case report

Stabilization of acute myeloid leukemia with a dendritic cell vaccine

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Acute myelogenous leukemia (AML), the most common adult acute leukemia, is characterized by the clonal expansion of myeloblasts initiating from rare leukemic stem cells.[1] An estimated 31 490 new cases of AML and 45 090 deaths due to this disease occurred in 2008 in the US.[2] Despite recent advances in the AML therapy, induction failure happened in more than 40% of patients and recurrences occurred in 50% to 70% even after complete remission. Among patients who had complete remission only 20% to 30% have long-term disease-free survival.[3,4]

The higher recurrence rates after chemotherapy are caused by the persistence of leukemia cells with high growth potential.[5] When this happen there is no golden standard treatment for relapsed AML patients.[6] Dendritic cells (DC) are increasingly being used for anti-cancer therapy.[7-10] Many pre-clinical studies have been performed to establish a strategy for the manufacture of a DC vaccine for AML immunotherapy.[11,12] Advances in culture techniques and AML-DC characterization have justified clinical application. We present a case of AML disease stabilization following therapy with dendritic-tumor cell hybrid vaccine.

CASE

A 56-year-old white female was diagnosed with AML subtype M2 (WHO) in 2004. She was initially treated with daunorubicin plus cytosine arabinoside (3+7) regimen followed by high-dose cytarabine. No further therapy was given. She went into complete remission but relapsed one year later. Immunophenotypic analyses revealed CD33+ in 80% of blasts. The patient was given gemtuzumab ozogamicin 9 mg/m^2 (day 1 and 14) followed by high dose cytarabine. She remained well until January of 2007 when she relapsed. We harvested 100 mL of the patient's bone marrow containing 60% blasts to use in preparing a hybrid dendritic-tumor cell vaccine in a manner previously described.[10] Vaccine was applied intradermally in the arm every 4 weeks from January 2007 to August 2007. No side effects were seen at the vaccination site or systemically. She had stable disease (roughly 16% blasts) for 9 months under vaccine treatment until the disease progressed and she expired.

DISCUSSION

Our patient relapsed even after receiving first- and second-line therapy for AML. As there is no golden standard treatment for relapsed AML[6] we decided to use a DC-based vaccine. This therapy has the advantage of no adverse effects, thus providing a high quality of life to patients, in contrast to the usual chemotherapy that is associated with serious side effects, which can even lead to death. Immunotherapeutic approaches, such as therapeutic vaccines, are being used to try to combat this disease. Phase I/II clinical trials showed that AML-derived peptides were safe, and specific immune responses were detected.[13-16] DC-based vaccination was also shown to be feasible in AML patients, but only a few clinical trials have been performed, mostly using leukemia-derived DCs.[17-19] In addition, a phase I/II trial using WT1 mRNA-electroporated DCs are being performed by Van de Velde et al.[20]

An advantage of the DC-tumor hybrid vaccine is that it induces a potent antileukemia response without the need to identify the HLA haplotype of the patient, which is necessary for other approaches such as the pulsing of DCs with specific peptides or antigens.[21] Moreover, allogeneic monocyte-derived DCs showed higher expressions of several molecules (HLA-DR, CD80, CD83 or CD86), higher production of IL-12 and a higher capacity to stimulate allogeneic T cells compared to both leukemic DCs and autologous monocyte-derived DCs.[11]

Our case report illustrates an effective response to allogeneic DC-autologous tumor cell vaccine with disease control for 9 months followed by disease progression. Considering the stabilization of the disease, even for a short period, we see this as a promising result, in view of the aggressive behavior of AML. The main challenge in treating AML is not in inducing remission after

diagnosis, but in preventing relapse.[22] It is desirable to use DC therapy to eliminate the residual tumor cells on the first remission after standard chemotherapeutic treatment.[23] Then, vaccination in early stage disease has the potential to promote more significant clinical benefits in AML patients by preventing relapse.

REFERENCES

1. Ishikawa F, Yoshida S, Saito Y, Hijikata A, Kitamura H, Tanaka S, Nakamura R, Tanaka T, Tomiyama H, Saito N, Fukata M, Miyamoto T, Lyons B, Ohshima K, Uchida N, Taniguchi S, Ohara O, Akashi K, Harada M, Shultz LD. Chemotherapy-resistant human AML stem cells home to and engraft within the bone-marrow endosteal region. Nat Biotechnol. 2007;25(11):1315-21.

2. Surveillance Epidemiology and End Results. National Cancer Institute Web site. http://seer.cancer.gov. Accessed 17 November 2008.

3. Hann IM, Stevens RF, Goldstone AH, Rees JK, Wheatley K, Gray RG, Burnett AK. Randomized comparison of DAT versus ADE as induction chemotherapy in children and younger adults with acute myeloid leukemia. Results of the Medical Research Council's 10th AML trial (MRC AML10). Adult and Childhood Leukaemia Working Parties of the Medical Research Council. Blood. 1997;89(7):2311-8.

