BLADDER CANCER TREATMENT REGIMENS (Part 1 of 3)

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)[1]

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 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[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 a maximum of 6 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 PO 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 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.[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 who are not candidates for cisplatin, there are no data to support a recommendation for perioperative chemotherapy.

First-Line Chemotherapy for Metastatic Disease[1]

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.

continued

BLADDER CANCER TREATMENT REGIMENS (Part 2 of 3)

First-Line Chemotherapy for Metastatic Disease[1] (continued)

DDMVAC with growth factor support[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 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[1]*

Preferred Treatment

- Single-agent taxane or gemcitabine

Additional Single-Agent Treatment Options

- Cisplatin
- Carboplatin
- Doxorubicin
- 5-fluorouracil (5-FU)
- Ifosfamide
- Pemetrexed
- Methotrexate
- Vinblastine

First-Line Radiosensitizing Chemotherapy Regimens[1†]

Cisplatin[13]	Cisplatin 100mg/m² IV every 2 weeks for 3 cycles.
Cisplatin + 5-FU[14,15]	**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[15-17]	**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[17]	**Days 1, 8 and 15:** Paclitaxel 50mg/m² **Days 1–3, 8–10, 15–17:** Cisplatin 15mg/m²; **followed by** twice-daily radiotherapy for 8 days‖

Radiosensitizing Chemotherapy with Conventionally Fractionated radiation[1§]

- 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.

continued

BLADDER CANCER TREATMENT REGIMENS (Part 3 of 3)

References

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology™. Bladder Cancer. v 1.2014. Available at: http://www.nccn.org/professionals/physician_gls/PDF/bladder.pdf. Accessed April 4, 2014.
2. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med.* 2003;349(9):859–866.
3. Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. *J Clin Oncol.* 2001;19(10):2638–2646.
4. Dash A, Pettus JA, Herr HW, et al. A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. *Cancer*. 2008;113(9):2471–2477.
5. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol.* 2000;18(17):3068–3077.
6. von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol.* 2005;23(21):4602–4608.
7. Griffiths G, Hall R, Sylvester R, et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. *J Clin Oncol.* 2011;29(16):2171–2177.
8. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. *Eur Urol*. 2005;48(2):202–205.
9. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. *Eur Urol*. 2005;48(2):189–199.
10. Sternberg CN, de Mulder P, Schornagel JH, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. *Eur J Cancer.* 2006;42(1):50–54.
11. Soto Parra H, Cavina R, Latteri F, et al. Three-week versus four-week schedule of cisplatin and gemcitabine: results of a randomized phase II study. *Ann Oncol.* 2002;13(7):1080–1086.
12. Bellmunt J, von der Maase H, Mead GM, et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. *J Clin Oncol.* 2012;30:1107–1113.
13. Coppin CM, Gospodarowicz MK, James K, et al. Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. *J Clin Oncol.* 1996;14:2901–2907.
14. Kaufman DS, Winter KA, Shipley WU, et al. The initial results in muscle-invading bladder cancer of RTOG 95-06: phase I/II trial of transurethral surgery plus radiation therapy with concurrent cisplatin and 5-fluorouracil followed by selective bladder preservation or cystectomy depending on the initial response. *The Oncologist.* 2000;5:471–476.
15. James ND, Hussain SA, Hall E, et al; BC2001 Investigators. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med.* 2012;366:1477–1488.
16. Hussain SA, Stocken DD, Peake DR, et al. Long-term results of a phase II study of synchronous chemoradiotherapy in advanced muscle invasive bladder cancer. *Br J Cancer.* 2004;90:2106–2111.
17. Mitin T, Hunt D, Shipley W, et al. Transurethral surgery and twice-daily radiation plus paclitaxel-cisplatin or fluorouracil-cisplatin with selective bladder preservation and adjuvant chemotherapy for patients with muscle invasive bladder cancer (RTOG 0233): a randomized multicentre phase 2 trial. *Lancet Oncol.* 2013;14:863–872.

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