BONE CANCER TREATMENT REGIMENS (Part 1 of 5)

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.

General Treatment Notes[1]

- Chemotherapy for Ewing's sarcoma and osteosarcoma should include growth factor support.
- Conventional chondrosarcoma (Grades 1–3) has no known standard chemotherapy options.
- Mesenchymal chondrosarcoma: follow Ewing's sarcoma regimens (category 2B).

Chordoma[1]

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

REGIMEN	DOSING
Imatinib[2,3]	Imatinib 800mg orally once daily.
Imatinib + cisplatin[4]	Imatinib 400mg orally once daily + cisplatin 25mg/m^2 weekly.
Imatinib + sirolimus[5]	Imatinib 400mg orally once daily + sirolimus 2mg orally once daily.
Erlotinib[6]	Erlotinib 150mg orally once daily.
Sunitinib[7]	Sunitinib 37.5mg orally once daily.
Lapatinib for epidermal growth factor receptor (EGFR)-positive chordomas (Category 2B)[8]	Lapatinib 1,500mg orally once daily.

Ewing's Sarcoma and Mesenchymal Chondrosarcoma[1]

First-line Therapy (Primary/Neoadjuvant/Adjuvant)

VAC/IE (vincristine + doxorubicin† + cyclophosphamide alternating with ifosfamide + etoposide)[9]	**Alternating VAC and IE cycles** *VAC cycles* **Day 1:** Vincristine 2mg/m^2 (max 2mg) IV + doxorubicin 75mg/m^2 IVP + cyclophosphamide 1,200mg/m^2 IV. Dactinomycin 1.25mg/m^2 IV can be substituted for doxorubicin when a total doxorubicin dose of 375mg/m^2 is reached. *IE cycles* **Days 1–5:** Ifosfamide 1,800mg/m^2 IV + mesna + etoposide 100mg/m^2 IV. Repeat each cycle every 3 weeks for 17 cycles.
VAIA (vincristine + dactinomycin [actinomycin D] + ifosfamide + doxorubicin)[10,11]	**Day 1:** Vincristine 1.5mg/m^2 IV **Days 1-3:** Ifosfamide 2,000mg/m^2 IV + mesna **Days 1, 3, and 5:** Dactinomycin 0.5mg/m^2 IV **Days 2 and 4:** Doxorubicin 30mg/m^2 IV. Repeat cycle every 21 days for 4 cycles, then proceed to local therapy. After local therapy, high-risk patients should receive 10 additional cycles of VAIA; standard-risk patients should receive 10 additional cycles of VAIA of 10 cycles of VACA: **Day 1:** Vincristine 1.5mg/m^2 IV + cyclophosphamide 1,200mg/m^2 IV + mesna **Days 1, 3, and 5:** Dactinomycin 0.5mg/m^2 IV **Days 2 and 4:** Doxorubicin 30mg/m^2 IV. Repeat cycle every 21 days for 10 cycles. **OR** **Days 1, 8, 15, and 22:** Vincristine 1.5mg/m^2 IV **Days 1, 2, 22, 23, 43, and 44 :** Ifosfamide 3,000mg/m^2 IV + mesna **Days 1, 2, 43, and 44 :** Doxorubicin 30mg/m^2 IV **Days 22, 23, and 24:** Dactinomycin 0.5mg/m^2 IV After completion of one 9-week cycle, proceed to local therapy. High-risk patients should then receive 3 additional cycles.
VIDE (vincristine + ifosfamide + doxorubicin + etoposide)[12]	**Day 1:** Vincristine 1.5mg/m^2 (max 2mg) IV push **Days 1–3:** Doxorubicin 20mg/m^2 IV + ifosfamide 3g/m^2 IV + mesna continuous IV infusion + etoposide 150mg/m^2 IV. Repeat cycle every 3 weeks for up to 6 cycles.

continued

BONE CANCER TREATMENT REGIMENS (Part 2 of 5)

Ewing's Sarcoma and Mesenchymal Chondrosarcoma[1] (continued)

