



NEW DRUGS AND NEW APPROACHES IN METASTATIC BLADDER CANCER

Joaquim Bellmunt Molins

Servicio de Oncología Médica
Hospital General Universitari Vall d' Hebron. Barcelona

With new agents becoming available, substantial single agent activity has been demonstrated for several single agents, as the antifolate piritrexim, the multi-targeted antifolate MTA, the taxanes paclitaxel and docetaxel, and gemcitabine ⁽¹⁻¹⁴⁾. Responses in phase II trials with either paclitaxel or docetaxel and gemcitabine in patients not previously treated with chemotherapy ranged from 25 to 40%, which compare favorably with the 17% obtained with single-agent cisplatin ^(1,3,6). Initial phase II studies of 2 drug combinations of docetaxel, or paclitaxel, with cisplatin, have shown activity in untreated patients, with response rates that are in the same range as is obtained with MVAC ⁽¹⁵⁻²⁰⁾, but to date there are no published comparative data with MVAC. In addition, several studies have tested the combination of paclitaxel with carboplatin, but again, and in line with the previous observation suggesting suboptimal efficacy of carboplatin-based chemotherapy, with several studies showing median survival figures of 8.5 - 9.5 months ⁽²¹⁻²⁶⁾, there is concern whether carboplatin should be substituted for cisplatin in those patients who are sufficiently fit to tolerate a cisplatin-based regimen. A SWOG phase II trial ⁽²⁴⁾ in 29 patients and an ECOG phase II trial ⁽²⁶⁾ in 42 patients reported a response rate of only 21% (8% - 40%, 95% CI) and 20.6% (8.9% - 38.9%, 95% CI). In terms of response rate, these results are substantially poorer than the previous trials. Nevertheless, the median overall survival time was 9 and 8.7 months, a figure similar to previously mentioned studies and also similar to the carboplatin-methotrexate-vinblastine ⁽²⁷⁾. Two small and underpowered randomized studies have suggested suboptimal efficacy of carboplatin-methotrexate-vinblastine chemotherapy when compared with cisplatin-based combinations ^(28,29). Although the results with carboplatin-paclitaxel combinations may reflect enrollment of patients with poor prognostic features, there is concern whether carboplatin should be substituted for cisplatin in those patients who are sufficiently fit to tolerate cisplatin-based therapy. Gemcitabine is a new antimetabolite that has been tested in one phase I and four phase II studies in locally advanced and metastatic urothelial cell cancer ⁽⁸⁻¹²⁾.

An alternative approach is the use of the two-drug regimen of gemcitabine and carboplatin. This combination has been evaluated in "unfit" bladder cancer patients in a dose finding study. Using this combination we ⁽³⁰⁾ reported an overall response rate of 43.5% with a median time survival of 14.4 months in 16 patients ineligible for the cisplatin-based regimen ("unfit" patient population). The preliminary results found in this phase II trial using the carboplatin/gemcitabine doublet prompted an EORTC randomized phase II/III trial comparing carboplatin/gemcitabine with methotrexate/ carboplatin/vinblastine (M-CAVI) in patients ineligible for cisplatin-based chemotherapy, which is ongoing.

In view of evidence of synergistic effects between cisplatin and gemcitabine ^(26,31) the 2-drug combination of gemcitabine and cisplatin (GC) was studied. The two largest studies were recently published ^(32,33). Overall response rates in these studies were 41% and 57% respectively, and median survival was 14.3 and 13.2 months, respectively. Based upon the results obtained a large multinational phase III trial comparing GC with MVAC was conducted ⁽³⁴⁾. With a median follow-up of 19 months, overall survival was found to be similar on both arms, GC 13.8 months, MVAC 14.8 months as were time to progressive disease (7.4 months on both arms), and overall response (GC, 49%; MVAC, 46%). Although the study failed to detect a significant difference in survival, which was the primary endpoint after all, the favorable risk-benefit ratio justifies considering these results. Therefore GC is a valuable alternative for the vast majority of patients with metastatic bladder cancer with the benefit of fewer side effects.

