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Cytokine Release Syndrome (CRS) Reporting and Mechanism in Immuno-Oncology Clinical Trials

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Abstract

Allogeneic hematopoietic cell transplantation using HLA haploidentical donors and post-transplantation The benefits of cyclophosphamide (PT/Cy-haplo), including its inexpensive cost, high likelihood of finding a compatible donor, and quick availability of donors, make it a widely utilised drug. In patients receiving PT/Cy-haplo, particularly when peripheral blood is used, cytokine release syndrome (CRS), caused by bidirectional alloreaction between host and donor, frequently occurs. The immunosuppressive humanised monoclonal antibody CAMPATH 1-H, which recognises CD52 on lymphocytes and monocytes, is clinically linked to a first-dose cytokine-release syndrome involving TNFa, IFNg, and IL-6. Since cytokine release is isotype dependent, in vitro models have been used to identify the cellular source and mechanism responsible for it. Rat IgG2b and human IgG1 isotypes induce the highest levels of cytokine release, which is inhibited by an antibody to CD16, the low affinity Fcreceptor for IgG (FcgR).

Keywords: HLA haploidentical; Immunosuppressive; Immunotherapies; Natural killer (NK) cell; Hyperinflammatory

Introduction

Lymphocyte and monocyte counts drop sharply within the first hour of its infusion, and a lengthy period of lymphopenia lasts for more than two years. Due to its capacity to debulk circulating tumour cells and avoid renal allograft rejection, CAMPATH 1-H has been widely employed in the serotherapy of leukaemias and lymphomas. Cancer immunotherapies are soon becoming the norm of care for many malignancies, and the pipeline of immuno-oncology (IO) drugs is still expanding. Importantly, as we gain more clinical experience with these immunotherapeutic drugs, we are becoming more aware of a number of toxicities specific to immunotherapies that are uncommonly seen with conventional cytotoxic drugs [1]. With the effectiveness of more recent immunotherapies such T cell engagers and chimeric antigen receptor (CAR) T cells in treating a number of hematologic malignancies, cytokine release syndrome (CRS) is being increasingly recognised as a separate clinical entity. One of the most frequent toxicities of these treatments is cytokine release syndrome, which can occur with different immunotherapeutic drugs and manifest itself differently in terms of frequency, severity, and presentation [2].

Infusion reactions and CRS have more clinical experience: Since the discovery of lymphokine-activated killer cells, interest in the production and immunobiology of natural killer (NK) cell immunotherapies for cancer has significantly increased. Although both the lymphocyte compartment's T-cell and NK cell subsets have cytotoxic subsets that destroy transformed and virally infected cells via cytotoxic (perforin/granzyme) or apoptotic (FAS ligand, TRAIL) pathways, there are a number of functional distinctions that affect how antigenic they are. NK cells, which are innate immune system CD3+/CD56+ lymphocytes, release cytokines and kill target cells without the need for prior sensitization [3]. They don't require MHC-mediated antigen presentation or the rearrangement of antigen-specific surface receptors. CRS is an immune system-driven supraphysiologic reaction. As a side effect of T cell-mediated therapy or in reaction to other treatments like COVID-19 mRNA vaccines, it has frequently been seen in sepsis and other infections, including those associated to COVID-19. T cell activation triggers CRS, which is then mediated by cytokines made by macrophages and other myeloid cells. An immunotherapeutic can be infused many hours to days later, although CRS normally doesn't manifest until 14 days have passed since treatment began [4].

CD-19 relevant factors: One of the most common and potentially lethal haematological malignancies is acute lymphoblastic leukaemia (ALL). Significant advancements have been achieved in the treatment of ALL in recent years, and the majority of patients achieve complete remission (CR) following induction chemotherapy; nonetheless, the outlook for patients who relapse or are resistant to chemotherapy is still dismal. Studies have shown that individuals treated with CAR-T cells that target CD19 had remarkable results, but the problems that followed, such as cytokine release syndrome (CRS), neurotoxicity, hematologic toxicity, and coagulation abnormalities, could be fatal. The cytokine release syndrome (CRS), which is characterised by high levels of acute phase reactants and inflammatory cytokines, particularly interleukin-6, is present in patients with severe coronavirus disease 2019 (COVID-19). Treatment for CRS brought on by chimeric antigen receptor T-cell therapy involves the interleukin-6 receptor inhibitor tocilizumab [5].

