Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Clinical Development of Temozolomide: An Anticancer Drug that Improves Survival of Patients with Brain Cancer (Glioma)

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

Temozolomide is a major UK anti-cancer drug development success story. Following chemical synthesis at Aston University, early clinical evaluation of temozolomide carried out at Imperial College optimised how temozolomide was scheduled and delivered to patients to ensure maximum efficacy balanced acceptable side effects. Imperial's early trials demonstrated how the drug could be used effectively to treat patients with a type of brain cancer, glioma, and was pivotal to its subsequent market licensing. ESMO and NICE guidelines recommend temozolomide for use in patients with recurrent glioma and for patients with newly diagnosed Grade IV glioma. Glioma is a relatively rare cancer yet annual sales of temozolomide have been in excess of £900 million per year since 2009. Temozolomide given during and following radiotherapy is now standard of care for glioma and has improved survival compared to previous treatments or radiotherapy alone.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor Ed Newlands, Professor of Cancer Medicine (1974-2004)
Professor Mark Bower, Professor of Oncology (1997-present)
Professor Pat Price, Clinical Professor (1989-2000), Honorary Professor (2001-present)
Dr Cathryn Brock, Research Fellow (1994-1998), Consultant Medical Oncologist Charing Cross Hospital (2003-2013), Honorary Clinical Senior Lecturer (2008-present)

Following chemical synthesis of temozolomide by colleagues at Aston University, in the early 1990s Professor Newlands and colleagues at Imperial continued the preclinical evaluation of temozolomide and conducted the first in-man trials that established the use of Temozolomide in primary brain tumours (glioma, also referred to as glioblastoma), based on an effective and safe treatment schedule.

In an Imperial study in 1993, of 28 patients with glioma given 750-1000mg/m^2 divided over five days, radiological changes were observed in 5/10 patients with recurrent glioma following surgery and 4/7 patients with newly diagnosed astrocytomas, a subtype of glioma (confirming the temozolomide dosage established in the Phase I trial conducted by Professor Newlands in 1992) (1). Temozolomide was well tolerated with predictable myelosuppression and its activity in primary brain tumours led to the establishment of a multicentre phase II study in high-grade (rapidly growing) glioma, conducted under the auspices of the Cancer Research Campaign.

In 1997, an Imperial-led phase II trial to evaluate the efficacy and toxicity of temozolomide recruited 103 patients with progressive or recurrent supratentorial high-grade glioma. Patients received temozolomide 150-200mg/m^2/day for 5 days repeated every 28 days. Of the 103 patients enrolled, 11% showed an objective response (radiological tumour improvement and improvement in neurological symptoms and status by at least one grade on the MRC neurological status scale) and 47% showed stable disease (neither radiological change nor improvement or deterioration in neurological status) over an 8 week period. The median response duration was 4.6 months and response rates were similar for anaplastic astrocytomas (grade III) and glioblastoma multiforme (grade IV) tumours (2).

The observations of the multi-centre Phase II study supported further investigation of temozolomide in high-grade glioma, and a phase I study to evaluate continuous use of temozolomide for a 6-7 week period showed it was well tolerated with the main tumour responses seen in the recurrent glioma group (3). In parallel, Imperial researchers performed a preclinical

examination of temozolomide with concurrent radiotherapy, *in vitro*, in the human glioma cell line (U373MG), demonstrating an additive effect of the drug on the radiation dose-response curve (4). Dr Brock and Imperial colleagues concluded the recommended dose as 75-85mg/m^2/day for 7 weeks on a continuous schedule which could be combined with radiotherapy, on the basis of the Imperial preclinical data, for the treatment of primary glioma.

Imperial researchers also investigated innovative imaging to quantitatively measure metabolic changes in the brain as a surrogate measure of clinical and subclinical response to temozolomide in 2000. Using [18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), the metabolic uptake of glucose was measured (before and after temozolomide treatment) and a 25% reduction in glucose uptake was observed in patients responding to treatment. This indicated that changes in tumour metabolism could reflect the degree of cell kill following chemotherapy (5). Labelling of temozolomide with carbon-13 enabled researchers at Imperial, in 2006, to visualise its distribution in humans and find that the drug was concentrated in and around the brain tumour (6). Imperial confirmed the drug's mechanism of action using radiolabelled temozolomide and showed that early changes to the tumour metabolic rate of glucose could predict the response to temozolomide treatment (6).

These Imperial clinical trials, including use of innovative imaging approaches, defined the safety profile, patient response, dose schedule and mechanism of action for Temozolomide. These trials subsequently provided the basis for registration trials of the drug and its subsequent use world-wide.

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

(1) O'Reilly, S.M., Newlands, E.S., Glaser, M.G., Brampton, M., Rice-Edwards, J.M., Illingworth, R.D., Richards, P.G., Kennard, C., Colquhoun, I.R., Lewis, P., et al. (1993). Temozolomide: a new oral cytotoxic chemotherapeutic agent with promising activity against primary brain tumours. *Eur J Cancer*, 29A (7), 940-942. DOI. Times cited: 201 (as at 1st October 2013 on ISI Web of Science). Journal Impact Factor: 5.06

(2) Bower, M., Newlands, E.S., Bleehen, N.M., Brada, M., Begent, R.J., Calvert, H., Colquhoun, I., Lewis, P., Brampton, M.H. (1997). Multicentre CRC phase II trial of temozolomide in recurrent or progressive high-grade glioma. *Cancer Chemother Pharmacol*, 40 (6), 484-488. DOI. Times cited: 105 (as at 1st October 2013 on ISI Web of Science). Journal Impact Factor: 2.79

