Institution: King's College London

Unit of Assessment: 1- Clinical Medicine

Title of case study: Better diagnosis and treatment for patients with myeloproliferative neoplasms

1. Summary of the impact

Myeloproliferative neoplasms (MPN) are a group of blood disorders that affect more than 9,000 people in the UK every year. King's College London (KCL) research on the biology, diagnosis and treatment of MPN has had the following significant impacts:

- International criteria for diagnosing MPN were revised to incorporate testing for specific mutations.
- The treatment of patients with two specific types of MPN, essential thrombocythaemia and myelofibrosis, has changed and been incorporated into national and international guidelines. Changes to treatment of essential thrombocythaemia are saving the NHS an estimated £20 million/year while the first specific therapy for myelofibrosis - a drug called ruxolitinib - has been introduced and is benefitting patients.
- International guidelines for the management of pregnant women with MPN have been changed based on KCL research.

2. Underpinning research

MPN: People with MPN make far too many blood cells, but these are mostly defective and not able to do their job properly. The specific type of MPN depends on whether too many red blood cells, white blood cells, or platelets are being made. As the number of extra blood cells increases, the patients run an increased risk of strokes, heart attacks and blood clots, as well as an increased risk of acute leukaemia. The result is that their quality of life deteriorates and they are likely to die early. Treatment is based on the type of MPN the patient has, since some are more aggressive than others. This means it is important to diagnose MPN correctly in order to plan treatment.

KCL research to improve the diagnosis of MPN: The research has been led by Professor Claire Harrison (KCL and Guy's and St Thomas' Hospitals [GSTT], 2001-present). Biological analyses originally performed by Professor Harrison at University College London Hospitals (UCLH) showed that essential thrombocythaemia, one of the six types of MPN, is not always a clonal disorder – it does not always derive from uncontrolled reproduction of a single aberrant cell, as previously thought (1). The research showed that when the cause of essential thrombocythaemia was non-clonal, patients had less risk of thrombosis.

After moving to KCL, Professor Harrison and her colleagues together with collaborators in Cambridge analysed the prevalence and clinical impact of genetic mutations in a large group of MPN patients (2,3,4). Samples were generated at KCL and in Cambridge, laboratory work was performed in Cambridge and jointly analysed at KCL. This research provided important biological insights regarding specific mutations in a protein called JAK, that led to changes to international diagnostic and treatment criteria.

Work directed by Professor Harrison with collaborators in Cambridge, and performed at KCL/GSTT, systematically analysed bone marrow biopsies from MPN patients. This research demonstrated critical inadequacies in the World Health Organization (WHO) diagnostic criteria in use at the time (5). The researchers also discovered novel prognostic features for predicting likely outcomes for patients (6).

Clinical trials that demonstrated superior treatments: The Medical Research Council Primary Thrombocythaemia 1 (MRC-PT1) trial which started in 1997 was developed at KCL/GSTT and in Cambridge. Professor Harrison joined the trial team as joint leader in 2001 (based at KCL), and has joint oversight of the trial and the scientific and clinical work arising from it. MRC-PT1 comprises three clinical trials, two of which are still ongoing. The first trial was reported in 2005 (7)

and showed that hydroxyurea and aspirin were superior to anagrelide and aspirin in treating high-risk essential thrombocythemia.

Novel treatment for myelofibrosis: KCL researchers led the European phase III trial COMFORT II, one of two first-ever phase III trials for drugs treating myelofibrosis, another MPN. This trial was among the most significant trials of novel drugs known as JAK (or janus kinase) inhibitors (8). Professor Harrison led study design, data collection, interpretation and publication of findings from this trial. The trial evaluated the JAK inhibitor ruxolitinib and showed it prolonged the life of patients with myelofibrosis. This was the first time that any drug had been shown to do this. The trial was reported in the *New England Journal of Medicine* in 2012 and directly contributed to the approval, in 2012, of ruxolitinib as the first targeted therapy for myelofibrosis.

Clinical research to improve the management of MPN in pregnancy: KCL researchers analysed half of all reported cases worldwide of another MPN, polycythaemia vera (9), as well as cases of idiopathic myelofibrosis (10), in pregnant women. They showed that there were appreciable negative health effects for both mother and foetus unless the mother received aggressive management to normalise blood parameters. They proposed a management strategy which has been adopted in treatment guidelines internationally.

