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Checkpoint inhibitors as potential therapeutics in acute myeloid leukemia

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Abstract

Despite recent progress in treatment methods, acute myeloid leukemia (AML) continues to pose significant clinical challenges and is associated with generally unfavorable prognoses. Patients considered fit for intensive therapy are usually treated with cytarabine-anthracycline-based induction chemotherapy. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is recommended for patients with adverse-risk AML and most patients with intermediate-risk AML. The standard therapy for patients who are deemed too poorly for intensive treatment is the combination of azacitidine and venetoclax. AML cells can escape the immune system through various mechanisms, including reduced expression of MHC complex molecules, ligand shedding, manipulation of chemical signaling, and enhanced inhibitory ligand expression. Increased expression of ligands for T-cell-regulation checkpoints is present in AML cells and correlates with worse outcomes. Therefore, this article reviews the current research progress in immune checkpoint inhibitors in AML.

Keywords: checkpoint inhibitors, therapy, acute myeloid leukemia, survival

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Introduction

Despite recent progress in treatment methods, acute myeloid leukemia (AML) continues to pose significant clinical challenges and is associated with generally unfavorable prognoses, with an estimated 5-year overall survival (OS) rate of c.30% that varies between different age groups [1].

Prognosis estimation in AML involves a multi-faceted assessment that considers various clinical and biological aspects, including patient characteristics, disease-related factors, and disease ontogeny. Based on the patient's disease history, AML can be classified into two groups: *de novo* AML and secondary AML. Secondary AML that arises from a pre-existing hematological disease or following treatment with chemotherapy or radiation accounts for 15–30% of all cases, and has a generally worse prognosis compared to primary AML [2]. Biological factors such as cytogenetic abnormalities, gene mutations, and chromosomal aberrations are the basis for the European Leukemia Net (ELN) criteria that stratify AML into categories of favorable, intermediate, or adverse risk. The ELN criteria are dynamic and were last updated in 2022 due to novel molecular findings. Risk stratification strongly influences treatment decisions [3].

Currently, the treatment regimen for young, transplant-eligible patients with AML who are considered to be fit for intensive treatment consists of two phases: complete remission (CR) induction and a consolidation phase. CR induction usually involves cytarabine-anthracycline-based induction chemotherapy, commonly following the '7+3' regimen [4]. If the leukemia fails to respond sufficiently to the initial induction therapy, a second induction is started.

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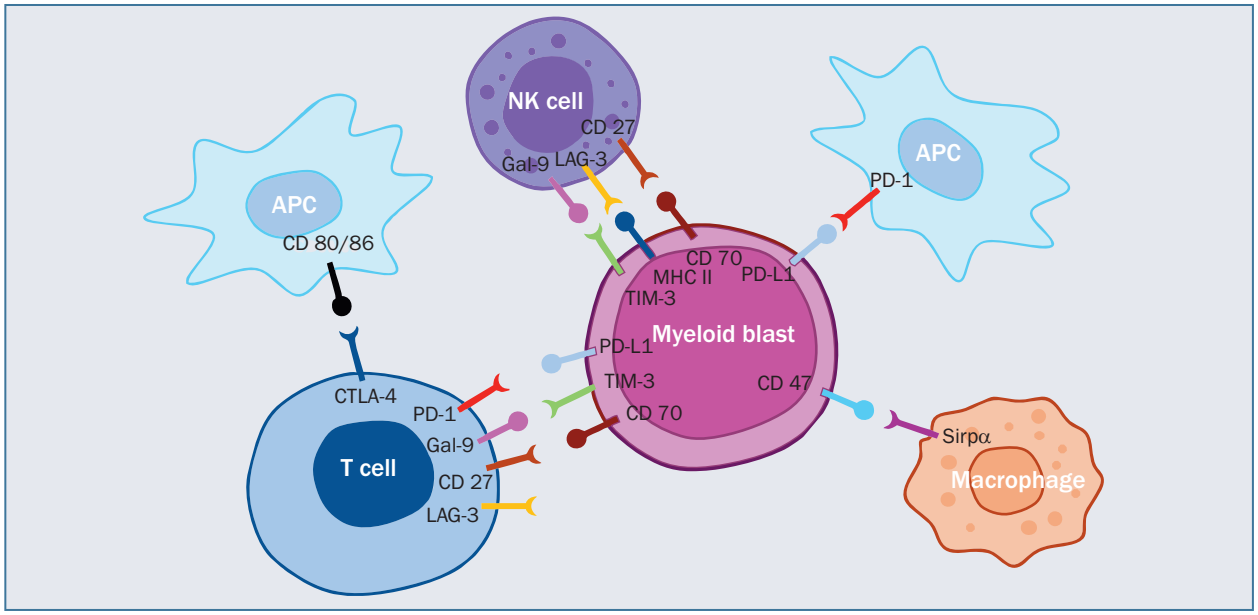

