

Impact case study (REF3b)

Institution: University College London
Unit of Assessment: 1 - Clinical Medicine
Title of case study: Lung cancer research at UCL/UCLH sets standards of care
<p>1. Summary of the impact</p> <p>UCL has conducted a series of national lung cancer trials, which have led to wide-scale changes in clinical practice. Two trials compared different platinum based therapies, which led to centres switching from using chemotherapy with cisplatin to carboplatin-based chemotherapy instead. Carboplatin can be given as an outpatient, and has fewer side effects, and has been (and still is) recommended as an alternative to cisplatin in the UK and US.</p>
<p>2. Underpinning research</p> <p>Lung cancer is the most common cause of cancer death in the UK and other developed countries. The CR-UK & UCL Cancer Trials Centre (CTC), with the London Lung Cancer Group (LLCG), has an established history (almost 30 years) of conducting large scale national trials in lung cancer treatment and screening. The chair of the LLCG is Professor Siow Ming Lee, based at UCL/UCLH.</p> <p>Gemcitabine/carboplatin as first-line treatment for lung cancer (known as studies 10 and 11)</p> <p>These were two national clinical multicentre trials in lung cancer, initiated, developed and conducted through UCL, to examine the efficacy and safety of gemcitabine/carboplatin (gem/carbo) in two different types of lung cancer. The Chief Investigator was Professor Siow Ming Lee. Both trials were independently peer-reviewed by Cancer Research UK and were conducted through the UK National Cancer Research Networks. All of the trials were large collaborative multicentre studies involving as many as 95 hospitals across the UK.</p> <p>Study 10 (extensive or limited stage small cell lung cancer (SCLC) with poor prognosis): compared gem/carbo with standard cisplatin/etoposide (PE) in 241 patients. This was the first randomised study comparing these two chemotherapy regimens for patients with poor-prognosis small cell lung cancer (SCLC). It showed that gem/carbo had similar survival outcomes to PE, but was better tolerated. Patients given gem/carbo received more chemotherapy as outpatients (89% vs. 66%), and fewer had nausea and alopecia (the two most commonly reported side effects associated with lower quality of life) [1].</p> <p>Study 11 (stage IIIb or IV non-small cell lung cancer (NSCLC)): gem/carbo was compared with standard mitomycin, ifosfamide, and cisplatin (MIC). This trial, based on 422 patients, showed for the first time that outpatient chemotherapy was more effective than conventional inpatient chemotherapy, improving median survival from 7.6 to 10.0 months (24% reduction in mortality) and one-year survival from 30% to 40%. Furthermore, quality of life was significantly improved, because patients given gem/carbo had fewer side effects [2]. An added advantage was that gem/carbo avoided the inconvenience and NHS cost of an overnight stay in hospital.</p>
<p>3. References to the research</p> <p>(Those in bold are UCL-based; James and Gower were in the clinical trials centre)</p> <p>[1] Study 10. Lee SM, James LE, Qian W, Spiro S, Eisen T, Gower NH, Ferry DR, Gilligan D, Harper PG, Prendiville J, Hocking M, Rudd RM. Comparison of gemcitabine and carboplatin versus cisplatin and etoposide for patients with poor-prognosis small cell lung cancer. <i>Thorax</i>. 2009;64(1):75-80. http://dx.doi.org/10.1136/thx.2007.093872</p> <p>[2] Study 11. Rudd RM, Gower NH, Spiro SG, Eisen TG, Harper PG, Littler JA, Hatton M, Johnson PW, Martin WM, Rankin EM, James LE, Gregory WM, Qian W, Lee SM. Gemcitabine plus carboplatin versus mitomycin, ifosfamide, and cisplatin in patients with stage IIIB or IV</p>

Impact case study (REF3b)

non-small-cell lung cancer: a phase III randomized study of the London Lung Cancer Group. *J Clin Oncol.* 2005 Jan;23(1):142-53. <http://dx.doi.org/10.1200/JCO.2005.03.037>

Funding for both trials: Eli Lilly

4. Details of the impact

The combination of mitomycin, ifosfamide, and cisplatin (MIC) was previously widely used in Europe for the treatment of advanced NSCLC. This required patients to stay in hospital overnight, and had adverse effects on quality of life. Cisplatin and etoposide (PE) were commonly used together to treat poor prognosis SCLC. However, major problems with cisplatin treatment were the administration time and significant symptomatic non-haematological toxicity.

Gemcitabine/carboplatin (gem/carbo) became popular because it was given as an out-patient treatment with short infusion time. It was also better tolerated, causing less emesis, renal impairment, hearing loss and neurotoxicity compared to other regimens. In addition, many NSCLC patients are elderly (median age 72) with poor performance status and have multiple co-morbidities, so clinicians often recommend carboplatin instead of cisplatin to treat this population group. Gem/carbo therefore became widely used as a first-line treatment in the UK and internationally to treat patients with advanced NSCLC (Lilly data). In 2009, NICE guidance recommended pemetrexed-based chemotherapy for NSCLC [a], and since that time, gem/carbo has been used mainly to treat SCLC (NICE guidelines TA26 [b] and CG121 [c]).

