

ONCOLOGY KNOWLEDGE HUB · FOR HEALTH PROFESSIONALS

Acute Lymphoblastic Leukaemia

A mini review for clinicians

For postgraduate residents (medical and haematology oncology, haematology, internal medicine, emergency medicine, critical care, pathology, transfusion medicine, radiation oncology), practising clinicians and medical students

Dr. Haritha Chiramana

MD (Internal Medicine), DM (Medical Oncology)

Senior Medical Oncologist & Hemato-Oncologist

C.R. Reddy Cancer Center, C.R. Reddy Superspeciality Hospital

17/406, Old Post Office Road, near Leela Mahal Road, Nellore, Andhra Pradesh 524003

Phone 0861 232 5344 · WhatsApp +91 79896 42272

info@drharitha.co.in · drharitha.co.in

Dr. Haritha teaches oncology to postgraduates and medical students. Colleges and departments may write to info@drharitha.co.in for teaching sessions.

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Updated 17 October 2026. Educational summary written in our own words from current guidelines and primary trials; no drug doses; not advice for an individual patient. Verify current guidelines and Indian regulatory approvals before treatment decisions. Patients and families: please see the patient guides at drharitha.co.in.

Acute Lymphoblastic Leukaemia

Haematological cancers, part 8 · Adults and AYA · B- and T-ALL · Ph+ ALL with TKIs · MRD and transplant · Blinatumomab, inotuzumab and CAR-T · Lymphoblastic lymphoma · Key points for clinicians · Last updated 17 October 2026

01 At a glance

- **ALL is a cancer of lymphoid precursors** (B lineage about 75%, T lineage about 25% of adult cases). It is mainly a disease of children, with a second peak after 60. Leukaemia and lymphoblastic lymphoma are the same disease: a mass with <20% marrow blasts is called lymphoma (LBL).
- **Suspect it** from cytopenias with blasts, bone pain, nodes, a big liver or spleen, or a mediastinal mass with breathlessness or facial swelling (T-ALL).
- **Stabilise first:** airway, superior vena cava and pericardium if there is a mass; tumour lysis (ALL is high or intermediate risk, never low); antibiotics for neutropenic fever. Leukostasis, DIC and infection care are shared with AML ([AML module, emergencies](#)).
- **Classify fast:** flow cytometry for lineage, BCR::ABL1 within days (it changes induction), karyotype and FISH, a Ph-like screen where available, and a lumbar puncture for CNS grade.
- **Ph-negative, fit:** paediatric-inspired, asparaginase-rich regimens up to about 40 (cure 60–80%), asparaginase regimens or hyper-CVAD at 40–65, rituximab for CD20+ disease; then **blinatumomab with consolidation** ([E1910](#)^[1]: 3-year survival 85% vs 68%) and 2 or more years of maintenance.
- **MRD decides:** MRD $\geq 10^{-4}$ after induction means high risk → blinatumomab, then allogeneic transplant for the fit ([BLAST](#)^[2]).
- **Ph-positive:** a TKI from day 1 to the end, with a steroid or low-intensity chemotherapy ([GRAAPH-2005](#)^[3]); chemotherapy-free dasatinib then blinatumomab is possible ([D-ALBA](#)^[4]).
- **Relapse:** blinatumomab, inotuzumab or CD19 CAR-T for B-ALL; revumenib for KMT2A-rearranged; nelarabine for T-ALL; then allogeneic transplant.
- **India:** many young adults; Indian AYA series report 40–60% survival on BFM-type protocols; abandonment (11–15%), resistant infections, cost and limited transplant access shape every decision ([Ganesan 2021](#)^[5]).

