

NCRI Bladder Clinical Studies Group

Introduction

Bladder cancer is a common cancer in the UK, with 10,025 new cases in 2004. Around 90% of bladder cancers are transitional cell carcinomas for which clinical management differentiates between non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC). The delivery of health care for patients with bladder cancer is expensive; the UK total annual cost is £200 million of which 40% is allocated to treatment of NMIBC and 20% to investigation of haematuria and detection of disease.

The Bladder Clinical Studies Group (Bladder CSG) has focused on developing a portfolio which spans the spectrum from NMIBC to muscle invasive disease. This strategy is vitally important to engage urologists and oncologists both within the CSG and the wider community. To achieve this, the Bladder CSG has developed subgroups and working parties (WPs) with membership from beyond the CSG. The formation of new WPs has enabled a number of trials to be developed. The remit of the WPs is to stimulate research activity, identify research areas of unmet need, develop links with industry and develop cross cutting collaborations with other CSGs with an objective to broaden the spectrum of trials within the portfolio.

The portfolio continues to expand and having opened four large trials (BOXIT, LAMBS, SELENIB and SPARE) a focus has been to develop a pipeline of early phase trials testing novel agents and combination therapies. The aim is to have studies which can accrue and report early providing a pipeline for the development of future phase III trials. The portfolio is now broadly balanced enabling the Group to explore and develop trials in new areas including diagnostics, surgical technologies and early detection and prevention.

The Group was reviewed in April 2008. As part of the future planning, the CSG conducted a SWOT (strengths, weaknesses, opportunities and threats) analysis in 2009 which was productive and has helped to develop a strategy to be developed over the next 5 years.

Membership and structure

There are 18 clinical research members, (five urologists, eleven clinical or medical oncologists, one radiologist, and one clinical trials unit statistician), two consumer representatives and five observers or funding body representatives on the Bladder CSG. Membership is structured to represent the multidisciplinary nature of NMIBC and MIBC.

Professor John Kelly was appointed Chair in 2007 and will serve until 2010. The Group are indebted to Mr Andrew Thorpe, Mr Vinod Nargund and Dr Helen Patterson who stepped down in 2009. The appointment of new members has been very successful; Professor Malcolm Masson, Mr Hugh Mostafid and Mr Vijay Sangar have joined the CSG in 2008 and new appointments will be made in August 2009. Together they build on the multidisciplinary skill mix to strengthen the Group.

The Bladder CSG has two subgroups Chemotherapy and Penile Cancer. Three WPs were established in 2008/9 Early Phase Trials, Imaging and Radiobiology and a Disease Detection and Prevention to address key areas of strategic importance. Membership of subgroups and WPs has extended involvement of the research

community in the Group's work including representation from pathology, imaging as well as non-clinical expertise in molecular genetics.

The Chemotherapy Subgroup, chaired by Dr Ben Mead focuses on the development of phase III trials in localised and advanced MIBC. It is the longest established of the two subgroups and it encompasses chemo-radiotherapy trials and metastatic disease. The Penile Subgroup, established in February 2006, is chaired by Dr Jim Barber. Penile cancer is relatively uncommon and clinical management is provided as a supra-regional service in 12 UK Centres. The subgroup draws its core membership from the designated Penile Cancer Centers across the UK and enlists active participation from up to 20 specialists representing andrology, pathology, radiology and oncology who have attended meetings.

The Early Phase WP was set up because the Bladder CSG recognised a need to investigate novel agents through engagement with industry and access to the CRUK novel compounds pipeline. It is chaired by Dr Rob Jones and has resulted in a successful interaction between the CSG and an initiative between the NCRN and AstraZeneca. One study has been funded through CTAAC by this route and a second funding application is pending. The early phase WP has close links to the chemotherapy subgroup which itself has been successful in developing and funding two additional early phase trials. Investing in bladder cancer has not been viewed as high priority by pharma and links to initiatives such as the NCRI/AZ group are seen as vital and important to sustain development. As such, the early WP will remain active through 2009/10.

