

Advancing the treatment of myelodysplastic syndrome: a focus on immunotherapy and nanotherapy

Yaoyao Wang^{1,2}, Ting Yang^{1,2,*}

¹ Department of Hematology, National Regional Medical Center, Binhai Campus of the First Affiliated Hospital, Fujian Medical University, Fuzhou, Fujian 350212, China;

² The Second Department of Hematology, the First Affiliated Hospital, Fujian Medical University, Fuzhou, Fujian 350005, China.

ABSTRACT

Myelodysplastic syndrome (MDS) is a heterogeneous clonal disorder of hematopoietic stem cells (HSCs), characterized by abnormal differentiation and maturation of myeloid cells. Current treatment options for MDS mainly include conventional methods such as supportive treatment, chemotherapy and hematopoietic stem cell transplantation (HSCT). Although these therapies can alleviate symptoms to some extent, numerous limitations persist. In recent years, immunotherapy has emerged as a promising method for MDS patients. By activating or regulating the body's own immune system to target and eliminate abnormal cells, this therapy shows great potential for clinical application. In addition, nanotherapy, as an emerging technology, also shows broad development prospects in the field of MDS.

Keywords: myelodysplastic syndrome, T cell-based therapy, immune checkpoint inhibitor, chimeric antigen receptor T cell therapy, nano immunotherapy

INTRODUCTION

Myelodysplastic syndrome (MDS) comprises a group of heterogeneous clonal hematopoietic stem cell (HSC) neoplasms, defined by ineffective hematopoiesis, refractory cytopenias, and a risk of progression to acute myeloid leukemia (AML) of up to 40%. Primarily affecting the elderly, MDS leads to mortality predominantly *via* infection or bleeding caused by cytopenias, highlighting a significant unmet therapeutic need^[1].

Current MDS management relies on risk stratification (IPSS-R/IPSS-M). Low-risk MDS is

managed with supportive care or anemia-directed therapies (*e.g.*, luspatercept), while high-risk MDS receives first-line treatment with hypomethylating agents (HMAs), such as azacitidine (AZA)^[2–3]. However, HMA monotherapy achieves only a 30%–40% response rate in high-risk MDS, with a median overall survival (OS) of 15 to 24 months^[4]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT), the sole curative option, is limited by factors including age (> 65 years), comorbidities, and donor scarcity. Consequently, patients with HMA-refractory disease face a dismal median OS of less than 6 months^[5].

Dysregulation of the immune microenvironment is

*Corresponding to: Ting Yang, Department of Hematology, National Regional Medical Center, Binhai Campus of the First Affiliated Hospital, Fujian Medical University, 999 Huashan Road, Wansha Village, Zhanggang Street, Changle District, Fuzhou, Fujian 350212, China. E-mail: yang.hopeting@gmail.com.

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central to MDS pathogenesis, underscoring the limitations of current therapies. Chronic inflammation remodels the bone marrow microenvironment (BMM), where mesenchymal stromal cells exhibit increased secretion of transforming growth factor-beta (TGF- β) and programmed death ligand 1 (PD-L1), and myeloid-derived suppressor cells (MDSCs) drive T-cell exhaustion. Together, these mechanisms impair normal hematopoiesis and facilitate the clonal expansion of malignant cells^[6].

Emerging therapies are addressing the unmet needs in MDS. The combination of bexmarilimab (a Clev-1 inhibitor) and AZA has achieved an 80% response rate and a median OS of 13.4 months in relapsed and/or refractory (R/R) patients. Advancements in nanobiotechnology further enhance treatment efficacy: modular nanocarriers have been shown to increase drug accumulation in the bone marrow eightfold, thereby improving HMA targeting and reducing toxicity^[7].

Nanobiotechnology, a pivotal subfield of nanotechnology in biology and biotechnology, employs nanomaterials and biomaterials to create multi-functional platforms that enhance anticancer immunity by stimulating robust immune responses^[8]. Its applications in oncology encompass drug delivery, therapeutic intervention, and cutting-edge treatment modalities^[9]. Nano-drug carriers enhance targeting efficiency, reduce side effects, and overcome poor blood-brain barrier penetration, offering new potential to improve patient outcomes^[10].

MDS-RELATED IMMUNE DISORDERS

Immune dysregulation stands as a central driver in the pathogenesis of MDS, contributing not only to ineffective hematopoiesis but also to disease progression and transformation to AML^[11–12]. Within the MDS BMM, both innate and adaptive immune systems exhibit functional abnormalities, accompanied by dysregulated cytokine and chemokine signaling (*Fig. 1*). These collective perturbations foster an immunosuppressive niche that enables the evasion of malignant clones, making the characterization of these immune alterations critical for the development of targeted immunotherapeutic strategies^[13–14].

T cell-mediated adaptive immunity in MDS exhibits subtype-specific abnormalities that impact both prognosis and treatment response. MDS-derived monocytes drive CD4⁺ T cell polarization toward the T helper 2 (Th2) phenotype, disrupting the Th1/Th2 balance^[15]. Cytokines such as interleukin (IL)-4 and

IL-10, secreted by Th2 cells, weaken Th1-mediated cellular immune responses, which is evidenced by reduced secretion of interferon-gamma (IFN- γ) and tumor necrosis factor-alpha (TNF- α), thereby compromising the clearance of malignant clones^[16]. Th1 and Th2 are specialized CD4⁺ T cell lineages: Th1 differentiation is driven by T-bet (secreting IFN- γ , TNF, and granulocyte-macrophage colony-stimulating factor (GM-CSF) for cellular immunity); Th2 differentiation is governed by GATA binding protein 3 (GATA3) (secreting IL-4, IL-5, and IL-13 for humoral immunity, while IL-10 is not Th2-specific). Under physiological conditions, the Th1/Th2 balance is maintained by T-bet/GATA3 crosstalk; however, in MDS, Th2 polarization predominates, partly due to monocyte-mediated skewing of naïve T cells toward the Th2 lineage.

Regulatory T cells (Tregs) exhibit context-dependent functions in MDS. In low-risk MDS, expanded bone marrow Tregs impair early anti-tumor immunity, whereas increased Th17 cells—likely driven by upregulated ROR γ t—foster a pro-inflammatory environment that exacerbates ineffective hematopoiesis. Thus, although the absolute Th17/Treg ratio may be lower in low-risk MDS, the critical alteration lies in the relative imbalance marked by an increase in Th17 cells alongside a reduction in Treg infiltration, which fundamentally disrupts immune homeostasis. In high-risk MDS, substantial Treg accumulation directly suppresses effector T cell function. These Tregs actively inhibit CD8⁺ T cells through multiple mechanisms, including secretion of IL-10 and TGF- β , metabolic interference, and cell-contact-mediated suppression^[17–19], thereby fostering an immunosuppressive environment conducive to malignant clone expansion.

In high-risk MDS, CD8⁺ cytotoxic T lymphocytes (CTLs) undergo exhaustion driven by chronic antigen stimulation and persistent inflammatory signaling within the BMM. This exhaustion is characterized by elevated expression of inhibitory receptors such as programmed death protein 1 (PD-1) and T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), along with a substantial decline in cytotoxic function, including reduced secretion of perforin and granzyme, as well as impaired cytokine production. Collectively, these changes result in compromised anti-tumor immunity^[20]. Concurrently, the PD-1 ligand (PD-L1) is upregulated on tumor cells. This co-expression of PD-1 on CD8⁺ T cells and PD-L1 on myeloid cells weakens T cell receptor (TCR)-mediated cytotoxicity, facilitating tumor immune evasion.

