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Treatment of Acute Myeloid Leukemia: A Concise Overview

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Abstract

Acute myeloid leukemia (AML) is a disease characterized by hematopoietic and progenitor stem cells disorder, resulting in their proliferation and accumulation in bone marrow which leads to hematopoietic failure. It is an aggressive form of cancer that typically demands quick decision-making. In case of AML, the addition of drug efflux inhibitors to the chemotherapeutic regimen may improve outcomes in patients. With the advancement in treatment strategies, patients can now receive chemotherapy, radiation therapy or additional stem cell transplants. Specific genetic mutations in leukemic cells provide the direction for treatment and determine the overall survival rate of patients. Older patients have adverse treatment consequences as age is an important factor in AML prognosis. We critically reviewed multiple existing therapies for AML. Optimization of traditional therapies remain major concern of scientists. However, little bit advancement has been made in current years. There is immense need of novel and targeted therapies to treat AML and reduce its relapse chances.

Keywords: AML, Leukemia, Treatment

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1. INTRODUCTION

Therapy needs good diagnostics, in case of AML different features are involved like molecular, cytogenetic, immunologic and morphology of cells[1]. Most common leukemia in adults is AML which has lowest survival rate of all leukemias[2]. Different prognostic factors of AML are identified which includes organ dysfunction, performance status, age, karyotype and other distinct molecular abnormalities[3,4]. Different molecular and heterogenous alterations are identified in AML, as it is a heterogenous disease[1]. Chromosomal specific abnormalities are established as specific and strong survival prognostic markers[4]. Treatment of AML includes minimum one course of intensive induction chemotherapy, which is followed by an intensive consolidation and maintenance therapy. Patients can be deal with allogenic transplantation of stem cells, many compounds are currently in their clinical trials for AML[5,6].

Treatment of AML declines with increase in age[7,8], high relapse rate after complete remission is very worrisome[9,10] till date no significant advancement is observed in treatment of AML[11]. Leukemic cells are maintained by stem cells of leukemia which has role in pathogenesis[12]. Those patients who are diagnosed with higher number of leukemic stem cells have high risk of relapse then those who are having a smaller number of leukemia stem cells[13]. Early mutations lead normal progenitors and hematopoietic stem cells to pre-leukemic hematopoietic stem cells, which have advantage of better cloning over normal hematopoietic stem cells, they have not lost their multilineage differentiation ability. Later on, pre-leukemic cells are transformed to leukemic stem cells and initiates AML[14]. In certain subgroups of younger patients, intensive chemotherapy plus hematopoietic stem cell transplant greatly improves the outcomes yet almost 80% of the adult AML patients die of [17]. For example, the Mixed Lineage Leukemia (MLL) gene leads to treatment resistance and poor prognosis, thus, highlighting the significance of transcriptional deregulation in AML pathogenesis. Recently, targeting epigenetic modifying enzymes has gain attention due to structurally rigid motifs and/or involvement of their catalytic domains in AML pathogenesis. Despite our advancement in understanding AML genetics, very little has been translated into clinics, and the same highly toxic and ineffective chemotherapies developed over half a century ago are still being used. Therefore, there is an urgent need to identify novel venues for more potent and effective drug development to tackle this formidable disease.

2. HISTONE ACETYLATION AND DNA METHYLATION IN AML: EPIGENETIC THERAPY

Change in heritable phenotypes irrespective of change in the sequence of DNA is known as epigenetics[18]. DNA methylation that causes silencing of genes is common in Leukemia and other cancers too. Decitabine

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and Azacytidine are FDA approved DNA methyltransferase inhibitors (DNMTi) which are used for certain myelodysplastic syndrome and AML[19]. Different pan-histone deacetylase inhibitors, which induces re-expression of tumor suppressor gene and remodel chromatin, are in use to treat AML[20]. In clinical trials, combination of DNMTi or Ara-c with histone deacetylase inhibitors showed synergistic effects[21,22]. To find novel targets for epigenetic therapies, recent research focuses on systematic analysis of Leukemia carrying mutations that affect histone methylation-modifying enzymes or chimeric transcription factors.