Figure 1. Checkpoint inhibitors and ligands in acute myeloid leukemia; APC — antigen-presenting cell; CTLA-4 — cytotoxic T-lymphocyte associated protein 4; Gal-9 — galectin-9; LAG-3 — lymphocyte-activation gene 3; MHC II — class II major histocompatibility complex; PD-1 — programmed cell death protein 1; PD-L1 — programmed cell death ligand 1; SIRPα — signal regulatory protein alpha; TIM-3 — T-cell immunoglobulin and mucin domain-3

Daunorubicin + AraC + cladribine (DAC) and cladribine + + AraC + mitoxantrone (CLAM) are equally effective [5].

Research by the Polish Adult Leukemia Group has shown the beneficial effect of adding cladribine to the '7+3' regimen in newly diagnosed AML patients, including those under 60 years old [6] as well as those over 60 [7]. In elderly patients unfit for intensive chemotherapy, the combination of cladribine with low-dose cytarabine has been proved to be a more effective therapeutic option compared to low-dose cytarabine alone [8]. Additionally, gemtuzumab ozogamicin can be used in combination therapy with daunorubicin and cytarabine for the treatment of patients aged 15 years and older with previously untreated *de novo* CD33 positive AML, except acute promyelocytic leukemia [9].

For patients with a therapy-related AML (t-AML), or AML with myelodysplasia-related changes (AML-MRC), CPX-351, a liposomal formulation of daunorubicin and cytarabine, is an alternative to the classical regimen. The use of targeted therapy is standard for leukemia with specific mutations. The IDH1 and IDH2 inhibitors ivosidenib and enasidenib are approved for patients with AML with mutations of the respective genes [10]. Midostaurin — a type I first-generation fms-like tyrosine kinase 3 (FLT3) inhibitor — is approved in combination with standard induction and consolidation chemotherapy for *FLT3* mutation-positive patients. Gilteritinib — a second-generation FLT3 inhibitor — can be used for relapsed/refractory AML in the same group of patients [11, 12].

Lower-intensity therapy with azacitidine and venetoclax for patients who do not tolerate intensive remission induction therapy might prolong survival, but only rarely results in long-term disease control [13].

Recurrence of AML is the most significant negative prognostic factor, occurring in c.30% of pediatric patients and reducing the 5-year OS to below 30% [14]. In the adult population, relapse is the most common cause of treatment failure, with a 5-year OS rate of c.10% for patients with disease recurrence [15].

To prevent relapse, post-remission consolidation therapy with high-dose cytarabine (HiDAC) is commonly used to eliminate residual, undetectable disease, although the optimal number of cycles and the timing remain under evaluation [16].

Allo-HSCT remains the most effective option due to its graft-versus-leukemia (GVL) effect. However, in many cases, the toxicity might outweigh the benefit [17], and in 30–70% of patients, allo-HSCT fails due to disease relapse, which significantly lowers the survival rate [18]. Therefore, the therapy is recommended for patients with adverse-risk AML and for most patients with intermediate-risk AML.

The curative potential of allo-HSCT is one of the reasons behind the growing interest in the potential role of immunotherapies in treating myeloid neoplasms, including AML.

AML cells can escape the immune system through various mechanisms, including reduced expression of MHC complex molecules, ligand shedding, manipulation of chemical signaling, and enhanced inhibitory ligand expression [19, 20].

