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Pancytopenia Post Allogeneic Hematopoietic Stem Cell Transplant

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Abstract

Panytopenia following allogeneic hematopoietic stem cell transplant (allo-HSCT) can vary in presentation based on the timing after the procedure. The duration and pattern of cytopenia often help clinicians to identify underlying causes and tailor management. Early post-transplant (day 0–30) pancytopenia is usually related to conditioning regimen toxicity, marrow aplasia, or acute infection. It is usually reversible. Pancytopenia in the engraftment phase (day 30–100) is usually due to delayed or failed engraftment, infections, GvHD, or drug toxicity. Etiology of late post-transplant (>100 days) pancytopenia are chronic GvHD, infections (e.g., CMV, EBV), Graft failure or rejection, relapse of disease or secondary marrow aplasia.

Keywords: Pancytopenia; Graft Failure; Poor Graft Function; Allo-HSCT

Abbreviations: Allo-HSCT: Allogeneic Hematopoietic Stem Cell Transplant; TA-TMA: Transplant-Associated Thrombotic Microangiopathy; GvHD: Graft Versus Host Disease; SOS: Sinusoidal Obstruction Syndrome; HCT: Hematopoietic Cell Transplantation, PRCA: Pure Red Cell Aplasia; HLH: Hemophagocytic Lymphohistiocytosis; RIC: Reduced-Intensity Conditioning; EBV: Epstein-Barr Virus

Introduction

Successful engraftment is first indicated by the emergence of monocytes and neutrophils in the blood, typically following 1–3 weeks of profound pancytopenia, and is subsequently marked by a rise in platelet count. The marrow cellularity gradually returns towards normal. The marrow reserve remains impaired for 1–2 years and in some cases is impaired permanently [1].

Causes of pancytopenia post stem cell transplant

Cytopenia following allogeneic hematopoietic stem cell transplantation (allo-HSCT) can involve single lineage or multiple lineages. Cytopenia can be temporary or long-lasting depending upon the cause. It contributes to increased chances of both morbidity and mortality. Older age of the recipient, low CD34 stem cell dose, transplant from an unrelated donor and viral infections, particularly CMV infection are all risk factors for cytopenias after SCT [2]. Cytopenia post allo-HSCT can result from a variety of causes, often overlapping. Understanding the common etiologies is crucial for appropriate management [2].

Post-SCT cytopenias are often secondary to:

Drug toxicity

High-dose chemotherapy or radiation used in conditioning regimen before transplant can cause marrow aplasia, leading to transient or prolonged cytopenia. Ganciclovir and Valganciclovir (prodrug of ganciclovir) are particularly prone to cause neutropenia. Ganciclovir-related neutropenia stems from its dose-dependent inhibition of DNA-polymerase, an enzyme essential for viral replication, in hematopoietic progenitor cells. It occurs in up to 40% of allograft recipients and may increase the risk of invasive bacterial and fungal (aspergillosis) infections (3).

Viral infections especially CMV and Epstein-Barr virus (EBV) infection [3].

Graft Verus Host Disease (GvHD)

Up to 50% of patients undergoing HSCT may develop GvHD. Donor T lymphocytes become activated and proliferate by

antigen-presenting cells in the transplanted patient resulting in an alloreactive T-cell response to recipient tissues mediated by cytotoxic T cells and inflammatory cytokines. Commonly affected organs are the skin, liver, gastrointestinal tract, and bone marrow [4].

Relapse

Cytopenia can result from marrow infiltration due to recurrence of the original hematologic malignancy. When pancytopenia emerges one year or more following allo-HSCT, relapse of the underlying disease becomes the leading diagnostic consideration [5].

Hepatic Sinusoidal Obstruction Syndrome (SOS)

Hepatic SOS is a systemic endothelial disease typically presents in the days or weeks after HSCT with refractory thrombocytopenia, hepatomegaly, ascites, and jaundice. It can rapidly progress to multiorgan dysfunction and high mortality rate. Maintaining a high degree of clinical suspicion for hepatic SOS, along with prompt and effective management, is essential for minimizing morbidity and mortality [6].

Transplant-Associated Thrombotic Microangiopathy (TA-TMA)

TA-TMA is observed in 7-39% of allo-HSCT recipients. It is clinically characterized by the TA-TMA triad: thrombocytopenia, microangiopathic hemolytic anemia, and organ damage (primarily involving the kidneys or central nervous system). ADAMTS13 activity is usually normal or only mildly decreased in TA-TMA and, therefore, cannot be used as a diagnostic marker of the disease. The two-hit hypothesis is true for TA-TMA. The second hit exacerbates endothelial injury. Frequently identified secondary triggers (second hits) include chemotherapy conditioning protocols, recipient age, donor-related factors, use of calcineurin or mTOR pathway inhibitors, presence of GvHD, and infectious complications. Data suggest involvement of increased complement activation and possible genetic predisposition in the pathophysiology of TA-TMA in both adult and pediatric patients [7].

Poor Graft Function

It is defined as cytopenias beyond 28 days in at least two cell lines in patients with complete donor chimerism in the absence of other explanations such as relapse or severe GvHD. Contributing factors to poor graft function include immune-related complications, impaired marrow microenvironments, defects in graft-derived progenitor cells, and the characteristics of the underlying disease. Chimerism testing can differentiate between graft failure and poor graft function. Loss of donor cell engraftment—whether partial or complete—defines graft failure and manifests as mixed or complete host chimerism, while, in cases of poor graft function, complete donor cells is observed post-transplant in the host (full donor chimerism post-transplant) but these donor cells exhibit ineffective function [2].

