Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: HIV Associated Multicentric Castleman's Disease: Translating Biology to Improved Patient Survival

1. Summary of the impact (indicative maximum 100 words)

HIV associated plasmablastic multicentric Castleman's disease (MCD) has emerged as an uncommon disease over the last decade that is a significant cause of mortality in people living with HIV infection. Advances in our understanding of the epidemiology, virology and immunology of this disease led Professor Bower to recognise the potential for using targeted monoclonal antibody therapy. This has dramatically improved the survival of patients with MCD and is now advocated in the national treatment guidelines and is widely adopted in clinical practice globally. Moreover, the use of plasma Kaposi's sarcoma herpesvirus virus levels as a tumour marker for MCD has been developed.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor Mark Bower, Professor of Oncology (1997-present)
Professor Brian Gazzard, Professor of HIV Medicine at Chelsea and Westminster Hospital, Honorary with Imperial (1998-present)
Dr Mark Nelson, Consultant HIV Medicine at Chelsea and Westminster Hospital, Honorary Clinical Senior Lecturer (2001, 2007-present)
Professor Kikkeri Naresh, Professor Histopathology, Hammersmith Hospital, Honorary Professor (2003-present)

Although a few case reports of Multicentric Castleman's Disease (MCD) in people living with HIV were published in the 1990s, the discovery of Kaposi's sarcoma herpesvirus (KSHV) and the finding that it was present in the monotypic polyclonal plasmablasts that characterise MCD greatly improved the diagnostic consensus. The enhanced diagnostic accuracy by immunostaining for KSHV latent nuclear antigen (LANA) enabled Professor Bower and colleagues to establish the epidemiology of MCD and demonstrate that the incidence was rising following the improved treatment of HIV with combination antiretroviral therapy (cART) (1). This was in contrast to Kaposi sarcoma which although caused by the same virus, Professor Bower and others had shown was falling in incidence. This work was based on analyses of the Chelsea & Westminster Hospital HIV cohort (1984-2008) of over 10,000 people living with HIV with over 56,000 patient years of follow-up and was in collaboration with Professor Gazzard and Dr Nelson.

In 2002 the only published case series of MCD was from Paris and recorded a median survival of 14 months and the median survival of our own patients at that time was 8 months (2). Immunophenotypic investigation of the KSHV infected plasmablasts in lymph nodes affected by MCD undertaken both by other groups and in collaboration with Professor Naresh (revealed expression of CD20 which we identified as a potential therapeutic target (3, 4).

Imperial researchers first reported the use of Rituximab in a patient with HIV associated MCD leading to clinical regression of symptoms, radiological shrinkage of lymph nodes and declines in cytokines in 2004 (3). Subsequently, Professor Bower led a phase II multi-site clinical trial that established the place of Rituximab as a potent treatment for MCD. This clinical trial was performed with collaborators at St Bartholomew's Hospital and Royal Sussex County Hospital, Brighton (4). For the first time in a series of 21 consecutive patients a 2 year overall survival of 95% was recorded. We have also shown in subsequent studies that patients may be successfully treated at relapse with the same agent. We also identified high plasma levels of many host immune cytokines and KSHV derived virokines in patients with active MCD and that these levels decline with successful treatment of MCD (5).

A further aspect of the work that has been translated into clinical care is the identification of raised plasma levels of KSHV in patients with active disease allowing this measurement to act as a tumour marker for disease diagnosis, and to monitor disease activity. Indeed the use of this assay in follow-up can predict relapse of MCD allowing earlier therapy at relapse (6).

The advance in the clinical management of KSHV-associated MCD is one of the apotheoses of HIV medicine in the post cART era. Prior to the introduction of rituximab-based therapy, nearly half of all HIV seropositive patients with HHV8-associated MCD died within a year, whilst nowadays over 90% are alive 5 years following the diagnosis.

