

TRANSPLANT- RELATED COMPLICATIONS IN THALASSEMIA

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ABSTRACT

Hematopoietic stem cell transplantation (HSCT) is the only effective therapeutic modality for patients affected by major hemoglobinopathies such as thalassemia major and sickle cell anemia. Although improvements in transplant technology a substantial group of patients continue to have post transplant complications which increase morbidity and mortality. Optimizing outcomes through prevention or early detection of post transplant complications and mitigation of disability are important issues. In this presentation transplant-related complications commonly seen in patients with thalassemia will be discussed.

Introduction

More than 60.000 children with thalassemia major are born annually worldwide. Although lifelong red blood cell transfusion and chelation have significantly improved survival of patients with thalassemia (1,2), this remains a progressive disease with disease and treatment related complications progressing over time. In fact, thalassemic patients with increasing age currently experience poor outcome even in the developed world (3,4). The situation in the developing world where most of these patients reside is even worse where the life expectancy of almost all patients is less than 20 years.

Hematopoietic stem cell transplantation (HSCT) is the only cure currently available for patients with thalassemia (5-7). The presence or absence of three factors such as hepatomegaly more than 2 cm below costal margin, portal fibrosis and an irregular chelation history could predict transplant outcome (6,7). On the basis of these risk factors patients are categorized into 3 classes of risk : class 1 (good risk), class 2 (intermediate risk) and class 3 (poor risk) patients. With current treatment protocols class 1, class 2, and class 3 younger patients (age <17 years) have the probability of thalassemia-free survival of 87%, 85% and 82% respectively.

Transplant-related complications continue to be a common cause of morbidity and mortality following stem cell transplantation. HSCT recipients experience certain infections at different times post transplant, reflecting the host defence impairments. Immune system recovery takes place in three phases. The pre-engraftment phase (0-30 days after transplant) is characterized by prolonged neutropenia and damage to mucocutaneous barriers; the early post transplantation phase or engraftment phase (30-100 days post-transplant) is characterized by impairment of cellular immunity; and the late post-transplant phase (>100 days post-transplant) is characterized by immune recovery. During the pre-engraftment phase oral, gastrointestinal, and skin flora are sources of infection. In this phase prevalent pathogens include **Candida species**, **Aspergillus species**, herpes simplex reactivation and bacterial infections. Phase II is dominated by impaired cell-mediated immunity and following engraftment **CMV** reactivation is most frequent infection. **Pneumocystis carini** and **Aspergillus species** are also dominant pathogens in this phase. During phase III most patients have cell-mediated and humoral immunity defects along with impaired reticuloendothelial system function. In this phase patients are at risk for infections which include **CMV**, **varicella zoster virus**, **EBV**-related posttransplant lymphoproliferative disease,

community-acquired respiratory virus and infections with encapsulated bacteria (**Ha. Influenzae**, **Stre. Pneumoniae**).

POSTTRANSPLANT COMPLICATIONS

Pulmonary complications.

Pulmonary complications are among the most frequent transplant-related complications occurring in 25%-50% of allogeneic stem cell transplant recipients, and can account for approximately 50% of transplant related deaths. Pulmonary non-infectious complications include pulmonary edema, pleural effusion, air leak syndrome, radiation pneumonitis and fibrosis, transfusion-related acute lung injury, medication-related lung injury, post-transplant lymphoproliferative disorders, idiopathic pneumonia syndrome and related disorders, pulmonary vascular complications and chronic GVHD-related lung complications.

Pulmonary edema is often occurs due to aggressive hydration, although infection, irradiation and chemotherapy induced cardiac and renal dysfunction also play a role. Pleural effusion may occur from aggressive hydration, hepatic VOD, pulmonary infection, medication and surgical interventions. Air leak syndrome (pneumothorax, pneumomediastinum, and subcutaneous emphysema) can occur in patients with chronic GVHD from obliterative bronchiolitis, or restrictive lung disease due to idiopathic pneumonia syndrome (8,9). Pneumothorax may also result from surgical procedures and lung biopsy, or central line placement. Radiation or chemotherapy-related pneumonitis usually develops 2-3 months after therapy.

