Leukemia-derived dendritic cells: towards clinical vaccination protocols in acute myeloid leukemia

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The ability of acute myeloid leukemic (AML) blasts to differentiate into leukemic dendritic cells (DC) thus acquiring the potential to present known and unknown leukemic antigens efficiently, holds promise as a possible new treatment for AML patients with minimal residual disease. Recent advances in culture methods have made the clinical use of leukemic DC feasible. However, additional measures appear to be essential in order to potentiate vaccines and to overcome the intrinsic tolerant state of the patients immune system. This review describes ways to improve AML-DC vaccines and discusses critical aspects concerning the development of clinical vaccination protocols.

Key words: leukemia, immunotherapy, dendritic cells, clinical vaccination

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Although intensive chemotherapy-based approaches including stem cell transplantation induce complete remission in 80% of patients with acute myeloid leukemia (AML), many patients relapse due to persistence of minimal residual disease (MRD) resulting in survival rates of 30-40%.[1] The presence of MRD after induction chemotherapy and stem cell transplantation is highly predictive of relapse. MRD can be assessed by flow cytometry in 80% of AML patients, by using leukemia-associated phenotypes.[2] A considerable body of evidence points to the critical role of T-cell immunity in the control of leukemia. The most well-known example is the reinduction of complete remission after infusion of donor T cells (in the form of donor lymphocyte infusion [DLI]) in patients with relapsed leukemia after allogeneic stem cell transplantation.[3,4] In the early 1970s it was shown that adding immunotherapy to chemotherapy, consisting of vaccination with irradiated autologous AML blasts, resulted in an increased survival of patients.[5] More recent data highlight a role for vaccination strategies in the eradication of MRD.[6-8]

Dendritic cells (DC) are known for their unique antigen-presenting capacity and their ability to activate naïve T-cells.[9,10] DC reside in peripheral tissues in an immature state where they capture and process antigens for presentation in the context of MHC molecules.[11] Microbial agents, inflammatory stimuli or T-cell-derived stimuli all induce a complex process of morphological, phenotypic and functional changes, commonly referred to as the DC maturation process, which enables the DC to activate T cells efficiently through interaction with co-stimulatory molecules.[12,13] Immature DC, unable to provide co-stimulatory signaling, induce a tolerogenic response and cause T-cell anergy.[14] Attracted by lymphoid chemokines, mature DC migrate towards areas of T cells in the lymph nodes where they initiate the immune response.[15] These features make DC ideal candidates for cellular immunotherapy.

DC can be generated from monocytes and $CD34^+$ bone marrow precursors and can be either pulsed, fused or transformed with relevant tumor antigens. Remarkably, AML and chronic myeloid leukemia (CML) cells can be differentiated into leukemic DC, conserving their leukemia-specific antigen-repertoire while acquiring full antigen presenting capacity. Vaccination with leukemic DC could, therefore, represent a potent new treatment modality for patients with MRD in AML and CML.

In vivo targeting of DC could seem preferable since it avoids laborious *ex vivo* DC preparation. Administration of Flt-3L results in increased numbers of circulating DC subsets, which could potentially be targeted with tumor antigens.[16,17] However, in the case of hematologic malignancies DC may be affected by the disease itself resulting in abnormalities in the numbers and function of DC.[18-20] Circulating DC subsets of AML patients show quantitative imbalances and impaired functional ability to mature, to stimulate T-cell proliferation and to produce cytokines.[20] Thus *in vivo* targeting of DC does not, in fact, seem to be the best approach in the case of leukemia.

The aims of this review are to discuss: (i) methods to culture leukemic DC; (ii) procedures to improve leukemic DC vaccines; and (iii) development of clinical vaccination protocols in AML (Figure 1).

