor survival [11]. Combined, these observations underline that prevention and treatment of elderly MDS/AML are an urgent unmet clinical need.

More recently, myeloid neoplasms have been linked to premalignant, clonal hematopoietic disorders in otherwise healthy individuals, including clonal hematopoiesis of indeterminate potential (CHIP) and clonal cytopenia of undetermined significance (CCUS). Like MDS/AML, the burden of clonal hematopoiesis increases with age. CHIP is infrequent (~1 %) in individuals less than 50 years of age but is exhibited in 10 % of otherwise healthy individuals 65 years or older. The presence of CHIP puts patients at a 13-fold higher risk of a subsequent hematologic malignancy, suggesting that CHIP mutations may be the initiating clonal event. However, more than two-thirds of patients with AML have CHIP predating the diagnosis by years or decades, highlighting the essential role for premalignant clonal expansions in the pathogenesis of myeloid neoplasms [17].

Like MDS/AML, t-MN patients are older and, having received prior therapies, tend to be frail and less likely to be offered and/or receive intensive chemotherapies [4,18]. Median survival following t-MN diagnosis is approximately 1 year, with less than 10 % of patients surviving beyond 5 years [19]. Commonly used MDS/AML-directed therapies such as hypomethylating agents, the BCL2 inhibitor venetoclax, and allogeneic stem cell transplant do not meaningfully improve survival in t-MN [20–23]. While poor survival and aggressive disease of t-MN can be explained at least in part by the enrichment of leukemia with TP53-mutation and/or complex karyotype in t-MN—both of which are known to be associated with chemo-refractoriness and decreased duration of response, the role of clonal selection in the presence of extrinsic selection pressures such as chemotherapy or radiation is emerging [24–26]. In a study of lymphoma patients undergoing autologous stem cell transplant, approximately 30 % had a coexistent CH. The presence of CH predicted a 3.3-fold (14.1 % vs. 4.3 % at 10-years) risk of t-MN as well as a higher risk of death from cardiovascular diseases compared to those without CH. A similar pattern was observed in the setting of diverse solid malignancies – the presence of CH in presumptive leukemia driver genes (CH-PD) was associated with both a shorter survival and a subsequent increase in hematological neoplasms. This finding, however, is not universal—a similarly designed study in multiple myeloma, as well as a population-based study of lymphoma patients undergoing transplant, did not confirm these findings [27–30].

While the presence of CHIP is unequivocally associated with an increased risk of subsequent myeloid neoplasms, the proportion of individuals who harbor CHIP that do not progress to an overt myeloid neoplasm supports the contribution of additional non-genetic factors. Historically, the focus of study was primarily on HSCs. However, evidence suggests that t-MN is driven by the synergistic effects on HSCs and the BMME [7,8]. Among the contenders are non-genetic HSC-intrinsic factors (e.g., epigenetic) as well as extra-HSC factors such as immune editing and altered BMME selective pressure [4,31].

3. Senescence in the bone marrow microenvironment

Given that advanced age is a substantial risk factor for MDS/AML, there has been much interest in investigating how age-related changes in the BMME may drive disease initiation and progression [14]; to this end, the accumulation of senescent cells with aging has emerged as a potential mechanism by which selective pressures drive hematopoietic clonal expansion.

Cellular senescence is defined as a state of stable/irreversible growth-arrest induced by cell stress (e.g., DNA damage). While it was originally characterized through the study of human fibroblasts undergoing replicative exhaustion *in vitro*, senescence has since been shown to occur in many different cell types, including terminally differentiated and non-proliferative cells [32,33]. In addition to growth arrest, senescent cells are characterized by their senescence associated secretory phenotype (SASP) which reinforces the senescence growth arrest phenotype and recruits immune cells to clear damaged cells and tissue [34]. Through these functions, senescent cells play a crucial role in protecting against tumorigenesis, as well as in development and wound healing [33,35]. However, senescent cell accumulation with aging drives numerous age-related pathologies, including cancer [36]. The paradoxical effect of senescence to promote cancer progression is linked to SASP-mediated matrix remodeling, angiogenesis, inflammation, stem-like reversion, epithelial-to-mesenchymal transition (EMT), and immune suppression [37]. Indeed, senescence is now recognized as a hallmark of cancer [38].

