# BONE CANCER TREATMENT REGIMENS (Part 1 of 4)

**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).
- High-grade undifferentiated pleomorphic sarcoma (UPS) of bone and dedifferentiated chondrosarcoma: follow osteosarcoma 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 with cisplatin**[4] | Imatinib 400mg orally once daily and cisplatin 25mg/m$^2$/week. |
| **Imatinib with sirolimus**[5] | Imatinib 400mg orally once daily and sirolimus 2mg/day orally once daily. |
| **Erlotinib**[6] | Erlotinib 150mg orally once daily. |
| **Sunitinib**[7] | Sunitinib 37.5mg orally once daily. |
| **Lapatinib for 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)

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|---|---|
| **VAC/IE (vincristine + doxorubicin† + cyclophosphamide alternating with ifosfamide + etoposide)**[9] | **Alternating VAC and IE cycles**<br>*VAC cycles*<br>**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.<br>*IE cycles*<br>**Days 1–5:** Ifosfamide 1,800mg/m$^2$ IV + mesna + etoposide 100mg/m$^2$ IV.<br>Repeat each cycle every 3 weeks for 17 cycles. |
| **VAI (vincristine + ifosfamide + dactinomycin + doxorubicin)**[10] | **Day 1:** Vincristine 1.5mg/m$^2$ IV<br>**Days 1–3:** Ifosfamide 2,000mg/m$^2$ IV + mesna<br>**Days 1, 3, and 5:** Dactinomycin 0.5mg/m$^2$ IV<br>**Days 2 and 4:** Doxorubicin 30mg/m$^2$ IV.<br>Repeat cycle every 3 weeks. |
| **VIDE (vincristine + ifosfamide + doxorubicin + etoposide)**[11] | **Day 1:** Vincristine 1.4mg/m$^2$ (max 2mg)<br>**Days 1–3:** Doxorubicin 20mg/m$^2$ IV + ifosfamide 3mg/m$^2$ IV + mesna 3g/m$^2$ continuous IV infusion + etoposide 150mg/m$^2$ IV.<br>Repeat cycle every 3 weeks for up to 6 cycles. |

### Primary Therapy for Metastatic Disease at Initial Presentation

| | |
|---|---|
| **VAC/IE (vincristine + doxorubicin† + cyclophosphamide alternating with ifosfamide + etoposide)**[9] | **Alternating VAC and IE cycles**<br>*VAC cycles*<br>**Day 1:** Vincristine 2mg/m$^2$ (max 2mg) IV + doxorubicin 75mg/m$^2$ IV bolus + 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.<br>*IE cycles*<br>**Days 1–5:** Ifosfamide 1,800mg/m$^2$ IV + mesna + etoposide 100mg/m$^2$ IV.<br>Repeat each cycle every 3 weeks for 17 cycles. |
| **VAI (vincristine + ifosfamide + dactinomycin [actinomycin D] + doxorubicin)**[10] | **Day 1:** Vincristine 1.5mg/m$^2$ IV<br>**Days 1–3:** Ifosfamide 2,000mg/m$^2$ IV + mesna<br>**Days 1, 3 and 5:** Dactinomycin 0.5mg/m$^2$ IV<br>**Days 2 and 4:** Doxorubicin 30mg/m$^2$ IV.<br>Repeat cycle every 3 weeks. |

*continued*

# BONE CANCER TREATMENT REGIMENS (Part 2 of 4)

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

### Primary Therapy for Metastatic Disease at Initial Presentation (continued)

| REGIMEN | DOSING |
|---|---|
| **VIDE (vincristine + ifosfamide + doxorubicin + etoposide)**[11] | **Day 1:** Vincristine 1.4mg/m² (max 2mg)<br>**Days 1–3:** Doxorubicin 20mg/m² IV + ifosfamide 3mg/m² IV + mesna 3g/m² continuous IV infusion + etoposide 150mg/m² IV.<br>Repeat cycle every 3 weeks for up to 6 cycles. |
| **VAdriaC† (cyclophosphamide + vincristine + doxorubicin OR dactinomycin)**[12] | **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).<br>Repeat cycle every 3 weeks for 17 cycles. |

