LETTER TO THE EDITOR

Maintenance of complete remission after allogeneic stem cell transplantation in leukemia patients treated with Wilms tumor 1 peptide vaccine

Blood Cancer Journal (2013) 3, e130; doi:10.1038/bcj.2013.29; published online 2 August 2013

The prognosis of patients after allogeneic hematopoietic stem cell transplantation (HSCT) is still not satisfactory because, while treatment-related mortalities have decreased, relapse after HSCT remains a major concern. The effectiveness of allogeneic HSCT for hematological malignancies is the result of immunologic rejection of recipient leukemia cells by donor T cells, known as the graft-versus-leukemia (GVL) effect. It is thus obviously important to be able to exploit the GVL effect while minimizing graft-versus-host disease (GVHD). A targeted anti-leukemic immunotherapy, such as use of a leukemia vaccine, is a promising strategy to boost the GVL effect.

Wilms tumor 1 (WT1) protein is one of the best targets for leukemia vaccines. Overexpression of the wild-type WT1 gene has been detected in all types of human leukemia. We performed a phase I clinical study of immunotherapy targeting the WT1 protein in patients with leukemia, and were able to show that WT1 vaccination was safe and could induce WT1-specific cytotoxic T lymphocyte (CTL). Furthermore, reduction of minimal residual disease (MRD) was observed in some leukemia patients who were given the WT1 vaccine.

This report presents the results of phase I clinical study of WT1 vaccination for HLA-A*2402: WT1 patients who were at high risk of relapse (HSCT in non-CR and 2nd HSCT for post-transplant relapse) or had already relapsed. The HLA-A*2402-restricted 9-mer WT1 peptide (amino acids 235–243 CYTWNQMNL) was emulsified with Montanide ISA51 adjuvant. Patients were intradermally injected with 1.0 mg (three patients: UPNs 1, 4 and 6) or 3.0 mg (other six patients) of WT1 peptide four times weekly. When no adverse effects and no obvious disease progression were observed after the fourth injection, further WT1 vaccinations at 2-week intervals were administered.

Nine patients (five with acute myeloid leukemia (AML), one each with acute lymphoblastic leukemia, chronic myelomonocytic leukemia, multiple myeloma and T-cell lymphoblastic lymphoma) were enrolled in this study (Supplementary Tables 1 and 2). Local inflammatory response was observed at the vaccine injection sites of all patients. One patient (UPN5) suffered mild hypoxia (PaO2 65 mm Hg at room air) and restrictive pulmonary dysfunction (FEV1,10% 40%) 65 days after the start of WT1 vaccination (day 199 after HSCT; Figure 1a). He was diagnosed with bronchiolitis obliterans (BO), which was a symptom of chronic GVHD. The patient recovered soon after administration of inhaled steroids. While early and sudden discontinuation of prednisolone and tacrolimus (day 103 after HSCT) were considered to be the reason for development of BO, the possibility of an association between BO and WT1 vaccination cannot be entirely ruled out. In other eight patients, no severe toxicities related to WT1 vaccine were observed (Table1).

Three AML patients (UPN1–3), who had undergone HSCT in non-CR, started WT1 vaccine in CR (Supplementary Tables 1 and 2). They started WT1 vaccination on post-HSCT days 141, 76 and 93 and have remained in CR for 1038, 973 and 662 days, respectively (as of 8 April 2013; Table1), suggesting the potential of WT1 vaccination as a maintenance therapy after HSCT.

Six patients started WT1 vaccination in non-CR and two of them became CR after WT1 vaccination. One B-ALL patient (UPN4) with MLL-AF4 underwent bone marrow transplantation from an HLA-matched unrelated donor during the first CR. On post-HSCT day 111, MLL-AF4 and WT1 mRNA in peripheral blood (PB) had increased to 16 000 and 15 000 copies/μg RNA, indicating that the disease had relapsed. Tacrolimus and prednisolone doses were tapered off to induce GVL effects. The expression levels of MLL-AF4 and WT1 mRNA in PB had decreased to 2700 and 190

Figure 1. Clinical course of patients who attained CR after the start of WT1 peptide vaccination. (a) Clinical course of UPN5 who achieved CR after administration of WT1 vaccine but stopped vaccination because of the development of bronchiolitis obliterans. (b) Clinical course of UPN4. Residual leukemia cells that were detected by MLL-AF4 expression disappeared after the start of WT1 vaccination. In both cases, rapid tapering of immune-suppressive drugs preceded WT1 peptide vaccination.
Our results suggest that WT1 vaccination should be started when the leukemia burden is minimal. The timing of the start of WT1 vaccination may be also important. For the cases with good outcomes, WT1 vaccination was started 76–140 days after transplantation (UPNs 1–5) and at later times (days 299–1815) for PD cases (UPNs 6–9). A lymphopenic environment a few months after transplantation may be favorable for rapid and extensive expansion of tumor antigen-specific CTLs.

In summary, this report suggests that WT1 vaccine can be safely administrated for post-HSCT patients with hematological malignancies and has potential as a maintenance therapy. Clinical benefit of WT1 vaccination for post-HSCT patients will be evaluated in the subsequent phase II trials.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Table 1. Patient outcomes

| UPN | Disease | Status before vaccination | Adverse events | Number of vaccine doses | Outcome | Additional therapy | Survival |
|-----|---------|--------------------------|----------------|------------------------|---------|-------------------|---------|
| 1   | AML (M4) | CR                       | None           | 54                     | CR      |                   | 1179 + 1038 + |
| 2   | AML(M4, DEK/CAN +) | CR | PLT ↓ | 52                     | CR      |                   | 1049 + 973 + |
| 3   | AML | CR                       | None           | 38                     | CR      |                   | 759 + 662 + |
| 4   | B-ALL (M4/AF4 +)  | Molecular relapse       | None           | 71                     | CR      |                   | 1312 + 1179 + |
| 5   | AML (M4)  | Relapse                  | Amylase ↑, bronchileitis obliterans (cGVHD) | 2 | CR      |                   | 972 + 842 + |
| 6   | CMMoL     | Relapse                  | None           | 25                     | PD +    | Chemo             | 2265 381 |
| 7   | MM        | PD                       | None           | 19                     | PD      | Chemo             | 1301 + 804 + |
| 8   | T-LBL     | Relapse                  | None           | 4                      | PD      | Second transplant | 955 656 |
| 9   | AML (M2)  | Relapse                  | None           | 17                     | PD      | Second transplant | 1544 + 749 + |

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CMMoL, chronic myelomonocytic leukemia; CR, complete remission; CGVHD, chronic graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; MM, multiple myeloma; PD, progressive disease; T-LBL, T-cell lymphoblastic lymphoma. (8 April 2013). A causal relationship between vaccination and this event was not strongly suspected, but could not be ruled out. Vaccination was discontinued. (The last injection was on post-HSCT day 60). Size of the subcutaneous tumor decreased, but the disease relapsed in axial lymph nodes and stomach.
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Supplementary Information accompanies this paper on Blood Cancer Journal website (http://www.nature.com/bcj)