Chemotherapy for Invasive Bladder Cancer

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New agents for advanced disease: FDA approved anti-angiogenic drugs investigated for advanced bladder cancer, among these: Sunitinib malate (www.sutent.com) and Sorafenib/Nexavar.

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Update April 2006: The prestigious Cochrane Review Meta-analysis reports a survival benefit for post-op chemo: The review "...suggests a 25% relative reduction in the risk of death for chemotherapy compared to that on control."

Abstract and article at the

Cochrane Library site (full article $25.00, abstracts are free)

Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Adjuvant chemotherapy for invasive bladder cancer (individual patient data). The Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD006018. DOI: 10.1002/14651858.CD006018.

May, 2005:

Cochrane Review, Pub Med Abstract: Neoadjuvant chemo provides a survival benefit of 5% at five years

{/niftybox}NEWS '05: MDAnderson researchers report that further, post-op (adjuvant) chemotherapy can increase survival in cases of lymph node-positive cystectomy recipients who have had pre-operative (neoadjuvant) chemotherapy below

Traditional chemo: M-VAC (methotrexate, vinblastine, doxorubicin [adriamycin], and cisplatin below)

Gemzar + Cisplatin(Platinol) - The new gold standard of chemotherapy (below)

Gemzar and Carboplatin (GC) vs. Gemzar and Cisplatin (CP) (below)

Single Agent Gemcitabine for Elderly Bladder Cancer Patient (below)

Gemzar + Taxotere (docetaxel)-phase II results, below

FOLFOX-4- oxaliplatin, fluorouracil, folinic acidin pre-treated patients with advanced, below

Sequential gemcitabine and cisplatin followed by docetaxel as first-line treatment below

Japanese research into intra-arterial chemotherapy, below

Some chemotherapeutic agents in use; M-VAC (methotrexate, vinblastine, doxorubicin [adriamycin], and cisplatin); flourouracil (5FU), gemcitabine (Gemzar); paclitaxel (Taxol); ifosfamide-taxol-cisplatin; Carboplatin; docetaxel (Taxotere).

In patients with invasive bladder cancer, radical cystectomy and more recently radical cystectomy plus adjuvant or neoadjuvant (post or pre-operative) chemotherapy appear to provide improved survival. The role of adjuvant chemotherapy, however, still remains controversial. 1

Although numbers differ widely depending on the study, roughly half of all people who undergo cystectomies will later develop metastases. An important factor is the stage of the cancer at the time of surgery; the higher the stage (or deeper the invasion), the higher the risk of developing metastases. For a graph depicting stage/risks click here

Detection of micro metastases at the time of surgery is not yet an exact science. Pathology is subjective, and since opinion may often differ as to the exact stage, cell type, and grade of a tumor specimen, second pathology opinions are a wise thing to have done. Cell types other than transitional cell carcinoma are usually more difficult to treat with drugs, perhaps because there is much less information about what's been used with success.

Some urologists/oncologists prefer to wait until there is definite evidence of disease (ie: lymph node involvement, regional or distant spread or recurrence) before administering chemotherapy, while others prefer to act more aggressively in the hope of delaying or halting any possible progression. Either way, it's a difficult decision to make without certain evidence of spread outside the bladder. Response to chemotherapy is a very individual thing, is not predictable up front and there are no guarantees. Reactions are also individual; some people have no side effects, or very little, while others have great difficulty tolerating the same drugs. Physical health at the time of diagnosis is an important factor to consider before choosing a chemotherapy protocol.

MVAC (methotrexate, vinblastine, doxorubicin [adriamycin], and cisplatin) has been the standard of care for advanced bladder cancer since the late 1980's/early 1990's. When combined with aggressive surgical intervention to lessen the tumor load, MVAC regimens have resulted in complete response in more than one-third of the patients. Unfortunately two thirds of the good responders relapse within two years. CMV (cisplatin, methotrexate, and vincristine), and CISCA (cisplatin, cyclophosphamide, and doxorubicin) regimens have also been used as both neoadjuvant and adjuvant (pre- and post operative) therapy with the possibility that disease-free survival and cancer-specific survival might be enhanced, and results have shown a prolonged interval of disease-free survival. But the toxicity is high, and the data that is coming in after more than a decade is shedding doubts on whether these regimens are ultimatley reducing cancer deaths. Predictors of survival include performance status, histology (cell type and grade/differentiation), and the presence of liver or bone metastasis. In one study, only 3.7% of the patients randomized to M-VAC were alive and continuously disease-free at 6 years. Long-term follow-up evaluation of the trial confirms that durable progression-free survival after M-VAC and CMV is rare.2