3. References to the research

The work in papers 2–7 was carried out in collaboration with Cambridge University. Professor Harrison was co-chief investigator for the research published in papers 4-7. Co-author Dr Wilkins and Dr van der Walt are also at KCL/GSTT

1. **Harrison CN**, Gale RE, Machin SJ, Linch DC. A large proportion of patients with a diagnosis of essential thrombocythemia do not have a clonal disorder and may be at lower risk of thrombotic complications. *Blood* 1999;93:417–24.

2. Campbell PJ, Scott LM, Buck G, Wheatley K, East CL, Marsden JT, Duffy A, Boyd EM, Bench AJ, Scott MA, Vassiliou GS, Milligan DW, Smith SR, Erber WN, Bareford D, Wilkins BS, Reilly JT, **Harrison CN**, Green AR; United Kingdom Myeloproliferative Disorders Study Group; Medical Research Council Adult Leukaemia Working Party; Australasian Leukaemia and Lymphoma Group. Definition of subtypes of essential thrombocythaemia and relation to polycythaemia vera based on JAK2 V617F mutation status: a prospective study. *Lancet* 2005;366:1945–53.

3. Scott LM, Tong W, Levine RL, Scott MA, Beer PA, Stratton MR, Futreal PA, Erber WN, McMullin MF, **Harrison CN**, Warren AJ, Gilliland DG, Lodish HF, Green AR. JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. *N Engl J Med*. 2007;356:459–68.

4. Campbell PJ, Baxter EJ, Beer PA, Scott LM, Bench AJ, Huntly BJ, Erber WN, Kusec R, Larsen TS, Giraudier S, Le Bousse-Kerdilès MC, Griesshammer M, Reilly JT, Cheung BY, **Harrison CN**, Green AR. Mutation of JAK2 in the myeloproliferative disorders: timing, clonality studies, cytogenetic associations, and role in leukemic transformation. *Blood* 2006;108:3548–55.

5. Wilkins BS, Erber WN, Bareford D, Buck G, Wheatley K, East CL, Paul B, **Harrison CN**, Green AR, Campbell PJ. Bone marrow pathology in essential thrombocythemia: interobserver reliability and utility for identifying disease subtypes. *Blood* 2008;111:60–70.

6. Campbell PJ, Bareford D, Erber WN, Wilkins BS, Wright P, Buck G, Wheatley K, **Harrison CN**, Green AR. Reticulin accumulation in essential thrombocythemia: prognostic significance and relationship to therapy. *J Clin Oncol*. 2009;27:2991–9.

7. **Harrison CN**, Campbell PJ, Buck G, Wheatley K, East CL, Bareford D, Wilkins BS, van der

Walt JD, Reilly JT, Grigg AP, Revell P, Woodcock BE, Green AR; United Kingdom Medical Research Council Primary Thrombocythemia 1 Study. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. *N Engl J Med*. 2005;353:33–45.

8. **Harrison C**, Kiladjian JJ, Al-Ali HK, Gisslinger H, Waltzman R, Stalbovskaya V, McQuitty M, Hunter DS, Levy R, Knoops L, Cervantes F, Vannucchi AM, Barbui T, Barosi G. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med*. 2012;366:787–98.

9. Robinson S, Bewley S, Hunt BJ, Radia DH, **Harrison CN**. The management and outcome of 18 pregnancies in women with polycythemia vera. *Haematologica* 2005;90:1477–83.

10. Tulpule S, Bewley S, Robinson SE, Radia D, Nelson-Piercy C, **Harrison CN**. The management and outcome of four pregnancies in women with idiopathic myelofibrosis. *Br J Haematol*. 2008;142:480–2.

4. Details of the impact

Marked improvements in diagnosis and treatment for people with MPN: Improved diagnosis and treatment of MPN are the greatest impacts resulting from this research. The existing WHO diagnostic criteria for these disorders were difficult to interpret and were not applied consistently by haemato-pathologists. KCL research contributed to changes in UK, European and WHO guidelines for diagnosis as well as treatment. The research has also lowered the costs of therapy, improved management of MPN in pregnancy, and raised public awareness of MPN and MPN treatments.

Findings used to improve international diagnostic criteria: The studies carried out by the KCL team together with collaborators in Cambridge have radically changed the understanding (11) of MPN - as neoplasms or clonal cancers rather than simply “disorders” - and identified specific mutations and subtypes. As a direct result, WHO improved and expanded its diagnostic criteria for MPN, incorporating the JAK2 V617F mutation testing into diagnostic processes (12). More accurate diagnosis directly affects patients, as correct diagnosis ensures that they receive appropriate treatment and prognosis. Refining diagnostic criteria and the criteria for assessing improvements (response criteria) also leads to better standardisation of clinical trials, and makes it easier to compare treatments.