3. LYSINE DEMETHYLASES ROLE IN TREATMENT RESPONSE

APL is the only AML subgroup with a well-established targeted therapy where all trans retinoic acid (ATRA) can induce transcriptional de-repression and leukemia differentiation. ATRA refractory cells are sanitized to treatment by pharmacological activation of *PHF8's* which is a histone lysine demethylase whereas its suppression cause resistance[23]. A combination of ATRA and the *LSD1* inhibitor TCP (family of transcription factors) initiated cell differentiation of non-APL AML cells[24]. However, *KDM1A* i-e *LSD1* is also the part of *RARa* fusions repression and inhibition that increase histone post transcriptional modification (*HEK4me2*) level on genes promoters of myeloid differentiation.

4. HISTONE METHYLASES AS POTENTIAL THERAPEUTIC TARGET

DOT1L is targeted by histone methyltransferase inhibitor; same as that of histone lysine methyltransferase, EPZ4777 in AML[25] and also its second-generation derivatives, i.e EPZ5676 showed selective inhibitory effects on cells with MLL fusions and H3K79 methylation [26]. Disease latency can be extended with AMI-408 and *PRMT1* in mouse models carrying *MOZ-IF2* or *MLL-GAS7* fusion[27]. shRNA or genetic approaches are better than *PRMT1* and *DOT1L* inhibitors in suppressing leukemia. It is reported that reduced tumour burden in the MLL-AF9 leukemia model by targeting Enhancer of Zeste Homolog 2 (*EZH2*), responsible for H3K27 methylation. DZNep, an *EZH2* inhibitor, reactivates thioredoxin interacting protein which result in accumulation of ROS (Reactive Oxygen Species) in cells of AML and lead it to apoptosis[28,29]. Tranylcypromine (TCP) independently or in combination with ATRA has been used for suppressing *LSD1* activity in MLL[30] or non-MLL leukemia[31]. GSK2879552 which is a TCP derivative, has already entered phase I clinical trials for relapsed AML (ClinicalTrials.gov identifier: NCT02177812) but at its effective doses, it showed severe toxicity. SP2509 non-monoamine oxidase inhibitor was developed as compared to TCP that blocked interactions between CoREST (a co-repressor) and LSD1. It effectively triggered apoptosis, induced cell differentiation and also suppressed colony formation in cells of AML with mutant NPMI but no fusions of MLL[32]. *LSD1* and *DOT1L* are essential for HSCs and normal development, hence a combination approach with lower dose may be beneficial[27]. Leukemogenesis is effectively diminished by pharmacological inhibition of KDM4 in vivo, SD70 (a KDM4C inhibitor) has limited toxicity in preclinical models, which highlights its therapeutic potential for treatment of AML.

Table. Emerging epigenetic drugs for AML treatment[33]

Compound	Target	Mechanism	Development
***DOT1L* inhibitor**	H3K79 methyltransferase *DOT1L*	Depletion of H3K79me2, leading to repression of MLL fusion targets	Preclinical EPZ4777 25. Phase I clinical trial EPZ5676 (NCT01684150, MLL leukaemia)
***PRMT1* inhibitor**	H4R3 methyltransferase *PRMT1*	Depletion of H4R3me2a, leading to repression of MLL fusion targets	Preclinical AMI-408
***EZH2* inhibitor**	H3K27 methyltransferase *EZH2*	Suppression of H3K27me3, leading to de-repression of polycomb targets (for example, CDKN2A, TXNIP)	Preclinical DZNep 34 UNC1999 35
MOA	H3K4	Unknown mechanism in	Clinical trials

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inhibitor TCP, TCP derivatives	demethylase KDM1A (LSD1)	AML enhances H3K4me1/2?	GSK2879552 (NCT02177812, refractory AML) ORY-1001 (EudraCT 2013-002447-29, refractory acute leukemia)
Non-MOA inhibitor	H3K4 demethylase KDM1A (LSD1)	Blocking the interaction of LSD1 and CoREST	Preclinical SP2509 32
KDM4C inhibitor	H3K9 demethylase KDM4C (JMJD2C	Increase in H3K9me3, leading to repression of MLL fusion or MOZ-TIF2 Targets	Preclinical SD70 27
BET inhibitor	Bromodomain-containing proteins, BRD family	Displacement of BRD family from chromatin	Phase I clinical trials OTX015 (NCT01713582, acute leukaemia and various haematological malignancies) CPI-0610(NCT02158858, acute leukemia and MDS) GSK525762(NCT01943851, relapsed haematological malignancies)

