CASE REPORT

Relapsed Diffuse Large B-Cell Lymphoma Treated by Reduced-Intensity Allogeneic Stem Cell Transplantation with Donor Lymphocyte Infusion

Qamar-un-Nisa Chaudhry[1], Parvez Ahmed[1], Khalil Ullah[1], Tariq Mehmood Satti[1], Shahid Raza[2], Syed Kamran Mehmood[2], Mohammed Akram[3] and Suhaib Ahmed[4]

ABSTRACT

A 42 years old male with relapsed diffuse large B-cell lymphoma was given second-line chemotherapy followed by reduced intensity allogeneic stem cell transplantation from HLA matched brother. Twelve weeks posttransplant, his disease relapsed evidenced by the appearance of lymphoma cells in the peripheral blood and declining donor chimerism. Donor lymphocyte infusion was given that induced complete lymphoma remission. The patient is well 3 years posttransplant with his disease in complete remission.

Key words: *Relapsed non-Hodgkin's lymphoma. Reduced-intensity conditioning transplantation. Donor lymphocyte infusion. Diffuse B-cell lymphoma.*

INTRODUCTION

Outcome for relapsed or refractory non-Hodgkin's lymphomas (NHL) after conventional and high dose chemotherapy with autologous haemopoietic stem cell transplantation (HSCT) remains poor.[1] Allogeneic HSCT can achieve prolonged disease control due to the graft-versus-malignancy (GVM) effect but because of high transplant related mortality and morbidity, improvement in overall survival (OS) has been insignificant.[2]

Over the last decade, non-myeloablative or reduced intensity conditioning regimens (RIC) have been developed to reduce the toxicity of allogeneic transplantation and patients who are ineligible for conventional myeloablative conditioning due to older age or co-morbidities can also benefit from allo HSCT.[3,4] In this kind of transplant, the anti-neoplastic effect of high-dose myeloablative conditioning is substituted with the GVM effect of donor lymphocytes. RIC transplants have been used in the treatment of several haematological malignancies including CML, relapsed/refractory acute leukaemias, myeloma and lymphomas.[3] Recently, allo-HSCT with reduced intensity preparative regimens has been reported to induce a curable GVM effect for lymphomas with a lower incidence of treatment related toxicity.[4]

[1] *Department of Haematology/Medical Oncology[2]/ Anaesthesiology[3], Armed Forces Bone Marrow Transplant Centre, Rawalpindi.*

[4] *Department of Haematology, Armed Forces Institute of Pathology, Rawalpindi.*

***Correspondence:** Dr. Qamar-un-Nisa Chaudhry, Armed Forces Bone Marrow Transplant Centre, Near CMH, Rawalpindi. E-mail: qammarchaudhry@yahoo.com*

Received August 04, 2009; accepted October 27, 2009.

We hereby report a case of diffuse large B-cell lymphoma (DLBCL) which was successfully treated using a reduced intensity conditioning regimen (RIC) followed by donor lymphocyte infusion (DLI).

CASE REPORT

A 42 years old male with diffuse large B-cell lymphoma was referred to our hospital in June 2006 for haemopoietic stem cell transplant (HSCT). He had relapsed 8 months after 6 x R-CHOP and was given second line chemotherapy x 3 cycles following which he was in complete remission (CR2). His Karnofsky performance score was 80% and there were no co-morbidities. He was given conditioning with a reduced intensity regimen consisting of alemtuzumab (Campath-1H) 20 mg/d on days -8 to -4, fludarabine 30 mg/m^2 on days -7 to -3 and melphalan 140 mg/m^2 on day 2. G-CSF mobilized peripheral blood stem cells from HLA matched sibling donor were given at a dose of 4.5 x 10^8 mononuclear cells (MNC)/kg body weight of the recipient. Graft versus host disease (GVHD) prophylaxis was with ciclosporin. Except for mild renal impairment necessitating dose reduction of ciclosporin and addition of mycophenolate mofetil and a brief episode of neutropenic fever which responded to first line antibiotics, he remained well during the early post-transplant period. Neutrophil engraftment was documented on day +16 and platelet engraftment on day +19. Four weeks posttransplant, he developed microangiopathic hemolysis with indirect hyper-bilirubinemia, high serum LDH (2600 IU/l), schistocytes in the peripheral blood, impaired renal function and fever. This episode responded to plasmapheresis, steroids and dose reduction of ciclosporin. Bone marrow aspiration and trephine biopsy done 8 weeks posttransplant showed posttransplant engraftment and polymerase chain

