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Review

Immunotherapy for acute myeloid leukemia (AML): a potent alternative therapy

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ABSTRACT

The standard therapy of AML for many years has been chemotherapy with or without stem transplantation. However, there has not been any tangible improvement in this treatment beyond induction through chemotherapy and consolidation with allogeneic stem cell transplantation or chemotherapy. Residual AML cells which later cause relapse mostly persist even after rigorous standard therapy. It is imperative therefore to find an alternative therapy that can take care of the residual AML cells. With a better understanding of how the immune system works to destroy tumor cells and inhibit their growth, another therapeutic option immunotherapy has emerged to address the difficulties associated with the standard therapy. Identification of leukemia-associated antigens (LAA) and the fact that T and NK cells can be activated to exert cytotoxicity on AML cells have further introduced diverse immunotherapeutic development strategies. This review discusses the merits of current immunotherapeutic strategies such as the use of antibodies, adoptive T cells and alloreactive NK cell, and vaccination as against the standard therapy of AML.

1. Introduction

Acute myeloid leukemia (AML) also called acute myelocytic leukemia, acute myelogenous leukemia, acute granulocytic leukemia, or acute non-lymphocytic leukemia is a kind of leukemia that starts in the myeloid cells. These cells are capable of self-renewing and sustaining malignant populations as well as producing subclones [1]. Acute myeloid leukemia (AML) is considered acute because it progresses quickly if no suitable intervention is found, and can be very fatal in a short period [2]. Available data point to the fact that AML is the most common acute leukemia among adults, and its incidence increases with age [3,4]. Acute myeloid leukemia (AML) is reported to account for roughly 1.2% of cancer deaths in the United States although relatively rare [5,6]. Notwithstanding, the incidence of AML is expected to increase as the population ages. Considering these alarming indicators, it is imperative to devote time and resources in finding appropriate interventions, and creating awareness.

The symptoms of AML are as a result of the replacement of normal bone marrow with leukemic cells which causes a drop in red blood cells, white blood cells and platelets [7,8]. Early and common symptoms associated with AML are fatigue, dypnoea, ostealgia, arthralgia, hemorrhage, and increased risk of infection [9]. There are other signs which are peculiar to the individual. Typical example is the swelling of the gingivae which may be experienced by some patients due to infiltration of leukemic cells into the gum tissue [10]. Interestingly, some patients do not exhibit any of these symptoms, therefore the condition is discovered accidentally during a routine blood test. A number of risk factors have been implicated in AML development, however, blood disorders, chemical exposures, ionizing radiation, and genetics are the most cited risk factors [11].

Treatment of AML is divided into induction phase and consolidation phase. Induction phase of AML treatment seeks to clear the blood of blasts and reduce the number of blasts in the bone marrow. Currently, the induction phase involves high dose induction chemotherapy with cytarabine and an anthracycline [12–14]. Consolidation chemotherapy is then administered to destroy residual leukemic cells after the patient

Abbreviations: AML, acute myeloid leukemia; GO, gemtuzumab ozogamacin; PBD, pyrrolobenzodiazepine; HuM196, humanized murine 196; CARs, chimeric antigen receptors; LAA, leukemia associated antigens; TCRT, cell receptor; NKG2D, natural killer group 2 D; MHC, major histocompatibility complex (MHC); MIC, major histocompatibility complex class I molecules; KIR, killer immunoglobulin-like receptor; ADAM10/17, disintegrin And metalloproteinase 10/17; HIF-1α, hypoxia-inducible factor 1-alpha; GM-CSF, granulocyte-macrophage-colony stimulating factor; WT1, wilms tumor 1; CTLs, cytotoxic T lymphocytes; RHAMM, receptor for hyaluronic acid mediated motility; PRTN3, proteinase 3

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has recovered from induction [15]. Although chemotherapy with remission and induction phases is the first option, this treatment mode is usually associated with high toxicity and high risk of relapse [16]. This is because, the AML stem cell is reportedly resistant to chemotherapy and responds to different selection pressures from chemotherapeutic drugs [17,18]. Stress cells including cancer cells express stress proteins which are recognized by the immune system through immunosurveillance. This leads to the elimination of these stress cells. Nevertheless, cancer cells are able to escape this immunosurveillance through various mechanisms including the shedding of the stress proteins [19,20]. Therefore, for cancer conditions such as AML, the best therapeutic option is immunotherapy, where specific immune cells are activated to re-establish the immunosurvielling activity of the immune system against these cancer cells.

