Chemotherapy for bladder cancer: an update

HEATHER A. PAYNE, RHONA McMENEMIN, JAMES GREEN, BENJAMIN W. LAMB, CARYS THOMAS, JAWAHER ANSARI AND JODIE BATTLEY

This report is based on a workshop seminar held during the 8th Annual Meeting of the British Uro-oncology Group. The workshop covered a range of topics in bladder chemotherapy, from a discussion of the use of multidisciplinary teams in this area, to a review of UK practice and an international update on second-line treatment of metastatic bladder cancer. The session closed with the presentation of two bladder cancer case histories.

Dr Rhona McMenemin emphasised the importance of bladder cancer in most urology practices by stating that an estimated 104,400 incident cases of bladder cancer were diagnosed in Europe in 2006, representing 6.6 per cent of the total cancers in men and 2.1 per cent in women.1 The most common form of bladder cancer is transitional cell carcinoma of the urothelium (TCCU), which represents around 90 per cent of all bladder cancers and is associated with a median survival of four to six months if left untreated.2

However, in spite of its prevalence and aggressiveness, very few new options for the management of TCCU have emerged over recent years, and the five-year survival rate in England and Wales actually appears to have declined over the period 1991–2006.3

Although TCCU is a chemosensitive tumour, there are no new drugs and very few treatment options, compounded by a prevalence of performance status-2 patients in the first- and second-line setting.

Dr McMenemin suggested that another possible reason for the lack of recent progress in management options for bladder cancer is competition from other urological cancers, particularly prostate and renal cancer, in which rapid advances are currently being made.

MULTIDISCIPLINARY TEAM ASPECTS OF TREATING ADVANCED BLADDER CANCER

Decisions in surgical oncology are increasingly being made by multidisciplinary teams (MDTs), which are now widely accepted as the preferred model for cancer service delivery. In the UK, all new cases of suspected or diagnosed bladder cancer must be referred to the MDT for discussion. However, if patients who have already been discussed at the MDT meeting suffer progression or recurrence, there is no requirement for re-referral.

Dr Lamb presented results of an online survey of 50 clinical oncologists, 29 cancer nurse specialists and five surgeons, which investigated the usual clinical practice of treating advanced bladder cancer among the specialists surveyed, and explored current attitudes to the management of advanced disease by the MDT.
**THE BRITISH URO-ONCOLOGY GROUP**

The British Uro-oncology Group (BUG) was formed in 2004 to meet the needs of clinical and medical oncologists specialising in the field of urological cancers. As the only dedicated professional association for uro-oncologists, its overriding aim is to provide a networking and support forum for discussion and exchange of clinical management, research and policy ideas. The group's objectives continue to be achieved in a number of ways, including regular newsletters (BUG Bytes), an interactive website (www.bug.uk.com), regional themed meetings, production of learning aids in the form of written guidelines and information DVDs for healthcare professionals and patients. A primary focus for BUG is its annual meeting for its entire membership, with plenary sessions and smaller group seminars with open debate on topical and challenging issues, all led by leading experts.

The results of the survey highlighted the variation in the way cases of advanced bladder cancer were treated among the respondents, particularly regarding the timing of staging investigations, treatment with second-line chemotherapy and referral to the MDT for advice on managing advanced bladder cancer.

Most respondents confirmed that attending the urology MDT meeting required a significant proportion of time, with many devoting two to three hours per week. However, around two-thirds of respondents reported that they found the meetings useful in terms of saving time later, particularly by being up-to-date with plans and results.

Drs James Green and Ben Lamb described frustrations with their own MDT until they began collecting formal metrics to assess its effectiveness and then implemented a series of interventions to improve internal processes. Similar ideas for streamlining the urology MDT meeting, such as prioritising cases, or treating simple cases by protocol, were popular among respondents, although splitting the MDT meeting by tumour type or complexity was not seen as a good idea.

