Institution: Newcastle University

Unit of Assessment: UoA1

Title of case study: Innovations in the treatment of chronic myeloid leukemia have almost doubled 5-year survival rates.

1. Summary of the impact

A new class of drug known as tyrosine kinase inhibitors for the treatment of chronic myeloid leukemia (CML) has been tested in Newcastle-led international clinical trials. One of these drugs, imatinib, was found to almost double five-year survival rates and significantly improve quality of life with few side effects. Subsequent follow up studies found an estimated eight-year overall survival of 85%. Imatinib is now recommended in national and international guidelines and is used increasingly to treat patients with CML.

2. Underpinning research

Key Newcastle research staff

Professor Stephen O'Brien was the sole member of Newcastle University research staff involved. He was senior lecturer 1999-2010, and Clinical Professor of Haematology from 2010 to date.

The challenge of chronic myeloid leukaemia

Chronic myeloid leukaemia (CML), a cancer of the white blood cells, is characterised by overproduction of myeloid cells in the bone marrow. In around 90% of cases, it is caused by a genetic fault known as the Philadelphia chromosome, where the ABL gene is inadvertently translocated to the BCR gene on another chromosome, creating the fusion gene BCR-ABL, a dysregulated tyrosine kinase responsible for the disease (see R1).

CML is relatively rare, with a prevalence of 2500 new cases a year in England (EV f). It is often asymptomatic or presents with generic symptoms such as weight loss and headaches. As a consequence, CML is often only diagnosed as a result of a blood test. At the onset of research described below, the prognosis for the disease was relatively poor, with a five-year survival rate of 57% in patients given interferon alpha plus cytarabine (see R1). The only cure is bone marrow transplant, but this carries substantial risks and, in any event, is an option in only 25% of patients (see R1).

The development of imatinib

Clinical development of tyrosine kinase inhibitors (TKIs) directed at the cancer-causing gene BCR-ABL began in the 1990s. The first phase 3 trial was the IRIS trial (ClinicalTrials.gov number NCT00006343). Professor Stephen O'Brien was the lead investigator for this study, which was conducted in 106 centres in 16 countries. The first paper to be published (R1) compared imatinib to interferon alpha plus cytarabine (the previous standard of care) in 1106 patients. As well as being better tolerated, imatinib produced significantly higher rates of cytogenetic response, where the Philadelphia chromosome disappears (87.1% vs 34.7%). A five-year follow up study (R2) found an estimated 89% survival rate at 60 months, with few side effects. The eight-year follow-up study (R3) found that 92% of patients given imatinib and who continued treatment were free from progression to accelerated-phase or blast crisis phase, and overall survival was estimated to be 85%; if causes of death other than CML are excluded, then overall survival was estimated to be 93% at eight years.

Further work (R4) investigated the link between eventual outcome and early response to imatinib. Results showed that a major cytogenetic response – where bone marrow cells have returned to normal and no longer have the Philadelphia chromosome – was predictive of long-term event-free survival. Specifically, patients who achieved major cytogenetic response within 18 months showed no progression to the advanced phases of CML, and seven-year event-free survival was 95% in these patients.

3. References to the research (Scopus citation data as at July 2013, Newcastle researchers in **bold**)

R1. **O'Brien SG**, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, Cornelissen JJ, Fischer T, Hochhaus A, Hughes T, Lechner K, Nielsen JL, Rousselot P, Reiffers J, Saglio

G, Shepherd J, Simonsson B, Gratwohl A, Goldman JM, Kantarjian H, Taylor K, Verhoef G, Bolton AE, Capdeville R, Druker BJ. Imatinib Compared with Interferon and Low-Dose Cytarabine for Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia. 2003. *The New England Journal of Medicine*. 348 (11):994-1004. DOI: 10.1056/NEJMoa022457. **Citation count 1746**

