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Cancer Immunology Research

Priority Brief

Long-term Complete Remission Following Radiosurgery and Immunotherapy in a Melanoma Patient with Brain Metastasis: Immunologic Correlates

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Abstract

A melanoma patient with brain metastases was treated by gamma-knife radiosurgery and immunotherapy with autologous tumor-lysate–loaded dendritic cells (DC). Ten years after the combined treatment, the patient remains in complete remission. Remarkable immunologic correlates to the clinical development were the transient induction of NY-ESO-1 antibody and the durable expansion of MAGE-A1$_{p161-169}$ EADPTGHSY–specific CD8$^+$ T cells. Although the induction of NY-ESO-1 antibody most likely resulted from gamma-knife–mediated "auto-vaccination," the persistence of circulating MAGE-A1–specific T cells, which are still detectable *ex vivo* in the absence of any tumor manifestation, coincides with DC-based vaccination administered monthly until today.

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Introduction

The discovery of "cancer-testis" antigens, such as MAGE-A1 and NY-ESO-1, has led to the development of vaccine-based interventions against cancer that rely on the stimulation of effective tumor-specific immune responses (1–3). The recent clinical success of the dendritic cell (DC)–based cancer vaccine sipuleucel-T (Provenge; Dendreon) for prostate cancer and the immunomodulatory anti–CTLA-4 antibody ipilimumab (Yervoy; Bristol-Myers Squibb) for advanced melanoma has renewed interest in immunotherapy targeting cellular responses to cancer antigens (4, 5). Although promising results on prolongation of overall survival have been reported, the optimal strategy for cancer immunotherapy to control tumor growth has yet to be determined. Mounting evidence suggests that immunotherapy might synergize with radiotherapy and is most successful in patients with a limited tumor burden (6, 7). In this regard, radiotherapy and the use of DC-based vaccines represent a promising treatment combination capable of inducing *de novo* and enhancing preexisting tumor-specific T-cell and antibody responses (8).

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Melanoma is one of the most frequent metastatic cancers with increasing incidence worldwide and very limited treatment options in advanced stages. Patients with melanoma brain metastases carry a very poor prognosis with a median overall survival of about 4 to 5 months (9).

We report here on a patient with brain metastatic melanoma, who experienced complete and sustained remission to the aforementioned treatment combination of radiosurgery and immunotherapy. In our approach, the vaccine consists of autologous tumor-lysate–loaded DCs (TL-DC) delivered into the skin by intradermal injections. Focusing on MAGE-A and NY-ESO-1, we provide a 12-year immunologic and clinical follow-up with remarkable correlations between treatment-induced immune responses and long-term disease-free survival.

Materials and Methods

Preparation of the TL-DC vaccine

DCs were generated from CD4 and CD8 T-cell–depleted peripheral blood mononuclear cells by adherence to plastic in 25-cm^2 tissue culture flasks and cultured in serum-free X-VIVO 15 medium (BioWhittaker) supplemented with granulocyte macrophage colony-stimulating factor (GM-CSF) and interleukin (IL)-4 (1,000 U/mL). After 5 days, 5×10^5 DCs were pulsed with 10 μL tumor lysate for 6 to 8 hours. The tumor lysate was prepared from the patient's lymph node metastasis by three freeze–thaw cycles of pulverized and homogenized tumor tissue (200 mg/200 μL water). For safety, the tumor lysate was irradiated at 200 Gy. TL-DCs were matured for 12 to 24 hours by adding a cytokine cocktail consisting of IL-6, IL-1β, and TNF-α (10 ng/mL). Matured TL-DCs were washed twice and used for intradermal vaccination. Remaining TL-DCs were frozen for subsequent vaccinations.

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Monitoring of immune responses

Longitudinal measurement of serum antibodies was performed by standard ELISA as described previously (10). *Ex vivo* or *in vitro* analysis of T cells was performed by IFN-γ enzyme-linked immunospot (ELISPOT) assay and by fluorescence-activated cell sorting (FACS) analysis using peptide-MHC class I tetramer complexes as described previously (11). Further details and information about these analyses are provided in the Supplementary Methods.