Transfusion-related acute lung injury (TRALI) is an acute event which is characterized by bilateral infiltrates and a PaO₂/FiO₂ ratio <300 mm Hg, without evidence of left atrial hypertension, that develop within 6 hr of receiving blood transfusion (10). The characteristic pulmonary edema is mediated by increased vascular permeability, probably due to antibody-antigen interactions between donor and patient. Supportive care, diuretics and steroids could be effective.

Idiopathic pneumonia syndrome (IPS) is defined as the clinical syndrome of diffuse lung injury after HSCT in the absence of an identifiable infectious cause (11). Both interstitial pneumonia and diffuse alveolar damage are seen in patients with this syndrome. Possible factors contributing to IPS include effects of pre-transplant chemotherapy regimens, immune mediated and inflammation-related lung injury, and possibly occult infections. On chest radiography and CT scan multilobar infiltrates are seen. BAL and open lung biopsy could help to define diagnosis. Treatment includes supportive care and empiric steroids, although the efficacy of the latter is unproven.

Diffuse alveolar hemorrhage (DAH) is characterized by cough, hypoxia, progressive dyspnoea, hemoptysis, and diffuse interstitial and alveolar infiltrates occurring in the absence of detectable infection (12). Symptoms typically appear 1-4 weeks after transplantation, coinciding with engraftment, and rapidly progress. On BAL progressive bloodier fluid is observed. The incidence in pediatric patients is 4%-6% (12). Hypoxic respiratory failure requiring mechanical ventilation is typical. Recombinant VII factor has been suggested as a potential therapy.

Engraftment syndrome (ES) is usually present around the time of neutrophil recovery with fever and an erythrodermatous rash (13). Pulmonary involvement is manifested by a range of findings from mild infiltrates to non-cardiogenic pulmonary edema to ARDS. The pathogenesis of ES is due to increased capillary permeability from cytokine release that accompanies engraftment. The incidence could be as high as 19% in pediatric patients with overall mortality of 23% (14). Steroid therapy is usually helpful in treating of ES.

Among pulmonary vascular complications pulmonary cytotoxic thrombi, pulmonary thromboembolus, pulmonary veno-occlusive disease, and pulmonary arterial hypertension could occur in HSCT patients.

Obliterative bronchiolitis (OB) is one of the most important late lung complications after HSCT that occurs in 2% to 10% of patients (15). It is frequently associated with chronic GVHD. Partial or complete obstruction of small airways due to inflammation and fibrosis are the main histopathological finding of OB. The pathogenesis of OB associated with GVHD likely involves T-lymphocytes directly attacking bronchiolar epithelium. Chest CT scan and open lung biopsy are essential for definitive diagnosis. BAL is important to rule out infectious causes. Immunosuppressive therapy along with high-dose pulse corticosteroids are used to treat this complication. Overall OB has a high mortality rate.

Bronchiolitis obliterans organizing pneumonia (BOOP) has also been reported in HSCT recipients. GVHD has been reported as a risk factor for developing BOOP, although cases in pediatric patients without GVHD have been reported. OB and BOOP may frequently occur simultaneously making their differential diagnosis difficult. CT scan findings include nodular, patchy infiltrates bilaterally. Lung biopsy is essential for diagnosis. The true incidence of this complication in pediatric patients is unknown mainly because of difficulty of diagnosis.

Common infectious lung complications in HSCT patients are invasive pulmonary aspergillosis, interstitial pneumonia due to CMV, HHV-6, respiratory syncytial virus, and *Pneumocystis carini*.

Invasive pulmonary aspergillosis can occur in 4.5% to 38% of patients after BMT. On lung CT scan the so-called "halo sign" during the first 2- 3 weeks of infection could be seen. Detection of aspergillus spp either by cytologic identification or by culture of BAL fluid can be difficult but should be done. Galactomannan assay and aspergillus-PCR assay could be informative for early diagnosis of aspergillus in HSCT recipients. High dose amphotericin B formulations, voriconazole or echinocandins are effective to treat aspergillosis (16).

Although the CMV reactivation in HSCT patients is high (up to 65%) the incidence of CMV pneumonia is decreased (10%) due to pre-emptive anti viral therapy (17). Nonetheless the mortality rate from CMV pneumonia is still high (35% to 48%). The detection of CMV antigenemia, or CMV DNA by PCR on blood and/or BAL fluid are important for timely diagnosis of CMV pneumonia. Treatment includes ganciclovir, vidarabine or cidofovir with or without specific hyperimmunoglobulins.

