**Institution:** University College London

**Unit of Assessment:** 1 - Clinical Medicine

**Title of case study:** Standard of care established for advanced biliary tract cancer

## 1. Summary of the impact

Before 2010, there was no accepted standard treatment for patients with advanced biliary tract cancer. The ABC02 trial showed that the combination of two drugs (gemcitabine and cisplatin) significantly improves survival, with acceptable side effects. Consequently, national and international guidelines have been revised to recommend this regimen as a standard of care. Furthermore, in ongoing trials of novel therapies, gemcitabine/cisplatin has become the comparator group, and the aim is to improve survival above what this can already achieve.

## 2. Underpinning research

The prognosis for patients with advanced biliary tract cancer (cholangiocarcinoma) is poor, with only half of them surviving to about eight months. UCL/UCLH is one of the main UK centres for treating these patients, and has been involved in several associated research projects over the years. One of these involved developing and participating in a randomised phase II study **[1]** to examine whether doublet chemotherapy (gemcitabine and cisplatin) is better than gemcitabine alone (UCL/UCLH Principal Investigator, Dr John Bridgewater, Consultant Oncologist; Chief Investigator Dr Juan Valle, Christie Hospital Manchester). This study showed very promising results for the doublet regimen, and was used to justify and design a large phase III trial (ABC02).

ABC02 successfully received funding from Cancer Research UK, with Bridgewater as the Chief Investigator. Professor Allan Hackshaw (CRUK-UCL Cancer Trials Centre) had oversight of the design and statistical analyses. The trial concept originated from Bridgewater and Valle, with support through the NCRN Lower Gastrointestinal Cancer Clinical Studies Group. UCL was responsible for trial design, study conduct and statistical analyses, and was the trial Sponsor.

This study was one of the first large scale national studies in biliary tract cancer in the UK, involving 37 recruiting hospitals (410 patients recruited 2002–8). It was independently peer-reviewed by Cancer Research UK, conducted across the UK National Cancer Research Networks (NCRN) and published in the New England Journal of Medicine **[2]**. These attributes confirm the high quality of this seminal trial.

The ABC02 trial showed that the combination of two drugs (gemcitabine and cisplatin) significantly improves survival, with acceptable side effects. Following the success of ABC02, and the implementation of doublet therapy into routine care, UCL has designed, conducted and sponsored all subsequent UK national trials in biliary tract cancer developed through the NCRN Clinical Studies Group (ABC03, ABC04 and ABC05).

## 3. References to the research

[1] Valle JW, Wasan H, Johnson P, Jones E, Dixon L, Swindell R, Baka S, Maraveyas A, Corrie P, Falk S, Gollins S, Lofts F, Evans L, Meyer T, Anthoney A, Iveson T, Highley M, Osborne R, Bridgewater J. Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study - The UK ABC-01 Study. Br J Cancer. 2009 Aug;101(4):621-7. http://dx.doi.org/10.1038/sj.bjc.6605211

[2] Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010

Apr;362(14):1273-81. http://dx.doi.org/10.1056/NEJMoa0908721

Funding: Cancer Research UK (2005–9)

Title: Gemcitabine, alone or in combination with cisplatin, in patients with advanced or metastatic cholangiocarcinomas and other biliary tract tumours: a multicentre, randomised phase III study.

Applicants: J Bridgewater, J Valle, H Wasan

Value: £220,000

Sponsor: University College London

## 4. Details of the impact

About 1,200 people are diagnosed with biliary tract cancer each year in the UK and 12,000 in the US. For the majority of patients, it is an incurable cancer and before 2010 there was no established standard of care; some patients had best supportive care, others single agent drugs. Therefore, there was an urgent need to find effective treatments.

Our research showed that the doublet regimen of gemcitabine and cisplatin increases the median survival from 8.2 months (gemcitabine alone) to 11.7 months, i.e. an extra 3.5 months of life on average. This is equivalent to reducing the chance of dying by 36%. Importantly, the side effects/harm associated with the doublet therapy were similar to the single agent. This improvement in patient outcomes led to revised international guidelines on treating biliary tract cancer, recommending this doublet therapy as routine care since 2011:

- The European Society for Medical Oncology (ESMO), following the first presentation of the ABC02 results in 2011, stated that the trial "set a new standard of care", and assigned it Level II evidence ('Evidence is obtained from at least one well-designed experimental study') **[a]**.

- In 2012, the British Society of Gastroenterology recommended the doublet therapy for advanced or metastatic unresectable cholangiocarcinoma (with Grade A evidence) **[b]**.

- The United States NCCN Clinical Practice Guidelines recommended the use of gemcitabine/cisplatin and assigned the trial as 'Category 1 evidence' ("Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate") **[c]**.

The recommendations have been endorsed by the International Liver Cancer Association **[d]**. Subsequent national trials for biliary tract cancer must now examine new treatments in addition to gemcitabine/cisplatin **[e]**. The treatment is recommended on NHS Choices **[f]**, and by Macmillan **[g]** as standard chemotherapy for biliary tract cancer. In August 2013, we surveyed 43 key centres treating biliary tract cancer, of whom 12 responded. All of these had adopted the new regime as standard of care, reporting improved survival and a well-tolerated regime. This amounted to over 230 patients treated **[h]**.

The ABC02 trial data were used to examine cost-effectiveness by an independent research group **[i]**. Total Quality Adjusted Life Years (QALYs) for gemcitabine/cisplatin (0.751) was greater than for gemcitabine alone (0.561), with total costs of $44,885 and $33,653 respectively. Gemcitabine/cisplatin had an incremental cost-effectiveness ratio of $59,480 per QALY gained, compared to gemcitabine alone. The authors concluded that the doublet therapy "is a cost-effective treatment alternative to gemcitabine monotherapy by currently accepted standards of willingness to pay".

## 5. Sources to corroborate the impact

[a] Eckel F, Brunner T, Jelic S; ESMO Guidelines Working Group. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2011;22 Suppl 6:vi40-

4.

[b] Khan SA, Davidson BR, Goldin RD, Heaton N, Karani J, Pereira SP, Rosenberg WM, Tait P, Taylor-Robinson SD, Thillainayagam AV, Thomas HC, Wasan H; British Society of Gastroenterology. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. Gut. 2012;61(12):1657-69. doi: 10.1136/gutjnl-2011-301748. Epub 2012 Aug 15.

[c] United States National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, version 2.2012: hepatobiliary cancers. Available on request.

[d] http://www.ammf.org.uk/2012/03/13/international-cc-guidelines

[e] Examples of ongoing national clinical trials in the UK, USA and Germany which use gemcitabine/cisplatin as the control/standard treatment for biliary tract cancer are:

- http://clinicaltrials.gov/ct2/show/NCT00939848
- http://clinicaltrials.gov/ct2/show/NCT01242605
- http://clinicaltrials.gov/ct2/show/NCT00919061
- http://clinicaltrials.gov/ct2/show/NCT01679405

[f] NHS Choices website on treatment for biliary tract cancer which refers to the results of our trial: http://www.nhs.uk/Conditions/Cancer-of-the-bile-duct/Pages/Treatment.aspx

[g] Macmillan page on biliary tract cancer, referencing Valle et al 2010: http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Bileduct/Bileductcancer.aspx

[h] Internal survey conducted among those centres who had taken part in the ABC trials. Full survey data available on request.

[i] Roth JA, Carlson JJ. Cost-effectiveness of gemcitabine + cisplatin vs. gemcitabine monotherapy in advanced biliary tract cancer. *J Gastrointest Cancer* 2012;43:215–23. http://dx.doi.org/10.1007/s12029-010-9242-0