Unlike chemotherapy and radiotherapy, immunotherapy is more specific in its activity and therefore associated with low toxicity [21]. This specificity is the core of immunotherapy that eliminates cancer cells without harming normal cells. Immunotherapeutic agents specifically inhibit cancer cell proliferation, recruit effector cells to eliminate the cancer cells or induce apoptosis in the cancer cells [22]. More importantly, many suitable AML associated antigens that can be targeted by immunotherapy to exert its activity have been identified, translating into construction and production of more efficient immunotherapeutic agents.

2. Chemotherapy, the common treatment option for AML

Chemotherapy is the use of anticancer drugs for the treatment of cancer condition such as AML. It is the standard treatment option because chemotherapeutic drugs are readily available and affordable. More common routes of drug administration include intravenous, intrathechal or subcutaneous. Administration can also be done orally [23]. These drugs have high bioavailability and thus, are able to spread throughout the body, making it useful for the treatment of cancers such as AML. Chemotherapy of AML is usually done in two phases induction and consolidation [24]. The level of intensity of this treatment depends on the age and health state of the patient. Younger patients usually go through a more intensive chemotherapy compared to older patients who are mostly above the age of 60 [25]. Common drugs that are usually used in the induction phase are cytarabine, anthracycline, and cladribine [26]. In younger patients who are usually under the age of 60, cytarabine and anthracycline can be administered together and in certain situations, a third drug cladribine can be added [27,28]. In the case of patients above age 60 as well as those with a poor health condition such as poor heart function, fludarabine and topotecan are the preferred drugs [27]. Nevertheless, the induction destroys most of the normal bone marrow cells alongside the leukemia cells, resulting in low blood counts in the patients [29]. In view of this, drugs that raise white blood cell counts are also administered alongside the anticancer drugs.

The induction phase is not able to destroy all the possible leukemia cells and therefore consolidation treatment phase is required to complete the treatment to prevent possible relapse [13]. The consolidation phase basically destroys any remaining leukemia cells which escaped the induction phase. Consolidation is an important step in the treatment of AML as it helps prevent a relapse [30]. Unlike the induction therapy, only one drug at very high dose is used in consolidation therapy. Cytarabine is the preferred drug for this purpose. Mostly, the drug is given over 5 days and repeated every 4 weeks for a total of 3 or 4 cycles [31]. This treatment regimen is most appropriate for younger patients. Older patients and those in poor health are not able to cope with the treatment regime of consolidation therapy. As such the number of treatment cycles is reduced from 4 to 1 or 2 but a high dose of the drug is maintained in such patients. Alternatively, 1 or 2 cycles of standard dose cytarabine possibly combined with idarubicin, daunorubicin or mitoxantrone are adopted in the treatment of AML in a special group of patients [32]. Other treatment options such as radiation therapy and surgery (stem cell transplant) can be resorted to in the treatment of AML. Radiation therapy might be used when the AML spreads to the brain or spinal cord. Also, in certain situations, a stem cell transplant is recommended [33].

