Institution: University College London

Unit of Assessment: 2 - Public Health, Health Services and Primary Care

Title of case study: Neoadjuvant chemotherapy for invasive bladder cancer

1. Summary of the impact

Researchers at the MRC Clinical Trials Unit conducted a systematic review and meta-analysis of individual patient data on neoadjuvant chemotherapy for invasive bladder cancer. This work has been cited as evidence in 19 national and international clinical practice guidelines from 2008 to 2013. In most cases, the guidelines citing this review substantiate their clinical recommendations by directly quoting the review content.

2. Underpinning research

Bladder cancer is the second most common cancer of the genitourinary system. Worldwide there are estimated to be about 336,000 new cases per year, of which about one third are likely to be invasive or metastatic disease.

Invasive bladder cancer, where the tumour has spread into (or invaded) the muscle layer of the bladder, is likely to spread to other parts of the body. At the time this project was initiated, standard treatment for invasive bladder cancer was surgery to remove the tumour, and part or all of the bladder and nearby lymph nodes and other tissues. Alternatively, radiotherapy was also given instead of or in addition to surgery. However, giving (neoadjuvant) chemotherapy before surgery and/or radiotherapy offered the potential to reduce tumour size and control cancer spread. Furthermore, if chemotherapy is given before these potentially debilitating treatments, it might be better tolerated than chemotherapy given after them, so that patients are more likely to comply with their chemotherapy treatment, allowing higher doses of drug to be administered. However, most randomised trials investigating the use of neoadjuvant chemotherapy were modestly sized and inconclusive about its effects, although results of the largest trial, the MRC Clinical Trials Unit BA06 trial looked encouraging. Subsequent systematic reviews and meta-analyses based on aggregate or summary data from publications of these trials were limited by the availability and quality of data and were similarly inconclusive.

We therefore initiated a systematic review and meta-analysis of individual patient data (IPD). This international collaborative project collected and analysed the original trial data from all patients included in all the relevant trials, including BA06. This IPD approach can bring about substantial improvements to the quality of the data and analysis, leading to more reliable and robust results than a standard systematic review of summary, and is considered the 'gold standard'.

The research was carried out at the MRC Clinical Trials Unit by the project management group on behalf of the Advanced Bladder Cancer (ABC) Collaboration. This group was responsible for formulating the questions; developing the protocol; collecting, checking and analysing data; presenting and discussing the preliminary results and preparing the manuscript. At the time their positions at the MRC Clinical Trials Unit were:

- Claire Vale, Research Scientist (Now Senior Research Scientist)
- Jayne Tierney, Senior Research Scientist (Now Meta-analysis Group Lead)
- Lesley Stewart, Meta-analysis Group Head (Now Centre for Reviews and Dissemination Director)
- Mahesh Parmar, Cancer Group Head (Now MRC Clinical Trials Unit Director)

An advisory group provided input and advice at all stages of the project (NW Clarke, UK; JT Roberts, UK; R Sylvester, Belgium; D Raghavan, USA) and the following supplied IPD and/or contributed to discussion of the results and commented on the drafts of the publication: H Abol-Enein, Egypt; P Bassi, Italy; AV Bono, Italy; M Boyer, Australia; ML Coppin, Canada; E Cortesi,

Italy; PJ Goebell, Germany; S Groshen, USA; RR Hall, UK; A Horwich, UK; P-U Malmström, Sweden; JT Roberts, UK; L Sengeløv, Denmark; A Sherif, Sweden; M Stockle, Germany; FM Torti, USA; DMA Wallace, UK).

3. References to the research

The results were published in the name of the Advanced Bladder Cancer (ABC) Collaboration.

[1] Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet. 2003 Jun 7;361(9373):1927-34. http://dx.doi.org/10.1016/S0140-6736(03)13580-5

[2] Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data. European Urology. 2005;48(2):202-6. http://dx.doi.org/10.1016/j.eururo.2005.04.006

[3] Advanced Bladder Cancer Overview Collaboration. Neoadjuvant chemotherapy for invasive bladder cancer. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD005246. http://dx.doi.org/10.1002/14651858.CD005246

This research was initially funded as part of the MRC Clinical Trials Unit Meta-analysis programme of research via two MRC programme Grants (1997-1999: £346,464; 2000-2002: £429,826), and subsequently via core support for the programme which was awarded following the Unit's 2003 Quinquennial Review.

