Pergamon

European Journal of Cancer, Vol. 33, Suppl. 1, pp. S23–S26, 1997

Printed in Great Britain
0959–8049/97 $17.00+0.00

PII: S0959-8049(96)00337-1

Metastatic Bladder Cancer: Advances in Treatment

W.M. Stadler,[1] T.M. Kuzel,[2] D. Raghavan,[3] E. Levine,[3] N.J. Vogelzang,[4] B. Roth[5] and F.A. Dorr[6]

[1]Section of Hematology/Oncology, University of Chicago, Chicago, Illinois; [2]Robert H. Lurie Cancer Center, North-Western University, Chicago, Illinois; [3]Roswell Park Memorial Institute, Buffalo, New York; [4]University of Chicago, Chicago, Illinois; [5]Indiana University, Indianapolis; [6]Eli Lilly and Company, Indianapolis, U.S.A.

At present, a combination of cisplatin, methotrexate, vinblastine and doxorubicin is the most widely used chemotherapy for metastatic bladder cancer. However, long-term follow-up shows that this combination may have little effect on survival. In addition, this regimen is toxic. New agents are needed which combine efficacy with good safety profiles. Agents which have been investigated include gallium nitrate, interferon-α and paclitaxel both as single agents and in combination with established cytotoxic drugs. A number of studies have been conducted in bladder cancer with the novel nucleoside analogue, gemcitabine. Response rates of up to 33% have been recorded in two phase II studies. Gemcitabine was well tolerated in both studies with few of the side-effects normally associated with cytotoxic drugs. A third study is ongoing. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: clinical trials, bladder cancer, gemcitabine, chemotherapy, review
Eur J Cancer, Vol. 33, Suppl. 1, pp. S23–S26, 1997

INTRODUCTION

BLADDER CANCER is a common disease estimated to strike > 50 000 patients in the United States in 1995 [1]. Most patients present with localised disease, but despite adequate surgical resection, 20–50% of patients with muscle invasive disease eventually progress [2]. Based on a number of randomised studies over the last 5 years, standard therapy for metastatic bladder cancer is cisplatin-based combination chemotherapy [3–5]. The most extensively studied of these regimens remains the combination of cisplatin, methotrexate, vinblastine and doxorubicin (MVAC).

This regimen was first published in 1985 [5] and has been the subject of numerous subsequent reports. Initial reports were very enthusiastic with response rates of 70% and complete response rates of 18% [5, 6]. More recently, this enthusiasm has been tempered by results from multi-institutional randomised studies. In one of the largest such studies, MVAC was compared to single-agent cisplatin in a total of 246 patients [3]. Although there was a clear benefit in the MVAC arm in both response rate as well as overall survival, only 39.5% of the MVAC-treated patients responded and the median survival was only 12.5 months. In addition, long-term follow-up has shown that many responses are not durable [7, 8]. Finally, it should be noted that response rates and survival in patients with metastatic disease involving liver and/or bone are even lower [3, 6].

The administration of MVAC in full doses is also associated with significant toxicities, especially in the elderly population in whom this disease is most prevalent. Alopecia is almost universal, some degree of nausea and vomiting occurs in most patients and is severe in 12% [3]. Grade 3 or 4 anaemia occurs in 1%, greater than or equal to grade 3 neutropenia occurs in 24–58% (with 10–25% experiencing febrile neutropenia), greater than or equal to grade 3 mucositis occurs in 13–17%, and 7% experience significant renal insufficiency [3–6]. Fortunately, more serious toxicities such as cardiac toxicity, requirements for dialysis and death are rare but do occur in 1–5% of patients.

There have been a number of efforts to decrease the toxicity or increase the effectiveness of this regimen, but no dramatic improvements have been accomplished. Although the administration of colony-stimulating factors ameliorates some of the neutropenia and mucositis and decreases antibiotic usage, overall toxicity and hospital stay have not been significantly affected [9, 10]. In addition, despite the use of these agents, dose escalation of standard MVAC has not been possible [11–13]. As such, a consensus is emerging that new, more effective and less toxic regimens for this disease need to be developed [14].

Newer regimens

A number of new agents and combination regimens for metastatic bladder cancer have been described over recent years. Although not complete, a brief overview of some of these is illustrative.

The success of cisplatin-based therapy in this disease has prompted evaluation of other transition metal compounds as therapeutic agents. Gallium nitrate was first noted to have

Correspondence to T.M. Kuzel.