May, 2001 information about neoadjuvant (pre-op) MVAC has had urologists talking, debating and re-thinking. Read about the controversy on a separate page, here: chemocontroversy

Selecting patients for chemotherapy, particularly for more aggressive regimens like CMV or M-VAC requires a great deal of clinical judgment, taking into account such aspects as kidney inefficiency and the overall health of the patient. Cytoprotectant drugs have been developed which can help protect against undesirable side effects. When aggressive chemotherapy is not an option, irradiation directed to symptomatic sites of metastases may be the appropriate treatment.

However, recent evidence confirms that age alone should not be used as a contraindication to aggressive therapy, nor as a contraindication to radical surgery. 1 3

Results of trials published in 2000 are showing that M-VAC is a toxic regimen, and G-CSF should be used prophylactically in all patients receiving this regimen. If G-CSF is used, M-VAC can be given every 2 weeks but is still associated with a 3% to 5% toxic death rate. **

Several new agents such as gemcitabine (Gemzar) and paclitaxel (Taxol) may have promise as single agents in the treatment of metastatic bladder cancer, and patients are reporting that these are better tolerated. Gemcitabine has shown good single agent activity with acceptable toxicity in patients who have failed cisplatin regimens.4

Gemcitabine also provided subjective symptomatic relief from pain, cystitis, dysuria, haematuria and peripheral oedema. Out of 31 evaluable study participants, 4 patients achieved a complete response (12.9%), 3 a partial response (9.6%) and 13 (42%) were stable for at least 4 weeks (overall response 22.5%). 2 patients with complete response are still alive with no evidence of disease after 14 and 21 months. Gemcitabine has a mild toxicity profile and warrants further investigation.5

Gemzar + Cisplatin - The new gold standard of chemotherapy?

Gemcitabine=Gemzar, Cisplatin=Platinol (GP)

Update: Feb. 2006: Data from a large randomized phase III study of GC versus MVAC were updated; "Long-term overall and progression-free survival after treatment with GC or MVAC are similar. These results strengthen the role of GC as a standard of care in patients with locally advanced or metastatic TCC. The 5-year overall survival rates for patients with and without visceral metastases were 6.8% and 20.9%, respectively."

Long-Term Survival Results of a Randomized Trial Comparing Gemcitabine Plus Cisplatin, with Methotrexate, Vinblastine, Doxorubicin, Plus Cisplatin in Patients with Bladder Cancer; H. von der Maase, L. Sengelov, J.T. Roberts, S. Ricci, L. Dogliotti, T. Oliver, M.J. Moore, A. Zimmermann, M. Arning J Clin Oncol, 23: 4602–4608, 2005

As reported at the American Society of Clinical Oncology meeting in New Orleans (May 2000): Preliminary results of a large, randomized phase III trial- comparing M-VAC to Gemcitabine + cisplatin show that bladder cancer may respond best to therapy made up of only two drugs, gemcitabine (Gemzar) and cisplatin (Platinol).

Results indicate that the combination of gemcitabine and cisplatin delivers similar results as the M-VAC regimen in terms of response rate and overall survival, however, it is associated with significantly less toxicity. "This better risk-benefit ratio should change the standard of care for patients with locally advanced and metastatic transitional-cell carcinoma from methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) to gemcitabine and cisplatin (GC)," Dr. Hans von der Maase, of Aarhus University Hospital, in Denmark, and a multinational team recommends in the journal. J Clin Oncol 2000;17:3068-3077.