The Imaging and Radiobiology WP was set up in the first quarter of 2008 and is chaired by Dr Bernadette Carrington. The members met to discuss and identify areas of opportunity. The WP has established links with a clinical trials unit to further ideas with a view to developing a study in muscle invasive bladder cancer. The future of the Imaging and Radiobiology WP was discussed at the spring CSG meeting and with the advent of novel applications including PET imaging the view from the CSG was that the WP should continue through 2009/10. The Disease Detection and Prevention WP is chaired by Professor John Kelly and has produced a report setting out the current status relating to disease detection and prevention and highlighting areas for research. With the anticipation that funding will become available through national funding organisations the WP will remain active pending applications for primary research.

Dr Tom Powles represents the Group on the Translational CSG and is the representative for the EORTC. Several members have been active in exploring cross cutting themes. Dr Alison Birtle has established links with the Primary Care and Palliative Care CSDGs and Mr Leyshon Griffiths with the Lung CSG.

The Bladder CSG appointed a project officer, Dr Sarah Stearn who completed an audit to identify problems relating to recruitment of patients to surgical trials. The audit was helpful and identified a need for close working relationships between research staff and clinical nurse specialists. The audit was presented to the CSG Chairs Forum in June 2009.

The Bladder CSG is grateful for the support from the NCRI CSGs Secretariat which has been very helpful in the organisation of meetings and for circulation of items including agendas and minutes. In particular the support offered by Dr Eileen Loucaides is much appreciated. Dr Eileen Loucaides, Ms Elliann Fairbairn and Ms Ulla Ventham worked tirelessly to organise the GU Trials day. The UK Clinical Trials Units (CTUs) play a pivotal role supporting individual investigators and protocol

development. Selection of CTUs to develop and host trials is based on investigator links, CTU availability and remit and several CTUs, (Birmingham, Cardiff, ICR London and Southampton) are involved with the portfolio.

Portfolio and accrual

The Bladder CSG has 19 trials within the portfolio. Four are in NMIBC, eight in MIBC, six in Translational Research and one in Penile Cancer. Table 1 provides a summary of the trials portfolio and details of individual trials respectively.

Table 1: Bladder CSG portfolio

Acronym	Title	UK PI(s)	Status
BOXIT (Bladder COX-2 Inhibition Trial)	A randomised phase III placebo-controlled trial evaluating the addition of celecoxib to standard treatment of transitional cell carcinoma of the bladder	Prof John Kelly, Dr Emma Hall	Open
BS06*	A randomised study of radical radiotherapy in the management of pT1G3 NxM0 transitional cell carcinoma of the Bladder	Dr Stephen Harland	Closed - Reported
HYMN	A randomised trial of hyperthermia plus mitomycin versus BCG or Institutional standard in patients with high risk NMIBC	Mr John Kelly	Open
ODMIT C	A multicentre, prospective, randomised study to the value of a single dose of intravesical mitomycin in preventing the development of bladder tumours following nephroureterectomy for transitional cell carcinoma of the upper urinary tract	Mr Ralph Beard, Mr Tim O'Brien	Closed - in follow-up
SELENIB	Randomised controlled trial of selenium and vitamin E in the recurrence and progression of non muscle invasive bladder cancer (part of the Bladder Cancer Prognosis Programme)	Prof KK Cheng	Closed - in follow-up
BA11	Randomised phase III study comparing Paclitaxel/Cisplatin/Gemcitabine and Cisplatin/Gemcitabine in patients with metastatic or locally advanced urothelial cancer without prior systemic therapy [EORTC 30987	Closed - in follow-up	Closed - in follow-up
BC2001*	A randomised phase III study radiotherapy with and - without synchronous chemotherapy in muscle invasive bladder cancer.	Closed - in follow-up	Dr Robert Huddart, Prof Nicholas James
BCON*	A multicentre randomised trial of radical radiotherapy with carbogen in the radical radiotherapy of locally	Closed - in follow-up	Prof Peter Hoskin

