PERGAMON

European Journal of Cancer 36 (2000) S1–S6

European Journal of Cancer

www.ejconline.com

Advanced bladder and urothelial cancers

D. Raghavan *

University of Southern California, Norris Comprehensive Cancer Center, 1441 Eastlake Avenue, Los Angeles, CA 90033, USA

Abstract

After more than 40 years of use, cytotoxic chemotherapy has an evolving role in the management of advanced bladder cancer. Standard single-agent regimens, such as methotrexate, doxorubicin, vinblastine and cisplatin, have produced objective response rates of 15–25%, and combination chemotherapy causes objective regression in 50–75% of cases. Novel compounds such as ifosfamide, the taxanes and gemcitabine are now being incorporated into combination regimens, having shown activity in this disease, both in previously treated and untreated cases. The phenomenon of stage migration, with increased precision of imaging, leads to the inclusion of different populations of patients with advanced disease into protocols of assessment of chemotherapy. This may cause an artifact of improved outcome, when in fact the higher response rates and longer survival figures may reflect a reduced burden of disease and case selection. It is thus essential to validate novel approaches in well structured, randomised clinical trials that compare new strategies against established standard protocols. Historical comparisons serve only to confuse the issue by introducing errors from case selection bias, stage migration and differences in duration of follow-up and supportive technologies.

Keywords: Bladder cancer; Chemotherapy; Clinical trials

1. Introduction

In the past 25 years, there has been a slow and steady progress in the management of advanced bladder cancer. Objective response rates to combination chemotherapy as high as 65–75% have been recorded in the past few years, in contrast to single-agent response rates of only 10–15% in the first recorded series of chemotherapy for bladder cancer. Similarly, median survival figures have increased from 3–4 months up to 18–20 months, with long-term survival of 20–30%, depending on the characteristics of the patients receiving treatment.

Although only 20% of bladder cancer cases are clinically advanced at presentation, many patients with superficial or locally invasive disease eventually recur or develop metastases. Thus, the management of advanced, inoperable cancer of the urinary tract is a much more common problem than would be inferred from the published incidence figures for metastatic bladder cancer alone.

The median survival of patients presenting with metastatic cancer of the urinary tract who do not receive cytotoxic chemotherapy is only 3–4 months [1]. Despite the more than doubling of the median survival figures since the introduction of chemotherapy [1,2], more than 80% of such cases will result in death from cancer, thus more effective treatment is required. This supplement reviews some of the recent progress in the management of advanced bladder cancer, with a specific focus on gemcitabine, one of the more promising of the novel compounds recently introduced into the management of bladder cancer.

2. Biology of advanced bladder cancer

There is a continuum between superficial and advanced bladder cancer, and little information is available regarding the specifics of the biology of advanced disease. In general, advanced disease is associated with less differentiated histology, aneuploidy and advanced T stage of the primary tumours. Where loss of heterozygosity of chromosome 9 appears to be associated with the initiation of bladder carcinogenesis in superficial disease, advanced cancer appears to require the presence of aberrations of *TP53* in most instances. The common sites of metastases include regional lymph nodes, bone, lung, skin and liver, and less frequently brain, meninges, vagina and the organs within the peritoneal cavity [3–5].

* Tel.: +1-323-865-3962; fax: +1-323-865-0061.

0959-8049/00/$ - see front matter
PII: S0959-8049(00)00075-7

The initial presentation depends on the sites of involvement, but may also reflect the non-specific constitutional features of advanced malignancy, such as asthenia, weight loss, malaise and fatigue. When planning treatment, it is important to recognise that the distribution of metastases correlates with prognosis. More prolonged survival is seen in patients with lymph node and soft tissue disease, and a substantially worse prognosis in those with liver and bone metastases [2,6,7].

This issue is also of importance when attempting to set different series into context. Thus, the use of various staging technologies may contribute to different distributions of cancer being treated in different series (the phenomenon of stage migration) [8]. For example, in the early series of the 1970s and 1980s, clinical examination and relatively crude imaging techniques led to the identification of metastatic disease and entry into treatment programmes for metastatic bladder cancer (essentially representing 'high volume' disease). In contrast, in more recent series, computerised tomographic or magnetic resonance imaging scans, with a much higher resolving power, may identify tiny metastatic deposits, which may be confirmed as being malignant via positron emission tomography. This, in turn, leads to patients being entered into trials of chemotherapy for metastatic disease who may have a much smaller tumour burden and a concomitantly better prognosis. These factors are of import when attempting to assess the true benefits of novel treatments, and justify using randomised trial design to achieve this.