Table 1. Single-agent response rates in bladder cancer

Agent	Number of patients	Response rate (%)	95% CI	Reference
Cisplatin	242	35	29–41	22–31
Methotrexate	236	29	23–35	32–39
Vinblastine	28	18	6–37	40
Vincristine	62	23	13–35	41, 42
Doxorubicin	248	17	12–23	43–47
5-Fluorouracil	105	15	18–22	46, 48–50
Paclitaxel	26	42	23–63	21
Gallium nitrate	73	25	15–36	15, 16, 51
Ifosfamide	101	28	19–38	42, 52, 53

activity in bladder cancer in studies performed through the Southwest Oncology Group and at the University of Colorado [15, 16]. Further development was slowed by the toxicities of this agent which included hypocalcaemia, hypomagnesaemia, nephrotoxicity, hearing loss and optic neuritis. More recently, Indiana University and the Eastern Cooperative Oncology Group have successfully introduced gallium into a combination regimen with vinblastine and ifosfamide [17, 18]. In 67 patients from two trials, there were 24 partial and 11 complete responses giving an overall response rate of 52%. Toxicities of this combination were formidable, however, and, even with dose reductions in high-risk patients, included febrile neutropenia in 13%, severe cardiac toxicity in 13%, severe neurotoxicity in 5% and 2 treatment-related deaths [18].

A combination programme of interferon-α, cisplatin and 5-fluorouracil has also been investigated at the MD Anderson Cancer Center. They treated 28 previously treated patients and reported a response rate of 61% (7% complete response) [19]. Similar results were observed in a Greek study of previously untreated patients [20].

Paclitaxel has also been investigated in this disease. In the initial study, 26 previously untreated patients were treated at a dose of 250 mg/m^2 over 24 h on a 21-day schedule [21]. There were 11 responses including 7 complete responses for an overall response rate of 42%. Severe toxicities included granulocytopenia fever in 2 patients, grade 3 mucositis in 3 patients, grade 3 neuropathy in 3 patients and grade 4 diarrhoea in 1 patient. Combination trials with paclitaxel are currently underway.

Table 1 summarises the response rates of various single agents used in the treatment of metastatic and locally advanced bladder cancer. It should be noted that this represents a compilation of multiple, different studies, testing different patient populations, tumour stages, study designs and various degrees of rigour to confirm responses. For example, in the recent multi-institutional, randomised study of single-agent cisplatin versus MVAC in patients with metastatic disease, the response rate to cisplatin alone was only 11.6% [3]. The response rates quoted in Table 1 thus tend to be optimistic when applied to patients with widely metastatic disease. Nevertheless, single-agent response rates of $> 30\%$ are unusual.

Gemcitabine in bladder cancer

As detailed in other reports in this issue, gemcitabine has been shown to have impressive single-agent activity in a number of solid tumours. In addition, this agent is very well tolerated, and can be administered to elderly, chronically ill patients with minimal side-effects.

It has also been noted that a number of patients with metastatic bladder cancer who were enrolled in a phase I study of gemcitabine in Europe responded [54]. In that study, 15 patients (14 previously treated with MVAC, 1 chemotherapy naive patient) were treated with at least 875 mg/m^2 weekly for 3 weeks every 28 days. There were 1 complete and 3 partial responses for an overall response rate of 27%. We thus elected to perform a phase II study of gemcitabine in previously untreated patients with bladder cancer.

38 patients (27 male/11 female) have been enrolled in this study through four participating clinical centres. Patients were eligible if they had metastatic transitional cell cancer, had normal laboratory values, a Karnofsky performance status of 60–100%, and had not been previously treated with chemotherapy for metastatic disease. Prior adjuvant or neoadjuvant therapy was allowed if at least 6 months had elapsed since the completion of therapy. Patient characteristics are detailed in Table 2 and include a median age of 70 years (range: 42–88), and a median Karnofsky performance status of 90%. 6 patients (16%) had received previous cisplatin-containing adjuvant or neoadjuvant therapy. Treatment consisted of 1200 mg/m^2 gemcitabine i.v. weekly for 3 weeks on a 28-day cycle. There were no withdrawals or dose reductions due to toxicity. In 27 evaluable patients there were 7 partial and 2 complete responses for an overall response rate of 33% (11 patients were not evaluable because their treatment was ongoing). Toxicity was generally mild and consisted mostly of WHO grade 1 and 2 neutropenia and nausea. Only a few grade 3 or 4 toxicities were noted (Table 3).