Graft failure or rejection

Graft failure refers to the lack of successful hematopoietic cell engraftment following autologous or allogeneic HSCT. The frequency of graft failure is increased by the presence of HLA mismatch, low stem cell dose, T cell depletion and reduced intensity conditioning regimens. Graft rejection represents a major contributor to graft failure. Post–allo-HSCT graft failure is categorized into two types: primary and secondary. Primary graft failure is characterized by the absence of detectable engraftment of donor cells. There is failure to achieve an absolute neutrophil count (ANC) $>0.5 \times 10^9$ /l within 28 days of stem cell infusion.

Platelet engraftment is often indicated by recovery of a platelet count of at least 20×10^9 /l in the absence of platelet transfusion for 7 consecutive days. Red cell engraftment has been defined as hemoglobin level ≥8 g/dl without transfusion support [2]. Secondary graft failure is characterized by the loss of donor-derived hematopoietic cells following initial successful engraftment. The required criteria are ANC $\geq 0.5 \times 10^9$ /l on three successive days with subsequent decline to $<0.5 \times 10^9$ /l for three or more consecutive days, and a platelet count that declines to $<20 \times 10^9$ /l, after achieving the threshold. Secondary graft failure can result from several factors, including graft rejection related to residual host immune cells, progressive disease, low donor stem cell count, side effects of medications, infections or GvHD [2].

ABO Incompatibility Induced Pure Red Cell Aplasia (PRCA)

PRCA occurs only after major ABO incompatible HSCT. The reduced-intensity conditioning (RIC) regimens allows the persistence of recipient B cells and plasma cells for much long period allowing recipient cells to produce antibodies for a long period until immunoglobulin (IgG and IgM) levels of recipient antibodies fall to 1:1. The plasma cells keep producing antibodies against donor RBC precursors and colony forming unit-erythroid (CFU-E) as these contain ABH antigens. The earlier burst forming unit-erythroid (BFU-E) are not affected as they do not contain ABH antigens [2]. Severe pancytopenia may be observed in some patients. ABO antigens are expressed on or adsorbed from plasma on granulocytes and platelets, and these may be affected by isohemagglutinins. Neutropenia and thrombocytopenia resolve after resolution of red cell aplasia in the majority of patients [8].

Hemophagocytosis

Post transplant hemophagocytic lymphohistiocytosis (HLH) is a form of secondary HLH that can be either early-onset (<30 days post-transplant) or late-onset (≥30 days post-transplant). It is a rare entity of post allo-HSCT. It is seen commonly posttransplant in both benign and malignant conditions. The pathogenesis of post-transplant HLH involves hypercytokinemia precipitated by host tissue damage, interaction between host antigen presenting cells and donor lymphocytes or viral infections. The Imashuku

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criteria for post-transplant HLH comprise (1) fever, (2) raised ferritin level, (3) elevated LDH, (4) cytopenias and (5) presence of hemophagocytosis in the bone marrow.

Post transplant HLH is commoner in allo-HSCT compared to autologous HSCT as well as in those receiving RIC. The use of G-CSF causes increased content of T cells and monocytes in the graft leading to higher predisposition to HLH. The CD34 stem cell dose greater than 9 x10^6 cells/kg also correlates with higher incidence of post-transplant HLH occurrence. It should be suspected in all patients with pancytopenia associated with an unexplained, culture-negative febrile illness and ongoing coagulopathy. A remarkably high ferritin level most accurately reflects a possibility of post-transplant HLH. Soluble IL-2 receptor (SIL2R) is another promising biomarker as it indicates T-cell activation [9].

Post-Transplant Lymphoproliferative Disorders (PTLD)

PTLD is a serious complication that can occur after allo-HSCT. According to the International Consensus Classification of Mature Lymphoid Neoplasms, the term PTLD encompasses 4 groups of lymphoproliferative disorders: nondestructive PTLDs, polymorphic PTLDs (pPTLDs), monomorphic PTLDs (mPTLDs), and classic Hodgkin lymphoma PTLDs (HL-PTLDs). Most PTLDs arise from B cells. Latent EBV infection is present in 52% to 80% of cases. The incidence of PTLD after HSCT is 1% but it is more common in transplant cases that use profound T-cell depletion, which increases the risk of EBV reactivation, in which it can occur in >10% [10].

Autoimmune Cytopenia After Stem Cell Transplantation

Autoimmune phenomena post-transplant can lead to destruction of blood cell lineages (autoimmune cytopenia, AIC). It is a rare complication. Nonmalignant disease, alemtuzumab use, and CMV reactivation are risk factors. The cytokine pattern observed in patients with AIC is indicative of a predominant T-helper 2 (Th2) pathway activation. Rituximab, bortezomib, and sirolimus are promising step-up therapies [11].

Cytopenia of unknown cause after allo-HSCT may have a worse outcome possibly due to a higher risk of acute GvHD and infections [12].

Other causes include sepsis and thrombotic thrombocytopenic purpura

Management of pancytopenia following stem cell transplantation is tailored to the underlying etiology and may include discontinuation of myelotoxic drugs, treatment of infections, administration of CD34+ stem cell boosters in cases of poor graft function, or consideration of a second stem cell transplant in the event of graft failure [2].

Conclusion

Cytopenias persisting beyond 6 months to 1 year may indicate severe complications like GvHD or marrow failure. Persistent cytopenia after 3–6 months should prompt investigations for GvHD, infections, marrow infiltration, or rejection.

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