The following recommendations are from the NICE website (accessed 30 April 2013), based on the findings of the UCL trials:

SCLC [d]:

“Early stage (broadly T1–2a, N0, M0) or limited disease (broadly T1–4, N0–3, M0)

Consider carboplatin if renal function impaired, poor performance status (WHO 2 or more) or significant comorbidity”

Extensive disease (broadly T1–4, N0–3, M1a/b)

Offer platinum-based combination chemotherapy (maximum 6 cycles) if patient can receive chemotherapy”.

NSCLC [e]:

“For advanced NSCLC, offer a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (either carboplatin or cisplatin).”

As a result of the national guidance, gem/carbo was used as a reference regimen in the BTOG 2 trial (a large national clinical trial of 1,350 NSCLC patients) to compare low dose and high dose platinum regimens [f]. The study shows gem/carbo was well tolerated and superior to low dose cisplatin but has similar outcome compared to high dose cisplatin regimen [g].

The Study 10 findings are also quoted in the US National Comprehensive Cancer Network (NCCN) guidelines to support the use of carboplatin to treat extensive SCLC [h]. Individual patient data from Study 10 were used for the meta-analysis comparing the efficacy of cisplatin versus carboplatin in the first-line treatment of SCLC [i]. There is also reference to Study 10 in Canadian guidelines on bladder cancer [j].

Approximately 4,000 new cases of SCLC are diagnosed in the UK each year. The majority of these patients have extensive SCLC and poor performance status and hence many are treated with a carboplatin-based regimen instead of a cisplatin-based treatment. A carboplatin regimen can be easily administered as an out-patient regimen reducing chair time usage and avoiding the

Impact case study (REF3b)

inconvenience of prolonged hydration or overnight stay associated with cisplatin and also fewer of the adverse effects that are commonly seen with cisplatin administration.

The Systemic Anti-Cancer Therapy (SACT) Dataset, within the National Cancer Intelligence Network, has been recording data on types of treatments for lung cancer since April 2012. For 2012 there were 3,686 SCLC cases recorded in England and Wales. The SACT dataset shows that between April 2012 and March 2013, 710 patients with SCLC received carboplatin, though only around 80% of trusts had uploaded data so the actual number is likely to be nearer 900, meaning that 26% of SCLC patients received carboplatin [k].

5. Sources to corroborate the impact

- [a] NICE: The diagnosis and treatment of lung cancer. April 2011. NICE Clinical Guideline 121. <http://www.nice.org.uk/nicemedia/live/13465/54202/54202.pdf>
- [b] NICE Guideline TA26. <http://guidance.nice.org.uk/TA26>
- [c] NICE Guideline CG 121. <http://www.nice.org.uk/CG121>
- [d] <http://pathways.nice.org.uk/pathways/lung-cancer/treatment-for-small-cell-lung-cancer#content=view-node%3Anodes-first-line-and-maintenance-treatment> Full guideline references our studies.
- [e] <http://pathways.nice.org.uk/pathways/lung-cancer/treatment-for-non-small-cell-lung-cancer#content=view-node%3Anodes-chemotherapy-for-advanced-or-metastatic-non-small-cell-lung-cancer> Full guideline references our studies.
- [f] BTOG 2 trial. <http://clinicaltrials.gov/ct2/show/NCT00112710>
- [g] Ferry et al. British Thoracic Oncology Group Trial, BTOG2: Randomised phase III clinical trial of gemcitabine combined with cisplatin 50mg/m² (GC50) versus cisplatin 80mg/m² (GC80) versus carboplatin AUC 6 (GCb6) in advanced NSCLC. Presented at the World Conference on Lung Cancer 2011. <http://abstracts.webges.com/wclc2011/myitinerary> [put 'BTOG2' in the search field, and the Ferry et al abstract will be shown]
- [h] US NCCN Guideline: Kalemkerian GP, Akerley W, Bogner P, Borghaei H, Chow LQ, Downey RJ, Gandhi L, Ganti AK, Govindan R, Grecula JC, Hayman J, Heist RS, Horn L, Jahan T, Koczywas M, Loo BW Jr, Merritt RE, Moran CA, Niell HB, O'Malley J, Patel JD, Ready N, Rudin CM, Williams CC Jr, Gregory K, Hughes M. Small cell lung cancer. J National Comprehensive Cancer Network. 2013;11(1):78-98. Available on request.
- [i] Rossi A, Di Maio M, Chiodini P, Rudd R, Okamoto H, Skarlos DV, Früh M, Qian W, Tamura T, Samantas E, Shibata T, Perrone F, Gallo C, Gridelli C, Martelli O, Lee SM (2012). Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer. The COCIS meta-analysis of individual patient data. Journal of Clinical Oncology 2012; 30(14):1692-8. <http://dx.doi.org/10.1200/JCO.2011.40.4905>
- [j] Moretto et al. Management of small cell carcinoma of the bladder: Consensus guidelines from the Canadian Association of Genitourinary Medical Oncologists (GAGMO). Can Urol Assoc J 2013;7:E44-E56. <http://dx.doi.org/10.5489/cuaj.220>
- [k] Data and estimated data provided by Clinical Lead, National Cancer Intelligence Network (NCIN). Copy available on request.