Table I. Overview of discussed immune checkpoints, their physiological function, and corresponding immune checkpoint inhibitors (ICIs)

Immune checkpoint	Physiological function	ICIs
CTLA-4	Inhibition of T-cell activation through competition with CD28 for binding to CD80/86 ligands	Ipilimumab
PD-1/PD-L1 axis	Inhibition of T-cell activation, proliferation and cytokine production	Nivolumab, pembrolizumab, durvalumab, avelumab, atezolizumab
TIM-3/Galectin-9 axis	Promotion of T-cell exhaustion; enhancement of treg cells	Sabatolimab
LAG-3	Reduction of T-cell proliferation and cytokine production upon binding to MHC class II and other ligands	Relatlimab
CD27/CD70 axis	Promotion of T-cell activation and proliferation in healthy individuals or immunosuppressive effect resulting from tumor-associated CD70 overexpression and chronic stimulation of axis	Cusatuzumab
CD47/SIRPα axis	Prevention of phagocytosis of healthy cells	Magrolimab, evorpacept, lemzoparlimab

CD27/CD70 — cluster of differentiation 27/cluster of differentiation 70; CD47 — cluster of differentiation 47; CTLA-4 — cytotoxic T-lymphocyte associated protein 4; LAG-3 — lymphocyte-activation gene 3; PD-1 — programmed cell death protein 1; PD-L1 — programmed cell death ligand 1; SIRPα — signal regulatory protein alpha; TIM-3 — T-cell immunoglobulin and mucin domain-3

Increased expression of ligands for T-cell-regulation checkpoints, including cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), B7-H3, and T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), is present in AML cells and correlates with worse outcomes [21].

Implementing immune checkpoint inhibitors (ICIs) has been successful in many solid tumors, but the same cannot be said about myeloid malignancies. The main reasons behind the limited progress in this area are likely a lower mutational burden and higher heterogeneity than solid tumors [19, 22]. This review will present the current research progress in immune checkpoint inhibitors in AML.

CTLA-4 blockade

Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a receptor from the CD28 family present on activated T-cells. It inhibits T-cell maturation and differentiation by competing with the T-cell co-stimulatory receptor CD28 in binding to CD80 and CD86 ligands. Its high expression has been demonstrated on CD4+ cells, CD8+ cells, and Treg cells. High expression of CTLA-4 on Treg cells might play a key role in the induction of immunological self-tolerance [23]. Around 80% of AML samples express CTLA-4 [24]. Preclinical studies have demonstrated that CTLA-4 blockade enhances cytotoxic T-cells function and increases the proportion of T-cells producing IFN-γ [25]. In murine models, CTLA-4 blockade has triggered a graft-versus-leukemia (GVL) effect after allo-HSCT but without leading to graft-versus-host disease (GVHD) [26].

Ipilimumab

Ipilimumab is the first FDA-approved CTLA-4 inhibitor. It is indicated as monotherapy or in combination with nivolumab for melanoma. Additionally, when combined with nivolumab, it is approved for the treatment of several other malignancies including renal cell carcinoma, colorectal cancer, non-small cell lung cancer, hepatocellular carcinoma and head and neck squamous cell carcinoma [27]. Data on its *in vivo* activity in AML is still very limited. Davids et al. [28] investigated the response to single-agent ipilimumab therapy in patients with relapse after allo-HSCT in a phase I/Ib multicenter study (median age 58 years, range 22–75). Two out of twenty-two patients had a partial response, and 5/22 had a complete response, with four of them experiencing a durable response for more than 12 months. In another clinical study, ipilimumab showed limited activity in patients after HMA failure (mean age, 67.3, standard deviation 7.9 years). One patient (3.4%) achieved a marrow complete response for three months and seven patients (24%) achieved stable disease lasting more than 46 weeks [29]. Another open-label study assessed the efficacy of ipilimumab in a group of 29 patients with relapse of solid and hematological malignancies after allo-HSCT (median age 43 years, range 21–65). No disease regression was observed in AML patients [30].

