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Chemotherapy for Metastatic or Unresectable Bladder Cancer

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Cisplatin, methotrexate, doxorubicin, and vinblastine (M-VAC) combination chemotherapy has been the historic standard of care in patients with advanced urothelial tumors. Phase III trials have evaluated new combinations such as gemcitabine/cisplatin (GC), carboplatin/paclitaxel, docetaxel/cisplatin, and interferon-α/5-fluorouracil/cisplatin. However, these new regimens have failed to demonstrate superiority in terms of overall survival when compared with classic M-VAC. The GC doublet has proved to be a new standard treatment alternative based on an improved toxicity profile and similar survival results. The addition of a third agent (paclitaxel) to this regimen is the focus of a phase III trial. However, long-term follow-up with classical and new regimens (doublets and triplets) still show limited efficacy and emphasize the need to identify more active treatment. For "unfit" patients, ie, those unable to receive cisplatin-based regimens, conventional regimens include methotrexate, carboplatin, and vinblastine (M-CAVI), carboplatin-gemcitabine, carboplatin-paclitaxel, gemcitabine-taxane, or monotherapy with either gemcitabine, carboplatin, or a taxane. New drugs, including pemetrexed and vinflunine, are now being studied for salvage therapy. In addition to new active drug combinations and targeted therapies, chemotherapy optimization using molecular characteristics to predict chemosensitivity is emerging.
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Approximately 15% of patients who present with bladder cancer will be found to have regional or distant metastasis. In addition, infiltrating tumors will develop distant metastases in up to 30% to 40% of cases despite standard treatment with radical cystectomy. Single chemotherapeutic agents and combinations of drugs have shown that a significant number of patients with metastatic bladder cancer will respond partially or completely. Cisplatin is the single most active agent, with improved response rates when combined with other agents. Herein, we summarize evidence-based data from randomized trials, as well as address current questions and hypothesize as to possible future treatment strategies.

The Classical Chemotherapy Regimen: M-VAC

The standard treatment for invasive bladder cancer is radical cystectomy, whereas patients with metastatic or locally advanced urothelial cancer are usually treated with chemotherapy. Systemic chemotherapy is the only modality that has been shown to improve survival in patients with advanced bladder cancer.[1,2] In randomized trials, the cisplatin, methotrexate, doxorubicin, and vinblastine (M-VAC) regimen has produced a modest though significant survival benefit when compared with cisplatin as a single agent, CISCA (cisplatin, doxorubicin, and cyclophosphamide) or carboplatin-based regimens.[1-3] The M-VAC regimen was first reported in 1985 by investigators from the Memorial Sloan-Kettering Cancer Center (MSKCC). It combined the four most active drugs at that time, and revealed that urothelial carcinoma was sensitive to chemotherapy.[4,5] Patients with measurable lesions were found to have a remarkably high response rate of 72%, with 36% attaining complete remission (CR).[5] This chemotherapy combination was more effective in patients with only nodal disease than in those with visceral metastases.[2,4] Overall survival for the whole group was 13.1 months.[4]

Other extensively studied combination regimens in metastatic urothelial carcinoma are cisplatin and methotrexate (CM), and CMV (with vinblastine).[6-8] CMV was shown to be superior to methotrexate and vinblastine (MV) in a randomized study of 214 patients undertaken by the Medical Research Council.[9] The median survival was 7 months versus 4.5 months, and the overall survival hazard ratio (HR) was

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0.48 in favor of CMV. This study demonstrated the significant survival impact of cisplatin, and has supported the routine use of cisplatin-based combination chemotherapies. Although CM, CMV, and M-VAC have never been compared in randomized studies, most centers consider M-VAC to be the standard regimen.

Toxicity, however, has been one of the major limitations of the M-VAC regimen. Myelosuppression can be reduced with the simultaneous use of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF), which allows more patients to receive the originally planned dose of the conventional M-VAC regimen, and even an intensified M-VAC schedule.[10-13] Unfortunately, dose intensification of the M-VAC regimen has not translated into a clinical benefit in terms of improved survival. In a phase III European Organization for Research and Treatment of Cancer (EORTC) Genitourinary Group trial, high-dose M-VAC (HD-MVAC) given every 2 weeks with G-CSF was compared with conventional M-VAC.[14] This trial revealed less toxicity with HD-MVAC due to the routine addition of G-CSF. It was possible to deliver twice the dose of cisplatin and doxorubicin with less toxicity, fewer dose delays, and in half the time. Although median survival did not significantly differ, there were significant differences in favor of HD-MVAC in response rate (RR) and CR rate. Two-year survival was 35% with HD-MVAC compared with 25% using M-VAC. Because cycle length is much shorter and it is delivered in half the time than the traditional M-VAC, this schedule might be useful both in the neoadjuvant and the adjuvant setting.