FUTURE DIRECTIONS

The next logical question to address is how to further optimize the therapy, incorporating the new active agents in two, three or multiple drug combinations and also, to define several new approaches as: chemotherapy optimization using molecular markers predicting chemosensitivity, dose intensification of conventional agents, dose-dense sequential administration of new agents, alternating chemotherapy schedules, the use of non-cisplatin containing combinations, and the use of the new biologicals to enhance the activity of the chemotherapy. In addition, the role of post-chemotherapy surgery in advanced disease is increasingly being recognized.

Several triple chemotherapy schedules such as the combination of taxanes, gemcitabine and either cisplatin or carboplatin⁽³⁵⁻³⁷⁾ or the addition of taxanes to the classic combination of cisplatin/ifosfamide or to methotrexate combined either with cisplatin or carboplatin⁽³⁷⁾ or to the combination of cisplatin/epirubicin⁽³⁶⁾, have been also investigated in first and second line with a reported response ranging from 40% to 78%.

The encouraging results of these new combinations have prompted the consecution of large phase III clinical trials (as EORTC 30987), in which they are compared with the standard GC combination, in order to define the possible role of these new schedules in the treatment of advanced bladder cancer patients. In this last trial (EORTC 30987), stratification by predefined prognostic factors derived from the analysis of the triplet trial has been added⁽³⁸⁾.

PREDICTION OF CHEMOSENSITIVITY

Studies on P-glycoprotein, glutathione⁽³⁹⁾ and metalloprotein⁽⁴⁰⁾ expressions in tumor specimens of metastatic urothelial disease have indicated that these parameters could predict resistance and toxicity to chemotherapy. Recent data have also suggested that altered expression of p53 may correlate with increased resistance to the MVAC combination regimen⁽⁴¹⁾. Response to paclitaxel-based chemotherapy regimens has been shown to be independent of the p53 mutation in some reports⁽⁴²⁾. Further molecular research studies may help to determine new prognostic factors to predict outcome and enable the clinician to more accurately choose the best treatment program for each individual patient.

DOSE INTENSIFICATION

Studies with increased dosages of conventional agents using M-VAC with and without recombinant human granulocyte colony-stimulating factor in patients with advanced urothelial carcinoma yielded disappointing results. Favorable findings were reported in a recent EORTC phase III study⁽⁴³⁾ of 263 patients with metastatic urothelial carcinoma randomized to receive high-dose M-VAC (134 patients) or classical M-VAC (129 patients). The response rate for high-dose M-VAC patients was 81/111 (73%) with 27 (24%) complete responses; the response rate for M-VAC was 64/111 (58%), with 12 (11%) complete responses (Chi-squared test on complete response rates: $P=0.008$). Progression-free survival was significantly better for high-dose M-VAC (9.1 months as opposed to 8.2 months; $P=0.03$). Time to progression and overall survival rates were similar in both groups. The levels of toxicity were also similar, but there was more grade 3–4 mucositis in classical M-VAC patients. Further follow-up is needed to establish definitive conclusions regarding the benefits of high-dose M-VAC in patients with metastatic urothelial carcinoma.

DOSE DENSE SEQUENTIAL SCHEDULES

Investigators at MSKCC have investigated the addition of ifosfamide to the two-drug combination of cisplatin/paclitaxel in patients with metastatic or unresectable transitional cell carcinoma^(44,45). Subsequently these investigators continued with the concept of dose-dense-sequential chemotherapy using the two-drug regimen of doxorubicin and gemcitabine (AG) administered every 15 days with G-CSF support followed by the three-drug regimen of ifosfamide, paclitaxel and cisplatin (ITP). In the phase I study⁽⁴⁶⁾ with 15 patients, AG was well tolerated at all dose levels and no grade 3 or 4 myelosuppression was observed. In the phase II trial⁽⁴⁷⁾ in 21 patients, the overall response rate reported was 86%. The same approach is being evaluated in patients with impaired renal function using AG but followed by paclitaxel and carboplatin⁽⁴⁸⁾. More mature results of

this approach are awaited. The concept of alternating chemotherapy using non-cross resistant agents, i.e. the alternating sequence of the TCG triplet with HD-MVAC, has been discussed as a potential alternative in the frame of SOGUG group.