Within the BMME, several cell lineages have been demonstrated to exhibit elevated senescence with aging. We have previously demonstrated an increase in senescent osteocytes, which are mesenchymal lineage cells that become embedded within bone late in osteoblast differentiation and serve as regulators of bone resorption and formation; we further demonstrated through genetic and pharmacologic models that the accumulation of senescent osteocytes contributes to age-related bone loss through effects on bone resorption and bone formation [39,40]. Others have shown that senescence within bone-forming osteoblasts and their mesenchymal stem cell (MSC) progenitors also contribute to decreased bone formation and increased bone marrow adiposity with aging [41–43].

MSCs committed to the osteoblast lineage are crucial for normal hematopoiesis [44–47], which is further demonstrated by reports that increased myelopoiesis in several mouse models of AML correlates with reduced osteoblasts [48–50], and activation of inflammation in osteoblasts via altered serotonin receptor signaling can facilitate the progression to AML [51]. Of interest, MDS patient-derived bone marrow stromal cells (BMSCs)– a heterogeneous stromal population that contains multipotent MSCs– have been shown to exhibit reduced

Table 1
Cancer chemotherapies with identified senescence-inducing action in nonmalignant tissues.

Drug/ Compound	Mechanism of action [79]	Cancer indications [79]	Senescence detected in non-malignant cell/ tissue	References
Alkylating agents				
Busulfan	DNA cross-linker/ alkylator	CML	Mouse bone marrow cells, human fetal lung fibroblasts (WI-38), rat bone marrow stromal cells, mouse ovarian tissue	Meng et al. 2003 [80], Probin et al. 2007 [81], Qi et al. 2012 [82], Li et al. 2023 [83]
Carboplatin	DNA cross-linker/ alkylator	Ovarian, germ cell, head and neck, SCLC, NSCLC, bladder, relapsed/ refractory acute leukemia, endometrial	Human peritoneal mesothelial cells and fibroblasts	Rutecki et al. 2024 [84]
Cisplatin	DNA cross-linker/ alkylator	Testicular, ovarian, bladder, head and neck, esophageal, SCLC, NSCLC, NHL, trophoblastic neoplasms	Mouse renal tubular epithelial cells, mouse pre-thecal cells, mouse pre-granulosa cells, human prostate fibroblasts, human ovarian fibroblasts, rat kidney fibroblasts (NRK-49F), mouse hepatocytes	Jin et al. 2019 [85], Li et al. 2019 [86], Marcozzi et al. 2019 [87], Pardella et al. 2022 [88], Yu et al. 2022 [89], Kumar et al. 2024 [90]
Cyclophosphamide	DNA cross-linker/ alkylator	Breast, NHL, CLL, ovarian, bone/soft tissue sarcoma, rhabdomyosarcoma, neuroblastoma, Wilm's tumor	Human fetal lung fibroblasts (TIG-7), mouse pre-thecal cells, mouse pre-granulosa cells, mouse granulosa cells, human granulosa cells, mouse ovarian tissue	Palaniyappan 2009 [91], Marcozzi et al. 2019 [87], Xu et al. 2023 [92], Li et al. 2023 [83]
Doxorubicin	DNA intercalator, DNA topoisomerase II inhibitor	Breast, Hodgkin's lymphoma, NHL, soft tissue sarcoma, ovarian, SCLC, NSCLC, bladder, thyroid, hepatoma, gastric, Wilm's tumor, neuroblastoma, ALL	Rat liver tissue, mouse bone marrow $CD45^{-}CD31^{-}$cells, mouse cardiac tissue, rat cardiomyocytes (H9c2), mouse liver tissue, mouse kidney tissue, human fetal lung fibroblasts (WI-38), human CD3 + T-cells, mouse hepatocytes	Aljobaily et al. 2020 [93], Yao et al. 2020 [94], Huang et al. 2021 [95], Sun et al. 2022 [96], Bientinesi et al. 2022 [97], Kasamatsu et al. 2023 [98], Kumar et al. 2024 [90]
Epirubicin	DNA intercalator, DNA topoisomerase II inhibitor	Breast, gastric	Human umbilical vein endothelial cells (hUVEC)	Eakin et al. 2020 [99]
Etoposide	DNA topoisomerase II inhibitor	Germ cell, SCLC, NSCLC, NHL, Hodgkin's lymphoma, gastric	Rat astrocytes, mouse hepatocytes	Bang et al. 2019 [100], Kumar et al. 2024 [90]
Irinotecan	DNA topoisomerase I inhibitor	Colorectal, NSCLC, SCLC	Human colonic fibroblasts, human colonic mucosa cells	Rudolf et al. 2012 [101]
Melphalan	DNA cross-linker/ alkylator	Multiple myeloma, breast, ovarian, polycythemia vera	Human CD3 + T-cells	Kasamatsu et al. 2023 [98]
Antimetabolites				
Azacitidine	DNA methyltransferase inhibitor	MDS, CML	Mouse hepatocytes	Kumar et al. 2024 [90]
Capecitabine	Thymidylate synthase inhibitor, DNA/RNA destabilizer	Breast, colorectal, colon, gastric, gastroesophageal, gastrointestinal	Human endothelial cells (EA.hy926)	Altieri et al. 2017 [102]
5-Fluorouracil	Thymidylate synthase inhibitor, DNA/RNA destabilizer	Colorectal, breast, anal, esophageal, gastric, pancreatic, head and neck, hepatoma, ovarian, basal cell cancer of skin, actinic keratosis	Human endothelial cells (EA.hy926), human intestinal epithelial cells (HIEC), human umbilical vein endothelial cells (hUVEC)	Altieri et al. 2017 [102], Xia et al. 2022 [103], Li et al. 2023 [104]
Other antineoplastic agents				
Arsenic trioxide	Various [105]	APL	Human bone marrow stromal cells, human articular chondrocytes (HC-a)	Cheng et al. 2011 [106], Chung et al. 2020 [107]
Hydroxyurea	Ribonucleotide reductase inhibitor	CML, polycythemia vera, AML, head and neck, ovarian	Human foreskin fibroblasts, human dental follicle stem cells, human peripheral blood mesenchymal stromal cells, human bone marrow stromal cells, mouse hepatocytes	Yeo et al. 2000 [108], Zhai et al. 2017 [109], Bjelica et al. 2019 [110], Kapor et al. 2021 [111], Kumar et al. 2024 [90]
Paclitaxel	Tubulin depolymerization inhibitor	Ovarian, breast, SCLC, NSCLC, head and neck, esophageal, prostate, bladder, Kaposi's sarcoma	Rat kidney fibroblasts (NRK-49F), human cerebromicrovascular endothelial cells (CMVEC), mouse cerebromicrovascular endothelial cells, human peritoneal mesothelial cells and fibroblasts	Yu et al. 2022 [89], Ahire et al. 2023 [112], Rutecki et al. 2024 [84]
Docetaxel	Tubulin depolymerization inhibitor	Breast, NSCLC, SCLC, prostate, gastric, head and neck, ovarian, bladder	Human prostate fibroblasts, human ovarian fibroblasts	Pardella et al. 2022 [88]
Methotrexate	Dihydrofolate reductase inhibitor, thymidylate synthase inhibitor	Breast, head and neck, osteogenic sarcoma, ALL, NHL, primary CNS lymphoma, meningeal leukemia, carcinomatous meningitis, bladder, gestational trophoblastic	Human granulosa cells (KGN)	Fu et al. 2021 [113]

