TRILICLICL (G1T28), A CDK4/6 INHIBITOR, PRESERVES T LYMPHOCYTE FUNCTION FROM DAMAGE BY CYTOTOXIC CHEMOTHERAPY

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ABSTRACT #439

BACKGROUND

While chemotherapy-induced tumor cell death can be immunogenic (e.g. through the release of neoantigens), many chemotherapeutic agents negatively impact the immune system leading to reduced anti-tumor efficacy. Recently, we have identified a critical consequence of chemotherapy that occurs via the direct killing of lymphocytes, as well as through hematopoietic stromal cell (HSC) damage and advanced myeloid-biased differentiation (Sclenotic marrow exhaustion). Persistent lymphopenia is associated with worse clinical outcomes following chemotherapy, and may result in long-term clinical complications and impaired anti-tumor immunity. Efforts to maintain the anti-tumor efficacy of immune checkpoint inhibitors have led to the clinical development of combinations with chemotherapy.

METHODS

CLINICAL LYMHCYTE COUNTS

As a clinical biomarker of immune system function, we evaluated the baseline lymphocyte counts from patients with small cell lung cancer (SCLC) who received one of the following regimens: carboplatin-etoposide (n=234) or carboplatin-etoposide+trilaciclib (n=52). Lymphocyte counts were performed by transplanting 1:1 of CD45.1+ recipient bone marrow (BM) cells into lethally irradiated (25 rads) secondary recipient mice. Peripheral blood (PB) and BM lymphoid/myeloid cell ratios were determined 13 months after the fourth dose of chemotherapy. Patients were enrolled into the two trilaciclib SCLC trials. Peripheral blood lymphocytes were analyzed by flow cytometry using antibodies against CD3, CD4, CD8, CD19, CD20, and CD45.1. The frequencies of donor CD45.1+ cells in each blood lineage were measured by analyzing the PB of secondary recipients 4- to 6-week post-transplantation. T LYMPHOCYTE STIMULATION ASSAY

C57Bl/6 mice were treated with 3 daily intraperitoneal (IP) doses of 50 mg/kg 5FU was collected from recipient mice 4 weeks after transplantation. 32 weeks after initial transplantation, peripheral blood (PB) was collected from an ongoing 1st line SCLC clinical trial treated) SCLC patients. Serial lymphocyte counts from two ongoing SCLC clinical trials testing the combination of trilaciclib with the following chemotherapy regimens (1st line, carboplatin-etoposide, NCT02499770; and 2nd line, topotecan, NCT02514447). In addition, serial lymphocyte counts were evaluated from patients enrolled into the two trilaciclib SCLC trials.

RESULTS

FIGURE 2. TRILACILIB PRESERVES HSC FUNCTION FROM PROLIFERATIVE EXHAUSTION

Eight-week-old female B6.SJL-Ptprca/BoyAiTac (CD45.1) mice were treated with vehicle or 150 mg/kg 5FU. BM cells from mice that were not transplanted. Data represent mean ± SEM. Statistical significance was assessed using two tailed Student’s t-test (P < 0.05).

CONCLUSIONS

1. Chemotherapy-associated bone marrow toxicity results from HSC damage and premature exhaustion. 5. In the clinic, trilaciclib maintains lymphocyte counts in patients receiving multiple cycles of 1st or 2nd line chemotherapy: i.e. “exhaustion”, myeloid-biased differentiation, and consequent lymphopenia.

2. Trilaciclib administered prior to chemotherapy preserves HSC function, thereby ameliorating the long-term toxicity associated with serial exposure to chemotherapy agents: i.e. “exhaustion”, myeloid-biased differentiation, and consequent lymphopenia.

3. In the clinic, trilaciclib maintains lymphocyte counts in patients receiving multiple cycles of 1st or 2nd line chemotherapy: i.e. “exhaustion”, myeloid-biased differentiation, and consequent lymphopenia.

4. Chemotherapy-induced lymphopenia is a well-known phenomenon following exposure to chemotherapy. While chemotherapy-induced tumor cell death can be immunogenic (e.g. through the release of neoantigens), many chemotherapeutic agents negatively impact the immune system leading to reduced anti-tumor efficacy. Recently, we have identified a critical consequence of chemotherapy that occurs via the direct killing of lymphocytes, as well as through hematopoietic stromal cell (HSC) damage and advanced myeloid-biased differentiation (Sclenotic marrow exhaustion). Persistent lymphopenia is associated with worse clinical outcomes following chemotherapy, and may result in long-term clinical complications and impaired anti-tumor immunity. Efforts to maintain the anti-tumor efficacy of immune checkpoint inhibitors have led to the clinical development of combinations with chemotherapy.

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