NON-CISPLATIN COMBINATIONS

The use of non-cisplatin combinations is a relatively novel approach also tested in other cisplatin-sensitive diseases⁽⁴⁹⁾, whose main aim is to diminish cisplatin –related gastrointestinal and renal toxicity and other side effects while maintaining the therapeutic benefit in the palliative setting. Looking for the design of non-platinum-containing regimens, paclitaxel and gemcitabine combination chemotherapy has been tested in bladder cancer in four studies using different schedules⁽⁵⁰⁻⁵³⁾. Unfortunately, data to support the use of these agents as an effective and safe palliative therapy are still scanty, and to date the prescription of one of these compounds should be based upon individual patient tailored decisions. Recently a triple platinum free combination using paclitaxel, methotrexate and gemcitabine has been reported showing to be feasible and preliminarily active⁽⁵⁴⁾. Other studies using platinum free combinations as the combination of MTA/Gemcitabine or with the new platinum analog oxaliplatin /gemcitabine are ongoing.

INCORPORATING THE NEW BIOLOGICALS IN BLADDER CANCER

Improved understanding of the molecular biology of urothelial malignancies will enable to define the role of new prognostic indices and can be a useful tool to direct appropriate therapeutic options. Advances in the molecular biology may allow the identification of specific genetic lesions and biochemical pathways upon which future therapeutic approaches can be focussed⁽⁵⁵⁾. Epidermal growth factor receptors (EGFRs), normally found only on the basal layer of bladder epithelial cells are also distinctly expressed on the superficial layers of malignant tissue. EGFR gene is over-expressed in high-grade invasive tumors and is associated with a more aggressive clinical behavior⁽⁵⁶⁻⁵⁸⁾. EGFR-inhibitors have been tested, alone or in combination with chemotherapy⁽⁵⁹⁻⁶²⁾ in several EGFR-positive tumors. Hence, there is a strong scientific and clinical rationale to study the feasibility of compounds like ZD 1839 (Iressa, a novel orally available epidermal growth factor receptor tyrosine kinase inhibitor) or monoclonals like C225 in combination with new chemotherapy agents in the treatment of locally advanced or metastatic transitional cell carcinoma⁽⁶³⁻⁶⁵⁾.

Her-2/neu is also over-expressed in bladder cancer. Her-2/neu over-expression was detected by immunohistochemistry in 36% and 48 % of patients with high grade or metastatic transitional-cell carcinoma of the bladder^(66,67). Preclinical and clinical data have shown marked enhancement of the antitumor activity of chemotherapy when combined with the monoclonal antibody against Her-2/neu (Herceptin)⁽⁶⁸⁾. Several strategies are now being initiated combining carboplatin + paclitaxel +/- gemcitabine with Herceptin, in Her-2/neu positive advanced bladder cancer patients.

Several other strategies have been designed to target other elements involved in the activation of the cascade of biochemical and physiologic responses that are involved in the mitogenic signal transduction pathways. Preliminary results of oral SCH66336 (a Farnesyl Protein Transferase Inhibitor) have indicated limited activity in previously treated patients with advanced/metastatic urothelial tract tumors⁽⁶⁹⁾. An already finished study by the Early Clinical Study Group (ECSG) of the EORTC of the combination of SCH663366 with gemcitabine as second line treatment in patients with advanced/metastatic urothelial tract tumors has tested the potential role of this new agent with chemotherapy (exciting results to be presented at ASCO this year).

Upcoming series of studies already underway should be able to assist us in defining the role of these new promising agents and strategies in the treatment of advanced bladder cancer.

POST-CHEMOTHERAPY SURGERY

Urologist should consider post-chemotherapy surgical resection of residual cancer in some selected patients with locally advanced bladder cancer who likely succumb to disease without surgery. Optimal candidates

