Review Article

Effective Dendritic Cell-based Immunotherapeutic Vaccines for Acute Myeloid Leukemia (AML)

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ABSTRACT

Acute myeloid leukemia (AML) is a type of poor prognosis hematological malignancies characterized by heterogeneous clonal expansion of myeloid progenitors. Leukemic stem cells are thought to form the majority of a cell population in minimal residual diseases (MRDs) which are resistant to current chemotherapeutic regimens and mediate disease relapse. Current therapeutic vaccine strategies have developed to mount effective anti-leukemic immunity and eradicate the MRDs. Dendritic cells (DCs) are the most professional antigen-presenting cells to elicit efficient anti-leukemic immune responses. In this review article, we present the possibility of generating AML blast-targeted DCs, especially leukemia-derived DCs and their appropriate maturation protocols and particularly the synergistic effects of TLR agonists. We also discuss about the *in vitro* evaluation of the generated DCs, some reported outcomes of DC-based clinical trials as well as the possibility of combination therapy to improve the efficacy of DC-based vaccines in AML patients.

KEYWORDS: AML-DC, DC-based cancer vaccine, acute myeloid leukemia (AML)

INTRODUCTION

Hematological malignancies are cancers that affect blood and different organs like bone marrow and lymph nodes. Considering the close relationship between the immune system cells, a disease disturbing one of the three compartments will often influence the others as well [1]. While unusual in solid tumors, chromosomal translocations are a common cause of liquid tumors. This feature leads to a different approach in diagnosis and treatment of hematological malignancies [2]. AML is a type of hematological malignancies characterized by heterogeneous clonal disorder of hematopoietic progenitor cells and the most common acute leukemia in adults, with a poor prognosis and an overall survival rate of only 23.6 % at 5 years [3, 4]. It is also known by an increase in the number of myeloid cells in the marrow and an arrest in their maturation, frequently resulting in hematopoietic insufficiency (*i.e.* granulocytopenia, thrombocytopenia, or anemia) with or without leukocytosis [5].

Recent studies have revealed that the heterogeneity of malignant cells relates to the previously defined immature progenitors within the bulk of leukemic cells which are intrinsically resistant to chemotherapy and are able to repopulate the stem cells [6]. These newly-adopted "leukemia stem cells (LSCs)" share the most relevant features of the normal hematopoetic stem cells (HSCs) such as the self-renewal potential and dormant status. It would be difficult to find various pools of leukemic stem cells within the individual patients which differ both phenotypically and molecularly [7, 8].

Despite intensive consolidation chemotherapy in AML patients, the relapses occur in 50% of the patients due to the presence of minimal residual disease (MRD) [3, 9, 10]. Since leukemic stem cells are thought to consist the most of cell population in MRDs, their study also has potentially promising clinical implications. On the other hand, while achieving complete remission (CR) mainly depends on high-dose chemotherapy, the maintenance protocols as well as different strategies for the induction or restoration of the immune pressure against LSCs are needed for several months or years after intensive chemotherapies [3]. Based on the major role of the immune system in the prevention and control of leukemia, alternative therapeutic approaches other than intensive chemotherapy or hematopoietic stem cell transplantation (HSCT) have been explored to modulate the immune system [1, 11, 12].

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Regarding the prominent role of a tumor-specific T cell response in relapse prevention, there is a need to explore alternative treatments for notably maintaining the remission phase in AML patients. It would be a promising treatment approach to reverse the tumor-mediated immunosuppression as a consequence of different rationales such as a lack of adequate expression of costimulatory molecules, major histocompatibility complex (MHC) molecules, or tumor-associated antigens (TAAs) on cancer cells [13].Recent studies or clinical trials have been focused on active cancer immunotherapy approaches like cell-based therapies. Dendritic cell (DC)-based vaccination with the ability to elicit cytotoxic T cell (CTL) responses that can eliminate residual tumor cells is therefore of great interest [14].

