Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Improving treatments for non-Hodgkin lymphomas

1. Summary of the impact

Clinicians and scientists at UCL have been central to the design and management of single centre and multi-centre lymphoma trials within the UK and internationally. The trials have enabled a balanced approach to the non-Hodgkin lymphomas (NHL), supporting more conservative strategies in certain well-defined situations but also providing evidence for the value of very intensive therapy in appropriate patients. These trials have contributed to patient survival, quality of life and appropriate resource utilisation.

2. Underpinning research

The non-Hodgkin lymphomas (NHL) are malignancies of the cells of the lymphoid system. They are the sixth most common cause of cancer and the reported incidence has risen dramatically over the last 40 years. There are many different types of NHL with variable speeds of progression, response to treatment and ultimate cure rates. Broadly there are those that are aggressive but respond well to chemotherapy, including in many cases resulting in cure. Conversely there are variants that progress slowly, and although the chances of cure are small, patients can survive many years with their disease.

In aggressive NHL (Diffuse Large B-Cell Lymphomas; DLBCL), one of the commonest types of NHL, our major contribution has been to establish the role of autologous stem cell transplant (ASCT) in patients who relapse after primary chemotherapy. 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 patient's blood) **[1]**. This regime has been the mainstay of treatment for relapsed NHL since 1995. Our subsequent studies have confirmed that relapsed patients are the most appropriate candidates for ASCT as there is no advantage to using ASCT earlier in the treatment path **[2]**. Chemotherapy alone remains the optimal first-line treatment and we have shown that intensifying chemotherapy (the combination of cyclophosphamide, doxorubicin, vincristine and prednisolone with rituximab; R-CHOP) on a two-weekly as opposed to a less intensive three-weekly regimen **[3]** does not improve outcome. In a recent international trial (the CORAL trial) we demonstrated that after an autograft for relapsed and resistant DLBCL there is no added benefit of rituximab administered as maintenance therapy **[4]**.

In indolent NHL, we showed that for asymptomatic patients, a policy of watchful waiting allows chemotherapy to be postponed by an average of two and a half years with no reduction in survival rates **[5]**. This became standard care for the 30-40% of all follicular lymphoma patients who are asymptomatic at the time of diagnosis. Subsequently in 2010 we reported on results of a trial to compare rituximab therapy with watchful waiting. We found that treatment with rituximab has advantages over watchful waiting: at three years, 54% of patients in the watch-and-wait arm had required chemotherapy compared to only 18% in the rituximab arm and there was improved quality of life **[6]**. As a result, since this work was presented in abstract form in 2010, monotherapy with rituximab alone is now widely used in this situation.

Lastly, for patients who relapse after ASCT, we refined optimal usage of allogenic stem cell transplantation in NHL. Allogeneic transplantation (where the stem cells are from a donor rather than the patient's own) had been demonstrated to be associated with a graft-versus-lymphoma activity in a number of retrospective registry reviews performed by the European Group for Blood and Marrow Transplantation, an effect of the foreign stem cells that were infused to repopulate the bone marrow. However this procedure was too toxic in NHL, 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). We introduced reduced intensity transplants (RITs) incorporating depletion of the harmful GvHD-inducing immune cells with alemtuzumab but preserving those that had anti-lymphoma effects**.** This greatly reduced the toxicity and mortality associated with allogeneic transplantation **[7]**. In 2010, in the setting of relapsed follicular lymphoma, we showed that excellent results (not bettered anywhere world-wide) are achieved with RIT, augmented by donor lymphocyte transfusions, resulting in progression-free survival at four years of 76% (90% if there is a matched sibling donor) **[8]**.

3. References to the research

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[5] Ardeshna KM, Smith P, Norton A, Hancock BW, Hoskin PJ, MacLennan KA, Marcus RE, Jelliffe A, Vaughan G, Hudson, Linch DC. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. Lancet. 2003 Aug 16;362(9383):516-22. http://dx.doi.org/10.1016/S0140-6736(03)14110-4

[6] Ardeshna KM, Qian W, Smith P, Warden J, Stevens L, Pocock C, Miall F, Cunningham D, Davies J, Walewski J, Ferhanoglo AB,Bradstock K, Linch DC. An intergroup randomised trial of Rituximab vs a watch and wait strategy in patients with Stage II,III,IV, asymptomatic non-bulky follicular lymphoma (Grades I, II and IIIa). A preliminary analysis. Blood. 2010;116:21(Abstr 6) (Presidential Symposium)

[7] Thomson KJ, Morris EC, Bloor A, Cook G, Milligan D, Parker A, Clark F, Yung L, Linch DC, Chakraverty R, Peggs KS, Mackinnon S. Favorable long-term survival after reduced-intensity allogeneic transplantation for multiple-relapse aggressive non-Hodgkin's lymphoma. J Clin Oncol. 2009 Jan 20;27(3):426-32. http://dx.doi.org/10.1200/JCO.2008.17.3328

