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. 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. 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, 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, 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 in 29 patients and an ECOG phase II trial 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 combination. Two small and underpowered randomized studies have suggested suboptimal efficacy of carboplatin-methotrexate-vinblastine chemotherapy when compared with cisplatin-based combinations. 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.

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 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, the 2-drug combination of gemcitabine and cisplatin (GC) was studied. The two largest studies were recently published. 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. 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 (38), 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 (59-63) 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 SCH66336 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%). 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.

**BIBLIOGRAFÍA**