Primary Therapy for Metastatic Disease at Initial Presentation

REGIMEN	DOSING
VAC/IE (vincristine + doxorubicin† + cyclophosphamide alternating with ifosfamide + etoposide)[9]	**Alternating VAC and IE cycles** *VAC cycles* **Day 1:** Vincristine 2mg/m² (max 2mg) IV + doxorubicin 75mg/m² IV bolus + cyclophosphamide 1,200mg/m² IV + mesna. Dactinomycin 1.25mg/m² IV can be substituted for doxorubicin when a total doxorubicin dose of 375mg/m² is reached. *IE cycles* **Days 1–5:** Ifosfamide 1,800mg/m² IV + mesna + etoposide 100mg/m² IV. Repeat each cycle every 3 weeks for 17 cycles.
VAIA (vincristine + dactinomycin [actinomycin D] + ifosfamide + doxorubicin)[10,11]	**Day 1:** Vincristine 1.5mg/m² IV **Days 1-3:** Ifosfamide 2,000mg/m² IV + mesna **Days 1, 3, and 5:** Dactinomycin 0.5mg/m² IV **Days 2 and 4:** Doxorubicin 30mg/m² IV. Repeat cycle every 21 days for 4 cycles, then proceed to local therapy. After local therapy, high-risk patients should receive 10 additional cycles of VAIA; standard-risk patients should receive 10 additional cycles of VAIA of 10 cycles of VACA: **Day 1:** Vincristine 1.5mg/m2 IV + cyclophosphamide 1,200mg/m² IV + mesna **Days 1, 3, and 5:** Dactinomycin 0.5mg/m² IV **Days 2 and 4:** Doxorubicin 30mg/m² IV. Repeat cycle every 21 days for 10 cycles. **OR** **Days 1, 8, 15, and 22:** Vincristine 1.5mg/m² IV **Days 1, 2, 22, 23, 43, and 44 :** Ifosfamide 3,000mg/m² IV + mesna **Days 1, 2, 43, and 44 :** Doxorubicin 30mg/m² IV **Days 22, 23, and 24:** Dactinomycin 0.5mg/m² IV. After completion of one 9-week cycle, proceed to local therapy. High-risk patients should then receive 3 additional cycles.
VIDE (vincristine + ifosfamide + doxorubicin + etoposide)[12]	**Day 1:** Vincristine 1.5mg/m² (max 2mg) IV push **Days 1–3:** Doxorubicin 20mg/m² IV + ifosfamide 3g/m² IV + mesna continuous IV infusion + etoposide 150mg/m² IV. Repeat cycle every 3 weeks for up to 6 cycles.
VAdriaC† (vincristine + doxorubicin + cyclophosphamide + dactinomycin)[13]	**Day 1:** Vincristine 2mg/m² IV + cyclophosphamide 1,200mg/m² + doxorubicin 75mg/m² (the first 5 cycles) **OR** dactinomycin 1.25mg/m² IV (subsequent cycles). Repeat cycle every 3 weeks for 17 cycles.

Second-line Therapy (Relapsed/Refractory Disease or Metastatic Disease)

Cyclophosphamide + topotecan[14–17]	**Days 1–5:** Cyclophosphamide 250mg/m²/day IV + topotecan 0.75mg/m²/day IV, each given as a 30-minute infusion once daily for 5 days. Repeat cycle every 3 weeks for 12–14 cycles.
Irinotecan ± temozolomide[18–24]	**Days 1–5:** Temozolomide 100mg/m²/day orally, **plus** **Days 1–5 and 8–12:** Irinotecan 10–20mg/m²/day IV at least 1 hour after temozolomide. Repeat cycle every 3 or 4 weeks.
Ifosfamide (high dose) ± etoposide[25,26]	**Days 1–5:** Ifosfamide 1,800mg/m²/day IV + mesna **Days 1–5:** Etoposide 100mg/m²/day IV. Repeat every 3 weeks for 12 cycles.
Ifosfamide + carboplatin + etoposide[27]	**Days 1 and 2:** Carboplatin 400mg/m²/day IV, **plus** **Days 1–5:** Ifosfamide 1,800mg/m²/day IV + mesna + etoposide 100mg/m²/day IV. Repeat cycle every 3 weeks for up to 12 cycles (median 1 cycle).
Docetaxel + gemcitabine[28]	**Days 1 and 8:** Gemcitabine 675mg/m² IV, **plus** **Day 8:** Docetaxel 75–100mg/m² IV. Repeat cycle every 3 weeks for up to 13 cycles (median 4 cycles).