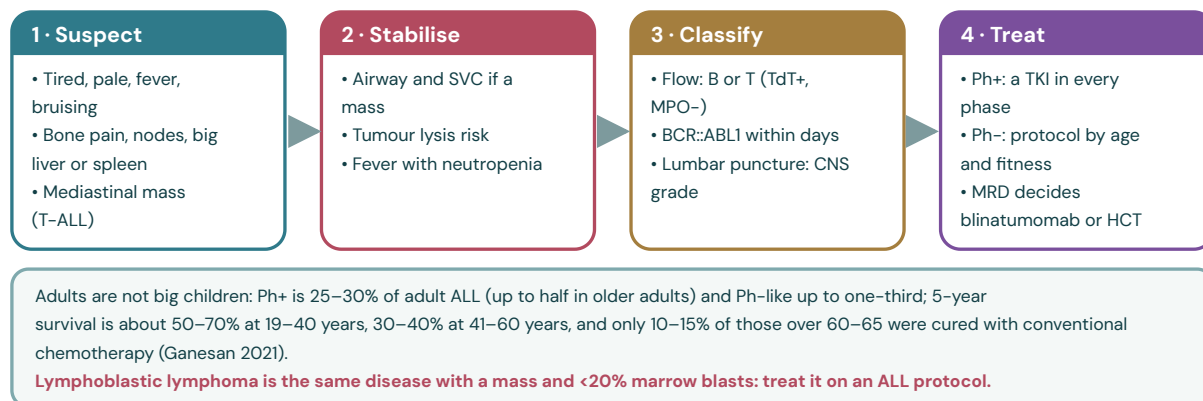
ALL in one picture: suspect, stabilise, classify, then treat by Ph status, age, fitness and MRD

Figure 1. The four steps (UpToDate ALL diagnosis and induction reviews; Ganesan 2021 for age-specific survival).

02 Clinical presentation, common traps & causes

How ALL and lymphoblastic lymphoma present in adults

B-ALL

- Anaemia, infections, bleeding
- Bone or joint pain
- Liver, spleen or nodes in up to half
- White count low, normal or very high
- CNS: cranial nerve palsy, headache

T-ALL

- Young men (2:1); 25% of adult ALL
- Anterior mediastinal mass in 50–75%
- Effusions, SVC obstruction, stridor
- High white count; CNS more often
- Testes involved more often

Lymphoblastic lymphoma

- A mass with <20% marrow blasts
- T-LBL: >80% stage III–IV
- B symptoms in about half
- About 60% later become leukaemic
- B-LBL: bone, skin, nodes

CNS involvement is present at diagnosis in 3–7% of adults; without CNS-directed therapy more than half develop CNS leukaemia, with prophylaxis fewer than 20%. The tempo varies: some present over weeks to months, others within days. Bone pain and big nodes point to ALL rather than AML.

Figure 2. Presentation (UpToDate B-ALL and T-ALL diagnosis reviews; CNS rates from the Ph-negative induction review).

Who gets it, and why

- **Age:** world incidence 1–5 per 100,000 a year; three-quarters of B-ALL occurs before age 6, with a second peak after 60. T-ALL peaks in adolescents and young adults, with a 2:1 male excess.
- **Causes:** unknown in most. Associations: ionising radiation, Down syndrome and other constitutional disorders, rare familial variants (PAX5, ETV6, TP53), and common inherited polymorphisms (ARID5B, IKZF1, CEBPE, CDKN2A/B, GATA3). Ph-like ALL is commoner in people of Hispanic ancestry.
- **Adults vs children:** adults carry more adverse genetics (Ph+ 25–30%, rising to about half in older adults; Ph-like up to one-third) and tolerate asparaginase, steroids and vincristine less well ([Roberts 2017^{\[6\]}](#)).
- **India:** India has the world's largest adolescent and young adult population, so most centres treat many AYA patients; multidrug-resistant infections during intensive therapy are a recurring problem ([Ganesan 2021^{\[5\]}](#)).

