LEUKEMIA TREATMENT REGIMENS:
Acute Lymphoblastic Leukemia (ALL) (Part 1 of 4)

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Drug dose modifications and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, and comorbidities. Thus, the optimal delivery of anticancer agents requires a healthcare delivery team experienced in the use of such agents and the management of associated toxicities in patients with cancer. The cancer treatment regimens below may include both FDA-approved and unapproved uses/regimens and are provided as references only to the latest treatment strategies. Clinicians must choose and verify treatment options based on the individual patient.

Ph(+) AYA (Age 15–39 years)[1]

Clinical trial OR chemotherapy + TKI[2]

Induction Therapy	**Weeks 4–6:** 3- or 4-drug induction therapy consistent with pediatric cooperative group (Children's Cancer Group [CCG] or Pediatric Oncology Group [POG]).
Consolidation Therapy	Block 1 (3 weeks) **Day 1:** Methotrexate (MTX) intrathecally (IT), etoposide 100mg/m²/day IV, ifosfamide 3.3g/m²/day IV. **Days 1–21:** Imatinib 340mg/m²/day orally. **Days 6–15:** Filgrastim 5mcg/kg/day SC. **Day 8:** CNS leukemia only: MTX IT, hydrocortisone IT, cytarabine IT. **Day 15:** CNS leukemia only: MTX IT, hydrocortisone IT, cytarabine IT. Block 2 (3 weeks) **Day 1:** Age adjusted: MTX IT, hydrocortisone IT, cytarabine IT. **Day 1:** MTX 5g/m² IV over 24 hrs. **Days 1–21:** Imatinib 340mg/m²/day orally (hold imatinib if patient does not achieve count recovery within 2 weeks of last dose of previous course). **Days 2–3:** Leucovorin 75mg/m² 36 hrs after MTX followed by 15mg/m² IV or orally every 6 hrs for 6 doses. **Days 2–3:** Cytarabine 3g/m²/dose IV every 12 hrs for 4 doses. **Days 4–13:** Filgrastim 5mcg/kg/day SC.
Reinduction Therapy Block 1 (3 weeks)	**Day 1:** Vincristine 1.5mg/m² IV. **Day 1:** Age adjusted: MTX IT, hydrocortisone IT, cytarabine IT. **Days 1–2:** Daunorubicin 45mg/m²/day IV bolus. **Days 1–21:** Dexamethasone 6mg/m²/day orally. **Days 1–21:** Imatinib 340mg/m²/day orally (hold imatinib if patient does not achieve count recovery within 2 weeks of last dose of previous course). **Days 3–4:** Cyclophosphamide 250mg/m²/dose IV every 12 hrs for 4 doses, **plus** mesna 125mg/m²/dose IV every 12 hrs for 4 doses. **Days 4, 6, 8, 10, 12, 15, 17, 19, and 21:** L-asparaginase 6,000 units/m² IM. **Days 5–14:** Filgrastim 5mcg/kg/day SC. **Day 8:** Vincristine 1.5mg/m² IV. **Day 15:** Vincristine 1.5mg/m² IV. **Day 15:** Age adjusted: MTX IT, hydrocortisone IT, cytarabine IT.
Intensification Therapy Block 1 (9 weeks)	**Day 1:** Age adjusted: MTX IT, hydrocortisone IT, cytarabine IT. **Day 1:** MTX 5g/m² IV over 24 hrs. **Days 1–63:** Imatinib 340mg/m²/day orally (hold imatinib if patient does not achieve count recovery within 2 weeks of last dose of previous course). **Days 2–3:** Leucovorin 75mg/m² 36 hrs after MTX, **followed by** 15mg/m² IV or orally every 6 hrs for 6 doses. **Day 8:** MTX 5g/m² IV over 24 hrs. **Days 9–10:** Leucovorin 75mg/m² 36 hrs after MTX, **followed by** 15mg/m² IV or orally every 6 hrs for 6 doses. **Day 15:** Age adjusted: MTX IT, hydrocortisone IT, cytarabine IT. **Days 15–19:** Etoposide 100mg/m²/day IV **+** cyclophosphamide 300mg/m²/day IV **+** mesna 150mg/m²/day IV. **Days 20–29:** Filgrastim 5mcg/kg/day SC. **Days 36–37:** Cytarabine 3g/m² IV. **Day 37:** L-asparaginase 6,000 units/m² IM. **Days 43–44:** Cytarabine 3g/m² IV. **Day 44:** L-asparaginase 6,000 units/m² IM.
Reinduction Therapy Block 2 (3 weeks)	Repeat Block 1.
Intensification Therapy Block 2 (9 weeks)	Repeat Block 1.