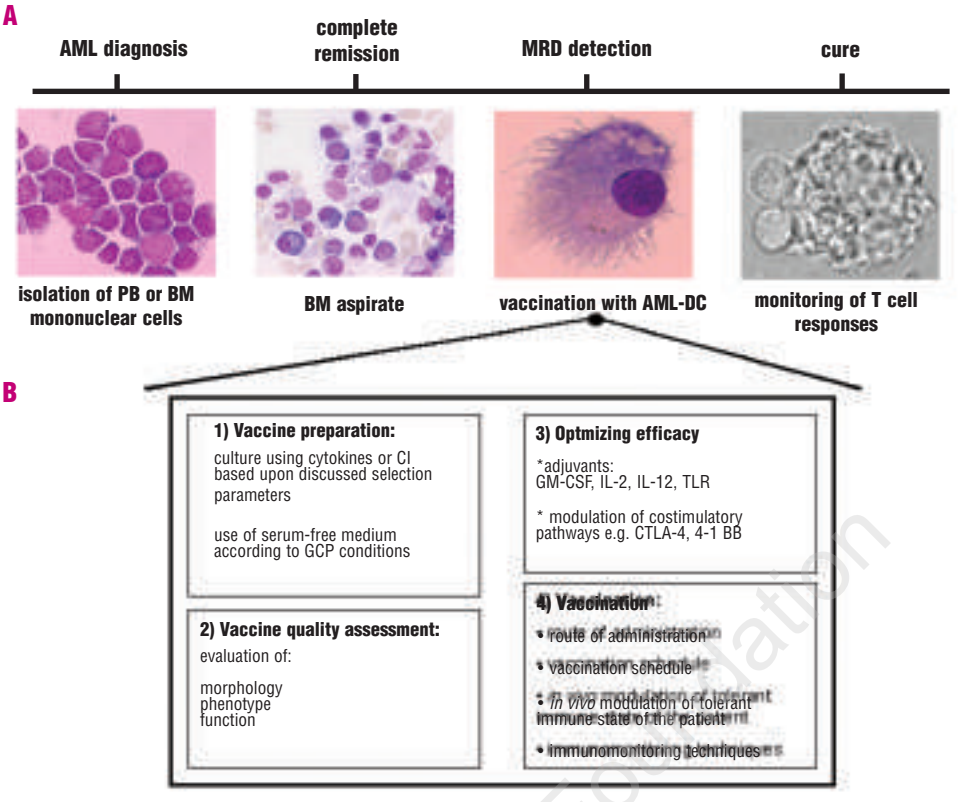

Figure 1. A. Time schedule of an AML-DC vaccination programs. **B.** Steps in designing AML-DC vaccination programs. At diagnosis peripheral blood (PB) or bone marrow (BM) mononuclear cells are isolated. After preparing the AML-DC vaccine using the best method, the quality of the vaccine should be determined according to pre-defined criteria. The efficacy of DC vaccines could be optimized, as discussed in the text. Patients are vaccinated in complete remission with cultured AML-DC with the aim of eradicating of minimal residual disease (MRD). Immune responses are evaluated according to accepted techniques. CI: calcium ionophore; TLR: toll-like receptor.

Preparing leukemic DC for vaccination

For the majority of human cancers it remains unclear which antigens represent the most important tumor rejection antigens.[21] However, leukemic blasts express tumor antigens capable of eliciting high avidity T-cell responses, such as bcr-abl, WT-1, PR3, PML-RARα and PRAME.[22] Cytotoxic responses elicited by WT-1 and PR3 have been observed and WT-1-specific antibodies may be identified in 15-25% of AML patients.[23,24] Unfortunately, these antigens are not uniformly expressed by each individual leukemia. The unique property of leukemic blasts to differentiate into DC, under the proper conditions, provides the opportunity to generate antigen-presenting cells (APC) that harbor the full range of potential, still unidentified tumor antigens specific for that particular leukemia.

Culture of leukemic DC

Co-culturing leukemic blasts for 14 days with various combinations of cytokines, including granulocyte-monocyte colony-stimulating factor (GM-CSF), tumor necrosis factor (TNF)-α, stem cell factor (SCF), Flt3-L, interleukin (IL)-3 and IL-4 results in the blasts differentiating towards leukemic DC-like APC.[6-8,25-32] These cytokine-cultured AML-DC can be matured to an extent that they are comparable to their normal counterparts, i.e. DC derived from $CD34^+$ progenitors, by incubating them for another 2 days with a mixture of inflammatory cytokines (TNF-α, IL-1β, IL-6 and PGE_2) or by adding CD40L.[33,34] Alternative methods for inducing the maturation of leukemic DC are gamma irradiation of the cultured blasts and adenoviral TNF-α gene transfer: both methods induce CD80 and CD86 expression and increase T-cell proliferation capacity.[35,36] Monocytes and $CD34^+$ hematopoietic progenitors but also CML cells and AML blasts respond to calcium-mobilizing agents (calcium ionophores) far more rapidly than to cytokines making these agents a more time and cost effective method.[7,37-41] However, although AML-DC cultured with calcium ionophores are more mature and more potent stimulators of T-cell proliferation, they are less viable than AML-DC generated in the presence of cytokines.[7] Consequently, the calcium ionophores-based method can only be applied if large numbers of AML blasts are available.