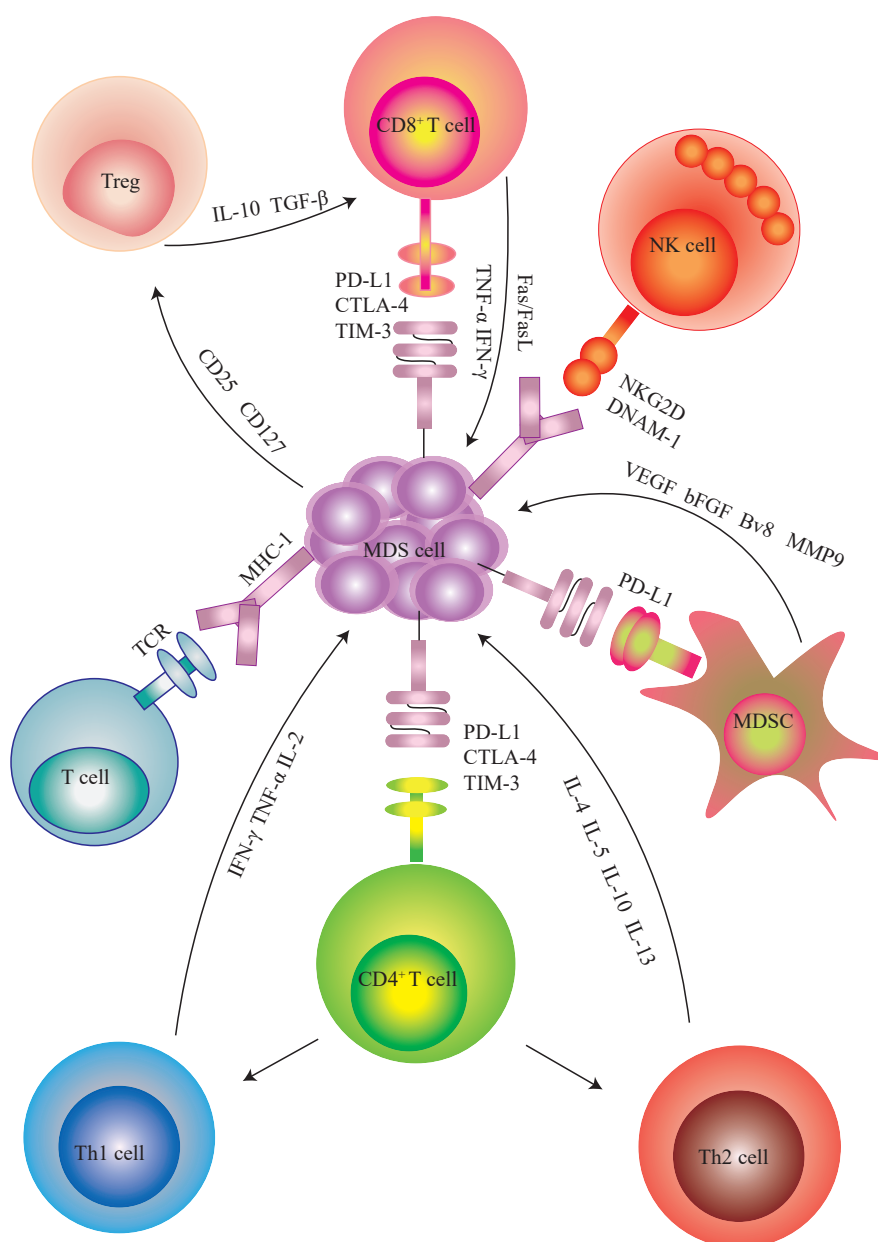


Fig. 1 Immune disorders in the pathogenesis of MDS. The pathogenesis of MDS involves a complex process of immune dysregulation, which is characterized by the dysfunction of various immune cells such as T cells, NK cells and DCs, accompanied by the imbalance of cytokines and chemokines, which further aggravates the immunosuppressive state of the body. MDS: myelodysplastic syndrome; NK cells: natural killer cells; DCs: dendritic cells; Treg: regulatory T cell; IL-10: interleukin-10; TGF- β : transforming growth factor-beta; PD-L1: programmed death ligand 1; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; TIM-3: T cell immunoglobulin and mucin domain-containing protein 3; TNF- α : tumor necrosis factor-alpha; IFN- γ : interferon-gamma; VEGF: vascular endothelial growth factor; bFGF: basic fibroblast growth factor; MMP9: matrix metalloproteinase 9; MHC-I: major histocompatibility complex class I; TCR: T cell receptor; MDSC: myeloid-derived suppressor cell; Th1: T helper 1.

Key mediators of clonal surveillance, which are defective in innate immune cells, contribute to the early escape of malignant clones in MDS. Natural killer (NK) cells, critical innate effectors responsible for eliminating abnormal hematopoietic cells, exhibit progressive functional decline in MDS. Patients with high-risk MDS show downregulated expression of activating receptors (*e.g.*, NKG2D, DNAM-1) on NK

cells, which disrupts the balance between activating and inhibitory signals and significantly reduces cytotoxicity against CD34⁺ MDS blasts^[21–22]. NK cell dysfunction is already apparent in pre-malignant conditions such as clonal cytopenia of undetermined significance (CCUS), establishing a foundation for subsequent disease progression. MDSCs are significantly expanded in the bone marrow of MDS

patients and mediate immunosuppression through multiple mechanisms. These include the release of reactive oxygen species (ROS) and nitric oxide (NO) to impair T cell function, depletion of essential amino acids such as tryptophan to inhibit T cell proliferation, and high expression of PD-L1 that binds to PD-1 on hematopoietic stem and progenitor cells (HSPCs), exacerbating hematopoietic cell apoptosis and ineffective hematopoiesis^[23–24]. Additionally, MDSCs secrete factors such as vascular endothelial growth factor (VEGF) and matrix metalloproteinase 9 (MMP9) to remodel the BMM, further promoting the expansion of malignant clones.

Dendritic cells (DCs), which serve as central antigen-presenting cells (APCs) bridging innate and adaptive immunity, exhibit functional impairments that disrupt immune crosstalk in MDS. Both mature and immature DC subsets are significantly reduced in the bone marrow of MDS patients and exhibit diminished antigen-presenting capacity, resulting in ineffective activation of naïve T cells. In low-risk MDS, DCs erroneously present antigens derived from apoptotic normal HSCs, inducing autoreactive T cells to target and eliminate normal HSCs, thereby promoting the dominance of malignant clones. In high-risk MDS, DC numbers declines further, impairing the initiation of immune responses and exacerbating the immunosuppressive state.

MDS-RELATED IMMUNOTHERAPY

Currently, MDS treatment mainly involves supportive care or HMA-based therapy. Allo-HSCT is the only potentially curative option, eliminating MDS clones through its graft-versus-tumor (GVT) effect. However, this approach is limited to approximately 15% of young, fit patients due to its high toxicity^[10–11]. HMA constitute the first-line treatment for transplant-ineligible patients with intermediate-to-high-risk or transfusion-dependent MDS^[3]. HMA failure leads to poor prognosis (median OS: 5.6 months) and there is no established standard for subsequent therapy, while immunotherapy shows promise for improved remission rates and survival outcomes^[18].

T cell-based therapies

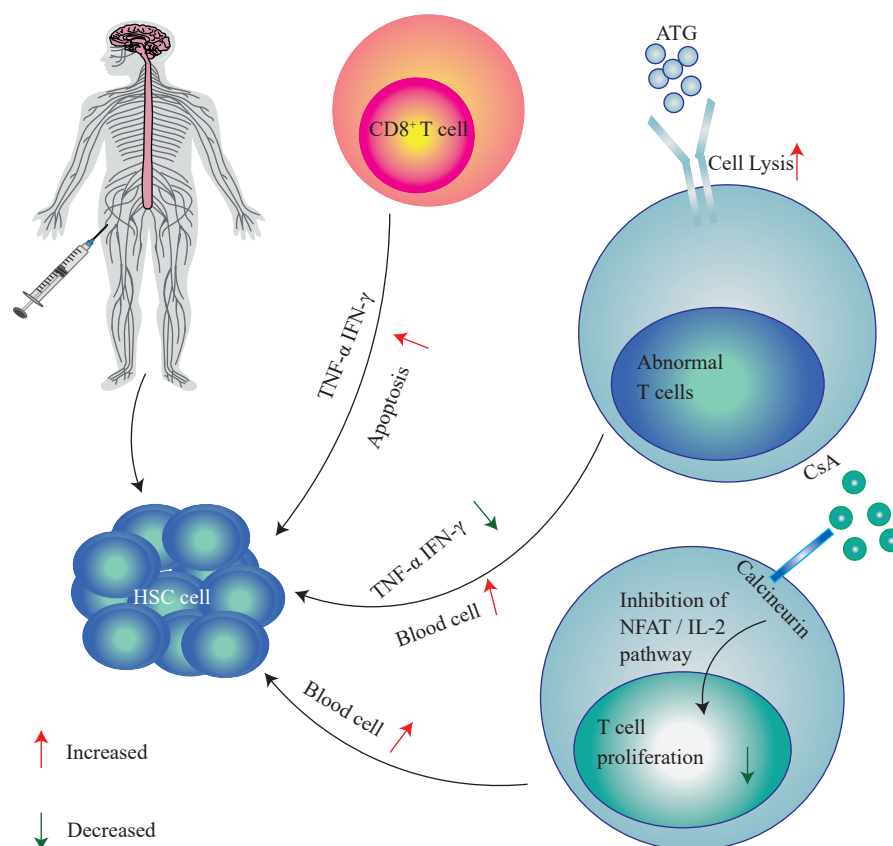
The central role of T cells in MDS pathogenesis is underscored by the efficacy of T cell-targeted therapies such as antithymocyte globulin (ATG) and cyclosporine (CsA), particularly in refractory anemia (**Fig. 2**). ATG, a polyclonal IgG preparation derived from rabbits or horses, induces complement-mediated lysis or apoptosis of T cells, whereas CsA inhibits calcineurin. The combination of these agents has