Treatment guidelines influenced by KCL research: Findings of the long-term Medical Research Council clinical trial MRC-PT1, which assessed the value of a new treatment for essential thrombocythaemia (ET), demonstrated that hydroxycarbamide with aspirin should be the first line of treatment for ET rather than a newer, more expensive drug, anagrelide. These have been incorporated into national and international treatment guidelines (13,14,15,16).

New class of drugs developed for myelofibrosis and first JAK inhibitor approved: Trials of a new class of drugs, JAK inhibitors, prompted by the findings of the biological studies have paved the way for targeted therapies. The KCL-led phase III trial, COMFORT II, showed that the JAK inhibitor ruxolitinib prolonged the life of patients with myelofibrosis (8). This is a major advance because patients with myelofibrosis have the most symptoms and the worst prognosis among the different MPN. The US Food and Drug Administration (FDA) approved ruxolitinib in November 2011 and Europe approved it in 2012 (17,18). Ruxolitinib is the first approved medication for myelofibrosis.

Lower costs for health systems: The research showing that hydroxycarbamide is a more effective treatment than the more expensive drug anagrelide for essential thrombocythemia (7) has altered management of this disease and been estimated to save the NHS alone around £20 million/ year (£20k pa treatment costs and a conservative estimate of 1000 high risk ET patients). Since these changes have been incorporated into international guidelines, this also means lower

costs internationally.

Improved management of pregnant women with MPN: The work of KCL researchers on pregnant women with polycythaemia vera and myelofibrosis resulted in a new management strategy that has been taken up in treatment guidelines nationally and internationally (13,14,15,16). The KCL researchers were also instrumental in setting up a European Union-wide reporting process to gather information on MPN in pregnancy, with the aim of improving outcomes.

Improved awareness of MPN and patient advocacy: Professor Harrison and her colleague at GSTT Dr Deepti Radia set up MPD Voice (19, 20), the UK patient advocacy group for MPN to educate both physicians and patients. MPD Voice has over 1500 members and the website receives over 100,000 hits a year.

5. Sources to corroborate the impact

Improvements in diagnosis

11. Barosi G, Birgegard G, Finazzi G, Griesshammer M, Harrison C, Hasselbalch HC, Kiladjian J-J, Lengfelder E, McMullin MF, Passamonti F, Reilly JT, Vannucchi AM and Barbui T. Response criteria for essential thrombocythemia and polycythemia vera: result of a European LeukemiaNet consensus conference. *Blood* 2009;113:4829–33. (Cites ref [7] p. 4829, 4831)

12. Vardiman JW, Thiele J, Arber DA *et al*. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood* 2009;114:937–51. (Cites ref [3] p.940, ref [5] p.941))

International guidelines influenced by the work of KCL researchers

13. Barbui T, Barosi G, Birgegard G *et al.* Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet*. J Clin Oncol.* 2011;29:761–70. (Cites ref [6] p.762, ref [7] p.764)

14. Reilly JT, Mcmullin MF, Beer PA *et al.* Guideline for the diagnosis and management of myelofibrosis*. Br J Haematol.* 2012;158:453-71 (Cites ref [5] p.454; ref [7] p. 460, ref [8] p.464, ref [10] p.464).

15. Harrison CN, Bareford D, Butt N *et al.* Guideline for investigation and management of adults and children presenting with a thrombocytosis*. Br J Haematol* 2010;149:352–75.

16. Mcmullin MF, Reilly JT, Campbell P *et al.* Amendment to the guideline for diagnosis and investigation of polycythaemia/erythrocytosis*. Br J Haematol* 2007;138:821–22.

FDA and European approval for ruxolitinib as a treatment for myelofibrosis

17. US Food and Drug Administration. 2011. FDA approves first drug to treat a rare bone marrow disease. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm280102.htm

18. UK Medicines Information. 2012. New Drugs Online Report for ruxolitinib. http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=4830

Public-facing communication about MPN

19. MPD Voice is a registered UK charity under the auspices of Guy's and St Thomas' Charity. www.mpdvoice.org.uk

20. Spotlight on MPN - an international website on myeloproliferative neoplasms, intended for patients and caregivers. http://www.spotlightonmpn.com/sompn/MPN/symptoms-and-management/what-are-the-symptoms.aspx