

Graft Versus Host Disease

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Allogeneic stem cell transplantation (SCT) has significant therapeutic benefit for many patients with haematopoietic disorders. Unfortunately the benefits of SCT are limited by significant morbidity and mortality related to graft versus host disease. GvHD remains one of the major complications of allogeneic SCT and a major determinant of outcome.¹

The acute form occurs within 100 days from HSCT, whereas chronic form develops beyond day+100. Acute GvHD develops in approximately 30% to 60% of patients. Acute GvHD results from an interaction of donor T lymphocytes with recipient antigens. Variety of lymphokines (TNF- α , IL-1, IL-12, IFN- α) are released, which activate both donor and recipient mononuclear cells. These activated cells produce non-specific tissue destruction of target organs especially skin, gut and liver.²

Chronic graft versus host disease GvHD is the most important cause of late transplants related morbidity and mortality. Between 30 and 50% of patients surviving 6 months or longer after an HLA identical sibling transplant, develop evidence of chronic GvHD. The major manifestations of chronic GvHD resemble several naturally occurring autoimmune disorders.³

Two basic approaches for GvHD prophylaxis after stem cell transplantation are either treatment of the recipient with pharmacologic agents (Cyclosporine, Prednisolone, Methotrexate, ALG) or in vitro purging of donor T lymphocytes from the marrow. Despite state of art prophylaxis, acute GvHD develops in about 50% of all HLA identical transplants. When the donor and recipient are unrelated or histo incompatible, the incidence of acute GvHD is much higher (40% to 90%) and in nearly 100% of non identical transplants.⁴

Initial treatment for acute GvHD routinely consists of intensifying the dose of corticosteroids and cyclosporin. Furthermore, steroid-resistant (SR) acute GvHD develops in 30-60% of patients, necessitating secondary intervention. Anti thymocyte globulin (ATG) is commonly used as first line therapy in this setting. Chronic GvHD remains a significant cause of late morbidity and mortality following allogeneic stem cell transplantation. However, patients with chronic GvHD are very heterogeneous, making evaluation and treatment difficult. Corticosteroids remain the most effective primary treatment of this condition.⁵

The transplant related mortality, defined as death without relapse has been found to be significantly high in

patients with acute GvHD (grade-II or more). The morbidity and mortality associated with acute GvHD correlate with the severity of the organ involvement. The mortality as a direct or indirect consequence of acute GvHD may be as high as 50%. EBMT working party analysis shows 25% mortality in patients with grade 0-I acute GvHD. The mortality related to Grade-II-IV GvHD ranged from 65% to 93%.⁶

The incidence of transplant related mortality due to chronic GvHD depends upon the progressive type, onset, extensive stage of GvHD and thrombocytopenia ($<100 \times 10^9/L$). The accumulative incidence of transplant related mortality due to chronic GvHD has been reported to be 7-8%. Prolonged immunosuppression to treat severe chronic GvHD results in a potential increase in the risk of opportunistic fatal infection.⁷

A recent analysis of 4174 HLA identical sibling transplants shows that early and long term outcome is influenced by severity of acute GvHD and at 3 years survival was 74, 64, 37 and 10% respectively for patients with grade-I, II, III and IV acute GvHD respectively.⁸

There are two major bone marrow transplant centers in Pakistan namely Bismillah Taque Institute of Health Sciences and Blood Disease Centre, Karachi and Armed Forces Bone Marrow Transplant Centre, Rawalpindi. Uptill now both the centers have carried out more than 250 allogeneic bone marrow transplants for various haematological disorders. The initial results are quite encouraging. However post transplant complications are the main causes of transplant related morbidity and mortality. Graft Versus Host Disease remains one of the major post transplant complications.

Author has reported 50% acute GvHD (Grade II-IV) in allogeneic stem cell transplantation in β -Thalassaemia and Chronic Myeloid Leukaemia in his initial series of transplant. The incidence of chronic GvHD was 5.2% in β -Thalassaemia and 18.1% in Chronic Myeloid Leukaemia.^{9,10} Author has also reported 44.2% acute GvHD and 14% chronic GvHD in a series of eighty six patients, transplanted for various haematological disorders. A retrospective analysis of acute GvHD in one hundred twenty five patients subjected to allogeneic stem cell transplantation for various haematological disorders at Armed Forces Bone Marrow Transplant Centre, showed 34% acute GvHD and 13% chronic GvHD. (To be presented in APBMT- 2005 Congress in China).

In this issue of JPMA Tahir Shamsi et al. have given a very low incidence of acute GvHD (29%) and chronic GvHD (24.3%) in a series of hundred patients under going allo - SCT for various haematological disorders. This shows the excellent GvHD prophylaxis strategy in their transplant setup. However the incidence of mortality was high in Grade III-IV acute GvHD and chronic extensive GvHD which is comparable to other international studies.

In a developing country the performance of these two transplant centers is excellent and are providing state of art transplant facility to the nation. Though the transplant programme in Pakistan is still in evolution, sooner of later the transplant facility will be available to majority of the critically sick patients at a much cheaper rate as compared to USA, European and other neighboring countries.

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