R2. Druker BJ, Guilhot F, **O'Brien SG**, Gathmann I, Kantarjian H, Gattermann N, Deininger MW, Silver RT, Goldman JM, Stone RM, Cervantes F, Hochhaus A, Powell BL, Gabrilove JL, Rousselot P, Reiffers J, Cornelissen JJ, Hughes T, Agis H, Fischer T, Verhoef G, Shepherd J, Saglio G, Gratwohl A, Nielsen JL, Radich JP, Simonsson B, Taylor K, Baccarani M, So C, Letvak L, Larson RA. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. 2006. *The New England Journal of Medicine* 355(23):2408-17. DOI: 10.1056/NEJMoa062867. **Citation count 1440.**

Newcastle contribution: Professor O'Brien was heavily involved in the design of the original study, recruited patients and contributed data. Crucially, together with Professors Druker, Guilhot and Larson, he was part of the Study Management Committee (SMC) for this trial. The SMC managed to study and approved all crossovers.

R3. Deininger M, **O'Brien SG**, Guilhot F, Goldman JM, Hochhaus A, Hughes TP, Radich JP, Hatfield AK, Mone M, Filian J, Reynolds J, Gathmann I, Larson RA, Druker BJ. International Randomized Study of Interferon Vs STI571 (IRIS) 8-Year Follow up: Sustained Survival and Low Risk for Progression or Events in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Treated with Imatinib. 2009. *Blood*: 51st Annual Meeting of the American Society of Hematology. 114 (22): 462. Peer-reviewed conference abstract. https://ash.confex.com/ash/2009/webprogram/Paper23968.html.

Newcastle contribution: Prof O'Brien was heavily involved in the design of the original study, recruited patients and contributed data. Together with the other authors of the SMC, Professor Deininger and colleagues from Novartis, Professor O'Brien led the data analysis for this abstract/presentation.

R4. Hughes TP, Hochhaus A, Branford S, Müller MC, Kaeda J, Foroni L, Druker BJ, Guilhot F, Larson RA, **O'Brien SG**, Rudoltz MS, Mone M, Wehrle E, Modur V, Goldman JM, Radich JP. Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS). 2010. Blood 116: 3758-3765. DOI: 10.1182/blood-2007-10-116475 **Citation count 133.**

Newcastle contribution: Prof O'Brien was heavily involved in the design of the original study, recruited patients and contributed data. As above, he was a member of the SMC who contributed to the data analysis, presentation and manuscript writing and revision.

Relevant funding awards

- The work was supported by ten awards from Novartis Pharmaceuticals UK, totalling **£752,179**

4. Details of the impact

Impact of Newcastle research on patient survival and quality of life

The drug has led to a near doubling of patient survival rate (R3), which was reported in two national and European guidelines. In 2010, the European Society for Medical Oncology published Clinical Practice Guidelines (EV a) that include R1 and R2, stating, "*The update of the IRIS study has confirmed and extended the earlier results, reporting a progression-free survival of 84% and an overall survival of 88% after 6 years*."

These results are also reported in NICE Technology Appraisal 251 (EV b), which states:

"*Standard-dose imatinib is associated with improved survival, with the latest results of the*

follow-up of the IRIS (International Randomised Study of Interferon versus STI571) trial (8-year follow-up) [R3] *showing overall survival of 85%. After the introduction of imatinib into routine clinical practice, 5-year relative survival increased from 27.1% in 1990–92 to 48.7% in 2002–04, for all age groups combined (p<0.0001)*".

A January 2013 report from the National Cancer Intelligence Network (EV c) showed that deaths from CML in men reduced from 163 in 2001-2003 to 105 in 2006-2008. This report confirms that the increase in survival is due to the introduction of imatinib: "*The improvement in prognosis seen is due to the introduction of a new drug – Imatinib which was being used increasingly to treat patients with CML.*"

According to a 2011 study (EV d), imatinib is well-tolerated and has few side-effects. This study used the cancer-specific questionnaire FACT-BRM (functional assessment of cancer therapy-biologic response modifiers) to assess patient quality of life, including physical function and well-being. The mean score increased significantly from 75.5 at baseline to 85.2 at six months, where an increase of >5 represents a clinically significant improvement. Scores for fatigue, emotional and cognitive dysfunction and side effects all decreased significantly from baseline to six months.

