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Managing Cytokine Release Syndrome Associated With Novel T Cell-Engaging Therapies

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Abstract

Chimeric antigen receptor (CAR)-modified T cells and bispecific T cell–engaging antibodies have demonstrated dramatic clinical responses in recent clinical trials. The hallmark of these novel highly active immunotherapies is nonphysiologic T cell activation, which has correlated not only with greatly increased efficacy but also with notable toxicity in some cases. We and others have observed a cytokine release syndrome (CRS), which correlates with both toxicity and efficacy in patients receiving T cell–engaging therapies. In addition to elevations in effector cytokines, such as interferon-γ, cytokines associated with hemophagocytic lymphohistiocytosis or macrophage activation syndrome, such as interleukin (IL)-10 and IL-6, may also be markedly elevated. Whereas corticosteroids may control some of these toxicities, their potential to block T cell activation and abrogate clinical benefit is a concern. Detailed studies of T cell proliferation and the resultant immune activation produced by these novel therapies have led to more targeted approaches that have the potential to provide superior toxicity control without compromising efficacy. One approach we have developed targets IL-6, a prominent cytokine in CRS, using the IL-6R antagonist tocilizumab. We will review the pathophysiology and management options for CRS associated with T cell–engaging therapies.

Keywords

Acute lymphoblastic leukemia; chimeric antigen receptor; blinatumomab; cytokine release syndrome

T cell–engaging therapies have shown remarkable promise for highly refractory B-cell malignancies; however, this type of immunotherapy presents unique challenges in toxicity management. By linking target antigen-expressing malignant cells to cytotoxic T cells, T

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cell–engaging therapies harness the cell-mediated immune response and direct it against cancerous cells, bypassing the major histocompatibility complex. T cells engineered to express a chimeric antigen receptor (CAR) with CD19 specificity and blinatumomab, a bispecific antibody linking $CD3^+$ T cells with $CD19^+$ cells, are 2 such therapies that have shown dramatic responses in early-phase clinical trials for relapsed/refractory B-cell leukemias and lymphomas.[1–5] These trials have demonstrated high complete response (CR) rates; however, CRs have been associated with cytokine release syndrome (CRS), which ranges from mild to life threatening.

Our group has shown that some patients develop clinical and laboratory findings similar to patients with macrophage activation syndrome/hemophagocytic lymphohistiocytosis (MAS/HLH) and that cytokine-directed therapy can abrogate life-threatening CRS symptoms without compromising efficacy.[2,6] This review will focus on the clinical manifestations and management of CRS associated with novel T cell–engaging therapies.

CART-19/CTL019 CLINICAL ACTIVITY

Chimeric antigen receptor–modified T cells (CART) use adoptive transfer of T lymphocytes engineered to express a single-chain fragment variable region (scFv) domain linked to the signaling domain of the T cell receptor (TCR),[7] plus various costimulatory domains such as CD28 and CD137 (4-1BB).[1,8–12] For CART-19, the scFv is directed against CD19, an attractive target for most B-cell malignancies, owing to its near-universal expression on malignant cells and specificity for the B-cell lineage. CD19 is expressed throughout B-cell development from the early pro-B stage through mature B cells.[13] Whereas the expression of chimeric antibodies in T cells was first described by Eshhar et al[14] more than 20 years ago, poor expansion and persistence of the engineered T cells limited clinical efficacy for many years. However, we and others have shown that CART therapy has promising activity in both chronic lymphocytic leukemia (CLL) and acute lymphoblastic leukemia (ALL). Porter et al were the first to report that CART-19 was effective in adults with refractory CLL. In 3 patients with high disease burdens, CART-19 therapy produced sustained CRs in 2 patients and a partial response in the third.[1] Our group also reported striking efficacy in relapsed pediatric B-ALL.[2] As recently reported at the ASH meeting (December 2013), we have treated 22 pediatric patients with relapsed/refractory ALL with CART-19 with a CR rate of 86% (19/22) at day 28. Sustained remissions of 2 to 20 months have been achieved in 12 of 17 evaluable patients with a median follow-up of 3.6 months. More than 70% of these patients had relapsed after allogeneic stem cell transplant, and none experience graft versus host disease despite a median donor T cell chimerism of 100%.[15] Other groups also have reported striking efficacy of CAR-modified T cells in relapsed/refractory CLL and ALL.[8,10,16]

