Institution: University of Oxford

Unit of Assessment: UOA5

Title of case study:

The use of alemtuzumab in stem cell and organ transplantation

1. Summary of the impact

Alemtuzumab, a humanised therapeutic antibody, is a major addition to the repertoire of immunosuppressive agents used for organ and stem cell transplants. Administered as an induction agent in a short course of treatment, alemtuzumab reduces the incidence of graft rejection without preventing recovery of the patient's ability to fight infection. Alemtuzumab also decreases graft versus host disease, a vital factor in the treatment of aplastic anaemia and acute leukaemias. Furthermore, its important role in minimising immunosuppressive therapy helps prevent treatment-associated problems for the patient. Currently used off-licence for transplants, alemtuzumab improves patient survival and healthcare.

2. Underpinning research

Effective immunosuppression of the host immune system plays a pivotal role in the successful transplantation of organs or stem cells. While a successful transplant requires the patient's immune system to be suppressed, to minimise both short and long-term graft versus host disease (GVHD), the immune system must still retain its ability to reconstitute itself to fight infection. The humanised anti-CD52 monoclonal antibody alemtuzumab was created in Cambridge University in the 1980s but extensively developed as an immunosuppressant in the period 1994-2007 by Professor Herman Waldmann and colleagues after they moved to Oxford University. Short-term use of alemtuzumab depletes lymphocytes actively involved in causing GVHD and organ rejection, but allows the patient's haematopoietic stem cells to survive enabling immune recovery. Funding from the Medical Research Council and the USA-based companies LeukoSite Inc and ILEX Oncology enabled the production of clinical grade alemtuzumab in Oxford for use in clinical trials.

The efficacy of alemtuzumab in reducing the immune response to donor organs (minimising graft rejection) was demonstrated in a variety of settings, including kidney and liver transplants. In 1999 Professor Waldmann reported that while the use of alemtuzumab was of equivalent benefit to conventional triple therapy (cyclosporine or tacrolimus, azathioprine and prednisolone) in kidney transplants, it had the additional advantage of minimising treatment for the patient[1]. Later reports confirmed that alemtuzumab was safe and effective, allowing long-term remission, and was beneficial when compared to conventional triple therapy[2]. Its use during the induction period prior to transplant permitted low levels of cyclosporine A to be used for maintenance therapy, reducing treatment-associated adverse side effects.

The value of alemtuzumab was also highlighted in allogeneic stem cell transplants in diseases such as Hodgkin's lymphoma and myeloma[3]. Its use minimised the administration of toxic immunosuppressive drugs during the pre-transplant conditioning treatment whilst still resulting in durable long-term remission. The immunosuppressive activity did not significantly affect the transplanted stem cells responsible for repopulating, or engraftment of the immune system[4]. Yet another important aspect of alemtuzumab concerned its effectiveness at depleting lymphocytes through 'in the bag' techniques. The removal *ex vivo* of T cells using this technique outside the patient has been shown to be a simple and reliable method for the prevention of GVHD[5].

In 1995, Oxford University established a User Group consisting of bone marrow transplant centres from the UK, Europe, Israel, Australia and South Africa. This informal group met annually until 2007 and provided data from more than 4,264 patients to be pooled to develop effective treatment protocols[6]. Oxford also maintained the group databases, performing and reporting the beneficial and adverse effects of alemtuzumab.

3. References to the research

1. Calne R, Moffatt SD, Friend PJ, Jamieson NV, Bradley AJ, Hale G, Firth J, Bradley J, Smith KG, Waldmann H. (1999) CAMPATH-1H allows low-dose cyclosporin monotherapy in 31 cadaveric renal allograft recipients. Transplantation 68: 1613-1616. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10589966 ***First report of efficacy of alemtuzumab compared to conventional triple therapy in kidney transplants.***

2. Watson CJE, Bradley JA, Friend PJ, Firth J, Taylor CJ, Bradley JR, Smith KGC, Thiru S, Jamieson NV, Hale G, Waldmann H, Calne R. (2005) Alemtuzumab (CAMPATH 1H) Induction Therapy in Cadaveric Kidney Transplantation-Efficacy and Safety at Five Years. Am J Transplant 5: 1347-1353. doi: 10.1111/j.1600-6143.2005.00822.x ***A paper reporting results from a single centre study suggesting that alemtuzumab induction permitted satisfactory long-term patient and graft survival compared to that obtained using standard treatments, whilst avoiding problems associated with steroid therapy.***