4. Details of the impact

Initial results were based on 2,688 patients, from ten randomised trials, and updated to include 3,005 patients, from 11 trials, including the MRC Clinical Trials Unit BA06 trial. This represents 98% of the available randomised evidence. We showed that people with invasive bladder cancer who had multi-drug, platinum-based chemotherapy before surgery and/or radiotherapy lived longer than those who had just surgery and/or radiotherapy. After five years, 50 out of every 100 people who received additional chemotherapy were still alive compared with 45 out of every 100 who just had surgery and/or radiotherapy. They were also less likely to have their cancer recur or spread to other parts of the body. These effects were independent of the whether neoadjuvant chemotherapy was added to surgery or radiotherapy. There was no evidence to support the use of neoadjuvant chemotherapy based on a single platinum-based drug.

The research has been cited as evidence in 19 national and international guidelines from 2008 to 2013. In most cases, the guidelines citing this review substantiate their clinical recommendations by directly quoting the review:

European Association of Urology (2008/2009/2010/2011/2012/2013) "Neoadjuvant cisplatin containing combination chemotherapy should be considered in muscle invasive bladder cancer irrespective of definitive treatment" **[a]**.

European Society for Medical Oncology (2008/2009/2010/2011) "A meta-analysis supports the use of neoadjuvant chemotherapy before cystectomy for T2 and T3 disease. The demonstrated survival benefit encourages the use of platinum based combination chemotherapy for patients with invasive bladder cancer before radical cystectomy or definitive radiotherapy" **[b]**.

National Comprehensive Cancer Network (2010/2011) "In the most recent meta-analysis, a statistically significant decrease in the death rate was seen corresponding to an improvement in overall survival. The NCCN Bladder Cancer panel members recommend considering cisplatin-based neoadjuvant combination chemotherapy" **[c]**.

Japanese Urological Association (2010) "At present, a definite improvement in survival rates has

been shown only for preoperative cisplatin-based combination chemotherapy" **[d]**.

Associazione Urologi Italiani (2010) "High-quality clinical evidence shows that neoadjuvant cisplatin-based chemotherapy has acceptable toxicity and increases the survival rate by 5–6.5%" **[e]**.

Saudi Oncology Society (2011) "Neoadjuvant cisplatin-based chemotherapy improved overall survival by 5–7% at 5 years and this option should be offered to patients especially with locally advanced disease (T3,T4)" **[f]**.

Our systematic review and meta-analysis of IPD was also cited as evidence in these guidelines:

British Columbia Cancer Agency (2008) [g].

Association of Comprehensive Cancer Centres (2009) [h].

Alberta Health Services (2011) [i].

Spanish Society of Medical Oncology (2011) [j].

In addition, the routine use of neoadjuvant chemotherapy in the management of locally advanced bladder cancer has been discussed in a number of recent articles. Notably, it was the topic of a panel discussion at the 11th Annual Meeting of the Society of Urologic Oncology, where the international experts concluded that the current standard of care for patients with muscle invasive bladder cancer is cisplatin-based neoadjuvant chemotherapy followed by radical surgery **[k]**. Use of neoadjuvant chemotherapy for patients with muscle-invasive bladder cancer has also increased. For example, a study published in 2011, which reviewed treatment patterns across the USA using data from the National Cancer Database, showed that the percentage of American patients receiving neoadjuvant chemotherapy had more than doubled during the period from 2003-2007. The authors attributed this to the increase in data supporting neoadjuvant treatment **[l]**.

One of the recommendations of the IPD meta-analysis was that neoadjuvant cisplatin-based chemotherapy should be used as the control arm in any subsequent trials in this population. Whilst no recently initiated randomised controlled trials could be identified, neoadjuvant chemotherapy continues to be the subject of a number of ongoing and recently reported trials. These studies have explored the use of novel therapeutic agents (including bevacizumab, sunitinib and sorafenib) alongside standard neoadjuvant, cisplatin-based chemotherapy; explored modifications to the dose or duration of standard neoadjuvant chemotherapy regimens or used novel drug combinations in attempts to further reduce side effects and improve outcomes for patients with muscle invasive disease **[m]**.

5. Sources to corroborate the impact

[a] **European Association of Urology**. The 2013 guidelines confirm that the three meta-analyses conducted by the authors established that neoadjuvant chemotherapy reduced mortality rate (p.30-1). There are no other references in this source that confirm this result. See references 35 and 37 (p.33-4). http://www.uroweb.org/gls/pdf/07_Bladder%20Cancer_LRV2.pdf.