Children are different: why childhood ALL results do not transfer directly to adults

Children

- The commonest childhood cancer; three-quarters of B-ALL before age 6
- More than 90% cured
- Favourable genetics common (hyperdiploidy, ETV6::RUNX1)
- Risk by age, WBC (50,000/ μ L), genetics, MRD
- Asparaginase, steroids, vincristine well tolerated

Adults

- Second peak after 60
- Ph+ 25–30%; Ph-like up to one-third
- More toxicity from asparaginase, steroids and vincristine
- Survival falls with every decade
- Transplant used more often

Adolescents and young adults do better on paediatric-type, asparaginase-rich regimens: 23 observational studies favour them (hazard ratio for 5-year survival 1.40), the basis of the 2026 ASH guideline for AYA ALL. Indian AYA series report 40–60% survival on BFM-type protocols.

Figure 3. Childhood vs adult ALL (UpToDate childhood diagnosis, risk and treatment reviews; DuVall 2026; Ganesan 2021). Childhood ALL is covered here only as a contrast.

Common traps

- **A normal or low white count does not exclude ALL:** look at the smear and ask for flow cytometry.

- **Bone pain, limp or joint pain with odd counts** may be leukaemia rather than arthritis.
- **A young man with cough, orthopnoea or facial swelling:** think anterior mediastinal mass (T-ALL/T-LBL) and image before any procedure that needs sedation or lying flat.
- **Myeloid markers (CD13, CD33) do not exclude B-ALL;** myeloperoxidase does. Mixed-phenotype leukaemia and CML in lymphoid blast phase are differentials.

SHARE WITH PATIENTS: SYMPTOMS AND SUSPICION

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

Leukaemia occurs only in children?

Leukaemia always causes a very high white blood cell count?

If there are no swollen lymph nodes, leukaemia is impossible?

Frequent fever always means an ordinary infection?

A normal haemoglobin level rules out leukaemia?

03 Diagnosis, workup & staging essentials

The first 24–48 hours: safety first, then the tests that decide treatment

Now (hours)

- CBC, smear, PT/aPTT, fibrinogen, D-dimer
- Potassium, phosphate, calcium, urate, creatinine, LDH
- Chest X-ray; CT if cough, chest pain or a widened mediastinum
- Fever: cultures and antibiotics at once
- Mass: airway, SVC and pericardium first

Within 24–48 hours

- Marrow: morphology, flow, karyotype, FISH
- BCR::ABL1 by RT-PCR or FISH
- Ph-like screen where available
- Store the diagnostic sample for MRD
- Mass, little marrow disease: core or excision biopsy

Before induction starts

- Central line with 2–3 lumens
- ECG and echocardiogram
- HBV, HCV, HSV, CMV; pregnancy test
- Sperm banking, fertility counselling
- HLA type the patient and siblings

Tumour lysis: ALL is HIGH risk with WBC $\geq 100,000/\mu\text{L}$ or LDH $\geq 2\times$ the upper limit, otherwise INTERMEDIATE (never low). High risk: IV fluids + rasburicase (not in G6PD deficiency); intermediate: fluids + allopurinol. A 3–7-day steroid prephase (with cyclophosphamide in some protocols) debulks very high counts.

First lumbar puncture: once blasts have cleared from the blood, given with the first intrathecal dose; at once if there are neurological signs.

Figure 4. Initial steps (UpToDate induction reviews; tumour lysis risk groups from the UpToDate TLS review and Perissinotti 2023). No doses.

Making the diagnosis

- **Blood and marrow:** CBC and smear, immunophenotyping of blood or marrow, and a marrow aspirate and biopsy with flow cytometry, karyotype and FISH.
- **Lineage:** lymphoblasts are TdT-positive and myeloperoxidase-negative. B lineage: CD19, cytoplasmic CD79a and CD22. T lineage: cytoplasmic or surface CD3 with CD7. Antigen-receptor gene rearrangements are not lineage-specific, so immunophenotype decides.
- **ALL or LBL:** $\geq 20\%$ marrow blasts = ALL (with or without a mass); a mass with $<20\%$ marrow blasts = LBL. Biopsy a node or mediastinal mass (core or excision) only when blood, marrow or an effusion cannot give the diagnosis.
- **Genetics that change treatment now:** BCR::ABL1 (RT-PCR or FISH, within days); KMT2A, hypodiploidy, complex karyotype and TP53 (risk and transplant decisions); Ph-like screen; CD20, CD19 and CD22 expression for antibody choice.
- **CNS:** every patient needs a lumbar puncture, generally once blasts have cleared from the blood and together with the first intrathecal dose; urgent imaging and LP for neurological signs.
- **Before treatment:** echo and ECG; HBV, HCV, HSV and CMV serology; pregnancy test; fertility counselling and sperm banking (induction does not usually cause sterility in younger patients); HLA typing of transplant-eligible patients and their siblings; a central line with 2–3 lumens.