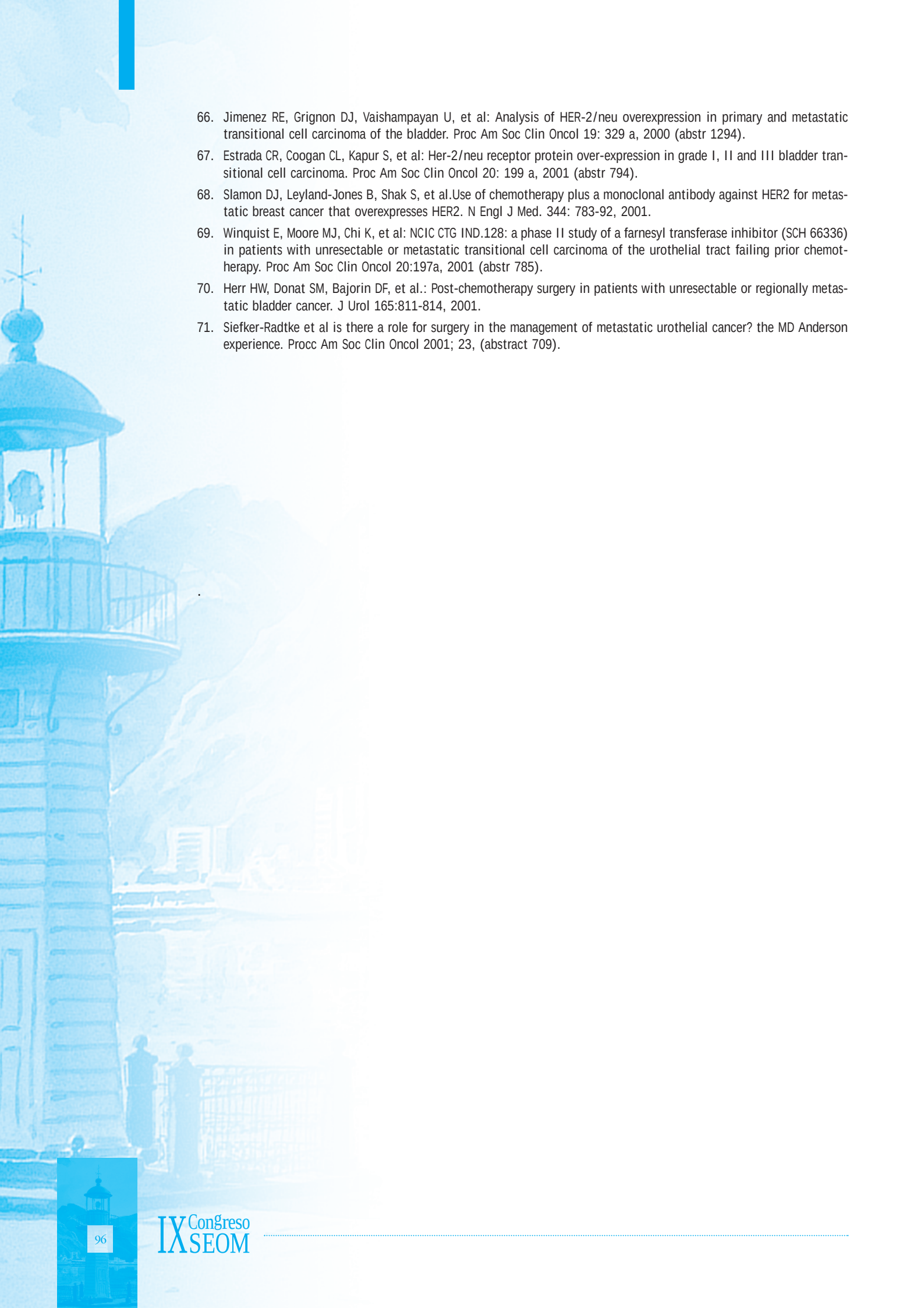
include those in whom the prechemotherapy sites of disease are restricted to the bladder and pelvis or regional lymph nodes, and who have a major response to chemotherapy. In a report of 207 patients who underwent postchemotherapy surgery, no cancer was present in 24 of 80 (30%) patients. Of the 24 patients, 14 (58%) survived 9 months to 5 years. Residual tumor was completely resected in 49 (61%) patients with 20 surviving (41%)⁽⁷⁰⁾. In another report from MD Anderson, 25 patients with metastatic urothelial cancer underwent metastasectomy (lung in 20 (80%), brain in 2 (8%), and distant lymph nodes in 3 (12%). The median survival from time of metastasectomy was 23 months and the median time to progression following metastasectomy was 6.5 months with 35% of patients being alive at 5 years post metastasectomy⁽⁷¹⁾.