continued

BONE CANCER TREATMENT REGIMENS (Part 3 of 5)

Giant Cell Tumor of Bone[1]

REGIMEN	DOSING
Denosumab[29,30]	Denosumab 120mg subcutaneously every 4 weeks with additional doses on Days 8 and 15.
Interferon alfa[31-33]	Interferon alpha-2 or beta (3,000,000 units/m^2) 48 to 72 hours postoperatively **OR** increasing dosage from 4 x 10^6 units 3 times a week to 9 × 10^6 units 3 times a week.
Peginterferon[33]	Peginterferon alfa-2a 1.0µ/kg SQ injection weekly.

Osteosarcoma[1]

First-line Therapy (Primary/Neoadjuvant/Adjuvant Therapy or Metastatic Disease)

Cisplatin + doxorubicin[34-36]	**Days 1–3:** Doxorubicin 25mg/m^2/day IV, **plus** **Day 1:** Cisplatin 100mg/m^2 IV continuous IV infusion. Repeat cycle every 3 weeks for 6 cycles.
MAP (high-dose methotrexate + cisplatin + doxorubicin)[37,38]	**Preoperative Chemotherapy** **Days 1 and 28:** Methotrexate 8g/m^2 IV followed by citrovorum factor rescue **Days 7-9 and 34-36:** Cisplatin 120mg/m^2 by intra-arterial infusion for 72 hours **Days 9 and 36:** Doxorubicin 60mg/m^2 IV starting 8 hours after the beginning of cisplatin. **Postoperative Chemotherapy (Necrosis ≥90%)** **Days 1, 48, 96, and 144:** Doxorubicin 45mg/m^2/day for 2 consecutive days in a 4-hour IV infusion **Days 21, 69, and 117:** Methotrexate 8g/m^2 IV followed by citrovorum factor rescue **Days 27, 75, and 123:** Cisplatin 120mg/m^2 by intra-arterial infusion for 72 hours. **Postoperative Chemotherapy (Necrosis <90%)** **Days 1, 69, 138, and 207:** Doxorubicin 45mg/m^2/day for 2 consecutive days in a 4-hour IV infusion **Days 21, 90, and 159:** Ifosfamide 2g/m^2/day IV for 5 consecutive days in 90 minutes + mesna **Days 42, 111, and 180:** Methotrexate 8g/m^2 IV followed by citrovorum factor rescue **Days 48, 117, and 186:** Etoposide 120mg/m^2/day in a 1-hour infusion for 3 days.
Doxorubicin + cisplatin + ifosfamide + high-dose methotrexate[39]	**Days 0, 6, 18, 27, and 36:** Methotrexate 12g/m^2 as a 4-hour infusion, increased by 2g/m^2 if the hour-4 level of serum methotrexate in the previous course was <1000 µmol/L **Days 1, 7, 19, 28, and 37:** Cisplatin 60mg/m^2/day as a 48-hour continuous IV infusion (total dose 120mg/m^2) **Days 1 and 7:** Doxorubicin (preoperative): 75mg/m^2 as a 24-hour continuous IV infusion **Day 12:** Surgery **Days 13, 22, and 31:** Doxorubicin (postoperative): 90mg/m^2 as a 24-hour continuous IV infusion **Days 4, 10, 16, 25, and 34:** Ifosfamide: 3 g/m^2/day as a 120-hour (5-day) continuous IV infusion (total dose 15g/m^2).
Ifosfamide + cisplatin + epirubicin[40]	**Day 1:** Epirubicin 90mg/m^2 IV + cisplatin 100mg/m^2 IV **Days 2–4:** Ifosfamide 2.0g/m^2 with an equivalent dose of mesna, repeated every 21 days. Six cycles of this combination regimen were administered (3 cycles preoperatively and 3 cycles postoperatively).