Most chemotherapeutic drugs are designed to inhibit the perpetual growth associated with cancer cells. They achieve this perpetual growth by dividing quickly and continuously. Interestingly, other important cells in the body including cells in the bone marrow, epithelial lining of the intestinal and oral mucosae, and the hair follicles are known to divide quickly and therefore are likely to be affected by the chemotherapy which was originally targeted at the cancer cells. These could lead to side effects such as alopecia, mouth sores, loss of appetite, nausea, vomiting, constipation or diarrhea and leukopenia which can result in increased risk of infection, bleeding and fatigue [34]. Another side effect although not common is lysis tumor syndrome which occurs in patients who have large numbers leukemia cells. During the chemotherapy, these large numbers of cancer cells break open and release their cytoplasmic contents into the bloodstream which overwhelm the kidneys, and therefore becomes impossible to get rid of these substances at a go. Accumulation of these excess substances has an adverse effect on the heart and the nervous system. However, it can be checked by taken extra fluid during the treatment [35]. These side effects largely depend on dose and type of chemotherapeutic drug and the duration of the drug use [36]. Although chemotherapy is mostly the first treatment option for AML, the disease has a high possibility of relapse, unless a more specific therapeutic strategy is employed afterward. This is because chemotherapy is only successful at inducing remission of AML. One of the best strategies that can be used to prevent relapse is immunotherapy [37].

3. Immunotherapy as alternative treatment for AML

Immunotherapy also known as targeted therapy is arguably the most effective intervention for AML. Cancers including AML can only progress if they are able to escape the immunosurveillance of the immune system [38]. Stress cells including these cancer cells express stress proteins that stimulates the immune system into action. These stress proteins are specific and therefore attract the attention of specific immune cells. Specific immune cells are able to recognize these stress proteins and are therefore recruited to the site of cancer to exert their effector function [39]. Notwithstanding, cancer cells including AML are able to escape this immune surveillance by shedding off these stress proteins from their surface or by blocking any receptor or ligand expressed (stress proteins) on the cancer cells that serve as recognition structures for specific immune cells to exert their effector function. Immunotherapeutic agents, therefore, come in to facilitate the recruitment and activation of the appropriate immune cells to act on the cancer cells by remedying the system changes employed by the cancer cells to evade routine surveillance activity of the immune systems. It can therefore be inferred that, the immunotherapeutic agents which are mostly biologics exert their activity by aiding in the activation or recruitment of the specific immune cells which have hitherto been rendered insensitive to the activities of the cancer cells due to certain inhibitory mechanisms employed by the cancer cells. Treatment of AML using immunotherapy employs several immunological systems and techniques that engage specific immune cells. These include the use of antibody therapy, adoptive T cell therapy, therapeutic vaccines, cytokines and alloreactive NK cells [40].

3.1. Antibodies

AML cells express a variety of surface antigens including CD33, CD123, CD47, and CD64 that serve as targets for antibody therapy [41,42]. These antibodies are usually designed to identify these specific antigens to help in the destruction of the cancer cells. Thus, the antibody mediates destruction of the cancer cells by recruiting appropriate