BIBLIOGRAFÍA

1. Wit de R, Kaye SB, Roberts JT, et al: Oral piritrexim, an effective treatment for metastatic urothelial cancer. *Br J Cancer* 67: 388-390, 1993.
2. Bellmunt J, de Wit R, Albiol S, et al: New drugs and new approaches in metastatic bladder cancer. *Crit Rev Oncol Hematol* 2003 (in press).
3. 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 (E1892). *J Clin Oncol* 12: 2264-2270, 1994.
4. Papamichael D, Gallagher CJ, Oliver RTD, et al: Phase II study of paclitaxel in pretreated patients with locally advanced/metastatic cancer of the bladder and ureter. *Br J Cancer* 75: 606-607, 1997 Broome CM, Hussain M, Gutheil J, et al: Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. *Proc Am Soc Clin Oncol* 19: 351, 2000 (abstr 1381).
5. Bellmunt J, Cos J, Cleries R, et al. Feasibility trial of methotrexate-paclitaxel as a second line therapy in advanced urothelial cancer. *Cancer Invest.*20:673-85, 2002.
6. Wit de R, Kruit WHJ, Stoter G, et al: Docetaxel (Taxotere): an active agent in metastatic urothelial cancer; results of a phase II study in non-chemotherapy-pretreated patients. *Br J Cancer* 78: 1342-1345, 1998.
7. 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* 15: 1853-1857, 1997.
8. Pollera CF, Ceribelli A, Crecco M, et al: Weekly gemcitabine in advanced bladder cancer: a preliminary report from a phase I study. *Ann Oncol* 5: 182-184, 1994.
9. Stadler WM, Kuzel T, Roth B, et al: Phase II study of single-agent gemcitabine in previously untreated patients with metastatic urothelial cancer. *J Clin Oncol* 15: 3394-3398, 1997.
10. Moore MJ, Tannock IF, Ernst DS, et al: Gemcitabine: A promising new agent in the treatment of advanced urothelial cancer. *J Clin Oncol* 15: 3441-3445, 1997.
11. Lorusso V, Pollera CF, Antimi M, et al: A phase II study of gemcitabine in patients with transitional cell carcinoma of the urinary tract previously treated with platinum: Italian Cooperative Group on Bladder Cancer. *Eur J Cancer* 34: 1208-1212, 1998.
12. Bellmunt J, Albiol S. New chemotherapy combinations for advanced bladder cancer. *Curr Opin Urol.*11:517-22, 2001.
13. Albers P, Siener R, Perabo FG, et al: Gemcitabine monotherapy as 2nd-line treatment in cisplatin refractory transitional cell carcinoma. *Proc Am Soc Clin Oncol* 19: 346a, 2000 (abstr 1360).
14. Paz-Ares L, Tabernero J, Moyano A, et al: A phase II of the multi-targeted antifolate, MTA (LY231514), in patients with advanced transitional cell carcinoma of the bladder. *Proc Am Soc Clin Oncol* 17:339a, 1998 (abstr 1307).
15. Murphy BA, Johnson DR, Smith J, et al: Phase II trial of paclitaxel and cisplatin for metastatic or locally unresectable urothelial cancer. *Proc Am Soc Clin Oncol* 15: 245, 1996 (abstr 617).
16. Burch PA, Richardson RL, Cha SS, et al: Phase II trial of combination paclitaxel and cisplatin in advanced urothelial carcinoma. *Proc Am Soc Clin Oncol* 18: 329, 1999 (abstr 1266).
17. Dreicer R, Manola J, Roth B, et al: phase II study of cisplatin and paclitaxel in advanced carcinoma of the urothelium: an Eastern Cooperative Oncology Group (ECOG) study. *J Clin Oncol* 18:1058-1061, 2000.
18. Dimopoulos MA, Bakoyannis C, Georgoulas V, et al: Docetaxel and cisplatin combination chemotherapy in advanced carcinoma of the urothelium: a multicenter phase II study of the Hellenic Cooperative Oncology Group. *Ann Oncol* 10: 1385-1388, 1999.
19. Sengeløv L, Kamby C, Lund B, et al: Docetaxel and cisplatin in metastatic urothelial cancer: a phase II study. *J Clin Oncol* 16: 3392-3397, 1998.