Results

Case report

In June 2001, a 44-year-old woman was diagnosed with a 1.2-mm Breslow primary nodular melanoma located in the right upper arm. She underwent wide local excision. The disease was classified as pT2NXMX, Clark level IV according to the American Joint Committee on Cancer (AJCC) 2001 staging system. Within 1 year, the disease recurred twice in the right axilla and three times in the clavicular lymph node region. Lymph node metastases were surgically resected repeatedly. The disease further progressed to the brain. Four lesions with volumes of 1, 3.7, 0.1, and 0.1 cm^3 were radiologically treated with 45 Gy each by gamma-knife surgery in August 2002. Brain metastases completely regressed and did not recur, as confirmed by routine magnetic resonance tomographic (MRT) images every year until today. Sixteen months later, in December 2003, the patient relapsed again with several mesenteric lymph node metastases that were removed by partial resection of the small intestine. Since then, the patient has remained free of disease for nearly 10 years.

Apart from the primary surgical treatment, the patient successively received adjuvant high-dose IFN-α2a (HDI) therapy for 8 weeks in 2002, followed by four injections of melanoma antigen-3 (MAGE-A3)–associated peptide within the LUD01–006 clinical study in June 2002. Because of rapid disease progression, the patient was removed from the study. Subsequently, immunotherapy with autologous TL-DCs was initiated in August 2002 on a compassionate-use basis. Routinely, 5×10^5 autologous TL-DCs have been injected intradermally in turn on the left upper arm and left or right upper thigh once a month until today. Up to this time, the patient has received a total of 133 vaccines. The patient is still in complete remission. The course of disease under treatment is presented in Fig. 1A.

Induction of NY-ESO-1 antibody after gamma-knife radiosurgery

By the time of tumor progression to the brain, there were no antibody responses against the tumor antigens MAGE-A1, MAGE-A3, or NY-ESO-1, which were expressed as assessed by reverse transcriptase PCR in previously resected lymph nodes (Supplementary Table S1). After gamma-knife surgery of brain metastases, the patient developed NY-ESO-1 antibodies that persisted for a year and a half until the removal of the mesenteric lymph node metastases in December 2003 (Fig. 1B). During the time of antibody persistence, we identified NY-ESO-1 antibody specificities against two different antigenic B-cell epitopes. Induction of the NY-ESO-1 antibody against epitope p31–50 located in the N-terminal part of the protein coincided with tumor destruction of the brain metastases, and the presence of the NY-ESO-1 antibody against epitope p161–180 located in the C-terminal region of the protein coincided with the development and subsequent resection of mesenteric lymph node metastases. Thus, NY-ESO-1 antibody responses of distinct specificities were triggered by different tumor manifestations and potentially through different ways of tumor antigen release (Fig. 2).

Expansion of MAGE-A1$_{p161–169}$–specific CD8$^+$ T cells

On the basis of the antigenic profile of the tumor and the patient's HLA haplotype, A1, A11, B13, B35, Cw4, and Cw6, we analyzed the CD8$^+$ T-cell responses against NY-ESO-1, MAGE-A1, MAGE-A3, and MELAN-A. CD8$^+$ T cells from different time points were presensitized *in vitro* with the following antigenic peptides: NY-ESO-1$_{p91–110}$ YLAMPFATPMEAELARRSLA, MAGE-A1$_{p161–169}$ EADPTGHSY, MAGE-A3$_{p168–176}$ EVDPIGHLY, and Melan-A$_{p26–35}$ EAAGIGILTV, as shown in the peptide database from van der Bruggen and colleagues (12). Cellular immune responses were detectable after *in vitro* presensitization in May 2002 early in the course of the disease (Fig. 3A); however, the frequency of these antigen-specific CD8$^+$ T cells was low and not detectable *ex vivo* from the peripheral blood (Fig. 3B). We analyzed lymphocytes of the first blood sample available after radiotherapy and immunotherapy with TL-DC in June 2004 and found that cellular responses were higher to all antigens tested, while levels of MAGE-A1$_{p161–169}$–specific CD8$^+$ T cells had increased significantly and had become clearly detectable *ex vivo* (Fig. 3A and B). A frequency of 0.4% of circulating MAGE-A1$_{p161–169}$–specific CD8$^+$ T cells was determined by both ELISPOT assay for IFN-γ secretion and FACS analysis for peptide/MHC tetramer binding. The robust MAGE-A1–specific CD8$^+$ T-cell response was maintained throughout immunotherapy and is still detectable *ex vivo* in the patient's peripheral blood without any evidence of detectable disease (Fig. 1C). The ability of MAGE-A1$_{p161–169}$–specific CD8$^+$ T cells to recognize naturally processed MAGE-A1 was shown at the clonal level by specific MZ2-MEL tumor cell lysis in ^{51}chromium release assays as described previously (Fig. 3C; ref. 1). To test whether the TL-DC vaccine could stimulate the patient's peripheral blood lymphocytes, we assessed IFN-γ secretion of circulating T cells in *ex vivo* ELISPOT. As shown in Fig. 3D, the vaccine was efficiently recognized by CD4 and CD8 T cells.

