Institution: University of Oxford

Unit of Assessment: UOA5

Title of case study:

Effective treatment of chronic lymphocytic leukaemia

1. Summary of the impact

Research led by University of Oxford scientists has resulted in widespread use of the humanised therapeutic antibody, Campath (alemtuzumab), in patients with chronic lymphocytic leukaemia (CLL). Licensed by both the European and American regulatory authorities in 2004 for the treatment of CLL, Campath is used as first-line treatment for patients with aggressive forms of the disease and following relapse. It can induce long-term clinical remission even in cases resistant to other drugs. Campath has now been used in approximately 15,000 patients, and has generated revenues of approximately £750 million from the licensed treatment of CLL.

2. Underpinning research

B-cell chronic lymphocytic leukaemia (B-CLL) is the most common leukaemia in the Western world and a major health problem, accounting for 25% of leukaemias and with an annual incidence rate of 4.3 per 100,000 people. The US National Institutes of Health estimate that in the USA, 15,680 people will be diagnosed with, and 4,580 people will die of CLL in 2013.

Most commonly occurring over the age of 50, in 50% of patients CLL has an indolent clinical course that may not require treatment for many years. In the remaining patients, however, CLL progresses rapidly and does not respond to current therapy. The most frequent form of treatment is combination chemotherapy. There are, however, patients whose disease is treatment resistant and the majority of these patients die within one year. New treatment options are therefore imperative.

In the late 1990s and early 2000s, Professors Herman Waldmann and Geoff Hale at the University of Oxford, in collaboration with approximately fifty clinical teams worldwide, designed and coordinated a series of international clinical trials using Campath in CLL. In 1997, the researchers showed that Campath, through its action of targeting the CD52 antigen (absent on stem cells but present on normal cells and malignant white blood cells) was capable of eradicating minimal residual disease in CLL[1]. This early trial was critically dependent on Campath that was manufactured at the University of Oxford.

In 2002, a phase II trial involving the Oxford University team confirmed the efficacy of Campath as a first-line treatment for CLL[2]; and in 2004, Campath was shown to be an effective second-line treatment for patients who had relapsed following conventional treatment for CLL with fludarabine[3]. An important outcome from these trials was the demonstration that Campath could be administered subcutaneously rather than intravenously[2, 3].

As a result of the research driven by the University of Oxford team, Campath was approved as a first-line treatment for adult CLL in 2007[4]. Genzyme (now Sanofi-Aventis/Genzyme) and Bayer Healthcare obtained exclusive worldwide rights to market Campath.

3. References to the research

1. Dyer MJS, Kelsey SM, MacKay HJ, Emmett E, Thornton P, Hale G, Waldmann H, Newland AC, Catovsky D. (1997) In vivo "purging" of residual disease in CLL with CAMPATH-1H. Brit J Haematol. 97: 669-672. doi: 10.1046/j.1365-2141.1997.1062924.x ***First report that Campath is effective in removing residual tumour cells from patients.***

2. Lundin J, Kimby E, Bjorkholm M, Broliden P-A, Celsing F, Hjalmar V, Mollgard L, Rebello P, Hale G, Waldmann H, Mellstedt H, Osterborg A. (2002) Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukaemia (B-CLL). Blood 100: 768-773. doi: 10.1182/blood-2002-01-0159 ***Example of the use of Campath for the first-line (initial) treatment of CLL and the efficacy of its subcutaneous administration.***

3. Hale G, Rebello P, Brettman L, Fegan C, Kennedy B, Kimby E, Leach M, Lundin J, Mellstedt H, Moreton P, Rawstron A, Waldmann H, Osterborg A, Hillmen P. (2004) Blood concentrations of alemtuzumab and antiglobulin responses in patients with chronic lymphocytic leukaemia following intravenous or subcutaneous routes of administration. Blood 104: 948-955. doi: 10.1182/blood-2004-02-0593 ***Example of Campath (alemtuzumab) as a treatment for relapsed CLL that had failed prior treatment. The trial also demonstrated the clinical value of the subcutaneous administration of Campath.***

4. Websites describing the various international approvals for Campath in CLL.
National Cancer Institute. FDA Approval for Alemtuzumab. Available from: http://www.cancer.gov/cancertopics/druginfo/fda-alemtuzumab ***NCI confirms FDA approval for alemtuzumab in September 2007.***

BTG plc: Campath® approved for first-line use in Adult Leukemia. Available from: http://www.btgplc.com/page/4872/btg-plc-campathsup174/sup-approved-for-first-line-use-in-adult-leukemia ***Press release 20 Sep 2007 describing the approval of Campath for the first-line treatment of CLL.***

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4. Details of the impact

Campath is now a treatment of choice for many cases of CLL and for patients who have relapsed from their disease. It benefits patients and is cost-effective relative to other agents. Financially, its use in the treatment of CLL has generated substantial income for both the pharmaceutical industry and the university sector in the UK.

Benefit to patients with CLL
The specificity of Campath means it is well tolerated compared with conventional cytotoxic chemotherapy; it is effective at stabilising disease or inducing clinical remission; and it has been shown to improve survival and quality of life.