Abbreviations: ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, APL = acute promyelocytic leukemia, CLL = chronic lymphocytic leukemia, CML = chronic myelogenous leukemia, MDS = myelodysplastic syndromes, NHL = non-Hodgkin's lymphoma, NSCLC = non-small cell lung cancer, SCLC = small cell lung cancer.

proliferation and osteogenic potential, along with reduced ability to support CD34 + HSCs in long-term culture, and BMSCs from these patients also exhibited senescence markers, including senescence-associated (SA) β-galactosidase activity, expression of the cell cycle checkpoint inhibitor CDKN2B, and altered global DNA methylation. This supports that senescence in the BMSC population may contribute to altered hematopoiesis in myeloid neoplasms [52]. These findings may also apply to other models of accelerated myeloid neoplasms. For

example, it was shown in a transplant model of *Nras*-mutant chronic myelomonocytic leukemia that disease progression was accelerated in older mice following BM transplant, with potential contributions from both aged and oncogene-driven BMSCs, both of which show proliferative defects and indications of senescence [53].

As discussed previously, cytotoxic therapies that induce DNA damage to ablate rapidly proliferating tumor cells are non-specific, and can invariably induce cellular senescence in non-tumor cells and tissues (Table 1) [1,2], leading to senescent cell accumulation that drives various aging pathologies. In bone, chemotherapy (mitotic inhibitors, anti-metabolites, topoisomerase inhibitors, etc.) and radiotherapy have been shown to damage osteoprogenitors, with consequent reduction in osteoblast number, increases in BM adiposity, and deterioration of bone architecture [3]. Notably, these changes mirror those seen in physiological aging, reinforcing how therapy-induced senescence presents as a form of accelerated aging which can drive cell dysfunction and bone loss [54]. The contribution of these altered BMSCs to t-MN development, however, remained largely unexplored until recently.

