Clinical Trials: The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment. Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies. These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

### Perioperative Chemotherapy (Neoadjuvant or Adjuvant)

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| **Dose-dense methotrexate + vinblastine + doxorubicin + cisplatin (DDMVAC) with growth factor support**<sup>2,3</sup> | **Day 1:** Methotrexate 30mg/m<sup>2</sup> IV  
**Day 2:** Vinblastine 3mg/m<sup>2</sup> IV, plus doxorubicin 30mg/m<sup>2</sup> IV, plus cisplatin 70mg/m<sup>2</sup> IV  
**Day 4:** Granulocyte colony-stimulating factor (G-CSF) 240μg/m<sup>2</sup> SQ for 7 consecutive days (days 4 through 10). May be extended for up to a total of 14 consecutive days. Repeat every 2 weeks for 3–4 cycles. |
| **Gemcitabine + cisplatin**<sup>4–6</sup> | **Days 1, 8 and 15:** Gemcitabine 1,000mg/m<sup>2</sup> IV over 30–60 minutes  
**Day 2:** Cisplatin 70mg/m<sup>2</sup>. Repeat every 4 weeks for a maximum of 6 cycles. |
| **Cisplatin + methotrexate + vinblastine (CMV)**<sup>7</sup> | **Day 1:** Methotrexate 30mg/m<sup>2</sup> IV bolus plus vinblastine 4mg/m<sup>2</sup> IV bolus  
**Day 2:** Cisplatin 100mg/m<sup>2</sup> IV infusion; followed by hydration; followed by leucovorin 15mg PO or IV every 6 hours for 4 doses (commencing 24 hours after methotrexate on day 1).  
**Day 8:** Methotrexate 30mg/m<sup>2</sup> IV bolus plus vinblastine 4mg/m<sup>2</sup> IV bolus.  
**Day 9:** Leucovorin 15mg PO every 6 hours for 4 doses after methotrexate on day 8. Repeat every 3 weeks for 3 cycles. |

### Principals of Chemotherapy Management

- Randomized trials and meta-analyses show a survival benefit for cisplatin-based neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer.<sup>2,8,9</sup>
- Meta-analysis suggests a survival benefit to adjuvant therapy for pathologic T3, T4 or N+ disease at cystectomy.<sup>9</sup>
- Neoadjuvant chemotherapy is preferred over adjuvant-based chemotherapy on a higher level of evidence data.
- DDMVAC is preferred over standard MVAC based on category I evidence showing DDMVAC to be better tolerated and more effective than conventional MVAC in advanced disease.<sup>3,10</sup> Based on these data, the traditional dose and schedule for MVAC is no longer recommended.
- Perioperative gemcitabine and cisplatin is a reasonable alternative to DDMVAC based on category I evidence showing equivalence to conventional MVAC in the setting of advanced disease.<sup>5,6</sup>
- For gemcitabine/cisplatin, both 21- and 28-day regimens are acceptable. Better dose compliance may be achieved with fewer delays in dosing using the 21-day schedule.<sup>11</sup>
- Neoadjuvant chemotherapy may be considered for select patients with upper tract urothelial carcinoma, particularly for higher stage and/or grade tumors, as renal function will decline after nephroureterectomy and may preclude adjuvant therapy.
- Carboplatin should not be substituted for cisplatin in the perioperative setting.
- For patients with borderline renal function or minimal dysfunction, a split-dose administration of cisplatin may be considered (such as 35mg/m<sup>2</sup> on days 1 and 2 or days 1 and 8; category 2B). Although safer, the relative efficacy of the cisplatin-containing combination administered with such modifications remains undefined.
- For patients who are not candidates for cisplatin, there are no data to support a recommendation for perioperative chemotherapy.

### First-Line Chemotherapy for Metastatic Disease

| Gemcitabine + cisplatin<sup>5</sup> | **Days 1, 8 and 15:** Gemcitabine 1,000mg/m<sup>2</sup> IV over 30–60 minutes  
**Day 2:** Cisplatin 70mg/m<sup>2</sup>. Repeat every 4 weeks for a maximum of 6 cycles. |

*continued*
First-Line Chemotherapy for Metastatic Disease

DDMVAC with growth factor support

Day 1: Methotrexate 30mg/m² IV
Day 2: Vinblastine 3mg/m² IV, plus doxorubicin 30mg/m² IV, plus cisplatin 70mg/m² IV
Day 4: G-CSF 240μg/m² SQ for 7 consecutive days (days 4 through 10). May be extended for up to a total of 14 consecutive days.
Repeat every 2 weeks for 3–4 cycles.

OR
Day 1: Methotrexate 30mg/m² IV
Day 2: Vinblastine 3mg/m² IV, plus doxorubicin 30mg/m² IV, plus cisplatin 70mg/m² IV
Day 3: G-CSF SQ for 5 consecutive days (days 3 through 7).
Repeat cycle every 15 days.

Principals of Chemotherapy Management

• The presence of both visceral metastases and Eastern Cooperative Oncology Group performance score ≥ 2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy.

• For most patients, the risks of adding paclitaxel to gemcitabine and cisplatin outweigh the limited benefit seen in the randomized trial.¹²

• A substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities.

› Participation in clinical trials of new or more tolerable therapy is recommended.

› Carboplatin-/taxane-based regimens, or single-agent therapy can be considered as alternative regimens for these patients.

Second-Line (Palliative) Chemotherapy for Metastatic Disease

Preferred Treatment

• Single-agent taxane or gemcitabine

Additional Single-Agent Treatment Options

• Cisplatin

• Carboplatin

• Doxorubicin

• 5-fluorouracil (5-FU)

• Ifosfamide

• Methotrexate

• Vinblastine

• Pemetrexed

First-Line Radiosensitizing Chemotherapy Regimens

Cisplatin

Cisplatin 100mg/m² IV every 2 weeks for 3 cycles.

Cisplatin + 5-FU

Days 1, 2, 3, 15, 16, and 17: IV hydration at a rate of 500mL/hour; followed by 5-FU 400mg/m² IV push; followed by cisplatin 15mg/m² IV over 1 hour as induction and consolidation therapy.†

5-FU + mitomycin C

Day 1 of radiotherapy: Mitomycin 12mg/m² IV bolus, plus Week 1 (fractions 1–5) and Week 4 (fractions 16–20) of radiotherapy: 5-FU 500mg/m² continuous IV infusion (10 days total).

Cisplatin + paclitaxel

Days 1, 8 and 15: Paclitaxel 50mg/m²; followed by twice-daily radiotherapy for 8 days

Radiosensitizing Chemotherapy with Conventionally Fractionated radiation

• Cisplatin

• Docetaxel or paclitaxel

• 5-FU

• 5-FU and mitomycin C

• Capecitabine

• Low-dose gemcitabine

* No standard therapy exists in this setting, thus participation in clinical trials of new agents is recommended.
† For bladder-preserving chemoradiation following a maximal transurethral resection of bladder tumor.
‡ On days 1, 3, 15, and 17, radiation was given immediately following the chemotherapy using twice-a-day 3 Gy per fraction cores to the pelvis for a total radiation dose of 24 Gy (with at least a 4-hour inter-fraction interval).
§ For palliation of metastases or for pelvic recurrence after cystectomy.
∥ Upon complete or near complete response, patients received consolidation chemoradiation consisting of 1.5 Gy pelvic radiotherapy twice a day for 8 days to 24 Gy (total dose: 64.3 Gy to the tumor and 44.8 Gy to the pelvic lymph nodes) and paclitaxel 50mg/m² days 1 and 8 and cisplatin15mg/m² on days 1, 2, 8, and 9.