5. MOLECULAR TARGETTED THERAPIES

5.1. Enasidenib

Mitochondrial IDH2 is mutated in 8 to 19% cases of AML patients[36,37]. R172 and R140 mutations in AML generate an oncometabolite 2-Hydroxyglutarate or 2-HG[36,38]. R140 is frequent mutation and in comparison to R172, results in high CR and OS rates[39,40]. Moreover, R172 mutation was suggested to have a role in high WBC count and intermediate karyotype[40]. In a cohort study by Papaemmanuil and co-workers, mutations R172 in AML patients (3%) and their long-term outcome resembled biallelic (NPM1 and CEBPA) mutated patients[41]. However, it's hard to determine overall impact of *IDH2* mutations in AML prognosis. First IDH inhibitor to enter clinical trials is Enasidenib, it effectively inhibits a-ketoglutarate conversion into 2-HG[42,43].

5.2. Gilteritinib

30% of patients with normal cytogenetics have mutations in the FLT3 gene; mostly internal tandem duplication (ITD) and only 7% affect the tyrosine kinase domain. To inhibit mutated FLT3, tyrosine kinase inhibitors Sunitinib, Lestaurtinib, Sorafenib, Midostaurin, Quizartinib, Gilteritinib, and Crenolanib have been studied [44 - 47]. FLT3 inhibitors vary in their mechanism of action: type I inhibitors (Gilteritinib, Midostaurin) inhibit both ITD and TKD mutations; whereas, the type II inhibitor (Quizartinib) inhibits the ITD-mutated FLT3. Gilteritinib showed promising results in preclinical studies and it has been approved by the FDA to treat refractory or relapsed (FLT3-mutated) AML[48].

5.3. Glasdegib

The Hedgehog (Hh) signaling pathway relays signal transmission from cell surface to the nucleus and maintains organ development, homeostasis, and role in malagnancies[49-52]. This complex pathway modulates target genes through Glioma (Gli) transcription factors[53] among which *GLI1/GLI2* are expressed in leukemic cells. Previously it was thought that inhibiting the Hh pathway did not cause marked toxicity[54,] but it is found that its inhibition increased cytarabine-induced cytotoxicity[55]. However, in vivo suppression of the Hh pathway did not cause cytopenias[56].

The role of the Hh pathway in definitive and primitive hematopoiesis is controversial[57]. Studies did not show a direct effect of Hh inhibitors on AML cells[58] instead this pathway may have a role in a cross-talk

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between non-hematopoietic bone marrow cells and LSCs[58]. In a clinical trial of patients with haematological malignancies, Glasdegib (Hh inhibitor) demonstrated promising results by binding to the Smoothened protein[59]. Moreover, Glasdegib along with intensive remission induction chemotherapy in FLT3+ patients produced an augmented response.

5.4. Venetoclax

Proteins with an antiapoptotic role as well as proapoptotic initiators/effectors belongs to BCL-2 protein family of B cell lymphoma[60] and plays a very important role in cell fate. In several hematological malignancies BCL-2 proteins are overexpressed that's why their pharmacological inhibitors are of great interest[61]. Venetoclax interact weakly with some members of BCL-2, to increase its affinity and inhibitory activity it was reverse engineered[61,62]. Although predominantly venetoclax showed prominent results in lymphoid malignancies and BCL-2 has important role in AML[63].

5.5. Ivosidenib

IDH1 mutations were detected by comparing AML samples with normal cytogenetics to skin-derived samples and this was an important discovery in context of AML. Incidence of *IDH1* mutation has been variable among reports[64,65] generally 6%-10%, but higher in some studies[66] confirmed conversion of alpha-ketoglutarate to 2-hydroxyglutarate (2-HG) is due to gain-of -function IDH1 mutations, 2-HG modulates histone and DNA methylation and prevents cell differentiation[67-69]. Ivosidenib being oral inhibitor of *IDH1*, is more potent against mutant IDH1 than wild type IDH1, and without any activity against *IDH2*.