immune cells, blocking particular signaling pathway relevant to cancer cell growth by binding to the related receptor or ligand, or delivering attached chemotherapeutic agents to the cancer cells. Antigen CD33 is expressed by about 80% of AML cells. This therefore makes CD33 the most suitable antigen for targeted therapy in AML [43,44]. Identifying other suitable antigens on AML for targeted immunotherapy is a challenge because most of the potential antigens are found on both AML cells and healthy myeloid precursors which can easily result in off-tumor target effect in AML treatment, leading to prolonged thrombocytopenia [45]. This explains why the antigens including CD33, CD123, CD47, and CD64 are the most investigated, as far as immunotherapy of AML is concerned [46]. Studies elsewhere have shown that CD33 is underexpressed on normal hematopoietic stem cells or mature granulocytes, as such it is the most appropriate antigen for targeted therapy [47]. Thus, AML cells are selectively eliminated as against normal stem cells when CD33 is targeted. Antibody therapy against AML has not always been successful, especially when used unconjugated, unlike other leukemia types [48]. However, such antibodies can also be used to deliver drugs or radioisotopes to the cancer cells. As the antibody targets and binds to a particular antigen on the cancer cell, the anticancer agent is delivered. This is one of the efficient ways to use antibodies in the fight against AML. Conjugated antibodies specifically direct the attached anticancer agent to the cancer cells [49]. This strategy decreases the toxicity of these agents to normal cells and rather enhances the potency of the treatment since the cancer cells are selectively targeted. Lintuzumab, an unconjugated humanized version of murine (M195) monoclonal antibody which was constructed based on the framework of a humanized IgG1 inculcated with murine CDR was tested on AML affected patients [50]. However, the clinical trials proved unsuccessful. Therefore, the development and use of lintuzumab were discontinued after a phase III trial [51]. It became clear afterward that naked antibody was not appropriate agent for the treatment of AML, and therefore needed an alternative with relatively low toxic level. With this obvious limitation associated with unconjugated or naked antibodies, there was the need to modify these naked antibodies to be able to carry and deliver antitumor agents to the AML cells. Construction and development of conjugated antibodies then took the center stage. Gemtuzumab ozogamacin (GO), also known as Mylotarg, conjugated to antitumor antibiotic calicheamycin, was the first humanized anti-CD33 approved by the Food and Drug Administration (FDA) [52]. Initially, just like lintuzumab, it was used as a single agent, however, clinical trials as a single agent achieved only 15% remission [53]. However, when used with other agents in the treatment of relapse, the outcome was very promising. FDA, therefore, approved the use of gemtuzumab ozogamacin (GO) conjugated to calicheamycin in 2009 [54]. Unfortunately, in 2010 it became necessary to withdraw GO from the market because the toxic level became uncharacteristically high coupled with the fact that it did not improve the clinical outcomes during a phase III study [55]. Notwithstanding, further studies and modification are being done on GO knowing the potential it possesses, with some showing improved clinical outcome, contrary to what was reported in the phase III trial of the initial test that necessitated its withdrawal from the market [56]. This presupposes that GO could be reintroduced onto the market anytime soon [57]. There is another anti-CD33 conjugate Vadastuximab talirine (SGN−CD33A), which is conjugated with pyrrolobenzodiazepine (PBD), a DNA-binding agent (Fig. 1) [58]. The antibody part of the conjugate binds to the CD33 and result in the formation of a complex which is then internalized. Following the internalization, the PBD derivative is released into the myeloid cell and binds to DNA located in the minor groove, leading to disruption in DNA double-strand and apoptosis of myeloid cells [59]. This potential drug is in phase III of clinical trials as of 2016 August. This therapeutic agent represents a novel strategy that targets antigen CD33 expression on the AML cells (Fig. 1) [60]. Evidently, antibody conjugated with an antitumor agent is more potent and promising compared to the naked or unconjugated antibody as far as treatment of AML is concerned. Nevertheless, there have been efforts to modify the structure of cancer therapeutic antibodies to be able to deliver similar efficiency as conjugated antibodies [61]. The focus is now on genetic manipulation of antibody structure to increase the interaction with activating Fc receptors in order to improve antibody-dependent cytotoxicity mediated by specific immune cells such as NK cells (Fig. 1) [62]. Antibodies with engineered Fc targeting antigen such as CD33 on AML antigens have been tested in the preclinical phase, with some specific constructs targeting antigens such as CD33 (MAb 33.1, BI 836858) at the clinical phase [63].

Another way an antibody can be used in the treatment of AML is by conjugating to it a radioisotope that has antitumor activity. Key factors to consider when choosing the best isotope are the half-life of the radioisotope, the availability of a suitable chelator on the antibody to attach the radionuclide, and the type of particle(s) emitted by the radioisotope [64]. Isotopes that emit β and α particles are commonly used for this purpose. Beta (β) particles have become more useful for large tumor burdens because it has a relatively long range which allows the radiation to be delivered to both the target and surrounding cells [65]. This explains why isotopes that emit β particles are the preferred and most used agent for this purpose [66]. One common and frequently used β particle emitters is Iodine-131 which was first used in combination with murine anti-CD33 in a phase 1 trial in patients with AML, which subsequently had about 89% success [67], demonstrating how efficient this therapeutic strategy is. On the other hand, α particle emitters are known to have shorter range and therefore useful targeting specific tumor cells and for that matter smaller tumor burdens but not the surrounding cells [68]. Unfortunately, because of limited availability or lack of appropriate chelators, this potential therapeutic strategy has not been explored extensively over the past years [69]. However, more studies are being done to improve its efficiency and make it user-friendly, and these have yielded positive results in recent times. To this end, bismuth-213 conjugated to humanized murine 196 (HuM196) tested in patients with relapsed AML was the first study with α-particle emitter in human (Fig. 1) [70]. Significant success was achieved when 14 of the treated 18 patients recorded decreased leukemic blast in the bone marrow [71]. There have been other studies with α-particle emitters which have demonstrated appreciable level of treatment success [72], suggesting the potential this treatment strategy presents, therefore, needed the required attention to derive the full potential.