demonstrated a 51% response rate in low-risk MDS, reflecting their immunomodulatory effects and broad therapeutic benefit across MDS subtypes^[1,3,25]. Hematologic responses following CsA and ATG treatment are characterized by gradual yet sustained improvements in blood cell counts. Patients typically begin to reduce or discontinue red blood cell (RBC) and platelet transfusions approximately 6 weeks after treatment initiation, with optimal outcomes observed within 3 to 6 months. In a study of 256 selected patients, predominantly with low-risk MDS, ATG treatment yielded responses in half of the patients, including complete remission (CR) in 11.2% of cases. In international studies, horse ATG (h-ATG) combined with CsA has been shown to be more effective than rabbit-derived ATG or CsA-free ATG.

Immune checkpoint inhibitors

Immune checkpoint inhibitors block inhibitory signals to restore the immune system's ability to target and eliminate cancer cells, demonstrating efficacy in numerous solid tumors (**Fig. 3**)^[26]. Recently, their efficacy has also been evaluated in clinical trials for MDS and AML^[27]. Compared with healthy individuals, T cells from patients with refractory MDS exhibit significantly higher expression of immunosuppressive receptors such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), TIM-3, PD-1, and inducible T-cell co-stimulator (ICOS). Therapies targeting the PD-1, PD-L1, or CTLA-4 pathways have shown a certain degree of efficacy in the treatment of MDS^[28–29]. Clinical trials of immune checkpoint inhibitors in MDS have demonstrated limited efficacy and considerable toxicity, as outlined in **Table 1**.

The PD-1/PD-L1 signaling pathway primarily modulates T cell activity by inhibiting TCR signaling after T cells exit the circulation and infiltrate tumor tissues, thereby playing a crucial role in maintaining peripheral tolerance. The efficacy of PD-1/PD-L1 inhibitors, such as pembrolizumab, is under investigation for new indications or combination regimens. Several monoclonal antibody drugs targeting PD-1/PD-L1 are now available on the market. In an early trial involving 28 MDS patients refractory to epigenetic therapy (93% with intermediate- or high-risk IPSS), pembrolizumab monotherapy demonstrated a 6-month OS rate of 49%, with OS rates of 29% and 22% observed in the high- and low-risk IPSS groups, respectively^[29–30]. The intermediate-1 risk group achieved a 1-year OS rate of 87%. The overall response rate (ORR) for ipilimumab monotherapy in HMA-resistant MDS was approximately 3.4% (clinically estimated as 4%) in a multicenter phase Ib trial. No ORR data are available for pembrolizumab in



this specific HMA-resistant MDS population. A study evaluated the phase II clinical efficacy of AZA combined with pembrolizumab in patients with intermediate-risk-1 or higher-risk MDS^[28]. In a nivolumab trial, treatment-naïve patients ($n = 17$) exhibited a 76% ORR, compared to 25% in patients who had failed prior HMA therapy ($n = 20$). The drug was evaluated for treating MDS relapse post-HSCT^[31–33]. A study reported that a total of 35 patients across two cohorts were treated with either nivolumab monotherapy or in combination with HMA. In the R/R MDS group ($n = 15$), nivolumab monotherapy demonstrated poor efficacy, leading to early trial closure, and was associated with frequent grade ≥ 3 adverse events (AEs). Conversely, the frontline cohort ($n = 20$) treated with nivolumab plus AZA achieved a 50% rate of CR/CR with incomplete platelet recovery (CRp). Another study explored nivolumab combined with ipilimumab (with or without AZA) in MDS patients. The frontline cohort ($n = 15$) showed a 67% ORR, including 5 CR and 5 hematologic improvements (HI), whereas the HMA-failure cohort ($n = 11$) achieved a 36% ORR, including 1 CR, 1 CR

with incomplete count recovery (CRI), and 2 HI^[34]. A subsequent phase II trial evaluated durvalumab plus AZA versus AZA monotherapy in 84 untreated high-risk MDS patients. No statistically significant differences were observed in ORR (61.9% vs. 47.6%, $P = 0.18$) or median OS (11.6 vs. 16.7 months, $P = 0.74$). Only the marrow complete remission (mCR) rate was numerically higher in the combination arm (35.7% vs. 19.0%). The combination arm experienced more grade 3–4 hematologic AEs (89.5% vs. 68.3%) and 7 durvalumab-related immune-mediated AEs. AZA increased PD-L1 expression on bone marrow granulocytes/monocytes (not blasts) in both arms, and patients with TP53 mutations exhibited lower ORR compared to wild-type individuals (41% vs. 61%)^[35–36]. In a phase Ib trial, the addition of atezolizumab to AZA did not significantly improve ORR, progression-free survival (PFS), or OS compared to AZA alone in high-risk MDS, despite acceptable tolerability and comparable ORR (47% in both groups). This trial enrolled older MDS patients stratified by treatment history but was terminated early due to high rates of grade ≥ 3 AEs (57%–71%)