BLINATUMOMAB CLINICAL ACTIVITY

Blinatumomab, a member of a new class of bispecific antibodies, links CD19-expressing target cells with T effector cells.[17] Resultant cytotoxic T cell engagement leads to target cell lysis. Owing to its short half-life, blinatumomab is given by continuous intravenous infusion in 4-week cycles. In the first clinical trial of blinatumomab, efficacy was demonstrated in

adults with refractory lymphomas, with a 35% objective response rate.[3] In a phase 2 study of adults with minimal residual disease–positive ALL, 16 of 21 patients became negative for minimal residual disease.[4] Of the 11 patients who did not subsequently receive allogeneic hematopoietic stem cell transplant, 6 patients remain in remission with a median follow-up of almost 3 years.[18] Early data from a phase 2 dose escalation trial in adults with refractory/relapsed ALL suggest a 75% CR rate in patients with significant disease burden at the start of treatment.[4] Finally, early data from a phase 1 dose-escalation trial of blinatumomab in children with relapsed/refractory B-ALL (NCT01471782) demonstrate a 47% CR rate,[19] and a phase 2 trial for relapsed/refractory pediatric ALL opened in October 2013.

CYTOKINE RELEASE SYNDROME AND HLH AFTER T CELL–ENGAGING THERAPIES

The most common toxicity associated with the novel immunotherapies CART-19 and blinatumomab is CRS, a constellation of inflammatory symptoms resulting from cytokine elevations associated with T cell engagement and proliferation. In most patients, CRS symptoms are mild and flulike, with fevers and myalgias. However, some patients experience a severe inflammatory syndrome, including vascular leak, hypotension, pulmonary edema, and coagulopathy, resulting in multiorgan system failure; and recently, a CRS-related death after blinatumomab was reported.[19] Cytokine elevations are measurable in most patients, but the degree of elevation may not correlate with severity of CRS or response to therapy. Moreover, some patients experience symptoms without marked cytokine elevation, whereas others demonstrate laboratory findings out of proportion to clinical symptoms.[20]

The management of CRS can be challenging. Fulminant CRS may be life threatening; however, some degree of cytokine release is likely a necessary consequence of T cell activation and therefore efficacy. Corticosteroids are an obvious choice to blunt CRS owing to their known efficacy in disorders that involve activated T cells, such as graft versus host disease and inflammatory processes.[21] Indeed, corticosteroids have been incorporated into the routine supportive care for blinatumomab therapy. However, the potential negative impact on therapeutic T cell proliferation remains a concern for cellular therapies. In the original report of CART-19 efficacy, Porter et al[1] observed a partial response in a patient who received corticosteroids early after CART-19 infusion. Yet, our group and Brentjens et al[2,10] have since used short-term steroids to treat life-threatening CRS in some cases without compromising CART proliferation or efficacy. In vitro, steroids reduce cytokine levels without affecting the T cell activation produced by bispecific T cell engagers.[22] However, the potential to blunt efficacy with corticosteroid use remains a concern, which needs to be balanced with their well-documented benefit in disorders of excess inflammation.

Another strategy to manage CRS is to target elevated cytokines directly. The most significantly elevated cytokines in the CRS associated with CART-19[1] and blinatumomab[20] are IL-10, IL-6, and IFN-γ. IL-10, primarily produced by monocytes/macrophages, regulates both innate and cell-mediated immunity by inhibiting activated macrophages.[23] IL-10 can also be produced by mast cells, B cells, regulatory T cells, and helper T cells (T_H2), but not commonly by cytotoxic T lymphocytes. As a negative regulator, IL-10 may not be an ideal

cytokine to target in CRS. Conversely, IL-6 is an inflammatory cytokine involved in a large number of processes, both within the immune system, such as neutrophil trafficking, acute phase response, angiogenesis, B cell differentiation, and autoantibody production, and outside it, such as bone and lipid metabolism.[24] IL-6 is produced by monocytes/macrophages, dendritic cells, T cells, fibroblasts, keratinocytes, endothelial cells, adipocytes, myocytes, mesangial cells, and osteoblasts. Interferon-γ, also an inflammatory cytokine, is involved in macrophage activation, T_H1 differentiation, major histocompatibility complex class 1 induction, and B-cell isotype switching; and it is produced by cytotoxic T cells, helper T cells (T_H1), and natural killer cells.[25] As an effector cytokine released by activated cytotoxic T cells after engagement, IFN-γ elevations are both anticipated and likely required for efficacy, making it a potentially undesirable target for toxicity management. Whereas it is not known if IL-6 plays a role in T cell proliferation through a feedback loop, it is thought to be primarily involved in the inflammatory process.