### Second-Line Therapy (Relapsed/Refractory Disease or Metastatic Disease)

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|---|---|
| **Cyclophosphamide + topotecan**[13–16] | **Days 1–5:** Cyclophosphamide 250mg/m²/day IV + topotecan 0.75mg/m²/day IV.<br>Repeat cycle every 3 weeks for 12–14 cycles. |
| **Irinotecan ± temozolomide**[17–23] | **Days 1–5:** Temozolomide 100mg/m²/day orally, **plus**<br>**Days 1–5 and 8–12:** Irinotecan 10–20mg/m²/day IV at least 1 hour after temozolomide.<br>Repeat cycle every 3 or 4 weeks. |
| **Ifosfamide + etoposide**[24] | **Days 1–5:** Ifosfamide 1,800mg/m²/day IV + mesna<br>**Days 1–5:** Etoposide 100mg/m²/day IV.<br>Repeat every 3 weeks for 12 cycles. |
| **Ifosfamide + carboplatin + etoposide**[25] | **Days 1 and 2:** Carboplatin 400mg/m²/day IV, **plus**<br>**Days 1–5:** Ifosfamide 1,800mg/m²/day IV + mesna + etoposide 100mg/m²/day IV.<br>Repeat cycle every 3 weeks for up to 12 cycles (median 1 cycle). |
| **Docetaxel + gemcitabine**[26] | **Days 1 and 8:** Gemcitabine 675mg/m² IV, **plus**<br>**Day 8:** Docetaxel 75–100mg/m² IV.<br>Repeat cycle every 3 weeks for up to 13 cycles (median 4 cycles). |
| **Irinotecan, temozolomide + cefpodoxime**[23] | **Days 1–5 and Days 8–21:** Irinotecan 20–30mg/m² IV with continuous oral cefpodoxime 10mg/kg/day divided BID starting 2 days prior to irinotecan. |
| **Cyclophosphamide + sirolimus**[27] **(Category 2B)*** | **First cycle of treatment**<br>**Days 1–7 and 15–21:** Cyclophosphamide 100mg oral twice daily from first cycle of treatment<br>**Days 1–7:** Sirolimus 1mg orally once daily<br>**Days 8–14:** Sirolimus 1mg orally twice daily<br>**Days 15–21:** Sirolimus 1mg orally three times daily.<br>**Second cycle of treatment**<br>**Days 1–7 and 15-21:** Cyclophosphamide 100mg oral twice daily from first cycle of treatment<br>**Days 1–21:** Sirolimus 1mg orally three times daily.<br>Repeat cycle every 4 weeks |

## Giant Cell Tumor of Bone[1]

| | |
|---|---|
| **Denosumab**[28,29] | Denosumab 120mg subcutaneously every 4 weeks with additional doses on Days 8 and 15. |
| **Interferon alfa**[30,31] | Interferon alpha-2 or beta (3,000,000 units/m²) 48 to 72 hours postoperatively **OR** increasing dosage from 4 x 106 units 3 times a week to 9 × 106 units 3 times a week. |

## Osteosarcoma[1]

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

| | |
|---|---|
| **Cisplatin + doxorubicin**[32–34] | **Days 1–3:** Doxorubicin 25mg/m²/day IV, **plus**<br>**Day 1:** Cisplatin 100mg/m² IV continuous IV infusion.<br>Repeat cycle every 3 weeks for 6 cycles. |
| **MAP (high-dose methotrexate + cisplatin + doxorubicin)**[35,36] | **Day 1:** Methotrexate 8g/m² IV (with leucovorin rescue 15mg every 6 hours for 11 doses, starting 24 hours after beginning methotrexate), **followed by**<br>**Days 7–9:** Cisplatin 120mg/m²/day intra-arterially, **followed by**<br>**Day 9:** Doxorubicin 60mg/m² IV (48 hours after start of cisplatin infusion).<br>Repeat cycle once after 4 weeks. |

