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General AML

Dendritic cell-based immunotherapy of acute myeloid leukemia

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The five-year overall survival rate of acute myeloid leukemia (AML) is less than 10% for most patients above the age of 65 years, with the main reason being relapse, even after complete remission (CR) is achieved through chemotherapy. Relapse arises from the persistent presence of a small number of treatment-resistant leukemic stem cells (LSCs),[1] known as minimal residual disease (MRD) which then may develop into clinical relapse.

Despite being the cornerstone of current AML therapy, chemotherapy and allogeneic hematopoietic stem cell transplantation (allo-HSCT), are both associated with significant mortality and morbidity.[2] For patients who are unfit for transplant, or for those with no donor options, there is no standard post-remission therapy to treat MRD and avoid relapse.[3]

These observations emphasize the need for less toxic and more effective treatment options to improve the long-term outcomes of AML. Recently, immunotherapy has been used to induce anti-leukemic immunity; where immune cells recognize and eliminate AML cells, resulting in the graft-versus-leukemia (GVL) effect.[4]

Dendritic cells (DCs) have recently been researched for their potent and unique ability to utilize the anti-leukemic activity of both leukemia antigen-specific $CD8^+$ cytotoxic T-lymphocytes (CTLs) and natural killer (NK) cells. CTLs and NK cells are the main immune effector cells that attack and destroy AML cells.[4] DCs are able to stimulate both adaptive and innate immune responses to AML cells through various methods.

Heleen Van Acker from the Laboratory of Experimental Hematology, Vaccine and Disease Institute at the University of Antwerp, BE, and colleagues reviewed the processes surrounding the use of DCs for the treatment of AML. In a previous study,[5] the same researchers found DC therapy following chemotherapy to be a cost-effective treatment.

The majority of studies conducted[6] have used DCs derived from autologous peripheral blood monocytes (moDCs), with other studies using allogeneic DCs. Autologous leukemic blast cells were also used as precursor cells for DC generation (AML-DCs).[6]

While AML-DCs generated from a leukemic cell line present the full antigen repertoire of the leukemic blasts and do not need an antigen loading step, their effectiveness may be hampered by the lack of co-stimulatory ligands such as 4-1BBL, a vital ligand for co-stimulation.

For moDCS, one or more AML antigens are required to be loaded, using one of the following methods:

1. Messenger RNA electroporation

2. Fusing of the DCs with leukemic blasts
3. Pulsing with apoptotic AML cells or lysates
4. Exogenous pulsing with a peptide

MoDCs are more effective in activating autologous leukemia-specific T cells, and due to these advantages, the use of moDCs are preferred over the use of AML-DCs.

Both non-specific and antigen-specific immunological effects have been identified in patients treated with DCs. Non-specific effects included:

- Delayed-type hypersensitivity (DTH) skin test reactions[7]
- Increases in $CD4^+$ and/or $CD8^+$ T cell frequencies during or after DC administration[8]
- Enhanced activation of $CD4^+$ T cells[9]
- Elevations in plasma levels of immunostimulatory or T_H1-polarizing cytokines (such as interleukin (IL)-2)[7,8,9]

Specific effects that were identified through *ex vivo* tetramer analysis, included DC-induced immune responses that resulted in responses within a single patient being directed against multiple antigens, or also against multiple epitopes in a particular antigen.[7]

DC Vaccinations

DC vaccines have been used in three settings:

1. HSCT (e.g. to treat relapsed AML after allo-HSCT)

One study[10] manufactured multi-genetically modified moDCs (Ad-siSSF) based on adenovirus delivery:

i) Secretory flagellin, a Toll-like receptor (TLR)-5 agonist including DC maturation

ii) Surviving-MUC1 fusion protein with two leukemia-associated antigens

iii) SOCS1 shRNA, an RNA interference moiety overriding the immune checkpoint molecule SOCS1

- 48 patients with post-transplant AML relapse were treated with either Ad-siSSF or donor lymphocyte infusions (DLI)
- The vaccine was found to be safe and induced a three-year overall survival of 48.9%, in comparison to 27.5% in the DLI arm
- 57% (13 of 23) patients treated with the Ad-siSSF DCs plus DLI achieved complete remission, in comparison to 48% (12 of 25) in the DLI arm

2. Advanced disease

Clinical responses in patients with relapsed or refractory AML where other options had failed, were limited to disease stabilization or transient reductions in leukemic load before eventually progressing.[9] One study[8] reported CR and partial remission (PR) in the relapsed/refractory setting.

3. MRD

For patients with low disease burden, MRD or after chemotherapy-induced remission of AML, the DC vaccine was administered as consolidation therapy to prevent or postpone relapse. Longer than usual CRs were reported in all post-remission DC vaccine studies, along with remarkably long progression-free survival (PFS) times.[11] A study focusing on 17 patients who achieved remission with chemotherapy, and were vaccinated with moDCs fused to AML cells, resulted in a 72% relapse-free survival at a median follow-up of 57 months.[12]

The combination of results from the detailed studies along with outcomes of the research teams' own trial,[13] has resulted in a follow-up randomized phase II trial comparing DC vaccination with the standard of care in the post-remission setting of AML (NCT 01686334).

Conclusions

The researchers concluded that DC-based immunotherapy has the potential to result in clinical responses in patients with AML. Outcomes have been shown to be particularly remarkable in post-remission stages of AML, but have not benefited every patient, indicating a need for further investigation. Patients who failed to mount an immune response to DC vaccination often had inferior clinical outcomes compared with immune responders.

The randomized phase II clinical trial is currently ongoing, and may provide insight into the effectiveness of combined hypomethylating agent treatment with DC vaccination.

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