3. Kottaridis PD, Milligan DW, Chopra R, Chakraverty RK, Chakrabarti S, Robinson S, Peggs K, Verfeuth S, Pettengell R, Marsh JCW, Schey S, Mahendra P, Morgan GJ, Hale G, Waldmann H, Ruiz de Elvira MC, Williams CD, Devereux S, Linch DC, Goldstone AH, Mackinnon S. (2000) In vivo CAMPATH-1H prevents graft-versus-host disease following nonmyeloablative stem cell transplantation. Blood 96: 2419-2425. Available from http://bloodjournal.hematologylibrary.org/content/96/7/2419 ***A reference describing the efficacy of alemtuzumab in patients with haematological malignancies who had been treated with reduced immunosuppressive treatment regimen prior to stem cell transplantation. The use of alemtuzumab was associated with durable engraftment and reduced GVHD and minimal treatment-associated toxicity.***

4. Hale G, Jacobs P, Wood L, Fibbe WE, Barge R, Novitzky N, du Toit C, Abrahams L, Thomas V, Bunjes D, Duncker C, Wiesneth M, Selleslag D, Hidajat M, Starobinski M, Bird P, Waldmann H. (2000) CD52 antibodies for the prevention of graft-versus-host disease and graft rejection following transplantation of allogeneic peripheral blood stem cells. Bone Marrow Transplant 26: 69-76. Available from http://www.nature.com/bmt/journal/v26/n1/full/1702477a.html ***Paper with 5 below, showing that in vitro T-cell depletion using alemtuzumab 'in the bag' reduced GVDH and increased rapid immune reconstitution, improving outcome in patients.***

5. Chakrabarti S, MacDonald D, Hale G, Holder K, Turner V, Czarnecka H, Thompson J, Fegan C, Waldmann H, Milligan DW. (2003) T-cell depletion with Campath-1H "in the bag" for matched related allogeneic blood stem cell transplantation is associated with reduced graft-versus-host disease, rapid immune reconstitution and improved survival. Br J Haematol. 121: 109-118. doi: 10.1046/j.1365-2141.2003.04228.x ***See Paper 4, above.***

6. Hale G, Cobbold S, Novitzky N, Bunjes D, Willemze R, Prentice HG, Milligan D, Mackinnon S, Waldmann H. (2001) CAMPATH-1 antibodies in stem-cell transplantation. Cytotherapy 3: 145-64. doi: 10.1080/146532401753173981 ***Meeting report of the users' group.***

Funding for research: Funding of approximately £6.3M until 2007 was awarded in grants from the Medical Research Council, and the USA-based companies LeukoSite Inc. and ILEX.

4. Details of the impact

The number of organ and stem cell transplants taking place is increasing year by year. In 2010, in the USA alone, 16,898 kidney and 6,291 liver transplants were performed[7] while in excess of 50,000 stem cell transplants are performed annually worldwide. Although more than 90% of renal transplants survive for one year, this figure drops to less than 50% after 10 years[8], thus emphasising the urgency for the availability of improved therapies for supporting transplant patients.

The increasing use of alemtuzumab (now manufactured by Genzyme), used off-label, continues to represent a major advance forward in the field of tissue transplantation. Used increasingly in the induction period, it is considered to be 'the most potent currently used lymphoid depleting antibody'[9].

The Users' Group meetings, organised by the University of Oxford and clinical teams involved in transplantation, have provided invaluable information that continues (i.e. post-2008) to be critical for the effective use of alemtuzumab. The establishment of this resource for clinicians, and the efficacy of the antibody, have resulted in alemtuzumab being recognised as an important therapeutic antibody not only for allogeneic organ transplants including kidney[10], heart[11] and intestinal transplants[12], but also in stem cell transplants in diseases such as lymphoma[13], acute leukaemia[14] and aplastic anaemia[15].

The use of alemtuzumab continues to have major impacts in the following areas:

- Improvements in the conditioning treatments used before stem cell transplants or as part of the induction period prior to organ transplantation. The use of alemtuzumab reduces the intensity of these regimes, with faster recovery of the immune system's ability to fight infection, and fewer adverse health problems, such as cancer, diabetes or bone disease.
- The promotion of improved survival of patients following transplantation due to reduced acute and chronic GVHD, and fewer deaths arising from infection.

The outcome of alemtuzumab use is a reduction in treatment-associated toxicity for the patient. Combined with its selective immunosuppressive properties, this has resulted in patients requiring less hospitalisation, and has increased access to cost-effective treatment.

Current treatment costs of the recognised off-licence use of alemtuzumab (brand name Campath, MabCampath, Campath-1H or Lemtrada) currently manufactured by Sanofi-Aventis/Genzyme are greatly reduced compared to many other transplant therapeutic regimens currently in use. For example, when used as an induction agent in kidney transplants, the cost of alemtuzumab is approximately £264 compared to £1684 - £3100 for other therapeutic monoclonal antibodies[16].