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# BONE CANCER TREATMENT REGIMENS (Part 3 of 4)

## Osteosarcoma[1] (continued)

### First-Line Therapy (Primary/Neoadjuvant/Adjuvant Therapy or Metastatic Disease) (continued)

| REGIMEN | DOSING |
|---|---|
| **Doxorubicin + cisplatin + ifosfamide + high-dose methotrexate**[37] | **Days 0, 6, 18, 27, and 36:** Methotrexate (MTX) 12g/m² as a 4-hour infusion, increased by 2g/m² if the hour-4 level of serum MTX in the previous course was <1000 µmol/L<br>**Days 1, 7, 19, 28, and 37:** Cisplatin 60mg/m²/day as a 48-hour continuous IV infusion (total dose 120mg/m²)<br>**Days 1 and 7:** Doxorubicin (ADM1) (preoperative): 75mg/m² as a 24-hour continuous IV infusion<br>**Day 12:** Surgery<br>**Days 13, 22, and 31:** Doxorubicin (ADM2) (postoperative): 90mg/m² as a 24-hour continuous IV infusion<br>**Days 4, 10, 16, 25, and 34:** Ifosfamide: 3 g/m²/day as a 120-hour (5-day) continuous IV infusion (total dose 15 g/m²). |
| **Ifosfamide + cisplatin + epirubicin**[38] | **Day 1:** Epirubicin 90mg/m², cisplatin 100mg/m²<br>**Days 2–4:** Ifosfamide 2.0 g/m² with an equivalent dose of mesna, repeated every 21 days. Six cycles of this combination regimen were administered (3 cycles prior to surgery and 3 cycles postoperatively). |

### Second-Line Therapy (Relapsed/Refractory or Metastatic Disease)

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|---|---|
| **Carboplatin + ifosfamide + etoposide**[25] | **Days 1 and 2:** Carboplatin 400mg/m²/day IV, **plus**<br>**Days 1–5:** Ifosfamide 1,800mg/m²/day IV + mesna + etoposide 100mg/m²/day IV.<br>Repeat cycle every 3 weeks for up to 12 cycles (median 1 cycles). |
| **Gemcitabine + docetaxel**[26] | **Days 1 and 8:** Gemcitabine 675mg/m² IV, **plus**<br>**Day 8:** Docetaxel 75–100mg/m² IV.<br>Repeat cycle every 3 weeks for up to 13 cycles (median 4 cycles). |
| **Cyclophosphamide + topotecan**[16] | **Days 1–5:** Cyclophosphamide 250mg/m²/dose followed by topotecan 0.75mg/m²/dose), each given as a 30-minute IV infusion once daily for 5 days. |
| **Sorafenib**[39] | Sorafenib 400mg orally twice daily. |
| **Ifosfamide + etoposide**[24] | **Days 1–5:** Ifosfamide 1,800mg/m²/day IV and etoposide 100mg/m²/day; 5-day cycles every 3 weeks for 12 cycles. |
| **Cyclophosphamide + etoposide**[40] | **Day 1:** Cyclophosphamide 4000mg/m² 3-hour IV infusion<br>**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**[41] | **Days 1 and 8:** Gemcitabine 1,200mg/m² IV.<br>Repeat cycle every 21 days. |
| **High-dose methotrexate + etoposide + ifosfamide**[42] | **Weeks 1, 2, 3, 7, 8, 12, and 13:** High-dose methotrexate IV<br>**Weeks 4 and 9:** Etoposide 75mg/m²/day IV + ifosfamide 3g/m²/day + mesna 3.6mg/m²/day continuous IV infusion for 4 days. |

* Indicated for high-grade chondrosarcoma for systemic recurrence.

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

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