In a similar trial reported by De Lena and colleagues, 18 patients with metastatic bladder cancer that had failed one prior cisplatin-containing regimen were treated with 1250 mg/m^2 weekly for 3 weeks on a 28-day cycle [55]. In 15 evaluable patients there were 3 complete and 1 partial response for an overall response rate of 27%. Toxicities were also mild with no WHO grade 3 or 4 neutropenia, 33% grade 3 or 4 thrombocytopenia, 20% grade 3 or 4 anaemia and 13% elevated liver enzymes. A third trial of gemcitabine in patients with metastatic bladder cancer is being performed in Canada, but has not yet been reported (M. Moore, Princess Margaret Hospital, Canada).

Table 2. Characteristics of patients in a phase II study of gemcitabine in bladder cancer

Sex (M/F)	27/11
Race (Caucasian/African American)	36/2
Age—median (range)	70 (41–88) years
Karnofsky performance status	90 (70–100)
Prior adjuvant/neoadjuvant therapy	6

Table 3. Summary of WHO grade 3 and 4 toxicities in a phase II study of gemcitabine in bladder cancer

Toxicity	WHO grade 3	WHO grade 4
Neutropenia	1	1
Thrombocytopenia	1	0
Nausea/vomiting	2	0
Deep venous thrombosis	2	0
Fever	1	0
Hypokalaemia	1	0
Oedema	1	0

CONCLUSION

Metastatic bladder cancer, although a 'chemosensitive' disease, remains a frustrating tumour to treat. The best standard regimen, MVAC, produces a good response rate (40–70%), but disappointing long-term survival and excessive toxicity. The identification of a number of new agents with excellent single-agent response rates is, however, very encouraging. Paclitaxel, ifosfamide and gemcitabine all produce response rates of > 25%. There are at least two trials confirming the high response rate for gemcitabine [54, 55], and the low toxicity associated with this agent makes it particularly attractive to investigate in multi-agent studies. A number of such studies are being planned and their results as well as the results of long-term follow-up in the current studies must be awaited before definitive recommendations on the use of gemcitabine or these other agents in metastatic transitional cell cancer can be made.

