Institution: Newcastle University

Unit of Assessment: UoA1

Title of case study:
Reducing the toxicity of pemetrexed treatment in malignant pleural mesothelioma.

1. Summary of the impact

Malignant pleural mesothelioma (MPM) is a treatable but incurable cancer that originates in the cells lining the lungs. Over 14,000 people worldwide are diagnosed annually with MPM. Antifolates are often used in cancer therapy, but side effects are a major issue. A retrospective analysis of cancer trials and phase 1 trial of MPM patients, carried out by Newcastle in collaboration with Eli Lilly Pharmaceuticals, determined that plasma homocysteine levels were a good predictor of drug toxicity in cancer patients treated with the antifolate pemetrexed, and that this drug was well tolerated by patients with low homocysteine levels. It was also determined that pemetrexed treatment should be supplemented with vitamin B12 as well as folic acid, to reduce drug toxicity. Ultimately, this permitted the continued development of pemetrexed, which otherwise would have been too toxic for clinical use. It is now the only licensed drug for MPM treatment in combination with platinum-based chemotherapy.

2. Underpinning research

Key Newcastle researchers
(Where people left/joined the university in 1993-2013, years are given in parentheses)

AV Boddy (1998 onwards), lecturer/senior lecturer 1998-2006, then professor of cancer pharmacology; AH Calvert (1990-2009), professor of medical oncology; NJ Curtin, lecturer/senior lecturer 1998-2006, then professor of experimental cancer therapeutics; DR Newell, professor of cancer therapeutics; R Plummer (2001 onwards), clinical lecturer/senior lecturer of oncology 2001-2008, and then clinical professor of experimental cancer medicine.

Background
Malignant pleural mesothelioma (MPM) is a cancer that originates in the pleura (the lining of the lungs). Over 14,000 people worldwide are diagnosed annually with this incurable disease, which is most often caused by past exposure to asbestos. It is therefore particularly prominent in industrialised regions closely connected with shipbuilding, mining, and construction.

Antifolates are drugs that are toxic to rapidly dividing cells such as malignant cells; therefore, many are used in cancer therapy. However, a major problem with antifolates is significant side effects, which include severe bone marrow suppression (leading to reduced immunity and thus increased risk of infection) and gastrointestinal toxicity: a combination that carries a high mortality risk.

Research
Antifolate use in cancer treatment has been a major research area for some time. Newcastle research into the cellular activity of a multitargeted antifolate (LY231514), now known as pemetrexed or Alimta [e.g. R1], led to supportive laboratory studies being performed and an important early-phase clinical trial of pemetrexed.

Pemetrexed prevents cell replication by interfering with folate-dependent processes; thus, it also affects normal cells; side effects include low white and red blood cell counts, nausea, fatigue, shortness of breath, and anaemia. It was recognised that the ability to predict patients more likely to experience drug-associated toxicity could lead to significant improvements in the management of this problem. Thus, in a collaborative study, Newcastle and Eli Lilly Pharmaceuticals retrospectively analysed plasma samples from 246 patients treated with pemetrexed, combined with folic acid in Phase I and II trials (1995) for cancers other than malignant pleural mesothelioma. The aim was to identify potentially predictive factors of severe drug toxicity [R2]. This analysis identified a positive correlation between plasma homocysteine levels and pemetrexed toxicity, suggesting that measuring pre-treatment homocysteine levels could identify patients likely to experience severe toxicity. These findings were incorporated into the protocol of an Eli Lilly–sponsored Phase I clinical trial of MPM therapy, which began at the same time as the retrospective analysis [R3]. This trial determined the safe dose of pemetrexed with carboplatin. The study enrolled patients with malignant pleural mesothelioma, and was the first prospective study to use

homocysteine levels as a marker to predict the potential adverse toxicity of an antifolate [R3]. This ensured that patients that were particularly vulnerable to pemetrexed toxicity could be excluded from the trial, leaving 27 eligible patients out of 40. The trial proved that pemetrexed was well tolerated in the trial patients at 500 mg/m^2 body surface area. There was also a substantial clinical benefit: significant tumour responses (size decrease) and rapid marked improvement of debilitating symptoms, e.g. shortness of breath and chest pain, in 84% of the patients [R3]. The Newcastle Phase I trial demonstrated that pemetrexed could be administered safely to patients in a platinum chemotherapy combination and, ultimately this was the first therapy to be approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) in 2004 for the treatment of malignant pleural mesothelioma.