In patients with severe CRS associated with T cell–engaging therapies, IL-6 levels peak during maximal T cell proliferation. We theorized that targeting IL-6 might reduce CRS toxicity without compromising clinical efficacy of T cell–engaging therapies. In our experience, IL-6 blockade by tocilizumab has resulted in rapid, dramatic reversal of life-threatening CRS in patients treated with CART-19 or blinatumomab.[2,6] Tocilizumab, a recombinant humanized monoclonal antibody against the IL-6 receptor, blocks IL-6 from binding to its receptor, both in membrane-bound and soluble states.[26,27] With a primary indication for juvenile idiopathic arthritis (JIA), tocilizumab is approved by the Food and Drug Administration for children as young as 2 years. It is also approved for adults with rheumatoid arthritis and for Castleman disease in Japan. Tocilizumab has been extensively studied in adults, with 8 randomized controlled trials treating more than 2000 patients,[26,27] and in children in phase 1 to phase 3 trials for JIA.[28–30] Tocilizumab was safely combined with other immunosuppressant medications in most of these trials, with the most common adverse events being liver enzyme elevations and cytopenias. Although grade 3 or greater transaminase elevations (>5× the upper limit of normal) are rare (italic>1%), some degree of liver enzyme elevation occurred in 34% to 41% of patients in the tocilizumab arm compared to 17% in the placebo arm; however, many of these studies combined tocilizumab with hepatotoxic agents, including methotrexate. Cytopenias, including neutropenia and thrombocytopenia, were reported with repeat dosing; however, less than 1% of patients developed severe neutropenia (bold>500/μL) or thrombo-cytopenia (<50,000/μL). Whereas tocilizumab is typically dosed every 2 to 4 weeks, extended treatment is not necessary in the management of CRS, which is self-limited.

In a subset of patients with severe CRS, we have observed a symptom pattern similar to that seen in HLH or MAS. In these patients, high fevers have been accompanied by hepatosplenomegaly, liver dysfunction, coagulopathy, hypofibrinogenemia, and profound hyperferritinemia. Furthermore, the cytokine profile observed in patients treated with CART-19 or blinatumomab mirrors that seen in HLH.[31–34] In addition to elevations in IL-10, IL-6, and IFN-γ, elevated IL-2R, MCP-1, and MIP1B are reported in patients treated with CART-19 and blinatumomab, with normal levels of IL-1B, IL-4, IL-5, IL-7, IL-12, IL-13, IL-17, tumor necrosis factor (TNF)-α, and granulocyte macrophage colony-stimulating factor (GM-CSF).[6,20,35] Whereas engagement of cytotoxic T cells would be

expected to produce high levels of IFN-γ, elevations of IL-6 and IL-10 are better explained by HLH/MAS. Individual cytokine levels can vary markedly between patients; however, the similarity of the patterns observed in patients receiving CART-19 or blinatumomab and the patients with HLH is quite striking. HLH is a rare disorder of immune regulation leading to pathologic immune activation and excessive inflammation. It is characterized by prolonged fever, splenomegaly, cytopenias, hyperferritinemia, hypertriglyceridemia, coagulopathy, decreased natural killer cell function, and elevated cytokines.[36] Primary HLH is an inherited disorder caused by defective cytolytic granule exocytosis. In patients with homozygous mutations in one of several genes, leading to loss of function of proteins involved in cytolytic granule exocytosis, HLH can present in infancy with minimal or no trigger. MAS is a form of secondary HLH triggered by immune-activating processes, such as infection, malignancy, or autoimmune diseases. Although MAS was initially thought not to be inherited, new data suggest that many patients with secondary HLH have heterozygous mutations in the same genes that are mutated in primary HLH, leading to mild dysfunctions in the same immune regulatory processes.[36–39] In these patients, HLH presents in childhood or adulthood after a significant immune-activating trigger. As seen later in the text, T cell–engaging therapies can provide such a significant trigger.