There are also clear differences in the results of treatment of transitional cell carcinoma, compared with the non-transitional cell types (adenocarcinoma and squamous carcinoma) of metastatic uroepithelial cancer [2,9]. The non-transitional histologies appear to be much less responsive to conventional chemotherapy. As reviewed by Khaled and colleagues (pp. S34–S37) in this supplement, novel compounds also appear to give lower objective response rates for schistosomiasis-associated non-transitional cell bladder cancer than for transitional cell carcinoma.

The dominant histology of most biopsied metastatic deposits is transitional cell carcinoma, but there is considerable occult heterogeneity within individual deposits of transitional cell cancer. This applies with respect to histology, growth kinetics, DNA content, gene expression and markers of cytotoxic response and resistance, and this may affect the outcome of chemotherapy [1,10]. Furthermore, the concept that bladder cancer has origins in a stem cell is becoming increasingly respected, and may explain some of the complexities in attaining cure in this disease [10]. This may explain the presence of mixed populations of transitional cell cancer and non-transitional histologies within individual metastatic deposits and even within primary tumours.

It has also become increasingly clear that specific determinants of response to chemotherapy can be identified in bladder cancer cells, including *P*-glycoprotein [11] and glutathione [12]. Recent data have also suggested the possibility that altered expression of p53 may correlate with increased resistance to combination chemotherapy regimens, such as methotrexate, vinblastine, doxorubicin, cisplatin (M-VAC) [13]. However, we have previously shown in bladder cancer cell lines that the expression of p53 itself may be upregulated by exposure to chemotherapy.

3. Conventional chemotherapy: single agents

Chemotherapy has been used for metastatic bladder cancer for the past 40 years. However, in early studies, the reproducibly quantifiable response rates were low and long-term survival was uncommon [14,15]. Most single agents yield objective responses in approximately 10–20% of cases, including complete responses in less than 5–10% [14–16].

It appears that the most rigorous assessment of response has been documented in randomised clinical trials. Thus, there was a paradoxical decrease in reported objective response rates from the 1960s to the 1980s, due largely to changing the precision of reporting. However, this was associated with apparent improvement in overall outcomes, as measured by median and long-term survival. Many of the cited randomised trials have been performed in more recent times, and consequently this improvement in outcomes could have been due to the phenomenon of stage migration or may also reflect an increased willingness to treat patients more aggressively and improved supportive care.

Most randomised trials of single-agent chemotherapy have produced response durations of less than 3–4 months. The most active 'standard' single agents against transitional cell carcinomas include cisplatin, methotrexate, vinblastine, mitomycin C and doxorubicin [1,14–16].

4. Conventional chemotherapy: combination regimens

Combination regimens were initially developed in an attempt to increase response rates and duration of survival. For more than a decade, the use of combination regimens appeared to improve response rates without a corresponding increase in survival, as reviewed in detail elsewhere [1]. Typical combination regimens that increased toxicity without a significant improvement of survival over single-agent therapy included cyclophosphamide/doxorubicin/cisplatin [17,18] and methotrexate/cisplatin [19].

With the development of regimens combining methotrexate, vinblastine and cisplatin (with or without doxorubicin), higher response rates with more durable remissions were achieved [20,21]. At the Memorial Sloan-Kettering Cancer Center in particular, the M-VAC regimen was even shown to yield complete pathological remissions in patients with liver and bone metastases, with long-term survival reported in more than 60–70% of complete responders [22].

A multicentre, randomised trial, which compared single-agent cisplatin with the M-VAC regimen, demonstrated for the first time a survival benefit from the combination regimen [2]. Cisplatin alone produced a median survival of 8 months, whereas the M-VAC regimen gave a median survival of 12 months, similar to the follow-up experience from the Memorial Sloan-Kettering Cancer Center and other non-randomised trials (Table 1) [23]. The tail of the survival curve at 2 years confirmed the superiority of the combination regimen, but a long-term follow-up study showed that the majority of patients in both arms were dead within 5 years [7]. It should be emphasised, however, that most of the long-term survivors were in the group treated with the M-VAC regimen.

In another randomised trial, Logothetis and colleagues [24] also demonstrated superiority of the M-VAC regimen, in this instance compared with the combination of cisplatin, doxorubicin and cyclophosphamide (CAP). This result was not surprising, given the lack of difference between CAP and single agents in a series of earlier randomised trials [17,18].