The number of injected AML-DC necessary to evoke an anti-leukemic immune response is currently not known and probably depends on antigenic density, T-cell receptor avidity, immune status of the patient and residual leukemic burden. Consequently, for the rational design of clinical studies it is of great importance to develop immunomonitoring tools that reliably predict clinical efficacy. Clinical outcome has been shown to correlate with the presence of specific T cells in delayed-

type hypersensitivity responses.[42] From the first DC-based vaccination study in CML patients it was concluded that at least 10×10^6 DC are required to elicit an immune response.[43] In a pilot study of autologous CML-DC vaccination 10×10^6 CML-DC could be generated for each of four vaccines, resulting in strong delayed-type hypersensitivity responses.[44] For AML, it was calculated that approximately 4×10^8 viable AML cells are needed at diagnosis assuming that an effective AML-DC vaccination regimen requires four vaccines of 10×10^6 cells each and that the average AML-DC yield is about 25%. This number of cells can be harvested from 70% of patients at diagnosis.[7] Clinical AML-DC vaccination programs rely on the possibility of culturing AML-DC under fetal calf serum -free conditions since the use of fetal calf serum carries the risk of presenting irrelevant antigens contained in this serum as well as anaphylactic complications.[45,46] Serum-free cultures can replace serum-enriched culture techniques to generate AML-DC. Various clinical grade serum-free media, such as Aim-V (Gibco-BRL, Gaithersburg, MD, USA), X-Vivo (Bio-Whittaker, Walkersville, MD, USA), CellGro (Cell-Genix, Freiburg, Germany) and StemSpan (Stemcell Technologies, Vancouver, Canada) are available nowadays and have successfully been tested in *in vitro* leukemic DC cultures.[31–33,47–50] Alternatively, human or autologous sera have been used.[29,51] However, these sera contain various identified and unidentified growth factors and tumor-derived suppressive factors that affect differentiation and maturation, thus making it impossible to standardize culture conditions.

Functional properties of leukemic DC

The leukemic origin of AML-DC has been confirmed by fluorescent *in situ* hybridization showing the original chromosomal abnormality in AML-DC and by quantitative polymerase chain reaction showing sustained or increased mRNA expression of leukemia-associated antigens such as PRAME and WT-1.[7,26,27,31, 52,53] In migration assays mature AML-DC exhibited potent migratory capacity towards the lymph node-associated chemokines SDF-1 and MIP-3β, implying their ability to migrate towards the lymph nodes.[34] The AML-DC proved to be potent inducers of T-cell stimulation in alloreactivity tests.[7,26,31,47] Preferably, AML-DC should evoke a Th1 response since Th1 cells are capable of stimulating $CD8^+$ cytotoxic T cells. Such a Th1 cytokine profile with interferon (IFN)-γ production without IL-4 and IL-10 production was indeed detected after co-culturing AML-DC with T cells.[7,33] Most importantly, T cells primed with autologous AML-DC demonstrated cytolytic capacity towards autologous AML blasts.[6,7,47]

To avoid the risk of infusing residual leukemic cells potentially causing relapse of the disease, AML-DC should be irradiated before injection. ^{3}[H] thymidine incorporation assays indicate that irradiated blasts and AML-DC are unable to proliferate, while AML-DC retain their capacity to induce T-cell proliferation.[54,7,32] As mentioned before, γ irradiation might even induce a more mature phenotype.[35] Accordingly, AML-DC maintain migratory capacity upon irradiation with 30Gy.[34] Thus, *in vitro* assays confirm the safety and the functional potential of AML-DC, which are instrumental in stimulating autologous cytotoxic T-cell responses.