Respiratory syncytial virus (RSV) is the most common community-acquired virus to cause respiratory tract infections in HSCT recipients. RSV infection can cause either mild respiratory tract infection or severe pneumonia with respiratory failure requiring mechanical ventilation. Both RSV antigen and DNA can be detected in BAL fluid. Therapy includes Ribavirin given i.v. and/or by nebulisation. The mortality rate is high.

Cardiac complications

Progressive heart failure, acute ventricular fibrillation and cardiac tamponade are among the reported cardiac complications of HSCT. Thalassemia patients often suffer from iron overload and decreased cardiac function prior to HSCT, and are at high risk for cardiac complications. Sudden cardiac tamponade has been observed in 2% of pediatric patients undergoing BMT for thalassemia (18). Nine pediatric thalassemia patients had sudden cardiac tamponade between -3 and +41 days from transplantation. The first six patients died from this complication and the diagnosis was made post mortem. Subsequently we introduced echocardiographic examination in our Center and in the last three patients early recognition of cardiac tamponade and pericardiocentesis resulted in a complete resolution of the complication. No characteristic clinical symptoms were present in these patients. The pathogenesis of this complication is unclear. In all patients viral and bacterial cultures were negative. Cardiac function in thalassemic patients given transplant should be monitored regularly and in case of unexpected arterial hypotension echocardiographic examination must be done.

Neurological complications.

One quarter of patients undergoing HSCT may develop neurological complications within the first year after transplantation, related to drug toxicity, hemorrhage or infections. Clinical manifestation includes tremor, headache, reversible posterior leucoencephalopathy syndrome, generalized tonic-clonic seizures, cerebellar or syndromextrapyramidal syndrome, and peripheral neuropathy. Neurotoxicity can be categorized into 3 grade: grade 1- mental status change, tremor, and headache; grade 2- visual disturbances and cortical blindness; and grade 3- seizure and coma. The incidence of grade 1, grade 2 and grade 3 neurotoxicity in patients with thalassemia was 13%, 6% and 10% respectively. Risk factors for grade 3 toxicity were high blood pressure, GVHD and use of methylprednisolone = >2 mg/kg/day (19).

Hemorrhagic cystitis

Hemorrhagic cystitis (HC) is one of the most common pos transplant complications after BMT. Severity of this complications could be classified as mild (gross hematuria without clots), moderate (gross hematuria with clots and dysuria), and severe (gross hematuria with clots and urethral obstruction). The incidence of moderate HC in patients with thalassemia who received bladder irrigation was 12% while it was 28% in patients not given bladder irrigation. Most late-onset HC occurring in 3,6% to 25% of patients are related to viral reactivation.

Gastrointestinal complications

Liver toxicity, liver VOD, biliary complications, acute pancreatitis, neutropenic enterocolitis, gastrointestinal hemorrhage and acute or chronic GVHD are common posttransplant complications (20). Despite existing iron overload and/or HCV related hepatopathy in most our thalassemic patients at the time of transplantation the incidence of hepatic VOD was very low.

Microangiopathy

Microangiopathy is one of the most serious complication after BMT which is observed in patients treated with cyclosporine or tacrolimus (21). Diffuse endothelial cell injury, tissue factor expression and platelet activation and aggregation are common features of microangiopathy. The overall incidence varies from 0,5% to 70%. Severe thrombocytopenia, hemolysis, schistocytosis on blood smear films, renal dysfunction and neurological complications are clinical and laboratory manifestations of this syndrome. Plasma exchange could be effective in few cases. No effective treatment is exist

Acute and chronic GVHD

The incidence of aGVHD in thalassemic patients treated with CSA+short MTX is significantly low than in patients given CSA+ methylprednisolone (17% vs 32%; p=0.001).

One of the major late complications of BMT is chronic GVHD that is the principal cause of morbidity and non-relapse mortality. Chronic GVHD has been reported to occur in 8-27% of patients receiving SCT from a compatible family donors for thalassemia. In most of these patients chronic GVHD was limited and the probability of moderate or severe form was only 8% and 2% respectively (22).

Graft failure or rejection

There is a substantial incidence of graft failure in patients with thalassemia after myeloablative conditioning regimens especially in class 3 patients in whom its incidence could be as high as 20% to 38,5%. Most patients with graft failure have recurrence of thalassemic marrow. Historically results of second transplants for thalassemia were poor because of a high rejection rate and/or increased transplanted related mortality (TRM).