20. Garcia del Muro, Marcuello E, Guma R, et al: Phase II study of docetaxel (D) and cisplatin (CDDP) in advanced urothelial cancer: preliminary results. *Proc Am Soc Clin Oncol* 19: 345a, 2000 (abstr 1356),
21. Pycha A, Grbovic M, Posch B, et al: Paclitaxel and carboplatin in patients with metastatic transitional cell cancer of the urinary tract. *Urol* 53: 510-515, 1999.
22. Droz JP, Mottel N, Prapotrich, et al: Phase II study of taxel (Paclitaxel) and carboplatin in patients with advanced transitional-cell carcinoma of the urothelium: preliminary results. *Proc Am Soc Clin Oncol* 17: 316a, 1998 (abstr 1219).
23. Bauer J, Stalder M, Roth A, et al: Phase II trial of paclitaxel (P) plus carboplatin (C) in advanced urothelial tract cancer (UTC). *Proc Am Soc Clin Oncol* 17: 326a, 1998 (abstr 1255).
24. 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* 16: 255-260, 1998.
25. Small EJ, Lew D, Redman BG, et al: Southwest Oncology Group study of paclitaxel and carboplatin for advanced transitional-cell carcinoma: the importance of survival as a clinical trial end point. *J Clin Oncol* 18: 2537-2544, 2000.
26. Redman BG, Smith DC, Flaherty L, et al: Phase II trial of paclitaxel and carboplatin in the treatment of advanced urothelial carcinoma. *J Clin Oncol* 16: 1844-1848, 1998.
27. Bellmunt J, Albanell J, Gallego O, et al. Carboplatin, Methotrexate, and Vinblastine in patients with bladder cancer who were ineligible for cisplatin-based chemotherapy. *Cancer* 1992;70: 1974-1979.
28. Petriolli R, Frediani B, Manganelli A, et al: Comparison between a cisplatin-containing regimen for recurrent or metastatic bladder cancer patients. *Cancer* 77:344-351,1996.
29. Bellmunt J, Ribas A, Eres N et al: Carboplatin based versus cisplatin-based chemotherapy in the treatment of surgically incurable advanced bladder carcinoma. *Cancer* 1997;80:1966-1972.
30. Bellmunt J, Wit de R, Albanell J, Baselga J. A feasibility study of carboplatin with fixed dose of gemcitabine in 'unfit' patients with advanced bladder cancer. *Eur J Cancer* 2001;37:2212-2221.
31. Peters GJ, Bergman AM, Ruiz van Haperen VW, et al: Interaction between cisplatin and gemcitabine in vitro and in vivo. *Semin Oncol* 22: 72-79, 1995 (suppl 11).
32. a. Von der Maase H, Andersen L, Crino L, et al: Weekly gemcitabine and cisplatin combination therapy in patients with transitional cell carcinoma of the urothelium: A phase II clinical trial. *Ann Oncol* 10: 1461-1465, 1999.
33. Moore MJ, Winquist EW, Murray N, et al: Gemcitabine plus cisplatin, an active regimen in advanced urothelial cancer: A phase II trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 17: 286-288, 1999.
34. Von der Maase H, Hansen SW, Roberts JT, et al: Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large randomized, multinational, multicenter, phase III study. *J Clin Oncol* 17: 3068-3077, 2000.
35. Bellmunt J, Guillem V, Paz-Ares JL, et al. A Phase I-II study of paclitaxel, cisplatin, and gemcitabine in advanced transitional-cell carcinoma of the urothelium. *J Clin Oncol*;18:3247-3255, 2000.
36. de Wit R, Bellmunt J. Overview of gemcitabine triplets in metastatic bladder cancer. *Crit Rev Oncol Hematol*. 45:191-7, 2003.
37. Bellmunt J, Guillem V, Paz-Ares L, et al. Gemcitabine/paclitaxel-based three-drug regimens in advanced urothelial cancer. *Eur J Cancer*. 36 (Suppl 2):17-25, 2000.
38. Bellmunt J, Albanell J, Paz-Ares L, et al Pretreatment prognostic factors for survival in patients with advanced urothelial tumors treated in a phase I/II trial with paclitaxel, cisplatin, and gemcitabine. *Cancer*. 95:751-7, 2002.
39. Pendyala L, Velagapudi S, Toth K, et al: Translational studies of glutathione in bladder cancer cell lines and human specimens. *Clin Cancer Res* 13:793-798, 1997.
40. Siu LL, Banerjee D, Khurana RJ, et al: The prognostic role of p53, metallothionein, P-glycoprotein and MIB-1 in muscle invasive urothelial transitional cell carcinoma. *Clin Cancer Res* 4:559-565, 1998.
41. Sarkis A, Bajorin D, Reuter V et al: Prognostic value of p53 nuclear overexpression in patients with invasive bladder cancer treated with neoadjuvant MVAC. *J Clin Oncol* 13(6):1384-1390, 1996.
42. Meyers FJ, Miller TR, Williams SG, et al.: Response to a taxol based chemotherapy regimen in advanced transitional cell carcinoma is independent of p53 expression. *Proc Am Soc Clin Oncol* 18:A1283, 1999.
43. Sternberg CN, Mulder de PHM, Schornagel J, et al: Randomized phase III trial in advanced urothelial tract tumors of high dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC. *J Clin Oncol* 19: 2638-2646, 2001.
44. Bajorin DF, McCaffrey JA, Hilton S et al Treatment of patients with transitional-cell carcinoma of the urothelial tract with ifosfamide, paclitaxel and cisplatin: A phase II trial. *J Clin Oncol* 16:2722-2727, 1998.

