TRANSFUSION ASSOCIATED GRAFT VERSUS HOST DISEASE
Masood Anwar, Farhat Abbas Bhatti*

Transfusion associated graft versus host disease (TA-GVHD) results from engraftment of viable donor T-lymphocytes in recipient that can not recognize or destroy them. It is seen in immunocompromised patients and pre-mature neonates. It can also occur in immunocompetent individuals receiving blood from first-degree relatives. It has emerged as single most common cause of death resulting from transfusion. Patients with B-cell malignancies appear to be especially at risk. TA-GVHD is associated with 80-90% mortality. Death most commonly occurs due to infection or haemorrhage secondary to pancytopenia. It is therefore important to prevent its occurrence. Prevention can be achieved either by complete removal of T-lymphocytes from donors blood or by abolishing their proliferating potentials. Available methods of leuko-depletion are not effective in preventing TA-GVHD. Only effective way is to inactivate T-lymphocytes. This can be achieved by irradiating blood product with gamma or X-ray irradiation. The concerns about malignant transformation of cells or reactivation of intracellular viruses have not been proved so far. Newer technologies for T-cell inactivation, which are not based on irradiation, are currently under trial.

Key words: Transfusion hazards, TA-GVHD, Graft versus Host Disease, Blood product irradiation, Transfusion to immunocompromised, Transfusion from first degree relatives

INTRODUCTION
Transfusion associated Graft versus Host disease (TA-GVHD) results from engraftment of viable donor T-lymphocytes present in cellular blood components, in a recipient that cannot recognize or destroy them. The susceptible patients who are at risk of developing this serious complication are immunocompromised and include recipients of allogeneic bone marrow transplantation and intrauterine transfusion, those undergoing treatment for various solid and haematological malignancies, premature neonates and children with congenital immunodeficiency states. TA-GVHD can also occur in immunocompetent individuals who receive blood products from first-degree relatives. In this scenario, the donor is homozygous for an HLA haplotype, shared by the recipient and the donor lymphocytes are not recognized as foreign leading to their engraftment. Although, patients of acquired immunodeficiency syndrome (AIDS) have defects in cellular immunity, TA-GVHD has not been reported in them. TA-GVHD emerged as the most common serious complication of transfusion of blood products, in the 5 years of SHOT (Serious Hazards of Transfusion) reporting from 1996/97-2000/01. Out of 38 cases whose death was definitely attributable to transfusion, 13 died due to TA-GVHD. Patients with B cell malignancies (6/13) appeared to be especially at risk. The most frequent reports of TA-GVHD in immunocompetent individuals are from Japan, where there is a greater HLA homogeneity in the general population. Blood collections in Pakistan are mainly derived from directed blood donors, resulting in increased possibility of blood products being transfused to first-degree relatives. Strict vigilance is therefore required in our set up, in order to recognize this almost fatal complication of transfusion.

PATHOGENESIS
There are several factors, which play a role in the pathogenesis of TA-GVHD.Billingham described 3 prerequisites for the development of GVHD, as follows: (1) the graft must contain viable immunocompetent cells, (2) the host antigens must be recognized as foreign by the graft, due to disparity in HLA antigens, and (3) the recipient must be incapable of mounting an immunological response against the graft tissue. New insights into the role of various lymphocyte sub-populations in the development of TA-GVHD have been gained. Different HLA antigens of the host are presented to donor T lymphocytes, by antigen presenting cells, such as dendritic cells or macrophages. Interleukin-1 (IL-1) produced by macrophages and thymocyte activating factor stimulate the T-helper cells. The T-helper cells in turn release interleukin-2 (IL-2), which stimulates the cytotoxic CD-8 positive T-lymphocytes. These lymphocytes destroy the host tissue carrying HLA class I molecules. Natural killer cells and macrophages have also been implicated in the development of TA-GVHD. There is increased expression of host histocompatibility antigens and other adhesion molecules (ICAM-1, VCAM-1) under influence of inflammatory cytokines, such as IL-1 and tumour necrosis factor a (TNF-a), released by damaged host tissue after radiotherapy, chemotherapy or infection. This leads to enhanced recognition of the host tissue by donor T-lymphocytes, thus amplifying the process.

DIAGNOSIS
TA-GVHD is associated with a high mortality of 80-90%. It is in contrast to a mortality rate of 10-20% seen in marrow transplant associated GVHD. This is because, in addition to liver, skin and gastrointestinal tract, the bone marrow is the main target of donor T-lymphocytes in TA-GVHD. Onset of symptoms is usually delayed for 1-2 weeks, after transfusion of cellular blood products. The clinical manifestations include fever, skin rash, diarrhoea and hepatitis with or without jaundice, pancytopenia, elevation of transaminases and raised bilirubin levels are observed. Histology
of the skin shows epidermal basal vacuolization and lymphoid infiltration. Donor T-lymphocytes may be detected by HLA typing, cytogenetic analysis or genetic fingerprinting. Their presence alone, however, does not indicate TA-GVHD, and must be correlated with other clinical and laboratory findings. Death usually is due to infection or haemorrhage secondary to pancytopenia. The features of TA-GVHD may be difficult to differentiate from primary infection and drug toxicity, which are common in immunocompromised patients.