At the time of the retrospective analysis and Phase I trial, it was known that folic acid supplementation could potentially reduce antifolate toxicity, but the underlying mechanism was unclear. However, the retrospective analysis, which included vitamin deficiency markers from patients, also demonstrated that high pemetrexed toxicity correlated with low folate and vitamin B12 levels [R2]. As folates and vitamin B12 are required for homocysteine metabolism, this offered an explanation of why increased homocysteine levels were correlated with increased drug toxicity; gastrointestinal pathology is thought to be present in the majority of patients with B12 deficiency. It was therefore inferred that these patients, with their background of gastrointestinal pathology might experience greater antifolate toxicity, as antifolates also have deleterious gastrointestinal side effects. These findings suggested that pemetrexed treatment should not only be supplemented with folic acid, but also vitamin B12, to reduce the toxic side effects of antifolates [R2]. Preliminary data of vitamin B12 intervention in a Phase II pemetrexed trial confirmed that administering folic acid and vitamin B12 reduced homocysteine levels and in turn significantly reduced the toxicity associated with pemetrexed therapy while maintaining, or even improving, efficacy [R2].

As a direct consequence of the retrospective analysis, all patients given pemetrexed in mesothelioma trials were also subsequently given folic acid and vitamin B12. Eli Lilly Pharmaceuticals supported a large multi-centre Phase III clinical trial and Newcastle was one of the participating centres [R4]. The protocol for this trial, which involved 456 patients, was revised in December 1999 to include supplementation treatment, thus 117 patients were not given folic acid and vitamin B12 and 339 patients were. This trial, which also incorporated the pemetrexed dose of 500 mg/m^2 body surface area, demonstrated the benefit of combining pemetrexed with cisplatin (another platinum drug similar to carboplatin) in patients with malignant pleural mesothelioma. It also confirmed that the addition of folic acid and vitamin B12 significantly reduced toxicity without affecting drug efficacy [R4].

3. References to the research

(Newcastle researchers in bold. Citation count from Scopus, July 2013)

R1. **Smith PG**, **Marshman E**, **Newell DR**, **Curtin NJ**. Dipyridamole potentiates the in vitro activity of MTA (LY231514) by inhibition of thymidine transport. Br J Cancer. 2000 Feb;82(4):924-30. DOI: 10.1054/bjoc.1999.1020. **Cited by 23**.

R2. Niyikiza C, Baker SD, Seitz DE, Walling JM, Nelson K, Rusthoven JJ, Stabler SP, Paoletti P, **Calvert AH**, Allen RH. Homocysteine and methylmalonic acid: markers to predict and avoid toxicity from pemetrexed therapy. Mol Cancer Ther. 2002 May;1(7):545-52. PMID: 12479273 **Cited by 186**.
(Prof Calvert was senior co-author for this paper and provided the oncology and antifolate expertise. He was a major driver of the study and a long-standing advisor to Eli Lilly for the development of pemetrexed and other antifolates.)

R3. **Hughes A**, **Calvert P**, **Azzabi A**, **Plummer R**, Johnson R, Rusthoven J, **Griffin M**, Fishwick K, **Boddy AV**, **Verrill M**, **Calvert H**. Phase I clinical and pharmacokinetic study of pemetrexed and carboplatin in patients with malignant pleural mesothelioma. J Clin Oncol. 2002 Aug;20(16):3533-44. DOI: 10.1200/JCO.2002.10.073. **Cited by 118**.

R4. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, Gatzemeier U, Boyer M, Emri S, Manegold C, Niyikiza C, Paoletti P. Phase III Study of Pemetrexed in Combination With Cisplatin Versus Cisplatin Alone in Patients with Malignant Pleural Mesothelioma. J Clin Oncol. 2003; 21(14):2636-2644. DOI: 10.1200/JCO.2003.11.136. **Cited by 1149**.