The M-VAC regimen has justifiably been viewed as a standard of care, with several series from the 1980s producing objective response rates in the broad range of 40–70%, but with reproducible median survival figures of approximately 1 year (Table 1) [2,22,24–27]. However, more recent experience suggests that the median survival may have increased by as much as 50% [27]. This calls into question the definition of what constitutes the 'standard of care' in the year 2000.

5. New agents for bladder cancer

Recently, several novel compounds have been shown to be active against transitional cell carcinoma, and are now being tested in combination chemotherapy trials. Several of these drugs have objective single-agent response rates of 25–30%, or have demonstrable anticancer effects in some patients who have previously received chemotherapy for metastatic disease. Some of the potentially promising innovations are reviewed in this supplement, and include ifosfamide [28], paclitaxel [29], docetaxel [30] and gemcitabine [31–33]. However, it should not be forgotten that some previous innovations appear to have failed to fulfil their early promise. For example, trimetrexate, mitoxantrone and gallium have not found their way into 'routine' management of advanced bladder cancer after many years of clinical trial experience.

Even the early promise of carboplatin, as summarised by D.J. Vaughn (pp. S7–S12), has recently come under a cloud in view of the disappointing single-agent response rates [34] and the median survival figures achieved from the doublet of paclitaxel and carboplatin in several clinical trials [35,36].

Thus, it is important that the agents discussed in this supplement be validated in well structured clinical trials, and in particular that randomised comparisons be carried out against standard treatments. For this purpose, the M-VAC regimen has been viewed as the 'gold standard', as it remains the one regimen proven to yield a survival benefit in randomised trials. However, as noted above, we must carefully consider what constitutes a 'standard' result from the M-VAC regimen in the year 2000. In past experience, as reviewed in Table 1, patients treated with the M-VAC regimen could expect a median survival of approximately 12 months. However, in more recent experience from the Memorial Sloan-Kettering Cancer Center, it appears that a more realistic median survival is in the range of 16–18 months [27]. At present, it is not clear whether this apparent increment is due to stage migration, improved supportive care, case selection or other factors.

In this supplement, D.F. Bajorin discusses the potential role of the combination of ifosfamide, paclitaxel and cisplatin (ITP), reporting preliminary results with a median survival of approximately 18 months. Whilst encouraging, these data must be taken in the context of the contemporary Memorial Sloan-Kettering Cancer Center experience with the M-VAC regimen. Thus, before we can accept the ITP regimen as a significant step forward, it must be tested against the M-VAC regimen or another appropriate standard.

Similarly, the important contributions from H. von der Maase and J. Bellmunt and colleagues (pp. S17–S25) effectively review the various combination regimens that incorporate gemcitabine, but cannot set them into a final context. Several groups have demonstrated

Table 1
International experience with M-VAC regimen [23]

Number of cases	Response CR (%)	Category total (%)	Median survival (months)	Series
121	26	72	13.4	Sternberg [22]
30	13	43	10.0	Tannock [25]
55	35	65	11.0	Logothetis [24]
67	19	57	13.0	Boutan-Laroze [26]
120	13	38	12.5	Loehrer [2]
17	12	94	18	McCaffrey [27]

CR, complete remission.

that gemcitabine can be administered effectively in combination programmes with agents such as cisplatin and paclitaxel [37–39]. However, it will remain for structured clinical trials to demonstrate whether any of these approaches represents a major step forward.

At present, the formal presentation of data from randomised trials comparing the M-VAC regimen against the combination of gemcitabine–cisplatin (sponsored by Eli Lilly and Company) and against the paclitaxel–carboplatin regimen (Eastern Cooperative Oncology Group) is awaited with interest. The rhetoric in reporting of phase II trials ignores the variables of case selection bias, and really does not clarify whether progress is truly being made and is, therefore, not an appropriate basis for changing routine standards of clinical care.

6. Changing roles for chemotherapy in locally advanced, clinically non-metastatic disease

In the past two decades, several studies have attempted to incorporate systemic chemotherapy into regimens that include definitive primary treatment, with the aim of reducing the symptoms and size of the primary tumour (thereby facilitating surgery or radiotherapy) and controlling occult systemic metastases [1]. The major approaches for combining systemic and local therapies have included the use of neoadjuvant (first-line) chemotherapy, adjuvant chemotherapy after the treatment of the primary tumour, and concurrent chemoradiation or schedules of perioperative chemotherapy.