Campath's importance in the treatment of relapsed CLL has been reinforced by clinical trials showing that its use in combination with chemotherapy (e.g. fludarabine or methlyprednisolone) and/or rituximab in the treatment of patients with CLL who had failed all available therapies, resulted in more effective clinical responses and increased survival[5]. Other large international clinical trials studies have shown its efficacy as first-line treatment for those patients who have CLL[6-8], particularly with genetic abnormalities associated with a poor prognosis, such as those affecting the tumour suppressor protein p53[6]. The following quote from this reference states that Campath '*combined with methylprednisolone is the most effective induction regimen hitherto reported in TP53-deleted CLL'* [8]. Low dose monotherapy using subcutaneously administered Campath has also been shown to be efficacious in poor prognosis CLL[8]. Subcutaneously administrated Campath simplifies treatment, opens up the options for patients requiring maintenance therapy to control their disease, and reduces costs[8-9].

More than 70 papers and/or reviews have been published since 2008 reporting the efficacy of Campath in CLL and, as further evidence of its widespread use for the treatment of CLL, patient access programmes have been established in 50 countries. In September 2012 Campath was no

longer commercially available for the treatment of CLL, because the manufacturer, Sanofi-Aventis/Genzyme, made a decision to surrender the licence so that Campath could be licensed for the treatment of multiple sclerosis (under the new name Lemtrada)[10]. Under the US Campath Distribution Program, Campath is provided free of charge by Sanofi-Aventis/Genzyme to appropriate patients, to ensure that CLL patients have continued access to treatment[11]. Currently, Campath is being used to treat ~1,500 patients/year with CLL[12].

Financial benefit to the pharmaceutical and university sectors

The $60,000 per patient average cost of a Campath course of treatment for CLL brought in a total of $76M in 2011, with cumulative worldwide sales of approximately $268M between 2010 and 2012[12]. Therefore, the income for the UK during the REF period is substantial, with 2% going to the UK university sector (including Oxford University), 2% going to British Technology Group (BTG, a company assigned rights to Campath), and 2% to GlaxoSmithKline (Campath was originally licensed to Burroughs Wellcome, a company later merging to form part of GSK).

5. Sources to corroborate the impact

5. Stilgenbauer S, Zenz T, Winkler D, Buhler A, Schlenk R, Groner S, et al. (2009) Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: Clinical results and prognostic marker analyses from the CLL2H study of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 27: 3994-4001. doi: 10.1200/JCO.2008.21.1128 ***Report of the efficacy of the use of Campath in combination with chemotherapy in a large German multicentre trial.***

6. Pettitt AR, Jackson R, Carruthers S, Dodd J, Dodd S, Oates M, et al. (2012) Alemtuzumab in combination with methylprednisolone is a highly effective induction regimen for patients with chronic lymphocytic leukemia and deletion of TP53: Final results of the National Cancer Research Institute CLL206 Trial. J Clin Oncol. 30: 1647-1655. doi: 10.1200/JCO.2011.35.9695 ***Report of the efficacy of the use of Campath in combination with chemotherapy in a large UK multicentre trial.***

7. Montillo M, Tedeschi A, Petrizzi VB, Ricci F, Crugnola M, Spriano M, et al. (2011) An open-label, pilot study of fludarabine, cyclophosphamide and alemtuzumab in relapsed/refractory patients with B-cell chronic lymphocytic leukemia. Blood 118: 4079-4085. doi: 10.1182/blood-2011-05-351833 ***Report of the efficacy of the use of Campath in combination with chemotherapy in a large Italian multicentre trial showing its efficacy in inducing clinical remissions.***

8. Cortelezzi A, Pasquini MC, Gardellini A, Gianelli U, Bossi A, Reda G, et al. (2009) Low-dose subcutaneous alemtuzumab in refractory lymphocytic leukaemia (CLL): results of a prospective, single-arm multicentre study. Leukemia 23: 2027-2033. doi: 10.1038/leu.2009.148 ***Description of low dose monotherapy using subcutaneously administered Campath and its efficacy in poor prognosis CLL.***

9. Wierda WG, Kipps TJ, Keating MJ, Brown JR, Gribben JG, Browning M, et al. (2011) Self-administered subcutaneous alemtuzumab to treat residual disease in patients with chronic lymphocytic leukemia. Cancer 117: 116-24. doi: 10.1002/cncr.25379 ***Report that self-administered subcutaneous Campath was safe and effective for the treatment of residual disease.***

10. Staton T. Sanofi pulls Campath to clear way for higher-priced Lemtrada. FiercePharma; 2012 A http://www.fiercepharma.com/story/sanofi-pulls-campath-clear-way-higher-priced-lemtrada/2012-08-21 ***Pharma industry newsletter FiercePharma reporting the costs of Campath for CLL.***

11. Genzyme Corporation. US Campath Distribution Program. 2009. Available from: http://www.campath.com/ ***Website of the US Campath programme reporting the***

distribution programme enabling Campath to be provided free of charge to CLL patients from September 2012 (after Campath was renamed Lemtrada for treatment of multiple sclerosis).

12. Evaluate Ltd. Campath Worldwide Sales 2010/11 Overview. http://www.evaluategroup.com/Universal/View.aspx?type=Entity&entityType=Product&id=54873&IType=modData&componentID=1002 ***Website providing the cumulative sales of Campath 2010-2011.***