(3) Brock, C.S., Newlands, E.S., Wedge, S.R., Bower, M., Evans, H., Colquhoun, I., Roddie, M., Glaser, M., Brampton, M.H., Rustin, G.J. (1998). Phase I trial of temozolomide using an extended continuous oral schedule. *Cancer Res*, 58 (19), 4363-4367. Times cited: 180 (as at 1st October 2013 on ISI Web of Science). Journal Impact Factor: 8.65

(4) Wedge, S.R., Porteous, J.K., Glaser, M.G., Marcus, K., Newlands, E.S. (1997). In vitro evaluation of temozolomide combined with X-irradiation. *Anticancer Drugs*, 8 (1), 92-97. DOI. Times cited: 99 (as at 1st October 2013 on ISI Web of Science). Journal Impact Factor: 2.23

(5) Brock, C.S., Young, H., O'Reilly, S.M., Matthews, J., Osman, S., Evans, H., Newlands, E.S., & Price, P.M. (2000). Early evaluation of tumour metabolic response using [18F]fluorodeoxyglucose and positron emission tomography: a pilot study following the phase II chemotherapy schedule for temozolomide in recurrent high-grade gliomas. *British Journal of Cancer*, 82 (3), 608-615. DOI. Times cited: 76 (as at 1st October 2013 on ISI Web of Science). Journal Impact Factor: 5.08

(6) Saleem, A., Brown, G.D., Brady, F., Aboagye, E.O., Osman, S., Luthra, S.K., Ranicar, A.S., Brock, C.S., Stevens, M.F., Newlands, E., Jones, T., Price, P. (2003). Metabolic activation of temozolomide measured in vivo using positron emission tomography. *Cancer Res*, 63 (10), 2409-2415. Times cited: 43 (as at 1st October 2013 on ISI Web of Science). Journal Impact Factor: 8.65

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

Impacts include: health and welfare, practitioners and services, commercial, public policy and services
Main beneficiaries include: patients, practitioners, industry

Brain tumours account for 2% of all cancers diagnosed in the UK. Around 4,500 people are diagnosed with a brain tumour each year in the UK, and around 3,500 die from the disease. Just over half, 52%, of brain tumours diagnosed in the UK are glioma. Prior to the clinical use of temozolomide, median survival of glioma patients was generally less than one year following diagnosis, where treatment included surgery and radiation therapy.

The significant improvement in survival of glioma patients in clinical trials, including those led by Imperial, supported the introduction of temozolomide as the standard of care for glioma. According to European Society of Medical Oncology (ESMO) guidelines in 2010, the use of temozolomide both during and post radiotherapy, as suggested by data from Imperial researchers, is now standard of care for newly diagnosed glioma (these concur with the current NICE recommendations) [1].

Following the licensing of temozolomide from Cancer Research Technologies to Schering-Plough annual sales of temozolomide (Temodal) reached $1 billion in 2009 (the use of the drug increasing by 50%) [2, 3], $935 million in 2011 and $917 million in 2012 [4].

A multi-centre Phase III trial, conducted by the pharmaceutical company independently from Imperial, confirmed that the addition of temozolomide to radiotherapy significantly improves survival among patients with newly diagnosed glioma. Analysis at 5 years, showed an overall survival of 9.8% with temozolomide and radiotherapy versus 1.9% with radiotherapy alone. The combined treatment benefit was seen in all clinical prognostic subgroups, including patients aged 60-70 years [5]. Prior to the introduction of temozolomide, it was very rare for a patient to survive 5 years from a diagnosis of glioma.

A retrospective study in the United States compared survival of adult glioma patients diagnosed during 2000-2003 prior to the use of temozolomide (n=6,673) to patients diagnosed from 2005-2008 after introduction of temozolomide (n=7,259), in order to evaluate pre-temozolomide and post-temozolomide periods. Statistical analysis of patient survival data showed that the survival of patients with newly diagnosed glioblastoma improved from 2000-2003 to 2005-2008 and the authors concluded that the improved patient survival is highly likely to be due to the introduction of temozolomide use [6].

Temozolomide has revolutionised the treatment of patients with recurrent high-grade glioma and newly diagnosed glioma. The team at Imperial, in conjunction with Cancer Research Campaign, played a pivotal role in the clinical development of this drug, its anti-tumour effect, scheduling and use which is now providing clinical and survival benefit to patients with high grade glioma.

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

[1] Stupp, R., Tonn, J.C., Brada, M., Pentheroudakis, G. on behalf of the ESMO Guidelines Working Group (2010). High-grade malignant glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, 21 (suppl 5), 190-193. DOI.

[2] Cancer Research Technology Press Release: Temozolomide sales reach $1 billion (Feb 2009) http://www.cancertechnology.com/temozolomide-sales-reach-1-billion. Archived on 7th November 2013.

[3] Uptake of temozolomide following NICE approval. http://www.nice.org.uk/newsroom/news/newsarchive/2009/reportshowsimprovementuptakeniceapprovedcancerdrugs.jsp. Archived on 7th November 2013.

[4] Tickerpot web-site: Temodar/Temodol mentioned by Merck & Co Inc (MRK): http://tickerpot.com/symbol/mrk/310158/topic/temodar

[5] Stupp, R., Hegi, M.E., Mason, W.P., van den Bent, M.J., Taphoorn, M.J., et al (2009). Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*, 10 (5), 459-466. DOI.

[6] Johnson, D.R., O'Neill, B.P. (2012). Glioblastoma survival in the United States before and during the temozolomide era. *J Neurooncol*, 107 (2), 359-64. DOI