To date, despite the publication of many promising phase I–II clinical trials, the vast majority of randomised assessments have failed to demonstrate any survival benefit from neoadjuvant cytotoxic chemotherapy. A meta-analysis of the early randomised trials has confirmed this observation [40]. Most recently, the first reports of large trials conducted, by the European Organization for Research and Treatment of Cancer–Medical Research Council (EORTC–MRC) Intergroup [41] and by the Radiation Therapy Oncology Group (RTOG) [42] respectively, have shown that initial chemotherapy with the combination of cisplatin–methotrexate–vinblastine does not substantially improve long-term survival.

Apart from a single randomised trial that demonstrated improved local control from the combination of cisplatin plus radiotherapy versus radiotherapy alone [43], there have been no randomised trials that have demonstrated improved overall survival from this approach. Shipley, one of the primary innovators in this field, has argued that the role of chemoradiation should only be to improve local control, and that it remains for systemic chemotherapy to change overall survival. At present, most studies appear to be concentrating on improving schedules of delivery and combinations of chemotherapy and radiation, rather than focusing on the important issue of whether this approach truly confers a survival benefit [44].

Strategies of adjuvant cytotoxic chemotherapy have also been tested. An early randomised trial from the University of Southern California reported a survival benefit from the use of adjuvant cyclophosphamide–doxorubicin–cisplatin [45], although the true utility of this approach has been heavily challenged. More recently, under-powered randomised trials have shown improved disease-free survival from the use of adjuvant CMV or M-VAC, but have failed to confirm an overall survival benefit [46,47]. At present, it appears most likely that survival may be improved by the use of adjuvant therapy. This hypothesis is being tested in a multicentre, randomised trial, conducted by the University of Southern California and Baylor College of Medicine, in which the molecular prognosticator, *TP53*, determines eligibility for chemotherapy for patients with invasive bladder cancer who have negative lymph nodes after surgery and lymphadenectomy. Patients are randomised to an observation arm or to adjuvant chemotherapy with the M-VAC regimen. This study will answer important questions regarding the utility of molecular prognostication, as well as defining the true utility of adjuvant chemotherapy for patients with invasive, node-negative disease.

With the availability of the various new cytotoxic agents discussed above, it is likely that investigators will begin to address the role of these agents in the treatment of locally invasive, clinically non-metastatic disease. The reduced profile of toxicity lends itself to multimodality combination approaches, especially as this may facilitate early use after radical surgery. However, caution will be required in combining the potent radiosensitisers, paclitaxel and gemcitabine, with radical radiotherapy. I believe that it is dangerous to introduce regimens that have not yet been validated in the context of metastatic disease into front-line, unstructured programmes of neoadjuvant or adjuvant chemotherapy. Whether paclitaxel–carboplatin, or gemcitabine–cisplatin, will prove to be more or less effective than the M-VAC regimen remains to be determined, and thus the role of these new combinations in adjuvant treatment for bladder cancer is still undefined. Thus, it will also be very important in this setting to complete the appropriate clinical trials (such as the current adjuvant trial of the Eastern Cooperative Oncology Group) before attempting to modify standards of care in the community.

Although important progress has been made in the management of invasive and metastatic bladder cancer in the past two to three decades, more than half the patients with invasive and metastatic disease are still destined to die of their disease, and thus there remains a real need for new treatment strategies. Although progress has been steady, it has been hampered sub-

stantially by the impediments to entry of patients into clinical trials, including the role of some health provider organisations and some physicians with a bias against structured clinical investigation.