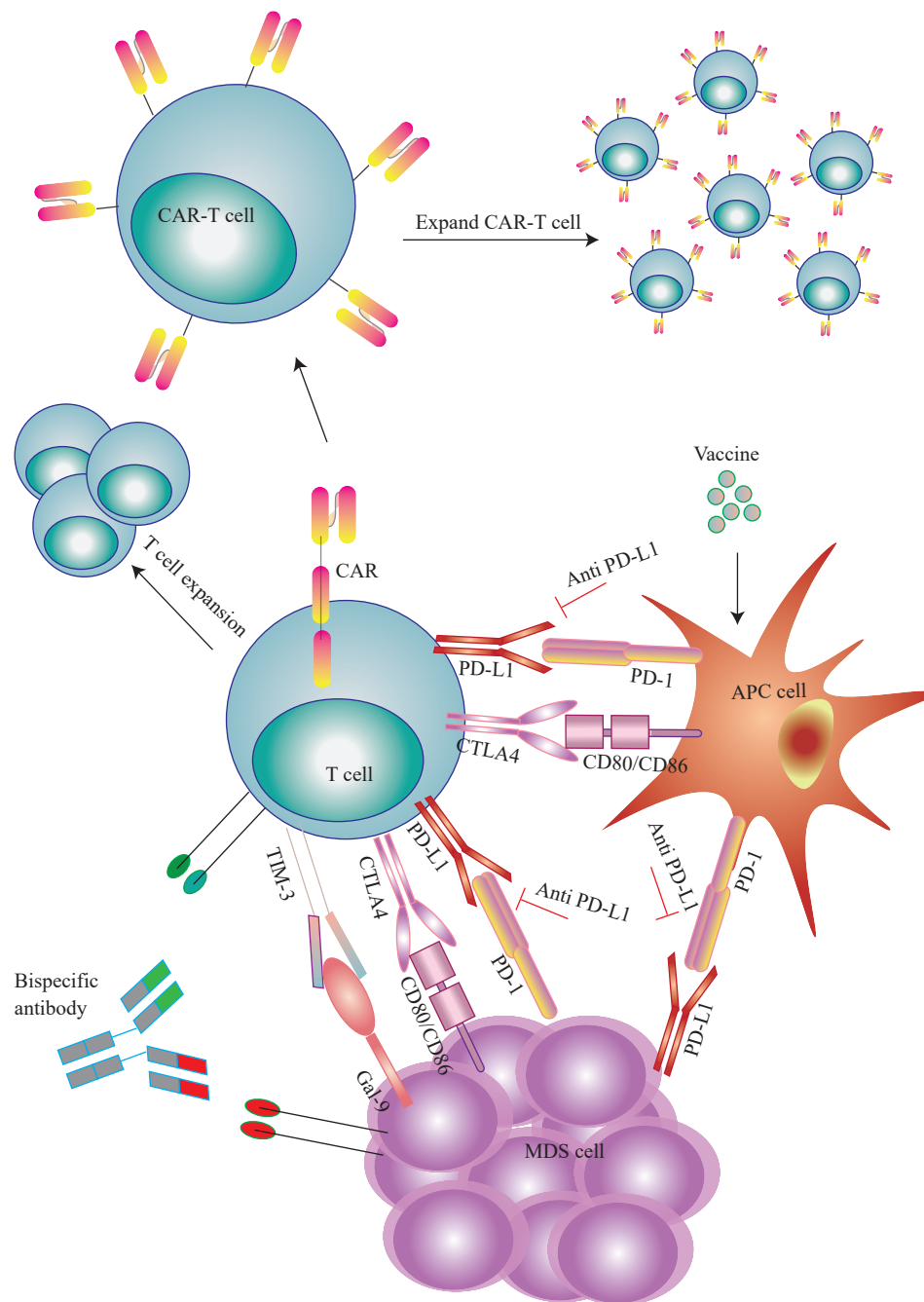


Fig. 3 Multiple immunotherapy for MDS. In the treatment of MDS, various immunotherapies are widely employed, including immune checkpoint inhibitors, CAR-T cell therapy, antibody therapy, and vaccine therapy. MDS: myelodysplastic syndrome; CAR-T: chimeric antigen receptor T; APC: antigen-presenting cell; PD-L1: programmed death ligand 1; PD-1: programmed death protein 1; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; TIM-3: T cell immunoglobulin and mucin domain-containing protein 3; Gal-9: galectin-9.

and early mortality (29%). In contrast, atezolizumab combined with guadecitabine was well-tolerated in a cohort of 9 patients with R/R MDS.

CTLA-4 is expressed on the surface of T cells and competitively binds to the ligands CD80 and CD86, thereby inhibiting the costimulatory activity of the T cell receptor CD28. By outcompeting CD28 for these shared ligands, CTLA-4 blocks CD28-mediated signal transduction, ultimately suppressing T cell activation,

differentiation, and maturation^[37–38]. Ipilimumab, a CTLA4 blocker has been shown to effectively attenuate the immunosuppressive function of Treg cells within lymph nodes and the tumor micro-environment (TME)^[39]. Ipilimumab monotherapy showed notable activity in high-risk MDS. Among the 9 R/R MDS patients treated with ipilimumab monotherapy, 2 patients achieved CR in the bone marrow, accompanied by significant HI^[40–42].

Table 1 Clinical trial of immune checkpoint inhibitors in the treatment of MDS

Study identifier	Phase	Drugs	Start date	Status	Study population	Number (n)	Study type
NCT02530463	II	Nivolumab and/or ipilimumab with or without azacitidine	2015-09-08	Active, not recruiting	MDS	99	Interventional
NCT03259516	I/II	Nivolumab combined with chemotherapy	2017-05-25	Terminated	Refractory MDS	2	Interventional
NCT03094637	II	Azacitidine and pembrolizumab (MK3475)	2017-11-06	Unknown	Higher-risk MDS	40	Interventional
NCT03092674	II/III	Azacitidine with or without nivolumab or midostaurin, or decitabine and cytarabine alone	2018-02-02	Completed	Newly diagnosed AML or high-risk MDS	76	Interventional
NCT03417154	II	Nivolumab and oral cyclophosphamide	2018-08-13	Completed	R/R AML and higher-risk MDS	12	Interventional
NCT06536959	II	PD-1 inhibitor in combination with venetoclax and hypomethylation agent	2024-07-18	Recruiting	R/R AML or high-risk MDS	67	Interventional
NCT04361058	I	Nivolumab	2020-04-13	Withdrawn	R/R AML/MDS	0	Interventional
NCT02936752	Ib	Pembrolizumab	2017-06-23	Completed	MDS	28	Interventional
NCT02508870	I	Atezolizumab (anti-PD-L1 antibody) administered alone or in combination with azacitidine	2015-09-30	Completed	MDS	46	Interventional
NCT01757639	I	Ipilimumab	2012-12-14	Completed	R/R high-risk MDS or AML	42	Interventional
NCT03969446	I	Pembrolizumab and decitabine with or without venetoclax	2020-05-04	Recruiting	Newly diagnosed, R/R AML or MDS	54	Interventional
NCT02935361	I/II	Guadecitabine and atezolizumab	2016-11-02	Active, not recruiting	R/R MDS or CMML	33	Interventional
NCT03358719	I	DEC-205/NY-ESO-1 fusion protein CDX-1401, poly ICLC, decitabine, and nivolumab	2018-03-27	Completed	MDS or AML	8	Interventional
NCT02890329	I	Ipilimumab and decitabine	2017-09-05	Active, not recruiting	R/R MDS or AML	54	Interventional
NCT03600155	Ib	Nivolumab and ipilimumab	2018-10-11	Completed	High risk R/R AML or MDS	29	Interventional

MDS: myelodysplastic syndrome; AML: acute myeloid leukemia; R/R: relapsed and/or refractory; PD-1: programmed death protein 1; PD-L1: programmed death ligand 1; CMML: chronic myelomonocytic leukemia.

TIM-3 is an inhibitory receptor expressed on both adaptive and innate immune cells, including T cells and macrophages. In preclinical models, its blockade reduces leukemia burden and eliminates leukemia-initiating cells, highlighting its therapeutic potential in AML and high-risk MDS^[43]. Sabatolimab (MBG453), a novel anti-TIM-3 monoclonal antibody, exerts anti-leukemia effects through multiple mechanisms^[44]. In an early-phase trial (NCT03066648), sabatolimab (anti-TIM-3) combined with decitabine demonstrated promising efficacy in 17 patients with high-risk MDS, with 8 of 16 evaluable patients achieving durable CR/CR with complete myeloid recovery (CRm). A subsequent phase Ib study established the recommended phase II dose as 400 mg every two weeks or 800 mg every four weeks, administered with standard HMAs for treating MDS, AML, or chronic myelomonocytic leukemia (CMML)^[45]. The combination of these two drugs did not impact the AZA schedule and demonstrated a manageable safety

profile, with few steroid-responsive immune-related AEs. For MDS patients, the regimen achieved a 57% ORR, including a 20% CR rate and a median remission duration of 17.1 months, which was consistent even in high-risk genetic subgroups such as those with *TP53* mutations or ELN high-risk classification^[46]. An ongoing trial (NCT03940352) is evaluating HDM201 combined with MBG453 or venetoclax in AML and high-risk MDS. Further randomized studies include the phase II/III STIMULUS-MDS programs (AZA ± MBG453). Additionally, a phase II trial (NCT04823) is exploring MBG453 monotherapy in low-risk MDS to assess the role of TIM-3 inhibition.

Antibody therapy and antibody-drug conjugate therapy

Tumor cells evade both T-cell attack and macrophage phagocytosis *via* the interaction between CD47 on tumor cells and signal regulatory protein alpha

(SIRP α) on macrophages^[47–48]. CD47 is overexpressed in high-risk MDS compared to normal HSCs. Its binding to SIRP α inhibits MDS cell phagocytosis, while disruption of this interaction enhances antibody-dependent cytotoxic phagocytosis of antibody-opsonized tumor cells^[49]. Early studies on the anti-CD47 monoclonal antibody magrolimab showed potential in enhancing phagocytosis and eliminating leukemia stem cells in AML and high-risk MDS models. Although its confirmatory phase III trial was subsequently discontinued. Currently, multiple drugs targeting the CD47-SIRP α pathway, including blocking antibodies and SIRP α -Fc decoys, are undergoing clinical trials^[50]. Magrolimab was shown to induce macrophage-mediated phagocytosis of AML cells *in vitro* and *in vivo*, achieving leukemia cell clearance and sustained remission in patient-derived xenograft (PDX) models^[51]. A phase Ib trial evaluated magrolimab combined with AZA in MDS/AML patients, this combination elicited objective responses in all treated newly diagnosed MDS patients and shortened the median time to remission by 1.9 months compared to AZA monotherapy. The phase I CAMELLIA trial further confirmed its tolerability and moderate activity in R/R AML, supporting further evaluation in the phase III ENHANCE trial (NCT04313881)^[52]. Other CD47-targeted agents include AK117, currently in a phase I/II trial for high-risk MDS (NCT04900350), and evorpaccept (ALX148), a high-affinity CD47-blocker designed to prevent RBC agglutination. In mice, ALX148 maintained stable blood counts (in contrast to significant reductions with control proteins), confirming its safety^[53]. Evorpaccept is under the phase I/II ASPEN-02 trial for high-risk MDS (NCT04417517), which determines the recommended phase II dose in combination with AZA, and the ASPEN-05 trial for AML (NCT04755244), where it is combined with AZA and venetoclax. A second stage of the ASPEN-02 trial will compare ALX148 plus AZA versus AZA monotherapy in newly diagnosed high-risk MDS patients.