	advanced bladder cancer		
BOLERO	A feasibility study to determine acceptance of randomisation between open and minimal access radical cystectomy	Open	Dr Ben Mead, Dr Peter Whelan
EORTC 30986	Randomised phase II/III study assessing gemcitabine with carboplatin and methotrexate with carboplatin and vinblastine in previously untreated patients with urothelial cancer ineligible for cisplatin based chemotherapy	Open	Dr Ben Mead, Dr Peter Whelan
EORTC 30994	Randomized phase III trial comparing immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4, and/or N+M0 transitional cell carcinoma (TCC) of the bladder	Open	Dr Michael Leahy
Gem v Mv	Randomised phase II study of Gemcitabine (Gem) or Methotrexate and Vinblastine (Mv) in advanced transitional cell carcinoma of the urothelium	Closed - in follow-up	Prof Peter Selby
LAMB	A phase II RCT of maintenance lapatinib versus placebo after 1st line chemotherapy in patients with Her 1/2 overexpressing locally advanced bladder cancer.	Open	Dr tom Powles
RT with Weekly GEM *	Phase II study of radiotherapy with concurrent weekly gemcitabine in muscle-invasive bladder cancer.	Closed - in follow-up	Dr Richard Cowan
SUCCINCT	A phase II trial of sunitinib in first line treatment of advanced / metastatic TCC .		
SPARE	SPARE - Randomised trial of Selective bladder Preservation Against Radical Excision (cystectomy) in muscle invasive T2/T3 transitional cell carcinoma of the bladder * feasibility study	Open	Dr Robert Huddart
TOTEM	A phase I/II trial of temsirolimus in 1st line advanced and metastatic TCC		
TOUCAN	A phase II trial of vandetanib plus gem carbo in patients with advanced/ metastatic TCC not eligible to receive cisplatin	In set up	Dr Rob Jones
ADVICE Study*	A feasibility study of molecular markers in patients with muscle invasive transitional cell carcinoma of the bladder entered into Neo-adjuvant chemotherapy trial	Open	Prof Nicholas James
BOXIT-T	Establishing a comprehensive bio-	Open	Prof John

	repositoruy linked to BOXIT		Kelly
BCPP	Bladder Cancer Prognosis Programme	Open	Prof KK Cheng
MCM5	Evaluation of urinary MCM5 as a diagnostic agent in genito-urinary malignancy.	Closed	Prof John Kelly
Pittsburgh Study	Investigation of suspected alterations in cytochrome activity in patients with bladder cancer by validated drug-cocktail protocol	Closed - in follow-up	Mr Raj Persad
SPARE-T	Establishing a comprehensive bio-repositoruy linked to SPARE	Open	Dr Rob Huddart
CPT11 and Cisplatin for penile carcinoma	International multicentre trial of Irinotecan (CPT11) and Cisplatin (CDDP) in metastatic or locally advanced penile carcinoma (EORTC 30992).	Closed - in follow-up	Prof Tim Oliver

The **BC20001** and **BECON** radiotherapy trials have completed successfully and together are the largest radiotherapy trials to have been conducted in bladder cancer in Europe or North America. These trials build on previous MRC trials track record in non-muscle invasive and invasive disease many of which have defined standards of care for patients within the spectrum of bladder cancer disease. Following on from these trials, the **SPARE** trial opened in 2007 and addresses, a key question; whether selective bladder preservation in patients who respond to neoadjuvant chemotherapy offer the same overall survival as radical cystectomy. The feasibility stage of this trial has been extended to determine whether it is possible to recruit patients to radical cystectomy versus radiotherapy arm. The trial aim to recruit 100 patients within 2 years will be extended to three years and measures of how equipoise is relayed to patients will be explored.