Discussion

The combination of radiotherapy with active immunotherapy may restore immunosurveillance in patients with advanced cancers, resulting in long-term tumor control. The effective stimulation of the immune system in the patient presented here is mainly characterized by the induction of high levels of MAGE-A1$_{p161–169}$–specific antitumor CD8$^+$ T cells. This finding matches with early T-cell data of our historical melanoma patient MZ2, in whom MAGE-A1$_{p161–169}$–specific T cells were first identified (13). In both cases, complete tumor eradication and long-term survival correlated with the presence of MAGE-A1–specific T cells, thus highlighting their potential to effectively control tumor growth. Analyzing early immune responses in the patient described herein, we found that T cells responding to tumor-associated antigens MAGE-

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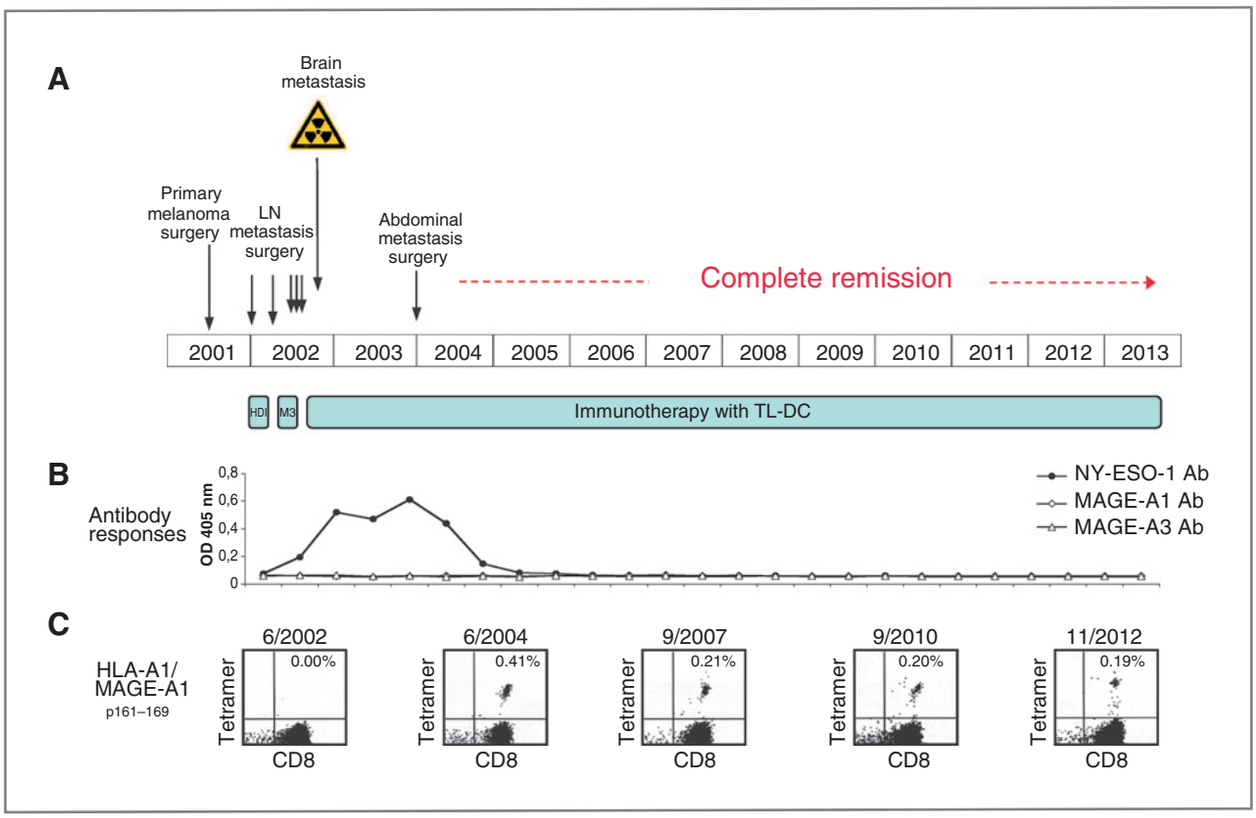