References

1. Raghavan D, Shipley WU, Garnick MB, *et al*. The biology and management of bladder cancer. *N Engl J Med* 1990, **322**, 1129–1138.
2. Loehrer PJ, Einhorn LH, Elson PJ, *et al*. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a Cooperative Group Study. *J Clin Oncol* 1992, **10**, 1066–1072.
3. Cooling CI. Review of 150 post-mortems of carcinoma of the urinary bladder. In Wallace DM, ed. *Tumours of the Bladder*. Edinburgh, E. and S. Livingstone, 1959, 171–186.
4. Babaian RJ, Johnson DE, Llamas L, *et al*. Metastases from transitional cell carcinoma of the urinary bladder. *Urology* 1980, **16**, 142–144.
5. Raghavan D, Chye RWM. Treatment of carcinomatous meningitis from transitional cell carcinoma of the bladder. *Br J Urol* 1991, **67**, 438–440.
6. Geller NL, Sternberg CN, Penenberg D, Scher H, Yagoda A. Prognostic factors for survival of patients with advanced urothelial tumors treated with methotrexate, vinblastine, doxorubicin, and cisplatin chemotherapy. *Cancer* 1991, **67**, 1525–1531.
7. Saxman SB, Propert K, Einhorn LH, *et al*. Long-term follow up of phase III intergroup study of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a Cooperative Group Study. *J Clin Oncol* 1997, **15**, 2564–2569.
8. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985, **312**, 1605–1608.
9. Sternberg CN, Swanson DA. Non-transitional cell bladder cancer. In Raghavan D, Scher HI, Leibel S, Lange PH, eds. *Principles and Practice of Genitourinary Oncology*. Philadelphia, Lippincott-Raven, 1997, 315–330.
10. Brown JL, Russell PJ, Philips J, Witherspoon J, Raghavan D. Clonal analysis of a bladder cancer cell line: an experimental model of tumour heterogeneity. *Br J Cancer* 1990, **61**, 369–376.
11. Petrylak DP, Scher HI, Reuter V, O'Brien JP, Cordon-Cardo C. P-glycoprotein expression in primary and metastatic transitional cell carcinoma of the bladder. *Ann Oncol* 1994, **3**, 835–840.
12. Pendyala L, Velagupudi S, Toth K, Glaves D, Creaven PJ, Raghavan D. Transitional studies of glutathione in bladder cancer cell lines and human specimens. *Clin Cancer Res* 1997, **3**, 793–798.
13. Bajorin D, Sarkis A, Reuter V, *et al*. Invasive bladder cancer treated with neoadjuvant M-VAC: the relationship of p53 nuclear overexpression with survival. *Proc Am Soc Clin Oncol* 1994, **13**, 232.
14. Carter S, Wasserman TM. The chemotherapy of urologic cancer. *Cancer* 1975, **36**, 729–747.
15. Yagoda A. Chemotherapy for metastatic bladder cancer. *Cancer* 1980, **45**, 1565–1572.
16. Young DC, Garnick MB. Chemotherapy in bladder cancer: The North American experience. In Raghavan D, ed. *The Management of Bladder Cancer*. London, Edward Arnold, 1988, 245–263.
17. Khandekar JD, Elson PJ, DeWys WD, Slayton RE, Harris DT. Comparative activity and toxicity of cis-diamminedichloroplatinum (DDP) and a combination of doxorubicin, cyclophosphamide, and DDP in disseminated transitional cell carcinomas of the urinary tract. *J Clin Oncol* 1985, **3**, 539–545.
18. Troner M, Birch R, Omura GA, *et al*. Phase III comparison of cisplatin alone versus cisplatin, doxorubicin and cyclophosphamide in the treatment of bladder (urothelial) cancer: a South Eastern Cancer Study Group trial. *J Urol* 1987, **137**, 660–662.
19. Hillcoat BL, Raghavan D, Matthews J, *et al*. A randomized trial of cisplatin versus cisplatin plus methotrexate in advanced cancer of the urothelial tract. *J Clin Oncol* 1989, **7**, 706–709.
20. Harker WG, Meyers FJ, Freiha FS, *et al*. Cisplatin, methotrexate, and vinblastine (CMV): an effective chemotherapy regimen for metastatic transitional cell carcinoma of the urinary tract: a Northern California Oncology Group study. *J Clin Oncol* 1985, **3**, 1463–1470.
21. Sternberg CN, Yagoda A, Scher HI, *et al*. Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium. *J Urol* 1985, **133**, 403–407.
22. Sternberg CN, Yagoda A, Scher HI, *et al*. Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. *Cancer* 1989, **64**, 2448–2458.
23. Levine E, Raghavan D. M-VAC for bladder cancer: time to move forward again. *J Clin Oncol* 1993, **11**, 387–389.
24. Logothetis CJ, Dexeus FH, Finn L, *et al*. A prospective randomized trial comparing M-VAC and CISCA chemotherapy for patients with metastatic urothelial tumors. *J Clin Oncol* 1990, **8**, 1050–1055.
25. Tannock K, Gospodarowicz M, Connolly J, *et al*. M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) chemotherapy for transitional cell carcinoma: the Princess Margaret Hospital experience. *J Urol* 1989, **142**, 289–292.
26. Boutan-Laroze A, Majhoubi M, Droz JP, *et al*. M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced carcinoma of the bladder. The French Federation of Cancer Centers Experience. *Eur J Cancer* 1991, **27A**, 1690–1694.
27. McCaffrey JA, Hilton S, Mazumdar M, *et al*. Phase II randomized trial of gallium nitrate plus fluorouracil versus methotrexate, vinblastine, doxorubicin, and cisplatin in patients with advanced transitional-cell carcinoma. *J Clin Oncol* 1997c, **15**, 2449–2455.
28. Witte RS, Elson P, Bono B, *et al*. Eastern Cooperative Oncology Group Phase II trial of ifosfamide in the treatment of previously treated advanced urothelial carcinoma. *J Clin Oncol* 1997, **15**, 589–593.
29. Roth BJ, Dreicer R, Einhorn LH, *et al*. Significant activity of paclitaxel in advanced transitional-cell carcinoma of the urothelium: a phase II trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 1994, **12**, 2264–2270.
30. McCaffrey JA, Hilton S, Mazumdar M, *et al*. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. *J Clin Oncol* 1997, **15**, 1853–1857.
31. Pollera CF, Ceribelli A, Crecco M, Calabresi F. Weekly gemcitabine in advanced bladder cancer: a preliminary report. *Ann Oncol* 1994, **5**, 132–134.
32. Stadler W, Kuzel T, Roth B, Raghavan D, Dorr FA. Phase II study of single-agent gemcitabine in previously treated patients with metastatic urothelial cancer. *J Clin Oncol* 1997, **15**, 3394–3398.
33. Moore MJ, Tannock I, Ernst DS, Huan S, Murray N. Gemcitabine: a promising new agent in the treatment of advanced urothelial cancer. *J Clin Oncol* 1997, **15**, 3441–3445.
34. Medical Research Council. A phase II study of carboplatin in metastatic transitional cell carcinoma of the bladder. *Eur J Cancer* 1987, **23A**, 375–377.
35. Redman B, Smith DC, Flaherty L, Du W, Hussain M. Phase II trial of paclitaxel and carboplatin in the treatment of advanced urothelial carcinoma. *J Clin Oncol* 1998, **16**, 1844–1848.
36. Vaughn DJ, Malkowicz SB, Zoltick B, *et al*. Paclitaxel plus carboplatin in advanced carcinoma of the urothelium: an active and tolerable outpatient regimen. *J Clin Oncol* 1998, **16**, 255–260.