3.2. Adoptive t cells and alloreactive NK cells

The use of adoptive T-cell firstly entails the identification and expansion of autologous or allogeneic T cells that exhibit antitumor activity. This specific T cell with these characteristics is subsequently administered to the patient with AML [73]. To prolong its activity and expansion *in vivo*, the T cell as a matter of necessity is administered alongside an appropriate growth factor. This specific T cell for immunotherapy can be isolated *in vivo* from leukemia patients or *in vitro* through LAA-loaded APC [74]. Additionally, the use of T cells expressing chimeric antigen receptors (CARs) or engineered T-cell receptor (TCR) genes for adoptive immunotherapy in AML has become a preferred option [75]. CAR is a construct of hybrid single-chain receptor constituted by an extracellular tumor antigen-recognizing domain connected to an intracellular component. This extracellular moiety is made up of the CD3 zeta chain with or without additional co-stimulatory endodomains to stimulate the immune cell during tumor cell binding [76]. Available data point to the fact that there are ongoing clinical trials to test CAR T cells, with one successful early report about a patient who had a transient decrease in marrow blasts after being treated with CD33-directed CAR T cells [77]. Another report that attests to the potency of this treatment strategy is when CD19-directed CAR T cell was used to induce high remission rates and durable remissions in children and adults with B lymphoblastic leukemia [78]. Unlike CAR T