The combination therapy of ipilimumab with HMA shows more promising results. In a multicenter phase I trial using ipilimumab and decitabine for patients with relapsed and/or refractory myelodysplastic syndrome (R/R MDS) or AML before and after allo-HSCT, Garcia et al. [31] reported an OS rate of 52% in allo-HSCT-naive patients and of 20% in patients post allo-HSCT.

PD-1/PDL-1 blockade

Programmed cell death protein 1 (PD-1) is a type I transmembrane protein primarily expressed in activated immune cells. It binds to the programmed cell death ligand 1 (PD-L1) and PD-L2. The expression of these ligands is regulated by pro-inflammatory cytokines involving IFN-γ, IL-12 and TNF-α [32]. The pathway's role is to inhibit immune responses. Even though PD-L2 has a greater affinity to PD-1 than to PD-L1, its role in immune regulation is smaller since PD-L1 is

present in many tissue types, while PD-L2 is found mostly in hematopoietic cells [33–35]. In patients with malignancies, an overexpression of PD-L1 molecules on the cells' surface of many tumors and PD-1 receptors on T-cells infiltrating the tumor has been observed. Interaction of PD-1 with PD-L1 on tumor cells inhibits apoptosis of malignant cells and suppresses the antitumor T-cell response by inducing their exhaustion and apoptosis. Blockade of this interaction restores T-cell activity and prevents the immune escape of neoplastic cells. These discoveries have allowed for the development of effective targeted therapies for multiple malignancies [36].

In AML, overexpression of PD-1 receptors has been observed in all T-cell populations [37]. The upregulation is more frequent in patients with relapses than in newly diagnosed patients [38], and also more frequent in non-respondents than in patients with complete remission [21]. Preclinical studies have demonstrated that disease progression leads to a higher proportion of Treg cells and increased PD-1 expression in CD8+ T-cells in murine AML models. PD-1 blockade, coupled with Treg lymphocyte depletion, prolonged the survival of the mice [39, 40]. In newly diagnosed AML patients, the modulation of PD-1/PD-L1 axis by combining anti-PD-1 and anti-PD-L1 antibodies with cytarabine was shown to enhance activation of Th and Tc cells, and thus positively affect the formation of an anti-cancer immune microenvironment, without influencing the blast cells [41].

Several anti-PD-1 antibodies (nivolumab, pembrolizumab, cemiplimab) and PD-L1 inhibitors (atezolizumab, avelumab and durvalumab) have been approved for various solid tumors, but their therapeutic use in hematological malignancies, including AML, is still under examination [42].

PD-1 inhibitors

Nivolumab

In 2016, Daver et al. [43] conducted a phase Ib/II study of the combination of nivolumab and azacitidine (AZA) with 51 enrolled patients who had failed prior therapy (median age 69 years, range 45–90). The median OS of the patients was 9.3 months, which compared favorably to the survival of similar patients treated only with AZA as salvage therapy [43].

In 2019, the same authors reported a phase II study in which 70 patients with R/R AML were treated with AZA and nivolumab (median age 70 years, range 22–90). In this trial, 65% of the patients had received prior HMA therapy. An overall response rate (ORR) of 33% was reported, involving 22% of CR or complete remission with incomplete count recovery (CRi) (four CR and 11 CRi). However, 58% of patients did not respond to the therapy. Prior HMA did not improve the outcome. The achieved ORR, CR/CRi and OS were significantly higher than in a historical cohort treated with HMA salvage therapy. In non-responders, CTLA-4 upregulation in CD4+ and CD8+ T-cell populations occurred, suggesting a role played by this mechanism in resistance to PD-1 blockade [44].

To further activate T-cell response, a second cohort of 31 patients was treated by the same authors with AZA, nivolumab, and ipilimumab (median age 71 years, range 26–86). The OS of 10.5 months was favorable compared to the first cohort and historical HMA-based clinical trial controls [45]. Due to the encouraging results, the authors are currently conducting phase Ib trials to study the efficacy of nivolumab and ipilimumab in patients with high-risk R/R AML or MDS after allo-HSCT (NCT03600155).

