

BLADDER CANCER TREATMENT REGIMENS (Part 1 of 5)

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.

Preferred Regimens

REGIMEN	DOSING
Dose-dense methotrexate + vinblastine + doxorubicin + cisplatin (DDMVAC) with growth factor support^{2,3}	<p>Day 1: Methotrexate 30mg/m² IV</p> <p>Day 2: Vinblastine 3mg/m² IV, plus doxorubicin 30mg/m² IV, plus cisplatin 70mg/m² IV</p> <p>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.</p> <p>Repeat every 2 weeks for 3–4 cycles.</p>

Gemcitabine + cisplatin⁴⁻⁶	<p>Days 1, 8, and 15: Gemcitabine 1,000mg/m² IV over 30–60 minutes</p> <p>Day 2: Cisplatin 70mg/m².</p> <p>Repeat every 4 weeks for 4 cycles.</p>
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Other Recommended Regimens

Cisplatin + methotrexate + vinblastine (CMV)⁷	<p>Day 1: Methotrexate 30mg/m² IV bolus plus vinblastine 4mg/m² IV bolus</p> <p>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)</p> <p>Day 8: Methotrexate 30mg/m² IV bolus plus vinblastine 4mg/m² IV bolus</p> <p>Day 9: Leucovorin 15mg orally every 6 hours for 4 doses after methotrexate on day 8.</p> <p>Repeat every 3 weeks for 3 cycles.</p>
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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 Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)^{1,a}

Cisplatin Eligible

Preferred Regimens

Gemcitabine + cisplatin (Category 1)⁶	<p>Days 1, 8, and 15: Gemcitabine 1,000mg/m² IV over 30–60 minutes</p> <p>Day 2: Cisplatin 70mg/m².</p> <p>Repeat every 4 weeks for a maximum of 6 cycles.</p>
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BLADDER CANCER TREATMENT REGIMENS (Part 2 of 5)

First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)^{1,a} (continued)

Cisplatin Eligible (continued)

Preferred Regimens (continued)

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.

Cisplatin Ineligible

Preferred Regimens

Gemcitabine + carboplatin¹²

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.

Atezolizumab¹³

Atezolizumab 1200mg IV infusion over 60 minutes every 3 weeks.

Pembrolizumab¹⁴

Pembrolizumab 200mg every 3 weeks.

Other Recommended Regimens

Gemcitabine¹⁵

Gemcitabine 1200mg/m² administered weekly x3 on a 4-week cycle.

Gemcitabine + paclitaxel¹⁶

Gemcitabine 2500mg/m² over 30 minutes, **plus** paclitaxel 150mg/m² over 3 hours given every 2 weeks.

Useful Under Certain Circumstances

Ifosfamide + doxorubicin + gemcitabine¹⁷

(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.

Principles of Chemotherapy Management

- The presence of both non-nodal metastases and ECOG performance score >2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy. The impact of these factors in relation to immune checkpoint inhibition is not fully defined, but they remain poor prognostic indicators in general.
- 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.

Subsequent Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV) (Post-platinum)^{1,a}

Preferred Regimens

Pembrolizumab (Category 1)¹⁹

Pembrolizumab 200mg every 3 weeks.

Alternative Preferred Regimens

Atezolizumab²⁰

Atezolizumab 1200mg IV infusion over 60 minutes every 3 weeks.

Nivolumab²¹

Nivolumab 3mg/kg IV every 2 weeks.

Durvalumab²²

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.

Other Recommended Regimens

Nab-paclitaxel²⁵

Nab-paclitaxel at 260mg/m² IV every 3 weeks.

Paclitaxel or docetaxel^{25,26}

Paclitaxel 80mg/m² every week
OR
 Docetaxel 100mg/m² over 1 hour every 21 days.

Gemcitabine¹⁵

Gemcitabine 1200mg/m² administered weekly x3 on a 4-week cycle.

Pemetrexed²⁷

Day 1: Pemetrexed 500mg/m² IV every 21 days, **plus** vitamin B₁₂, folic acid, and dexamethasone prophylaxis.