Gemzar and Carboplatin (GC) vs. Gemzar and Cisplatin (CP)

2007: Phase II randomized trial results confirm that the more easily tolerated Carboplatin + Gemzar was as effective as Gemzar and Cisplatin, although survival was slightly shorter. 15

Taxol and Carboplatin

A phase II trial conducted in 1994 demonstrated that paclitaxel (Taxol) was effective in locally advanced or metastatic transitional cell carcinoma of the urothelium with a complete response rate of 27%. Due to the lack of nephrotoxicity, and the ability to administer Taxol to patients with renal insufficiency, new regimens could provide potential advantages over the standard cisplatin-based regimens. 6 Paclitaxel-based combination regimens have recently been developed and reported, and paclitaxel plus carboplatin has been shown to be an active and tolerable for patients with advanced cancer. Ongoing cooperative group trials will help to further define the activity and toxicity of this regimen in previously untreated patients, patients with prior treatment, and patients with abnormal renal function. 7

Preliminary results suggest that the combination of paclitaxel and carboplatin as first-line therapy compared well with the outcome after MVAC, and with less toxicity. 8

The 1998 activated ECOG protocol E2895, 'Phase II Study of Cisplatin Plus Paclitaxel in Advanced Carcinoma of the Urothelium', is hoped to be the beginning of a new generation of combination chemotherapy agents for the treatment of advanced bladder cancer. 9

Cisplatin combined with paclitaxel, docetaxel (Taxotere), gemcitabine, or both paclitaxel and gemcitabine has been reported to have acceptable toxicity and response rates ranging from 60% to 90%. 10

Cisplatin or Carboplatin?

These two, related drugs are both analogues of the heavy metal, platinum. Cisplatin is toxic to the kidneys, and is not given if there is renal impairment. It is one of the hardest chemos to tolerate (nausea, neurotoxicity and hearing loss).

Carboplatin is much less toxic to the kidney, although if there is pre-existing kidney damage, one would want to be careful with it. It has taken over in many platinum regimens and has been found to be almost as effective as Cisplatin, and is beginning to replace it in many regimens.

More New Combinations

As a front-line (pre-op or in place of cystectomy) treatment for metastasised bladder cancer, Memorial Sloan Kettering physicians are using a new combination chemotherapy regimen of ifosfamide (Ifex), Taxol, and cisplatin. This combination appears to be more effective and to have fewer side effects than M-VAC, the standard therapy. MSK physicians also are evaluating sequential chemotherapy for bladder cancer, which potentially maximizes the effectiveness of the therapy by allowing patients to receive even higher doses of the most effective drugs.11

In a 1996 randomized trial from M.D. Anderson Cancer Center, comparings preoperative vs postoperative chemotherapy for bladder cancer, no survival advantage was found between neoadjuvant vs adjuvant M-VAC, but preoperative chemotherapy may increase the resectability of localized bladder cancer and contribute to organ preservation.12

Other drugs are being investigated and are believed to have potential, such as ifosfamide, bropirimine, gallium and docetaxel, but more studies are needed before specific conclusions can be drawn. Gemcitabine, the taxanes, ifosfamide, and gallium nitrate has each led to objective responses, including complete responses in both untreated and previously treated patients. More recent reports of combination regimens using these agents suggest that response rates are equivalent to those seen with MVAC but that there is significantly less toxicity. These observations, if confirmed in randomized trials, would signify an important advance in the therapy of metastatic bladder cancer.1

Intra-arterial chemotherapy Japanese investigations:

Japanese research into the use of intra arterial, or regional chemotherapy, has shown it's uselfulness in advanced bladder cancer. Patients are treated by chemotherapy with intermittent arterial infusion from an implanted reservoir and alteration of intrapelvic blood flow. The tip of an infusion catheter is inserted selectively into an internal iliac artery by an angiographic technique. Superior gluteal artery and the other internal iliac artery were then embolized with steel coils so that the drugs would perfuse throughout the tumor through a single catheter. Response rates of up to 80% have been reported. No serious side effects, such as severe myelosuppression or renal and/or liver dysfunction, were noted during treatment. These findings suggest that intermittent arterial chemotherapy with an implanted reservoir is clinically useful. This procedure appears safe and is easily performed in the outpatient clinic for the treatment of locally advanced bladder cancer.14 In 2007, Japanese experts reported 10 year follow up data on the combination of intra-arterial chemo plus radiation therapy, stating, "Combined cisplatin-based intra-arterial chemotherapy and radiotherapy was performed; the 5-year overall survival rate and cancer-specific survival rate for all patients were 81.6% and 85.6%, respectively. The 5-year overall survival rate for the radical cystectomy group (100%) was higher than that of the non-radical cystectomy group (70%). Conclusion: This combined chemo-radiotherapy was effective for local invasive bladder carcinoma, leading to the possibility of bladder preservation using this therapy. 16