T cell–engaging therapies, like CART-19 and blinatumomab, cause transient but profound T cell proliferation and cytokine release, which could trigger a cascade of immune activation sufficient to cause HLH/MAS, both in predisposed patients and patients with no known mutations in HLH-causing genes. The parallels in both clinical and laboratory findings between CRS and HLH/MAS suggest similar pathophysiology. In fact, CRS associated with T cell therapies may represent a spectrum of symptoms, with a subset of patients developing significant, if temporary, HLH/MAS. Disease burden, degree of T cell proliferation, or genetic predisposition may increase the risk of developing HLH/MAS in some patients. Further studies may find merit in screening for HLH-predisposing mutations in high-risk genes, such as *PRF1*, *MUNC13-4*, *STXBP2*, and *STX11* to predict patients at higher risk of developing HLH/MAS. Moreover, we propose prospective monitoring for HLH/MAS in patients treated with CART therapies and bispecific T cell–engaging antibodies and have incorporated this monitoring in our practice. HLH/MAS can develop whether T cells are activated through the native TCR, as is the case with blinatumomab, or a CAR that bypasses the TCR; therefore, this monitoring may be warranted in other cellular therapies as well.

Although tocilizumab has rapidly reversed life-threatening manifestations of CRS caused by CART-19 or blinatumomab, it should be noted that there is some concern that tocilizumab should be avoided if MAS is suspected. This concern stems from a case report suggesting that tocilizumab may temporarily mask or control clinical symptoms of MAS in patients with JIA, thereby delaying definitive therapy.[40] In MAS caused by an auto-immune disease, symptoms may flare when IL-6 blockade is lifted if definitive therapy is not initiated; however, this is less of a concern with the transient MAS associated with T cell therapies.

Other cytokine-directed approaches to managing CRS could be considered. Inhibitors of MCP-1 and MIP1B are in development, but not in clinical use, whereas inhibitors of IL-2R, IL-1R, and TNF-α have been used clinically. Tumor necrosis factor α is elevated in inflammatory syndromes but does not seem to be elevated after T cell therapy. Tumor

necrosis factor α can be targeted by etanercept, which has demonstrated efficacy in rheumatologic disorders[41] but showed no obvious clinical benefit in severe CRS after CART-19 therapy in a single pediatric patient with ALL.[2] Soluble IL-2 receptor (CD25) is elevated after blinatumomab or CART-19 treatment in some patients and is markedly elevated in patients with HLH. Daclizumab, a monoclonal antibody against CD25, has potential efficacy in HLH;[42,43] however, it is no longer commercially available, and targeting CD25, which is present on activated T cells, may compromise efficacy of the cell therapy. Elevated IL-1β is prominent in JIA, and anakinra, a recombinant form of the IL1 receptor antagonist (IL1Ra), has been used for HLH/MAS associated with JIA.[44] Whereas marked elevations in IL-1β have not been observed in our few patient observations to date after blinatumomab or CART-19 therapy, a subset of patients do have modest increases in IL-1α, raising the possibility that anakinra could have a role in managing CRS after T cell–engaging therapies.

In summary, there are a number of potential treatment options for CRS associated with T cell–engaging therapies; however, many of these carry the theoretical risk of inhibiting T cell activity and could impair treatment efficacy. Our data suggest that tocilizumab is effective at reversing CRS without inhibiting the efficacy of CART19 or blinatumomab.

CONCLUSION

As we enter the era of highly active T cell–engaging therapies, as exemplified by the bispecific T cell–engaging antibody blinatumomab and CAR-modified T cell therapies such as CART-19/CTL019, it has become apparent that the high degrees of T cell activation that result in dramatic clinical responses are accompanied by significant toxicities. Cytokine release syndrome is a potentially life-threatening complication of the nonphysiologic T cell activation that is a hallmark of T cell–engaging therapies. We have now demonstrated that nonphysiologic T cell activation can produce abnormal macrophage activation, mimicking HLH, a syndrome that may contribute significantly to these toxicities. The challenge in toxicity management is controlling symptoms without compromising efficacy. In the case of CAR-modified T cell therapies, significant clinical responses may require a high degree of in vivo proliferation, and it is the ability to achieve this proliferation that has resulted in both powerful efficacy results and increased toxicity. Targeted therapies may control CRS while maintaining efficacy. Our data suggest that IL-6 blockade by tocilizumab is effective at reversing CRS and controlling HLH/MAS without inhibiting the efficacy of CART-19 or blinatumomab. As T cell–engaging therapies show great promise, further studies are needed to determine optimal toxicity management.

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