DC vaccination: A cell-based cancer immunotherapy approach as an alternative medicine

Cancer immunotherapy is a collection of methods using the immune system to fight against the cancers. This can be either through the immunization of the patient (e.g., by administering a cancer vaccine) in order to train the patient's own immune system for recognizing and destroying the tumor cells or through the administration of therapeutic antibodies as drugs, to recruit the patient's immune system for fighting the tumor cells [15-18]. Cell-based immunotherapy is another major entity of cancer immunotherapy. This involves immune cells such as the natural killer cells (NK cells), lymphokine activated killer cells (LAK cells), CTLs, DCs, etc. which are either activated in vivo by administering certain cytokines such as interleukins or are isolated, enriched and transfused to the patient (ex vivo) to fight against the cancer. In this regard, one of the most exciting approaches involves the use of DC-based vaccines [14, 19-28].

The truth that our immune system can be exploited for control or even eradication of leukemia blasts has created a strong interest in manipulating therapeutic vaccine strategies to increase effective anti-leukemic immunity in AML patients. The rationale of vaccination against AML comes from the facts that AML cells carry leukemia-associated antigens (LAA) which allows them to be targeted and killed by LAA-specific CTL [20]. DCs are professional antigen presenting cells, capable of inducing anti-leukemic immune responses directed against leukemia-associated antigens. They are programmed to digest and present antigen fragments via major histocompatibility complex (MHC) molecules to T cells. In addition to presenting the antigens, DCs express co-stimulatory molecules to prime naïve CD8+ T cells into antigen-specific CTLs [29].

Recently, DC vaccination has been developed as a promising immunotherapy for cancers including hematological malignancies. Using DCs in clinical trials for therapeutic purposes in cancer patients has been started since the mid-1990s [30].These antigen presenting cells have the professional ability in orchestrating the immune system and triggering the appropriate immune responses. Culture of DCs ex vivo circumvents the immunosuppressive features of the tumor microenvironments and can lead to eradication of MRD which are a small reservoir of leukemic cells (mostly cancer stem cells) that are resistant to chemotherapy and may evolve to a full clinical relapse [14, 21, 28, 31].

Regarding the limiting use of HSCT to younger patients and no donor available in some patients, scientists are looking for effective and less toxic post-remission therapies to prevent the relapses and to prolong the survival rates. The feasibility of using DCs has been established in many cancers while both immunological and clinical responses have been reported in several clinical trials in cancer immunotherapy. Therefore, DCs are considered as attractive and potential candidates for anti-tumor or anti-leukemic vaccination strategies [32].These unique characteristics of DCs have made them exciting tools for generating vaccines that can activate the tumor-specific immune responses.

Possibility of generating blast-derived DCs

The main sources of DCs for clinical trials are: CD34+ blood, umbilical cord blood or bone-marrow-derived ancestors, blood DCs, monocytes as well as leukemic blast precursors [33-36].

A major advance arose with the description of a simple method to generate large numbers of blood-derived DC from monocytes by culture in the presence of granulocyte-macrophage colony stimulating factor (GM-CSF) and interleukin-4 (IL-4). This allocated the design of immunotherapeutic strategies using ex vivo-generated DC as an adjuvant. Monocyte-derived DCs are widely used in clinical trials, in shape of immature DCs (only cultured in IL-4 and GM-CSF) or mature DCs (matured by different factors like cytokine cocktail: IL-1β, IL-6, tumor necrosis factor-α (TNF-α) and Prostaglandin E2 (PGE2), often referred to as the "gold standard DCs"). Several pilot clinical trials indicate that mature DCs are superior to immature DCs, at least because of their T-cell stimulatory ability in contrast to regulatory T cell induction of immature DCs [37].

