Institution:
University of Cambridge

Unit of Assessment:
UoA1

Title of case study:
Defining first line therapy for high risk essential thrombocythemia

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

Essential thrombocythemia (ET) is a pre-leukaemic chronic myeloproliferative neoplasm (MPN) the management of which had been hampered by a lack of prospective randomised studies. Professor Green (University of Cambridge Department of Haematology) was Chief Investigator for the MRC primary thrombocythemia-1 (PT-1) study, initiated in 1997, which compared hydroxyurea plus aspirin with anagrelide plus aspirin in patients with ET at high risk of thrombosis. This clinical trial remains the world's largest randomised study of any MPN and its results demonstrated that hydroxyurea plus aspirin should be first line therapy, a result embedded in current guidelines. This outcome had a major effect on the world-wide use of anagrelide for patients with ET and is estimated to have saved the NHS over £22M per year in drug costs since the results of the trial were published in the NEJM.

2. Underpinning research (indicative maximum 500 words)

Professor Green (Department of Haematology, University of Cambridge 1991-date) has been chief investigator for the PT-1 suite of clinical trials since their inception in 1997, a role initially shared with Professor Tom Pearson and, following his retirement, with Dr Claire Harrison (both Dept of Haematology, St Thomas' Hospital). The study of patients at high risk of thrombosis remains the world's largest randomised trial of any MPN, having recruited over 800 patients from 138 centres in three countries. Low and intermediate risk PT-1 studies (also led by Professor Green) have been on-going since, each representing the world's largest study in their respective risk categories.

Prior to the high-risk PT-1 trial (NEJM 2005), use of the inexpensive drug hydroxyurea was being widely replaced by the newer and considerably more expensive drug anagrelide, an agent which selectively blocks megakaryocyte differentiation. Anagrelide had received FDA approval despite lack of evidence of efficacy from a randomised trial. Professor Green negotiated a subvention from the Department of Health to support the considerable additional drug costs associated with a randomised comparison of hydroxyurea with anagrelide. This multicentre study opened in 1997 and closed in 2003. The primary end point was the risk of arterial thrombosis, venous thrombosis, serious haemorrhage or death from thrombotic or haemorrhagic causes. The results were presented in a plenary talk by Professor Green at the American Society of Hematology in 2004 and were published in the New England Journal of Medicine the following year (ref 1). The results demonstrated a clear superiority for hydroxyurea plus aspirin in that anagrelide plus aspirin was associated with higher rates of arterial thrombosis, serious haemorrhage, transformation to myelofibrosis and treatment withdrawal. This trial defined hydroxyurea and aspirin as first line therapy.

A substantial body of work from the Green lab has utilised samples and clinical data from patients enrolled in PT-1, and has generated additional insights into the classification, diagnosis and management of ET. These include the demonstration that (i) JAK2 mutation status identifies two distinct sub-types of ET (ref 2), (ii) transformation to acute myeloid leukaemia is frequently associated with unexpected 'loss' of the JAK2 mutation, an observation thought to reflect the existence of a 'pre-JAK2' phase of disease (e.g. ref 3); (iii) the concept that prefibrotic myelofibrosis is an entity distinct form ET is of questionable utility since diagnostic criteria cannot be applied reproducibly (refs 4 and 5); (iv) MPL mutations define a subset of ET patients with clinico-pathological features distinct to those with JAK2 mutation-positive ET (ref 6); (v) a haplotype including the JAK2 locus itself accounts for much of the inherited predisposition to JAK2 mutation-negative as well as JAK2 mutation-positive MPNs.

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

Reference to research:

1. 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**. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia**. N Engl J Med** 353: 33-45, 2005.

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**. Definition of subtypes of essential thrombocythaemia and relation to polycythaemia vera based on JAK2 V617F mutation status: a prospective study. **Lancet** 366: 1945-1953, 2005.

3. Campbell PJ, Baxter EJ, Beer PA, Scott LM, Bench AJ, Huntly BJ, Erber WN, Kusec R, Larsen TS, Giraudier S, Le Bousse-Kerdiles MC, Griesshammer M, Reilly JT, Cheung BY, Harrison CN and **Green AR**. Mutation of JAK2 in the myeloproliferative disorders: timing, clonality studies, cytogenetic associations and role in leukemic transformation. **Blood** 108 (10): 3548-3555, 2006.

4. 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**, 111: 60-70, 2008. **(*joint authors**).

5. 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**, 27: 2991-2999 2009.

6. Beer PA, Campbell PJ, Scott LM, Bench AJ, Erber WN, Bareford D, Wilkins BS, Reilly JT, Hasselbalch HC, Bowman R, Wheatley K, Buck G, Harrison CN, **Green AR**. MPL mutations in myeloproliferative disorders: analysis of the PT-1 cohort. **Blood,** 112: 141-149, 2008.

Research grant support:

LLR programme grant funding held continually since 1997 by Professor Green.
Most recent renewal 01.04.2008 – 31.03.2013, Molecular pathogenesis of myeloproliferative disorders, £2,230,206.

LLS Specialized Center of Research held continually by Professor Green since 2006.
Most recent renewal with co-applicants Dr B Huntly, Dr B Gottgens & Dr P Campbell 01.10.2011 – 30.09.2016, $6,250,000.

CRUK grant funding to support PT-1 held continually by Professor Green since 2007.
Most recent CRUK CTAAC 01.05.2008 – 31.03.2013, A collaborative study of myeloproliferative disorders (COSMYD) (with Dr PJ Campbell, MF McMullin, CN Harrison, K Wheatley), £462,865.