4. Morgan MA, Reuter CW. Molecular target therapy in myelodysplastic syndromes and acute myeloid leukemias. Ann Hematol. 2006;85:139-63.

5. Kerncor W, Schoch C, Haferlach T, Schnittger S. Monitoring of minimal residual disease in acute myeloid leukemia. Critical Reviews in Oncology/Hematology. 2005;56:283-309.

6. National Comprehensive Cancer Network. www.nccn.org. Accessed 2 July 2008.

7. Mosca PJ, Lyerly HK, Clay TM, Morse MA, Lyerly HK. Dendritic cell vaccines. Front Biosci. 2007;12:4050-60.

8. Osada T, Clay TM, Woo CY, Morse MA, Lyerly HK. Dendritic cell-based immunotherapy. Int Rev Immunol. 2006;25(5-6):377-413.

9. Gilboa E. DC-based cancer vaccines. J Clin Invest. 2007;117(5):1195-203.

10. Barbuto JAM, Ensina LFC, Neves AR, Bergamini-Santos PC, Leite KRM, Marques R, Costa F, Martins SC, Câmara-Lopes LH, Buzaid AC. Dendritic cell-tumor hybrid vaccination for metastatic cancer. Cancer Immunol Immunother. 2004;53:1111-18.

11. Lee JJ, Choi BH, Kang HK, Kim SK, Nam JH, Yang DH, Kim YK, Kim HJ, Chung IJ. Monocyte-derived dendritic cells from HLA-matched allogeneic donors showed a greater ability to induce leukemic cell-specific T cells in comparison to leukemic cell-derived dendritic cells or monocyte-derived dendritic cells from AML patients. Leuk Res. 2008 May 21. [Epub ahead of print].

12. Royer PJ, Bougras G, Ebstein F, Leveque L, Tanguy-Royer S, Simon T, Juge-Morineau N, Chevallier P, Harousseau JL, Gregoire M. Efficient monocyte-derived dendritic cell generation in patients with acute myeloid leukemia after chemotherapy treatment: application to active immunotherapy. Exp Hematol. 2008;36(3):329-39.

13. Scheibenbogen C, Letsch A, Keilholz U, et al. CD8 T-cell responses to Wilms tumor gene product WT1 and proteinase 3 in patients with acute myeloid leukemia. Blood. 2002;100:2132-7.

14. Mailänder V, Scheibenbogen C, Keilholz U, et al. Complete remission in a patient with recurrent acute myeloid leukemia induced by vaccination with WT1 peptide in the absence of hematological or renal toxicity. Leuk. 2004;18:165-6.

15. Keilholz U, Scheinbenbogen C, Letsch A, Asemissen AM, Hofmann WK, Uharek L, et al. WT1-peptide vaccination shows high immunogenicity and clinical activity in patients with acute myeloid leukemia. Blood. 2005;106:406 [abstract].

16. Greiner J, Giannopoulos K, Li L, Liebisch P, Wendl C, Chen J, et al. RHAMM/CD168-R3 Peptide vaccination of HLA-A2+ patients with acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and multiple myeloma (MM). Blood. 2005;106:2781 [abstract].

17. Roddie H, Klammer M, Thomas C, Thomson R, Atkinson A, Sproul A, Waterfall M, Samuel K, Yin J, Johnson P, Turner M. Phase I/II study of vaccination with dendritic-like leukaemia cells for the immunotherapy of acute myeloid leukaemia. Br J Haematol. 2006;133(2):152-7.

18. Li L, Giannopoulos K, Reinhardt P, Tabarkiewicz J, Schmitt A, Greiner J, Rolinski J, Hus I, Dmoszynska A, Wiesneth M, Schmitt M. Immunotherapy for patients with acute myeloid leukemia using autologous dendritic cells generated from leukemic blasts. Int J Oncol. 2006;28(4):855-61.

19. Houtenbos I, Westers TM, Ossenkoppele GJ, van de Loosdrecht AA. Leukemia-derived dendritic cells: towards clinical vaccination protocols in acute myeloid leukemia. Haematologica. 2006;91:348-55.

20. Van de Velde ALR, Berneman ZN, Van Tendeloo VFI. Immunotherapy of hematological malignancies using dendritic cells. Bull Cancer. 2008;95(3):320-6.

21. Galea-Lauri J. Immunological weapons against acute myeloid leukaemia. Immunol. 2002;107(1):20-7.

22. Greiner J, Döhner H, Schmitt M. Cancer vaccines for patients with acute myeloid leukemia - definition of leukemia-associated antigens and current clinical protocols targeting these antigens. Haematologica. 2006;91:1653-61.

23. Houtenbos I, Westers TM, Ossenkoppele GJ, van de Loosdrecht AA. Feasibility of clinical dendritic cell vaccination in acute myeloid leukemia. Immunobiol. 2006;2116-8):677-85.