4. Senescence and t-MN

To evaluate the contribution of HSC-intrinsic vs. therapy-induced effects on stromal cells in the development of t-MN, Stoddart *et al.* developed a mouse model in which the bone marrow cells from donor mice exhibiting partial genetic components of del(5q) t-MN (*Egr1*$^{+/-}$, *Apc*$^{del/+}$) were subject to ex vivo *Trp53* knockdown (*EA-Trp53*) followed by transplantation into recipient mice. To model the impact of prior cytotoxic therapy on both the HSC and BMME compartments, the investigators employed the alkylating agent N-ethyl-N-nitrosurea (ENU) to donor mice prior to bone marrow harvest, as well as to recipient mice two–three weeks prior to transplant. Using this model in which both donors and recipients were administered ENU, along with control conditions in which only recipient or only donor mice received ENU, the authors demonstrated that cytotoxic effects in both the HSC population and the stromal BMME contributed to disease pathology [7]. The full MDS/AML pathology of the t-MN model required the HSC-intrinsic mutations, including *Egr1*$^{+/-}$, *Apc*$^{del/+}$, and *Trp53* knockdown; thus, these data support that synergistic chemotherapy-induced alterations in both the HSC and the BMME compartments are necessary to drive t-MN development.

In a separate set of experiments in which Trp53 was not knocked down (*Egr1*$^{+/-}$, *Apc*$^{del/+}$ donors), prior ENU treatment of recipient mice (or both recipient and donor mice) before transplant was sufficient to drive a t-MDS like phenotype. In contrast, treatment of *Egr1*$^{+/-}$, *Apc*$^{del/+}$ donor mice with ENU prior to bone marrow harvest and transplant, without ENU pre-treatment of recipients, was not sufficient to drive the MDS phenotype, suggesting a greater contribution of dysregulated BMME in driving t-MDS [7].

Consistent with previous studies that revealed senescence in myeloid neoplasm patient-derived BMSCs [52], ENU-treated mouse-derived BMSCs showed reduced DNA synthesis, enhanced SA-β-galactosidase activity, and elevated *CDKN1A/p21*, *CDKN2A/p16*, and *IL-6* (SASP factor). Gene set enrichment analysis confirmed enrichment of a SASP gene signature, highlighting a potential mechanistic role for BMSC SASP in driving t-MNs [7]. Interestingly, it has been shown previously that the SASP factors S100A8/9 secreted by BMSCs are sufficient to induce genotoxic stress in hematopoietic progenitors, and that this paracrine signaling axis is predictive of myelodysplastic evolution in patients [55]. On the other hand, it has been reported in a mouse model of clonal hematopoiesis that *Dnmt3a*-mutant hematopoietic stem/progenitor cells exhibit elevated pro-inflammatory cytokines that are sufficient to induce senescent features in primary BMSCs [56]. Additionally, RAB27B overexpression in human AML cell lines promotes senescence in BMSCs through enhanced release of exosomes [57]. Taken together, this suggests that clonal HSCs promote paracrine senescence in adjacent bone marrow stroma, resulting in a positive feedback loop that ultimately reinforces BMSC senescence and drives disease progression. This could explain the synergism of ENU-treated HSCs and BMME in driving MN development in the *EA-Trp53* model [7].

Kutyna *et al.* built off previous work to specifically examine patient BMSCs in the context of t-MN. In their study, the effects of cytotoxic therapy were isolated by a well-controlled selection of cohorts: 1) t-MN following chemotherapy for prior cancer, 2) primary myeloid neoplasm without previous cancer, 3) primary myeloid neoplasm with previous cancer and no chemotherapy, and 4) healthy controls. Consistent with previous studies, BMSCs from myeloid neoplasm cohorts were shown to have aberrant morphology, defective proliferation, and reduced HSC-supportive capacity, along with increased SA-β-galactosidase activity and SASP production. These effects were significantly magnified in t-MN, with significantly increased senescence even in comparison to primary MN. GSEA for multiple senescence related gene sets confirmed a distinct senescence profile compared to all other myeloid neoplasm cohorts. This suggests that exposure to cytotoxic therapy generates a very different senescent profile as compared to ones driven by age or by primary MN/other cancers. Finally, analysis of serial t-MN patient samples taken at diagnosis of primary disease, after chemotherapy, and at diagnosis of t-MN confirmed the induction of dysregulated features in BMSCs following chemotherapy consistent with previous studies [8].