In future, these agents in clinical trials may result in achievement of disease remission and prevention of chemotherapeutic toxicities in relapsed or refractory leukemia.

6. LSCs SPECIFIC TARGETING STRATEGIES

Pathogenesis and maintenance of leukemic cells is greatly influenced by leukemic stem cells (LSCs) following, increased risk of relapse in patients with higher number of LSCs at the time of diagnosis[13]. These LSCs evolve from normal HSCs firstly into pre LSCs during early mutations with ability of multi-lineage differentiation. With an increase in mutational burden, these pre-leukemic stem cells ultimately transformed into LSCs results in AML initiation[14]. LSCs retain the capability of uncontrolled self-renewal with prominent defect in differentiation and maturation[70,71]. A symmetrical division leads to an increase in overall number of leukemic stem cells and few amongst these further differentiate into mature cells[72]. Major obstacles in treatment of AML like minimal residual disease and relapse are mainly due to of the presence of LSCs. Since LSCs are generally dormant, chemotherapeutic treatment fails in their elimination[73]. Furthermore, anti-cancerous activity of drugs on LSCs is difficult, as LSCs resides in bone marrow microenvironment.[74,75]. Under these circumstances, optimum way to achieve higher CR rate along with lower chance of relapse is to design treatment strategies considering LSCs biological characteristics that might help in specific targeting of LSCs[76,77].

7. NATURAL PRODUCTS AND THEIR DERIVATIVES

7.1. Flavonoids

The role of Flavgline family as a cytotoxic agent against leukemic cells is proved by several methods [78,79] rocaglamide noticeably targets LSCs without interfering in the function of normal HSCs mainly as *ERK* inhibitor that leads to inhibit phosphorylation of eukaryotic initiation factor 4E[80].Another such agent silvestrol targets LSCs in FLT3-ITD positive AML by inhibiting overexpression of FLT3 and decreasing levels of miR-155[81]. Both rocaglamide and silvestrol cytotoxic action involve mechanisms such as translation inhibition, reduction of anti-apoptotic proteins, Myc protein downregulation and disrupting mitochondrial integrity unsettling LSCs renewal ability[82,83]. Alvocidib showed promising results in R/R AML, emerging as a CDK9 inhibitor and induces downregulation of *McL-1*, *Myc* and *cyclin D1*[84].

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7.2. Terpenes

Treatment with Triptolide (TPL); diterpenoid triperoxide leads to ROS production that results in KG1a cells apoptosis by down regulating *CXCR4*, *Nrf2*, the adhesion molecule *VLA-4*, and the tumor angiogenic transcription factor *HIF-1α* in *in vivo* experiments[85]. The downregulation of surface markers of stem cell and transcription and translation of *Myc* is shown by salt variant of TPL i.e. a hydrophilic disodium called Minnelide[86]. Parthenolide (PTL) (natural small sesquiterpene lactone molecule) can binds to IκB kinase and inhibit NF-κB by modifying the NF-κB subunits (p50 and p65) result in LSCs reduction in primary AML and increases ROS level by inhibiting glutathione system of mitochondria. Dimethylamino-parthenolide (DMAPT) is same as PTL but enhances PTL family application and overcome PTL poor solubility and availability[87].The 17-N-allylamino-17-demethoxy geldanamycin (17-AAG), is derivative of antibiotic geldanamycin known as tanespimycin, leads to LSCs apoptosis through inhibition of *HIF1α* activity (HSP90-mediated)[88].

7.3. Antibiotics

Apoptosis in cancer and leukemic cells may induce by antibiotics. Such as, HIF-1α is inhibited by Echinomycin. And LSCs show enhance vulnerability to echinomycin than AML blasts [89]. In mice it specifically targets leukemia initiating cells with syngeneic relapsed AML and normal HSCs survival is not affected[90].

7.4. Curcumin

Curcumin (a phenolic compound) reduces *BCL-X(L)* and *STAT3* mRNA levels in the KG1 cells due to its cytotoxicity towards leukemic cells as well as leukemic stem cells[91]. Also, within AML cells polyphenolic compound resveratrol activates caspase signalling besides Fas-mediated apoptosis by inhibiting the *STAT3* and down-regulating B cell lymphoma *BCL-2*[92].