**Group discussion**

Participants at the workshop felt that MDTs currently devote a lot of time to the in-depth discussion of a number of cases, which could actually be dealt with more quickly. Some commented that if a chairman's action is used to streamline cases too frequently, this can be raised as a concern during peer review. Dr Green commented that this was a widely held view, and that collecting formal metrics provides the evidence necessary to show that this system should be modified.

Dr Green also commented on the importance of attaching formal costings to MDT meetings when the time spent by all the senior staff required at these meetings is considered. He felt that this would provide a strong case for streamlining certain cases within these meetings.

Advance preparation was felt to be of critical importance prior to an MDT meeting so that more patient cases could be discussed, making the meeting more focused and less stressful for all participants.

Some participants felt that, in spite of the use of MDTs, some smaller centres were still managing bladder cancer with the available therapies, and not necessarily the optimal management strategy. The problem of bladder cancer care being delegated to junior doctors and nurse specialists rather than physicians with an interest in bladder cancer was also discussed.

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**UK PRACTICE AND INTERNATIONAL UPDATE ON SECOND-LINE TREATMENT OF METASTATIC BLADDER CANCER**

Dr Carys Thomas described current UK practice for treatment of metastatic bladder cancer, stating that a consensus in first-line therapy was well established, with most centres using gemcitabine/cisplatin. Gemcitabine/cisplatin plus paclitaxel has not generally been adopted, largely because of the high toxicity, while physicians are awaiting the results of the CALGB 90601 trial before adding in bevacizumab.

In terms of second-line therapy for metastatic bladder cancer, there is much more variance in treatments used. Choice of chemotherapy depends on first-line treatment used, prior chemosensitivity, duration of response and presence of visceral metastasis.

**Vinflunine**

Vinflunine is a third-generation vinca alkaloid, with a pharmacological profile that suggests it may offer advantages in bladder cancer.

Following two promising phase 2 studies, a large phase 3 European study was conducted in which patients with advanced TCCU who had experienced progression after a first-line platinum-containing regimen were randomised to treatment with best supportive care (BSC) plus vinflunine or BSC alone. Overall survival in the eligible intention-to-treat population was significantly higher in the BSC plus vinflunine group compared with BSC alone (6.9 versus 4.3 months, \( p = 0.04 \)). The updated survival analysis showed a 22 per cent reduction in risk of death after a 3.5-year follow-up (\( p = 0.02 \)). Importantly, quality-of-life data were collected in the trial and showed a trend towards improvement, although this did not reach statistical significance. Patients treated with vinflunine also reported significantly reduced pain, and required less palliative treatment.
On the basis of this study, the European Association of Urology has offered the following guidance: ‘Currently, vinflunine is the only approved second-line treatment; any other treatment should take place in the context of clinical trials’ (level of evidence 1b, recommendation A*).1

Dr Thomas concluded by highlighting the number of ongoing trials in this area, and emphasising what an exciting time this is in the development of new therapeutic options for first-line, second-line and maintenance treatment of metastatic bladder cancer (Table 1).

**CASE HISTORY 1**
Dr Jodie Battley presented a case of a 64-year-old man who presented to his GP in August 2009 with a six-week history of intermittent haematuria and polyuria with no medical comorbidities and an Eastern Cooperative Oncology Group score of 1. He was subsequently diagnosed with TCC of the bladder in September, with an initial clinical staging of at least cT2N0. However, following radical cystectomy and ileal pouch formation, he was restaged pathologically as pT3N2 (5/16 lymph nodes positive), stage IV disease, with an incidental finding of prostate adenocarcinoma (Gleason 3+4=7).

Treatment consisted of four cycles of adjuvant cisplatin/gemcitabine. However, restaging computed tomography (CT) after adjuvant chemotherapy in April 2010 showed disease progression with new liver metastases in at least three segments of the liver.

Treatment with vinflunine (320mg/m², 20-minute intravenous infusion every three weeks) was commenced in May 2010. The patient remained well during treatment, reporting some mild, grade 1 fatigue. No constipation was reported, although he was treated with regular prophylactic laxatives and encouraged to increase oral hydration around chemotherapy cycles. His energy levels were described as excellent, and he gained weight during chemotherapy.

