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CELL THERAPY

24MO Randomized, multicenter, open-label trial of autologous cytokine-induced killer cell immunotherapy plus chemotherapy for squamous non-small cell lung cancer

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Background: There is no multicenter clinical study about cytokine-induced killer (CIK) cells in lung cancer. This randomized, multicenter trial was designed to evaluate the efficacy of CIK cell immunotherapy combination with chemotherapy in patients with advanced squamous non-small-cell lung cancer (NSCLC).

Methods: In this phase II trial, 90 patients with untreated, stage IIIB/IV squamous NSCLC were randomized to autologous CIK cell immunotherapy plus gemcitabine and cisplatin (CIK-CT group, n = 45), or gemcitabine and cisplatin (CT group, n = 45). The primary endpoint was progression-free survival (PFS) and secondary endpoint was overall survival (OS) evaluated by Kaplan—Meier analyses and treatment hazard ratios (HRs) with the Cox proportional hazards model.

Results: After a median follow-up of 29.3 months, the median PFS was 8.7 months (95% CI, 7.1 to 10.3) in the CIK-CT group and 4.0 months (95% CI, 3.1 to 5.0) in the CT group (HR, 0.26; 95% CI, 0.16 to 0.43; P < .001). The median OS was 21.0 months (95% CI, 17.8 to 24.2) in the CIK-CT group and 10.3 months (95% CI, 7.9 to 12.1) in the CT group (HR, 0.22; 95% CI, 0.13 to 0.40; P < .001). The objective response rate was 62.2% (95% CI, 47.9% to 76.5%) in the CIK-CT group and 31.1% (95% CI, 17.4% to 44.8%) in the CT group (P < .001). The adverse events of grade 3 or higher were 33.3% and 42.2% in the CIK-CT group and CT group, respectively.

Conclusions: These data suggested that the addition of CIK cell immunotherapy to chemotherapy resulted in significantly longer PFS and OS than chemotherapy alone in patients with previously untreated, advanced squamous NSCLC.

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25P Improving efficacy and reducing toxicity of anti-PD-L1 treatment: T-cells as delivery vehicles for anti-PD-L1 blocking nanobodies

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Background: Cancer therapy has experienced a paradigm shift due to the clinical success of immune checkpoint inhibitors (ICI) such as anti-PD-L1 antibodies, yet ICI benefits remain limited to a minority of patients. On top of the resistance mechanisms limiting their efficacy, ICI are causing auto-immune side effects related to the activation of self-directed CD8 T cells. We propose a new approach using antitumoral T cells as vehicles to deliver anti-PD-L1 nanobodies specifically at the tumor site. Compared to antibodies, nanobodies offer the advantage of a good penetration ability in tissues while displaying a very short half-life in the blood stream. We evaluated whether this approach could improve efficacy and reduce toxicity compared to classical anti-PD-L1 antibody treatment.

Methods: Ovalbumin-specific OT-I T cells were engineered to secrete an anti-PD-L1 blocking nanobody. In MC38 Ova murine colon carcinoma model, adoptive transfer of nanobody-secreting T cells was compared with wildtype T cells alone or wildtype T cells in combination with an anti-PD-L1 antibody given by intraperitoneal injection. Treatment efficacy was assessed by measuring tumor growth over time. Flow cytometry and immuno-histochemistry (IHC) analysis on tumor, lymph nodes and spleen samples were performed to compare the distribution of the anti-PD-L1 treatment across different tissues.

Results: Intratumoral delivery of anti-PD-L1 nanobody improved tumor rejection compared to systemically given anti-PD-L1 antibody. According to flow cytometry and IHC analysis, anti-PD-L1 nanobody was enriched in the tumor compared to spleen and lymph nodes, while anti-PD-L1 antibody was rather enriched in spleen and lymph nodes and weakly detected in the tumor. This low systemic exposure to the nanobody could minimize the risk of developing auto-immune side effects.

Conclusions: Our study points out the poor penetration of anti-PD-L1 antibody in established tumors as a limitation factor for its efficacy in treating MC38 Ova tumors. Local delivery of an anti-PD-L1 nanobody could both overcome this limitation and reduce the risk of side effects as the nanobody is enriched in the tumor compared to the periphery.

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26P Cellulose beads prepared in deep eutectic solvent function as carrier and cytoprotective encapsulation matrix for CAR-T cells in T-cell therapy against glioblastoma cells

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Background: Malignant brain tumors, including glioblastoma, represent some of the most difficult to treat of solid tumors. Chimeric antigen receptor (CAR) T cells are a promising immunotherapeutic modality, which utilizes the tumor targeting specificity of any antibody or receptor ligand to redirect the cytolytic potency of T cells. The unique properties of the central nervous system limit T cell entry and risks of immune-based toxicities in highly sensitive environments. This is especially the case for CAR-T cells due to their lability during transfer, manipulation, and storage. Convection Enhanced Delivery (CED) is a technique used to infuse sensitive therapeutic agents directly into the intracranial area continuously under pressure with an improved turnover. Although CED successfully delivers small therapeutic agents, this technique has failed to effectively deliver cells largely due to cell sedimentation or destruction during delivery.

Methods: To overcome the described limitations, we developed a cellulose-based hydrogel matrix with the aid of deep eutectic solvents. The prepared cellulose beads were studied for improving the stability and efficacy of CAR-T cells when utilizing CED. CAR-T cells submitted to CED were counted and the efficiency of delivery was determined. In addition to delivery, the ability of the encapsulated CAR-T cells to migrate and induce cytotoxicity on U87MG-cells was evaluated, and their safety studied using preclinical animal models.