KRAS-MUTANT TUMORS

Known but poorly characterized consequence of CAR T-cell therapy to date in which 16 adult patients with relapsed or chemotherapy-refractory B-cell acute lymphoblastic leukemia (B-ALL) were treated with autologous T cells engineered to target the B-cell-specific antigen CD19. Consistent with previous results, CAR T-cell therapy was highly effective, producing complete responses in 88% of patients and molecular complete remissions in 75% of patients. However, a known but poorly characterized consequence of CAR T-cell therapy is a substantial increase in inflammatory cytokines with subsequent fever, hypotension, hypoxia, and neurologic changes, a severe but reversible phenomenon called cytokine release syndrome (CRS). The authors found that blockade of the interleukin-6 (IL-6) receptor with the monoclonal antibody tocilizumab ameliorated severe CRS symptoms without affecting expansion of CAR T cells, whereas steroid therapy reversed CRS symptoms but ablated CAR T cells. The authors also retrospectively analyzed patient serum samples and observed that only patients with high serum levels of C-reactive protein (CRP) showed signs of severe CRS, suggesting that CRP levels may be a surrogate for cytokine elevation that can potentially be used to predict which patients are at high risk for CRS. Of note, all patients in CAR T-cell–induced complete remission who were eligible for and received an allogeneic hematopoietic stem cell transplant have not relapsed, providing evidence that CAR T-cell therapy can be an effective bridge to curative therapy. In addition to providing strong support for further evaluation of CD19-targeted CAR T cells in B-ALL in a multicenter phase II study, these findings provide a framework for the management of patients treated with adoptive T-cell therapy.


C-REACTIVE PROTEIN MAY INDICATE RISK OF CAR T CELL-INDUCED TOXICITY

The adoptive transfer of tumor-specific, chimeric antigen receptor (CAR) T cells has emerged as a potentially effective therapy for hematologic malignancies. Davila and colleagues report complete findings from the largest phase I trial of CAR T-cell therapy to date in which 16 adult patients with relapsed or chemotherapy-refractory B-cell acute lymphoblastic leukemia (B-ALL) were treated with autologous T cells engineered to target the B-cell-specific antigen CD19. Consistent with previous results, CAR T-cell therapy was highly effective, producing complete responses in 88% of patients and molecular complete remissions in 75% of patients. However, a known but poorly characterized consequence of CAR T-cell therapy is a substantial increase in inflammatory cytokines with subsequent fever, hypotension, hypoxia, and neurologic changes, a severe but reversible phenomenon called cytokine release syndrome (CRS). The authors found that blockade of the interleukin-6 (IL-6) receptor with the monoclonal antibody tocilizumab ameliorated severe CRS symptoms without affecting expansion of CAR T cells, whereas steroid therapy reversed CRS symptoms but ablated CAR T cells. The authors also retrospectively analyzed patient serum samples and observed that only patients with high serum levels of C-reactive protein (CRP) showed signs of severe CRS, suggesting that CRP levels may be a surrogate for cytokine elevation that can potentially be used to predict which patients are at high risk for CRS. Of note, all patients in CAR T-cell–induced complete remission who were eligible for and received an allogeneic hematopoietic stem cell transplant have not relapsed, providing evidence that CAR T-cell therapy can be an effective bridge to curative therapy. In addition to providing strong support for further evaluation of CD19-targeted CAR T cells in B-ALL in a multicenter phase II study, these findings provide a framework for the management of patients treated with adoptive T-cell therapy.


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ImmunoTherapy

Major Finding: High CRP levels may predict which recipients of CART cells are at risk of cytokine release syndrome. Clinical Relevance: IL-6 blockade reduced cytokine release syndrome symptoms while retaining CART-cell expansion. Impact: These findings suggest guidelines for management of patients treated with CART-cell therapy.

