BLADDER CANCER TREATMENT REGIMENS (Part 1 of 4)

Clinical Trials: The National Comprehensive Cancer Network (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 NCCN 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)[1,a]

Note: All recommendations are Category 2A unless otherwise indicated.

REGIMEN	DOSING
Dose-dense methotrexate + vinblastine + doxorubicin + cisplatin (DDMVAC) with growth factor support[2,3]	**Day 1:** Methotrexate 30mg/m² IV **Day 2:** Vinblastine 3mg/m² IV, **plus** doxorubicin 30mg/m² IV, **plus** cisplatin 70mg/m² IV **Day 4:** Granulocyte colony-stimulating factor (G-CSF) 240µg/m² subcutaneous (SQ) injection 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[4–6]	**Days 1, 8, and 15:** Gemcitabine 1,000mg/m² IV over 30–60 minutes **Day 2:** Cisplatin 70mg/m². Repeat every 4 weeks for 4 cycles.
Cisplatin + methotrexate + vinblastine (CMV)[7]	**Day 1:** Methotrexate 30mg/m² IV bolus **plus** vinblastine 4mg/m² IV bolus **Day 2:** Cisplatin 100mg/m² IV infusion; **followed by** hydration; **followed by** leucovorin 15mg orally or IV every 6 hours for 4 doses (commencing 24 hours after methotrexate on day 1) **Day 8:** Methotrexate 30mg/m² IV bolus **plus** vinblastine 4mg/m² IV bolus **Day 9:** Leucovorin 15mg orally every 6 hours for 4 doses after methotrexate on day 8. Repeat every 3 weeks for 3 cycles.

Principles of Chemotherapy Management

- For patients who are not candidates for cisplatin, there are no data to support a recommendation for perioperative chemotherapy.
- Randomized trials and meta-analyses show a survival benefit for cisplatin-based neoadjuvant chemotherapy (3 or 4 cycles) in patients with muscle-invasive bladder cancer.[2,8,9]
- Meta-analysis suggests a survival benefit to adjuvant therapy for pathologic T3, T4, or N+ disease at cystectomy.[9]
- 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.[3,10] 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.[5,6]
- 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.[11]
- 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/m² 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 with borderline renal function, estimate glomerular filtration rate to assess eligibility for cisplatin.

First-Line Chemotherapy for Locally Advanced or Metastatic Disease[1,a]

Cisplatin Eligible (Standard Regimens)

Gemcitabine + cisplatin (Category 1)[6]	**Days 1, 8, and 15:** Gemcitabine 1,000mg/m² IV over 30–60 minutes **Day 2:** Cisplatin 70mg/m². Repeat every 4 weeks for a maximum of 6 cycles.
DDMVAC with growth factor support (Category 1)[3,10]	**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 injection 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 injection for 5 consecutive days (days 3 through 7). Repeat cycle every 15 days.

continued

BLADDER CANCER TREATMENT REGIMENS (Part 2 of 4)

First-Line Chemotherapy for Locally Advanced or Metastatic Disease[1,a] (continued)

Cisplatin Ineligible (Standard Regimens)

Gemcitabine + carboplatin[12]	**Days 1 and 8:** Gemcitabine 1,000mg/m² over 30 minutes IV **Day 1 (every 3 weeks):** Carboplatin (4.5 × [glomerular filtration rate + 25]) over 1 hour IV.
Atezolizumab[13]	Atezolizumab 1200mg IV infusion over 60 minutes every 3 weeks.
Pembrolizumab[14]	Pembrolizumab 200mg every 3 weeks.

Principles 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.[18]
- 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.

Cisplatin Ineligible (Alternative Regimens)

Gemcitabine[15]	Gemcitabine 1200mg/m² administered weekly x3 on a 4-week cycle.
Gemcitabine + paclitaxel[16]	Gemcitabine 2500mg/m² over 30 minutes, **plus** paclitaxel 150mg/m² over 3 hours given every 2 weeks.
Ifosfamide + doxorubicin + gemcitabine[17] (For patients with good kidney function and good performance status)	**Days 1–4:** Ifosfamide 1500mg/m² infused over 3 hours daily, **plus** MESNa 225mg/m² over 15 minutes at hours 0, 3, 7, and 11 **Day 3:** Doxorubicin 45mg/m² over 15 minutes via peripheral IV or up to 12–18 hours via central line on day 3 only **Days 2 and 4:** Gemcitabine 150mg/m² over 30 minutes.