Selected Funding Awards

- 1999-2003 *NECRC Cancer Research Unit Core Grants 2-5*. Cancer Research UK- £3,427,742

4. Details of the impact

It is estimated that over 14,000 people are diagnosed worldwide with malignant pleural mesothelioma each year, around 2,500 of which are in the UK. This disease most commonly develops between the ages of 50 and 70 years, affecting five times more men than women. Symptoms include shortness of breath, chest pains, fatigue, and weight loss. There is no cure and the prognosis is poor; over 2,000 people die annually from the disease in the UK.

Impact on Patients

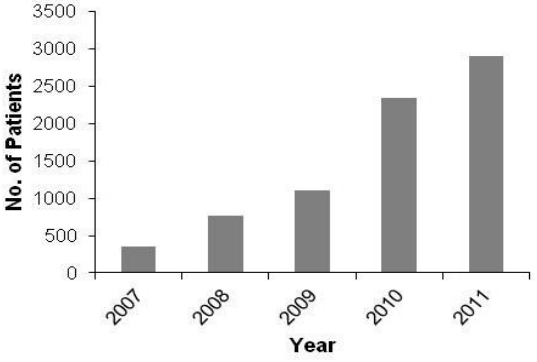
If not for the Newcastle research and collaboration with Eli Lilly Pharmaceuticals, pemetrexed toxicity, which includes severe bone marrow suppression, vomiting, fatigue, shortness of breath, and anaemia, would have led to its clinical development being discontinued [EV a]. Instead, it was demonstrated for the first time that pemetrexed could be used safely in patients and that the toxicity and side effects could be reduced by supplementation with not only folic acid, but also vitamin B12. A Vice President of Eli Lilly at the time the research was carried out confirms that during their collaborative work with the Newcastle group:

> *'…the identification of biomarkers related to folic acid and other vitamins* [including homocysteine] *has been fundamental to understand the toxicity of Pemetrexed. High levels of homocysteine were associated to higher risk of developing severe toxicity and in some instances toxic deaths. The supplementation of folic acid and vitamin B12, currently part of the label of Pemetrexed commercialized with the name of Alimta is the result of this collaboration*' [EV a].

Continuing, he says that this ultimately permitted *'…the completion of the development of Pemetrexed*' [EV a]. The supplementation treatment means that patients are better able to tolerate the drug and stand to benefit from this treatment.

Following the Newcastle Phase I trial, the collaborative retrospective study with Eli Lilly, and incorporating vitamin B12 supplementation in a Phase II trial [R2, R3, Section 2], a Phase III trial [R4, Section 2] included the supplementation treatment and 500 mg/m^2 body surface pemetrexed. This is recognised in the 2008 National Institute for Health and Care Excellence (NICE) guidelines for the treatment of malignant pleural mesothelioma, which states that *'…with effect from the date of the protocol change, all patients received supplementation*' [EV b, p. 8]. The trial confirmed that when pemetrexed was supplemented with folic acid and vitamin B12, incidences of severe toxicity, which include drug-related death, neutropenia (white blood cell reduction), febrile neutropenia, and diarrhoea, were significantly reduced, compared to when it was not [R4, Section 2; EV b]. Supplemented pemetrexed treatment combined with cisplatin also resulted in a significant increase in patients' quality of life by reducing disease symptoms, including pain, fatigue, anorexia, and cough [R4, Section 2; EV b].

Using pemetrexed with cisplatin also resulted in a significant survival benefit for patients with malignant pleural mesothelioma. In fully supplemented patients with advanced disease, median survival was 13.2 months when pemetrexed and cisplatin were administered, versus 8.4 months for patients given cisplatin alone [EV b]. Pemetrexed also increased tumour response rates to cisplatin (41.3% with pemetrexed versus 16.7% without) and the median time to progressive disease (defined as at least 20% growth in tumour size since the start of treatment) was significantly longer for patients who received pemetrexed and cisplatin as compared with patients who received just cisplatin (5.7 months versus 3.9 months, respectively) [EV b]. Notably, there has been a marked increase in the number of cancer (predominantly MPM) patients in the UK receiving pemetrexed treatment following the release of the 2008 NICE guidelines (bar chart) [EV c].