C-Reactive Protein May Indicate Risk of CAR T Cell-Induced Toxicity

The adoptive transfer of tumor-specific, chimeric antigen receptor (CAR) T cells has emerged as a potentially effective therapy for hematologic malignancies. Davila and colleagues report complete findings from the largest phase I trial of CAR T-cell therapy to date in which 16 adult patients with relapsed or chemotherapy-refractory B-cell acute lymphoblastic leukemia (B-ALL) were treated with autologous T cells engineered to target the B-cell-specific antigen CD19. Consistent with previous results, CAR T-cell therapy was highly effective, producing complete responses in 88% of patients and molecular complete remissions in 75% of patients. However, a known but poorly characterized consequence of CAR T-cell therapy is a substantial increase in inflammatory cytokines with subsequent fever, hypotension, hypoxia, and neurologic changes, a severe but reversible phenomenon called cytokine release syndrome (CRS). The authors found that blockade of the interleukin-6 (IL-6) receptor with the monoclonal antibody tocilizumab ameliorated severe CRS symptoms without affecting expansion of CAR T cells, whereas steroid therapy reversed CRS symptoms but ablated CAR T cells. The authors also retrospectively analyzed patient serum samples and observed that only patients with high serum levels of C-reactive protein (CRP) showed signs of severe CRS, suggesting that CRP levels may be a surrogate for cytokine elevation that can potentially be used to predict which patients are at high risk for CRS. Of note, all patients in CAR T-cell–induced complete remission who were eligible for and received an allogeneic hematopoietic stem cell transplant have not relapsed, providing evidence that CAR T-cell therapy can be an effective bridge to curative therapy. In addition to providing strong support for further evaluation of CD19-targeted CAR T cells in B-ALL in a multicenter phase II study, these findings provide a framework for the management of patients treated with adoptive T-cell therapy.


Signaling

Major finding: Activation of the DNA damage response by wild-type RAS contributes to mutant KRAS-driven oncogenesis. Concept: Wild-type HRAS activates the DNA damage checkpoint by antagonizing MAPK/AKT-mediated CHK1 inhibition. Impact: Inhibition of HRAS or CHK1 may sensitize KRAS-mutant tumors to genotoxic chemotherapy.

HRAS AND NRAS REGULATE THE DNA DAMAGE RESPONSE IN KRAS-MUTANT TUMORS

Mutation of the RAS genes (HRAS, NRAS, and KRAS) occurs frequently in cancer and leads to activation of multiple signaling pathways that promote tumorigenesis. Oncogenic mutations in KRAS are sufficient to drive tumor formation in vivo, but recent work suggests that the remaining wild-type HRAS and NRAS proteins may contribute to tumor growth, prompting Grabocka and colleagues to investigate the underlying mechanisms. Depletion of wild-type HRAS or NRAS specifically inhibited proliferation of KRAS-mutant cells in association with delayed mitotic progression and mitotic defects suggestive of damaged DNA. Indeed, silencing of HRAS led to increased DNA damage and abrogation of the G2/M cell-cycle checkpoint, which is required to provide cells adequate time to repair damaged DNA prior to entering mitosis. Recent evidence suggests that KRAS effector pathways may bypass antiproliferative responses by inactivating the DNA damage kinase CHK1, leading the authors to hypothesize that wild-type HRAS may reinforce DNA damage checkpoint control by antagonizing mutant KRAS-driven signaling. Indeed, HRAS depletion enhanced AKT and MAPK activation and increased inhibitory phosphorylation of CHK1. Moreover, knockdown of wild-type HRAS or inhibition of CHK1 with AZD7762 sensitized KRAS-mutant cells to DNA-damaging agents. To address whether HRAS-mediated modulation of the DNA damage response facilitates mutant KRAS-driven carcinogenesis in vivo, HRAS was knocked down in established KRAS-mutant xenografts. Although HRAS depletion increased mitotic abnormalities, loss of wild-type HRAS alone did not alter KRAS-mutant tumor growth. However, HRAS depletion in the presence of the chemotherapeutic agent irinotecan led to significant, sustained tumor regression in association with ERK and AKT hyperactivation and inhibitory CHK1 phosphorylation. This work highlights a role for wild-type RAS-mediated regulation of the DNA damage response in KRAS-mutant driven tumorigenesis and points to the RAS–CHK1 axis as a potential vulnerability of KRAS-mutant cancers.

C-Reactive Protein May Indicate Risk of CAR T cell-Induced Toxicity

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