Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Treatment of patients with Hodgkin lymphoma not responding to conventional dose therapy

1. Summary of the impact

Clinical research from UCL established 'salvage therapy' and autologous transplantation protocols for use in relapsed and resistant Hodgkin lymphoma and demonstrated the efficacy of such approaches. These treatments are now widely used standards of care. A reduced intensity transplant (RIT) regimen, incorporating alemtuzumab to reduce graft-versus-host disease, was also developed and a potent graft-versus-tumour effect was demonstrated. RIT treatments are now increasingly used in patients failing an autologous transplant and in those patients deemed to have a high risk of autograft failure, as determined by pre-transplant CT/PET scanning. We estimate that 5,000 patients have been cured in the REF period as a result of our research.

2. Underpinning research

Each year in the UK, around 1,600 people are diagnosed with Hodgkin lymphoma. Treatment is usually very successful, and most people can be cured, or the lymphoma can be controlled for many years. However for around a quarter of patients, this is not the case. Our research has developed new treatment strategies for those patients for whom conventional therapy had failed.

The regime we invented consists of two parts: initially high dose chemotherapy to ablate the bone marrow using the 'BEAM' regimen (a combination of carmustine, etoposide, cytarabine and melphalan) followed by autologous stem cell transplantation (ASCT; using stem cells harvested previously from the patients blood). In a randomised trial designed and managed by researchers at UCL, this strategy was compared with the same drugs at lower non-marrow-ablative doses, without ASCT (mini-BEAM). The trial proved the efficacy of BEAM plus ASCT and established it as the global standard treatment for all patients failing conventional chemo/radiotherapy **[1]**.

In the mid-1990s, the use of granulocyte-colony stimulating factor (G-CSF) became standard practice because of its effect to stimulate the bone marrow to produce stem cells, which could then be harvested from the blood. Our research established the factors that were predictive of successful stem cell harvests, including the dose of stem cells to be administered for successful engraftment. Defining this dose helped to ensure that engraftment of the infused stem cells would occur in the minimal time with the maximum chances of success. This reduced the time needed to support the patient during the period when their bone marrow was non-functional, so reducing the risk of serious infection and bleeding **[2]**.

Despite these major advances the use of BEAM plus ASCT only 'rescued' about 45% of patients. The remainder relapsed following autologous transplantation and had a dismal prognosis. Allogeneic transplantation (where the stem cells are from a donor rather than the patient's own) had demonstrated improved anti-lymphoma activity, an effect of the foreign stem cells that were infused to repopulate the bone marrow. However this procedure was too toxic in HL, with high mortality rates directly related to procedural toxicity. In addition, the donor stem cells mounted an immune response against not only the lymphoma, but other healthy tissues, so-called graft-versus-host disease (GvHD) which ranged from 45 to 60%. We introduced reduced intensity transplants (RITs) incorporating depletion of the harmful GvHD-inducing immune cells with alemtuzumab **[3]** but preserving those that had anti-lymphoma effects**.** This greatly reduced the toxicity and mortality associated with allogeneic transplantation. With safer transplants we were able to demonstrate the potential benefit of the allogeneic graft-versus-tumour effect in HL **[4]**.

Relapse of the patients' lymphoma became the primary cause for treatment failure. Researchers at UCL then pioneered the development of infusion of incrementally increasing doses of immune cells

from the donor (donor lymphocyte infusions, DLIs) at later time points following allogenic transplantation (when the risk of induction of GvHD is lower) as a means to reduce or treat disease relapse in HL **[5]**. These were combined with a novel strategy for monitoring patients for early signs of relapse following transplantation utilising positron emission tomography (PET) scanning **[6]**, enabling earlier delivery of DLIs. This combined approach delivered results that were significantly better than those seen in other countries, and has become standard practice throughout the UK. This difference has been widely ascribed to the novel strategy developed by UCL, relating both to the incorporation of T-cell depletion using the alemtuzumab antibody, and the strategy of post-transplant DLIs. Other countries are now evaluating similar strategies based on the research from UCL.