CD70 (CD27 ligand), a TNF superfamily member, is widely expressed on immune effector cells. Tumor-expressed CD70 triggers local immunosuppression^[54–55] and is abnormally expressed on leukemia progenitors, making it a potential target for both immunotherapy and direct leukemia treatment. The anti-CD70 antibody cusatuzumab has been investigated in MDS and AML (often in combination with AZA for MDS), but no specific response data for MDS patients have been reported^[56]. SEA-CD70, a humanized, non-fucosylated anti-CD70 antibody that

acts *via* antibody-dependent cellular cytotoxicity (ADCC) or antibody-dependent cellular phagocytosis (ADCP), is currently in a phase I trial for R/R MDS and other myeloid malignancies (NCT04227847).

CD123 (IL-3R α), a marker of leukemia-initiating cells, is overexpressed in the majority of myeloid malignancies, with expression levels increasing as MDS progresses to AML^[57]. It is overexpressed on MDS stem cells, particularly in high-risk MDS. Although CD123 chimeric antigen receptor T (CAR-T) cells effectively eliminated these cells *in vitro*, their efficacy was limited in low-risk MDS due to fewer CD34⁺CD123⁺ cells. Talacotuzumab (JNJ-56022473), an anti-CD123 IgG1 antibody that acts *via* NK cell-mediated ADCC^[58–59], was combined with decitabine for AML/MDS; however, the combination was discontinued due to poor efficacy and high toxicity^[60], leading to early termination of its SAMBA trial in AML and high-risk MDS^[61]. The CD123-targeted fusion protein tagraxofusp-erzs is being investigated in combination with AZA for MDS, AML, and blastic plasmacytoid dendritic cell neoplasm (BPDCN, NCT03113643). Although MDS results are pending, splenomegaly was reduced in 8 out of 10 CMML patients^[60,62].

Novel bispecific molecules, including Bispecific T-cell Engagers (BiTEs), Dual-Affinity Re-Targeting proteins (DARTs), and Trispecific Killer Engagers (TriKEs), bridge malignant cells and cytotoxic immune cells to promote targeted killing by simultaneously recognizing tumor-associated antigens (*e.g.*, CD123, CD33) and T cell-activating molecules (*e.g.*, CD3) (**Fig. 3**). A CD16 $\times$ CD33 BiTE reversed NK cell suppression in MDS *in vitro*. Flotetuzumab (CD123 $\times$ CD3 DART) achieved a 32.1% CR rate among 28 patients with refractory AML/MDS (phase I)^[63–64]. APVO436 (CD123 $\times$ CD3) had a 43% ORR in 28 patients with R/R AML/MDS (including 1 MDS patient who responded for over 11 cycles)^[65]. The dual CD3-CD122 inhibitor vibecotamab is currently in phase II clinical development (NCT05285813) for R/R MDS and AML, with enrollment requiring at least 20% CD123-positive abnormal myeloid cells.

Antibody-drug conjugates (ADCs), composed of an antibody, a linker, and a cytotoxic payload, deliver toxins to tumor cells precisely and represent a prominent focus of current research^[66]. Several ADCs targeting antigens relevant to MDS have been evaluated. Gemtuzumab ozogamicin (GO), an anti-CD33 ADC approved by the U.S. Food and Drug Administration (FDA) for AML, has been tested in high-risk MDS and secondary AML^[67–68]. The IAGO

regimen (idarubicin + cytarabine + GO) demonstrated limited efficacy^[68–69], whereas the combination of hydroxyurea, AZA, and low-dose GO achieved a 70% rate of CR/CRi in a cohort of 20 patients^[70–72]. The combination of decitabine and GO achieved CR/mCR in 15 out of 20 MDS patients; however, median survival remained suboptimal at 5.7 months^[73–74]. SGN-CD33A (vadastuximab talirine), a next-generation anti-CD33 ADC^[75], had its phase III trial (AZA + SGN-CD33A for AML) halted due to a higher incidence of early death and the combination had high 30-day and 60-day mortality in elderly and relapsed AML patients^[76]. BI 836858, a fully humanized anti-CD33 IgG₁ antibody, reduced MDSCs *via* ADCC preclinically. Although its phase I/II trial in transfusion-dependent low- or intermediate-1-risk MDS was terminated due to insufficient monotherapy response, this agent has been proposed to target MDSCs and modulate BMM in low-risk MDS^[77–78]. Brentuximab vedotin (BV), an anti-CD30 ADC approved for lymphomas, has been evaluated in a phase I trial for AML re-induction (NCT01830777) and a phase II trial for AML/MDS monotherapy (NCT01461538)^[79–80], however, its trial combining BV with AZA was terminated due to slow patient recruitment (NCT02096042). ADC ¹³¹I-BC Ab (Iomab-B, ¹³¹I-anti-CD45) was tested in 58 patients aged over 50 years with AML or high-risk MDS receiving low-intensity conditioning. The median OS and DFS were 199 and 159 days, respectively (206 and 189 days at the maximum tolerated dose), with infusion reactions. A follow-up phase I trial (90Y-DOTA BC8 + stem cell transplantation in high-risk AML/MDS, NCT01300572) is ongoing.

CAR-T therapy

CAR-T cells are T cells obtained and transduced from patients through viral vectors (**Fig. 3**). Viral vectors engineer T cells to express CAR, enabling major histocompatibility complex (MHC)-independent tumor antigen recognition. NKG2D, an immunomodulatory receptor on NK and CD8⁺ T cells, is a compelling CAR target as its ligands are exclusively expressed under pathological conditions and are largely absent on healthy tissues^[81]. NKG2D-CAR-T cells can not only specifically target and kill cancer cells but also modulate Tregs and MDSCs within the TME^[82–83]. A phase I dose-escalation trial evaluated the safety of CAR-T cell therapy targeting NKG2D ligands in 12 patients with previously untreated AML, MDS or R/R multiple myeloma (MM)^[84–85]. The therapy showed no dose-limiting toxicities or cytokine release syndrome (CRS). Efficacy was limited to transient HI observed at the

highest dose and to disease stabilization. Celyad's CYAD (NKR-2) is being evaluated in a multinational phase I THINK trial across various cancers. A study reported the results of 25 R/R patients (including 3 cases of MM, 19 cases of AML, and 3 cases of MDS) who received CYAD-01 CAR-T cell therapy without prior lymphocyte clearance chemotherapy (THINK test). Among three elderly, HMA-resistant MDS patients treated at the highest CYAD-01 dose level, one achieved a brief CR; however, all patients experienced disease progression within 12 weeks despite retreatment. A separate DEPLETHINK trial is evaluating a single CYAD-01 infusion following lymphodepletion with cyclophosphamide and fludarabine in R/R AML/MDS patients. Compared to the THINK trial, DEPLETHINK patients showed enhanced CAR-T expansion post-lymphodepletion, yet two MDS patients failed to respond. The increased expansion was dose-dependent and correlated with severe toxicity, including two cases of grade ≥ 3 CRS and neurotoxicity. Another phase I trial is investigating NKG2D ligand-targeting CAR-T cells in MDS (NCT02203825). The clinical data related to CAR-T treatment in MDS are shown in **Table 2**.

CD123, while not MDS-specific, is a marker of disease progression due to its upregulation. A CD123-targeting CAR-T construct effectively eliminated MDS cell lines within 48 hours of co-culture. Furthermore, when tested against primary cells from high-risk MDS patients, these CAR-T cells cleared 50%–100% of MDS stem cells while sparing normal hematopoietic cells and progenitors^[86]. Meanwhile, a novel FMS-like tyrosine kinase 3 (FLT3)-CAR-R2 with a rituximab-responsive off-switch demonstrated potent anti-leukemia activity *in vitro*, eliminating over 80% of AML blasts within 48 hours. This safety switch enabled controlled CAR-T cell depletion post-treatment to mitigate potential hematopoietic toxicity^[87].