Figure 1. Positive correlations between disease course and treatment-induced immune responses. A, the course of disease is shown above the timeline. Before radiotherapy and immunotherapy with TL-DC, the tumor rapidly progressed to regional lymph nodes (LN) and to the brain. After radiotherapy for brain metastases, the patient showed a prolonged time to progression of 16 months. Since December 2003, the patient has remained free of disease. Immunotherapeutic treatments are shown below the timeline. M3, MAGE-A3 peptide vaccination. Continuous vaccination with TL-DC correlated with long-term tumor control. B, antibody (Ab) responses against the cancer–testis antigens NY-ESO-1, MAGE-A1, and MAGE-A3. The patient developed NY-ESO-1 antibodies in November 2002 after gamma-knife radiation of brain metastasis. After surgical removal of mesenteric lymph node metastasis in December 2003, NY-ESO-1 antibody decreased and has not been detectable at all since July 2004. Antibody responses to MAGE-A1 and MAGE-A3 were not observed at any time. C, *ex vivo* tetramer analysis showing strong expansion of MAGE-A1$_{p161–169}$–specific CD8$^+$ T cells after radiotherapy and immunotherapy with TL-DC in 2004 that persisted throughout the course of immunotherapy and is still detectable *ex vivo* in the patient's peripheral blood without any evidence of detectable disease.

A1, MAGE-A3, NY-ESO-1, and Melan-A were present in the peripheral blood already in June 2002. However, the T-cell response at the time was ineffective and failed to prevent tumor progression. Upon local radiotherapy and immunotherapy with TL-DC, the patient's immune response shifted toward tumor recognition indicated by the development of NY-ESO-1 antibodies. It turned out that NY-ESO-1 antibody response was directed against two distinct epitopes, each of which was targeted at different time points and different tumor sites. Moreover, the antibody switch observed indicated an important evolution of the patient's antitumor immune response as NY-ESO-1$_{p161–180}$–specific antibody appeared independent of radiation, and spontaneously. Of note, subsequent to radiotherapy and vaccination with TL-DC, the patient showed a prolonged time to disease progression of 16 months, which was potentially mediated by the initiation of effective immune responses.

A major goal of active cancer immunotherapy is to induce T-cell–mediated antitumor immune responses with the potential to control tumor growth and to protect against tumor recurrence. To achieve this goal, DC-based vaccines represent a promising treatment approach as DC play a key role in the initiation and regulation of cellular immune responses (14). In our case, immunotherapy with TL-DC was initiated 1 week after gamma-knife surgery of brain metastases. Analysis of the first postvaccination blood sample revealed a strong *ex vivo* detectable MAGE-A1–specific antitumor CD8$^+$ T-cell response that was maintained at a relatively constant high level over time and is still present in the patient, who is alive without any evidence of disease. Therefore, it is likely that the durable expansion of MAGE-A1$_{p161–169}$–specific T cells has been maintained and is still being boosted by continued vaccination with TL-DC. However, evidence that the vaccine still enables the patient's immune system to protect against melanoma recurrence would only be provided by cessation of vaccination. Therefore, it remains uncertain whether the induced T-cell immune response still controls the outgrowth of residual tumor cells, thus keeping the patient's disease in a dormant state (15), or whether the strong anti-MAGE-A1 T-cell immune response has led to the complete elimination of residual tumor