Is it ALL, and which lineage? Flow cytometry first, genetics within days

Blasts on smear or marrow → flow cytometry: TdT positive, myeloperoxidase negative = lymphoblasts

B lineage (about 75%)

- CD19, cytoplasmic CD79a and CD22
- CD10 ± (CD10- = pro-B, high risk)
- CD20 >10–20% of blasts in ~40%
- CD13/CD33 may be present

T lineage (about 25%)

- Cytoplasmic or surface CD3, CD7
- CD1a, CD2, CD5, CD4/CD8 vary
- ETP: CD1a-, CD8-, weak CD5 with stem or myeloid markers
- Only surface CD3 is lineage-specific

Not ALL

- MPO positive: AML
- TdT negative, MYC: Burkitt
- Keratin+ mixed thymocytes: thymoma
- Polyclonal TdT+ cells: indolent T-lymphoblastic proliferation
- Recovering marrow: hematogones

Genetics: banded karyotype + FISH (ETV6::RUNX1 is cryptic on banding; KMT2A, BCR::ABL1), RT-PCR for BCR::ABL1 p190/p210 within days, a Ph-like screen (CRLF2 by flow, fusion panel or RNA sequencing), and NGS where available (TP53). Keep diagnostic material: PCR-based MRD needs it.

Figure 5. Work-up (UpToDate B-ALL and T-ALL diagnosis, classification and MRD reviews).

The central nervous system: grade it, protect it, treat it**CNS-1**

- No lymphoblasts in spinal fluid
- Prophylaxis per protocol

CNS-2

- Lymphoblasts with <5 WBC/μL
- Prophylaxis per protocol
- No routine cranial RT

CNS-3

- Lymphoblasts with ≥5 WBC/μL, or cranial nerve palsy
- More frequent intrathecal therapy until clear
- ± cranial RT 18 Gy later

Traumatic tap with blasts in blood: if the spinal-fluid WBC:RBC ratio is at least twice the blood ratio, call it CNS-3. Prophylaxis uses intrathecal methotrexate, cytarabine ± steroid and CNS-penetrating systemic drugs (high-dose methotrexate, cytarabine, asparaginase) as the protocol defines. In 1,508 adults, 5% had CNS disease at diagnosis; 90% still reached remission and survival did not differ significantly.

Figure 6. CNS (UpToDate Ph-negative induction and relapsed/refractory reviews). Radiotherapy in Gy only.

Not ALL: the differentials to exclude

- **AML** (myeloperoxidase-positive; Auer rods) and mixed-phenotype acute leukaemia.
- **Burkitt lymphoma/leukaemia**: mature B cells (surface immunoglobulin, TdT-negative) with MYC rearrangement; treated differently (see the aggressive B-cell module).
- **Thymoma (type B1)**: a mediastinal mass with many immature T cells, but keratin-positive epithelium and polyclonal thymocytes of all stages.
- **Indolent T-lymphoblastic proliferation**: TdT-positive but non-clonal, normal-pattern T cells, often in the upper aerodigestive tract.
- **T-lymphoblastic lymphoma with eosinophilia**: a myeloid/lymphoid neoplasm with a tyrosine-kinase gene rearrangement (PDGFRA/PDGFRB) that responds to TKIs.
- **Reactive**: hematogones in regenerating marrow, infections, and CML in lymphoid blast phase (BCR::ABL1 with a chronic-phase history).