A recently developed new treatment protocol for second transplantation in patients with thalassemia recurrence significantly reduced the incidence of graft failure and increased thalassemia-free survival rate (23)

Natural history of liver fibrosis progression

Analysis of the natural history of liver fibrosis following BMT for thalassemia showed that iron overload and hepatitis C virus infection are independent risk factors for liver fibrosis progression, and their concomitant presence results in a striking increase in risk (24). Therefore, the toxic effect of iron overload contributing to progression of already present organ damages should be avoided as soon as possible using posttransplant iron depletion. Either regular phlebotomy or chelation therapy can successfully remove excess iron from the body with normalizing the iron pool which resulted in marked improvement in liver and cardiac function (25-27).

Growth and development

Growth failure and endocrine dysfunction are common in thalassemia major patients treated by conventional treatment. While the endocrine dysfunction is usually due to iron overload as a result of chronic transfusions, in growth failure lifelong desferrioxamine treatment also plays a negative role in these patients. It has been shown that busulfan-containing regimens did not adversely affect growth velocity in patients receiving BMT for malignancies but can cause gonadal damage. In β -thalassemia major patients the age at time of transplant has been reported to be important predictor of growth after BMT. Children receiving transplant before age of 8 years regain a normal growth rate while older children, class III patients and patients who developed chronic GVHD have impaired growth (28).

Gonadal damage is a common side effect of busulfan- cyclophosphamide conditioning. Indeed, approximately one third of boys and two third of girls failed to spontaneously enter puberty following transplant (29). Nevertheless some patients can restore their fertility after transplant which is supported by our observations of five successful pregnancies and three spontaneous paternity in our patients. These data demonstrate that patients exposed to BUCY regimen are not inevitably infertile.

Postransplant malignancies

With the increasing number of transplant survivors there is a risk for secondary malignancies. Patients who received BMT for β -thalassemia and sickle cell disease had a low incidence (0.8%) of malignancies (30). The type of malignancies observed in our patients consisted of three early and one late non Hodgkin lymphomas, and four solid tumors (spinocellular cancer, Kaposi's sarcoma, melanoma and colon cancer respectively). Four of these patients are alive and well.

Summary

Most post transplant complications in patients with thalassemia are similar to those observed in malignant BMT setting. Establishing the correct diagnosis early is crucial to prevent or minimize both morbidity and mortality. More reliable early diagnostic markers and more specific therapies are needed.