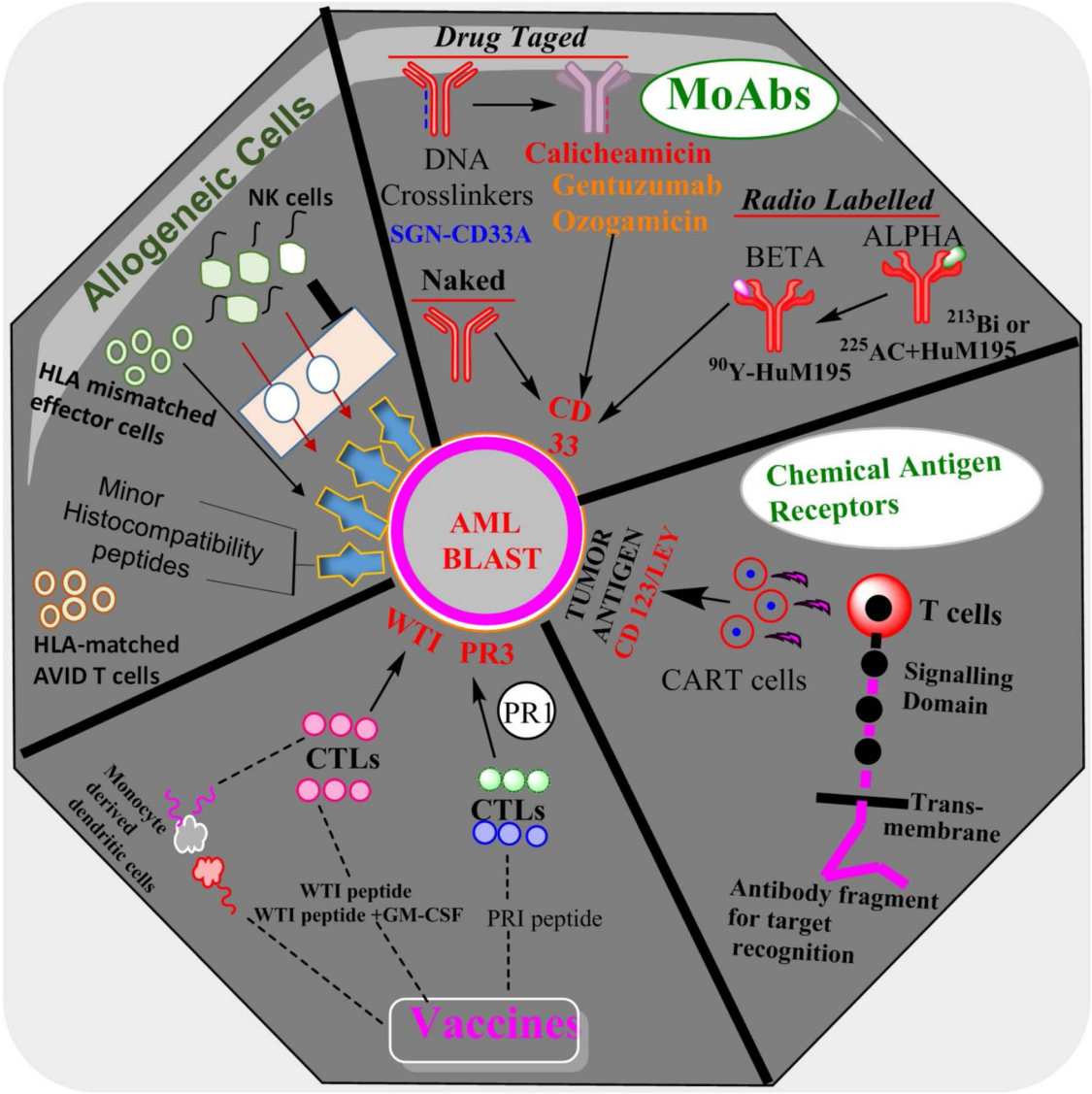

Fig. 1. Illustrations of Different Immunotherapeutic options to AML.

cells, T cells with engineered TCR genes have not received enough attention. However in the few instances that it has been tested, it has shown that it can efficiently induce physiological activation and offer a better option for the recognition of intracellular epitopes expressed on the cell surface [79].

NK cells express receptor Natural Killer Group 2 D (NKG2D) that binds to major histocompatibility complex (MHC) class I molecules (MIC) expressed on the surface of stressed cells including cancer cells to initiate cytotoxicity in these cells [80]. However, as presented in Fig. 2, tumor cells that down-regulate the expression of MIC or shed the MIC off its surface escapes the immune surveillance and for that matter cytotoxicity by NK cells [81]. Notwithstanding, NK cells might recognize the missing expression of the MIC when they encounter mismatched allogeneic cells, and it is referred to as missing self-recognition [82]. Potential NK cells for alloreaction make use of the inhibitory killer cell immunoglobulin-like cell receptors to recognize the missing expression or under-expression of self-MIC. This explains why NK cells alloreactions are activated between cells that are killer immunoglobulin-like receptor (KIR) ligand-mismatched. Studies have demonstrated that AML is susceptible to alloreative NK cells *in vitro* [83]. Additionally, donor versus recipient NK cell alloreactivity in haploidentical transplants reduced the risk of relapse in clinical trials on AML patients [84]. Alloreactive NK cells could, therefore, be employed to get rid of AML cells.

3.3. Vaccines

A vaccine against AML is intended to actively stimulate a patient's immune system to pick out and destroy AML cells via the introduction of a tumor antigen [85]. The first attempt of vaccine for AML was in the late 1960s and was created by combining tuberculosis peptide bacilli Calmette- Guérin antigen and irradiated AML cells to actively stimulate the immune system [86]. Largely, the attempt failed to produce any significant results as three out of the four control trials recorded no significant outcome. Thus, one of the four trials did increase survival and remission duration of vaccination maintenance immunotherapy after induction and consolidation. However, there has been a significant improvement in the construction and production of vaccines recently [87]. Development and production of AML vaccine are through the use of intact AML cells attenuated through radiation, or antigens on the tumor cells which can be categorized either as leukemia-associated antigen (LAA) or leukemia-specific antigens (LSA) [88]. Currently, four vaccine types have been identified for AML targeting. These are peptide vaccines, granulocyte-macrophage-colony stimulating factor (GM-CSF) vaccines, dendritic cell (DC) vaccines and whole tumor cell vaccines [89] (Fig. 1).