45. Bajorin DF, McCaffrey JA, Dodd PM, et al: Ifosfamide, paclitaxel and cisplatin for patients with advanced transitional cell carcinoma of the urothelial tract: final report of a phase II trial evaluating two dosing schedules. *Cancer* 88: 1671-1678, 2000.
46. Dodd PM, McCaffrey JA, Hilton S, et al: Phase I evaluation of sequential doxorubicin + gemcitabine then ifosfamide + paclitaxel + cisplatin for patients with unresectable or metastatic transitional-cell carcinoma of the urothelial tract. *J Clin Oncol* 18: 840-846, 2000.
47. Maluf FC, Hilton S, Nanus M, et al: Sequential doxorubicin/gemcitabine and ifosfamide, paclitaxel and cisplatin chemotherapy in patients with metastatic or locally advanced transitional cell carcinoma of the urothelium. *Proc Am Soc Clin Oncol* 19: 342 a, 2000 (abstr 1344).
48. Novick S, Higgins G, Hilton S, et al: Phase I/II sequential doxorubicin plus gemcitabine followed by paclitaxel plus carboplatin in patients with transitional cell carcinoma and impaired renal function. *Proc Am Soc Clin Oncol* 19: 361 a, 2000 (abstr 1423).
49. Isla D, Rosell R, Sanchez JJ, et al: Phase II trial of paclitaxel plus gemcitabine in patients with locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 19:1071-1077, 2001.
50. Marini L, Sternberg CN, Sella A, et al: A new regimen of gemcitabine and paclitaxel in previously treated patients with advanced transitional cell carcinoma. *Proc Am Soc Clin Oncol* 18:346a, 1999 (abstr 1335).
51. Meluch AA, Greco FA, Burris HA, et al: Paclitaxel and gemcitabine chemotherapy for advanced transitional cell carcinoma of the urothelial tract: a phase II trial of the Minnie Pearl Cancer Research Network. *J. Clin Oncol* 19:3018-3024, 2001.
52. Kaufman DS, Stadler WM, Carducci MA, et al: Gemcitabine and paclitaxel every two weeks: a multicenter phase II trial in locally advanced or metastatic urothelial cancer. *Proc Am Soc Clin Oncol* 19:341a, 2000 (abstr 1341).
53. Parameswaran R, Fisch MJ, Ansari RH, et al: A hoosier oncology group phase II study of weekly paclitaxel and gemcitabine in advanced transitional cell carcinoma of the bladder. *Proc Am Soc Clin Oncol* 20:200a, 2001 (abstr 798).
54. Law LY, Lara PN, Meyers FJ, et al: Platinum free combination chemotherapy in locally advanced and metastatic transitional cell carcinoma: phase I/II trial of gemcitabine, paclitaxel, methotrexate. *Proc Am Soc Clin Oncol* 20:192 a, 2001 (abstr 767).
55. Bellmunt J, Hussain M, Dinney C.P. Novel approaches with targeted therapies in bladder cancer Therapy of bladder cancer by blockade of the epidermal growth factor receptor family . *Crit Rev Oncol Hematol* 2003 (in press).
56. Izawa JI, Slaton JW, Kedar D, et al . Differential expression of progression-related genes in the evolution of superficial to invasive transitional cell carcinoma of the bladder. *Oncol Rep* 8: 9-15, 2001.
57. Ravery V, Grignon D, Angulo J, et al. Evaluation of epidermal growth factor receptor, transforming growth factor alpha, epidermal growth factor and c-erbB2 in the progression of invasive bladder cancer. *Urol Res* 25: 9-17, 1997.
58. Chow NH, Chan SH, Tzai TS, et al. Expression profiles of erbb family receptors and prognosis in primary transitional cell carcinoma of the urinary bladder. *Clin Cancer Res* 7: 1957-1962, 2001.
59. Rubin MS, Shin DM, Pasmatier M, et al: Monoclonal antibody IMC-C225, an anti-epidermal growth factor receptor, for patients with EGFR-positive tumors refractory to or in relapse from previous therapeutic regimens. *Proc Am Soc Clin Oncol* 19: 474 a, 2000 (abstr 1860).
60. Ferry D, Hammond L, Ranson M, et al: Intermittent oral ZD 1839 (Iressa), a novel epidermal growth factor receptor tyrosine kinase inhibitor, shows evidence of good tolerability and activity: finals results from a phase I study. *Proc Am Soc Clin Oncol* 19: 3 a, 2000 (abstr 5E).
61. Shack S: Overview of the Traztuzumab (Herceptin) anti-HER2 monoclonal antibody clinical program in HER2-overexpressing metastatic breast cancer. *Sem Oncol* 26 (supply 12): 71-77, 1999.
62. Weiner LM: An overview of monoclonal antibody therapy of cancer. *Sem Oncol* 26 (supply 12): 71-77, 1999.
63. Sirotnak FM, Zakowski MF, Miller VA, et al .Efficacy of cytotoxic agents against human tumor xenografts is markedly enhanced by coadministration of ZD1839 (Iressa), an inhibitor of EGFR tyrosine kinase. *Clin Cancer Res* 6: 4885-4892, 2000.
64. Inoue K, Slaton JW, Perrotte P, et al.Paclitaxel enhances the effects of the anti-epidermal growth factor receptor monoclonal antibody ImClone C225 in mice with metastatic human bladder transitional cell carcinoma. : *Clin Cancer Res* 6: 4874-4884, 2000.
65. Miller V A, Johnson D, Heelan R T, et al. A pilot trial demonstrates the safety of ZD1839 ('iressa'), an oral epidermal growth factor receptor tyrosine kinase inhibitor (EGFr-TKI), in combination with carboplatin (c) and paclitaxel (p) in previously untreated advanced non-small cell lung cancer (nsccl). *Procc Am Soc Clin Oncol* 20: 326a, 2001 (abstr 1301).

