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Pilotstudy with a trifunctional bispecific antibody in patients with Head and Neck Cancer

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Bispecific antibodies are promising immunological tools for the elimination of tumor cells in minimal residual disease situations. We have applied a newly constructed trifunctional antibody (triomab) which targets EpCAM present on head and neck squamous cell cancer with its one arm, T lymphocytes via CD3 with its second arm and accessory cells via its Fc-region. In a clinical protocol untreated resectable patients with hypopharyngeal cancer UICC IV were treated with three increasing doses (max. 40µg) of triomab i.v.. To date, eleven patients tolerated the application of the antibody fairly well, showing side effects from a mild Cytokine Release Syndrome (CRS) to a mild Systemic Inflammatory Response Syndrome (SIRS) due to the increased cytokine release predominantly of IL6 and TNF alpha. Laboratory data showed strong increase of all liver enzymes due to a cytokine induced cholestasis and moderate signs of hemolysis. Most striking were the kinetics of the white blood cells, which almost completely disappear from the periphery after 1-2 hours after triomab infusion in a dose-dependent manner and start to reappear to pretreatment values within 24-48 hours. The initial pilot study with intravenous application reveals induction of a tumor specific cytotolytic T cell response as well as tumorspecific B cell response after treatment with triomab leading to a significantly prolonged survival in patients with hypopharyngeal cancer stage UICC IV. A relevant limiting effect in the antibody treatment consist of the immunosuppressive effect of the therapies following surgery, e.g. radiotherapy, chemotherapy, which eliminate or drastically reduce the effect of the triomab treatment. Future plans therefore cover a continued application of triomab following standard treatment.

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Induction of an Effective Immune Response against Tumor-Cell-Spheroids Induced by the Trifunctional Antibody BiUIII (anti-EpCAM X anti-CD3)

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Bispecific antibodies are an innovative strategy in cancer therapy. They recognize tumor antigens with one arm and effector cells with the other redirecting immune cells towards tumors. The trifunctional Ab BiUIII has one arm binding to the Epithelial Cell Adhesion Molecule (EpCAM), the other recognizes CD3 on T cells. Because of an unique Fc-region, this Ab format simultaneously binds and activates Fc-receptor + cells. Thereby, the formation of a tri-cell-complex of tumor cell, T cell and Fc-receptor+ cell was postulated. To clear that point, Cell-cell-interactions were studied using immunocytochemically stained cytospins of single cell suspensions consisting of EpCAM+ tumor cells and effector cells (PBMCs). Moreover, tumor cell spheroids (TCS) were treated with PBMC and BiUIII to investigate whether 3-dimensional structures can also be eliminated. Immunohistochemistry was performed using TCS-cryocuts. Viability of tumor cells was tested by FACS-analysis and in replating experiments. PBMC-activation was monitored by testing supernatants in a TNF-alpha bioassay. For the first time, we could show the formation of a tri-cell-complex by immunostaining and provide evidence for phagocytosis as one BiUIII-mediated effect. Using the TCS model we investigated the immune cell infiltration and observed significant changes in the infiltrate following BiUIII-treatment resulting in an effective elimination of TCS. Since micrometastases are supposed to play an important role in tumor development this new Ab format may be a promising approach especially in minimal residual disease