Impact of Newcastle research on guidelines

The use of imatinib is recommended in two European guidelines and UK-wide NICE guidelines. Clinical Practice Guidelines from 2010 (EV a), published by the European Society for Medical Oncology, (ESMO) state "*On the basis of a randomized trial of imatinib… (IRIS study,* [R1, 2]), *imatinib 400 mg daily has been established as standard, frontline treatment of all patients with CP CML*." The updated ESMO guidelines from 2012 (EV e) directly cite R1 and R2 as two of the "*high quality reports of phase 2 and phase 3 studies, single-arm, and randomized, that have been published in peer-reviewed journals over the last 10 years*" that inform the guidelines: of these, R1 was the first to be published. These guidelines recommend imatinib, stating "*Imatinib was the first TKI to be used and is still the gold standard of first-line treatment worldwide.*"

Imatinib is recommended in NICE Technical Appraisal 251 (EV f), published in April 2012. The evidence that informs this report includes two papers (Saglio *et al.*, DOI: 10.1056/NEJMoa0912614 and Kantarjian *et al.* DOI: 10.1056/NEJMoa1002315 both 2010 *N Eng J Med*) that are based on Newcastle research: the former cites R2, and the latter cites both R1 and R2.

The Technical Appraisal states:

- "*…the progression of CML can be slowed by imatinib. Imatinib produces high rates of remission in the chronic phase*." (pg 3)
- "*The primary outcome was complete cytogenetic response within 12 months.*" (pg 10)
- "*The primary outcome was major molecular response at 12 months. Secondary outcomes included complete cytogenetic response by 12 months.*" (pg 11, from Saglio *et al.*)
- "*Standard-dose imatinib is recommended as an option for the first-line treatment of adults with chronic phase Philadelphia-chromosome-positive chronic myeloid leukaemia (CML)*," (pg 53, from Kantjarian *et al.*)

In summary, Newcastle research found that imatinib had a higher cytogenetic response and was better tolerated than the previous standard of care. This work almost doubled five-year survival rates, improved patient quality of life and adoption of the drug into guidelines.

5. Sources to corroborate the impact

EV a. Baccarani M and Dreyling M. (2010). Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 21 Suppl 5:v165-7. doi: 10.1093/annonc/mdq201. http://annonc.oxfordjournals.org/content/21/suppl_5/v165.full.pdf

EV b. NICE Technology Appraisal Guidance 251 April 2012.

http://www.nice.org.uk/nicemedia/live/13716/58911/58911.pdf

EV c. National Cancer Intelligence Network report January 2013. www.ncin.org.uk/view?rid=1787

EV d. Aziz Z, Iqbal J, Aaqib M, Akram M, Saeed A. (2011) Assessment of quality of life with imatinib mesylate as first-line treatment in chronic phase-chronic myeloid leukemia. *Leukaemia and lymphoma*. 52(6):1017-23. doi: 10.3109/10428194.2011.560310.

EV e. Baccarani M, Pileri S, Steegmann JL, Muller M, Soverini S, Dreyling M. (2012). Chronic myeloid leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. Suppl 7:vii72-7. doi:10.1093/annonc/mds228. http://annonc.oxfordjournals.org/content/23/suppl_7/vii72.full.pdf+html

EV f. NICE technology appraisal guidance 241 January 2012.

http://publications.nice.org.uk/dasatinib-nilotinib-and-standard-dose-imatinib-for-the-first-line-treatment-of-chronic-myeloid-ta251/evidence-and-interpretation