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66. Jimenez RE, Grignon DJ, Vaishampayan U, et al: Analysis of HER-2/neu overexpression in primary and metastatic transitional cell carcinoma of the bladder. *Proc Am Soc Clin Oncol* 19: 329 a, 2000 (abstr 1294).
 67. Estrada CR, Coogan CL, Kapur S, et al: Her-2/neu receptor protein over-expression in grade I, II and III bladder transitional cell carcinoma. *Proc Am Soc Clin Oncol* 20: 199 a, 2001 (abstr 794).
 68. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 344: 783-92, 2001.
 69. Winquist E, Moore MJ, Chi K, et al: NCIC CTG IND.128: a phase II study of a farnesyl transferase inhibitor (SCH 66336) in patients with unresectable or metastatic transitional cell carcinoma of the urothelial tract failing prior chemotherapy. *Proc Am Soc Clin Oncol* 20:197a, 2001 (abstr 785).
 70. Herr HW, Donat SM, Bajorin DF, et al.: Post-chemotherapy surgery in patients with unresectable or regionally metastatic bladder cancer. *J Urol* 165:811-814, 2001.
 71. Siefker-Radtke et al is there a role for surgery in the management of metastatic urothelial cancer? the MD Anderson experience. *Procc Am Soc Clin Oncol* 2001; 23, (abstract 709).