The initial-response scan at 12 weeks showed improvement in all lymph metastases (a partial response) and no evidence of new disease. The patient completed 13 cycles of treatment and remained clinically well throughout. On the restaging CT scan in January 2011, however, he reported lethargy and was found to have progression of disease in the liver and new retroperitoneal nodes.

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<td>- Double-blind, international randomised phase 2</td>
<td>- Pazopanib versus paclitaxel</td>
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<td>- Cisplatin + gemcitabine + sunitinib</td>
<td>- HER1 and/or HER2 over-expressing metastatic or locally advanced bladder cancer</td>
<td>German study</td>
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<td>Vinflunine + pazopanib</td>
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<td>- Patient achieved objective response or stable disease with first-line chemotherapy</td>
<td>Vinflunine + Phase 1/2 single arm</td>
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<td>- Carboplatin + gemcitabine + vandetanib</td>
<td>- Randomised to maintenance lapatinib versus placebo</td>
<td>NUCOG3 Scandinavian study</td>
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<td>Vinflunine + sorafenib</td>
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<td>- Maintenance vinflunine following objective response or stable disease with first-line gemcitabine/cisplatin</td>
<td>NUCOG2 Scandinavian study</td>
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<td>- Cisplatin + gemcitabine + temsirolimus</td>
<td>- European study</td>
<td>Vinflunine versus vinflunine + pemetrexed</td>
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Table 1. Planned and ongoing studies in first-line, second-line and maintenance treatment of metastatic bladder cancer
Although the benefit of third-line chemotherapy in this setting was considered to be small, because of his excellent performance status and level of motivation, the patient was commenced on treatment with single-agent paclitaxel. Unfortunately, this was not well tolerated and he died in hospital in March 2011, having received just four treatments.

This case highlights how patients with advanced metastatic TCC can have a prolonged response to vinflunine with minimal toxicity.

CASE HISTORY 2
Dr Jawaher Ansari presented a case of a 64-year-old patient who presented in May 2007 with G3 pT1 TCC bladder. A CT scan performed in December 2009 showed pelvic and para-aortic lymph node metastases. Because the patient did not have muscle-invasive disease at presentation, he had a laparoscopic biopsy, which confirmed that he had metastatic TCC. Although he had some degree of hypertension and hypercholesterolaemia, he was otherwise fit and a non-smoker.

He was commenced on first-line treatment with gemcitabine (1250mg/m² on days 1 and 8) and cisplatin (70mg/m² on day 1) intravenous every 21 days, receiving six cycles between February and June 2010. A CT scan following this treatment indicated that the disease had stabilised.

Within four months, the patient presented with a left supraclavicular fossa lymph node mass (7×5cm) and right hip pain (grade 6/10). CT scan showed extensive metastases involving mediastinal, pelvic and para-aortic lymph nodes along with a large deposit over the psoas muscle.

The patient received vinflunine (320mg/m², 20-minute intravenous infusion every three weeks) on a named-patient basis. Treatment was tolerated well, with mild constipation and nausea being managed effectively medically.

The patient received significant clinical, symptomatic and radiological benefit from vinflunine chemotherapy. After just one cycle, he reported that his pain had disappeared. The para-aortic lymph nodes were shown to have reduced in size considerably. The patient experienced a progression-free interval of eight months. However, a recent scan showed the original tumour to be larger in size than at initial presentation, and other clinical signs have also deteriorated.

The patient will be offered best supportive care, palliative radiotherapy, and possibly third-line chemotherapy.

This case highlights the potential benefit of vinflunine in prolonging progression-free survival in appropriately selected patients.

Declaration of interests
The British Uro-oncology Group seminar ‘Update on bladder cancer’ was sponsored by an educational grant from Pierre Fabre. Pierre Fabre was involved in the selection and briefing of speakers, and the payment of speaker honoraria, but had no editorial control over any publications arising from the meeting.

REFERENCES