3. References to the research

[1] Linch DC, Winfield D, Goldstone AH, Moir D, Hancock B, McMillan A, Chopra R, Milligan D, Hudson GV. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. Lancet. 1993 Apr 24;341(8852):1051-4. http://dx.doi.org/10.1016/0140-6736(93)92411-L

[2] Watts MJ, Sullivan AM, Jamieson E, Pearce R, Fielding A, Devereux S, Goldstone AH, Linch DC. Progenitor-cell mobilization after low-dose cyclophosphamide and granulocyte colony-stimulating factor: an analysis of progenitor-cell quantity and quality and factors predicting for these parameters in 101 pretreated patients with malignant lymphoma. J Clin Oncol. (1997 Feb;15(2):535-46. http://jco.ascopubs.org/content/15/2/535.long

[3] Kottaridis PD, Milligan DW, Chopra R, Chakraverty RK, Chakrabarti S, Robinson S, Peggs K, Verfuerth S, Pettengell R, Marsh JC, Schey S, Mahendra P, Morgan GJ, Hale G, Waldmann H, de Elvira MC, Williams CD, Devereux S,Linch DC, Goldstone AH, Mackinnon S. In vivo CAMPATH-1H prevents graft-versus-host disease following nonmyeloablative stem cell transplantation. Blood. 2000 Oct 1;96(7):2419-25. http://dx.doi.org/10.1080/146532401753174025

[4] Peggs KS, Hunter A, Chopra R, Parker A, Mahendra P, Milligan D, Craddock C, Pettengell R, Dogan A, Thomson KJ, Morris EC, Hale G, Waldmann H, Goldstone AH, Linch DC, Mackinnon S. Clinical evidence of a graft-versus-Hodgkin's-lymphoma effect after reduced-intensity allogeneic transplantation. Lancet. 2005 Jun 4-10;365(9475):1934-41. http://dx.doi.org/10.1016/S0140-6736(05)66659-7

[5] Peggs KS, Thomson K, Hart DP, Geary J, Morris EC, Yong K, Goldstone AH, Linch DC. Dose-escalated donor lymphocyte infusions following reduced intensity transplantation: toxicity, chimerism, and disease responses. Mackinnon S. Blood. 2004 Feb 15;103(4):1548-56. http://dx.doi.org/10.1182/blood-2003-05-1513

[6] Lambert JR, Bomanji JB, Peggs KS, Thomson KJ, Chakraverty RK, Fielding AK, Kottaridis PD, Roughton M, Morris EC, Goldstone AH, Linch DC, Ell PJ, Mackinnon S. Prognostic role of PET scanning before and after reduced-intensity allogeneic stem cell transplantation for lymphoma. Blood. 2010 Apr 8;115(14):2763-8. http://dx.doi.org/10.1182/blood-2009-11-255182

4. Details of the impact

Our research since 1993 has developed new treatments for HL and has improved outcomes for patients who do not respond to conventional therapy. Firstly, we demonstrated the advantages of autologous stem cell transplantation, then refined this technique by establishing the correct dose range for the infused stem cells. Secondly, for the subset of these patients who subsequently relapsed after autologous stem cell transplantation, we pioneered allogenic stem cell

transplantation to exploit the graft versus tumour effect of foreign stem cells. In particular, we developed reduced intensity allogenic transplants (RITs), which are less toxic than standard allogenic transplants, and which could be boosted by additional infusion of donor cells once the graft was established.

High dose therapy and autologous transplantation, as developed at UCL, are currently the standard treatment for relapsed and resistant HL. This recommendation was confirmed in 2012 in the updated clinical practice guidelines of the National Comprehensive Cancer Network (USA) **[a]**, and remains the standard throughout Europe **[b]**. Peggs recently chaired the expert panel on behalf of British Committee for Standards in Haematology for the development of guidelines in relapsed and resistant HL, which confirmed this position in the UK **[c]**.