SHARE WITH PATIENTS: TESTS AND DIAGNOSIS

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

A routine blood test alone can identify every type of leukaemia?

A bone marrow test makes leukaemia spread?

All leukaemias are the same disease?

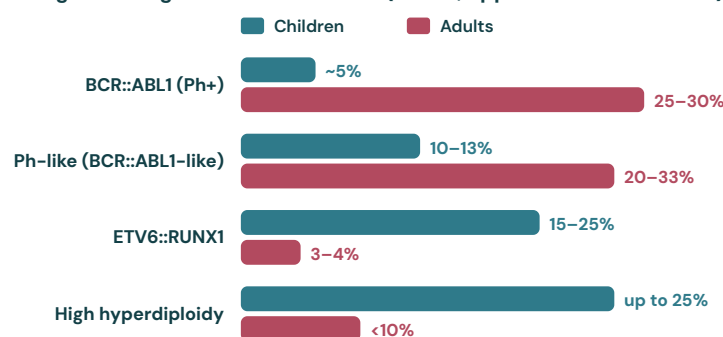
Blood cancer is always hereditary?

o4 Biology and biomarkers that change treatment

Biology in brief

- **B-ALL** is classified by genetics (WHO 5th edition and ICC 2022 differ only modestly). Up to 30% of cases lack a defined subgroup; RNA sequencing finds further fusions (DUX4, ZNF384, MEF2D and others), especially in young adults.
- **Ph-like ALL** has the expression profile of BCR::ABL1 ALL without the fusion; most cases carry kinase-activating changes (ABL-class, JAK2, CRLF2 with JAK-STAT or RAS mutations). It is 10–13% of childhood, about 21% of adolescent and up to one-third of adult B-ALL; frequency data: [Roberts 2017^{\[6\]}](#). In one single-institution series of 148 adults, five-year survival was 23% with Ph-like ALL vs 59% for other Ph-negative B-ALL. Targeted drugs are being tested; enrol in trials.
- **T-ALL**: NOTCH1/FBXW7 activation, TAL1 and other transcription-factor rearrangements, and CDKN2A deletion are typical. In adults, NOTCH1/FBXW7 mutation without RAS or PTEN changes (about half) predicts longer survival ([Trinquand 2013^{\[7\]}](#)); TP53 mutation (10–15%) predicts resistance. Early T-cell precursor (ETP) ALL is 5–10% of adult T-ALL and historically high risk ([Jain 2016^{\[8\]}](#)); it depends on BCL-2, which is why venetoclax is studied.
- **Outcome in adult T-ALL**: in UKALL XII/ECOG 2993 (356 adults) CR was 94% and 5-year survival 48%; survival after relapse was only 6.5% ([Marks 2009^{\[9\]}](#)).

The genetic map changes with age: children vs adults (B-ALL, approximate % of cases)



Favourable in children: hyperdiploidy and ETV6::RUNX1. Adverse: BCR::ABL1 (now treated with TKIs), Ph-like, KMT2A rearrangement (5–7% overall; 60–80% of infants), hypodiploidy (<5%), iAMP21 (2%, older children) and TP53 mutation.

T-ALL: NOTCH1/FBXW7 mutation without RAS/PTEN changes (about half of adults) predicts longer survival; TP53 mutation (10–15%) and ETP phenotype (5–10% of adult T-ALL) predict failure.

Figure 7. Subtype frequencies (UpToDate classification/cytogenetics, MRD-detection and T-ALL reviews; Roberts 2017; Trinquand 2013). Bars show mid-points of the published ranges.