continued

LEUKEMIA TREATMENT REGIMENS:
Acute Lymphoblastic Leukemia (ALL) (Part 2 of 4)

Ph(+) AYA (Age 15–39 years)[1] (continued)

Clinical trial OR chemotherapy + TKI (continued)

Maintenance Therapy

Cycles 1-4 (8 weeks)
Day 1: Age adjusted: MTX IT, hydrocortisone IT, cytarabine IT.
Day 1: Vincristine 1.5mg/m² IV.
Day 1: MTX 5g/m² IV over 24 hrs.
Days 1–5: Dexamethasone 6mg/m²/day orally.
Days 1–56: Imatinib 340mg/m²/day orally (hold imatinib if patient does not achieve count recovery within 2 weeks of last dose of previous course).
Days 2–3: Leucovorin 75mg/m² 36 hrs after MTX, **followed by** 15mg/m² IV or orally every 6 hrs for 6 doses.
Days 8–28: 6-mercaptopurine (MP) 75mg/m²/day.
Day 8: MTX 20mg/m²/week orally.
Day 15: MTX 20mg/m²/week orally.
Day 22: MTX 20mg/m²/week orally.
Day 29: Age adjusted: MTX IT, hydrocortisone IT, cytarabine IT.
Day 29: Vincristine 1.5mg/m² IV.
Days 29–33: Dexamethasone 6mg/m²/day orally.
Days 36–40: Etoposide 100mg/m² IV.
Days 36–40: Cyclophosphamide 300mg/m² IV.
Days 41–50: Filgrastim 5mcg/kg/day SC.

Cycles 5-12 (8 weeks)
Cycle 5 only: Cranial irradiation 12 Gy.
Day 1: Vincristine 1.5mg/m² IV.
Days 1–5: Dexamethasone 6mg/m²/day orally.
Days 1–14: Imatinib 340mg/m²/day orally (hold imatinib if patient does not achieve count recovery within 2 weeks of last dose of previous course).
Days 8, 15, and 22: MTX 20mg/m²/week orally.
Days 8–28: 6-MP 75mg/m²/day.
Days 29–42: Imatinib 340mg/m²/day orally (hold imatinib if patient does not achieve count recovery within 2 weeks of last dose of previous course).
Day 36: MTX 20mg/m²/week orally.
Day 43: MTX 20mg/m²/week orally.
Day 50: MTX 20mg/m²/week orally.
Day 29: Vincristine 1.5mg/m² IV.
Days 29–33: Dexamethasone 6mg/m²/day orally.
Days 36–56: 6-MP 75mg/m²/day.

Ph(+) Adult (Age ≥40 years)

Patients <65 years with no substantial comorbidities

Induction Therapy

4 cycles Hyper-CVAD alternating with 4 cycles of high dose cytarabine and MTX.
Days 1–14 of each cycle: Dasatinib 50mg orally twice daily (or 100mg daily),[3] **OR** imatinib 400mg orally daily.[4]

OR

Day 1: Cyclophosphamide 1,200mg/m² IV over 3 hrs.
Days 1–3: Daunorubicin 60mg/m² IV over 1 hr.
Days 1–21: Prednisolone 60mg/m² orally.
Days 1, 8, 15, and 22: Vincristine 1.3mg/m² IV bolus.
Days 8–63: Imatinib 600mg orally.
Day 29: MTX 15mg IT, cytarabine 40mg IT, dexamethasone 4mg IT.[5]

OR

Pretreatment for 7 days: Prednisone at increasing doses from 10-40mg/m²/day.
Days 1–45: Imatinib 800mg orally daily.
Days 1–45: Prednisone 40mg/m² daily (patients >60 years).[6]