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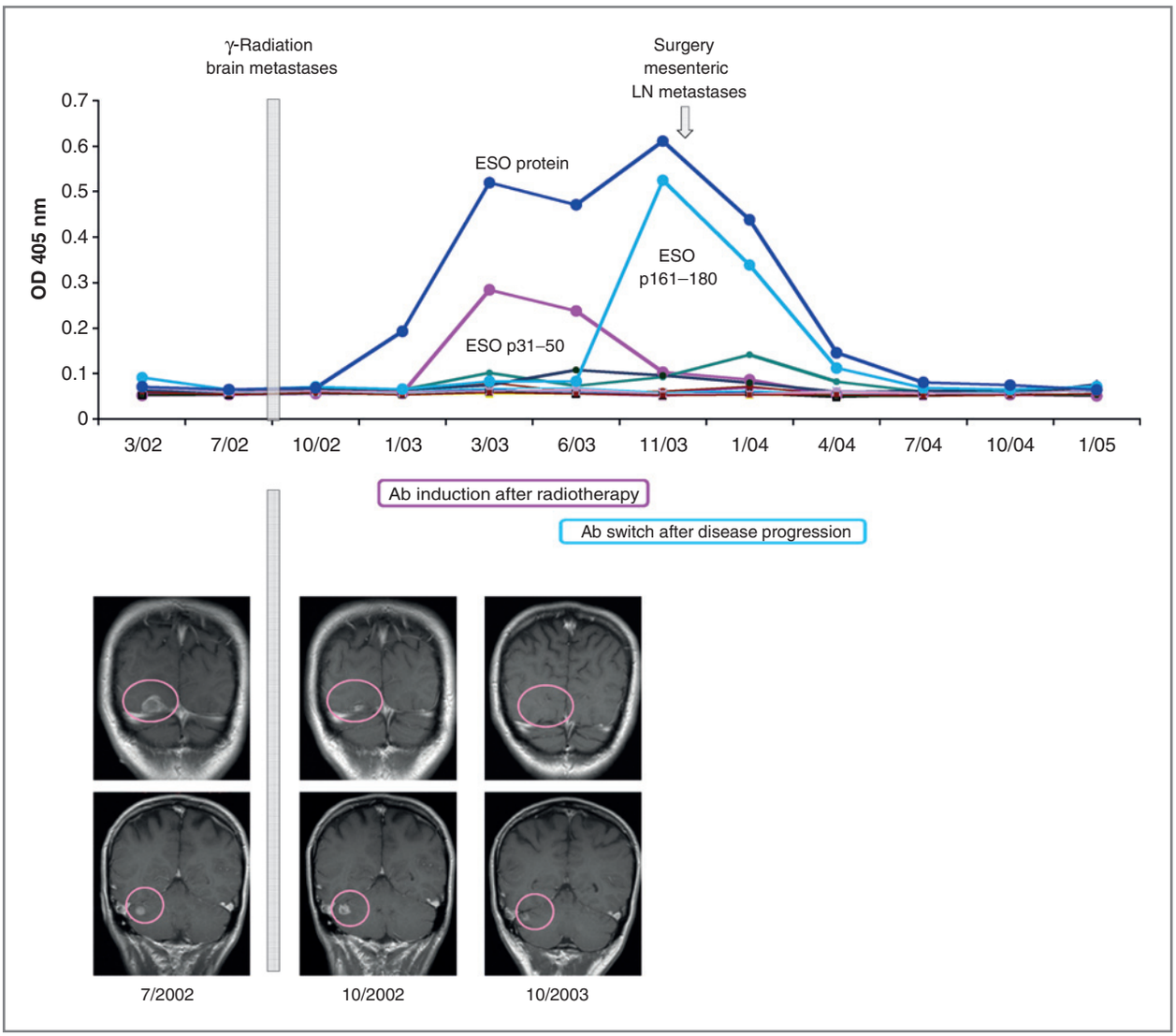