Ph-negative ALL in adults: who is high risk?**High risk (any one)**

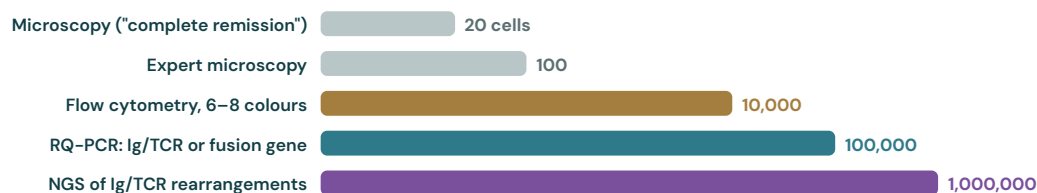
- Age over 60
- WBC >30,000/ μ L (B) or >100,000/ μ L (T)
- t(4;11) KMT2A::AFF1 or t(1;19)
- Ph-like signature
- Pro-B (CD10-negative) blasts
- More than 4 weeks to remission
- MRD $\geq 10^{-4}$ after induction

Standard risk

- None of the high-risk features
- Other favourable signs: age <30, WBC <30,000, mediastinal mass, T phenotype
- Old trial (UKALL XII/ECOG 2993): 5-year OS 54% standard vs 29% high risk

MRD is the strongest single predictor (GMALL)

Figure 8. Risk (modified Hoelzer criteria in the UpToDate post-remission review; Goldstone 2008; Gökbuget 2012; Brüggemann 2006).

MRD: how deep can each test see? (one leukaemic cell among ...)**Where**

- Marrow preferred for B-ALL: blood is 1–3 logs lower
- T-ALL: blood and marrow similar
- First 2–5 mL of the aspirate

When

- End of induction
- After consolidation
- Before and after transplant
- Ph+: BCR::ABL1 qPCR serially

What it changes

- $\geq 10^{-4}$ = high risk
- Blinatumomab clears MRD in about 78%
- Persistent MRD → transplant
- Reappearance: confirm on a second sample

"MRD-negative" means below the limit of that test: a decision needs an assay that reaches 10^{-4} on a good first-pull sample. MRD negativity halves the risk of death or more (hazard ratio for survival 0.28 in adults; 39 studies, 13,637 patients).

Figure 9. MRD (UpToDate MRD detection and clinical-use reviews; Berry 2017; Gökbuget 2018). Bar length is on a log scale.

Markers that change treatment

Marker	Frequency	What it changes
BCR::ABL1 (Ph+)	25–30% of adults; ~5% of children	TKI in every phase; MRD by BCR::ABL1 qPCR; transplant decisions
Ph-like / CRLF2	Up to one-third of adults	High risk; trials of ABL/JAK inhibitors
KMT2A rearrangement	5–7%; most infants	High risk (favour transplant); revumenib at relapse
Low hypodiploidy, complex karyotype, TP53	Uncommon	High risk; favour transplant in first remission
CD20 on >10–20% of blasts	About 40% of B-ALL	Add rituximab (under 65)
CD19 / CD22	Nearly all B-ALL / >90%	Blinatumomab, CAR-T / inotuzumab; check again at relapse (antigen loss)

Marker	Frequency	What it changes
ETP phenotype; NOTCH1/FBXW7, RAS/PTEN	5–10% of adult T-ALL	Prognosis; trials (venetoclax)
MRD after induction	Positive in many adults	$\geq 10^{-4}$: blinatumomab, then transplant if fit
TPMT / NUDT15	Variants in a minority	Thiopurine (6-mercaptopurine) dose in maintenance (CPIC 2019 ^[10])

05 Local therapy: radiotherapy, surgery & procedures

Radiotherapy

- **CNS leukaemia (CNS-3 or cranial nerve palsy):** more frequent intrathecal therapy until the spinal fluid clears; cranial RT can be added in later phases, typically 18 Gy in 1.8–2.0 Gy fractions to the whole brain and the posterior globes, down to C2, as the protocol defines. It is not used routinely for CNS-1 or CNS-2 disease in current adult protocols.
- **CNS relapse:** cranial RT 24 Gy (2 Gy fractions) with at least six intrathecal treatments.
- **Testes:** examine at diagnosis; testicular disease that has not resolved by the end of induction → RT 24 Gy to both testes, usually with the first maintenance cycle.
- **India:** some Indian centres still give prophylactic cranial RT (12 Gy) to adults on BFM-type protocols to lower CNS relapse, accepting the late effects ([Ganesan 2021^{\[5\]}](#)). This is a protocol decision, not routine practice in current Western adult regimens.
- **Residual mediastinal mass in lymphoblastic lymphoma:** the supplied sources do not settle whether mediastinal RT is needed; follow the protocol and discuss at the tumour board (question for Dr. Haritha in review).

