Abstract: P1223

Title: POLATUZUMAB VEDOTIN-INDUCED INNATE IMMUNE CELL INFILTRATION CONTRIBUTES TO ITS ANTITUMOR EFFECT IN A HUMAN DLBCL XENOGRAFT MODEL

Abstract Type: Poster Presentation

Topic: Lymphoma biology & translational research

Background:

Polatuzumab vedotin (Pola) is an antibody–drug conjugate (ADC) comprising an anti-CD79b antibody conjugated with monomethyl auristatin E (MMAE). It is approved in many countries for diffuse large B-cell lymphoma (DLBCL) in first-line and relapsed/refractory (r/r) settings. Upon binding to CD79b expressed on B cells, Pola is internalized leading to the release of MMAE within B cells, where it exerts potent anti-tumor activity by inhibiting cell proliferation and inducing apoptosis. In addition, some vedotin-based ADCs have the potential to alter the tumor microenvironment through MMAE-mediated immunogenic cell death,1, 2 and a recent study has shown that the lymphoma microenvironment, including innate and acquired immune cells, may influence patient survival.3 However, few studies have focused on the interaction between the anti-tumor effect of Pola and the tumor immune microenvironment in DLBCL.

Aims:

We investigated the relationship between Pola treatment and immune status using xenograft mouse models, focusing on innate immune cells such as natural killer cells (NK) and macrophages (MΦ) in the tumor microenvironment.

Methods:

C.B-17/Icr-scid/scidJcl (scid) and NOD/Shi-scid,IL-2RγKO (NOG) mice were subcutaneously inoculated with human DLBCL DB cells. Human IgG or Pola (2–5 mg/kg) was administered intravenously on day 1. For immunohistochemistry, sections of tumor paraffin blocks (harvested on day 4) were stained with NCR1 and CD68 antibodies to detect NK and MΦ, and apoptotic cells were assessed by TUNEL assay. Depletion of NK and MΦ was achieved by administration of clodronate liposomes and anti-asialo GM1. Tumor cells with *in vivo*-specific low Pola sensitivity (#5-1 cells) were established from DB tumors by long-term administration of Pola in a scid mouse. #5-1 tumors in scid and NOG mice were analyzed using the same methods as DB tumors.

Results:

In the scid mouse model, regression of DB tumors was observed in the 2 mg/kg Pola treatment group (6 out of 6 mice) on day 22, and levels of MΦ and NK infiltration were significantly higher than in the ctrl IgG group on day 4. No significant anti-tumor effect of Pola was observed under MΦ and NK-depleted conditions, although it was observed under non-depleted conditions by TUNEL assay on day 4. This indicates that Pola-induced infiltrating immune cells could contribute to the anti-tumor effect on DB tumors. To further investigate the influence of the tumor microenvironment on Pola efficacy, we compared DB tumors with #5-1 tumors. In the #5-1 tumors of scid mice, the intratumoral infiltration of MΦ and NK after 2 mg/kg Pola treatment was significantly lower than in the DB tumors on day 4, and regression of #5-1 tumors was not observed in the 2 mg/kg Pola treatment group on day 22. Furthermore, the difference between DB and #5-1 in tumor regression by Pola treatment (2, 3 and 5 mg/kg) was diminished in the NOG mouse model, which lacks mature NK cells and has reduced MΦ function, suggesting that the difference in Pola effect between DB and #5-1 tumors could be caused by Pola-induced immune cell infiltration.

Summary/Conclusion:

In the DB xenograft model, Pola increased the infiltration of MΦ and NK cells into the tumor tissues, and these

immune cells contributed to its anti-tumor effect. This suggests that the interplay between Pola and immune cells plays a crucial role in the anti-tumor effect of Pola.

1. Heiser RA, et al., *Mol Cancer Ther.* 2024;23:68-83.
2. Gray E, et al., *J Immunother Cancer.* 2023; 11:e007572.
3. Kotlov N, et al., *Cancer Discov.* 2021;11:1468–89.

Keywords: Tumor immunology, Mouse model, DLBCL, Innate Immunity