Figure 2. Induction of NY-ESO-1 antibody (Ab) after gamma-knife radiation. Changes in NY-ESO-1 antibody response were investigated by measuring serum immunoglobulin G (IgG) against recombinant full-length NY-ESO-1 protein and against 17 different synthetic 20 mer overlapping NY-ESO-1 peptides as antigens in standard ELISA. Before radiotherapy, the patient had not developed NY-ESO-1 antibodies. After gamma-knife radiation of brain metastasis, the patient sero-converted for NY-ESO-1 antibody. B-cell epitope mapping of NY-ESO-1 antibody response revealed that the presence of NY-ESO-$1_{p31–50}$–specific antibody coincided with tumor cell destruction of brain metastasis. The presence of NY-ESO-$1_{p161–180}$–specific antibody coincided with the development and subsequent surgical removal of mesenteric lymph node (LN) metastasis in December 2003. MRT images with coronal view on two of the brain metastases are shown before gamma-knife radiation (July 2002) and 2 months (October 2002) and 14 months (October 2003) after radiotherapy. Top images show the regression of the right occipital lesion, and bottom images show the transformation and subsequent regression of the right cerebellar lesion. OD, optical density.

cells. The clinical efficacy of our treatment approach may be due to several factors. The use of autologous whole tumor cell lysate as the source of antigens to load DC generates a broad immune response covering all relevant antigens of the individual's disease (16). In this regard, the antigenic material obtained from the abdominal metastases in December 2003 was highly effective in stimulating T-cell responses *in vivo* (Fig. 3D). For the timing of vaccination, it is assumed that patients with large tumor burdens are less likely to clinically respond to therapeutic cancer vaccines because of immunosuppressive mechanisms released by the tumor microenvironment. Furthermore, a minimum time is required to generate a sufficient immune response. Vaccination with TL-DC in our patient was initiated after gamma-knife surgery in a status of minimal residual disease and was even continued beyond tumor recurrence and the subsequent surgery in December 2003. Finally, our data suggest that immunotherapy may synergize well with radiotherapy, especially hypofractionated radiosurgery. Our patient developed tumor antigen–specific antibody and T-cell responses that were not detectable before treatment, suggesting that radiation has led to the release of tumor-associated antigens and DC activation, which in turn may have supported the

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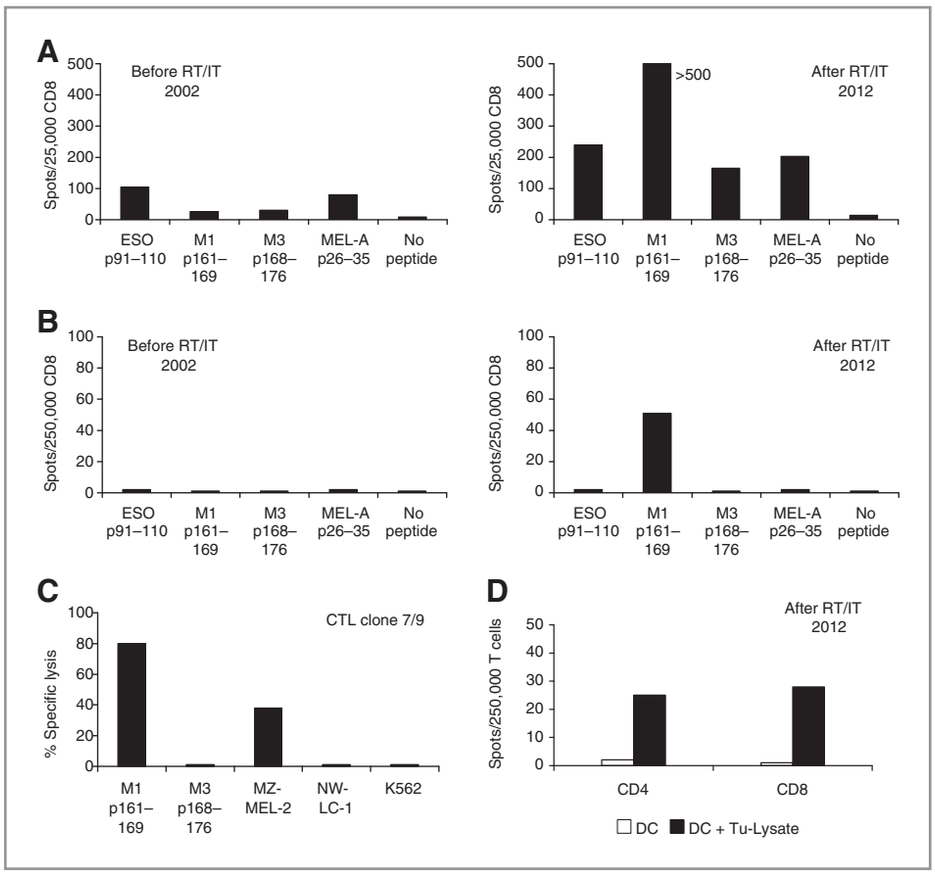

