ELSEVIER

Blood 142 (2023) 2825–2826

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

605.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: LYMPHOID NEOPLASMS

Photoablation with the Aurolase System Reduces T Cell Exhaustion and Synergizes with Immunotherapies in Lymphoma

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Introduction: Immunotherapy is less active in non-Hodgkin lymphoma due to immune evasion from the tumor microenvironment. For diffuse large B cell lymphoma (DLBCL), the overall response rates (ORR) for immune checkpoint inhibitors (ICIs) were low (4-18%). Bispecific antibodies (BiAb), such as FDA-approved Epcoritamab and Glofitamab, had a complete response (CR) rate of 39% for DLBCL. Methods that alter local and systemic immune microenvironments are needed to improve the response to immunotherapy. Unlike radiation, photothermal therapy (PTT) can generate a strong T-cell activation signal. PTT is created by irradiating specially designed gold nanoparticles with near-infrared (NIR) light. The nanoparticles absorb the light and transfer the energy into heat, leading to very localized ablations. The local high heat stimulates a cascade of pro-inflammatory cytokines, including IL-6, IL-1β, TNF-α, G-CSF, GM-CSF, and CCL2. We previously found that PTT with toll-like receptor 9 agonists had a significantly higher CD8 to CD4 ratio, cytotoxic T cell to regulatory T cell ratio, and effector memory T cells in a murine lymphoma model. The AuroLase system, which uses silica gold nanoshells and an FDA-cleared laser, has been undergoing clinical trials for various solid tumors. Here, we explore the systemic immune effects of the PTT device in a lymphoma murine model and evaluate its synergistic effects with ICIs and BiAbs.

Methods: The AuroLase system and AuroShells were provided by Nanospectra. The lymphoma model uses A20 cells implanted in Balb/c mice. Single flank tumors were used for immunophenotyping, and a dual tumor model was used to evaluate the systemic anti-lymphoma effects of PTT and combination therapies. PTT (day 0) was performed by injecting 20ul of nanoshells intratumorally and then irradiating the tumor with the laser at 4W for 30sec-1min. Spleens were collected on days (d) 1, 4, and 8 for immunophenotype by flow cytometry. For systemic immune response, we used a dual tumor model and treated the left side with PTT on d0. Anti-PD1 (aPD1) antibodies and the CD20xCD3 BiAbs were injected intraperitoneally on d1, 3, and 5.

Results: In a single tumor lymphoma model, PTT did not change the size of the spleen or the total T cell count, including CD4, CD8, and regulatory T cell (Treg), compared to tumor naïve or tumor-bearing mice. However, the treatment reduced splenocyte T cell PD1 levels on d1 & 4 post-ablation, down to the level of tumor naive mice, and returned to elevated levels by d8, similar to untreated mice. CD4 and CD8 T cell PD1 levels dropped from 3.49% to 0.78% and 28% to 0.45%, respectively, post-ablation ($p<0.001$). Treg PD1 levels also dropped from 11.5% to 2.4%. There was a reduction of the central memory T cells ($CD44^{hi}$ $CD62^{hi}$) population on d1&4 post-ablation but started to increase by d8. The PD1 expression pattern was similar to the prior, with a reduction on d1&4 and recovery by d8. The effector memory T cells ($CD44^{hi}$ $CD62^{lo}$) had an increased population by d8 with the same PD1 reduction pattern. The B cell population didn't change, but there was an increase in B cell maturation ($CD80^{+}$) on d1&4. As for the myeloid cells, there is a sharp increase in dendritic cell population on d1 and increased maturation/activation on d1&4. There was an increased population of macrophages on d4. There was a reduction of myeloid-derived suppressor cells on d1. In the dual tumor model, the treated tumor had a dramatic loss of tumor volume due to PTT. The untreated tumor did not have a tumor reduction with PTT alone. However, when combined with anti PD1 (aPD1) therapy with just three doses, the untreated side had significant tumor growth reduction. By day 20, the PTT+aPD1 group had a tumor size of 378 mm^3, while the PTT alone and aPD1 alone groups were 1207 and 985 mm^3, respectively. There was also a survival advantage with PTT+aPD1. Similarly, we found that PTT+BiAb significantly delayed tumor growth compared to PTT only. Survival data is still ongoing.

Conclusion: PTT in lymphoma is understudied and can effectively activate an anti-lymphoma response. PTT resulted in a marked reduction in PD1 expression on all T cells and activated several myeloid immune cells. We found that PTT combined with aPD1 therapy or BiAbs had improved tumor suppression in a lymphoma model. This system provides a platform and opportunity to translate PTT into the clinics.

Disclosures Gordon: *Janssen:* Other: data and safety monitoring board ; *nanoparticles:* Patents & Royalties: nanoparticles for cancer therapy (HDL NP As Inducers of Ferroptosis in Cancer, PCT/US2020/051549; *Nanostructures:* Patents & Royalties: Nanostructures for Treating Cancer and Other Conditions, PCT/US2013/027431); *Zylem Biosciences:* Other: co-founder; *Kite Pharmaceuticals:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Bristol Meyers Squibb:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Ono Pharmaceuticals:* Consultancy.

https://doi.org/10.1182/blood-2023-185400