[8] Thomson KJ, Morris EC, Milligan D, Parker AN, Hunter AE, Cook G, Bloor AJ, Clark F, Kazmi M, Linch DC, Chakraverty R, Peggs KS, Mackinnon S. T-cell-depleted reduced-intensity transplantation followed by donor leukocyte infusions to promote graft-versus-lymphoma activity results in excellent long-term survival in patients with multiply relapsed follicular lymphoma. J Clin Oncol. 2010 Aug 10;28(23):3695-700. http://doi.org/fhcz6g

4. Details of the impact

Our research has changed the way patients with NHL are managed in the UK and worldwide. This work has resulted in improved patient survival, quality of life and appropriate resource utilisation.

In relapsed and resistant DLBCL our research has helped to establish the benefit of ASCT in this situation. The subsequent CORAL trial indicated that there was no benefit to post-ASCT rituximab maintenance therapy and this saves approximately £18,000 per patient. In the front line treatment of DLBCL, the finding that R-CHOP given every three weeks is as effective as the more intensive two-weekly R-CHOP, which requires growth factor support, has allowed discontinuation of this more expensive strategy.

In advanced follicular lymphomas, our research provided the trial data that has underpinned the policy of withholding chemotherapy until symptoms intervene. The advantage of this is to avoid toxicity of treatment. The subsequent evidence we provided of the effect of rituximab in these patients improved the treatment for these patients still further. These policies have been incorporated into UK guidelines, which state that: "*Observation remains an appropriate approach in patients with asymptomatic advanced stage follicular lymphoma in an attempt to delay the need for chemotherapy. This is particularly the case for patients over 70 years of age*" **[a]**. In the US, guidelines from the National Comprehensive Cancer Network state that: "*Observation may be appropriate in Stage I and II disease where potential toxicity of involved field radiotherapy outweighs potential clinical benefit*" and in patients with more advanced disease who are asymptomatic, "*Watchful waiting is the only approach advised*" **[b]**. The European Society for Medical Oncology also made similar recommendations in their 2010 guidelines **[c]**. Based on the incidence of indolent forms of NHL, since 2008 approximately 900 patients per year in the UK have been able to delay chemotherapy with its attendant toxicities **[d]**. This strategy also conserves resources without detriment to the patients. The average age of presentation of follicular lymphoma approaches 70 years of age, and up to 40% of surviving asymptomatic patients above this median age at presentation will not have need of any chemotherapy over the following 10 years **[e]**, a period during which competing causes of death will have intervened.

Our studies have established the role of allogeneic RITs in patients with relapsed and resistant lymphomas. The BCSH guidelines state that "*Reduced Intensity Conditioning allogeneic transplants should be considered for younger follicular lymphoma patients who have relapsed*" **[a]**, and a similar statement is contained in the European guidelines **[c]**. The US NCCN guidelines **[b]** advocate a similar approach and suggest that allogeneic stem cell transplants should be considered in selected cases such as those patients who have failed an autograft, did not mobilise sufficient stem cells for such a procedure or who had persisting bone marrow disease.

In summary, the establishment of allogeneic transplantation strategies in relapsed and resistant non-Hodgkin's lymphomas, both indolent and DLBCL, is undoubtedly saving lives. Based on European Group for Blood and Marrow Transplantation (EBMT) activity data for the period spanning 2006 to 2011 **[f, g]**, we estimate that 26,000 patients with NHL underwent autologous and 6,000 underwent allogeneic transplants. From prior EBMT publications on transplantation for lymphoma that 60% of these transplants were performed for indolent NHL or DLBCL. We can therefore estimate that approximately 6,500 patients with have been cured, and in the case of indolent lymphoma 2,000 patients have attained durable remissions, following autologous and allogeneic transplantation.

5. Sources to corroborate the impact

[a] British Committee for Standards in Haematology guidelines on: The Investigation and Management of Follicular Lymphomas. Found at: www.bcshguidelines.com. Our studies are extensively cited in this document.

[b] The US 2013 NCCN guidelines

http://www.nccn.org/professionals/physician_gls/f_guidelines.asp Copy available on request.

[c] Tilly H, Dreyling M; ESMO Guidelines Working Group. Diffuse large B-cell non-Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010 May;21 Suppl 5:v172-4. http://dx.doi.org/10.1093/annonc/mdq203

[d] http://www.cancerresearchuk.org/cancer-info/cancerstats/types/nhl/incidence/ (incidence) http://www.cancerresearchuk.org/cancer-info/cancerstats/types/nhl/treatment/#Indolent (treatment of indolent sub-types)

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This gives the state of the art in 2011 and our work is supported and highly referenced.

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