3. References to the research (indicative maximum of six references)

(1) Powles, T., Stebbing, J., Bazeos, A., Hatzimichael, E., Mandalia, S., Nelson, M., et al. (2009). The role of immune suppression and HHV-8 in the increasing incidence of HIV-associated multicentric Castleman's disease. *Ann Oncol*, 20 (4), 775-779. DOI. Times cited: 36 (as at 6th November 2013 on ISI Web of Science). Journal Impact Factor: 7.38

(2) Bower, M., Newsom-Davis, T., Naresh, K., Merchant, S., Lee, B., Gazzard, B., et al. (2011). Clinical Features and Outcome in HIV-Associated Multicentric Castleman's Disease. *J Clin Oncol*, 29 (18), 2481-2486. DOI. Times cited: 16 (as at 6th November 2013 on ISI Web of Science). Journal Impact Factor: 18.03

(3) Newsom-Davis, T., Bower, M., Wildfire, A., Thirlwell, C., Nelson, M., Gazzard, B., et al. (2004). Resolution of AIDS-related Castleman's disease with anti-CD20 monoclonal antibodies is associated with declining IL-6 and TNF-alpha levels. *Leuk Lymphoma*, 45 (9), 1939-1941. DOI. Times cited: 20 (as at 6th November 2013 on ISI Web of Science). Journal Impact Factor: 2.30

(4) Bower, M., Powles, T., Williams, S., Davis, T.N., Atkins, M., Montoto, S., et al. (2007). Brief communication: rituximab in HIV-associated multicentric Castleman disease. *Ann Intern Med*; 147(12):836-9. DOI. Times cited: 56 (as at 6th November 2013 on ISI Web of Science). Journal Impact Factor: 13.97

(5) Bower, M., Veraitch, O., Szydlo, R., Charles, P., Kelleher, P., Gazzard, B., et al. (2009). Cytokine changes during rituximab therapy in HIV-associated multicentric Castleman disease. *Blood*, 113 (19), 4521-4524. DOI. Times cited: 14 (as at 6th November 2013 on ISI Web of Science). Journal Impact Factor: 9.06

(6) Stebbing, J., Adams, C., Sanitt, A., Mletzko, S., Nelson, M., Gazzard, B., et al. (2011). Plasma HHV8 DNA predicts relapse in individuals with HIV-associated multicentric Castleman disease. *Blood*; 118(2):271-5. DOI. Times cited: 12 (as at 6th November 2013 on ISI Web of Science). Journal Impact Factor: 9.06

Key funding:

- Medical Research Council (MRC; 2004-2008; £700,000), Principal Investigator (PI) M. Bower, F. Gotch, B. Gazzard and C. Boshoff, KSHV infection and immunity.
- MRC (2009-2013; £1,128,355), PI M. Bower, F. Gotch, B. Gazzard and C. Boshoff, KSHV infection and immunity extension.
- St Stephen's AIDS Trust (2009; £5,000), PI M. Bower, Investigation of cytokines in Castleman's disease.
- Chelsea & Westminster Healthcare Trust (2012; £45,000), PI M. Bower, KSHV immunology study.

4. Details of the impact (indicative maximum 750 words)

Impacts include: health and welfare, practitioners and services, public policy and services
Main beneficiaries include: patients, practitioners, British HIV Association and international

guideline bodies

Multicentric Castleman's disease (MCD) is an infrequent lymphoproliferative disorder first described in 1954. The original reports were of a relatively indolent illness, however a more aggressive and disseminated form of the illness, plasmablastic MCD, was found in people living with HIV and is associated with the presence of KSHV in the pathological plasmablasts. These patients present with rapidly progressing life threatening systemic symptoms attributable to cytokine release and many require intensive care treatment. No standard treatment was established and combination antiretroviral therapy had no influence on the incidence or course of the illness with only half the patients surviving a year. Over the last decade due to the research described, the combination of pathophysiology based diagnostics and rational targeted therapy has dramatically improved survival.