Another phase II study assessed the combination of nivolumab and induction chemotherapy with idarubicin and cytarabine in patients with newly diagnosed AML (n = 42) or high-risk MDS (HR-MDS) (n = 2) (median age 54 years, range 26–66). The median OS of all patients and of those who underwent allo-HSCT was 18.5 months and 24 months, respectively. However, there was no difference between patients who continued the therapy after remission and those who bridged to allo-HSCT, suggesting nivolumab's ability to restore antitumor immune activity. The ORR was 78% including 64% of CR and 14% of CRi. The therapy was well tolerated, and no excess immune-related adverse events (irAEs) and mortality were reported [46].

Liu et al. [47] studied the potential of nivolumab alone to eliminate MRD and as maintenance therapy in patients with AML after chemotherapy in a multi-center phase II study. Eighty patients were randomized to a treatment or a placebo arm (mean age 64.4 years, range 29–80). The 2-year PFS was identical (30%) in both arms. Nivolumab also failed to improve the 2-year OS, which was 60% in the treatment arm and 54% in the observation arm (p = 0.23). AEs were more common in the nivolumab arm, although they were expected and manageable. The authors concluded that patients with AML after chemotherapy did not benefit from nivolumab on its own [47].

Pembrolizumab

The therapeutic use of pembrolizumab combined with AZA was investigated in a phase II study in patients with R/R and newly diagnosed AML. In the first cohort of 37 R/R patients (median age 65 years, range 19–83), 29 (78%) were eligible for response evaluation. Among them, 14% achieved CR/CRi and 4% achieved PR. The median OS was 10.8 months. In the second newly diagnosed cohort, 8/17 evaluable patients (median age 75 years, range 67–83) showed CR/CRi (47%), 2/17 showed PR (12%), and the median OS was 13.1 months. In the first cohort, 24% of patients showed grade 3/4 irAEs, while in the second cohort, they were observed in 11% of patients [48].

Goswami et al. [49] tested the potential synergy of pembrolizumab and decitabine combination therapy in R/R

AML patients. The cohort included 10 previously treated patients (median age 62 years, range 30–81). One patient achieved a morphological leukemia-free state. Three had stable disease, and two were in CR. The median OS was 10 months. The AEs were consistent with a single-agent decitabine therapy, except for two patients who experienced irAEs [49].

Pembrolizumab was also tested in combination with HiDAC to examine whether PD-1 inhibition improves the outcomes of intensive chemotherapy in R/R AML. The ORR, CR rate, and median OS of the 37 enrolled patients were 46%, 38%, and 11.1 months, respectively (median age 54 years, range 24–70). Both patients with R/R AML and those receiving the treatments for the first time had good outcomes (13.2 and 11.3 months of median OS, respectively). The irAEs were, in general, self-limiting and easily resolved [50]. Nine of the examined patients were bridged to allo-HSCT. In a retrospective analysis, they were compared to a historical group of 18 AML patients after allo-HSCT without prior ICI therapy. OS was comparable between the two groups (67% vs. 78%). However, in contrast to the control cohort, the ICI group showed no 100-day mortality (0% vs. 17%) and no chronic GVHD [51].

No publication on cemiplimab in AML has yet been released. One study is currently recruiting (NCT03017820).

PD-L1 inhibitors

Durvalumab

A randomized, open-label study investigated the combination of AZA and durvalumab in HR-MDS and AML patients (median age 76 years, range 65–89). Both AML and HR-MDS patients were randomized into two arms to receive either AZA and durvalumab, or AZA alone. The difference in ORR between the arms in either cohort was insignificant. The authors concluded that the combination of drugs does not bring significant clinical benefits compared to AZA alone [52].

Another study, FUSION-AML-001, compared AZA with or without durvalumab as a first-line treatment for patients with AML or HR-MDS. Patients with AML were enrolled in two arms of 64 and 65 patients, respectively. In both arms, ORR, OS, and duration of response were similar [53]. The HR-MDS cohort was divided into two arms, each of 42 patients, with no significant differences in ORR and median OS between them [54].