Subsequent Systemic Therapy for Locally Advanced or Metastatic Disease[1,a]

Standard Regimens

Pembrolizumab (Category 1)[19]	Pembrolizumab 200mg every 3 weeks.
Atezolizumab[20]	Atezolizumab 1200mg IV winfusion over 60 minutes every 3 weeks.
Nivolumab[21]	Nivolumab 3mg/kg IV every 2 weeks.
Durvalumab[22]	Durvalumab 10mg/kg once every 2 weeks up to 12 months, unacceptable toxicity, or confirmed progressive disease.
Avelumab[23,24]	Avelumab 10mg/kg IV over 1 hour every 2 weeks.
Paclitaxel or docetaxel[25,26]	Paclitaxel 80mg/m² every week **OR** Docetaxel 100mg/m² over 1 hour every 21 days.
Gemcitabine[15]	Gemcitabine 1200mg/m² administered weekly x3 on a 4-week cycle.
Pemetrexed[27]	**Day 1:** Pemetrexed 500mg/m² IV every 21 days, **plus** vitamin B_{12}, folic acid, and dexamethasone prophylaxis.

Alternate Regimens for Select Patients

Nab-paclitaxel[28]	Nab-paclitaxel at 260mg/m² IV every 3 weeks.
Ifosfamide[29]	Ifosfamide to 1,500mg/m² IV with MESNa 750 mg/m² IV for 5 days every 3 weeks, with doses modified for hematologic, renal, and central nervous system toxicity.
Methotrexate	Follow usual protocols.
Ifosfamide + doxorubicin + gemcitabine[17]	**Days 1–4:** Ifosfamide 1500mg/m² infused over 3 hours daily, **plus** MESNa 225mg/m² over 15 minutes at hours 0, 3, 7, and 11 **Day 3:** Doxorubicin 45mg/m² over 15 minutes via peripheral IV or up to 12–18 hours via central line on day 3 only **Days 2 and 4:** Gemcitabine 150mg/m² over 30 minutes.
Gemcitabine + paclitaxel[16]	Gemcitabine 2500mg/m² over 30 minutes, **plus** paclitaxel 150mg/m² over 3 hours given every 2 weeks.
Gemcitabine + cisplatin[5]	**Days 1, 8, and 15:** Gemcitabine 1,000mg/m² IV over 30–60 minutes **Day 2:** Cisplatin 70mg/m². Repeat every 4 weeks for a maximum of 6 cycles.
DDMVAC[3]	**Day 1:** Methotrexate 30mg/m² IV **Day 2:** Vinblastine 3mg/m² IV, **plus** doxorubicin 30mg/m² IV, **plus** cisplatin 70mg/m² IV Repeat every 2 weeks for 3–4 cycles.

First-Line Radiosensitizing Chemotherapy Regimens[1,a,b]

First-line Standard Chemotherapy Regimens (Doublet Preferred)

Cisplatin[c] **+ 5-FU**[30]	**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.

continued

BLADDER CANCER TREATMENT REGIMENS (Part 3 of 4)

First-Line Radiosensitizing Chemotherapy Regimens[1,a,b] (continued)

First-line Standard Chemotherapy Regimens (Doublet Preferred) (continued)

Cisplatin[c] + paclitaxel[30,31]	**Days 1, 8, and 15:** Paclitaxel 50mg/m^2 **Day 1–3, 8–10, 15–17:** Cisplatin 15mg/m^2; followed by twice-daily radiotherapy for 8 days.[f]
5-FU + mitomycin[32]	**Day 1 of radiotherapy:** Mitomycin 12mg/m^2 IV bolus, **plus** Week 1 (fractions 1–5) and Week 4 (fractions 16–20) of radiotherapy: 5-FU 500mg/m^2 continuous IV infusion (10 days total).[d]

Alternate Regimens

Cisplatin[c] alone[33]	Cisplatin 100mg/m^2 IV every 2 weeks for 3 cycles.
Low-dose gemcitabine (Category 2B)[34,35]	Gemcitabine 75mg/m^2 IV weekly given concurrently with radiotherapy.

Radiosensitizing Chemotherapy With Conventionally Fractionated Radiation[1,a,e]

Cisplatin[c]
Taxane (docetaxel or paclitaxel; Category 2B)
5-FU ± mitomycin (both Category 2B)
Capecitabine (Category 3)
Low-dose gemcitabine (Category 2B)

[a] Participation in clinical trials of new agents is recommended.

[b] For bladder-preserving chemoradiation following a maximal transurethral resection of bladder tumor.

[c] Carboplatin in not an effective radiation sensitizer and should not be substituted for cisplatin with radiation.

[d] 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 interfraction interval).

[e] For palliation of metastases or for pelvic recurrence after cystectomy.

[f] 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/m^2 days 1 and 8 and cisplatin 15mg/m^2 on days 1, 2, 8, and 9.

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