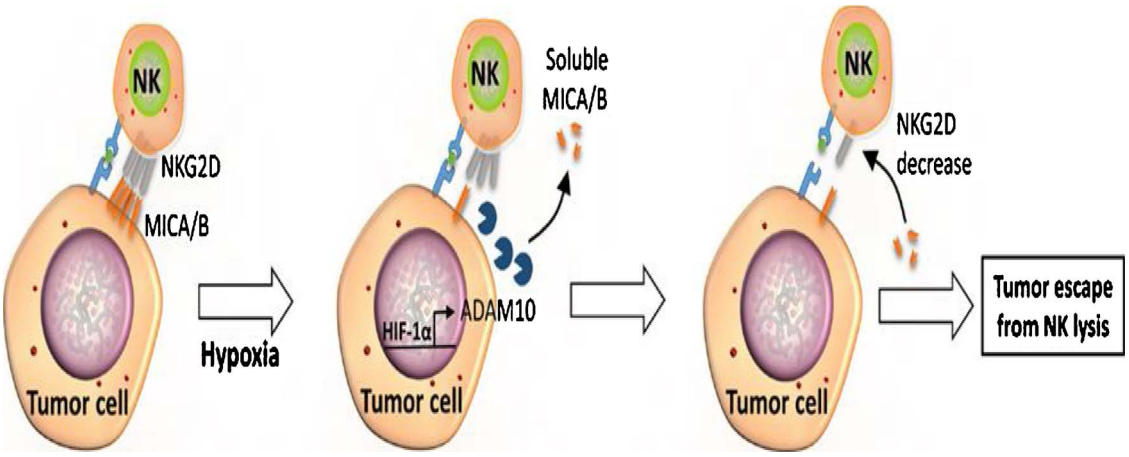

Fig. 2. Soluble MIC regulates NKG2D receptors on the surface of NK cells. Under hypoxic stress condition, tumor cells induce expression through HIF-1α which results in the release of A Disintegrin And Metalloproteinase 10/17 (ADAM10/17). Released ADAM10/17 cleaves MIC ligands on the surface of tumor cells. The resultant soluble MIC downregulates the expression of NKG2D on the surface of NK cells, leading to tumor escape from NK-mediated cytotoxicity.

3.3.1. Peptide vaccines

AML vaccination using peptide has been investigated extensively but the results have always been disappointing [90]. However, with the recent identification of suitable receptors for this purpose, encouraging results have been recorded. [70]. To derive the full benefit of this therapeutic option, the peptide vaccine binds specifically to the antigen-expressing AML cells but not normal cells which do not express the targeted antigen. Wilms tumor 1 (WT1) antigen which is overexpressed on AML cells is a suitable target for peptide vaccines and has accordingly been tested in several peptide vaccine investigations, and has demonstrated to be potent in treating and managing WT1 expressing AML cells [91]. Binding of peptide vaccine to this antigen stimulates cytotoxic T lymphocytes (CTLs) against AML cells expressing WT1 (Fig. 1). Proteinase 3 is also an important serine protease mostly overexpressed on AML cell. It is therefore targeted with a peptide vaccine designed and developed from proteinase 3 (PRTN3) which stimulates CTLs against AML cells [92]. Although using peptide vaccine derived from proteinase 3 has not produced tangible success, combining PR1 (a 9 amino acid-long peptide derived from the myeloid proteins proteinase 3) and WT1 peptide vaccines in a combination therapy increased the potency of both PR1 and WT1 [93], demonstrating that the two peptide vaccines function synergistically. Another important antigen for this purpose is the receptor for hyaluronic acid mediated motility (RHAMM) which has shown potent immune activity against AML cells that express this antigen (Fig. 1) [94].