Procedures for improving leukemic DC vaccines

Culture methods

Cultured AML-DC harvested from an array of AML patients form a heterogeneous population with a variable expression of co-stimulatory molecules. To optimize leukemic DC yield, the best DC culture method must be chosen for each patient individually. In a large cohort of patients we found that DC differentiation capacity is independent from the FAB subtype (*Houtenbos et al. unpublished data*). However, it was possible to predict the outcome of culture systems by the expression of defined surface markers on AML blasts.[55-57] High TNFα-RI expression on AML blasts was predictive for the DC differentiation capacity of blasts cultured in the presence of cytokines.[57] In addition, it is the $CD14^+$ leukemic blast population that can be induced to differentiate into leukemic DC *in vitro*, not the $CD14^-$ population.[56] Interestingly, we observed that induction of DC differentiation in $CD14^-$ blast is possible if these blasts express TNFα-RI.[58] Alternative culture methods, for example the calcium ionophore-based method, can be used to induce DC differentiation in $CD14^-$ and TNFα-RI^- AML samples.[57] Besides the expression of surface markers, the presence of a Flt-3 internal tandem duplication is strongly associated with a diminished DC differentiation capacity in both culture methods.[59] Using these selection parameters the best culture protocol for the generation of AML-DC can be identified for each individual patient. A model to predict AML-DC culture outcome is currently being developed in our department.

Adjuvants

Genetically modified AML cells that express immunomodulatory cytokines used to enhance antigenicity, such as IL-12 or GM-CSF proved to be potent vaccines that are able to cure leukemia in mice.[60-64] Whereas systemic administration of IL-12 caused systemic toxicities, these vaccines did not.[65] Transducing DC with genes encoding for GM-CSF and IL-12 may be another way to enhance T-cell stimulation, as shown by the induction of strong T-cell responses in a murine melanoma model.[66]

Toll-like receptors

Triggering toll-like receptors (TLR) of DC promotes the maturation and activation of these cells, resulting in the expression of co-stimulatory molecules and IL-12 production, as well as increasing their life span.[67] Additionally, TLR seem to be essential for Th1 responses.[68] For these reasons, triggering of TLR, with clinically applicable CpG, is currently being used as an adjuvant in clinical vaccination trials.[69] The receptor for CpG, TLR9, is mainly expressed on B cells and plasmacytoid DC.[70] Myeloid DC have been reported to lack TLR9, although it was recently suggested that myeloid DC might upregulate TLR9 upon stimulation with IFN-γ.[71,72] Thus, incubating of AML-DC with IFN-γ might induce TLR9 expression and CpG could then be used as adjuvant treatment to enhance T-cell responses.

Co-stimulatory signaling

Several studies have focused on the increased expression of the co-stimulatory molecules CD80 and CD86 on AML blasts caused either by transduction of AML blasts with genes encoding for co-stimulatory molecules or by differentiation of the blasts into AML-DC, leading to greater activity of cytotoxic T lymphocytes.[73-76] The weak immune responses elicited by many tumors can be potentiated by blocking the inhibitory co-stimulatory pathway of CTLA-4, a strategy which is currently being tested in clinical settings.[77] However, susceptibility seems to be correlated with the inherent immunogenicity of the tumor.[78] Therefore, a combined strategy, for example with DC vaccination, is advantageous.

4-1BB is an inducible activating co-stimulatory molecule expressed on activated T cells. In addition to its role in promoting the expansion of antigen-specific T cells, 4-1BB signaling, produced by administration of agonistic 4-1BB monoclonal antibodies or by 4-1BB ligand, can also prevent T-cell anergy as well as activation-induced death of $CD8^+$ cells.[79-82] The combined approach of DC-based vaccines with co-administration of the 4-1BB monoclonal antibody improved antitumor responses.[83] Similarly, *in vitro* studies of AML-DC cocultured with T cells with targeting of 4-1BB show an increased proliferation of $CD8^+$ cells capable of producing IFN-γ. This effect may be exploited in leukemic DC vaccination strategies (*Houtenbos et al., unpublished data*). A more effective way to engage 4-1BB towards tumor destruction and avoid the complication of depressing antibody formation due to use of monoclonal antibodies, could be to transfect the tumor cells to express a cell-bound form of anti-4-1BB single chain Fv (scFv) fragments.[84-86] Thus, many options can be explored to improve leukemic DC vaccines further.