7.5. Lipids and other natural products

Avocatin B (avocado derived) a 17-carbon liquid is 1:1 mixture of avocadene and avocadyne that in LSCs selectively induces mitochondrial-mediated apoptosis. It causes glutathione system disorder in AML cells and increases ROS levels by affecting the citric acid cycle and inhibiting fatty acid oxidation[93].

8. IMMUNOTHERAPIES

8.1. Potential targets antibody therapies

For immunotherapy in the case of AML, CD123 and CD33 (sialic acid-binding immunoglobulin-like lectin) are frequent targets. CD33 binds to sialic acids and mediates cell interactions while inhibiting immune functions. Targeting CD33 is very difficult because of its overexpression in normal HSCs and LSCs. More specific than CD33 is CD123 (IL-3 receptor alpha chain) that is a surface marker in AML[94,95].

CD70 (tumor necrosis factor) present on active immune cells binds to its receptor; CD27 promoting lymphocyte activation and proliferation[96]. In bone marrow and peripheral blood CLL-1 is present on myeloid cells, leukemic cells and CD34+CD38- LSCs[97]. CD47 overexpression on leukemic stem cells leads to poor survival of patients and targeting signal regulatory protein alpha (SIRPα)-CD47 signalling in these cells leads to phagocytosis of LSCs, preferentially by macrophages reducing AML cells. [98-100].

8.2. Monoclonal Antibodies

Monoclonal antibodies are involved in cytolysis of leukemic cells through ADCC (antibody dependent phagocytosis), reverse ADCC and complement dependent cytotoxicity (CDC)[101]. Lintuzamab and BI 836858 both CD33 MAb are clinically tested for AML whereas, anti-CD123 first generation chimeric MAb CSL360 reached till stage 1 clinical tests but could not proceed further since no anti-tumour activity was reported in AML[102]. Second generation anti-CD123, CSL362 showed improved anti-tumour effects through increased ADCC in phase 1 AML trials after optimizing structure[103]. In order to achieve promising anti-tumour effect without any side effects, structural optimization is required as shown in clinical trials of CD47 MAb Hu5F9-G4, PD-L1 and TIM3[104].

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8.3. Bi-and tri-specific antibodies

Increasing the valency of antibodies as multivalent antibodies leads to targeting of tumour cells by binding to bi-tri-quadrispecific different epitopes of similar or diverse antigens stimulating CD3 and CD16 receptors on T cells and NK cells, respectively[105]. Over past few years special focus is laid on bispecific antibodies with designing nanobody, tandem diabody (T and Ab), dual-affinity re-targeting, bispecific T-cell engager (BiTE) 106. Bite is mainly regulated by PD-1/PD-L1 and CD80/CD86. Other noticeable BiTE AMG 330 and AMV-564 targets CD33 and CD3 presenting effective response in AML models at preclinical stage[107]. CD123 targeting bispecific antibodies MGD006, XmAb14045, and JNJ-63709178 amongst which mgd006 exhibited better therapeutic effect in refractory AML with CR rate of 31%[108] bsAb 1633, parallel in structure to BiTE targets CD16 on NK cells[109].

8.4. Immunotoxins

First antibody-drug conjugate, Gemtuzumab ozogamicin (GO) harnessed the ability of both monoclonal antibody and cell killing agent causing apoptosis in AML cells was however, withdrawn due to side effects of severe toxicity and an unstable linker [110]. IMGN779, anti CD33 MAb induces apoptosis through DNA damage and cell accumulation at G2/M stage[111] SL40, an immunotoxin comprises of recombinant human IL3 involved in anti-CD123 therapy effectively kills AML cells[112]. Another CD123 MAb, IMGN632 displayed efficient anti-tumour activity with low toxicity *in vitro*[113].