In order to trigger a tumor-specific T cell response in leukemic patients, it is common to pulse monocyte-derived DCs with tumor (or leukemic) antigens which imposes an additional manipulation to the DC generation process [24]. Since it is hard to isolate leukemia-specific antigens from different AML patients, immunogenic DCs can be successfully generated from blasts without needing antigen pulsing [34]. Furthermore, differentiation of blasts into leukemic DCs can elevate their immunogenicity, as demonstrated by the induction of anti-leukemic T cell responses. This clarifies the rationale for attempting to change the leukemic cells into efficient antigen-presenting cells [26]. The first report on successful generating of AML-DCs in vitro by Santiago-Schwartz and *et al*., opened a promising way toward a simple DC generation method from available blasts for future DC immunotherapy in AML patients [35, 38]. AML-DCs can differentiate from blasts in relapse phase and induce anti-leukemic T-cell responses [39, 40]. These cells can be successfully generated and regain the stimulatory capacity of mature monocyte-derived DCs (i.e. conventional DCs). Bagheri and his colleagues showed that blast-derived DCs can be sufficiently generated in all AML cases and the leukemic origin of them can be confirmed using the expression pattern of angiotensin-converting enzyme (CD143) which its expression is much higher on mo-DCs than AML-DCs [41]. Moreover, Kufner and his colleagues indicated the possibility of generating DCs in AML and MDS patients under serum-free condition, although not all blasts in culture could convert into DC. Besides, they recommended selecting leukemic-DCs for vaccinations or ex vivo T-cell activations to avoid contaminations with non-converted blasts and non-leukemia-derived DC and to improve the yield of specific, anti-leukemic T cells, as well [42]. Research efforts have now focused on optimizing in vitro culture conditions for generating antigen specific leukemic-DCs and their maturation protocols in order to maximize their potential to induce anti-leukemic immunity [19].

According to our previous studies on generating blast-derived DCs, we showed that blasts of more than 70 % of AML

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patients mostly with M4 or M5 phenotypes (French–American–British (FAB) classification) could differentiate to DCs (AML-DC) in a 5% AB serum culture condition. Those converted blasts displayed typical DC markers (e.g. CD40, CD86, CD1a, CD83 and CCR7) and revealed the other functional capacities of antigen presenting cells. We also tried to find the most efficient maturation cocktails among different combinations of TLR ligands as recently introduced potent adjuvants [43, 44].

Synergistic effect of TLR-agonists on DC maturation

Recent studies have focused on attempts to provide appropriate guidelines in order to generate optimally matured DCs with the ability of migration toward lymph nodes and response to licensing stimuli, following administration to a patient with cancer [14]. However, there are controversial reports on DC generation and maturation protocols. For instance, Sporri and his colleagues believed that inflammatory mediators in cytokine cocktail are insufficient for generating fully activated DCs and promote expansion of CD4+ T cell populations lacking a helper function due to negative regulation properties of PGE2 [45]. Therefore, applying the cytokine cocktail is not the only method used for maturation of human DCs. Kalinski and colleagues have introduced a "megacytokine cocktail" consisting of 5 reagents (TNF-α, IL-1β, Poly (I:C), IFN-α, and IFN-γ), conferring superior immunogenicity and more potent CTL responses [46]. As a result, cocktails containing synthetic TLR agonists such as Poly (I:C) (TLR3 agonist) or R848 (TLR7/8 agonists) came out as attractive alternatives for the induction of DC maturation and subsequent Th1 immune responses via high production of IL-12(p70) [47, 48].

The co-stimulatory features of DCs can be launched by triggering of pathogen recognition receptors (PRRs) such as Toll-like receptors (TLRs), which have a critical role in sensing microbial or viral structures called pathogen-associated molecular patterns (PAMPs) [49, 50]. Expression of at least 11 TLRs on normal or transformed cells of the human immune system has been well established [50, 51]. A variety of TLRs are also expressed by human AML-DCs [52]. Recent studies suggest that adjuvants, including TLR ligands are powerful stimulator for DC maturation by targeting distinct TLRs and their intracellular adaptors. After binding, DCs can directly mediate the innate immune responses by regulating the phagocytic function or differentiate to mature DCs and instruct the adaptive immune responses by secreting the effective cytokines [53, 54]. There are controversial reports on activation of different T cell subsets following TLR binding [55]. Overall, it appears that some ligands (e.g. TLR-3, -4, -5 and -7/8) can shift the immune response toward polarized Th1 responses and/or CTL induction while the others like TLR-2 ligands emerge a Th2 bias [56]. Thus, it can be possible to find appropriate combinations of TLR ligands with the most synergistic effect on DC maturation and function to stimulate a potent antitumor immune response. In addition to eliciting a desired immune response, it may also be accompanied with the strategies to overcome the immunosuppressive microenvironment in the tumor periphery [57].

