

Background Electrochemotherapy (ECT) exhibits high therapeutic effectiveness in the clinic, achieving up to 80% local tumor control but without a systemic (abscopal) effect. It was proposed that ECT elicits *in situ* vaccination; therefore, we investigated its immunological effects. Moreover, we designed a combination therapy consisting of ECT via intratumoral application of bleomycin, oxaliplatin or cisplatin with peritumoral gene electrotransfer of a plasmid encoding interleukin-12 (p. t. IL-12 GET). Our hypothesis was that p. t. IL-12 GET potentiates the effect of ECT on local and systemic levels and the potentiation varies depending on tumor immune status.

Materials and Methods The combination therapy was tested in three immunologically different tumor models: B16F10 malignant melanoma, 4T1 mammary carcinoma and CT26 colon carcinoma (U34401-1/2015/7, U34401-3/2022/11). Growth of primary treated tumors and of distant untreated tumors, mimicking a systemic disease, was followed. After the therapy, cytological and histological analyses were performed to detect the types of cell death and immunologically important biomarkers as tumor immune infiltrate, the expression of MHC-1, PD-L1 and danger signals.

Results ECT induced immunogenic cell death, changes in the expression of cell markers such as MHC-1 and PD-L1 and other immunologically important danger signals. Moreover, it attracted effector immune cells intratumorally. In poorly immunogenic B16F10 melanoma, IL-12 potentiated the antitumor effect of ECT with biologically equivalent low doses of cisplatin, oxaliplatin or bleomycin. The most pronounced potentiation was observed after ECT using cisplatin, resulting in a complete response rate of 38% and an abscopal effect. Compared to B16F10 melanoma, better responsiveness to ECT was observed in more immunogenic 4T1 mammary carcinoma and CT26 colorectal carcinoma. In both models, p. t. IL-12 GET did not significantly improve the therapeutic outcome of ECT using any of the chemotherapeutic drugs.

Conclusions Electrochemotherapy induces immunologically important changes intratumorally and the effectiveness of the combination therapy depends on tumor immune status. ECT was more effective in more immunogenic tumors, but GET exhibited a greater contribution in less immunogenic tumors. Thus, the selection of the therapy, namely, either ECT alone or combination therapy with p. t. IL-12 GET, should be predominantly based on tumor immune status.

Disclosure Information K. Ursic Valentinuzzi: None. U. Kamensek: None. S. Kos: None. S. Kranjc Brezar: None. M. Cemazar: None. G. Sersa: None.

P08.04 PHOTOTHERAPY WITH CANCER-SPECIFIC NANOPORPHYRIN POTENTIATES IMMUNOTHERAPY IN BLADDER CANCER

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10.1136/jitc-2022-ITOC9.50

Background Immune checkpoint inhibitors (ICIs) in general have shown poor efficacy in bladder cancer (BCa). The purpose of this project is to determine whether photodynamic therapy (PDT) with BCa-specific porphyrin-based PLZ4-nanoparticles (PNP) potentiated ICI.

Materials and Methods SV40 T/Ras double-transgenic mice bearing orthotopic BCa and C57BL/6 mice carrying syngeneic bladder cancer models were used to determine the efficacy and conduct molecular correlative studies.

Results PDT with PNP generated reactive oxygen species, induced protein carbonylation, and dendritic cell maturation. In SV40 T/Ras double-transgenic mice carrying orthotopic bladder cancer, the median survival was 33.7 days in the control, compared to 44.8 (p=0.0123), 52.6 (p=0.0054) and over 75 (p=0.0001) days in the anti-PD-1, PNP PDT and combination groups, respectively. At Day 75 when all mice in other groups died, only one in 7 mice in the combination group died. For the direct anti-tumor activity, compared to the control, the anti-PD-1, PNP PDT and combination groups induced a 40.25% (p=0.0003), 80.72% (p<0.0001) and 93.03% (p<0.0001) reduction, respectively. For the abscopal anti-cancer immunity, the anti-PD-1, PNP PDT and combination groups induced tumor reduction of 45.73% (p=0.0001), 54.92% (p<0.0001) and 75.96% (p<0.0001), respectively. The combination group also diminished spontaneous and induced lung metastasis. Potential of immunotherapy by PNP PDT is multifactorial.

Conclusions In addition to its potential for photodynamic diagnosis and therapy, PNP PDT can synergize immunotherapy in treating locally advanced and metastatic bladder cancer. Clinical trials are warranted to determine the efficacy and toxicity of this combination.

Disclosure Information C. Pan: E. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; LP Therapeutics. Z. Zhu: None. A. Ma: None. H. Zhang: None. T. Lin: None. H. Farrukh: None. Y. Li: None. K. Lam: E. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; LP Therapeutics.

P08.05 LENTIVIRAL PROTEIN VPX DELIVERY SYSTEMS AS POTENTIAL WEAPONS TO IMPROVE CYTARABINE TREATMENT RESPONSE AGAINST ACUTE MYELOID LEUKEMIA

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10.1136/jitc-2022-ITOC9.51

Background The effective treatment of the blood cancer type acute myeloid leukemia (AML) presents several challenges. One of them is resistance to Cytarabine (ara-C), which is the primary chemotherapeutic drug used as front-line treatment against AML. In 2017, it was reported that sterile alpha motif and HD-domain-containing protein 1 (SAMHD1) plays a role in ara-C resistance.¹ SAMHD1 is an enzyme that reduces the level of dNTPs in cells, thereby serving as an attractive target for AML treatment.¹ The lentiviral accessory protein Vpx, found in Simian Immunodeficiency Viruses (SIV) and Human Immunodeficiency Virus-2 (HIV-2), is known to target SAMHD1 for proteasomal degradation.² Hence, we aim to use Vpx to reduce SAMHD1 levels in AML cells to improve ara-C sensitivity.