Abstract

Peptides derived from human cancer antigens have proven successful for the induction and the monitoring of antigen-specific CD8+ T-cell responses in vivo and in vitro. Following intradermal injection, antigenic peptides were found to induce delayed-type hypersensitivity (DTH) reactions that correlate with the magnitude of peptide-specific CD8+ T-cell responses detectable in the peripheral blood. Strong DTH and CD8+ T-cell responses were associated with stabilization and regression of metastatic disease in single patients.

The identification of MHC class I and class II restricted NY-ESO-1 epitopes has set the basis for the monitoring of spontaneous and vaccine-induced cellular immune responses against NY-ESO-1. The NY-ESO-1 peptides p157-167, p157-165, and p155-163, which are presented by HLA-A2, were first to be evaluated for their immunogenicity in vivo in a clinical study. Twelve patients have received weekly intradermal injections of NY-ESO-1 peptides at a dose of 100 µg/injection for 4 weeks. After a 4-week treatment-free interval, the schedule of immunization was continued until disease progression was observed. GM-CSF was used as a systemic adjuvant starting with the third cycle of immunization. Peptide-specific CD8+ T-cell responses were induced in 4/7 NY-ESO-1 antibody negative patients during the first 4 months of vaccination, as assessed in ELISPOT and tetramer assays. DTH reactions at immunization sites reflected the onset and intensity of peptide-specific CD8+ T-cell responses present in the peripheral blood. In 5/12 NY-ESO-1 antibody positive patients, peptide-specific CD8+ T-cell responses detected at baseline were not significantly altered during the course of vaccination.

The impact of an intensive-course schedule of peptide immunization on the onset and magnitude of peptide-specific immune responses was evaluated in a subsequent study. NY-ESO-1 peptides p157-165 and p157-167 were administered intradermally for 5 consecutive days at a dose of 100 µg/injection. Immunizations were repeated every 3 weeks for 5 days, and combined with GM-CSF as a systemic adjuvant starting with the third cycle. In contrast to the weekly protocol, strong peptide-specific DTH reactions and CD8+ T-cell responses were induced in 8/9 NY-ESO-1 antibody negative patients as early as during the first 6 weeks of vaccination. In 9 NY-ESO-1 antibody positive patients, baseline DTH and CD8+ T-cell reactivity were not significantly changed during vaccination. These results indicate that the efficacy of cancer vaccines is closely related to the schedule of immunization. T-cell responses of high magnitude induced early during the course of vaccination may be most effective to eliminate NY-ESO-1-expressing cancer cells and to prevent immune escape in vivo.

Cancer vaccines may have more favorable effects by stimulating integrated immune responses involving CD4+ and CD8+ T-cell and B-cell responses. To broaden the immunogenic profile of NY-ESO-1 vaccines to both MHC class I and class II restricted epitopes, recombinant vaccinia- and fowlpox-NY-ESO-1 constructs were administered as a vaccine in a subsequent study. Vaccinia- and fowlpox-NY-ESO-1 constructs used at 2
different dose levels were shown to be safe after intradermal and subcutaneous injection at monthly intervals for 4 months. Since NY-ESO-1 antibody negative, HLA-A2 positive patients were recruited for the first study cohorts, the HLA-A2 restricted NY-ESO-1 epitopes p157-167 and p157-165 were used for DTH testing and to monitor CD8+ T-cell responses during the course of immunization. Twelve HLA-A2 positive patients were enrolled, 7 have completed 4 immunizations. Peptide-specific CD8+ T-cell responses were induced in all 7 patients who completed the protocol. The induction of NY-ESO-1 antibody was observed in 1 patient after 2 immunizations. There was no evidence of disease progression in 6 patients for >6 months after the start of immunization. Additional analyses for the identification of CD4+ and CD8+ T-cell responses directed against other NY-ESO-1 epitopes are ongoing in different international collaborative projects within the Ludwig Institute. The results will contribute important information on the efficacy of recombinant viral NY-ESO-1 constructs in inducing integrated NY-ESO-1-specific immune responses involving CD4+, CD8+ T cells, and antibody, and their impact on the clinical development of NY-ESO-1 positive disease.

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