A study assessing the efficacy and safety of the combination of AZA and durvalumab in previously untreated HR-MDS or AML elderly patients has been completed (NCT02775903). No studies are currently recruiting.

Avelumab

Zheng et al. [55] conducted a phase I study to assess the safety and tolerability of the combination of avelumab and decitabine in patients with untreated AML unfit for HiDAC. Seven patients were enrolled (median age 72 years, range 62–78). Two patients died of sepsis before the end of therapy, meaning that five patients were evaluated for response. One achieved CR, one showed disease progression, and the remaining three had stable disease. The median OS was 3.2 months. Regarding AEs, two patients developed grade three pneumonitis and five patients died of septic shock. The authors concluded the therapy did not bring about a clinical benefit and contributed to a significant increase in sepsis-related deaths [55].

The efficacy of avelumab with AZA in patients with R/R AML was assessed in a phase Ib/II clinical trial. Nineteen patients were treated (median age 66 years, range 22–83), 66% of whom had prior exposure to HMA. Two patients achieved CRi. The median OS was 4.8 months. The efficacy was comparable to the historical CR/CRi rate of 16% and the median OS of 6.7 months in a large cohort of R/R AML patients treated with AZA only. Mass cytometry performed in the same study revealed a higher expression of PD-L2 compared to PD-L1 on AML blasts with increasing PD-L2 expression during therapy, suggesting its role in AML immune escape [56]. No new studies are recruiting at the moment.

Atezolizumab

The safety of a combination of atezolizumab and gilteritinib (an FMS-like tyrosine kinase 3 inhibitor) was assessed in a phase I dose-escalation study by Altman et al. [57]. Eleven adults with relapsed or refractory FLT3-mutated AML were recruited (median age 82 years, range 68–84). Serious treatment-related AEs were reported in 10 patients (90.9%) and led to the withdrawal of study treatment in eight. In three patients, they led to death. The authors concluded that the combination had an acceptable safety profile with no new safety signals from either of the agents [57].

Another phase Ib study by Prebet et al. [58] evaluated the safety and efficacy of the combination of atezolizumab with guadecitabine in patients with R/R AML or newly diagnosed AML. All sixteen enrolled patients (median age 73 years, range 43–82) reported at least one AE and 15/16 reported an AE of grade 3 or higher. Eight patients died due to disease progression and six due to AEs. One patient achieved CRi. The overall benefit-risk profile of the drug combination was unfavorable [58].

Several clinical trials investigating the safety of drug combinations involving atezolizumab have been completed lately (NCT03390296, NCT03730012, NCT02892318).

TIM-3/Galectin-9 axis

T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) is a type I transmembrane protein found in various immune cells. It plays a crucial role in inhibiting Th1 responses and expressing inflammatory cytokines

such as TNF-α and IFN-γ. The ligand with the highest affinity to the TIM-3 domain is a soluble Galectin-9 (Gal-9). Their interaction triggers cell death in effector Th1 cells, reducing inflammation and promoting tumor cell evasion in malignant diseases [59]. In AML patients, TIM-3 expression on peripheral T cells significantly increases and positively correlates with a worse prognosis [60, 61]. In murine models after xenotransplantation, anti-TIM3 monoclonal antibodies eliminated LSCs able to reconstitute human AML [62]. Several anti-TIM3 monoclonal antibodies have been synthesized, but only MGB453 (sabatolimab) has demonstrated preliminary safety and efficacy in the context of AML [63]. Sabatolimab is a high-affinity, humanized IgG4 monoclonal antibody targeting TIM-3 on immune and leukemic cells [64].

The safety and response rate of the combination of sabatolimab and HMA in AML and HR-MDS were evaluated in a phase I study by Brunner et al. [66]. Fifty AML patients received sabatolimab + decitabine. Sixteen AML patients received sabatolimab + AZA. In the sabatolimab + decitabine cohort, three patients experienced irAEs of grade 3 or higher. In the sabatolimab + AZA cohort, no irAEs of grade 3 or higher were reported. For sabatolimab + decitabine, ORR was 41% and 24% in ND-AML and R/R-AML respectively. For MBG453 + AZA, ORR was 27% for ND-AML. Results for both combinations were encouraging [65]. A subsequent study discovered that R/R AML and HR MDS patients treated with the combinations of sabatolimab and HMA have favorable outcomes after HCT [66].