To date, there has not been an extensive evaluation of senescence in other BMME cell types that may contribute to *de novo* or therapy-related myeloid neoplasms. BM adipocytes, the fat-storing cells within the BMSC lineage, have been shown to be metabolically altered by AML blasts, ultimately allowing them to transfer fatty acids to the tumor cells to support their survival and proliferation [58]. Adipocytes have also been demonstrated to attract acute lymphoblastic leukemia (ALL) cells and protect them from chemotherapeutic agents daunorubicin and vincristine [59]. Arteriolar endothelial cells, which constitute the vasculature lining, have been shown to significantly expand in a mouse model of AML, suggesting tumor-driven angiogenesis to support further growth [60]. BM fibroblasts, which function primarily in the production and remodeling of extracellular matrix as well as support the long-term maintenance of HSCs/HSPCs, were shown to have reduced hematopoietic supportive capacity in the presence of AML cells [61]. Whether senescence in these non-hematopoietic cell types contribute to the specific development of t-MN following cytotoxic therapy, however, is vastly underexplored and deserving of further scrutiny.

5. Senescent cell targeting via senotherapeutics: Opportunities for intervention

Given the potential causal role for BMME senescence to drive clonal evolution that contributes to myeloid neoplasms, particularly in patients previously exposed to cytotoxic therapy, the natural question becomes whether pharmacologic ablation of senescent cells may be used therapeutically to prevent myeloid neoplasms in these patients. To this end, Drs. James Kirkland and Tamar Tchkonia have led the effort to identify pharmacologic agents that interfere with senescent cell anti-apoptosis pathways (SCAPs) to induce senolysis. By ablating senescent cells, these agents, dubbed “senolytics,” combat the pathogenic effects of senescent cell accumulation with aging [62].

The first proposed senolytic therapy discovered in the Kirkland-Tchkonia lab combined Dasatinib and Quercetin (D + Q), each of which induced senolysis of specific cell types as single agents through inhibition of SRC kinase/EFNB1/3 and PI3K, respectively; together D + Q exhibit a synergistic effect to activate senolysis across cell types [62]. D + Q has now been demonstrated in numerous animal models to reduce senescent cell burden across tissues, alleviate physical and cognitive dysfunction, and prevent age-related bone loss in naturally aged mice [40,63,64]. These effects have also been extended to humans in a phase I trial in which D + Q reducing senescent cell burden in patients with diabetic kidney disease [65]. D + Q has also been shown to reduce senescent cell burden following cytotoxic therapy, with D + Q reducing

Table 2
Natural, approved, or clinical trial stage agents with known senotherapeutic activity.

