Recent Developments in Chemotherapy for Bladder Cancer

Drs. Vaughn and Malkowicz provide a fairly extensive and balanced review of chemotherapy for metastatic bladder cancer. They highlight the results obtained with some of the most commonly employed regimens that have been evaluated over the past several years. Transitional carcinoma of the urothelium is clearly one of the most chemotherapy-responsive solid tumors, offering a wide variety of opportunities to test combined modalities and other innovative approaches designed to enhance tumor control and cure rates.

At present, there are at least 30 distinct multidrug regimens that have consistently demonstrated moderately high response rates (95% confidence intervals ranging from approximately 50%-80%) with similar response duration and survival rates in phase II studies. In addition, phase III trials have demonstrated the superiority of drug combinations over single agents in terms of response rates and survival, and have clearly illustrated that drug combinations have enhanced antitumor activity.

Toxicity in M-VAC vs Newer Combinations

The four-drug combination of M-VAC (methotrexate, vinblastine, doxorubicin [Adriamycin], cisplatin [Platinol]) represents the cornerstone of systemic chemotherapy for this disease. It has been considered the appropriate standard to which new treatments should be compared in prospective, randomized clinical trials in patients with metastatic disease. The main difference between newer combinations and M-VAC resides in the incidence and severity of acute/chronic toxicity.

A recently reported multi-institutional, international phase III trial has shown that one of the newest and most promising regimens—combination gemcitabine (Gemzar)/cisplatin—is comparable to M-VAC in terms of activity, but is associated with a significantly lower incidence of serious side effects.[1] Non-cisplatin-containing combinations based on taxanes and gemcitabine have shown activity in patients who had been previously treated with M-VAC or CMV (cisplatin, methotrexate, vinblastine), as well as in patients with impaired renal function who were not considered suitable candidates for cisplatin-containing regimens. Similarly, the substitution of pharmacologically planned doses of carboplatin (Paraplatin) with either paclitaxel (Taxol) or docetaxel (Taxotere) in patients with renal dysfunction has been shown to be feasible and effective.[2]

Unanswered Questions

As such treatment strategies continue to evolve, a number of interesting questions suggest opportunities for further research into metastatic bladder cancer. For example:

(1) As recently illustrated by Bajorin et al,[3] there is substantial heterogeneity in terms of outcome following chemotherapy among patients with metastatic transitional cell carcinoma. The extent of metastatic involvement, not unexpectedly, is a major predictor of response and survival. In the subset of patients with regional soft-tissue nodal metastasis (no visceral involvement and Karnofsky performance status of 80 or better), an overall chemotherapy response rate of about 75% (at least half of which were complete responses), as well as long-term disease-free and overall survival, have been reported (30%-35% 5-year survival). While these patients are usually not considered candidates for local therapy initially, it may not be unreasonable to ask whether there is a role for local treatment with surgery or radiation after a response to chemotherapy has been achieved in order to eradicate or maximally control the primary site of disease. Furthermore, not uncommonly, patients with responsive local tumors are at risk for developing problems such as obstruction and
bleeding.

(2) How can the treatment benefits of current regimens be enhanced? Should one simply add all active drugs into multidrug regimens? The evolving experience with taxane/gemcitabine combinations in patients for whom M-VAC or other platinum-containing regimens have failed suggests that there may be a significant salvage rate. In light of this, is there a role for designing regimens based on alternating or sequential non-cross-resistant combinations?

(3) Do all patients require treatment until they demonstrate evidence of disease progression? The experience with most active regimens suggests that maximal responses are evident within 3 to 4 months after the initiation of chemotherapy, or usually after three to six cycles of treatment. It also suggests that the magnitude of response is a major factor predicting outcome. Since toxicities that are more prone to leave significant debilitating and potentially irreversible sequelae, such as neurotoxicity, are frequently related to cumulative doses, a shorter duration of treatment may have a significant impact on quality of life. Discontinuation of treatment after a few cycles would allow for the earlier utilization of more active alternate regimens in nonresponding patients. Those who demonstrate major responses to treatment provide an excellent opportunity to assess the benefits of some of the new noncytotoxic compounds, which are more likely to exert their effects on tumor progression.

(4) Bladder cancer represents a unique model for translational research. Various phases of early tumor progression and metastasis, such as invasion and angiogenesis, can be sequentially evaluated by repeat biopsies of tumor and surrounding tissues—all part of the standard management of patients with primary bladder cancer. Molecular markers have been shown to correlate with outcome, and possibly, response to systemic treatment. Further characterization and definition of various molecular phenotypes would undoubtedly enhance new drug development efforts by providing critical information about potential intermediate end points with which to assess treatment effects and perhaps even treatment selection. The setting of local disease where repeat cystoscopes and biopsies are part of the standard follow-up in these patients, can offer the necessary opportunity for adequate correlational studies.

(5) Although fortunately less common than transitional cell carcinoma, "nontransitional" histologies derive relatively little benefit from chemotherapy. More efforts need to be made to identify new, active treatments for these patients.

**Adjuvant Treatment**

While not the major focus of their review, the authors briefly discuss the potential role of adjuvant treatment and various prognostic factors that are evaluated in patients with local disease. Among the ongoing adjuvant studies of major importance are two phase III trials by the National Cancer Institute (NCI): the long-awaited, high-priority SWOG 8710, which is comparing the role of three cycles of neoadjuvant M-VAC prior to radical cystectomy vs radical cystectomy alone in patients with muscle-invasive disease, and the NCI-sponsored randomized, postoperative adjuvant M-VAC study (which involves the administration of M-VAC for four cycles in patients with recurrent/invasive p53-positive disease). Based on these two trials, it would not be surprising if transitional cell carcinoma of the bladder is added to the list of tumors in which adjuvant chemotherapy for high-risk patients represents the standard treatment approach.

**References:**


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