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Should irradiated blood products be given routinely to all patients with aplastic anaemia undergoing immunosuppressive therapy with antithymocyte globulin (ATG)? A survey from the European Group for Blood and Marrow Transplantation Severe Aplastic Anaemia Working Party

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Keywords

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In view of the lack of guidance on the use of irradiated blood products (IBP) in patients with aplastic anaemia (AA) receiving immunosuppressive therapy (IST) with antithymocyte globulin (ATG) and ciclosporin, we conducted the first survey from European and USA centres to determine current practice on this issue. The routine use of pre-storage leucocyte-depleted blood products has reduced the risk of allosensitization in haematological malignancies, although data is lacking in AA [The Trial to reduce Alloimmunization to Platelets study group, 1997; Marsh et al, 2009].

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Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare but invariably fatal complication following transfusion of viable lymphocyte-containing blood products. It is abolished by the use of IBP in at-risk patients. For haematological patients, the routine use of IBP is recommended for all autologous and allogeneic haemopoietic stem cell tranplantation (HSCT) recipients, patients with congenital immune deficiency, Hodgkin lymphoma, and patients receiving purine analogues. In Germany, Non-Hodgkin lymphoma is also an indication for IBP [British Committee for Standards in Haematology (BCSH) Blood Transfusion Task Force, 1996; Williamson et al, 2007; Agbaht et al, 2007; The Board of the German Medical Association on the recommendation of the Scientific Advisory Board 2009]. Treatments with either ATG or Alemtuzumab (anti-CD52 monoclonal antibody) are also under consideration as an indication by the BCSH (J. Treleaven, Royal Marsden Hosptial, Sutton, UK, personal communication, 2009).

The rationales for considering giving only IBP to patients with AA are (1) to prevent TA-GVHD during ATG treatment and (2) to help reduce allo-sensitization, which occurs frequently in AA patients (Killick et al, 1997; Laundy et al, 2004). Animal data show that irradiation of all red cell and platelet transfusions before HSCT reduces the risk of sensitization to minor histocompatibility antigens and the risk of graft rejection after dog leucocyte antigen-identical marrow grafts [Bean et al, 1994]. It is likely, but unproven, that the routine clinical use of leucocyte-depleted blood products has helped to reduce this risk. Leucodepletion should also reduce the chances of a recipient developing TA-GVHD. There were 13 cases of TA-GVHD reported to Serious Hazards of Blood Transfusion (SHOT) in the UK between 1996 and 2005, and of these, 11 occurred after transfusion of non-leucocyte depleted products and 2 after transfusion of leucocyte-depleted products; there have been no reported cases since 2001 [Williamson et al, 2007].

We were not aware of any published cases of TA-GVHD following ATG treatment for haematological disorders. We therefore performed an email survey of 12 European Group for Blood and Marrow Transplantation (EBMT) centres and two USA centres in 2008. Questionnaires were sent to lead representatives who were also representatives on the EBMT Severe Aplastic Anaemia Working Party (EBMT SAAWP) from the following countries: UK, Switzerland, Germany, Italy, Sweden, Netherlands, Italy and France. Two large centres in the USA were also included, The National Institutes of Health and Medical College of Wisconsin, on account of their specialist interest in AA. Both adult and paediatric centres were included in the survey.

The questionnaire comprised the following questions: (1) Do you routinely give only IBP after ATG? (2) If so, how long for? (3) Which blood products do you irradiate? (4) What is/are your reason(s) for giving IBP? (5) Have you ever seen a case of TA-GVHD after ATG? (6) Do you have the same policy for children and (7) Any other comments to add?

The results are summarized in Figure 1. Twelve of 14 centres (85%) routinely only give IBP after ATG. Of these, 6 of 12 centres indicated that they give IBP to all AA patients regardless of treatment. The reason for not giving IBP at 2 centres was lack of published evidence. There was no consensus on how long to continue IBP after IST. Two of 12 centres gave IBP indefinitely, 5 until patients became transfusion independent, two for 6 months, two for 12 months and one until the lymphocyte count was $> 1.5 \times 10^9/1$. All of the 12 centres gave IBP to avoid TA-GVHD after ATG. Two centres had a universal IBP policy to avoid TA-GVHD for all haematology/oncology patients, to avoid possible errors of not giving IBP to patients known to be at risk. Only three centres indicated that reduction in allosensitization was another indication for giving IBP. Seven of 10 centres irradiated both red cell and platelet transfusions, and three irradiated red cells, platelets and fresh frozen plasma. Eight centres managed both children and adults with AA, and all reported the same

policy for children and adults. A patient with severe AA was reported to have developed probable TA-GVHD 20 years ago after treatment with ATG. A further case was reported in a liver transplant recipient more than 10 years ago. No further details on these two cases of TA-GVHD were available.

The risk of TA-GVHD post-ATG is not known but appears to be low. This may reflect irradiation practices, and the use of leucodepleted blood products, or it may be truly low. However, horse ATG (Lymphoglobuline) was routinely used as treatment for AA, but was withdrawn from the market in 2007. Rabbit ATG is more immunosuppressive than horse ATG. It causes a more prolonged lymphopenia, higher peak Epstein-Barr virus (EBV) viral levels post-ATG for AA than horse ATG [Scheinberg et al, 2007], more EBV post-transplant lymphoproliferative disease after HSCT [Scheinberg et al, 2007]. Therefore, there is concern that rabbit ATG might increase the risk of TA-GVHD compared with horse ATG.

Therefore, based on background information we have on the beneficial effect of IBP, and on the results of this survey, we propose that patients with AA should receive IBP during and after ATG treatment. This policy should probably be continued for at least as long as patients are receiving IST, such as ciclosporin.

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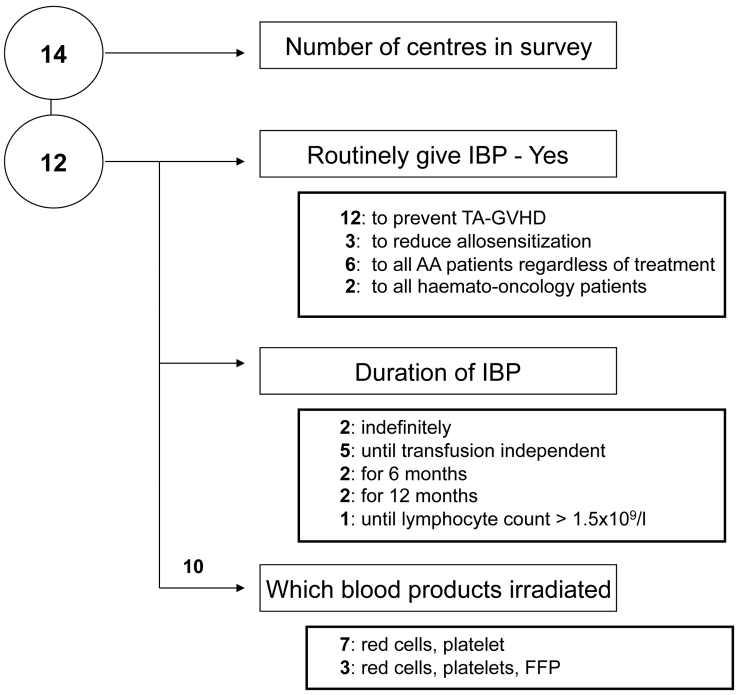

Figure 1.
Results of survey on the use of irradiated blood products in aplastic anaemia patients treated with immunosuppressive therapy.