Vaccine

The goal of cancer vaccines is to enable immune cells to identify tumor cells that evade detection through immune escape mechanisms (**Fig. 3**). As research into tumor-mediated immunosuppression deepens, combining cancer vaccines with other immunotherapies has demonstrated enhanced effectiveness in cancer treatment^[88].

Wilms' tumor 1 (WT1) is a highly immunogenic tumor-associated antigen overexpressed in various cancers. In MDS, elevated WT1 mRNA levels strongly correlate with increased bone marrow blast percentage, serving as a marker of disease progression

Table 2 Clinical trial of CAR-T in the treatment of MDS

Study identifier	Phase	Treatment	Start date	Status	Study population	Number (n)	Study type
NCT05457010	I	ARC-T cells	2022-11-28	Recruiting	R/R AML or high-risk MDS	24	Interventional
NCT06906380		ARD103 CAR-T cell therapy	2025-05-07	Not yet recruiting	R/R AML or high-risk MDS	49	Observational
NCT02203825	I	CM-CS1 T cells	2015-03	Completed	AML; Advanced MDS (MDS-RAEB) MM	12	Interventional
NCT06765876	I	CART123 T cells	2024-10-23	Recruiting	AML, MDS, ALL, or BPDCN	18	Interventional
NCT06680752	I/II	ARD103 CAR-T therapy	2025-03	Not yet recruiting	R/R AML or MDS	49	Interventional
NCT04156256	I	CD123-CD33 cCAR T cells	2018-03-01	Unknown status	R/R, high risk hematologic malignancies	20	Interventional
NCT03795779	I	CLL1-CD33 cCAR T cells	2018-03-01	Unknown status	R/R, high risk hematologic malignancies	20	Interventional

CAR-T: chimeric antigen receptor T; MDS: myelodysplastic syndrome; R/R: relapsed and/or refractory; AML: acute myeloid leukemia; MM: multiple myeloma; ALL: acute lymphoblastic leukemia; BPDCN: blastic plasmacytoid dendritic cell neoplasm; cCAR: composite chimeric antigen receptor.

toward AML^[89]. In a clinical study, two patients showed transient reductions in bone marrow blasts with hematologic recovery, while five patients with persistent T-cell activity survived beyond 12 months^[90–92]. In a separate study involving 26 MDS patients (22 evaluable), WT1-targeted therapy resulted in 1 mCR and 12 cases of stable disease, yielding a 18.2% ORR (defined as mCR plus any HI) and a 59.1% disease control rate^[93]. One patient exhibited a mild response with a 50% reduction in transfusion requirements and a decrease in bone marrow myeloid cells, achieving minimal transfusion dependence for approximately 14 months post-vaccination. Separately, WT1 vaccination led to complete neutrophil recovery in two patients, with the recovery being sustained for 10 months in one MDS case. PR1 is an HLA-A2-restricted peptide from proteinase 3 and neutrophil elastase. Similar to the WT1 vaccine, PR1 vaccine has shown promise in MDS, AML, and CML by inducing specific immune responses correlated with clinical remission.

To explore the immune response against MDS clones, researchers administered HLA-A2-restricted PR1 and WT1 peptide vaccines to two patients with MDS^[94]. Two patients generated PR1/WT1-specific T-cells following vaccination despite the absence of objective responses. Separately, HMA treatment upregulated NY-ESO-1 expression in AML and MDS cells in a time- and dose-dependent manner, enabling recognition by antigen-specific CD8⁺ CTLs in preclinical models and in circulating myeloid progenitors of HMA-treated patients^[95–96]. A study of 9 high-risk MDS patients combined decitabine with an HLA-unrestricted NY-ESO-1 vaccine to induce cytotoxic responses. All 7 patients completing the study showed NY-ESO-1 gene expression, with 6 and 4 patients mounting NY-ESO-1-specific CD4⁺ and CD8⁺ T-cell responses, respectively. Ongoing

research is exploring the combination of NY-ESO-1-directed immunotherapy and hypomethylated drugs.

Another therapeutic vaccine strategy for MDS uses transfected plasmids to enable patient-derived whole tumor cells (K562 cell line) to secrete GM-CSF^[97]. A phase I GVAX trial in four patients with MDS and one with CMML demonstrated good tolerability, with only grade 1 injection site reactions reported. One patient achieved major HI and another became transfusion-independent. However, the small cohort size constrained definitive efficacy evaluation.

APPLICATIONS AND PROSPECTS OF NANO IMMUNOTHERAPY

Advantages of nano-drug delivery systems

Nanoimmunotherapy is committed to fully tapping the therapeutic potential of immunotherapy through nanoparticle (NP) platforms and nanoengineering technologies to address the current challenges in cancer immunotherapy^[98]. By precisely co-delivering immunostimulants (e.g., toll-like receptor agonists) and antigenic components to APCs such as DCs, nanocarriers avoid the systemic dispersion of free immunostimulants and enhance their accumulation in lymphoid organs, thereby amplifying anti-tumor immune responses while minimizing off-target toxicity^[99]. Numerous preclinical studies have demonstrated that nanocarriers can safely and effectively enhance the activity of immunostimulants, underscoring their broad potential in the field of immuno-oncology^[99].

Nanotechnology bridges the gap between biological and physical sciences by applying nanostructures and nanophases across various scientific fields^[100–101]. In nanomedicine and nano-drug delivery systems, NPs have become a central focus of research (**Fig. 4**)^[102–103].

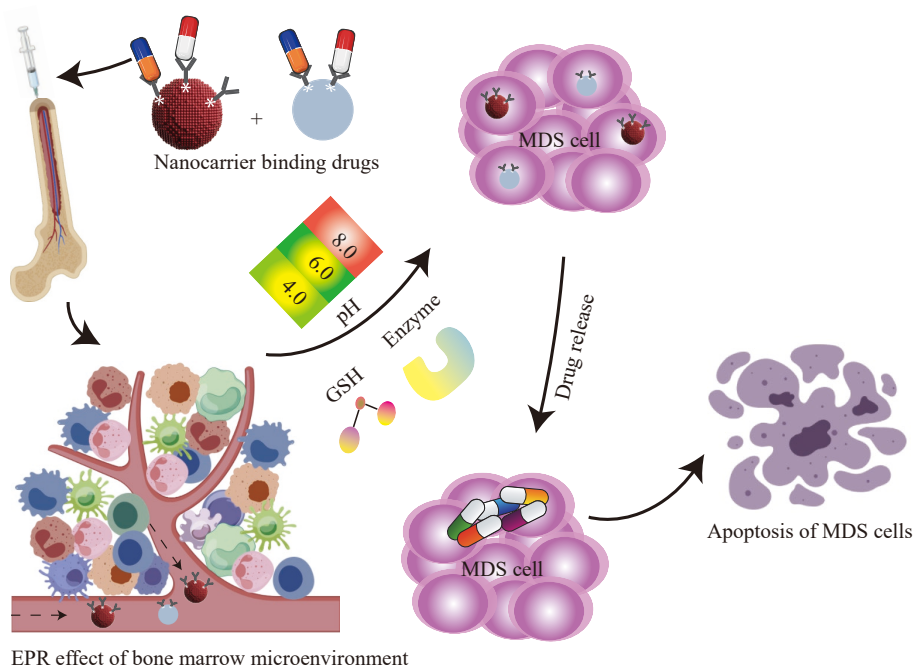


Fig. 4 Targeted precise drug delivery of NPs for MDS. NPs are designed to encapsulate chemotherapeutic drugs targeting the pathogenesis of MDS, and to achieve preferential delivery to malignant cells by binding to highly expressed receptors on the surface of MDS cells, while protecting healthy tissues, thereby minimizing AEs. In addition, stimuli-responsive NPs can be designed according to specific triggers (such as pH, temperature, or enzyme activity) in the TME to achieve precise drug release. NPs: nanoparticles; MDS: myelodysplastic syndrome; AEs: adverse effects; TME: tumor microenvironment; EPR effect: enhanced permeability and retention effect; GSH: glutathione.