OR

Pretreatment for 7 days: Prednisone at increasing doses from 10–60mg/m²/day.
Days 1–48: Dasatinib 70mg orally twice daily.
Days 1–24: Prednisone 60mg/m² daily (max 120mg daily).
Days 22 and 43: MTX IT.
Days 25–32: Prednisone taper.[7]

continued

LEUKEMIA TREATMENT REGIMENS:
Acute Lymphoblastic Leukemia (ALL) (Part 3 of 4)

Ph(+) Adult (Age ≥40 years) (continued)	
Patients <65 years with no substantial comorbidities (continued)	
Consolidation Therapy	Allogeneic hematopoietic stem cell transplant (HSCT), if a donor is available and consider post-HSCT TKI. **OR** Continue multi-agent chemotherapy **+** TKI.
Maintenance Therapy	**2–3 years** MTX weekly, **plus** 6-MP daily, **plus** Vincristine pulse monthly, **plus** Prednisone pulse monthly.
Ph(-) AYA (Age 15–39 years)[1]	
GRAALL-2003 regimen[8]	
Corticosteroid Prephase	**1–7 days before induction therapy:** Prednisone 60mg/m²/day. **4–7 days before induction therapy:** MTX 15mg IT.
Induction Therapy	**Day 1:** Cyclophosphamide 750mg/m²/day **+** vincristine 2mg IV. **Days 1–3:** Daunorubicin 50mg/m²/day. **Days 1–14:** Prednisone 60mg/m²/day. **Day 8:** Vincristine 2mg IV **+** L-asparaginase 6,000 units/m²/day. **Days 10, 12:** L-asparaginase 6,000 units/m²/day. **Day 15:** For Good Early Responders: Cyclophosphamide 750mg/m²/day, **OR** **Days 15–16:** For Poor Early Responders: Cyclophosphamide 500mg/m²/12 hrs. **Day 15:** Vincristine 2mg IV. **Days 15–16:** Daunorubicin 30mg/m²/day. **Day 17:** Lenograstim 150mcg/m²/day to myeloid recovery. **Days 20, 22:** L-asparaginase 6,000 units/m²/day. **Day 22:** Vincristine 2mg IV. **Days 24, 26, and 28:** L-asparaginase 6,000 units/m²/day.
Salvage Therapy	**Days 1–3:** Idarubicin 12mg/m²/day. **Days 1–4:** Cytarabine 2g/m²/12 hrs. **Day 9:** Lenograstim 150mcg/m²/day to myeloid recovery.
Consolidation Therapy Blocks 1, 4, 7	**Days 1–2:** Cytarabine 2g/m²/12 hrs. **Days 1–2:** Dexamethasone 10mg/12 hrs. **Day 3:** L-asparaginase 10,000 units/m²/day. **Days 7–13:** Lenograstim 150mcg/m²/day.
Consolidation Therapy Blocks 2, 5, 8	**Day 15:** MTX 3g/m² continuous infusion **+** vincristine 2mg IV **+** 6-MP 60mg/m²/day. **Day 16:** L-asparaginase 10,000 units/m²/day. **Days 16–21:** 6-MP 60mg/m²/day. **Days 22–27:** Lenograstim 150mcg/m²/day.
Consolidation Therapy Blocks 3, 6, 9	**Day 29:** MTX 25mg/m²/day. **Days 29–30:** Cyclophosphamide 500mg/m²/day. **Days 29–30:** Etoposide 75mg/m²/day. **Day 31:** Lenograstim 150mcg/m²/day to myeloid recovery.
Late intensification between consolidation blocks 6 and 7 For patients in CR after the first induction course	Lenograstim 150mcg/m²/day if neutrophils <0.5g/L. **Days 1–3:** Daunorubicin 30mg/m²/day. **Day 1:** Vincristine 2mg IV. **Days 1–14:** Prednisone 60mg/m²/day. **Day 8:** Vincristine 2mg IV. **Days 8, 10, and 12:** L-asparaginase 6,000 units/m²/day. **Day 15:** Vincristine 2mg IV **+** cyclophosphamide 500mg/m²/12 hrs. **Days 18, 20, and 22:** L-asparaginase 6,000 units/m²/day.
Late intensification between consolidation blocks 6 and 7 For patients in CR after salvage course	**Days 1–3:** Idarubicin 9mg/m²/day. **Days 1–4:** Cytarabine 2g/m²/12 hrs. **Day 9:** Lenograstim 150mcg/m²/day to myeloid recovery.
Maintenance Therapy	Months 1–12 **Day 1:** Vincristine 2mg IV. **Days 1–7:** Prednisone 40mg/m²/day. Months 1–24 **Daily:** 6-MP 60mg/m²/day. **Weekly:** MTX 25mg/m²/week.