Mechanism of Syndromal cytokine release: The systemic inflammatory condition known as CRS can develop in a lot of people up to two weeks after receiving immunotherapies that target malignant B cells. Chimeric antigen receptor (CAR) T cells and bispecific T-cell-engaging antibodies against CD19 were originally used to characterise this, and more recently, anti-CD22 CAR T cells. Since then, there has been a significant attempt to harmonise criteria of CRS and its severity, which initially varied between investigations.33 These definitions frequently share characteristics with those of HLH, MAS, and SIRS/sepsis [6]. (Figure 1)

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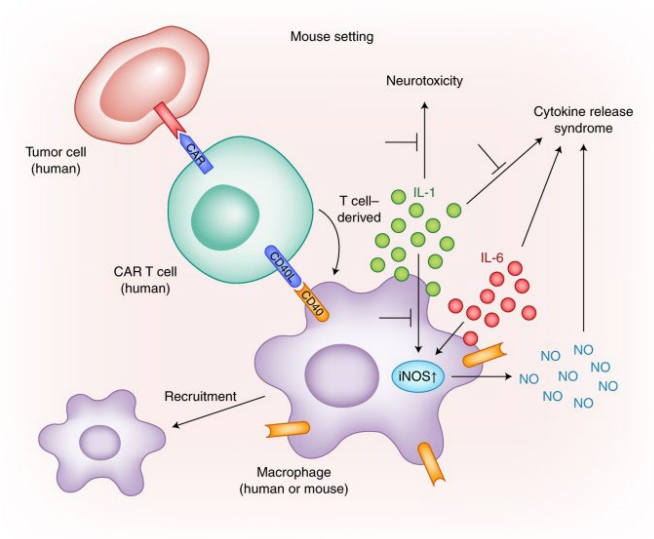

Figure 1: There is significant mechanistic commonality in the genetic abnormalities frequently linked to CSSs. LPI is for lysinuric protein intolerance; HPS stands for Hermansky-Pudlak syndrome; and XMEN stands for X-linked immunodeficiency with magnesium deficit, EBV infection, and neoplasia.

Material and Methods

Blood sampling and cytokine tests

Blood was drawn from CRS patients serially after CTL019 infusion and within a day of the infusion. For batch analysis, the blood was prepared as previously described, aliquoted, and frozen at 80°C. For the primary analysis, the first blood sample that was available was obtained three days after PICU admission. Blood was taken as soon as possible for sepsis patients following PICU admission, but no later than 48 hours after sepsis diagnosis. The specifics of the sample analysis have already been released. Forty-six cytokines were analysed including ANG2, CD163, EGF, Eotaxin, FGF-Basic, GCSF, GM-CSF, HGF, ICAM1, IFNγ, IFNα, IL10, IL12, IL13, IL15, IL17, IL1β, IL1RA, IL2, IL4, IL5, IL6, IL7, IL8, IP10 (CXCL10), MCP1, MIG (CXCL9), MIP1α, MIP1β, RANTES, sCD30, sEGFR, sgp130, sIL_1RI, sIL1RII, sIL2Ra, sIL4R, sIL6R, sRAGE, sTNFRI, sTNFRII, sVEGFR1, sVEGFR2, sVEGFR3, TNFα, and VEGF [7].

Study objectives

The trial's main goal was to determine whether TPE was effective in reducing CRP and cytokine load (IL-6, IL-8, IL-10, TNF, IFN, and GM-CSF) by monitoring these levels daily and right after TPE for a total of 14 days. Patients who experienced therapeutic benefit, improvement in oxygenation, and independence from mechanical ventilation or additional oxygen were considered secondary objectives [8].

Result

This molecule, which is constitutively expressed at high levels by NK cells (41), has been shown to be important in promoting effector-target interactions by these cellsAdditionally, it has been shown that some CD11a antibodies can work in concert with CD16 to inhibit NK cells' acute production of TNFa. This suggests that the participation of LFA-1 is subsequent to CD16 ligation because there was little indication of cytokine release in the absence of CD16 ligation. As a result, even while it is likely that CAMPATH 1-H is what builds the initial connection between CD52 on the targets coated with antibodies and CD16 on NK cells, other molecules, like CD11a on NK cells and its ligand ICAM, may later contribute to this contact [9].

Conclusion

A wide range of hyperinflammatory conditions with diverse genetic, viral, rheumatologic, oncologic, and pharmacological causes are included in CSSs. They all have an extremely active immune system, which, if it is not identified and treated promptly, frequently results in death. It is still difficult to diagnose using different criteria and biomarkers, but early treatment that addresses both the viral insult when present and the heightened immune response is essential for saving lives all over the world. The COVID-19 pandemic has shed new light on the issue and numerous new choices for diagnosis and treatment that, if used carefully, may calm the storm and rescue the patient, despite the fact that grappling with life-threatening immunopathology is a very old problem [10].

Acknowledgement

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