The high prevalence of NMIBC is a major contributor to the high health economic cost of bladder cancer. Several trials have opened in NMIBC and test agents which may reduce disease recurrence and, progression from non-invasive to invasive disease. **BOXIT** is a UK wide study recruiting patients with intermediate and high risk NMIBC to address the question whether addition of celecoxib to standard therapy is more effective than standard therapy plus placebo. **BOXIT** opened in 2007 and in May 2009 UK 30 centres had recruited 107 patients.

SELENIB is a phase III randomised controlled trail which will determine the benefit of addition of selenium plus vitamin E in patients with intermediate and high risk NMIBC. **SELENIB** is now open and has recruited 100 patients; the trial is a component of a larger tissue and bio-fluid collection study **BCBP** incorporating lifestyle measures and occupational history which is recruiting to target. The translational studies **BOXIT-T** and **BCBP** and **SPARE-T** opened in 2007 and are embedded within the clinical trials. The trials will establish a comprehensive bio-repository spanning the disease spectrum of non-invasive and invasive disease.

LAMBs is a phase III, randomised, two-arm comparison of maintenance lapatinib versus placebo in patients with HER 1 and/or HER 2 over-expressing metastatic bladder cancer. The trial opened in 2009 and aims to recruit 240 cases across the UK with potential to open in additional European centres.

HYMN is a randomised phase III trial of hyperthermia plus mitomycin-c versus a second course of BCG in patients with NMIBC with disease recurrence following

BCG. The study will open in 2009 and as with the LAMBs, study engagement with centres outside the UK is planned and a means of establishing links for future collaboration.

In penile cancer, the **TPF** study is a feasibility study chemotherapy for locally advanced and metastatic penile cancer. The study is the first to be developed by the Penile Subgroup and awarded funding by the FSC in late 2007. It was opened in 2009.

Recruitment to studies in 2008/9 was 5.1% of incidence cases. 4.4% was to RCTs and 0.7% was to non RCTs. In total 515 patients were recruited to studies.

The recruitment rate is well below the target accrual rate of 10% for all cancers. The growth in bladder trials has meant that the accrual rate is almost double that for the period 2007/8 and is expected to continue to grow. The new trials, which are in development in NMIBC and MIBC, will contribute to the improved accrual rates in the short to medium term. Accrual will also increase as new centres open and a network is established with centres feeding into bladder cancer trials.

Trials in Early Development

Five early phase and feasibility trials have been approved and are in set up. **TOTEM**, **SUCCINCT** and **TOUCAN** are phase I/II studies in 1st line advanced and metastatic disease. These studies which will incorporate novel agents (the mTOR kinase inhibitor Temsirolimus, multi-targeted receptor tyrosine kinase Sunitinib and Vandetanib) with cisplatin or carboplatin build on the novel agents currently being assessed in bladder cancer and will provide valuable information about the feasibility of future phase III studies in the disease. A phase I study of radiotherapy plus cetuximab has been funded by CTAAC and will open in 2009. The CSG is currently considering studies which will be attractive in 2nd line advanced and metastatic setting.

BOLERO is a surgical trial to determine the feasibility of randomising patients to open versus laparoscopic or robotic radical cystectomy approved by the FSC. **BOLERO** will determine whether a phase III study of minimal access technologies, which are now playing an important role in the management of invasive disease, should be considered.

Collectively these studies herald what will be an exciting decade to come and a new invigorating direction which seeks to improve the outcomes for bladder cancer through molecular targeting and introduction of novel surgical technologies. The search for new targets continues unabated through translational experimental research. Studies which aim to target critical processes involved in bladder cancer tumourigenesis, such as aurora kinase, are in development.

The CSG is keen to explore ways of improving outcomes for patients with NMIBC. Several novel technologies are available including hyperthermia (Synergo) and electro motive drug administration (EMDA). Both require validation and a phase III of EMDA versus BCG and Synergo versus BCG with cross comparisons of quality of life and health economic analysis is in development. Funding applications will be submitted in 2009 with a view to opening in 2010/11.