1. Wingo PA, Tong T, Bolden S. *Cancer Statistics CA* 1995, **45**, 8–30.
2. Raghavan D, Shipley WU, Garnick MD, *et al.* Biology and management of bladder cancer. *New Engl J Med* 1990, **322**, 1129–1138.
3. 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**, 1066–1073.
4. Logothetis CJ, Dexeus FH, Finn L, *et al.* A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. *J Clin Oncol* 1990, **8**, 1050–1055.
5. 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.
6. 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.
7. Conner JP, Olsson CA, Benson MC, *et al.* Long-term follow-up in patients treated with methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) for transitional cell carcinoma of the urinary bladder: cause for concern. *Urology* 1989, **34**, 353–356.
8. Igawa M, Kadena H, Usui T. Long term results with M-VAC for advanced urothelial cancer: high relapse rate and low survival in complete response patients. *J Urol* 1994, **151**, abstract no. 454.
9. Gabrilove JL, Jakubowski A, Scher H, *et al.* Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. *N Engl J Med* 1988, **318**, 1414–1422.
10. Moore MJ, Iscoe N, Tannock IF. A phase II study of methotrexate, vinblastine, doxorubicin, and cisplatin plus recombinant human granulocyte-macrophage colony stimulating factors in patients with advanced transitional cell carcinoma. *J Urol* 1993, **150**, 1131–1134.
11. Logothetis C, Sella A, Amato R, *et al.* Escalated MVAC ± rhGMCSF in patients with advanced metastatic transitional cell carcinoma of the bladder. *J Urol* 1993, **149**, abstract no. 318.
12. Loehrer PJ, Elson P, Dreicer R, *et al.* Escalated dosages of methotrexate, vinblastine, doxorubicin, and cisplatin plus recombinant human granulocyte colony-stimulating factor in advanced urothelial carcinoma: an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 1994, **12**, 483–488.
13. Seidman AD, Scher HI, Gabrilove JL, *et al.* Dose-intensification of MVAC with recombinant granulocyte colony-stimulating factor as initial therapy in advanced urothelial cancer. *J Clin Oncol* 1993, **11**, 408–414.
14. Levine E, Raghaven D. MVAC for bladder cancer-time to move forward again. *J Clin Oncol* 1993, **11**, 387–389.
15. Crawford ED, Saiers JH, Baker LH, *et al.* Gallium nitrate in advanced bladder carcinoma: A Southwest Oncology Group study. *Urology* 1991, **38**, 355–357.
16. Seligman PA, Crawford ED. Treatment of advanced transitional cell carcinoma of the bladder with continuous-infusion gallium nitrate. *J Natl Cancer Inst* 1991, **83**, 1582–1584.
17. Einhorn LH, Roth BJ, Ansari R, *et al.* Phase II trial of vinblastine, ifosfamide, and gallium combination chemotherapy in metastatic urothelial carcinoma. *J Clin Oncol* 1994, **12**, 2271–2276.
18. Dreicer R, Roth B, Propert K, *et al.* Vinblastine, ifosfamide, and gallium nitrate (VIG) in advanced carcinoma of the urothelium: a phase II trial of the Eastern Cooperative Oncology Group. *Proc Am Soc Clin Oncol* 1995, **14**, abstract no. 246.
19. Logothetis C, Dieringer P, Ellerhorst J, *et al.* A 61% response rate with 5-fluorouracil, interferon-α2b and cisplatin in metastatic chemotherapy-refractory transitional cell carcinoma. *Proc Am Assoc Cancer Res* 1992, **33**, abstract no. 221.
20. Bacoyiannis C, Skarlos D, Aravantinos G, *et al.* Cisplatin, interferon A2B and 5-fluorouracil for advanced urothelial cancer: a phase II study. *Proc Am Soc Clin Oncol* 1995, **14**, abstract no. 234.
21. 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.
22. Yagoda A. Phase II trials in patients with urothelial tumors: Memorial Sloan-Kettering Cancer Center. *Cancer Chemother Pharmacol* 1983, **11** (Suppl), 9–12.
23. Herr HW. Cis-diamminedichloride platinum II in the treatment of advanced bladder cancer. *J Urol* 1980, **123**, 853–857.
24. Peters PC, O'Neill MR. Cis-diamminedichloroplatinum as a therapeutic agent in metastatic transitional cell carcinoma. *J Urol* 1980, **12**, 375–377.
25. Merrin C. Treatment of advanced bladder cancer with cis-diamminedichloroplatinum II: a pilot study. *J Urol* 1978, **119**, 493–495.
26. Soloway MS, Ikard M, Ford K. Cis-diamminedichloroplatinum (II) in locally advanced and metastatic urothelial cancer. *Cancer* 1981, **47**, 476–480.
27. De Lena M, Lorusso V, Lacobellis U, Marzullo F, Maiello E, Crammarosa A. Cis-diamminedichloroplatinum activity in bidimensionally measurable metastatic lesions of bladder carcinoma. *Tumori* 1984, **70**, 85–88.
28. Oliver RTD, Newlands ES, Wiltshaw E, Malpas JS. A phase II study of cis-platinum in patients with recurrent bladder carcinoma. *Br J Urol* 1981, **53**, 444–447.
29. Rossof AM, Talley RW, Stephens RL, *et al.* Phase II evaluation of cis-dichlorodiammineplatinum (II) in advanced malignancies of the genitourinary and gynecologic organs: a Southwest Oncology Group study. *Cancer Treat Rep* 1981, **63**, 1557–1564.
30. Fagg SI, Dawson-Edwards P, Hughes MA, Latief TN, Rolfe EB, Fielding JWL. Cis-diamminedichloroplatinum (DDP) as initial treatment of invasive bladder cancer. *Br J Urol* 1984, **56**, 296–300.
31. Raghavan D, Pearson B, Cuval P, *et al.* Initial intravenous cis-platinum therapy; improved management for invasive high-risk bladder cancer. *J Urol* 1985, **133**, 399–402.
32. Turner AG, Hendry WF, Williams GB, Bloom HJG. The treatment of advanced bladder cancer with methotrexate. *Br J Urol* 1977, **49**, 673–678.
33. Hall RR, Bloom HJG, Freeman JR, Nawrocki A, Wallace DM. Methotrexate treatment for advanced bladder cancer. *Br J Cancer* 1977, **35**, 40–51.
34. Gad-el-Mawla NH, Hamsa R, Cairns J, Anderson T, Ziegler JL. Phase II analysis of methotrexate in carcinoma of the bilharzial bladder. *Cancer Treat Rep* 1978, **62**, 1075–1076.
35. Natale RB, Yagoda A, Watson RC, Whitmore WF, Blumenreich M, Braun DW. Methotrexate: an active drug in bladder cancer. *Cancer* 1981, **47**, 1246–1250.
36. Turner AG. Methotrexate for advanced bladder cancer. *Cancer Treat Rep* 1981, **62**, 183–186.
37. Oliver RTD. Methotexate as selvage or adjunctive therapy for primary invasive carcinoma of the bladder. *Cancer Treat Rep* 1981, **65**, 179–182.
38. Oliver RTD, England HR, Risdon RA, Blandy JP. Methotrexate in the treatment of metastatic and recurrent primary transitional cell carcinoma. *J Urol* 1984, **131**, 483–485.
39. Hall RR, Newling DWW, Ramsden PD, Richards B, Robinson MRG, Smith PH. Treatment of invasive bladder cancer by local resection and high dose methotrexate. *Br J Urol* 1984, **56**, 668–672.
40. Blumenreich MS, Yagoda A, Natale RB, Watson RC. Phase II trial of vinblastine sulfate for metastatic urothelial tract tumors. *Cancer*