continued

LEUKEMIA TREATMENT REGIMENS:
Acute Lymphoblastic Leukemia (ALL) (Part 4 of 4)

Ph(-) AYA (Age 15-39 years)[1] (continued)

GRAALL-2003 regimen[8] (continued)

CNS Therapy Prophylaxis	<u>Triple IT Injection</u> 1 IT injection at **Days 1 and 8** of induction; 1 IT injection at **Day 29** of each series of consolidation blocks; 1 IT injection at **Day 1** of late intensification. ▪ MTX 15mg IT. ▪ Cytarabine 40mg IT. ▪ Methylprednisolone 40mg IT. <u>Cranial Irradiation</u> 18 Gy before maintenance therapy initiation. 6-MP 60mg/m^2/day during irradiation.
CNS Therapy Treatment of patients with initial CNS involvement	<u>Triple IT Injection</u> 8 IT injections starting from 7 days before induction to **Day 21** of induction; 4 IT injections during the first 2 consolidation blocks; 1 IT injection at **Day 29** of consolidation blocks 3 and 6. ▪ MTX 15mg IT. ▪ Cytarabine 40mg IT. ▪ Methylprednisolone 40mg IT. <u>Cranial Irradiation</u> 15 Gy before HSCT or 24 Gy before maintanence therapy initiation. 6-MP 60mg/m^2/day during irradiation.

Ph(-) Adult (Age ≥40 years)

Consolidation Therapy **8 cycles alternating between 2 courses** <u>Course 1</u> **Day 1:** MTX 1g/m^2 IV. **Day 1:** MTX 15mg IT **+** cytarabine 40mg IT **+** dexamethasone 4mg IT. **Days 1–3:** Methylprednisolone 50mg IV over 1 hr for 2 doses. **Days 2–3:** Cytarabine 1–2g/m^2 IV over 3 hrs for 2 doses. <u>Course 2</u> **Day 1:** MTX 15mg IT **+** cytarabine 40mg IT **+** dexamethasone 4mg IT. **Days 1–28:** Imatinib 600mg PO.[5]	**COG AALL-0031 Regimen**[9] <u>Courses 1, 3, 5, and 7: Hyper-CVAD</u> **Days 1–3:** Cyclophosphamide 300mg/m^2 IV over 2–3 hrs every 12 hrs for 6 doses. **Days 1–3:** Sodium mercaptoethanesulfonate 2x cyclophosphamide dose by continuous infusion starting with cyclophosphamide and ending 12 hrs after last cyclophosphamide dose. **Days 1–4:** Dexamethasone 40mg. **Day 4:** Vincristine 2mg IV **+** doxorubicin 50mg/m^2 IV over 2 hrs. **Day 11:** Vincristine 2mg IV. **Days 11–14:** Dexamethasone 40mg. <u>Courses 2, 4, 6, and 8: HD-MTX-Ara-C</u> **Days 1–3:** Methylprednisolone 50mg IV twice daily. **Days 2–3:** Ara-C 3g/m^2 IV over 2 hrs every 12 hrs for 4 doses. **Day 1:** MTX 1g/m^2 IV over 24 hrs. **Day 2:** Citrovorum factor rescue 15mg infusion every 6 hrs initiated 12 hrs after completion of MTX for 8 doses. Increase to 50mg IV every 6 hrs if MTX level is ▪ >20µmol/L at 0 hrs. ▪ >1.0µmol/L at 24 hrs after MTX infusion ends. ▪ >0.1µmol/L at 48 hrs after MTX infusion ends.

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