Single-agent gemcitabine in previously untreated elderly patients with advanced bladder carcinoma: response to treatment and correlation with the comprehensive geriatric assessment. November, 2004

A study aimed at evaluating the activity and toxicity of gemcitabine monochemotherapy in a unselected series of elderly patients with advanced bladder cancer found that response evaluation showed 3 (13.5%) complete responses (CRs) and 7 (32%) partial responses (PRs), for an overall response rate of 45.5% Median overall survival was 8 months and median time to progression was 5 months. Treatment was generally well tolerated, with 1 patient having grade 3 gastrointestinal toxicity and 3 having grade 4 neutropenia. CONCLUSIONS: We conclude that gemcitabine can be safely administered in monochemotherapy, is effective and does not worsen the functional status of elderly patients with advanced bladder cancer.

Castagneto B, Zai S, Marenco D, Bertetto O, Repetto L, Scaltriti L, Mencoboni M, Ferraris V, Botta M. Department of Medical Oncology, S. Spirito Hospital, Casale Monferrato, Italy. Oncology. 2004;67(1):27-32.PubMed Abstract

Gemzar (gemcitabine) + Taxotere (docetaxel)

The recent (Feb. 2005) results from a phase II clinical trial reported: "gemcitabine and docetaxel is very active and well tolerated as a first-line treatment for advanced/relapsing or metastatic urothelial carcinoma. Although its relative efficacy and tolerance as compared to classic MVAC should be assessed in a phase III setting, the favourable toxicity profile of this regimen may offer an interesting alternative, particularly in patients with compromised renal function or cardiovascular disease."

Gemcitabine and docetaxel as first-line treatment for advanced urothelial carcinoma: a phase II study. Ardavanis A, Tryfonopoulos D, Alexopoulos A, Kandylis C, Lainakis G, Rigatos G. 11st Department of Medical Oncology, St Savas Anticancer Hospital, 171, Alexandras Avenue, 11522 Athens, Greece. PMID: 15685232

New Treament being studied for pre-treated, metastatic bladder cancer: "May 2005: FOLFOX-4 in pre-treated patients with advanced transitional cell carcinoma of the bladder" -oxaliplatin, fluorouracil, folinic acid in pre-treated advanced bladder cancer patients.

BACKGROUND: Despite recent progress in the treatment of advanced urothelial cancer, there continues to be a need to identify new active agents and their toxicity spectra. We conducted a study using FOLFOX-4 (oxaliplatin, fluorouracil, folinic acid) in pre-treated advanced bladder cancer patients.

METHODS: Sixteen eligible patients with advanced disease were treated with oxaliplatin (85 mg/m(3)) on day 1 followed by fluorouracil and folinic acid (De Gramont schedule) on days 1 and 2 every 14 days until disease progression. All patients received nutritional support to increase their caloric intake. Objective responses and toxicity were evaluated. Biochemical responses (reduction of markers) and nutritional parameters (increase in body weight and albumin, and reduction in ferritin and C-reactive protein) were also considered.

RESULTS: Three patients obtained an objective response (overall response rate 19%). Hematological toxicity and stomatitis were the most commonly noted side effects, but we observed only low (3-4) grade toxicity. In four patients (25%), we observed a reduction in tumoral markers (carcinoembryonic antigen and tissutal polypeptide antigen) and modified nutritional parameters.

CONCLUSIONS: Using these doses and schedules of FOLFOX-4 appears to be a promising therapy in patients pre-treated with platinum compounds. More studies are required to assess the possible role of this regimen in the treatment of advanced bladder cancer.