1982, **50**, 435–438.
41. Richards R, Newling D, Fossa S, *et al.* Vincristine in advanced bladder cancer; an EORTC phase II trial. *Cancer Treat Rep* 1983, **6**, 575–578.
42. Gad-el-Mawla N, Ziegler J, Hamza R, Elserafi M, Khaled H. Phase II chemotherapy trials of 5-FU, cyclophosphamide, ifosfamide, and vincristine in carcinoma of the bilharzial bladder. *Cancer Treat Rep* 1984, **68**, 419–420.
43. Pavone-Mascaluso M, EORTC Genitourinary Cooperative Group A. Single drug chemotherapy of bladder cancer with Adriamycin, VM-26, or bleomycin. *Eur Urol* 1976, **2**, 138–141.
44. O'Bryan RM, Baker LH, Gottlieb JE, *et al.* Dose–response evaluation of Adriamycin in human neoplasm. *Cancer* 1977, **39**, 1940–1948.
45. Yagoda A, Watson RC, Whitmore WF, Grabstald H, Middleman MF, Krakoff IH. Adriamycin in advanced urinary tract cancer; experience in 42 patients and review of the literature. *Cancer* 1977, **9**, 79–285.
46. Knight EW, Pagand EM, Hahn RG, Horton J. Comparison of 5-FU and doxorubicin in the treatment of carcinoma of the bladder. *Cancer Treat Rep* 1983, **67**, 514–515.
47. Gagliano R, Levin H, El-Bolkainy MN, *et al.* Adriamycin versus Adriamycin plus cis-dichlorodiammineplatinum (II) in advanced transitional cell bladder carcinoma; a Southwest Oncology Group study. *Am J Clin Oncol* 1983, **6**, 215–218.
48. Ducheck M, Edsmyr F, Naeslund I. 5-Fluorouracil in the treatment of recurrent cancer of the urinary bladder. In Pavone-Imacaluso M, Smith P, Edsmyr F, eds. *Bladder Tumors and Other Topics in Urologic Oncology*. New York, Plenum Press, 1980, 381–385.
49. Smalley RV, Bartolucci AA, Hemstreet G, *et al.* A phase II evaluation of a 3 drug combination of cyclophosphamide, doxorubicin, and 5-fluorouracil and of 5-fluorouracil in patients with advanced bladder carcinoma or stage D prostatic carcinoma. *J Urol* 1981, **125**, 191–195.
50. Fossa SD, Gudmundsun TE. Single-drug chemotherapy with 5-FU and Adriamycin in metastatic bladder carcinoma. *Br J Urol* 1981, **53**, 320–323.
51. Seidman AD, Scher HI, Heinemann MH, *et al.* Continuous infusion gallium nitrate for patients with advanced refractory urothelial tract tumors. *Cancer* 1991, **68**, 2561–2565.
52. Otaguro K, Ueda K, Niijima T, *et al.* Clinical evaluation of Z4942 (ifosfamide) for malignant urological tumors. *Hinyokika Kiyo* 1981, **27**, 459–462.
53. Witte R, Loehrer P, Dreicer R, *et al.* Ifosfamide in advanced urothelial carcinoma: an ECOG trial. *Proc Am Soc Clin Oncol* 1993, **12**, abstract no. 230.
54. Pollera CF, Ceribelli A, Crecco M, Calabresi F. Weekly gemcitabine in advanced bladder cancer: a preliminary report from a phase I study. *Ann Oncol* 1994, **5**, 182–184.
55. De Lena M, Larusso V, Amadori D, *et al.* Gemcitabine in resistant stage IV bladder cancer: a phase II study. *Proc ECCO* 1995, abstract no. 1146.

Acknowledgements—Studies were supported by research grants from Eli Lilly and Company.