References

1. Piga A, Longo F, Consolati A. Mortality and morbidity in thalassemia with conventional treatment. *Bone Marrow Transplant*. 1977; 19(Suppl.2):11-13.
2. Borgna- Pignatti C, Rugolotto S, DeStefano P et al. Survival and complications in patients with thalassemia major treated with transfusions and deferoxamine. *Haematologica*. 2004;89:1187-93.
3. Modell B, Khan M, Darlison M. Survival in beta-thalassemia major in the UK: data from the UK Thalassemia Register. *Lancet*. 2000; 355:2051-2052.
4. Cunningham MJ, Macklin EA, Neueld EJ, Cohen AR. Thalassemia Clinical Research Network. Complications of beta – thalassemia major in North America. *Blood*. 2002; 99:36-43.
5. Thomas ED, Buckner CD, Sanders JE et al. Marrow transplantation for thalassaemia. *Lancet*. 1982; ii: 227-9.
6. Lucarelli G, Galimberti M, Polchi P et al. Bone marrow transplantation in patients with thalassemia. *N Engl J Med*. 1990; 322: 417-21.
7. Lucarelli G, Andreani M, Angelucci E. The cure of thalassemia by bone marrow transplantation. *Blood Reviews*. 2002; 16:81-85.
8. Kudoh T, Suzuki N, Oda T et al. Pneumomediastinum, subcutaneous emphysema, and pulmonary fibrosis in a patient with idiopathic pneumonia syndrome after bone marrow transplantation. *Pediatr Hematol Oncol* 2000, 17:113-117
9. Suzuki T, Saijo Y, Ebina M et al. Bilateral pneumothoraces with multiple bullae in a patient with asymptomatic bronchiolitis obliterans 10 years after bone marrow transplantation. *Bone Marrow Transplant* 1999; 23:829-831.
10. Sanches R, Toy P. Transfusion related acute lung injury. A pediatric perspective. *Pediatr Blood Cancer* 2005; 45:248-255.
11. Clark JG, Hansen JA, Hertz MI et al. NHLBI workshop summary. Idiopathic pneumonia syndrome after bone marrow transplantation. *Am Rev Respir Dis*. 1993; 147:1601-1606.
12. Haggen J, West C, Olson E et al. Diffuse alveolar hemorrhage in pediatric hematopoietic cell transplant patients. *Pediatrics* 2002; 109:965-971.
13. Spitzer TR. Engraftment syndrome following hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2001;27:893-989.
14. Madero L, Vincent MG, Sevilla J et al. Engraftment syndrome in children undergoing autologous peripheral blood progenitor cell transplantation. *Bone Marrow Transplant* 2002;26:492-496.
15. Dudek AZ, Mahaseth H, DeFor TE et al. Bronchiolitis obliterans in chronic graft-versus-host disease: analysis of risk factors and treatment outcomes. *Biol Blood Marrow Transplant* 2003;9:657-666.
16. Wingard JR, Beals SU, Santos GW, et al. Aspergillus infections in bone marrow transplant recipients. *Bone Marrow Transplant* 1987; 2:175–181
17. Schmidt GM, Horak DA, Niland JC, et al. A randomized controlled trial of prophylactic ganciclovir for cytomegalovirus pulmonary infection in recipients of allogeneic bone marrow transplants. *N Engl J Med* 1991; 324:1005–1011
18. Angelucci E, Mariotti E, Lucarelli G et al. Sudden cardiac tamponade after chemotherapy for marrow transplantation in thalassemia. *Lanset* 1992; 339:287-289.
19. Erer B, Polchi P, Lucarelli G et al. CsA-associated neurotoxicity and ineffective prophylaxis with clonazepam in patients transplanted for thalassemia major: analysis of risk factors. *Bone Marrow Transplant* 1996; 18(1):157-62
20. Barker CC, Anderson RA, Sauve RS, Butzner JD. GI complications in pediatric patients post-BMT. *Bone Marrow Transplant* 2005; 36:51-58
21. Elliot MA, Nichols WL, Plumhoff EA et al. Posttransplant thrombotic trombocytopenic purpura: a single center experience and a contemporary review. *Mayo Clin Proc*. 2003;78:421-430.
22. Gaziev D, Polchi P, Galimberti M et al.: Graft-versus-host disease after bone marrow transplantation for thalassemia: an analysis of incidence and risk factors. *Transplantation* 1997, 63:854-860.
23. Gaziev J, Lucarelli G, Sodani P et al. High engraftment rate after second stem cell transplantation for thalassemia: a prospective study. *Blood* 2007,
24. Angelucci E, Muretto P, Nicolucci A et al.: Effects of iron overload and hepatitis C virus positivity in determining progression of liver fibrosis in thalassemia following bone marrow transplantation. *Blood* 2002, 100:17- 21.

25. Li CK, Lai DH, Shing MM, Chik KW, Lee V, Yuen PM. Early iron reduction programme for thalassaemia patients after bone marrow transplantation. *Bone Marrow Transplant* 2000, 25(6):653-656
26. Angelucci E, Muretto P, Lucarelli G et al.: Phlebotomy to reduce iron overload in patients cured of thalassemia by bone marrow transplantation. Italian Group for Phlebotomy Treatment of Transplanted Thalassemic Patients. *Blood* 1997, 90:994- 998.
27. Giardini C, Galimberti M, Lucarelli G et al.: Desferrioxamine therapy accelerates clearance of iron deposits after bone marrow transplantation for thalassemia. *Br J Haematol* 1995, 89:868-873.
28. Gaziev D, Galimberti M, Giardini C, Baronciani D, Lucarelli G. Growth in children after bone marrow transplantation for thalassemia. *Bone Marrow Transplant* 1993, 12(Suppl.1):100-101.
29. De Sanctis V, Galimberti M, Lucarelli G et al. Growth and development in ex-thalassemic patients. *Bone Marrow Transplant* 1997, 19(Suppl.2):126-127
30. Gaziev J, Polchi P, Giardini C et al.: Malignant complications after BMT for thalassemia. *Bone Marrow Transplantation* 2004, 33: P791