Combination of poly(I:C) binding as an TRIF activator via an MyD88-independent pathway, along with the bindings of TLR4 and TLR7/8 for MyD88-dependent pathway have been investigated on AML-DCs in our published study. Phenotypic evaluation of AML-DCs stimulated with LPS alone or in combination with R848 and/or poly(I:C) revealed, to some extent, a similar expression pattern of DC markers and costimulatory molecules expressed on conventional monocyte-derived DCs. We found that a combination of LPS + R848 and LPS + R848 + poly(I:C) provide the highest percentages of DCs expressing HLA-DR and CD86. High expression of these two molecules was accompanied with a strong allostimulatory capacity of the relevant AML-DCs in allo-MLR [43].

Similarly, Bohnenkamp *et al*. indicated that potent and efficient T-helper cell type 1 response can be elicited by monocyte-derived DCs after TLR engagement with poly(I:C) or LPS and R848 [58]. High levels of IL-12 (p70) production by monocyte-derived DCs prepared in the presence of TLR3 and TLR7/8 agonists have been reported in other studies [59, 60]. Although LPS by itself can induce recruitment of both MyD88/TIRAP and TRIF/TRAM adaptor proteins, our results showed that LPS alone is not sufficient to generate potent AML-DCs and needs to be accompanied with a synergized signal. In parallel, Roses *et al*. reported that multiple signals of agonists are required for commitment of the antigen presenting cells toward Th1 immune responses [65].

In vitro evaluation of generated DCs

There are different protocols for assessing the antigen presenting and T cell activating ability of in vitro-generated DCs. As minimum requirements for DC evaluation, it is common to assess the features described in Fig. 1.

Specific DC surface markers (immunophenotyping) change during the differentiation of DCs from the precursors (monocytes, bone marrow precursors, blasts, etc.). As a results of our and previous studies on AML-DCs, CD14+ and CD86+, blasts are more susceptible to be differentiated to AML-DCs [43, 61-63]. Contrary to CD14 which decreases during the differentiation of blast into immature and mature DCs, the expression pattern and especially mean florescent intensity (MFI) of CD86 increase gradually until full maturity of DCs. Elevating expression of CD11c, CD40, HLA-DR and CD83 (human DC maturation marker) following DC generation and subsequent maturation procedure can be found in AML-DC in parallel to the cognate monocyte-derived DCs. We also found that higher expression of CD1a occurs in the presence of 10% FBS instead of 5% AB serum-conditioned culture medium [43, 64].

Key cytokines which shift the immune response toward Th1, Th2, Th17 or Treg cells.

DCs produce different cytokines like IL-12, IL-10, IL-23, IL-6 and IL-1β, especially after stimulating with TLR agonists [65]. Attachment of cytokines to their matching receptors on T cells, triggers the internal signals in the direction of T cell activation corresponding to the required function for eliminating the pathogens or tumor cells [50, 66]. In cancer immunotherapy approaches, it is important to generate DCs with a sustained ability for producing Th1-shifting cytokines, especially IL-12. In our study, the production of IL-12(p70) was superior by AML-DCs matured using TLR4 and TLR7/8 agonists with or without adding TLR3 agonist (i.e. the best combinations) [44]. There are different methods with various sensitivities for intracellular (non-secreted) or secreted cytokine assessment including flow cytometry, ELISPOT/ELISA methods, respectively.

Allostimulatory function can be measured through the stimulatory capacity of irradiated DCs in a primary MLR assay (co-culture setting) with allogeneic T cells. Potent DCs especially those activated by TLR agonists can elicit a strong proliferation activity among T cells according to the allogenic differences between MHC on DCs and TCR on T cells [67]. There are different methods with various sensitivity for T cell proliferation assessment including MTT, XTT, Brdu labeling

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protocol (ELISA, Chemiluminescence or flow cytometry), live cell labeling (CFSE, orange dye, etc.). In addition, cytokine production of T cells (like IFN-γ, IL-4, IL-10, IL-17, etc.) is being assessed to find out the preferred T cell subsets in the co-culture system. Gamma interferon is a key cytokine of Th1-shifted T cells which are important in anti-leukemic responses. As a result of our study, AML-DCs matured with TLR4 plus TLR7/8 agonists with or without TLR3 agonist can stimulate allogeneic T cell responses more potently than the other conditioned cells [44].