3.3.2. Granulocyte-macrophage-colony stimulating factor (GM-CSF) vaccines

Granulocyte-macrophage-colony stimulating factor (GM-CSF) vaccine is another important agent which has been used to stimulate the immune system together with other AML vaccines [95]. A case in point is when GM-CSF was used in combination with HLA-A*0201–restricted WT1 peptide in the treatment of patients who were not eligible for chemotherapeutic induction. In this study, more than half of the subjects achieved stable disease levels, demonstrating the potency of GM-CSF when used in combination with AML vaccine (Fig. 1) [96]. Notwithstanding, more work is needed in this direction to further improve its potency.

3.3.3. Dendritic cell (DC) vaccines

Dendritic cells (DCs) which are antigen presenting cells (APCs) are capable of mediating the production of antigen-specific CTLs [97]. The use of these AML-specific DCs for vaccine development has generated keen interest among scientists in this field because of the strong immune response they generate. The source of these specific DCs is the host's monocytes that undergo *in vitro* differentiation to DCs in the presence of granulocyte macrophage colony stimulating factor and interleukin-4 and then primed by the introduction of LAAs through WT1 mRNA electroporation [98]. Combining monocyte-derived DC vaccines and WT1 has generated immense immune responses including specific molecular responses for some patients in partial remission, presenting as an appropriate treatment option (Fig. 1)[91]. As recent as 2015, a new vaccine produced, based on telomerase-focused DCs, AST-VAC1 was a success in a phase II trial. But for mild side effects such as headaches and fatigue, this vaccine was largely safe. With respect to efficacy, eleven out of the 19 patients in complete remission remained disease-free after 52 months of follow up [99]. This is, therefore, a potential therapeutic agent which should be subjected to further investigations to bring out the full potential.

3.3.4. Whole tumor cell vaccines

Another immunotherapeutic strategy which has been used is the whole tumor cell approach. Employing this strategy ensures simultaneous activation of immune responses against multiple TAAs [100]. The whole tumor cell approach for AML treatment seeks to circumvent factors such as immune escape mechanisms and the non-inflammatory leukemia microenvironment that inhibit effective immune responses, in order to promote their antigen-presenting capacity by increasing the number of inflammatory signals in the tumor cells microenvironment [101]. As demonstrated by most of the trials involving the whole cell approach, it is a suitable AML treatment option [102,103]. In the first report of active immunotherapy for patients with AML [104], patients received chemotherapy with or without immunotherapy. This consisted of intradermal injections of irradiated (attenuated) AML cell in combination with Bacillus Calmette-Guérin (BCG) as an adjuvant to elicit an immune response against the LAAs, delivered to competent APCs by the attenuated AML cells (Fig. 1). This immunotherapy was relatively successful, resulting in prolonged periods of first remission and longer survival after the first relapse. Notwithstanding, there were very few long-term survivors. Another study investigated the efficacy of a combined administration of human irradiation primary AML cells and exogenous proinflammatory stimuli [105]. A phase I clinical trial of this therapeutic option in which autologous irradiated AML cells were administered to relapsed or refractory AML patients in combination with the cytokines IL-2, IL-6, and GM-CSF resulted in complete remission in four and partial remission in five of 25 patients. This is the common trend with most whole tumor cell vaccines tested on AML patients [106]. It can, therefore, be inferred that whole tumor cell vaccine as an alternative therapeutic option for AML is patient specific.

4. Conclusion

Immunotherapies for AML have achieved some level of success in the various trials. Studies in this field have progressed and demonstrated that immunotherapy is a potential alternative to chemotherapy and radiotherapy in the treatment of AML. Considering the fact that many antigen-specific immunotherapeutics are currently under development, more potent immunotherapeutics will soon be available for the AML treatment. Another critical fact that has surfaced following many years of investigation is that AML is a heterogeneous disease and therefore it is unlikely that any single therapeutic regimen will constitute effective treatment. However, it has been established through investigation that there is room to successfully combine different immune approaches and with chemoradiotherapy, and determine the optimal timing of these therapeutics in the course of the treatment. This presents immunotherapy as the option of choice, therefore should be given the needed attention to derive the full benefits associated with it.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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