Drug/compound	Mechanism of action	Clinical status	References
Senolytics			
Dasatinib	Pan-receptor tyrosine kinase inhibitor	Phase I/II for Alzheimer's Disease (NCT04063124), Phase II for Alzheimer's Disease (NCT04685590), Phase II for skeletal health (NCT04313634), Phase II for frailty in adult survivors of childhood cancer (NCT04733534), Phase II for chronic kidney disease (NCT02848131), Phase II/III for obesity (NCT05653258)	Zhu et al. 2015 [62]
Quercetin	Numerous (BCL-2, PI3K inhibitor)	see Dasatinib, natural flavonoid	Zhu et al. 2015 [62]
Fisetin	PI3K/AKT/mTOR inhibitor	Phase I/II for femoroacetabular impingement and labral tear (NCT05025956), Phase I/II for vascular health (NCT06133634), Phase I/II for osteoarthritis (NCT04210986, NCT04815902,), Phase II for carpal tunnel syndrome (NCT05416515), Phase II for skeletal health (NCT04313634), Phase II for frailty in adult survivors of childhood cancer (NCT04733534), Phase II for frailty in older adults (NCT03430037, NCT03675724), Phase II for sepsis (NCT05758246), Phase II for frailty in breast cancer survivors (NCT05595499, NCT06113016)	Zhu et al. 2017 [69]
ABT-263 (Navitoclax)	Bcl-2 family inhibitor	Various for cancer	Chang et al. 2016 [114]
UBX0101	p53/MDM2 inhibitor	Phase II for osteoarthritis of the knee (NCT04129944, NCT04229225)	Chin et al. 2023 [115]
UBX1325	BCL-xL inhibitor	Phase I/II for diabetic macular edema (NCT04537884, NCT04857996, NCT05275205)	Tsuruda et al. 2021 [116]
Panobinostat	HDAC inhibitor	Approved for multiple myeloma	Samaraweera et al. 2017 [117]
Azithromycin	Autophagy/aerobic glycolysis inducer	Phase IV for lymphocytic bronchitis/bronchiolitis (NCT01109160), Phase II for pulmonary tuberculosis (NCT03160638), Phase IV for blepharitis (NCT00629590), Phase II for type 1 diabetes (NCT03682640), Phase III in chronic obstructive pulmonary disease (NCT01071161)	Ozsvari et al. 2018 [118]
Roxithromycin	Autophagy/aerobic glycolysis inducer	Phase IV for rheumatoid arthritis (NCT00439062), Phase III for bronchiectasis (NCT04122040),	Ozsvari et al. 2018 [118]
Procyanidin C1	Mitochondrial destabilizer, pro-apoptotic factor inducer	Natural antioxidant	Xu et al. 2021 [119]
Senomorphics			
Metformin	IKK, NF-κB inhibitor	Approved for type 2 diabetes	Moiseeva et al. 2013 [120]
Apigenin	NF-κB p65 subunit, IκB inhibitor	Natural flavonoid	Lim et al. 2015 [121]
Kaempferol	NF-κB p65 subunit, IκB inhibitor	Natural flavonoid	Lim et al. 2015 [121]
Rapamycin	mTOR inhibitor	Approved for immunosuppression	Herranz et al. 2015 [122], Laberge et al. 2015 [123]
RAD001	mTOR inhibitor	Approved for tuberous sclerosis complex-associated diseases	Zhang et al. 2018 [124]
Ruxolitinib	JAK inhibitor	Approved for graft-versus-host disease	Xu et al. 2015 [77]
NDGA	HSP90 inhibitor	Natural antioxidant	Harrison et al. 2014 [125]
Loperamide	HSP90 inhibitor	Approved for diarrhea	Fuhrmann-Stroissnigg et al. 2017 [126]
Cortisol	Suppresion of IL-6 secretion	Steroid hormone	Laberge et al. 2012 [127]
Anakinra	IL-1R inhibitor	Approved for rheumatoid arthritis	Ding et al. 2023 [128]
Canakinumab	IL-1β inhibitor	Approved for cryopyrin-associated periodic syndromes	Kuemmerle-Deschner et al. 2011 [129]
Rilonacept	IL-1α, IL-1β inhibitor	Approved for cryopyrin-associated periodic syndromes	Hoffman et al. 2008 [130]
Etanercept	TNF inhibitor	Approved for autoimmune diseases	Klareskog et al. 2004 [131]
Infliximab	TNF inhibitor	Approved for autoimmune diseases	Vlachogiannis et al. 2023 [132]
Tocilizumab	IL-6R inhibitor	Approved for autoimmune diseases	Emery et al. 2008 [133]
Siltuximab	IL-6 inhibitor	Approved for multicentric Castleman disease	van Rhee et al. 2014 [134]

Clinical trial information obtained from publicly available records on ClinicalTrials.gov.

BM adiposity and restoring bone architecture in an *in vivo* model of focal radiation [66,67].

More specifically to t-MN, Kutyna *et al.* demonstrated that D + Q treatment could rescue stromal cell differentiation potential in t-MN BMSCs, suggesting efficacy in restoring normal stromal function within the therapy-altered BMME [8]. Thus, senolytics may be effective in the mitigation of t-MN as the latter part of a "one-two punch" approach following cytotoxic therapy.

Another class of senolytic agents targets Bcl family proteins that are upregulated in senescent cells. Hellmich *et al.* demonstrated that treatment of aged mice with the ABT-263 (Navitoclax), which inhibits both BCL2 and BCLxL, reduced senescent BMSCs and restored hematopoietic progenitor cell metabolism and ability to properly expand in response to infection, providing evidence that selective elimination of senescent BMSCs can also have indirect effects on HSC normal function [68]. Several additional BCLxL inhibitors have been identified that may have improved safety profiles due to selective inhibition of BCLxL [69].