CTLs induction and target-specific killing activity of CTLs.

In cancer immunotherapy, it is very important to stimulate effector and specific CTLs for targeting malignant cells. CTL induction performs to mimic the in vivo capability of DCs for stimulating CTLs and the subsequent killing of the target cells [68]. For achieving such induction, autologous T cells should be taken in remission phase and be co-cultured with tumor specific DCs for 21 days (this may vary between different protocols). The cells also need to be re-stimulated by DCs and be replenished with IL-2/IL-7, every 3 days. After harvesting the CTLs, they are ready for killing the targets (tumor cells, blasts, etc.) [44]. Cytotoxicity can be measured by different methods. Some of them are chromium release assay, target cell labeling (CFSE, orange, etc.) and also detecting CD107a by flow cytometry for the effector cells.

Phagocytic function

Immature DCs have the highest capacity of phagocytosis which gradually decreases after maturation and starting of their migration. This phenomenon helps DCs to internalize foreign particles, process and subsequently present them in the presence of major histocompatibility molecules (MHCs) to naïve T cells. There are different methods to detect the phagocytic function of DCs. Most of them are based on the ingestion of fluorochrome-conjugated particles including carbohydrates (dextran) or bacteria (*E. coli* or *S. aureus*), detectable by flow cytometry. After releasing the statistical analyses of flow cytometric data, the proportion of phagocytic cells and the number of the ingested particles can easily be determined according to the percentage of gated cells and related mean florescent intensity (MFI), respectively.

Outcomes of DC vaccine trials in AML and lessons that could be learned

Cancer immunotherapy has recently been named in Science as "breakthrough of the year"; therefore, we have in our hand a promising strategy and potential weapon to harness the cancer patients' immune responses [69]. There are several clinical trials on AML patients containing DC-based vaccines which were registered in <www.ClinicalTrials.gov>. By a quick search in the website with the keywords: "dendritic cell vaccination in cancer/tumor", we could find 302 registered clinical trials. Of those, 13 clinical trials belonged to DC vaccination with or without conventional therapies for AML patients. Obviously, DCs should be produced in a good clinical practice (GCP) setting in order to be used in clinical trials (Fig. 1). For AML-DC vaccination, it is necessary to irradiate the cells prior to the administration for preventing the uncontrolled proliferation of probably undifferentiated blasts in the vaccine [70]. According to the results, there are controversial outcomes in immunological and clinical responses of DC-based vaccination in AML patients.

Apparently, it would be more effective to use the cancer vaccines in patients with minimal disease burden after conventional therapies rather than in newly diagnosed or non-treated relapsed patients with a compromised immune system [71]. Although there are several clinical trials using leukemic DCs [70, 72], a more thorough investigation is needed to establish a technical procedure for producing AML-DCs with a potent immunostimulatory activity in all subtypes of AML patients [11]. The preference of using monocyte-derived DCs, especially in AML patients with minimal residual disease, has been shown in recent studies,; although the first report was not successful in AML patients with high tumor burden [73]. In contrast, Van Tendeloo *et al*. observed complete remission in 8 patients with elevated WT1 mRNA level and 2 patients in partial remission (PR) following injections of full-length WT1 mRNA-electroporated DCs as a post-remission treatment. High numbers of WT1-specific CD8+ T cells were also in line with clinical responses [74]. Kitawaki *et al*. recently published two clinical studies on mo-DC vaccination subsequent to morphologic remission in elderly AML patients. In the first trial, they could induce immune response with stable condition in 2 of 4 patients following administration of TLR4 agonist activated mo-DCs, enableding to cross-present endocytosed autologous apoptotic leukemia cell antigens [75]. In the other report, although mo-DCs were pulsed with zoledronate and an HLA-A*24:02-restricted modified WT1 peptide (with higher affinity to HLA than natural WT1 peptide), the transient period of stabilization was observed in 2 of 3 evaluated patients, despite expansion of anti-WT1 CD8+ T cell response. More persistent CD8 T cells, specific for natural WT1 than modified peptide, indicated the preference of using the former molecule in DC-based vaccines [76].

