P02.03 MICROWAVE ABLATION ENHANCES TUMOR-SPECIFIC IMMUNE RESPONSE IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Background Thermal ablative therapies, such as microwave ablation (MWA) or radiofrequency ablation (RFA), are standard treatments for HCC. In addition to the local tumor destruction, abscopal effects (a reduction of a tumor mass in areas that were not included in the thermal ablation) could be observed. These systemic effects may be mediated by anti-tumor immune response, which has been described for RFA. MWA is rapidly replacing RFA, but systemic immunostimulatory effects of MWA treatment have been poorly studied.

Materials and Methods Patients receiving MWA for localized HCC were included in this study. Effects of MWA on peripheral blood mononuclear cells (PBMC) of HCC patients treated with MWA were analyzed by multicolor flow cytometry. Tumor-specific immune responses against 7 shared tumor antigens were analyzed using peptide pools in 3-color Fluorospot assays (Interferon- γ /Interleukin-5/Interleukin-10). The impact of type, density and localization of tumor-infiltrating lymphocytes was assessed by immunohistochemistry (IHC) of CD3, CD4, CD8, FoxP3, CD38 and CD20 and digital image analyses (Immunoscore) of tumor specimens in an additional cohort of patients who received combined surgical resection and thermal ablation.

Results While comprehensive flow cytometric analyses in sequential samples (day 0, 7 and 90) of a prospective patient cohort (n=23) demonstrated only moderate effects of MWA on circulating immune cell subsets, Fluorospot analyses revealed de novo or enhanced tumor-specific immune responses in 30% of these patients. This anti-tumor immune response was related to tumor control. Interferon- γ and Interleukin-5 T cell responses against cancer testis antigens were more frequent in patients with a long-time remission (>12 months) after MWA (7/16) compared to patients suffering from an early relapse (0/13 patients). Presence of tumor-specific T cell response (Interferon- γ and/or Interleukin-5) was associated to longer progression-free survival (15.0 vs. 10.0 months). Immunohistochemical analyses of resected tumor samples revealed that a high T cell infiltration in a second tumor lesion at the time of thermal ablation was associated with superior disease-free survival (37.4 vs. 13.1 months).

Conclusions Our data demonstrates remarkable immune-related effects of MWA in HCC patients. This study provides additional evidence for a combination of thermal ablation and immunotherapy in this challenging disease.

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P02.04 ABSTRACT WITHDRAWN

P02.05 INVESTIGATION OF A SYNGENEIC A-PD-1 ANTIBODY TO TREAT MURINE 4T1 MAMMARY CARCINOMA

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Background Many cancers acquire mechanisms to evade immunosurveillance by activating immune checkpoint pathways, which suppress the antitumor immune responses. Monoclonal antibodies (ab's) targeting immune checkpoints, such as CTLA-4 and PD-1, have shown excellent results in several cancers and are currently being investigated in clinical trials for various malignancies. The clinically tested a-CTLA-4 (Ipilimumab) and a-PD-1 (Nivolumab and Pembrolizumab) ab's are fully human or humanized ab's, respectively. However, most studies conducted in mice utilize a xenogeneic a-PD-1 ab originating from rat, IgG2a RMP1-14 clone. This has been proposed to cause adverse effects in the commonly used 4T1 mammary carcinoma model of triple negative breast cancer (TNBC). Repeated administration of xenogeneic a-PD-1 ab's in this model results in fatal hypersensitivity reactions in tumor bearing mice, and unlike human TNBC, the 4T1 cell line is generally poorly responsive to immune checkpoint inhibitors. Recently, a semi-syngeneic recombinant a-PD-1 ab has been developed by transferring the variable regions of RMP1-14 onto a murine IgG1e3 constant region.

Materials and Methods Testing xenogeneic and semi-syngeneic a-PD-1 ab with and without a-CTLA-4 ab in BALB/c mice carrying 4T1 luciferase positive tumors.

Results In this study, we compared a semi-syngeneic recombinant a-PD-1 ab to the original xenogeneic RMP1-14 clone for treatment of luciferase positive 4T1 carcinomas. Surprisingly, the semi-syngeneic a-PD-1 ab was not able to circumvent the fatal hypersensitivity reactions. Still, the combination therapy of a-CTLA-4 and the semi-syngeneic a-PD-1 ab significantly reduced tumor volume in 4T1-luciferase tumor bearing mice compared to isotype control-treated mice already from day 16 post tumor inoculation (day 8 post treatment-initiation). In contrast, xenogeneic a-PD-1/a-CTLA-4 treated mice did not show significant difference from the control group until 24 days post tumor inoculation and never to the same degree. Furthermore, analysis of the T cell responses towards the murine tumor-associated antigen AH-1, revealed that treatment with syngeneic a-PD-1/a-CTLA-4 ab gave a significantly stronger CD8⁺ T cell response over both control mice and mice treated with xenogeneic a-PD-1/a-CTLA-4 ab.