Procedures and their pitfalls

- **Mediastinal mass:** assess the airway, SVC and pericardium before any sedation, anaesthesia or lying flat; get the diagnosis from the least invasive source (blood, marrow, pleural fluid).
- **Central line:** two or three lumens at the start of treatment. Catheters (especially PICC lines) carry about half of asparaginase-related thromboses ([Mort 2025^{\[11\]}](#)).
- **Lumbar puncture:** correct platelets and clotting first; perform it once blasts have cleared from the blood, together with the first intrathecal dose.
- **Marrow at count recovery:** neutrophils >1,000/μL and platelets >100,000/μL; send the first 2–5 mL of the aspirate for MRD (later pulls are diluted with blood).
- **Before high-dose methotrexate:** drain pleural effusions and ascites where feasible; they act as a reservoir and delay clearance.

o6 Systemic therapy: indications & options

Ph-negative ALL: induction

Ph-negative ALL: induction is chosen by age and fitness, not by lineage

Fit, ≤40 years	Fit, 40–65 years	Older or unfit B-ALL	Everyone
• Paediatric-inspired, asparaginase-rich (CALGB 10403, DFCI) • CALGB 10403: 3-year OS 73%, treatment deaths 3% • Cure 60–80% • Obesity worsens results	• Asparaginase regimen (E1910, GRAALL-2005) or hyper-CVAD • GRAALL-2005: CR 92%, 5-year OS 59% • Hyper-CVAD + rituximab: 3-year OS 50% • Choose by toxicity and experience	• Inotuzumab + dexamethasone (>55 years): 3-year OS 73% • Mini-hyper-CVD + inotuzumab: 3-year OS 56%; liver VOD 8% • Mini-hyper-CVD + venetoclax (also T-ALL) • Frail: vincristine + steroid, POMP	• CD20+, under 65: add rituximab • CNS prophylaxis from the first LP • Steroid prephase if count very high • Marrow and MRD at count recovery

Rituximab (GRAALL-2005/R, ≥8 doses): 4-year EFS 55% vs 43%, fewer relapses, no overall survival difference. Inotuzumab is not for T-ALL (no CD22). Nelarabine helped children and young adults with T-ALL (COG AALL0434: 5-year DFS 88% vs 82%) but has not improved outcomes in adults.

Figure 10. Induction (UpToDate Ph-negative induction review; Stock 2019; Huguet 2018; Thomas 2010; Stelljes 2024; Kantarjian 2018; Maury 2016; Dunsmore 2020). No doses.

- **Principles:** induction is chosen by age and fitness; immunophenotype and genetics do not change it in fit adults up to 65, except rituximab for CD20+ disease (and a TKI for Ph+). Follow one published protocol closely, in a centre that can manage asparaginase and its complications.
- **Up to about 40 years:** paediatric-inspired, asparaginase-rich regimens ([CALGB 10403](#)^[12]: 295 patients aged 17–39, 3-year survival 73%, treatment deaths 3%, a quarter with raised liver enzymes, 5% thromboses; [DFCI](#)^[13]: CR 85%). Older adult-type regimens gave 5-year survival near 30%.
- **40–65 years:** an asparaginase regimen (E1910; [GRAALL-2005](#)^[14]: CR 92%, 5-year survival 59%) or hyper-CVAD ([with rituximab](#)^[15]: CR 95%, 3-year survival 50%). Asparaginase regimens bring liver, pancreas and clotting problems; hyper-CVAD more neutropenia and admissions.
- **Rituximab:** adding at least 8 doses for CD20+ B-ALL in patients under 65 improved 4-year EFS (55% vs 43%) without more toxicity ([GRAALL-2005/R](#)^[16]); four doses without CD20 selection did not help ([UKALL14](#)^[17]). In India cost often limits it ([Ganesan 2021](#)^[5]).
- **Response:** CR = marrow blasts <5%, cellularity >25% and normal counts; assess MRD at CR. No CR after induction = refractory disease (see relapse below).