Based on these promising results, a STIMULUS clinical trial program was initiated to evaluate multiple combination therapies with sabatolimab in AML, HR-MDS and CMML during phase II and III trials. STIMULUS-AML1 is a phase II, single-arm study of sabatolimab, venetoclax and AZA in newly diagnosed AML patients with a median age of 77 years. The interim results showed the safety profile was comparable to that of venetoclax + AZA therapy [67]. The STIMULUS-AML2 study tested sabatolimab (400 mg or 800 mg IV) alone or in combination with AZA for AML patients with MRD detected after allo-HSCT. Twenty-one patients with a median age of 59 years were enrolled, 10 at 400 mg and 11 at 800 mg. At data cut-off, in the 400 mg cohort, three patients were still ongoing, and seven had to discontinue due to relapse. In the 800 mg cohort, seven patients had to discontinue: due to relapse (five), AE (one), or new therapy (one). No cases of GvHD or irAEs were reported in either cohort [68].

LAG-3/MHC signaling

LAG-3 is a type I transmembrane glycoprotein with a similar domain structure to CD4 [69]. It binds to MHC class II with a higher affinity than CD4, downregulating T-cell activation, proliferation, and cytokine production [70]. LAG-3 also binds to galectin-3, a lectin-modulating T-cell activity that is expressed in many solid tumors. The interaction between LAG-3 and galectin-3 inhibits CD8 (+) effector T cell function by lowering levels of plasmacytoid dendritic cells [71]. Another MHC-II independent, functional ligand for LAG-3 is liver-secreted fibrinogen-like protein 1 (FGL1). Blockade of their interaction by monoclonal antibodies stimulates immune reaction to tumor cells [72]. High expression of LAG-3+ T cells has been found in patients with newly diagnosed AML [73]. LAG-3/PD-1 co-expression in AML correlates with poor OS and might be used as a potential target for novel therapies [74]. In an *in vitro* model, LAG-3 blocking antibodies diminished immune evasion of AML cells by increasing T cell activation, lowering the number of Tregs, and improving MHC-I mediated toxicity against tumor cells [75]. Currently, one clinical trial is investigating the use of the combination of 5-AZA, nivolumab and an anti-LAG-3 antibody i.e. relatlimab for the treatment of patients with R/R AML and older patients with newly diagnosed AML (NCT04913922).

CD27/70 interactions

CD27 and CD70 are members of the tumor necrosis factor superfamily. CD27 is generally found in naïve T, memory T cells, B cells, and NK cells. CD70, on the other hand, is only transiently expressed on activated cells. Upon binding to CD70, CD27 interacts with TNF receptor-associated factors (TRAFs), leading to activation of T, B, and NK cells through NF-κB. However, chronic triggering of CD27 leads to T-cell exhaustion [76]. In hematological malignancies, CD70 may be aberrantly expressed in tumor cells with co-expression of CD27. Riether et al. [77] investigated CD70/CD27 signaling in AML as a potential therapeutic target. They discovered that CD27 and CD70 were constitutively co-expressed on LSCs in contrast to healthy HSCs. Soluble CD27 was also significantly elevated in the serum of AML patients and proved to be an independent negative prognostic factor. It was also discovered that CD70/CD27 signaling triggers the Wnt pathway in AML, promoting tumor progression. Attempts to block the CD70/27 interaction in AML stem cells resulted in cell growth inhibition and differentiation induction *in vitro*. In AML xenotransplanted mice, blocking the CD70/CD27 interaction prolonged survival [77]. Preclinical trials showed that leukemia stem cells in AML upregulate CD70 in response to HMA treatment, leading to increased CD70/CD27 signaling. Targeting CD70-expressing LSCs with a human αCD70 monoclonal antibody with enhanced antibody-dependent cellular cytotoxicity activity (cusatuzumab) eliminated LSCs *in vitro* and in xenotransplantation experiments.