Clinical strategies with leukemic DC vaccination

The possibility of preventing or curing leukemia by using DC vaccinations has been tested in animal models.[87,88] Pawlowska *et al*. concluded that tumor-lysate pulsed DC could effectively prevent mice from developing leukemia when challenged; however, mice with established disease could not be cured, probably because of their high leukemia burden.[88] In a phase I pilot study on CML-DC vaccination in advanced stage disease delayed-type hypersensitivity responses, representing autologous CML-specific T-cell responses, could be detected.[44] A decrease in the number of bcr-abl$^+$ cells was shown in a CML patient treated with a CML-DC vaccination following autologous peripheral blood stem cell transplantation.[89] Additionally, infused CML-DC induced the appearance of T-cell clones expressing the same T-cell receptor as that on an anti-leukemic cytotoxic T-cell line derived from the same patient, suggesting that the immune repertoire included tumor-reactive T cells. In another study, intradermally injected, bcr-abl pulsed, monocyte-derived DC induced peptide-specific cellular responses, although without any clinical responses.[90] In these few patients treated so far, no toxic or auto-immune adverse effects were detected.

One clinical study on AML lysate-pulsed monocyte-derived DC in two patients has been published.[91] In this study positive delayed-type hypersensitivity responses were observed although the leukemic burden did not decrease. Another five patients injected with AML-DC showed no adverse side effects while leukemic-specific T-cell responses were detected.[92]

Challenges in DC vaccination

In order to establish the value of DC vaccination in leukemia patients some consensus on quality criteria and immune monitoring is essential. Recently, minimal quality criteria for DC vaccines were proposed.[93] The main focus is on the necessity to vaccinate mature DC, as defined by morphological, immunophenotypic, and functional criteria. An important argument for the use of only mature DC is that antigen-loaded immature DC silence T cells either by deleting them or by expanding regulatory T cells.[14, 94,95] However, the definition of the maturation status of DC in terms of cytokine secretion, is still a matter of debate. Shortly after activation, DC secrete larger amounts of cytokines but prolonged periods of maturation result in exhaustion of DC with considerably less cytokine production and an impaired capacity to stimulate Th1 responses.[96] Although leukemic DC meet most quality criteria proposed by Figdor *et al.,* it is not yet known what level of maturation is optimal to elicit an immune response and whether leukemic DC are capable of attaining such a state *in vivo* after being administered.[93]

Another unresolved question is the optimal route of administration. Intradermal or subcutaneous injections may lead to better T-cell responses than those following intravenous administration.[97,98] However, these routes of administration rely on the capacity of injected DC to migrate towards the lymph nodes. Intranodal administration circumvents this problem and allows delivery of a known amount of DC to the desired anatomic region, potentially leading to increased T-cell immunity.[99] On the other hand, intranodal vaccination requires technical expertise and includes the risk of damaging the architecture of the lymph node. Additionally, it has been suggested that the route of administration determines the location of the primary immune response, the distribution of memory cells, and the ability to control the outgrowth of tumors at different sites in the body.[100]

Immunotherapy is thought to be most effective in a context of MRD. The detection of residual leukemic cells, characterized by the presence of a leukemia-associated phenotype, is highly predictive for the occurrence of a relapse.[2] A cut-off of 0.1% detectable leukemic cells after the third course of chemotherapy identifies patients at risk of a fast-developing relapse. Patients with MRD of less than 0.1% should be monitored every 3 months in order to predict a possible relapse.[101] Depression of the immunological system after high-dose chemo- and radiotherapy is likely to influence the efficacy of immunotherapy. For example, following a stem cell transplant, $CD8^+$ T cells reappear more rapidly, i.e. within 6 months, than do $CD4^+$ T cells, which still show low levels even after 1 year.[102] However, studies performed by Bruserud *et al*. suggest that, after exposure to chemotherapy, T cells show increased responsiveness upon optimal co-stimulation, which compen-

sated for quantitative defects.[103] Additionally, cells executing the immune response after *in vitro* priming with AML-DC seem to differ at different time points during remission. During early remission, immune responses seem to be largely MHC-restricted whereas later on the immune response shifts towards being non-MHC-restricted.[104]

