Relapse of renal cell carcinoma with disappearance of HLA class I following hTERT peptide vaccination

A 74-year-old woman who had undergone right nephrectomy due to renal cell carcinoma (RCC) was found to have developed multiple lung metastasis of RCC 5 years after surgery. The patient was treated with interferon-α, but she was unable to tolerate this therapy because of fever and severe malaise. At this time, as molecular-targeted therapy, such as the multikinase inhibitor sorafenib, was not available, the patient was enrolled in a phase I/II clinical study of human telomerase reverse transcriptase (hTERT) peptide vaccination, as reviewed and approved by the Institutional Review Board of Ehime University Hospital. She received s.c. injection of 1 mg hTERT\textsubscript{324-332} (VYAETKHFL) peptide \cite{1} in Montanide ISA51 adjuvant biweekly. During the following 2 years, she received hTERT peptide vaccination a total of 20 times with some discontinuations. The protocol was well tolerated; only local erythema occurred at the peptide vaccine injection sites. As shown in Figure 1A, during vaccination with hTERT peptide for 2 years, the sizes of the RCC metastases did not change significantly. The results of enzyme-linked immunospot (ELISPOT) assay for monitoring hTERT\textsubscript{324-332}-specific CD8\textsuperscript{+} cytotoxic T lymphocytes (CTLs) in peripheral blood are shown in Figure 1B. The hTERT peptide-specific CTLs were not detectable in peripheral blood of the patient before hTERT peptide vaccination and became detectable after the fifth vaccination. The frequency of hTERT peptide-specific CTLs in peripheral blood appeared to increase as the vaccinations were repeated.
After the period of ~2 years during which the disease remained stable, a large mass became palpable on the inside of the patient’s right thigh (Figure 1C). Histology of the biopsied specimen revealed metastasis of RCC (Figure 1D). Histochemical analysis of the metastatic RCC using the anti-human leukocyte antigen (HLA) class I framework monoclonal antibody, EMR8-5 [2], revealed that most of the RCC cells in the metastasis appeared to lack HLA class I expression (Figure 1E). The multiple metastases subsequently progressed, and the patient died 6 months later.

In our phase I/II clinical trial of hTERT peptide vaccine, four patients with metastatic RCC and six patients with metastatic prostate cancer were enrolled. Although no severe adverse events occurred, no apparent clinical response was detectable in any of the patients except for the present one. In this case, multiple lung metastases remained in a stable state during the period.
of hTERT peptide vaccination, and hTERT-specific CTLs were generated. Although it is well known that RCC often remains stable for a long period, especially after treatment of the primary lesion, it can be speculated that in this case, an anti-RCC immune response resulting in a stable state might have been induced during the course of hTERT peptide vaccination. In spite of the clinical response shown by the metastatic lesions in the lungs, a new metastatic focus developed in the thigh with down-regulation of HLA class I expression.

Down-regulation of HLA class I is one of the mechanisms by which cancer can evade immunosurveillance. Down-regulation of HLA class I in cancer cells can be caused by impairment of the antigen-processing machinery, which is mediated by TAP1, TAP2, tapasin, LMP2, LMP7, and LMP10/MECL-1 [3], and down-regulation or deficiencies of TAP1, tapasin, LMP2, and LMP7 have been reported in RCC [4]. In addition, impaired epigenetic regulation of the β2-microglobulin gene is one of the main causes of HLA class I down-regulation in various cancers [5]. Overcoming the disappearance of HLA class I expression in cancer will be an essential step for establishing effective cancer immunotherapy regimens targeting tumor-associated-antigens recognized by tumor-specific CTLs.

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funding


acknowledgement

We thank Atsuro Sugita and Tatsuhiko Miyazaki for histological analysis and immunohistochemical analysis, respectively.

disclosure

The authors declare no conflicts of interest.

references


doi:10.1093/annonc/mdq544