Critically, many of the currently identified senolytics are natural compounds (e.g., quercetin, fisetin, procyanidin C1) or have prior FDA approval for other indications (e.g. Dasatinib), allowing an accelerated path to the clinic. Indeed, this is reflected in several planned and ongoing trials testing whether senolytics can alleviate age-related disease pathologies (Table 2) [70]. Numerous additional candidate senolytics are currently being tested in pre-clinical *in vitro* and *in vivo* models.

Of note, new modalities are being explored to allow greater tissue and cell specificity, thus limiting potential off-target toxicity and enhancing pharmacokinetics. A recent example is the use of small extracellular vesicles tagged with the bone-targeting peptide $(AspSerSer)_6$ to deliver a galactose-modified microtubulin inhibitor to senescent osteocytes, which subsequently cleave and activate the payload as a consequence of their increased SA β-galactosidase activity [71]. This bone-targeted approach has also been demonstrated with $(DSS)_6$ peptide-tagged liposomes loaded with Quercetin [72]. Another route being pursued for senescent cell ablation is immune mediated targeting of membrane proteins expressed by senescent cells, such as GPNMB [73], uPAR [74], and CD153 [75].

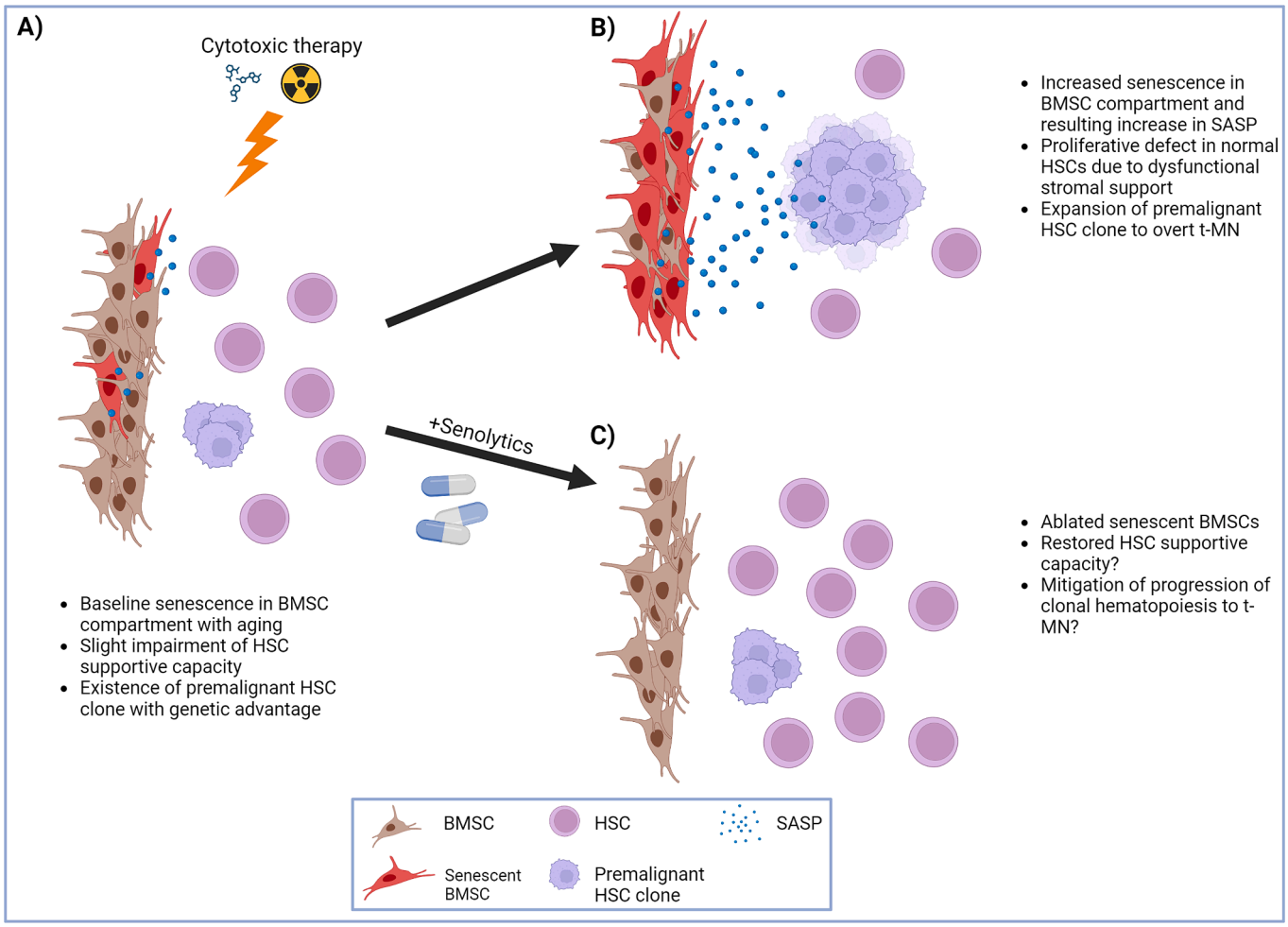

Fig. 1. Diagram of t-MN pathogenesis driven by therapy-induced senescence in the bone marrow microenvironment. State of bone marrow microenvironment (A) immediately prior to cytotoxic therapy, (B) after cytotoxic therapy without intervention, and (C) after cytotoxic therapy plus intervention with senolytics. Abbreviations: BMSC: bone marrow stromal cell, HSC: hematopoietic stem cell, SASP: senescence-associated secretory phenotype, t-MN: therapy-related myeloid neoplasm. Created with BioRender.com.

In addition to senescent cell ablation, several pharmacologic agents are available to modulate senescent cell function via the SASP. These agents are dubbed "senomorphics" and act by targeting various SASP pathways, such as NF-κB, mTOR, and p38-MAPK, or interfering directly with known SASP factors, such as IL-6 and TNF and/or their receptor signaling complexes. Thus, senomorphics block the pathological influence of senescent cells on their local microenvironment without inducing senescent cell clearance [76]. Currently identified senomorphics include many natural compounds or agents with prior FDA approval for other indications (Table 2). One example is the JAK inhibitor, ruxolitinib, a drug approved for myelofibrosis and other inflammatory conditions, which has been shown to suppress the pro-inflammatory SASP from senescent human primary preadipocytes and human vascular endothelial cells (hUVEC); treatment of aged mice with ruxolitinib reduced systemic inflammation and alleviated frailty [77].