reaction (PCR) for short tandem repeats (STRs), showed 95% donor chimerism (Figure 1). Immunosuppressives were tapered off over the next 2 weeks. He relapsed 4 weeks later with the appearance of lymphoma cells in the peripheral blood. PCR for STRs showed only 40% donor chimerism. At this time he was not receiving any immuno-suppressives. He was given lymphocytes from the sibling donor at a dose of 2 x 10^7 MNC/kg body weight. About 5 weeks after DLI, he developed extensive ulceration of the oral mucosa with grade-III hepatic and skin GVHD. He was treated with methyl prednisolone 5mg/kg body weight/day, ciclosporin, mycophenolate mofetil and oral steroid rinses. STRs at this point (5 months post-bone marrow transplant, 6 weeks post-DLI) showed 99% donor chimerism. Skin GVHD responded to immunosuppression but he remained deeply jaundiced with bilirubin 160 umol/l and alkaline phosphatase 800 IU/l. He was given daclizumab (1L-2 receptor inhibitor) 2 doses a fortnight apart. STRs again showed declining donor chimerism (85% donor). Further doses of daclizumab were withheld and immunosuppressives were tapered off. Repeat STRs 8 weeks later showed 99% donor chimerism but his hepatic GVHD gradually worsened with alkaline phosphatase 2000 IU/l. Two more doses of daclizumab were given 08 months post -DLI in July 2007 while other Immunosuppressives were gradually reduced. Although this period was complicated by several febrile episodes, derangement of renal function and impaired glucose tolerance, his hepatic GVHD gradually settled with normal liver function tests (bilirubin 18 umol/l and alkaline phosphatase 268 IU/l) by February 2008. At this point, he had minimal oral and ocular GVHD which were treated with local steroids and lubricants while systemic immunosuppressives were gradually tapered off. PCR for STRs done in May 2009 (3 years posttransplant) showed 99% donor chimerism (Figure 1).

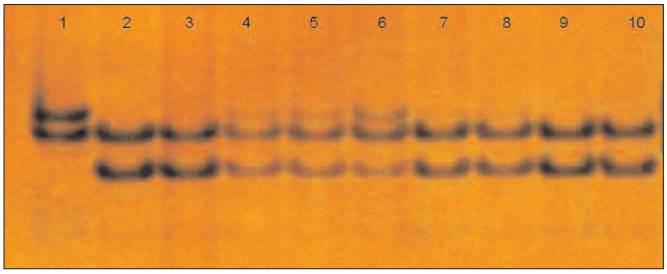

Figure 1: Photograph showing sequential polyacrylamide gel electrophoresis for short tandem repeats (STRs). Lane 1: recipient pre-transplant, lane 2: donor, lane 3: recipient post-transplant showing 95% donor chimerism, lanes 4, 5 and 6 show declining donor chimerism reflecting disease relapse, lanes 7, 8,9 and 10: sequential STRs following DLI showing donor chimerism.

Presently (October 2009) he is 39 months post-transplant. He is in complete remission with normal blood counts and has no active GVHD of the skin or liver.

DISCUSSION

RIC allogeneic transplantation has recently been used for a variety of haematological malignancies with the aim to reduce short-term morbidity and mortality.[3] The use of alemtuzumab (anti-CD52, Campath-1H), for *in vivo* lymphodepletion, allows durable engraftment while significantly reducing the risk for acute and chronic graft-versus-host disease (GVHD).[5] This type of intervention may have an adverse impact on disease response due to the positive correlation between GVHD and graft-versus-malignancy effect. Therefore, the use of DLI has been central to many RIC protocols. Peggs *et al.* have reported a strong evidence for a graft-versus-lymphoma effect by using RIC and DLI in lymphomas.[6] Currently, the role of RIC allo-HSCT in relapsed DLBCL is under investigation. There is emerging evidence for a graft-versus-lymphoma effect against DLBCL after allogeneic HSCT and following DLI.[7] Rezvani *et al.* used RIC allogeneic HSCT for 31 patients with DLBCL and concluded that this treatment could produce long-term disease free survival in patients who have failed or are not eligible for autologous HSCT.[8] A recent study on 48 patients with relapsed/refractory DLBCL, who underwent RIC allogeneic transplantation, documented progression free survival (PFS) and OS of 55% and 54% respectively at 4 years and concluded that there is a role for RIC allogeneic transplantation in relapsed DLBCL.[9]

In this case of relapsed DLBCL, the reasons for performing RIC transplant were early relapse within 8 months of completing R-CHOP x 6 cycles, relatively advanced age for conventional allogeneic transplantation and prior high dose chemotherapy.

RIC regimen was used consisting of fludarabine, melphalan and alemtuzumab. This regimen is more immunosuppressive and myelosuppressive than a number of other regimens and in a multi-centre study the most common toxicities observed were sepsis, post-transplantation lymphoproliferative disorder (PTLPD) and demyelinating neuropathy or Guillain-Barre' syndrome.[10] The patient had a brief episode of neutropenic fever which responded to intra-venous antibiotics, but he experienced severe microangiopathic hemolysis that was not seen in any of the 88 patients in the above mentioned study.[10]