8.5. Radioimmunoconjugates

Over the years, radiotherapy has been proved as a treatment modality for management of several types of cancer. Highly proliferative AML cells exhibit sensitivity towards radiation conferring to its survival benefits[114]. Total Body Irradiation (TBI), is a radiotherapeutic technique, predominantly utilized for haematological malignancies. TBI along with chemotherapy is employed as a preparative regimen for HSCT that promotes myeloablative therapy. Despite the apparent advantage, it comes with lethal toxicities for many body organs thus questioning the efficacy and safety of the process[115]. To enhance the therapeutic prospects of radiotherapy, radioimmunoconjugates are used to replace the side effects due to its target specific activity[116,117]. Initially, β-emitting radioactive nuclides, iodine-131 and Yttrium-90 were used for CD33 targeting in AML[114]. In contrast to β-emitting radionuclides, α-emitters (225Ac and 213Bi) showed higher efficacy, decrease in cell eradication as a consequence of cross-fire along with reduced toxicity[118] as evident from a trial in phase 1 and 2, where cytarabine was administered in combination with Lintuzumab Bi 213 continuously for five days. This, subsequently, led to remission in AML patients as well restricted extramedullary toxicity (NCT00014495)[119]. Similarly, a low Cytarabine and Lintuzumab Ac 225 dose is reported (NCT02575963) as a safe dose for elderly AML patients presenting an overall 28 % response rate[120]. Additionally, for R/R AML patients, 4 µCi/kg dose of Lintuzumab Ac 225 was determined tolerable without any noticeable renal toxicity[121]. Whereas phase 2 trial on newly diagnosed older patients demonstrated 1.5 µCi/kg of Lintuzumab Ac 225 as a dose with lower myelotoxicity and in turn a decrease response rate of 22%. Increasing this dose to a 2.0 µCi/kg lifted the response rate to 69% though myelosuppression of grade 4 was observed in more than 50 % of patients[122].

9. ADOPTIVE CELL THERAPY

Immune system itself has been the main focus of research for past few decades in regard to cancer treatment. To make this a potent option, immune system is modified in order to detect tumour cells precisely beneficial over lymphokine activated killer cells stimulated by IL-2 and CIKs that lack specificity for tumour[123,124] and Tumour-infiltrating lymphocytes (TILs), although, successful in treatment of metastatic melanoma fell short of advantages due to unstable extraction, amplification, and treatment effects[125]. For this purpose, T cells along with dendritic and natural killer cells acquired from either a patient or donor are transformed *in vitro*, then administered to the patient. In order to carry out this specific anti-tumour effect ACT is developed into T cell receptors (TCR), antigen stimulated cytotoxic T lymphocytes (CTLs), genetically modified T cells and chimeric antigen receptor T cells (CAR-Ts).

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9.1. Antigen stimulated TCR-Ts and CTL

Peptides specific to antigen stimulate the natural defence through the production of specific CTLs that can also be expanded *in vitro*. TCR therapy equipped with a specific TCR and engineered α and β chains personalized according to tumour antigen can identify tumour antigen peptides either intracellular or extracellular, attached to major histocompatibility complex MHC. Afterwards, activation in CD3 in association with co-stimulatory T cell molecules lead to tumour cytoreduction[126]. Several targets called as tumour-associated antigens TAAs are identified such as melanoma antigen PRAME, Wilms tumour protein 1 WT1[127] and cyclin-A1 are widely expressed in LSCs and bulk of leukemic cells [128] latter antigen with significantly higher expression than PRAME and WT1, specific CTLs of these three antigens are currently tested[128,129] making it a critical target for immunotherapy. Reportedly, WT1-specific CTLs eliminated AML cells and leukemic stem cells in AML animal models[130] and five out of ten R/R AML patients post HSCT showed event free survival prolonged for eight years[131]. Moreover, identification of numerous TAAs after HSCT increases the overall anti-leukemic effect leading to the evaluation of T cells for safety and efficacy against WT1/NY-ESO-1/PRAME/Survivin (NCT02494167) and WT1/PRAME/Survivin (NCT02203903), resultantly, former TAAs specific T cells sustained 11 out of 12 patients in CR with median of 12 months after receiving HSCT and in case of active AML patients one partial remission and a CR was observed among seven patients[132].