Di Lorenzo G, Autorino R, Giordano A, Giuliano M, D'Armiento M, Bianco AR, De Placido S.Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Seconda Universita degli Studi, Naples, Italy. Jpn J Clin Oncol. 2004 Dec;34(12):747-50 PMID: 15640506

Update 2005: MDAnderson experts release a retrospective study: Significance of lymph node positive disease in patients treated with neoadjuvant chemotherapy: Is adjuvant chemotherapy beneficial?

"It is commonly believed that persistent nodal disease in the surgical specimen after neoadjuvant chemotherapy is associated with poor prognosis, and patients are often offered adjuvant therapy only for palliative reasons. To improve understanding of this subgroup of patients and define outcomes with current management, we performed a retrospective review of our experience. ...out of 857cystectomies performed, 31 patients had viable tumor in lymph nodes after neoadjuvant chemotherapy. Adjuvant chemotherapy included protocol regimens such as MVAC, CGI, and TMP. In the presence of positive nodes after neoadjuvant chemotherapy, the only factor that correlated with improved recurrence-free survival was the use of adjuvant chemotherapy.

Conclusions: Contrary to current opinion, patients with positive lymph nodes after neoadjuvant chemotherapy may benefit from further adjuvant chemotherapy.

Wassim Kassouf*, Dan Leibovici, Xian Zhou, Colin P. Dinney, G. H. Barton, Arlene Siefker-Radtke, Louis L. Pisters, David A. Swanson, Ashish M. Kamat, Houston, TX; American Urological Association Annual Meeting May 21 - 26, 2005 San Antonio, Texas, USA Publishing #1317

November 2006: Sequential gemcitabine and cisplatin followed by docetaxel as first-line treatment of advanced urothelial carcinoma: a multicenter phase II study of the Hellenic Oncology Research Group.

Study treatment consisted of GMB (1000 mg/m(2), days 1 and 8) and CDDP (70 mg/m(2), day 1) (GP regimen), every 21 days for a total of four cycles followed by docetaxel (D; 100 mg/m(2), day 1) every 21 days for four cycles. The objective response rate was 55.2%. Five patients had complete response (13.15%) and 16 patients had partial response (42.1%), while nine patients had disease stabilization (23.7%). After a median follow-up period of 13 months (range 1.5-40.5 months), the median time to progression was 6.8 months (range 1-40.5 months), the median overall survival 13 months (range 1.5-40.5 months), and the 1-year survival rate 55.3%. CONCLUSION: The sequential administration of GP followed by D is active and well tolerated as first-line treatment of advanced urothelial carcinoma and merits to be further evaluated.

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Current treatment approaches in advanced bladder cancer

P.G.Harper, MD, Guy’s Hospital, London, United Kingdom

Adjuvant chemotherapy in muscle invasive bladder cancer: Current concepts D.F. Bajorin,MD, Memorial Sloan-Kettering Cancer Center, NY, USA

Overview of novel agents

Ch.Sweeney, MD, MBBS, Indiana University, Indianapolis, Indiana, USA

Future management of advanced bladder cancer

D. Raghavan, MD, PhD, University of Southern California Norris Comprehensive Cancer Center Los Angeles, California, USA

External Sites

For an article on the results of recent clinical trials which discusses MVAC see; Systemic Therapy for Invasive Bladder Cancer http://www.moffitt.usf.edu/pubs/ccj/v3n6/a2.html

And in the July/Aug '00 issue of the Moffit Cancer Journal: Progress in the Management of Metastatic Bladder Cancer (PDF file: 129Kb] http://www.moffitt.usf.edu/pubs/ccj/v7n4/toc.htm

Advances in the Treatment of Metastatic Bladder Cancer Nicholas J. Vogelzang, MD -- Writer: Michelle L. Plante, PharmD, online article at Medscape

Drug info: http://www.worldmegastore.com/cf/index.php?command=drugs

http://www.fda.gov/cder/consumerinfo/default.htm FDA's 'consumer info' for chemo drugs

Surviving chemo Click here for information on anti nausea medications as well as cytoprotectant drugs.

See also: Clinical Trials

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17..Sunitinib malate and sorafenib may be beneficial at the treatment of advanced bladder cancer due to their anti-angiogenic effects Mesrur Selcuk SilayCorresponding Author Informationemail address, Cengiz Miroglu March 2007; Medical Hypothesis Volume 69, Issue 4 Pages 892-895