Impact on Clinical Practice

In accordance with the 2008 NICE guidelines [EV b, p. 8], pemetrexed with cisplatin is currently the only chemotherapy regimen licensed for treatment of malignant pleural mesothelioma. The guidelines cite the Phase III trial [R4, Section 2] which adopted vitamin B12 with folic acid supplementation into its protocol as a result of the collaborative work between Newcastle and Eli Lilly [R2, Section 3] as the only identified randomised controlled pemetrexed trial in malignant pleural mesothelioma. The NICE guidelines clearly state that '*…in order to reduce toxicity, patients treated with pemetrexed must receive folic acid and vitamin B12 supplementation*' [EV b, p. 6]. This is also clearly stated in the 2004 FDA and EMEA approvals for pemetrexed (Alimta) and in its prescription information, and the maximum tolerated dose of 500 mg/m^2 body surface area [EV d]. Notably, the US National Guideline Clearinghouse website provides a link to the NICE guidelines [EV e]. A Phase II trial on the treatment of patients with malignant pleural mesothelioma with pemetrexed and carboplatin, recently reported that 70% of the 76 patients enrolled exhibited clinical improvement after just two courses and that the pemetrexed dose of 500 mg/m^2 body surface area was well tolerated [EV f].

The former Vice President of Eli Lilly states that to date:

> '*…Alimta has been used globally by hundreds of thousands of patients and it is standard of care in* [mesothelioma and non small cell lung cancer]. *The collaboration* [between Newcastle University and Eli Lilly] *has been crucial for the advancement of the knowledge in this field and the achievement of the introduction of a medicine that changed the modality of treatment for mesothelioma and lung cancer*' [EV a].

Pemetrexed treatment with folic acid and vitamin B12 supplementation was also adopted into the NICE guidelines for non-squamous non–small cell lung cancer (comprises most lung cancers) in December 2010 [EV g] and for maintenance treatment of this disease in 2012 [EV h].

Clinical Trials

There are currently 361 clinical trials (either open or completed in 2008-2013) registered on clinicaltrials.gov that use pemetrexed in accordance with the FDA and Eli Lilly guidelines. These include trials on malignant pleural mesothelioma, non–small cell lung cancer, squamous cell head and neck cancer, advanced urothelial carcinoma, ovarian carcinoma, and thyroid cancer, and involve over 58,000 patients [EV i].

5. Sources to corroborate the impact

EV a. Testimonial letter: Former VP of Eli Lilly Pharmaceuticals (Letter held at Newcastle).

EV b. NICE technology appraisal guidance 135 (2008): Pemetrexed for the treatment of malignant pleural mesothelioma**.** http://guidance.nice.org.uk/TA135/Guidance/pdf/English

EV c. Patient numbers extracted from NHS prescription data for pemetrexed: http://www.hscic.gov.uk/searchcatalogue?q=pemetrexed&area=&size=10&sort=Relevance in conjunction with statement in NICE guidelines on cost/patient for a course of pemetrexed treatment (EV a, p. 7).

EV d. Prescription information: http://www.lilly.com/products/human/Pages/human.aspx

EV e. http://guideline.gov/search/search.aspx?term=pemetrexed

EV f. Castagneto, B et al. Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma (MPM). Ann Oncol. 2008, 19:370-3. DOI: 10.1093/annonc/mdm501.

EV g. NICE technology appraisal guidance 181 (2010): Pemetrexed for the first-line treatment of non-small-cell lung cancer. PDF at: http://guidance.nice.org.uk/TA181/Guidance/pdf/English

EV h. NICE technology appraisal guidance 190 (2012): Pemetrexed for the maintenance treatment of non-small-cell lung cancer. PDF at: http://guidance.nice.org.uk/TA190/Guidance/pdf/English

EV i. Data extracted from: www.clinicaltrials.gov (Search words 'pemetrexed' 'alimta', '500 mg/m^2'; show results for trials open or completed 2008-2013)