With the rapid expansion and progression of senotherapeutic development over the last decade, there is much opportunity to explore treatment for senescence-associated diseases, including t-MN. However, additional research is required to determine the appropriate senotherapeutic drugs and optimize the timing of intervention.

6. Conclusion

It is becoming increasingly clear that myeloid neoplasms are diseases of multifactorial origin, and that the BMME is a critical driver of pathogenesis. Particularly, therapy-induced senescent BMSCs appear to play a significant role in the development of t-MN and represent a compelling target for therapeutic intervention with senolytics. Ablation of senescence in the post-therapy BMME may prevent senescence-induced BMSC dysfunction, restoring support of normal HSCs and mitigating the expansion of premalignant HSC clones that exhibit a selective advantage conferred by enabling mutations (Fig. 1).

Additional research is needed to define the specific contributions of therapy-induced senescence to t-MN pathogenesis, particularly as demonstrated by the profiling performed by Kutyna *et al.,* which demonstrated distinct senescence profiles in t-MN and primary myeloid neoplasms [8]. Furthermore, it is of pressing interest to examine the remodeling driven by various other primary malignancies and their standard of care treatment regimens to determine their specific impact on t-MN, as we have previously explored in the context of the immunome in multiple myeloma undergoing autologous stem cell transplant [78]. Given the current landscape of treatment for primary malignancies, including the expanding use of CAR based strategies, t-MN will continue to pose a substantial risk to patients. Targeting senescence may represent a valid strategy to work within current treatment framework and to block the negative effects of cytotoxic therapy on the BMME to drive secondary malignancy.

CRediT authorship contribution statement

Angelo Jose Guilatco: Writing – review & editing, Writing – original draft, Conceptualization. **Mithun Vinod Shah:** Writing – original draft, Conceptualization. **Megan Moore Weivoda:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Angelo Jose Guilatco reports financial support was provided by National Cancer Institute. Angelo Jose Guilatco reports financial support was provided by the University of Michigan. Megan Moore Weivoda reports financial support was provided by National Institute on Aging. Megan Moore Weivoda reports a relationship with National Institute of Arthritis and Musculoskeletal and Skin Diseases that includes: funding grants. Mithun Vinod Shah reports a relationship with AbbVie Inc that includes: funding grants. Mithun Vinod Shah reports a relationship with Bristol Myers Squibb Co that includes: funding grants. Mithun Vinod Shah reports a relationship with Astellas Pharma US Inc that includes: funding grants. Mithun Vinod Shah reports a relationship with MRKR Therapeutics that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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