9.2. CAR-Ts

Limitation presented by TILs and TCRs can be countered through CAR-T as in contrast it can bind to tumour cells even if antigens are not presented in MHC restricted manner by extracellular identification of antigens through scFv causing a broader penetration into tumour cells 126. Considerably evolved over the years, 1st generation CAR-Ts have limited signalling[133] while the generation 2nd coupled with co-stimulatory domain (CD28, 4-IBB, OX40 and ICOS), nonetheless, showed no sustained T cell activity[134]. Added potential of multiple co-stimulatory domains enhanced the overall anti-tumour activity of third generation CAR-Ts. Anti-leukemic activity in AML and haematopoietic toxicity of CD33 CAR -T was reported[135,136]. Consequently, reduction of leukemic cells was observed in one R/R AML patient after 2 weeks of infusing CD-33 CAR-T that later on reverted in 9 weeks (NCT01864902). Subsequently, GRADE IV level of toxicities have been reported corresponding to cytokine release syndrome[137]. According to researchers, CD33 CAR-T in coordination with CD33 knockout HSCT can be used to prevent damage of CD33 CAR-T aided by fact that -CD33 HSCs avoid damage and also CD33 absence did not affect activity of HSCs in any way[138]. On the other hand, AML cells and LSCs were killed in generation 1st of CD123 CAR-T[139] with the 2nd and 3rd generations also quite successful in AML xenograft mice model without affecting regular function of HSCs[140] making it safer to use rather than CD33 CAR-T[136]. One such CD123 CAR-T, MB-102 made its way into the clinical research stage. Results demonstrated its safety with no release of cytokines, however, anti-leukemic effect in AML is yet to be proved, also metallic nanoparticles have antimicrobial and anticancer activities, silver nanoparticles have antiproliferative and apoptosis-inducing properties, plants extracts can be used efficiently in its synthesis[141,142]. Another CD123 CAR-T considerably bio-degradable showed limited enlargement *in vivo*[143]. Several aspects shape the CAR-T designing and research, and although AML is characterized as a genetically heterogenous malignancy, multi or dual targeted CAR-T were also assessed in clinical trials (NCT03222674, NCT03631576, and NCT03795779). Noticeable results such as CLL-CD33 CAR-T (CR achieved in AML patients after 6 years of therapy)[144] CD123 and CD33 with CAR-T targeting in twin-fold showed effective anti-tumour activity with capacity to remove LSCs as described in a preclinical stage of study[145] also the recruitment of early phase 1 trial (NCT04156256). Another novel CD13×TIM3 CAR-T efficiently eliminated mice AML cells with reduced toxicity[141,102]. Unfortunately, reported results are not good enough for CAR-T in undergoing AML clinical trials with a hint of possibility towards myeloablative and related toxic effects such as CRs over period. While all these mixed results restrict the utilization of CAR-T to its maximum potential, better strategies have emerged including combinational target antigen recognition, suicide gene switch, synthesized notch receptors along with approaches involving gene editing techniques[146] can be employed in designing of 4th generation of CAR-T to optimize benefits while reducing the side effects[147].

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9.3. NK cells

In the patients of AML, NK cells lose their functions, doesn't identify and kill AML cells due to phenotypic changes [148]. In the microenvironment of bone marrow, the quick recovery of NK cells after HSCT is linked with satisfactory overall survival and extended progression-free survival[149], suggesting usage of ACT in AML NK cells. However, no human leukocyte antigen-compatibility or sensitization is needed for NK cells to kill tumour cells. Tumour cells are killed by NK cells by release of perforins and granzymes, death receptor mediated apoptosis and ADCC[150]. Whereas the NK cells with chimeric antigen receptor (CAR-NK) targets specific antigen and cause cytotoxicity.CD123+ targets in AML mice were effectively killed by CD123 CAR-NK[151]. Recently, trial is in progress for CD33 CAR-NK, where study of phase 1 demonstrated tolerability as well as safety at a dose of 5×109[152].

10. CONCLUSION

AML is a complex and heterogenous disease with multiple recurrently mutated genes. Increasing knowledge of AML pathogenesis put us in a state that we need multiple novel agents to treat this disease, as we can find out different active sites for drugs. Prognosis and treatment of AML had considerable advancement in last decades. Recently, novel agents have been explored to treat AML, and it has promising results. However, it is unlikely that all these agents will be helpful and curative as monotherapy, it is more likely that these agents will be used in combination with conventional therapy or other novel agents. Minimal gain and multiple failure are the history of AML drug development so far, it is a challenging task. However, in the current modern and genomic era a revolution is expected all the time in all subjects and fields.

CONFLICT OF INTEREST

Authors declared no conflict of interest

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