PREVENTION

TA-GVHD can be prevented either by complete removal of donor T-lymphocytes or abolishing their proliferative potential. Current methods of leucodepletion result in a 3 log removal of leucocytes and aim at a count of <5 x 10⁹/l. Although, this procedure is useful to prevent alloimmunisation to white cell and platelet antigens, it does not protect from TA-GVHD. With current technology, the only way to prevent TA-GVHD is to inactivate the T-lymphocytes present in the cellular blood components, thus inhibiting their blast transformation and mitotic activity. This is achieved with the help of gamma irradiation and the minimum dose required to achieve this effect is 25 Gy. The blood component bags can be irradiated using blood irradiators, which utilize either cobalt-60 or caesium-137 as the source of radiation. They can be installed in a conventional laboratory environment and the blood bags can easily be loaded and unloaded in purpose built canisters, by trained laboratory staff. Due to shielding by lead, the equipment is heavy, and may require strengthening of the floor at the time of installation. Caesium-137 is preferred as the radiation source, as it has a longer half-life. Irradiation of blood components can also be carried out in the allied radiotherapy department using X rays delivered by the linear accelerator. The blood bags are placed in groups under the projected X ray field and a tissue bolus equivalent is placed on top and bottom to provide ideal and uniform dosage. Associated problems include logistic management, additional transit time leading to exposure of blood components to inappropriate temperatures, adjustment with patients’ treatment schedules and lack of round the clock service.

TA-GVHD has developed following transfusion of red cells, platelets, and granulocytes. There have been no documented cases of TA-GVHD following the use of fresh frozen plasma and cryoprecipitate and these non cellular components do not require irradiation. Irradiation of red cells causes a rise in extracellular potassium, which may become significant in clinical settings like exchange transfusion and intrauterine transfusions. In such instances the red cells should be transfused within 24 hours of irradiation. Irradiation also results in a reduced post transfusion recovery of red cells, which becomes apparent after 24 days of storage in the blood bank. It is thus recommended that the red cells should be irradiated within 14 days of their shelf life, and then stored for a maximum of 28 days from the time of irradiation or the expiry date, whichever is first. It is, however, advisable to irradiate the blood components immediately prior to their usage. This ensures their utilization within the shelf life, with maximum clinical benefit and minimum adverse effects.

The various conditions in which irradiation of cellular blood products is required are listed in Table-1. All bone marrow and stem cell transplant recipients should start receiving irradiated cellular blood products from the onset of conditioning therapy. This needs to be continued until there is evidence of post transplant haematopoietic reconstitution. Patients undergoing autologous bone marrow / peripheral blood stem cell transplantation should receive irradiated blood components for 3 months and allograft recipients for at least 6 months after the transplant. Red cells, platelets and granulocytes derived from HLA matched donors and first degree relatives should be irradiated, as HLA sharing can cause TA-GVHD even in immunocompetent patients. Patients with Hodgkin’s disease and those who have received fludarabine should also receive irradiated blood products. As there have been recent reports of TA-GVHD in patients with B cell malignancies, irradiated blood must be administered to them whenever required. All intrauterine transfusions and blood given to patients with congenital cellular immune deficiency should be irradiated. From the preceding discussion, it is apparent that a multidisciplinary approach is required to organize irradiation of blood components in a medical setup. It is more convenient to install a blood irradiator centrally in the blood transfusion center, from where needs of different groups of patients is met round the clock.

Table-1: Indications for irradiated blood products

<table>
<thead>
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<th>Indication</th>
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<tr>
<td>Autologous bone marrow/stem cell transplant recipients</td>
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<tr>
<td>Allogeneic bone marrow/stem cell transplant recipients</td>
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<tr>
<td>Hodgkin’s disease</td>
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<tr>
<td>B-cell malignancies (non Hodgkin’s lymphoma, multiple myeloma, Waldensrom’s macroglobulinaemia, ALL)</td>
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<td>Fludarabine, Cldarbine therapy</td>
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<td>Directed donations from blood relatives</td>
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<tr>
<td>HLA matched platelets</td>
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<td>Congenital immunodeficiency disorders (SCID, Wiskott-Aldrich)</td>
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<tr>
<td>Intrauterine transfusions</td>
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<tr>
<td>Granulocyte transfusions in infants</td>
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<tr>
<td>Non Indications</td>
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<tr>
<td>AIDS / HIV infection</td>
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Full term neonates
Acute leukaemia without transplantation
Aplastic anaemia

There are concerns regarding radiation induced malignant change and reactivation of latent viruses subsequent to irradiation. No such instances have however, yet been described. Efforts are being made to develop alternate methods, which could prevent TA-GVHD. One such technology, for which trials are underway, is based on a small molecule (PEN 110) that binds to the RNA or DNA of the lymphocytes and any pathogens present in the blood. This irreversible (covalent) bond inhibits WBC proliferation, and also ‘kills’ the pathogens by preventing their replication. PEN 110 treatment can potentially be used to prevent development of TA-GVHD, because it has been shown to be as effective as γ irradiation. Moreover, PEN 110 pathogen reduction system can also be utilized to prevent transmission of bacteria, enveloped and non-enveloped viruses and potentially new transmissible agents through blood transfusion.

TA-GVHD is a serious complication of blood transfusion, and requires a high index of suspicion for early diagnosis and management. This is especially true in this country where donations from first degree relatives are quite frequent, increasing the risk of disease in immunocompetent recipients. Newer and simpler technologies may virtually eliminate this complication and enhance the safety of blood in the future.

REFERENCES

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