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Hematopoietic Stem Cell Transplantation In SCID and CID

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INTRODUCTION

- Inborn errors of immunity potentially life-threatening disorders caused by genetic defects that result in immune deficiency and/or immune dysregulation

- Various treatments are available depending upon the specific genetic defect and the parts of the immune system affected

INTRODUCTION

- Allogeneic hematopoietic cell transplantation is the treatment of choice for most cases of severe combined immunodeficiency (SCID)

- HCT is also a treatment option for several other forms of IEI including:
  - many combined immunodeficiencies
  - syndromic immunodeficiencies
  - immune dysregulatory disorders
  - phagocytic cell defects
  - some defects of innate immunity
  - a few autoinflammatory disorders

SCID

- The predominant clinical consequence of SCID is an increased frequency and severity of infection, often opportunistic in nature, resulting in death in the first year of two of life
- However, allogeneic hematopoietic cell transplantation (HCT) remains the primary curative treatment of choice for typical SCID

Atypical SCID

- There is increasing recognition of atypical forms of SCID that are either due to hypomorphic mutations or due to mutations in genes that inherently produce a less profound immunologic defect
- Atypical SCID includes both leaky SCID, characterized by diminished,but not absent, T cell number and function, as well as Omenn syndrome
- they also require allogeneic HCT to prevent sequelae from opportunistic infections

Donor choice

- HLA typing to evaluate potential donors should be performed on all available members of the patient's nuclear family as soon as a diagnosis of SCID is established
- An HLA-identical sibling is the preferred donor, if available
- Alternatives include a matched unrelated donor (URD), a haploidentical parent or other mismatched related donor(MMRD), or a UCB donor

PRETRANSPLANT CONSIDERATIONS

- The selection of an optimal donor for HCT for a patient with SCID is of critical importance since the other pretransplant decisions regarding stem cell source, conditioning, and GVHD prophylaxis strategies are all dependent upon the type of donor and the genotype of the patient
- Human leukocyte antigen (HLA) matched related donors are preferred for HCT in patients with SCID
- However, excellent survival is possible with any donor type if the HCT occurs in the first 3.5 months of life or before the onset of infection

Conditioning chemotherapy

- SCID is the only immunodeficiency in which the complete absence of T cell immunity sometimes allows HCT to be performed without chemotherapy in selected cases
- A consequence of *absence of host T cells* in SCID is that there is little or no resistance to incoming grafts for many SCID genotypes

Conditioning chemotherapy

- Myeloablative chemotherapy is typically unnecessary for T cell engraftment in patients with SCID with B cells such as is seen with defects IL-2RG, Janus kinase 3 (JAK3), or interleukin 7 receptor
- On the other hand, patients with SCID lacking B cells (T-B-SCID), such as is seen in patients with defects in (RAG) 1/2, have higher rates of T cell engraftment and long-term survival after some degree of myeloablation
- Patients with leaky SCID and Omenn syndrome also generally require some degree of myeloablative chemotherapy to achieve multilineage engraftment

RECONSTITUTION OF IMMUNE FUNCTION

- Thymic T cell output is restored following HCT for SCID and peaks in one to two years
- Recovery of B cell function is less consistent after HCT and does not occur in a substantial fraction of patients, especially if space-making chemotherapy conditioning is not administered

Mixed T cell chimerism

- Mixed chimerism is often defined as having donor-derived cells that account for less than 95percent of peripheral blood samples
- Following allogeneic HCT, especially if patients receive NMA conditioning or RIC, recipient marrow can recover alongside donor marrow engraftment

- T cells are 90 to 100 percent donor derived in almost all cases of successful HCT for SCID
- One exception is patients with natural killer cell-positive (NK+)SCID, who are more likely to have mixed T cell chimerism and poorer long-term recovery of CD4+ Tcell immunity
- This is probably because many patients with mutations in RAG1/2 are somewhat "leaky," allowing production of a small amount of dysfunctional host T cells if complete myeloablation is not achieved

COMPLICATIONS BEFORE AND AFTER HCT

- Infections
- Toxicity from cytoreductive chemotherapy
- Graft rejection
- Graft-versus-host disease (GVHD)
- Posttransplant lymphoproliferative disease

- The incidence of these adverse events varies with the type of HCT, conditioning regimen, and underlying disease

- Survival rates for patients with SCID who undergo HCT have continued to improve due to:
  - early identification through newborn screening (NBS) or by genetic testing for a known defect when there is a family history
  - the availability of an increasing pool of matched unrelated donors
  - advances in the methods of preparing hosts and donor stem cells
  - improved supportive and adjuvant therapies

SCID Survival Rates

- In the modern era, survival rates for patients with SCID are as high as 90 percent following HCT, with noninfected patients having survival of 95 percent