New Active Single Agents and Doublets in Bladder Cancer

The limited results with the classical M-VAC combination have led to the search for new treatment approaches aiming to improve outcome and treatment tolerance. Anti-tumor activity has been demonstrated with several single agents, although these have rarely produced an improvement in survival.[15-17] The RR to single-agent cisplatin is 17% in phase II trials and 12% in phase III trials.[18] Carboplatin also has been widely used because of its easy outpatient administration and milder toxicity profile (RR, 12% to 14% in phase II studies).[19,20] Oxaliplatin monotherapy, as in other tumors, has shown minimal activity in previously treated patients, but preliminary data have shown encouraging results when combined with gemcitabine in patients unfit to receive cisplatin.[21-23]

Antifolate compounds have also been tested in advanced bladder cancer. Witte et al reported a response rate of 17% for trimetrexate in patients who had received prior chemotherapy.[24] Piritrexim, an oral second-generation antimetabolite, demonstrated a 38% response rate when used as a single agent in chemotherapy-naive patients,[25] whereas responses dropped to 23% in previously treated patients.[26] Currently this compound is being evaluated in combination with gemcitabine.[27]

Several other chemotherapeutics, including gemcitabine, the taxanes (paclitaxel and docetaxel), ifosfamide, and recently, pemetrexed, the epothilones and vinflunine have demonstrated single-agent activity in urothelial carcinoma.[15,16,28-31] Testing novel agents in sequence with gemcitabine and cisplatin (GC) has been suggested as a feasible strategy to study new compounds in bladder cancer without compromising survival.[32]

Modern Doublet Chemotherapy

Gemcitabine is a highly active agent in bladder cancer, obtaining response rates from 23% to 28% in both pretreated patients and in those who have not had prior therapy.[31,33,34] Following several phase II studies,[35-37], the combination of gemcitabine and cisplatin (GC) was compared with M-VAC in a randomized international trial. This study revealed a similar efficacy with respect to response, time to disease progression, and overall survival.[38] Median survival was 13.8 months for GC-treated patients and 14.8 months for M-VAC–treated patients, with a HR of 1.04. Interestingly, however, GC was significantly less toxic than M-VAC, and therefore the risk–benefit ratio favored GC. Even though the study was designed to demonstrate a 4-month improvement in survival benefit with GC and not to show the equivalence of the two regimens, many researchers have interpreted the results as showing therapeutic noninferiority, and determined that any difference in survival was unlikely to be sufficiently large to offset the improvement in toxicity with GC.[38] Consequently, GC is currently considered the standard alternative to M-VAC.

Based on its effectiveness in advanced bladder cancer, cisplatin also has been tested in combination with the taxanes. The paclitaxel and cisplatin regimen, usually given every 3 weeks, has been evaluated in several phase II studies,[39-41] totaling more than 100 patients, resulting in overall RRs ranging from 50% to 70% (CR rates from 15% to 32%). Similarly, the combination of docetaxel and cisplatin every 3 weeks also has been evaluated.[42-44] In more than 120 patients, the overall RR was 52% to 62%, with median overall survival durations ranging from 8.2 to 13.6 months. Although these phase II studies have shown activity in untreated patients with similar response rates to M-VAC, a recent randomized study reported by the Hellenic Group, originally designed to detect an advantage for docetaxel and cisplatin, showed inferior activity and survival of the cisplatin/docetaxel combination compared with classic M-VAC. Because performance status (PS) was not used in this trial as a prospective stratification variable, the treatment arms might not have been appropriately balanced. When adjusted for prognostic factors, the difference in time to progression (TTP) remained significant in favor of M-VAC (HR 1.61; $P = .005$), whereas the survival difference was not significant at the 5% level (HR 1.31; $P = .089$)[45] (Table 1).

Studies with carboplatin (area under the curve [AUC] 5 to 6) and paclitaxel (150 to 225 mg/m^2) have reported RRs ranging from 21% to 63%, although many of the responses were partial remissions (PRs).[46-48] In a Southwest Oncology