Check(point) or Checkmate for AML?

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Title: Check(point) or Checkmate for AML?

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In this edition of *Haematologica*, Stroopinsky and colleagues report on the application of a personalized vaccine derived from fusing leukemia cells to autologous dendritic cells (FV, fusion vaccine) as a potential tool to overcome checkpoint blockade in AML (1). Acute Myeloid Leukemia (AML) is an aggressive hematologic malignancy with poor long-term outcomes despite recent treatment advances. The only potential curative therapeutic option for intermediate to high-risk acute myeloid leukemia is allogeneic stem cell transplantation through the induction of graft-versus tumor effect demonstrating the importance of cell-based immunotherapy (2).

Antibodies which block the programmed cell death protein 1 (PD-1) or programmed death-ligand-1 (PD-L1) inhibitory pathway have led to improvements in progression-free survival and overall survival in several solid tumors and Hodgkin’s Lymphoma leading to multiple clinical trials in other hematologic malignancies including AML (3). Daver and colleagues reported the overexpression of clinically targetable checkpoint inhibitor receptors PD-1 and OX40 in the bone marrow of patients with AML making checkpoint inhibition an interesting therapeutic option to further study. However to date, checkpoint inhibitor therapy for AML has yielded disappointing results (4,5).

In an immunocompetent murine AML model using the TIB-49 murine AML cell line genetically altered to express luciferase and mCherry, Stroopinsky and colleagues confirmed that treatment with single agent anti-PD1, anti-TIM3 or anti-repulsive guidance molecule b (RGMb) antibodies had little therapeutic efficacy compared to isotope controls. To overcome this resistance to checkpoint inhibition, these investigators tested a combinatorial approach whereby a FV was given in combination with checkpoint inhibitors. Personalized vaccines derived from patient-derived AML cells fused with autologous dendritic cells have been previously tested in 17 patients who achieved complete remission after chemotherapy (6). Rosenblatt and colleagues observed that vaccination induced an increase in circulating T-cells recognizing leukemia specific antigens that persisted for more than 6 months with 12 of 17 patients remaining alive without recurrence at a median follow-up of 57 months. This study demonstrated that personalized vaccination of AML patients could induce expansion of leukemia-specific T-cells which may have the potential to protect against leukemia relapse.

In the current study, Stroopinsky and colleagues hypothesized that the combination of a personalized fusion vaccine and checkpoint inhibitor therapy could elicit a unique synergistic response whereby vaccination induced leukemia specific T-cell populations while checkpoint inhibition enhanced the function and persistence of these anti-leukemic T-cells (1). Using an immunocompetent murine AML model, cohorts of mice were vaccinated 24 hours after being inoculated with murine leukemia cells followed by treatment with immune checkpoint inhibition every 3 days for 6 total doses. Rapid AML progression occurred by day 29 in all the control mice requiring euthanasia. Mice treated with checkpoint inhibition alone showed only a modest improvement in survival compared to the control cohort but all required euthanasia by day 44. Two of 5 mice
treated with the personalized vaccine alone remained leukemia free at day 90 of leukemia inoculation. Remarkably all the mice treated with vaccination and checkpoint blockade remained alive and leukemia free at day 90 after leukemia inoculation. Stroopinsky and colleagues showed that mice treated with the personalized vaccine alone showed variable expansion of tumor reactive T-cells, but mice treated with the combination of personalized fusion vaccine and checkpoint blockade demonstrated robust expansion of circulating tumor specific CD8+ T-cells. The enhanced expansion of tumor specific T-cells following vaccination and checkpoint blockade was confirmed in the splenocytes of mice euthanized 17 days after leukemia inoculation showing that combination vaccine with checkpoint inhibition resulted in induction of tumor specific immunity with prevention of leukemia engraftment. The investigators further found that combination treatment with FV and checkpoint inhibition induced a T cell memory response and increased clonal diversity along with a statistically significant decrease in CD4+/CD25+ FOXP3+ Tregs compared to single agent treatment with FV or checkpoint inhibition alone. The group also demonstrated that the combinatorial approach provided long-term protection from leukemia relapse even after rechallenge via retro-orbital inoculation of a lethal leukemia dose at day 90 after treatment.

Important questions remain such as whether these impressive pre-clinical results can be replicated in a broader range of murine leukemias. It is also unclear whether this combinatorial approach which utilizes a FV created with a “snapshot” of the leukemia at diagnosis can elicit effective and long-term immune responses against the genetically complex and clonally heterogeneous leukemic populations that characterize AML in humans. Relapses of AML are often due to emergence of treatment resistant clones that may be undetectable at diagnosis and may not be sufficiently immunogenic in this model. Nonetheless this study provides a strong scientific foundation for a clinical trial of combination therapy using personalized fusion vaccines and checkpoint inhibition. Results are eagerly awaited to determine if this novel approach can finally check(point) or even checkmate AML.

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