Based on these findings, Pabst et al. [78] performed a phase I/II trial in previously untreated older patients with AML with a single dose of cusatuzumab monotherapy

followed by combination therapy with AZA. Initial results show hematological response in all 12 patients, with a CR in eight of them and complete remission with Cri in two (median age 75 years, range 64–84). No dose-limiting toxicities were reported [78]. Due to the promising results, a phase II study of cusatuzumab + AZA was started in patients with newly diagnosed AML ineligible for intensive chemotherapy (NCT04023526). Another phase Ib study evaluating the combination of cusatuzumab with venetoclax and AZA in patients with AML not eligible for intensive chemotherapy is active but not recruiting (NCT04150887).

SIRPα/CD47 pathway

CD47 is a transmembrane protein expressed on the surface of every cell type, and its primary function is to inhibit phagocytosis. When CD47 binds to signal regulatory protein alpha (SIRPα) present on macrophages, it sends a "don't eat me" signal [79]. The level of CD47 expression is higher in LSC in AML than in normal HSCs, and has been proven to be a negative prognostic factor [80, 81]. Chao et al. [82] identified calreticulin as a highly pro-phagocyting signal expressed on LSCs but minimally on normal cells. Calreticulin expression in cancer cells correlates strongly with CD47 expression, suggesting the protective role of increased CD47 from calreticulin-mediated phagocytosis of cancer cells. This leads to high susceptibility of LSCs to anti-CD47 antibodies [82]. It has been shown that anti-CD47 antibodies enable phagocytosis of AML cells *in vitro* and eradicate human AML in xenografted mice, indicating the high potential of this new therapeutic agent [83].

Magrolimab

Magrolimab, previously known as 5F9, is a first-in-class humanized anti-CD47 antibody that enhances tumor cell phagocytosis by blocking CD47/ SIRPα interaction. Despite promising results of many studies investigating its therapeutic use in AML, magrolimab has demonstrated both futility and an increased risk of death in a population of patients with hematological malignancies. Therefore, the US Food and Drug Administration (FDA) has halted all clinical studies of magrolimab in AML and MDS [84].

Evorpacept

Evorpacept (ALX148) is a high-affinity CD47-blocking protein with an inactive modified Fc domain to prevent phagocytosis of red blood cells and thus minimize toxicity. There are currently two studies investigating evorpacept in AML. The ASPEN-05 phase I/II open-label multicenter study is evaluating the safety and tolerability of evorpacept in combination with standard venetoclax and AZA in AML. The results from phase Ia show that the combination is well-tolerated without dose-limiting toxicities. In all 12 assessed patients (median age 74 years, range 56–82), a reduction in bone marrow blasts has been observed [85]. The results of the second ongoing trial evaluating evorpacept + AZA for HR-MDS (NCT04417517) are yet to be published.

Lemzoparlimab

Lemzoparlimab is a second-generation anti-CD47 IgG4 antibody with a distinctive binding epitope that reduces the risk of anemia. A phase I/II study of lemzoparlimab as monotherapy in patients with AML or MDS has been completed. Four out of five patients developed treatment-emergent AEs, but only one of them developed a grade 3 AE [86]. A phase III trial of lemzoparlimab with AZA for previously untreated HR MDS patients is currently recruiting (NCT05709093).

Conclusions

Despite significant advances in the treatment of AML, it continues to be characterized by low rates of survival and high rates of relapse. Even though ICIs have brought long-lasting responses in many malignant diseases, none have yet been approved for AML treatment. Classical CTLA-4 and PD-1 inhibitors represent a promising frontier in AML treatment, but their clinical application is still limited by the mixed results obtained in clinical trials, with significant AEs in some cases.

However, the optimistic outcomes of combination therapies of ICIs and HMA encourage further research in this area. Furthermore, numerous ongoing clinical trials are evaluating the therapeutic potential of novel targets such as TIM-3 or LAG-3, and the synergistic effect of drug combinations, bringing optimism to the future perspectives of AML therapy.

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