In a recent review study on Wilms' tumor protein 1 (WT1)-targeted active specific immunotherapy, Driessche *et al*. showed objective clinical responses (including stable disease) in 46% and 64% and specific immunological responses in 35% and 68% of solid tumors and hematological malignancies, respectively. Due to achieving the first rank by WT1 (as a result of National Cancer Institute Prioritization Project) as well as considerable clinical results and minimal side effects, WT1-cancer vaccines have been shown to be a promising immunotherapy as a standard vaccination in patients with various tumor types [77]. Moreover, the possibility of producing fusion DCs and AML blast and the in vivo activity of fusion cells have been shown in a phase I clinical trial. The authors could find the expansion of bone marrow infiltrating AML reactive T cells in the patients [78]. In another study, a 23-month remaining in remission was reported in 9 of 13 evaluable AML patients who had received vaccination with DC/leukemia fusion cells after remission [79]. Hopeful investigations are ongoing to use the TLR-DCs in combination with the other modalities like blocking of checkpoint molecules (e.g. CTLA4) or dampening the immunosuppressive factors [78].

There are different results on overall survival rates of AML patients in various clinical trials; however, the best results are related to studies which have considered all important aspects of designing a vaccination protocol. These factors include the process of generating mature leukemic or monocyte derived antigen specific-DCs, overcoming the immunosuppressive milieu, timing of injection, route and dose of vaccination, overall tumor burden as well as knowing the characteristics of LSCs to target them [78]. Although the exact immunophenotype of the LSCs is still unclear, CD123 (IL-3R) is constitutively expressed on both LSCs and leukemic cells and is a promising therapeutic target for AML. Leukemic antigen specific-DCs can indeed provoke the immune

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responses in AML patients, nonetheless other modalities are required to potentiate the MRD-eradicating capacity of AML-DCs, such as steering the tolerized immunity toward immunized immunity [25]. More notably, few recent DC vaccinations studies after allo-HCT have shown to be safe and efficient regarding both clinical and immunological responses. Hopefully, the field is open for further investigations, especially with the current approaches in achievable combination therapies to lessen the relapse rates and improve the survival rates [80]. To wrap up, these reports point to the feasibility of using DC-based immunotherapy as an immunogenic adjuvant after remission-induction therapy in AML patients, although it necessitates further studies.

The importance of combination strategies in future therapeutic approaches

Although DCs are key orchestrators of the immune system to communicate with cells of both adaptive and innate immunity, a vaccine strategy for AML is presumably to be effective if it targets different anti-leukemic immune pathways. In this regard, DC vaccines can be designed to activate the key cells of innate immunity like NK cells or to be combined with the other immunotherapeutic approaches. Regarding the tumor control role of NK cells and their multiple defects in AML patients [81, 82], future research efforts should also concentrate on optimizing the NK cell activating properties of DC vaccines, in addition to improving their T cell stimulatory capacity.

In this point of view, it will be very interesting to investigate the IL-15-treated DCs for their capacity to activate NK cells or particularly restore the impaired NK cell functions of AML patients [19]. By the way, due to the immunosuppressive microenvironment in AML, it appears that DC vaccination by itself may not be sufficient to induce protective anti-leukemic immunity. Thus, it needs to reverse the immune suppression, using therapeutic agents in combination with DC-based vaccines.

One approach would be blocking the immune suppression-mediated molecules, like the PD/PDL interaction, CTLA-4, CD200, reactive oxygen species, IDO expression, CXCR4, or the KIR/class I interaction [83]. In a recent study conducted by Memarian *et al*, a considerable association between the expansion of Foxp3+ regulatory T cells and CD200 up regulation on blasts of Iranian AML patients was shown. Accordingly, the blockade of CD200-CD200R interaction could be a promising target for AML immunotherapy [84]. Indeed, DC vaccination plus CTLA-4 blockade (as a checkpoint molecule) was shown to be superior to vaccination alone in terms of eliciting an AML-specific T cell response in vitro [85]. While at first it seems to be an attractive strategy, it might have unfavorable effects than beneficial ones in vivo since CTLA-4 blockade can induce an undesired proliferation of regulatory T cells (Treg) [86]. Conceivably, a more clinically workable tactic for combination therapy is to apply Treg depletion before DC vaccination in order to avoid non-selective elimination of vaccine-induced T cells. Antibody-mediated removal of CD25+ Treg in a mouse model of AML significantly enhanced the efficacy of subsequent DC vaccination [87]. Apart from improving the immunostimulatory activity of DC vaccines, we should think about the immunoediting ability of blasts to protect them against the immune attacks which can weaken the vaccine efficacy [88]. There are different strategies to increase the immunogenicity of AML cells together with DC vaccination, such as cytokines like IFN-α or Toll-like receptor ligands like resiquimod (R848) as TLR7/8 ligand [89, 90]. Obviously, there are more possible combinations of anticancer agents than described here that can result to a considerable improvement in DC vaccine efficacy.