This interdisciplinary integration enables the engineering of carriers with customizable physico-chemical properties, such as tunable particle size (50 nm–200 nm for optimal enhanced permeability and retention effect), surface charge, and functional ligands. These can be tailored to overcome biological barriers and meet therapeutic demands^[104]. Nanotechnology employs nanoscale therapeutic agents to develop nanomedicines. NPs play a central role in advancing biomedical fields including nanobiotechnology, drug delivery, biosensing, and tissue engineering. Notably, their integration with diagnostic modalities, including MRI and fluorescence imaging, has given rise to "theranostic" platforms that enable real-time monitoring of drug distribution and treatment response^[101].

Nano-drug delivery systems have shown significant advantages in delivering natural active ingredients and chemotherapeutic drugs, including efficient embedding ability, prolonged circulation time, controllable release mechanisms, reduced drug resistance, and reduced adverse reactions of anticancer drugs (Fig. 4)^[105]. Their efficient embedding capability spans both hydrophilic drugs such as doxorubicin (DOX) and hydrophobic compounds like curcumin (CUR). For instance, porous inorganic nanocarriers

can achieve drug loading capacities exceeding 80% for lipophilic compounds, while liposomes form aqueous cores to encapsulate water-soluble drugs. Prolonged circulation is commonly achieved *via* surface modifications with polyethylene glycol (PEG) or biomimetic membranes such as RBC membranes, which shield NPs from phagocytic clearance and prolong blood circulation from hours to days^[106]. Controllable release mechanisms have advanced to "smart" responsive systems, including pH-sensitive polymers that degrade in the acidic TME or temperature-sensitive liposomes triggered by local hyperthermia, thereby ensuring that drug release is confined to pathological sites^[107]. These systems also mitigate drug resistance by enhancing cellular uptake to bypass efflux pumps and by targeting cancer stem cells (CSCs) through ligand-mediated recognition. Finally, by concentrating drugs at tumor sites rather than in healthy tissues, nano-delivery reduces systemic toxicities. For example, encapsulation of CD40 antibodies within membrane-adhesive nanoliposomes enhanced anti-tumor efficacy while reducing immunogenic adverse reactions^[108].

Nanocarriers in nano-drug delivery systems are mainly divided into two categories: organic and inorganic nanocarriers. Organic nanocarriers mainly

include polymers, liposomes and proteins. Inorganic nanocarriers include gold NPs (AuNPs), silicon NPs (SiNPs), iron NPs (e.g., iron oxide), and other inorganic salt NPs^[109]. Organic carriers excel in biocompatibility. Biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA) enable tunable drug release profiles, while protein-based carriers such as albumin NPs leverage the EPR effect for passive tumor targeting^[106]. Liposomes, composed of phospholipid bilayers, have been developed for clinical applications (e.g., PEGylated liposomal DOX) and can be modified with antibodies to achieve active targeting^[110]. Inorganic carriers, by contrast, offer high stability and multifunctionality. AuNPs serve as both drug carriers and photothermal agents; iron oxide NPs (IONPs) function as MRI contrast agents and drug delivery vehicles; and porous SiNPs enable high-capacity loading for combination therapies^[101]. Recent innovations have further integrated these categories through the development of hybrid organic-inorganic carriers, which combine the advantages of both classes for synergistic therapy^[107].

Classification and application of nanocarriers

Polymer carriers mainly include PLGA, PEG, polyethylenimine (PEI), and chitosan. These carriers typically exhibit a core-shell architecture, which is composed of a drug-loaded polymer core (center) and a functionalizable polymer shell (outer layer). Through rational structural design and synthesis, such carriers can achieve multifunctional drug delivery requirements. PLGA has garnered significant research interest due to its potential in controlled release, surface modification, prolonged circulation time, loading of both hydrophilic and hydrophobic drugs, and targeted delivery^[111]. A novel dual-drug CD33-targeted delivery system was designed based on PEGylated PLGA NPs to co-encapsulate and simultaneously deliver two drugs at a synergistically optimized ratio. The study further evaluated the therapeutic efficacy of the system in a CD33-positive pediatric AML cell model^[112]. PEGylated PLGA NPs loaded with chlorpromazine (CPZ) were developed for the treatment of AML. The study showed that CPZ can effectively mitigate effects on the central nervous system while preserving its anti-AML activity through nano-embedding technology^[113]. PEG is a flexible, hydrophilic polymer that can bind to peptides, proteins, nucleic acids, liposomes, or NPs through physical linkage. This binding can reduce renal clearance, prevent interactions between antibodies and protein binding sites, prolong the half-life of therapeutic molecules, and improve their efficacy^[114].

Ando H *et al.* prepared a novel PEG drug conjugate venetoclax and evaluated its AML cytotoxicity *in vitro* and *in vivo*. The results demonstrated a significant increase in tumor accumulation alongside a marked reduction in the non-specific distribution of venetoclax^[115]. The first PEGylated NP approved in the United States and Europe is liposomal DOX (Doxil[®]/Caelyx[®] [PLD]) for the treatment of Kaposi's sarcoma, recurrent ovarian cancer, and MM, with ongoing clinical trials for other indications.

Liposomes are a kind of biomimetic NP formed through self-assembly of concentric bilayer lipids, which enclose a water-soluble core. They are widely used as nanocarriers for drugs and diagnostic reagents^[116]. With nanoscale dimensions and a biological membrane structure, liposomes demonstrate good biocompatibility and relative stability^[117]. Liposomes are widely considered as efficient drug delivery vehicles due to their structural versatility, good biocompatibility, biodegradability, and non-toxicity and non-immunogenicity^[118]. Liposomes are primarily divided into the following four types: (1) conventional liposomes; (2) PEGylated liposomes; (3) ligand-targeted liposomes; and (4) therapeutic diagnostic liposomes. A nano-lipid carrier containing etoposide (ETP) and CUR (ETP-CUR-NLC) was prepared, which showed low cytotoxicity in normal tissues and high cytotoxicity *in vivo*. In addition, researchers constructed hyaluronic acid (HA)-modified nanoliposomes as a co-delivery carrier for paclitaxel (PTX) and DOX. The results of *in vitro* cytotoxicity experiments indicated that HA-modified NLC exhibited superior inhibitory effects on the drug-resistant breast cancer cell line (MCF-7/ADR) compared to unmodified BCL/DOX-NLC. Drug loading into liposomes can be achieved through both active and passive methods. Among them, the active method is to encapsulate drugs after the formation of liposomes, while the passive method incorporates drugs during the formation of liposomes. For hydrophilic drugs such as ampicillin and 5-fluorodeoxyuridine, encapsulation typically occurs within the aqueous core of liposomes. Therefore, their encapsulation efficiency is independent of adjustments to the drug-to-lipid ratio. A continuous flow system for liposome synthesis, functionalization, and purification has been reported. This study focused on vesicles smaller than 300 nm in the chip laboratory, which were considered ideal and cost-effective candidates for drug or protein encapsulation. Several liposome-based drug delivery systems have been approved by the FDA. CPX-351, a classical liposome composed of cytarabine and daunorubicin (DNR) in a

ratio of 5 : 1, enhances therapeutic synergy of drugs and reduces their antagonistic effects. It was utilized in the clinical treatment of AML^[119]. Studies have explored the efficacy of PLEKHA7 cRGD-mediated PEGylated cationic lipid NPs in delivery of PLEKHA7 in leukemia cells, as well as the regulatory effects of PLEKHA7 on AML behavior and growth changes. The results showed that PLEKHA7 plays a key role in modulating AML behavior and growth patterns^[120]. A6 peptide-functionalized biomimetic NPs (A6-NP) targeting HSP90 and CD44 were designed and prepared. The targeting ability and anticancer efficiency of A6-NP were evaluated by preparing A6-NP with different degrees of modification. The release of encapsulated G2111 from A6-NP was less than 5% within 12 hours, effectively minimizing off-target toxicity prior to cellular uptake. In addition, A6-NP retained the broad-spectrum anticancer properties of HSP90 inhibitors and exhibited significant targeting and anticancer effects in hematological malignancies and solid tumors^[121].

Nanoemulsions (NEs) are generally composed of water phase and oil phase, which can effectively address poor drug solubility by improving bioavailability, enhancing drug stability and reducing side effects of drug carriers^[122]. An oil-in-water NM was developed to successfully achieve the encapsulation of gambogic acid. The drug-loaded NM showed good stability in phosphate buffer solutions at pH 2.0, 5.8, and 7.4, respectively, and exhibited significant sustained release characteristics. Studies have demonstrated that it can prolong the survival of MV4-11 transplanted mice, improve their survival rate, and reduce the median lethal concentration of AML cell lines such as Jurkat and HL-60^[123].