[b] **ESMO guidelines Working Group**. *Bladder cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up* These guidelines confirm on p.vi46 that the use of neoadjuvant chemotherapy was effective in reducing mortality rates. There are no other references in this source that confirm this result. http://dx.doi.org/10.1093/annonc/mdr376. See references 7 and 8.

[c] **National Comprehensive Cancer Network**. The 2011 guidelines confirm on p.MS-12 that the meta-analyses conducted by the authors established that neoadjuvant chemotherapy caused a significant decrease in death rate. There are no other references in this source that confirm this result. *Document is available on request* (log in needed for online access). See reference 46.

http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

[d] **Japanese Urological Association** http://www.urol.or.jp/en/guideline.html The 2010 guidelines confirm on p.114 that the meta-analyses conducted by the authors established that neoadjuvant chemotherapy improves the overall survival rate by 5%, and the recurrence-free rate by 9%. There are no other references in this source that confirm this result. http://dx.doi.org/10.1111/j.1442-2042.2010.02486.x. See references 91 and 92.

[e] **Associazione Urologi Italiani** http://www.auro.it/documenti-iniziative/linee-guida The 2010 guidelines confirm on p.172 that the meta-analyses conducted by the authors established that neoadjuvant chemotherapy increases the survival rate by 5-6%. There are no other references in this source that confirm this result. http://dx.doi.org/10.1111/j.1464-410X.2010.09324.x See references 151, 152 and 153.

[f] **Saudi Oncology Society** http://www.oncology.org.sa/portal The 2011 guidelines confirm on p.57 that the meta-analyses conducted by the authors established that neoadjuvant chemotherapy improved overall survival by 5-7%. There are no other references in this source that confirm this result. http://dx.doi.org/10.4103/0974-7796.78549. See references 22 and 23.

[g] **British Columbia Cancer Agency: Cancer Management Guidelines**. The 2008 guidelines confirm on p.1 that the meta-analyses conducted by the authors established that neoadjuvant chemotherapy caused a 5% improvement in survival at 5 years. There are no other references in this source that confirm this result. *Document is available on request.* See references 18 and 20. http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/default.htm

[h] **Association of Comprehensive Cancer Centres** http://www.oncoline.nl/index.php The 2009 guidelines confirm on p.37-39 that the meta-analyses conducted by the authors established that neoadjuvant chemotherapy resulted in an absolute improvement in the 5-year survival of 5%. There are no other references in this source that confirm this result. *Document is available on request.* See reference 45.

[i] **Alberta Health Services**. The 2011 guidelines confirm in the section 'Discussion – Advanced Stage Disease' that the meta-analyses conducted by the authors established that neoadjuvant chemotherapy resulted in a 14% reduction in the risk of death and 5% absolute increase in overall survival at five years. There are no other references in this source that confirm this result. http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-gu002-bladder.pdf. See references 23, 45 and 46.

[j] **Spanish Society of Medical Oncology** http://www.seom.org/en/publicaciones/guias-clinicas The 2011 guidelines confirm on p.554-555 that the meta-analyses conducted by the authors established that neoadjuvant chemotherapy demonstrated an improvement of 5-6.5% in 5 year survival. There are no other references in this source that confirm this result. Document is available online: http://dx.doi.org/10.1007/s12094-011-0696-8. See references 16 and 18.

[k] Apolo AB, Grossman HB, Bajorin D, Steinberg G, Kamat AM. Practical use of perioperative chemotherapy for muscle-invasive bladder cancer: summary of session at the Society of Urologic Oncology annual meeting. Urol Oncol. 2012 Nov-Dec;30(6):772-80. http://dx.doi.org/10.1016/j.urolonc.2012.01.012.

[l] Fedeli U, Fedewa SA, Ward EM. Treatment of muscle invasive bladder cancer: evidence from the National Cancer Database, 2003 to 2007. J Urol. 2011 Jan;185(1):72-8. http://dx.doi.org/10.1016/j.juro.2010.09.015

[m] Meeks JJ, Bellmunt J, Bochner BH, Clarke NW, Daneshmand S, Galsky MD, Hahn NM, Lerner SP, Mason M, Powles T, Sternberg CN, Sonpavde G. A systematic review of neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer. Eur Urol. 2012 Sep;62(3):523-33. http://dx.doi.org/10.1016/j.eururo.2012.05.048.