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BLADDER CANCER TREATMENT REGIMENS (Part 3 of 5)

Subsequent Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV) (Post-platinum) ^{4,a} (continued)

Useful in Certain Circumstances Based on Prior Medical Therapy

Ifosfamide ²⁹	Ifosfamide to 1,500mg/m ² IV with MESNa 750 mg/m ² 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/m ² infused over 3 hours daily, plus MESNa 225mg/m ² over 15 minutes at hours 0, 3, 7, and 11 Day 3: Doxorubicin 45mg/m ² 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/m ² over 30 minutes.
Gemcitabine + paclitaxel ¹⁶	Gemcitabine 2500mg/m ² over 30 minutes, plus paclitaxel 150mg/m ² over 3 hours given every 2 weeks.
Gemcitabine + cisplatin ⁵	Days 1, 8, and 15: Gemcitabine 1,000mg/m ² IV over 30–60 minutes Day 2: Cisplatin 70mg/m ² . Repeat every 4 weeks for a maximum of 6 cycles.
DDMVAC with growth factor support ³	Day 1: Methotrexate 30mg/m ² IV Day 2: Vinblastine 3mg/m ² IV, plus doxorubicin 30mg/m ² IV, plus cisplatin 70mg/m ² IV Repeat every 2 weeks for 3–4 cycles.

Subsequent Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV) (Post-checkpoint inhibitor)

Cisplatin Ineligible

Preferred Regimens

Gemcitabine + carboplatin ¹²	Days 1 and 8: Gemcitabine 1,000mg/m ² over 30 minutes IV Day 1 (every 3 weeks): Carboplatin (4.5 × [glomerular filtration rate + 25]) over 1 hour IV.
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Cisplatin Eligible, Chemotherapy Naïve

Preferred Regimens

Gemcitabine + cisplatin ⁶	Days 1, 8, and 15: Gemcitabine 1,000mg/m ² IV over 30–60 minutes Day 2: Cisplatin 70mg/m ² . Repeat every 4 weeks for a maximum of 6 cycles.
DDMVAC + growth factor support ³	Day 1: Methotrexate 30mg/m ² IV Day 2: Vinblastine 3mg/m ² IV, plus doxorubicin 30mg/m ² IV, plus cisplatin 70mg/m ² IV Day 4: G-CSF 240µg/m ² 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/m ² IV Day 2: Vinblastine 3mg/m ² IV, plus doxorubicin 30mg/m ² IV, plus cisplatin 70mg/m ² IV Day 3: G-CSF SQ injection for 5 consecutive days (days 3 through 7). Repeat cycle every 15 days.

Other Recommended Regimens

Nab-paclitaxel ²⁸	Nab-paclitaxel at 260mg/m ² IV every 3 weeks.
Paclitaxel or docetaxel ^{25,26}	Paclitaxel 80mg/m ² every week OR Docetaxel 100mg/m ² over 1 hour every 21 days.
Gemcitabine ¹⁵	Gemcitabine 1200mg/m ² administered weekly x3 on a 4-week cycle.
Pemetrexed ²⁷	Day 1: Pemetrexed 500mg/m ² IV every 21 days, plus vitamin B12, folic acid, and dexamethasone prophylaxis.

Useful in Certain Circumstances Based on Prior Medical Therapy

Ifosfamide ²⁹	Ifosfamide to 1,500mg/m ² IV with MESNa 750 mg/m ² IV for 5 days every 3 weeks, with doses modified for hematologic, renal, and central nervous system toxicity.
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BLADDER CANCER TREATMENT REGIMENS (Part 4 of 5)

Radiosensitizing Chemotherapy Regimens for Organ-Preserving Chemoradiation^{1,a,b} (continued)

Cisplatin Eligible, Chemotherapy Naïve (continued)

Useful in Certain Circumstances Based on Prior Medical Therapy (continued)

Methotrexate¹	Follow usual protocols.
Ifosfamide + doxorubicin + gemcitabine¹⁷	Days 1–4: Ifosfamide 1500mg/m ² infused over 3 hours daily, plus MESNa 225mg/m ² over 15 minutes at hours 0, 3, 7, and 11 Day 3: Doxorubicin 45mg/m ² 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/m ² over 30 minutes.
Gemcitabine + paclitaxel¹⁶	Gemcitabine 2500mg/m ² over 30 minutes, plus paclitaxel 150mg/m ² over 3 hours given every 2 weeks.

Radiosensitizing Chemotherapy Regimens for Organ-Preserving Chemoradiation^{1,a,b}

Preferred Regimens (Doublet Preferred)

Cisplatin^c + 5-FU³⁰	Days 1, 2, 3, 15, 16, and 17: IV hydration at a rate of 500mL/hour; followed by 5-FU 400mg/m ² IV push; followed by cisplatin 15mg/m ² IV over 1 hour as induction and consolidation therapy.
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 + mitomycin³²	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

Other Recommended Regimens

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

Radiosensitizing Chemotherapy With Conventionally Fractionated Radiation for Palliation of Metastases or Recurrence^{1,a,e}

Preferred Regimens

Cisplatin^c

Other Recommended Regimens

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/m² days 1 and 8 and cisplatin 15mg/m² on days 1, 2, 8, and 9.

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