In the last five years approximately 880 patients with relapsed and resistant HL have been treated in the UK with ASCT **[d]** and we estimate that 400 patients have been cured. In Europe 9,500 patients with relapsed and resistant HL underwent ASCT 2006-10, most using the BEAM regimen **[e]**, with an estimated 4,300 cured.

Following the successful results published from UCL, the number of RITs in relapsed and resistant HL has steadily risen in the UK, from 14 per annum in 2003/4, to 38-44 by 2006/7, and 62-64 by 2010/11, a rise of over 300% **[d]**. This has also been the basis for the development of a prospective study in the UK (PAIReD), badged by both the NIHR Cancer Research Network (NCRN) and the British Society for Blood and Marrow Transplantation Clinical Trials Committee (BSBMT-CTC). Based on the outcomes achieved at our centre, we can predict that approximately 30-35 patients are cured per year in the UK as a result of the allogeneic RIT strategy (equivalent to 150-175 over a five-year period), and that this number will increase with earlier application in the treatment pathway.

As a result of the work at UCL, Peggs was asked to chair the BSBMT 'indications' panel for lymphomas. The indications-tables are used as a template for commissioning transplant services in the UK. Allogeneic transplantation is now designated a 'standard' therapy in patients with HL who have relapsed following ASCT, and as a 'clinical option' in those with primary resistant or relapsed disease who remain chemo-sensitive **[f]**. This ensures funding and equitable access to such therapies for all patients who might benefit from them across the UK.

5. Sources to corroborate the impact

[a] Morgan CH, et al. Hodgkin Lymphoma, Version 2.2012 Featured Updates to the NCCN Guidelines. JNCCN (2012) 10, 589-597. *The NCCN guideline confirms ASCT as the current standard therapy in chemo-sensitive relapsed or refractory Hodgkin lymphoma in North America.* (Copy available on request.)

[b] Sureda A. ESH/EBMT Handbook on Haematopoietic Stem Cell Transplantation: Ed. Apperley J, Carreras E, Gluckman E, Masszi T. Chapter 30 – HSCT for Hodgkin's lymphoma in adults. (2012). *The EBMT handbook also confirms ASCT as the current standard therapy in chemo-sensitive relapsed or refractory Hodgkin lymphoma in Europe.* http://www.ebmt.org/Contents/Resources/Library/EBMTESHhandbook/Pages/EBMT-ESH-handbook.aspx

[c] http://www.bcshguidelines.com/documents/classical_hodgkin_lymphoma_relapsed_combined.pdf. *The British Committee for Standards in Haematology (BCSH) 2013 guidelines confirm ASCT as the current standard therapy in chemo-sensitive relapsed or refractory Hodgkin lymphoma in the UK.*

[d] http://bsbmt.org/about-the-registry/ *Annual transplant activity figures are reported to the British Society for Blood and Marrow Transplantation and confirm the increased application of allogeneic transplantation.*

[e] Passweg JR, Baldomero H, Gratwohl A, Bregni M, Cesaro S, Dreger P, de Witte T, Farge-Bancel D, Gaspar B, Marsh J, Mohty M, Peters C, Tichelli A, Velardi A, de Elvira CR, Falkenburg F, Sureda A, Madrigal A; European Group for Blood and Marrow Transplantation (EBMT). The EBMT activity survey: 1990-2010. Bone Marrow Transplant. 2012 Jul;47(7):906-23. http://dx.doi.org/10.1038/bmt.2012.66. *Annual transplant activity figures are also reported to the European Bone Marrow Transplantation group, and reported according to disease and country.*

[f] http://bsbmt.org/wp-content/uploads/2012/03/Indications-Table-Updated-Feb-2012-Word-Version.pdf *The British Society for Blood and Marrow Transplantation provides guidance on indications for transplantation, which help to inform the commissioning process, and the most recent update (September 2013) confirms allogeneic transplantation is now considered a standard therapy in those with relapse following ASCT.*