A trial of surgery versus chemo-resection for low risk NMIBC has been proposed and a trial development group has been established. For low risk NMIBC there is potential to explore novel strategies to control disease and to test different surveillance protocols. The design of a study to test both aspects is currently under consideration. The development of future studies in NMIBC will focus on ways to

improve detection and may address issues relating to screening. The availability of biomarkers which may alter the positive predictive value offers an ideal opportunity and can be tested in these settings.

The CSG is considering how best to improve the management of upper tract disease. As an entity there is a paucity of high quality evidence regarding optimal management for muscle invasive, upper tract disease and a study of neo-adjuvant or adjuvant chemotherapy would be attractive in this setting. The disease is however relatively uncommon and plans to develop a study may require international collaborations to be successful.

Imaging studies are seen as integral to trials in the advanced disease setting and may answer questions such as the detection of occult nodal disease and accurate staging of disease. The Imaging and Radiobiology Working Party will seek to develop a study which can recruit across several trials to address this issue.

Meetings

In 2008/9, the Bladder CSG joined forces with the Prostate, Renal and Testes CSG for a National genitor-urinary (GU) Trials Day. The meeting was held in London and attended by about 300 delegates. The theme was survivorship and the program attracted delegates from nursing and medical backgrounds. Feedback was very good and highlighted a need for the GU groups to come together to explore common issues relevant to urological cancers. The success of the event has prompted the chairs to meet to discuss a second GU Trials day planned in early 2010.

The Bladder CSG has had a significant presence at the British Association of Urological Surgeons (BAUS) and the British Uro-Oncology Group (BUG) national meetings and the BAUS Section of Oncology meeting. These national meetings bring together the uro-oncology community and are important forums for raising the profile of the Group.

Collaborations

The Bladder CSG is actively welcoming researchers seeking to develop ideas and proposals and this is an important step towards becoming more integrated into the UK research community. Our links with other CSGs have been developed to move forward specific areas which are considered important, for example, with the Primary Care CSDG to develop studies around screening and early disease detection. New links are being developed and the CSG is working with the Colorectal CSG to explore agents which may be relevant to a secondary prevention trial and with the Palliative Care CSG to explore aspects of survivorship.

The role of the Early Phase Trials working party has been important in developing collaborative links with industry. It remains important to foster links with pharma and the CSG will continue to develop this aspect.

The Bladder CSG has links with the EORTC although to date the link has not established a common protocol. Dr Tom Powles has agreed to act as the Group's lead to develop the link and if possible to open a study which can be a test bed for future trials. Collaborations with several EU groups are established and the CSG has identified the LAMBS study as a test case for European collaborative links. We have also made contact with the Australian Prostate and Urological Group APUG and have agreement to explore the possibility of opening existing studies within our portfolios with a view to developing common trials.

3-year strategy

The key strategic elements for the next 3 years are set out below;

- Continue to promote awareness of the CSG, its portfolio and its potential to delivery high quality National Trials engaging Urologists, Oncologists and the Research Community.
 - Effective communication at National Meetings.
 - Dissemination of information at Regional workshops / meetings
 - Education and service development through trials meetings
 - Continue with an Annual National Trials Day in 2010

- Engage trials centres to establish a solid networked infrastructure
 - Ensure that current trials meet accrual targets
 - Continue to identify trials centres and investigators across UK networks

- Build upon the success of subgroups and ensure that working parties fulfil their remit to develop trials in key areas identified by subgroups and working parties
 - Imaging and radiobiology
 - Disease detection and prevention
 - Early phase trials

Priorities for next year

The Groups priorities for next year are to:

- Monitor recruitment to the new studies
- Engage the research community and raise the profile of the Group.
- Ensure that the studies which are currently funded and in set-up open and accrue on target.