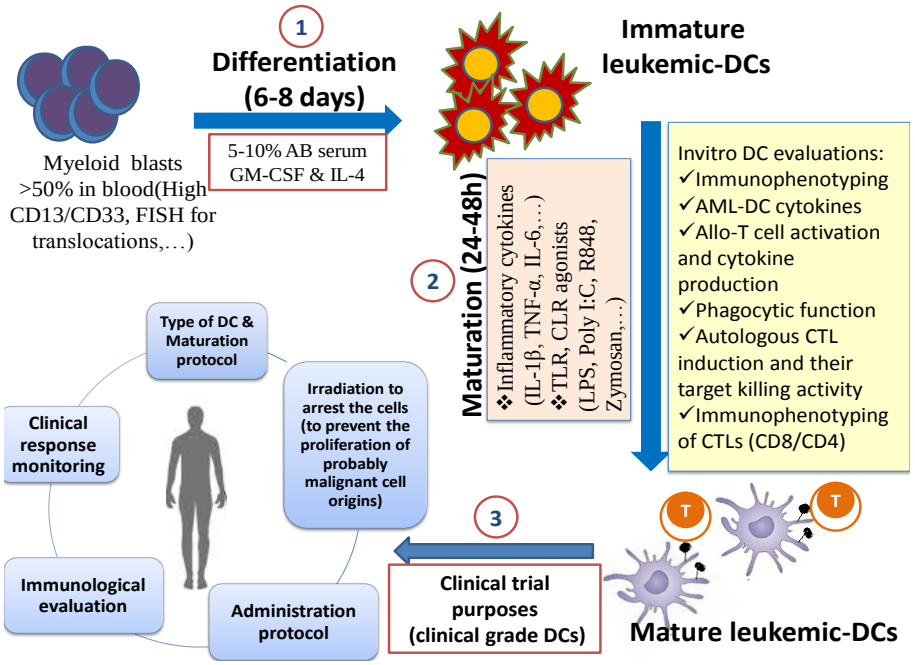

Fig. 1. A scheme of DC-based tumor vaccine preparation. DCs can be generated from peripheral blood or bone marrow blasts by culture in the presence of GMCSF and IL-4. AML-DCs do not usually need to be loaded with leukemic antigens and just need to be stimulated with maturation signals like cytokines and/or TLR agonists. Then, clinical grade DCs can be administered to the patient. There are many parameters that should be considered containing the source of DCs, maturation agents, and the route of administration.

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High incidence of relapse following chemotherapy in majority of AML patients is a powerful incentive for scientist to find alternative therapeutic approaches to improve the patients' endurance. Low rate of long-term survival can be largely attributed to the presence of minimal residual diseases (MRDs) despite intensive chemotherapy. Thus, it is indispensable to find effective interventions to control MRDs and prevent relapses. DCs can be generated from blasts of AML patients (especially in M4 and M5 patients) and be used as a post-remission therapy. To potentiate the vaccine efficacy, it may be combined with anticancer or immunomodulatory agents. More noticeably, in order to uncover the full potential capacity of DC vaccines, future studies comprising both experimental models and clinical trials will be needed.

AUTHOR'S CONTRIBUTION

Maryam Nourizadeh has written and Jamshid Hadjati has revised and edited the manuscript.

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CONFLICTING INTERESTS

We have no conflicts of interest to declare.

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