Abstracts

In this abstract, there is a mention of a study on patients with recurrent high-grade gliomas. The study used a peptide-based vaccine and adoptive transfer therapy using T-cells transduced with the H3.3.K27M-specific TCR. The H3.3.K27M mutation is shared by any known human protein. Intravenous administration of T-cells loaded with the synthetic H3.3.K27M epitope peptide but also recognized HLA-A2-negative cells. The H3.3.K27M epitope peptide, but not the non-mutant counterpart, induced an excellent affinity (Kd 13 nM) to HLA-A2 based on competitive binding inhibition assay. From CTL clones with high and specific affinities to HLA-A2-H3.3.K27M-tetramer, cDNAs for T cell receptor (TCR) and -chains were cloned into a retroviral vector. Human HLA-A2- T cells transduced with the TCR demonstrated antigen-specific reactivity as well as anti-glioma responses in vitro. Peptide titration assay suggested that the H3.3.K27M-specific TCR had the maximal reactivity for peptide recognition of around 100 nM. Furthermore, critically important for the efficacy of any adoptive cell application, alanine scanning demonstrated that a key amino-acid sequence motif in the epitope for the TCR reactivity is not shared by any known human protein. Finally, intravenous administration of T-cells transduced with the H3.3.K27M-specific TCR significantly inhibited the growth of Toca 511-H3.3.K27M-positive glioma xenografts in immune-deficient mice. These data provide us with a strong basis for developing peptide-based vaccines as well as adoptive transfer therapy using autologous T-cells transduced with the H3.3.K27M-specific TCR.

OS09.5 SYNERGISTIC EFFECT OF REIRRADIATION AND PD-1 INHIBITORS IN RECURRENT HIGH-GRADE GLIOMAS

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BACKGROUND: To date, studies of single agent PD-1 or PDL-1 inhibitors in recurrent high-grade gliomas (HGG) have shown infrequent responses (< 10%) and limited efficacy. Reirradiation is considered one of the standard salvage regimens for selected patients with recurrent gliomas but tumor responses are also infrequent (< 5%). Radiotherapy counteracts the immunosuppressive tumor microenvironment by increasing MHC class I expression and enhancing tumor neoantigen presentation and has a significant effect with PD-1 inhibition in preclinical models of glioma. METHODS: From December 2014 to June 2016, 20 patients (14 men, 6 women) with recurrent HGG were treated with the combination of reirradiation and PD-1 inhibitors. 18 patients had a glioblastoma, 1 anaplastic oligodendroglioma and 1 anaplastic oligoastrocytoma. The median KPS at the start of this regimen was 70 (50 to 80). The median number of prior treatments for recurrent tumor was 2 (1–4), 100% had prior radiation, 95% prior temozolomide and 55% prior bevacizumab. 8 patients received pembrolizumab (2 mg/kg every 3 weeks) and 12 patients received nivolumab (3 mg/kg or 240 mg flat dose every 2 weeks). Median reirradiation dose was 35 Gy (12 Gy to 35 Gy). RESULTS: There were 7 confirmed partial responses (35% objective response rate, ORR), 5 stable disease and 8 progressive disease. The median duration of response was 5.2 months (2.2 to 10.8 months). Median PFS was 4 months and median OS was 10 months. Most common side effects were increased ALT (3 patients) and fatigue (2 patients). There was no obvious case of cerebral edema related to treatment. Side effects were managed with dose reduction. Conclusions: Reirradiation in combination with re-irradiation in preclinical models of glioma. From December 2014 to June 2016, 20 patients (14 men, 6 women) with recurrent HGG were treated with the combination of reirradiation and PD-1 inhibitors. 18 patients had a glioblastoma, 1 anaplastic oligodendroglioma and 1 anaplastic oligoastrocytoma. The median KPS at the start of this regimen was 70 (50 to 80). The median number of prior treatments for recurrent tumor was 2 (1–4), 100% had prior radiation, 95% prior temozolomide and 55% prior bevacizumab. 8 patients received pembrolizumab (2 mg/kg every 3 weeks) and 12 patients received nivolumab (3 mg/kg or 240 mg flat dose every 2 weeks). Median reirradiation dose was 35 Gy (12 Gy to 35 Gy). RESULTS: There were 7 confirmed partial responses (35% objective response rate, ORR), 5 stable disease and 8 progressive disease. The median duration of response was 5.2 months (2.2 to 10.8 months). Median PFS was 4 months and median OS was 10 months. Most common side effects were increased ALT (3 patients) and fatigue (2 patients). There was no obvious case of cerebral edema related to treatment. Side effects were managed with dose reduction. Conclusions: Reirradiation in combination with re-irradiation. In the treatment-\intention to treat set and in the per protocol set. RESULTS: Between December 2008 and October 2012, a total of 180 patients were randomly assigned to the CIK immunotherapy group (n = 91) or control group (n = 89). In the intention-to-treatment analysis set, median PFS was 8.1 months [95% confidence interval (CI), 5.8 to 8.5 months] in the CIK immunotherapy group, as compared to 4.9 months in the control group (one-sided log-rank, p = 0.0401). Overall survival did not differ significantly between two groups. Grade 3 or higher adverse events, health-related quality of life and performance status between the two groups did not show a significant difference. In the intention-to-treatment set, the addition of CIK cells immunotherapy to standard chemoradiotherapy with TMZ improved PFS. However, the CIK immunotherapy group did not show a beneficial effect on overall survival.

OS09.7 PHASE III RADIATED TREATMENT OR NON-RADIATED CYTOKINE-INDUCED KILLER CELL IMMUNOTHERAPY FOR NEWLY DIAGNOSED GliOBLASTOMA IN KOREA

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INTRODUCTION: Adoptive cell immunotherapy involves an ex vivo expansion of autologous cytokine-induced killer (CIK) cells before their reinfusion into the host. We evaluated the efficacy and safety of CIK cell immunotherapy with radiotherapy-temozolomide (TMZ) for the treatment of newly diagnosed glioblastomas. MATERIALS AND METHODS: In this multi-center, randomized, phase 3 study, we randomized 231 patients with newly diagnosed glioblastoma to receive CIK cell immunotherapy combined with standard TMZ chemoradiotherapy (CIK immunotherapy group) or standard TMZ chemoradiotherapy alone (control group). The efficacy endpoints were analyzed in the intention-to-treat set and in the per protocol set:

RESULTS: Between December 2008 and October 2012, a total of 180 patients were randomly assigned to the CIK immunotherapy (n = 91) or control group (n = 89). In the intention-to-treatment analysis set, median PFS was 8.1 months [95% confidence interval (CI), 5.8 to 8.5 months] in the CIK immunotherapy group, as compared to 4.9 months in the control group (one-sided log-rank, p = 0.0401). Overall survival did not differ significantly between two groups. Grade 3 or higher adverse events, health-related quality of life and performance status between the two groups did not show a significant difference. In the intention-to-treatment set, the addition of CIK cells immunotherapy to standard chemoradiotherapy with TMZ improved PFS. However, the CIK immunotherapy group did not show a beneficial effect on overall survival.