Second-line Therapy (Relapsed/Refractory or Metastatic Disease)

Carboplatin + ifosfamide + etoposide[27]	**Days 1 and 2:** Carboplatin 400mg/m^2/day IV, **plus** **Days 1–5:** Ifosfamide 1,800mg/m^2/day IV + mesna + etoposide 100mg/m^2/day IV. Repeat cycle every 3 weeks for up to 12 cycles (median 1 cycles).
Gemcitabine + docetaxel[28]	**Days 1 and 8:** Gemcitabine 675mg/m^2 IV, **plus** **Day 8:** Docetaxel 75–100mg/m^2 IV. Repeat cycle every 3 weeks for up to 13 cycles (median 4 cycles).
Cyclophosphamide + topotecan[17]	**Days 1–5:** Cyclophosphamide 250mg/m^2/day IV + topotecan 0.75mg/m^2/day IV, each given as a 30-minute infusion once daily for 5 days. Repeat cycle every 3 weeks for 12–14 cycles.
Sorafenib[41]	Sorafenib 400mg orally twice daily until progression or unacceptable toxicity.

continued

BONE CANCER TREATMENT REGIMENS (Part 4 of 5)

Osteosarcoma[1] (continued)

Second-line Therapy (Relapsed/Refractory or Metastatic Disease) (continued)

Ifosfamide (high dose) ± etoposide[25,26]	**Days 1–5:** Ifosfamide 1,800mg/m²/day IV + mesna, **plus** **Days 1–5:** Etoposide 100mg/m²/day IV. Repeat every 3 weeks for 12 cycles.
Cyclophosphamide + etoposide[42]	**Day 1:** Cyclophosphamide 4,000mg/m² 3-hour IV infusion; all patients received mesna 1,400mg/m² before and after 4 hours and 8 hours from cyclophosphamide start **Days 2–4:** Etoposide 100mg/m² over 1 hour twice daily for 3 days on Days 2, 3, and 4 (total dose 600mg/m²).
Gemcitabine[43]	**Days 1 and 8:** Gemcitabine 1,200mg/m² IV. Repeat cycle every 21 days.
High-dose methotrexate + etoposide + ifosfamide[44]	**Weeks 1, 2, 3, 7, 8, 12, and 13:** High-dose methotrexate IV **Weeks 4 and 9:** Etoposide 75mg/m²/day IV + ifosfamide 3g/m²/day + mesna 3.6mg/m²/day continuous IV infusion for 4 days.
Sorafenib + everolimus[45]	Sorafenib 800mg orally + everolimus 5mg orally once daily until disease progression or unacceptable toxicity.
^{153}Sm-EDTMP (for relapsed or refractory disease beyond second-line therapy)[46]	Samarium-153 ethylene diamine tetramethylene phosphonate (^{153}Sm-EDTMP) 1.0, 3.0, 4.5, 6.0, 12.0, 19.0, or 30.0mCi/kg can be considered; however, the 30mCi/kg dosage requires peripheral-blood progenitor cell grafts with more than 2 x 10⁶ CD34(+)/kg to overcome the myeloablative effects of skeletal irradiation.
^{223}RA[47-49]	Three 75kBq/kg ^{223}RA infusion given in 4-week intervals (total administered dose of 14.44MBq or 0.390mCi); ^{223}RA doses of 50kBq/kg and 100Bq/kg are being investigated.

* Indicated for high-grade chondrosarcoma for systemic recurrence.

† Dactinomycin can be substituted for doxorubicin because of concerns regarding cardiotoxicity.

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