Since the introduction of rituximab based therapy and the use of plasma KSHV viral quantification in diagnosis and monitoring of disease activity the overall survival of patients treated at the National Centre for HIV Malignancy at Chelsea and Westminster Hospital (the largest cohort of MCD patients in the UK) has improved by almost 60%. For 49 patients treated with the Rituximab based approach since 2003, the overall survival at 5 years was 90% compared to 33% in the 12 patients treated before Rituximab was introduced [1]. These survival rates were supported by groups in France (5 year survival of 90% following rituximab treatment, compared with 47% in patients treated without rituximab) and Germany (confirmed the improvement in survival when rituximab was included in the treatment strategy [2, 3].

An additional benefit of the use of rituximab is a significant decrease in the risk of developing lymphoma in patients with HHV8-associated MCD treated with rituximab that was first observed at Imperial and was confirmed in France [2]. This remarkable breakthrough in the management of MCD has been widely accepted and Professor Bower was invited by the American Society of Haematology to write a position statement (their "How I treat" series published in Blood on the management of HIV associated MCD) [4].

The treatment strategy has been adopted into national treatment guidelines. The only evidence-based treatment guidelines for HIV associated MCD are published by BHIVA (British HIV association) in 2008 and advocate the use of Rituximab in MCD [5]. The approach is also recommended in the UptoDate guidelines [6]. Review publications from US and Europe similarly recommend adopting this strategy in the management of MCD [7-9].

This bench to bedside translational research development has had an enormous impact on the survival of a relatively small number of patients globally; very few oncological advances in the last decade have had such a dramatic effect, doubling 5 year overall survival.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[1] Bower, M., Newsom-Davis, T., Naresh, K., Merchant, S., Lee, B., Gazzard, B., et al. (2011). Clinical Features and Outcome in HIV-Associated Multicentric Castleman's Disease. *J Clin Oncol*, 29 (18), 2481-2486. DOI.

[2] Gerard, L., Michot, J.M., Burcheri, S., Fieschi, C., Longuet, P., Delcey, V., et al. (2012). Rituximab decreases the risk of lymphoma in patients with HIV-associated multicentric Castleman disease. *Blood*, 119 (10), 2228-2233. DOI.

[3] Hoffmann, C., Schmid, H., Muller, M., Teutsch, C., van Lunzen, J., Esser, S., et al. (2011). Improved outcome with rituximab in patients with HIV-associated multicentric Castleman disease. *Blood*, 118 (13), 3499-3503. DOI.

[4] Bower, M. (2010). How I treat HIV-associated multicentric Castleman disease. *Blood*, 116 (22), 4415-4421. DOI.

[5] Bower, M., Collins, S., Cottrill, C., Cwynarski, K., Montoto, S., Nelson, M., et al. (2008). British HIV Association guidelines for HIV-associated malignancies 2008. *HIV Med*, 9 (6), 336-388 http://www.bhiva.org/Malignancies2008.aspx. Archived on 6th November 2013.

[6] Up-to-date guidelines: http://www.uptodate.com/contents/castlemans-disease. Archived on 6th November 2013.

[7] Sullivan, R.J., Pantanowitz, L., Casper, C., Stebbing, J., Dezube, B.J. (2008). HIV/AIDS: epidemiology, pathophysiology, and treatment of Kaposi sarcoma-associated herpesvirus disease: Kaposi sarcoma, primary effusion lymphoma, and multicentric Castleman disease. *Clin Infect Dis*, 47 (9), 1209-1215. DOI

[8] Oksenhendler, E. (2009). HIV-associated multicentric Castleman disease. *Curr Opin HIV AIDS*, 4 (1), 16-21. DOI.

[9] Reid, E., Nooka, A., Blackmon, J., Lechowicz, M.J. (2012). Clinical use of rituximab in patients with HIV related lymphoma and Multicentric Castleman's disease. *Curr Drug Deliv*, 9 (1), 41-51. DOI.