Professor John Kelly, Chair

Appendix 1

2008/09 Publications and abstracts

Non Muscle Invasive Bladder Cancer

Kalsi J, Harland SJ, Feneley MR. Electromotive drug administration with mitomycin C for intravesical treatment of non-muscle invasive transitional cell carcinoma. *Expert Opin Drug Deliv.* 2008 Jan;5(1):137-45.

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Saeb-Parsy K, Veerakumarasivam A, Wallard MJ, Thorne N, Kawano Y, Murphy G, Neal DE, Mills IG, Kelly JD. MT1-MMP regulates urothelial cell invasion via transcriptional regulation of Dickkopf-3. *Br J Cancer.* 2008 Jul 29.

Veerakumarasivam A, Warren A, Wallard MJ, Scott HE, Neal DE, Collins VP and Kelly JD. High-Resolution Array-Based Comparative Genomic Hybridization of Bladder Cancers Identifies Mouse Double Minute 4 (MDM4) as an Amplification Target Exclusive of MDM2 and TP53. *Clin Cancer Res.* 2008 May 1;14(9):2527-34.

Horvath A, Mostafid H. Therapeutic options in the management of intermediate-risk nonmuscle-invasive bladder cancer. *BJU* 2008;103:726-769.

Dovedi SJ, Kirby JA, Atkins H, Davies BR, Kelly JD. Celecoxib has Potent Anti-Tumour Effects as a Single Agent and in Combination with BCG Immunotherapy in a model of Urothelial Cell Carcinoma. *Eur Urol.* 2008 Jan 15; 7;96(9):1384-93

C. Moynihan, E. Hall, R. Lewis, A. Birtle, G. M. Mead, R. Huddart, on behalf of the SPARE Trial Management Group; SPARE: A qualitative study investigating randomization barriers in a Selective Bladder Preservation trial (SBP) (ISCRCTN: 61126465). *J Clin Oncol* 27:15s, 2009 (suppl; abstr 5077)

Huddart R, Hall E, James N, Hussain S, Crundwell M, Jenkins P et al. Effect of radiotherapy volume of bladder toxicity: First report of the BC2001 trial: a multicentre phase III randomised trial of standard versus reduced volume radiotherapy trial ISCRCTN No. 68324339. *Radiother Oncol* 88[2], S19 #64. 2008. *Ref Type: Abstract*

Huddart R, Hall E, James N, Hussain S, Crundwell M, Tremlett J et al. BC2001; A multicentre phase III randomised trial of synchronous chemotherapy versus no chemotherapy and standard versus reduced volume radiotherapy in muscle invasive bladder cancer. *NCRI Cancer Conference 2008 #C164 Ref Type: Abstract*

Huddart RA, Hall E, James N, Crundwell M, Tremlett J, Jenkins P et al. Effect of Reducing Radiotherapy Volume on Bladder Toxicity: First Report of the BC2001 Trial; A Multicenter Phase III Randomized Trial of Standard versus Reduced Volume Radiotherapy Trial Iscrtn No. 68324339, Eudract No. 2004-000164-26. *International Journal of Radiation Oncology*Biology*Physics* 72[1, Supplement 1], S292-S293. 1-9-2008. *Ref Type: Abstract*

James N, Hussain S, Rawlings C, Jenkins P, Tremlett J, Crundwell M et al. BC2001; a multicentre phase III randomised trial of standard versus reduced volume

radiotherapy trial, with and without synchronous chemotherapy in muscle invasive bladder cancer. *NCRI Cancer Conference 2008 #A189 Ref Type: Abstract*

James ND, Hussain SA, Tremlett J, Crundwell M, Jenkins P, Rawlings C et al. First Toxicity Report of the BC2001 Trial: A Multicentre Phase III Randomised Trial of Radiotherapy with and without Synchronous Chemotherapy in Muscle Invasive Bladder Cancer ISCRTN No. 68324339, EUDRACT No. 2004-000164-26. *International Journal of Radiation Oncology, Biology and Physics* 72[1, Supplement 1], S7. 1-9-2008. *Ref Type: Abstract*