After RIC allografting, DLIs are given for a number of indications: first, to convert mixed chimerism into full donor chimerism which in turn reduces the chances of graft rejection and improves the graft versus-malignancy effect, second, to treat disease progression or partial remission, and third, and most recent, to eradicate minimal residual disease (MRD) and pre-empt relapse.[6] In the absence of any other disease marker to monitor MRD, PCR was used for highly polymorphic short tandem repeat units to document the patient's donor chimerism status and use this information to time DLI and tailor immunosuppression. The patient had early neutrophil and platelet engraftment and had 85% donor chimerism 8 weeks posttransplant. Donor chimerism

declined over the next 4 weeks which coincided with appearance of lymphoma cells in the peripheral blood. At this point DLI was given. In the study quoted above, 17 patients out of 88 had disease progression or disease relapse 1-3 months after transplant requiring DLI and out of 17, 7 patients responded.[10] This patient showed prompt response to DLI with 99% donor chimerism 6 weeks post-DLI, which coincided with the development of acute grade-III GVHD of the skin and liver. Marks *et al.* reported that 25% of patients given DLI developed grade II-IV GVHD while grade III-IV GVHD was seen in 15% patients.[6] About 75% of patients, who responded, developed GVHD indicating a substantial overlap between GVHD and GVM effect.[6] This patient developed grade-III hepatic and skin GVHD requiring heavy doses of steroids, ciclosporin and mycophenolate mofetil; later daclizumab was also added to manage grade-III GVHD.

Advanced investigative methods such as positron emission tomography (PET) scan are not available in Pakistan as yet. In the absence of a marker for monitoring disease status, STR analysis proved appropriate and useful for documenting chimerism and modulating immunosuppression. The fact that the patient is in remission 3 years posttransplant with no active GVHD supports the feasibility of this approach.

RIC followed by DLI is a safe and effective treatment modality for relapsed/refractory NHL in patients who are ineligible for or not likely to benefit from auto-HSCT due to progressive disease. The relatively low toxicity and high progression free survival make this an attractive up-front option in patients with relapsed/refractory DLBCL. This area is being intensively investigated at present, and current studies may help identify the subset of NHL patients most likely to benefit from this therapeutic modality.

REFERENCES

1. Gribben JG, Goldstone AH, Linch DC, Taghipour G, McMillan AK, Souhami RL, *et al.* Effectiveness of high-dose combination chemotherapy and autologous bone marrow transplantation for patients with non-Hodgkin's lymphomas who are still responsive to conventional dose therapy. *J Clin Oncol* 1989; **7**:1621-9.
2. Hale GA, Phillips GL. Allogeneic stem cell transplantation for the non-Hodgkin's lymphomas and Hodgkin's disease. *Cancer Treat Rev* 2000; **26**:411-27.
3. Giralt S, Thall PF, Khouri I, Wang X, Braunschweig I, Ippolitti C, *et al.* Melphalan and purine analog-containing preparative regimens: reduced intensity conditioning for patients with haematological malignancies undergoing allogeneic progenitor cell transplantation. *Blood* 2001; **97**:631-7.
4. Kogel KE, Macsweeney PA. Reduced intensity allogeneic transplantation for lymphoma. *Curr Opin Oncol* 2002; **14**:475-83.
5. Pérez-Simón JA, Kottaridis PD, Martino R, Craddock C, Caballero D, Chopra R, *et al.* Non-myeloablative transplantation with or without alemtuzumab: comparison between 2 prospective studies in patients with lymphoproliferative disorders. *Blood* 2002; **100**:3121-7.
6. Peggs KS, Thompson K, Hart DP, Geary J, Morris EC, Yong K, *et al.* Dose-escalated donor lymphocyte infusions following reduced intensity transplantation: toxicity, chimerism, and disease responses. *Blood* 2004; **103**:1548-56.
7. Bishop MR, Dean RM, Steinberg SM, Odom J, Pavletic SZ, Pittaluga SC, *et al.* Clinical evidence of a graft-versus-lymphoma effect against relapsed diffuse large B-cell lymphoma after allogeneic haematopoietic stem-cell transplantation. *Ann Oncol* 2008; **19**:1935-40.
8. Rezvani AR, Norasetthada L, Gooley T, Sooror M, Bouvier M, Sahebi F, *et al.* Non-myeloablative allogeneic haematopoietic cell transplantation for relapsed diffuse large B-cell lymphoma: a multicentre experience. *Br J Haematol* 2008; **143**:395-403.
9. Thomson KJ, Morris EC, Bloor A, Cook G, Milligan D, Parker A, *et al.* Favourable long-term survival after reduced-intensity allogeneic transplantation for multiple-relapse aggressive non-Hodgkin's lymphoma. *J Clin Oncol* 2009; **27**:426-32. Epub 2008 Dec 8.
10. Morris E, Thomson K, Craddock C, Mahendra P, Milligan D, Cook G, *et al.* Outcomes after alemtuzumab-containing reduced-intensity allogeneic transplantation regimen for relapsed and refractory non-Hodgkin's lymphoma. *Blood* 2004; **104**:3865-71. Epub 2004 Aug 10.