37. Moore MJ, Tannock I, Winquist E, *et al*. Gemcitabine (G) plus cisplatin (C): an active regimen in advanced transitional cell carcinoma (TCC). *Proc Am Soc Clin Oncol* 1998, **17**, 320a.
38. Stadler WM, Murphy B, Kaufman D, Raghavan D, Voi M. Phase II trial of gemcitabine (GEM) plus cisplatin (CDDP) in metastatic urothelial cancer (UC). *Proc Am Soc Clin Oncol* 1997, **16**, 323a.
39. Von der Maase H, Andersen I, Crino L, Weissbach L, Doglioti L. A phase II study of gemcitabine and cisplatin in patients with transitional cell carcinoma (TCC) of the urothelium. *Proc Am Soc Clin Oncol* 1997, **16**, 324a.
40. Ghersi D, Stewart LA, Parmar MKB, *et al*. Does neoadjuvant cisplatin based chemotherapy improve survival of patients with locally advanced bladder cancer? A meta-analysis of individual patient data from randomized clinical trials. *Br J Urol* 1995, **75**, 206–213.
41. International collaboration of trialists on behalf of the MRC Advanced Bladder Cancer working party, EORTC Genitourinary Group, Australian Bladder Cancer Study Group, *et al*. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer. A randomized controlled trial. *Lancet* 1999, **354**, 533–540.
42. Shipley WU, Winter KA, Kaufman DS, *et al*. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. *J Clin Oncol* 1998, **16**, 3576–3583.
43. Coppin CML, Guspodarowicz MK, James K, *et al*. Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. *J Clin Oncol* 1996, **14**, 2901–2907.
44. Raghavan D. Editorial: Bladder preservation in patients with bladder cancer–quality versus quantity of life? *J Urol* 1998, **160**, 1678–1679.
45. Skinner DG, Daniels JR, Russell CA, *et al*. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. *J Urol* 1991, **145**, 459–467.
46. Stockle M, Meyenburg W, Wellek S, *et al*. Advanced bladder cancer (stages pT3b, pT4a, pN1 and pN2): improved survival after radical cystectomy and 3 adjuvant cycles of chemotherapy: results of a controlled prospective study. *J Urol* 1992, **148**, 302–307.
47. Freiha FS, Reese J, Torti F. A randomized trial of radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. *J Urol* 1996, **155**, 495–500.