The Kay Kendall Leukaemia Fund, 01.09.2009 – 31.08.2012. Genome-wide characterization of somatic mutation in acute lymphoblastic leukaemia and myeloproliferative disorders (with co-applicants Professor M Greaves and Dr PJ Campbell). £1,632,075.

Cancer Research UK, project grant to Professor Green, 01.10.2011 – 30.09.2014. Investigation of interaction between germline and somatic genetics at the JAK2 locus in myeloproliferative neoplasms. £240,279

MRC support for PT-1 Clinical Trial, to Professor Green and Dr C Harrison, 01.05.2004 – 30.04.2006. £103,612

4. Details of the impact (indicative maximum 750 words)
Direct impact on patient management

The MRC high-risk PT-1 study (NEJM 2005) remains the world's largest randomised study of any MPN, defined first line therapy for patients with essential thrombocythemia and has been widely acknowledged as having had a major influence on the management of ET patients around the world (e.g. refs 1-4). Prior to the PT-1 trial, only a single much smaller randomised study of patients with ET had been reported, and this compared hydroxyurea with no cyto-reductive therapy. The approval of anagrelide by the FDA was having a major effect on prescribing patterns, with many clinicians using it as first line therapy despite the absence of randomised trial data. Publication of the results of the PT-1 trial firmly established hydroxyurea plus aspirin as first line therapy for patients with ET and a high risk of thrombosis (refs 1-6). The trial also demonstrated that anagrelide was less effective at reducing thrombosis than hydroxyurea, and was much less well tolerated, with twice as many patients withdrawing from treatment because of side effects. Importantly the PT-1 results showed that anagrelide increases the risk of myelofibrotic transformation and so, when anagrelide is used as a second-line agent, it is now recognised that patients need regular bone marrow trephine biopsies to look for the development of myelofibrosis. This trial defined hydroxyurea and aspirin as first line therapy, an outcome that is estimated to have saved the NHS over £22M per year in drug costs (based on cost of Anagrelide and hydroxyurea in 2005) and has influenced management of ET worldwide. The central role of the PT-1 study in defining current first-line therapy is described in multiple reviews (refs 1-4) and its findings were embedded in current national and international guidelines (e.g. refs 5 and 6) in 2010 and 2011, that remain current.

Impact on classification and diagnosis

Essential thrombocythemia has long been recognised to be a heterogeneous entity which overlaps with other MPNs, particularly polycythemia vera (PV) and primary myelofibrosis, but the demarcation between these various disorders was unclear. This led to difficulties in classifying individual patients and in determining optimum therapy. The banking of samples from the beginning of the PT-1 trial in 1997 combined with the collection of comprehensive prospective clinical data, generated a unique resource for studying the classification, diagnosis and pathogenesis of ET. Multiple studies by University of Cambridge researchers have utilised this resource over the past seven years, and the insights thus gained have altered the way ET is classified and how it is distinguished from other MPNs. Particular highlights with practical impact include: (i) the demonstration that JAK2 mutation status (now a routine diagnostic test; for example of usage see ref 7) identifies two distinct subtypes of ET with JAK2 mutation-positive patients resembling a *forme fruste* of PV – the realisation that JAK2-mutant ET forms a phenotypic spectrum with PV has led to simpler diagnostic algorithms that are embedded in guidelines (e.g. refs 5 and 6); (ii) the results of the PT1 trial also led to the concept that primary myelofibrosis in fact represents patients presenting in accelerated phase of an occult undiagnosed MPN; (iii) the demonstration that the WHO category "prefibrotic myelofibrosis" is not clearly distinguished from ET and may not exist as a distinct entity has resulted in a reduced requirement for bone marrow trephine histology in the BCSH diagnostic guidelines (ref 5); (iv) the demonstration that LDH levels are not useful in distinguishing ET from primary myelofibrosis; (v) the demonstration that reticulin levels provide an important prognostic marker in ET.

5. Sources to corroborate the impact (indicative maximum of 10 references)
Reviews that corroborate the impact of this research on clinical practice:

1. Barbui T, Finazzi MC, Finazzi G. Front-line therapy in polycythemia vera and essential thrombocythemia. Blood Rev, 26(5): 205-211, 2012.

2. Cervantes F. Management of essential thrombocythemia. Hematology AmSoc Hematol Educ Program 2011: 215-221, 2011.

3. Levine RL and Gilliland DG. Myeloproliferative disorders. Blood, 112(6): 2190-2197, 2008.

4. Tefferi A. Polycythemia vera and essential thrombocythemia: 2012 update on diagnosis, risk stratification and management. Am J Hematol, 87: 285-293, 2012

Guidelines that corroborate the impact of this research on clinical practice:

5. Harrison CN, Bareford D, Butt N, Campbell P, Conneally E, Drummond M, Erber W, Everington T, Green AR, Hall GW, Hunt BJ, Ludlam CA, Murrin R, Nelson-Piercy C, Radia DH, Reilly JT, Van der Walt J, Wilkins B, McMullin MF; British Committee for Standards in Haematology. Guideline for investigation and management of adults and children presenting with a thrombocytosis. Br J Haematol, 149(3): 352-375, 2010

6. Barbui T, Barosi G, Birgegard G, Cervantes F, Finazzi G, Griesshammer M, Harrison C, Hasselbalch HC, Hehlmann R, Hoffman R, Kiladjian JJ, Kröger N, Mesa R, McMullin MF, Pardanani A, Passamonti F, Vannucchi AM, Reiter A, Silver RT, Verstovsek S, Tefferi A. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. J Clin Oncol, 29(6): 761-770, 2011.

7. http://www.nbt.nhs.uk/sites/default/files/filedepot/incoming/JAK2_V617F_and_Exon_12_Service_at_BGL.pdf