Figure 3. Specificity, frequency, and effector function of $CD8^+$ T-cell responses before and after radiotherapy/immunotherapy (RT/IT). A, IFN-γ secretion of $CD8^+$ T cells following *in vitro* presensitization with peptides. Peptide-pulsed and unpulsed autologous monocyte-derived DC were used as antigen-presenting cells in ELISPOT. B, dominant MAGE-A1–specific $CD8^+$ T-cell response after RT/IT detectable *ex vivo* by IFN-γ ELISPOT analysis. C, lytic activity of MAGE-A1–specific $CD8^+$ T-cell clone NW1751–7/9 against MAGE-$A1_{p161–169}$ peptide-pulsed autologous EBV-B cells and against the MAGE-A1/HLA-A1–expressing tumor cell line MZ2-MEL in chromium release assay at 10:1 effector/target ratio. MAGE-$A3_{p168–176}$ peptide-pulsed autologous EBV-B cells, the MAGE-A1–negative tumor cell line NW-LC-1 (HLA-$A1^+$) and K562 were used as negative controls and were not recognized. D, recognition of the vaccine by circulating CD4 and CD8 T cells is shown in *ex vivo* IFN-γ ELISPOT assay. Unpulsed DC were not recognized.

initiation of a tumor-specific $CD8^+$ T-cell response (17, 7). In mice, it has been shown recently that eradication of murine colon adenocarcinoma under immunotherapy was successful only when preceded by radiotherapy (18).

The cancer immunoediting model by Dunn and colleagues describes the interaction between cancer development and a patient's immune response resulting in tumor elimination, equilibrium, or escape (19). It has been established that the immunoediting process can be affected significantly by therapeutic manipulations (20). In our patient, it seems probable that after the failure of immunosurveillance, the rapidly growing tumor was locally controlled by surgery and radiotherapy. However, long-term disease-free survival may have resulted from the induction of an antitumor T-cell response triggered by auto-vaccination effects of radiotherapy durably sustained by immunotherapy with TL-DC.

On the basis of the convincing evidence of effective tumor control following surgery, hypofractionated radiotherapy, and immunotherapy with TL-DC, we suggest considering conventional cancer treatments to be combined with active immunotherapy as a means to improve patient survival.

Disclosure of Potential Conflicts of Interest

S. Gnjatic has an ownership interest (including patents) in NY-ESO-1 peptide patents. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: J. Karbach, A. Knuth, E. Jäger
Development of methodology: J. Karbach, S. Gnjatic, K. Brandt, A. Knuth, E. Jäger
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Karbach, A. Atmaca, A. Knuth, E. Jäger
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Karbach, S. Gnjatic, E. Weidmann, H. Bernhard, A. Knuth, E. Jäger
Writing, review, and/or revision of the manuscript: J. Karbach, S. Gnjatic, M. Biskamp, E. Weidmann, H. Bernhard, A. Knuth, E. Jäger
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Karbach, C. Wahle, A. Knuth, E. Jäger
Study supervision: J. Karbach, M. Biskamp, E. Jäger

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