Based on the data discussed above, we hypothesize that AML-DC treatment schedules should start early after complete remission has been achieved. Patients with high levels of MRD after chemotherapy are particularly likely to benefit from an early start of a vaccination program. Moreover, we think that booster injections during a maintenance vaccination program could increase immune responses at a time that the immune system is further or fully recovered. Monitoring MRD as well as immune responses could provide guides to such a strategy. An alternative approach, circumventing the problem of T-cell deficiencies following chemotherapy, is the adoptive transfer of *ex vivo*-expanded leukemia-specific T cells, possibly by leukemic DC.[105] However, major drawbacks of this approach are the finite life span of T cells *in vitro*, a phenomenon called replicative senescence, and impaired engraftment and persistence *in vivo*.[106] Much has to be learnt to bring DC vaccination further into the clinic.[107] Most techniques for monitoring responses are indirect measurements of cytolytic activity of effector cells. Several clinical vaccination studies in cancer patients have reported T-cell responses in peripheral blood but usually only in a minority of patients or after prolonged antigenic restimulation *in vitro*.[108–111] Delayed-type hypersensitivity infiltrated T lymphocytes are able to show antigen-specific responses after short-term *in vitro* cultures without the need for antigen restimulation.[112] The newly developed tetramer technology enables sensitive detection of antigen-specific T cells. Also for leukemia, leukemia-associated antigens have been identified for which tetramers can be developed. However, except for CML, the leukemia-associated antigens are largely unknown and T-cell specificity needs to be determined in a more indirect way. The classical way of detecting cytotoxic T lymphocyte activity in a ^{51}Cr release assay might not be suitable in leukemia because of the high spontaneous release of ^{51}Cr by leukemic blasts. Recently, a flow cytometric assay using Syto-16/7-AAD staining to detect early apoptosis and secondary necrosis was developed; this assay is particularly suitable for detecting heterogeneous cell populations such as those in AML.[113] This technique can be used to determine the cytolytic capacity of effector cells induced by DC vaccination.

Efficacy of DC vaccines

Recently published reviews on clinical DC vaccination trials in a wide variety of malignancies, report data concerning types of DC vaccines, route of administration, side effects and clinical efficacy.[107,114] Although clinical response data are not conclusive yet, most studies report minimal antitumor effects.

New approaches seem required to make DC vaccines worthwhile in leukemia. Apart from developments in the selection of culture methods and manipulation of maturation and co-stimulatory pathways, leukemic DC need to be able to overcome the intrinsic tolerant state of the patient better.[20] Recruitment of leukemia-specific T cells to the microenvironment of AML blasts could be influenced by serum levels as well as local release of T-cell chemotactic chemokines, which have been reported to show wide variation among AML patients.[115] In addition, the microenvironment of leukemic blasts and also leukemic blasts themselves are known to produce factors that inhibit cytotoxic T cells and favor regulatory T-cell functions.[116,117] In contrast, AML blasts create an anti-apoptotic microenvironment that favors survival of malignant cells, but also of resting and stimulated T cells.[118]

Another mechanism to escape immune surveillance is the persistence of class II-associated invariant chain peptide (CLIP) in the antigen binding groove of the MHC class II molecule of AML blasts. A high CLIP expression on AML blasts proved to predict shortened disease-free survival.[119] Furthermore, it has been shown that residual leukemic cells upregulate certain co-stimulatory pathways that could protect them from the patient's immune response.[120] Strategies to *sensitize* residual leukemic cells and their microenvironment, for instance by blocking regulatory T cells, blocking inhibitory co-stimulatory pathways, or neutralizing antibodies to inhibitory interleukins, all deserve further exploration in order to increase the immune stimulatory effect of leukemic DC.[121]

Conclusion

The development of clinically applicable AML-DC vaccines offers a desired new treatment modality for patients with AML. Much has been achieved in preparing leukemic DC for vaccination and these cells do indeed provoke immune responses. It does, however, seem that additional strategies are required to potentiate the efficacy of AML-DC vaccines *in vivo*, by shifting the patients' immune state from tolarizing towards immunizing. Using vaccines in combination with immune modulatory and stimulatory agents could represent a powerful approach to eradicating MRD in patients with AML.

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