5. Sources to corroborate the impact

7. United States Census Bureau. The 2012 Statistical Abstract. Health & Nutrition. Available from: http://www.census.gov/compendia/statab/cats/health_nutrition/health_care_utilization.html ***Statistics on incidence of organ transplants from 1990-2009.***

8. Scientific Registry of Transplant Recipients. Annual Data reports. Available from: http://www.ustransplant.org/annual_reports/current/509a_ki.htm ***Survival statistics following renal transplants in the USA.***

9. Tan HP, Donaldson J, Basu A, Unruh M, Randhawa P, Sharma V, Morgan C, McCauley J, Wu C, Shah N, Zeevi A, Shapiro R. (2009) Two hundred living donor kidney transplantations under alemtuzumab induction and tacrolimus monotherapy: a 3-year follow-up. Am J Transplant 9: 355-366. doi: 10.1111/j.1600-6143.2008.02492.x ***Paper reporting the value of alemtuzumab in kidney transplants and describing it as the most potent currently used lymphoid depleting antibody (discussion paragraph 2, line 1).***

10. Hanaway MJ, Woodle SE, Mulgaonkar S, Peddi VR, Kaufman DB, Firist MR, Croy R, Holman J. (2011) Alemtuzumab inductions on renal transplantation. N Engl J Med 364: 1909-1914. doi: 10.1056/NEJMoa1009546 ***Paper describing 5-year results of a single centre study on kidney transplants confirming the efficacy of alemtuzumab used in induction therapy compared with standard triple immunosuppression while avoiding steroid therapy.***

11. Teuteberg JJ, Shullo MA, Zomak R, Toyoda Y, McNamara DM, Bermudez C, Kormos RL, McCurry KR. (2010) Alemtuzumab induction prior to cardiac transplantation with lower intensity

maintenance immunosuppression: One year outcome. Am J Transplant 10: 382-388. doi: 10.1111/j.1600-6143.2009.02856.x ***The inclusion of alemtuzumab in heart transplants results in increased freedom from graft rejection despite reduced therapy (including the use of steroids).***

12. Abu-Elmagd KM, Costa G, Bond GJ, Wu T, Murase N, Zeevi A, Simmons R, Soltys K, Sindhi R, Stein W, Demetris A, Mazariegos G. (2009) Evolution of the immunosuppressive strategies for the intestinal and multivisceral recipients with special reference to allograft immunity and achievement of partial tolerance. Transpl Int 22: 96-109. doi: 10.1111/j.1432-2277.2008.00785 ***Paper reporting that the use of alemtuzumab in visceral transplantation permitted improved graft success with 91% and 75% patients surviving after 1 and 5 years, respectively.***

13. Thomson KJ, Morris EC, Milligan D, Parker AN, Hunter AE, Cook G, Bloor AJC, Clark F, Kazmi M, Linch DC, Chakraverty R, Peggs KS, Mackinnon S. (2010) T-cell-depleted reduced intensity transplantation followed by donor leucocyte infusions to promote graft-versus-lymphoma activity results in excellent long-term survival in patients with multiply relapsed follicular lymphoma. J Clin Oncol 23: 3695-3700. doi: 10.1200/JCO.2009.26.9100 ***Paper describing the use of alemtuzumab in conditioning treatment prior to stem cell transplantation in follicular lymphoma.***

14. Shaw BE, Apperley JF, Russell NH, Craddock C, Liakopoulou E, Potter MN, Wynn R, Gibson B, Pearce RM, Kirkland K, Lee J, Madrigal JA, Cook G, Byrne JL. (2011) Unrelated donor peripheral blood stem cell transplants incorporating pre-transplant *in vivo* Alemtuzumab are not associated with any increased risk of significant acute or chronic graft-versus-host disease. Br J Haematol 153: 244-252. doi: 10.1111/j.1365-2141.2011.08615.x ***Paper describing the use of alemtuzumab in myeloid leukaemia and its efficacy in reducing GVHD.***

15. Marsh JC, Gupta V, Lim Z, Ho AY, Ireland RM, Hayden J, Potter V, Koh MB, Islam MS, Russell N, Marks DI, Mufti GJ, Pagliuca A. (2011) Alemtuzumab with fludarabine and cyclophosphamide reduces chronic graft-versus-host disease after stem cell transplantation for acquired aplastic anaemia. Blood 118: 2351-2357. doi: 10.1182/blood-2010-12-327536 ***Paper describing the value of (intravenous/subcutaneous) alemtuzumab in 50 patients with aplastic anaemia in reducing GVHD.***

16. Morgan R, O'Callaghan JM, Knight SR, Morris PJ. (2012) Alemtuzumab induction therapy in kidney transplantation: A systematic review and meta-analysis. Transplantation 93: 1179-1188. doi:10.1097/TP.0b013e318257ad41 ***Analysis of kidney transplants in 1233 patients in 10 trials.***