Polymeric micelles (PMs) are biodegradable, flexible, spherical NPs self-assembled from various amphiphilic diblock or triblock copolymers^[124–125]. Studies have demonstrated that PMs function as a multifunctional drug carrier due to their higher drug solubility, excellent biocompatibility, enhanced permeability, and lower toxicity^[126]. A research team developed a biocompatible nanomicelle drug delivery system capable of carrying multiple drugs. C-type lectin-like molecule 1 (CLL1)-targeted peptide-modified DNR nanomicelles exhibit high affinity for CLL1-expressing leukemia stem cells, thereby achieving efficient intracellular drug delivery and significantly improving the efficacy and safety of chemotherapy^[127]. In addition, a team prepared nanomicelles by combining chemically synthesized CXC chemokine receptor 4 antagonist peptide E5 with PEG-modified distearoyl phosphate ethanolamine^[128].

These nanomicelles can effectively inhibit the implantation of AML cells in the bone marrow and spleen in refractory AML mouse models, while inducing apoptosis and differentiation of AML cells, thereby prolonging the survival time of AML mice.

Numerous studies have indicated that metal NPs (MNPs) with different components show great potential for disease treatment, and their mechanisms include controlled drug release and local hyperthermia. Common therapeutic MNPs include AuNPs, silver NPs (AgNPs), and IONPs^[129]. One study proposed a coupling strategy based on the hydrophobic interactions between FLT3 inhibitors and poloxamer copolymers coated on the surface of NPs, successfully preparing FLT3 inhibitor-AuNP conjugates for the treatment of AML. In addition, IONPs were prepared through chemical coprecipitation, followed by silica deposition *via* the sol-gel method, and then cytarabine was further modified on the surface.

Nanocarrier strategies for MDS treatment

NP-based drug delivery systems represent a transformative strategy for MDS, enhancing drug targeting and reducing systemic toxicity. One prominent approach utilizes bone-targeted NPs for the co-delivery of synergistic agents such as decitabine and arsenic trioxide. In murine models, the system significantly prolonged circulation time and enhanced drug accumulation in the bone marrow, leading to improved hematological recovery and extended survival^[130]. Additionally, polymer-based NPs (*e.g.*, PLA-PEG) enable controlled drug release and support flexible combination therapies, a well-established strategy for optimizing chemotherapeutic efficacy^[131]. Albumin-based NPs further contribute by leveraging inherent biocompatibility and passive targeting to selectively deliver arsenic compounds to hematological malignancy cells, achieving targeted cytotoxicity while sparing normal lymphocytes^[132–133].

A key precision target in MDS is CD123 (interleukin-3 receptor α -subunit), which is highly expressed on high-risk MDS and leukemic stem cells but exhibits minimal expression on normal hematopoietic progenitors. A quantum dot (QD)-based delivery system conjugated with anti-CD123 antibodies and loaded with DNR (DNR-CdTe-CD123) was developed, demonstrating high encapsulation efficiency ($74.52\% \pm 1.81\%$) and drug loading capacity ($42.08\% \pm 0.64\%$)^[134]. This construct enables specific binding to CD123-overexpressing MUTZ-1 cells ($72.89\% \pm 10.67\%$) and induces apoptosis through upregulation of p53, cleaved

caspase-3/9, and BCL-2-associated X protein (BAX). In MDS mouse models, DNR-CdTe-CD123 suppressed tumor growth while mitigating DNR-induced cardiotoxicity. Beyond antibody-mediated targeting, peptide-functionalized nanocarriers using the CD123 antagonistic peptide PO-6 assembled into nanomicelles (mPO-6) block CD123/IL-3 signaling, reducing malignant cell infiltration and prolonging survival in refractory leukemia models—a strategy applicable to high-risk MDS^[135].

For molecularly defined subtypes such as SF3B1-mutant MDS, nanocarriers have been designed to exploit specific vulnerabilities, notably through exportin 1 (XPO1) inhibition^[136]. Recent studies support synergistic combinations of next-generation XPO1 inhibitors with BCL-2 antagonists such as venetoclax and navitoclax, prompting the development of co-delivery nanosystems^[137]. To address delivery challenges, bone-homing NPs have been designed to enhance eltanexor accumulation in marrow niches while minimizing systemic exposure^[138]. Nucleus-targeted nanocarriers facilitate site-specific drug release, capitalizing on altered nuclear transport mechanisms to amplify anti-leukemic effects^[139–140].

Expanding into immune modulation, acid-sensitive nanoplateforms co-delivering entinostat (an MDSC inhibitor) and PD-1/PD-L1 blockers can reprogram the immunosuppressive marrow microenvironment by polarizing macrophages toward the M1 phenotype, suppressing MDSCs, and reactivating cytotoxic T cells^[141–142]. Further innovating this approach, manganese-doped layered double hydroxide (MLDH) nanoplateforms activate the STING pathway to enhance anti-tumor immunity^[143].

Despite their considerable potential, immune-modulatory nanotherapies for MDS confront substantial translational challenges. These impediments are predominantly attributable to the profoundly immunosuppressive character of bone marrow niche and the considerable interpatient heterogeneity in somatic mutations and baseline immune constitution, which collectively contribute to variable and often suboptimal clinical responses^[144–145]. In response to these barriers, sophisticated NP platforms are being engineered for the spatially and temporally coordinated co-delivery of synergistic immuno-modulatory agents. One prominent strategy involves the bone marrow-targeted co-delivery of immune checkpoint inhibitors (*e.g.*, anti-PD-1/PD-L1) with HMAs such as decitabine. This approach not only exerts direct cytotoxic effects on malignant clones but also mitigates immune checkpoint upregulation and

potentiates tumor antigen presentation, thereby reinstating T cell-mediated immune surveillance^[28,146]. A parallel, complementary strategy focuses on the co-delivery of innate immune agonists, notably STING activators, with inhibitors of MDSCs. This combination activates the cGAS-STING pathway, initiating a robust type I interferon response while depleting a key cellular population responsible for T-cell suppression, thereby reshaping the immunological landscape of the marrow^[147–148]. Looking forward, the integration of predictive biomarkers, for instance, clonal T-cell receptor signatures or specific mutational profiles that correlate with immunotherapy susceptibility, into the fundamental design principles of nanocarriers represents a promising frontier for personalizing therapeutic interventions and optimizing efficacy across the clinically diverse spectrum of MDS patients.

Notably, the successful clinical application of nanocarrier-based strategies in AML, a disease that shares pathophysiological features with high-risk MDS, provides a supportive rationale for their development in MDS. For instance, the liposomal formulation of cytarabine and daunorubicin (CPX-351), which is approved for AML treatment, has demonstrated the potential of nanoscale drug delivery in improving therapeutic outcomes in myeloid malignancies^[149]. Although direct translation to MDS requires further validation, such as the adaptation of targeting fragments to MDS-specific surface markers and the optimization of drug combinations based on MDS molecular subtypes, these established nanotherapeutic approaches in AML provide a valuable conceptual and technical framework for accelerating MDS-specific nanomedicine development.

Collectively, these evolving nanocarrier technologies, which span bone-directed, molecularly targeted, and immune-modulatory strategies, address critical limitations of conventional MDS therapies like short drug half-lives and off-target toxicity, paving the way for more precise and effective treatments.

SUMMARY AND PROSPECTS

As a highly heterogeneous hematologic malignancy, MDS is witnessing a paradigm shift from conventional chemotherapy toward precision immunotherapy, with emerging modalities including antibody therapy, cancer vaccines, immune checkpoint inhibitors, CAR-T, and nano-immunotherapy offering diverse treatment options. These strategies share the common goal of precisely targeting malignant clones by activating the patient's immune system while

preserving normal tissues. Moving forward, addressing common challenges such as patient stratification, toxicity management, and the immunosuppressive TME will be crucial. The rational combination of complementary approaches, exemplified by pairing immune checkpoint inhibitors with agents targeting immunosuppressive cells, represents a highly promising direction for achieving durable responses and improving outcomes in MDS patients.

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Author contributions

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Ethics statement

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Informed consent statement

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Declaration of competing interest

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