- Though certain SCID genotypes may continue to have worse outcomes

Non-SCID combined immunodeficiencies

- The indications for HCT for non-SCID combined immunodeficiency primarily depend upon the severity of the specific disorder
- Combined immunodeficiencies for which HCT is often used include:
  - CD40 ligand (CD40L) deficiency,
  - dedicator of cytokinesis 8 (DOCK8) deficiency
  - zeta chain-associated protein kinase of 70 kD(ZAP-70) deficiency
  - major histocompatibility complex class II (MHC-II) deficiency

CD40L deficiency

- However, data from more recent transplants reveal higher quality-of-life scores and better survival in those who underwent HCT
- younger age at allogeneic HCT is associated with better outcomes
- Liver disease is a common complication observed in patients with CD40L deficiency and is a predictor of poor outcome when present at the time of allogenic HCT
- Successful sequential/combined liver transplantation and HCT has been reported

DOCK8 deficiency

- Dedicator of cytokinesis 8 (DOCK8) deficiency is a typically moderateto-severe IEI, and less than half of patients survive into their 20s
- Allogeneic HCT is often indicated
- Preexisting infections or other complications such as malignancy or central nervous system complications can impact care

ZAP-70 deficiency

- Deficiency of ZAP-70 causes a combined immunodeficiency (CID)
- Affected children present within the first two years of life with a history of recurrent infections, similar to infants with SCID
- However, diagnosis can be delayed because most patients with ZAP-70 deficiency have detectable lymphoid tissues and a normal lymphocyte count
- Patients with ZAP-70 deficiency require hematopoietic cell transplantation (HCT) to cure their CID
- Bone marrow from a HLA matched sibling is the optimal choice, with excellent survival
- However, most patients lack this option. In such situations, other histocompatible donors can be used

MHC (HLA) class II deficiency

- MHC II deficiency generally results in a clinical picture of SCID since MHCII plays a pivotal role in the maturation and function of both T and B cells
- Common disorders include pneumonitis, bronchitis, gastroenteritis, and septicemia
- Infections usually start in the first year of life and are associated with failure to thrive and diarrhea
- HCT can be curative, although the success rate is lower than for other combined immunodeficiency diseases
- The chances for success are higher if the transplant is performed in the first two years of life

Conditioning chemotherapy

- SCID is the only immunodeficiency in which the complete absence of T cell immunity sometimes allows HCT to be performed without chemotherapy in selected cases
- In all other conditions, there is sufficient host immunity to resist engraftment of allogeneic cells
- Thus, some type of pretransplant conditioning is always required to allow engraftment of donor-derived stem cells in non-SCID combined immunodeficiencies
- The patient's underlying genetic defect, health status, available donor HLA match, and other factors influence the type of conditioning chemotherapy used

Conditioning chemotherapy

- Conditioning regimens were historically classified as:
  - myeloablative (MAC)
  - nonmyeloablative(NMA)
  - reduced intensity (RIC)
- MAC regimens irreversibly ablate recipient hematopoietic stem cells (HSCs), and exogenous HSCs must be given in order to achieve count recovery
- NMA regimens do not result in irreversible marrow destruction, and autologous marrow recovery can occur
- RIC regimens fall somewhere in between MAC and NMA regimens and can also allow some autologous marrow recovery following transplant,which may result in mixed chimerism

Conditioning chemotherapy

- MAC regimens have the benefit of increased success of engraftment but are associated with higher toxicities compared with RIC regimens, which have fewer toxicities but can be associated with decreased stable engraftment

Conditioning serotherapy

- Conditioning regimens often also contain serotherapies such as alemtuzumab or antithymocyte globulin
- These agents deplete recipient T cells and help prevent graft rejection
- These agents also deplete donor graft T cells, which can help prevent graft-versus-host disease (GVHD)

Donor choice

- As with all allogeneic HCT, an HLA-matched related donor (MRD), such as an unaffected brother or sister, is considered the optimal choice for non-SCID HCT
- However,fewer than 20 percent of patients in the US have such a donor
- Alternatives include a matched unrelated donor (MUD/MURD), a mismatched unrelated donor (MMUD), a mismatched related donor (MMRD), or an umbilical cord blood (UCB) donor

COMPLICATIONS OF HCT

- Complications during and following HCT include:
  - infections
  - toxicities from cytoreductive chemotherapy
  - graft failure
  - graft-versus-host disease (GVHD)
  - transplant-associated thrombotic microangiopathy
  - and posttransplant lymphoproliferative disease
- Late effects such as endocrinopathies and fertility problems also occur
- The incidence of these adverse events varies with the type of HCT, conditioning regimen, and underlying disease

LONG-TERM PROGNOSIS

- The largest European collective report regarding allogeneic HCT outcomes for patients with a non-SCID IEI included 783 patients treated at 37 European centers
- The four-year probability of survival forall non-SCID patients who were transplanted between the years 2000 and 2005 was 69 percent
- A report from the Center for International Blood and Marrow Transplant Research included 1902 patients with non-SCID IEI
- Three-year overall survival in the 816 non-SCID patients transplanted between 2010 and 2016 was 75 percent