Ph-negative ALL: after remission

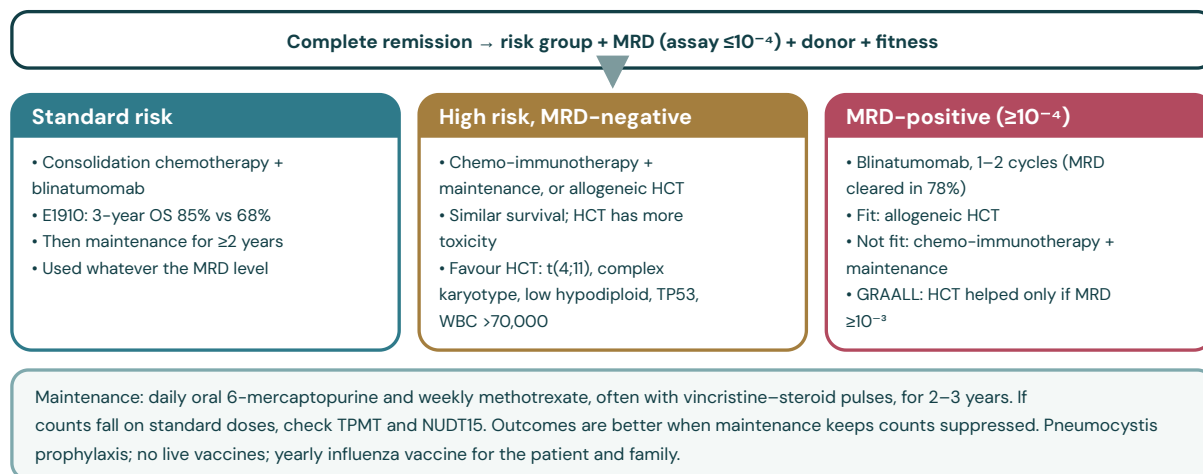
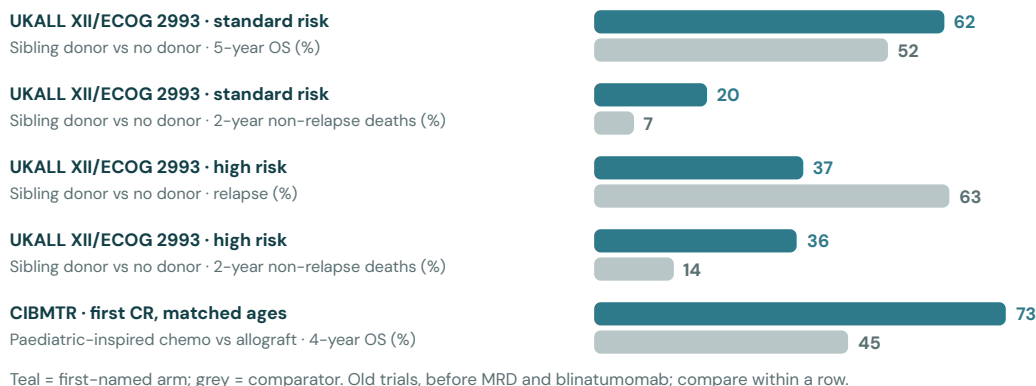
Ph-negative ALL in first remission: risk and MRD decide

Figure 11. After remission (UpToDate post-remission review; Litzow 2024; Gökbuget 2018; Dhédin 2015; Relling 2019).

- **Standard risk:** consolidation chemotherapy plus blinatumomab, rather than chemotherapy alone, blinatumomab alone or transplant. In E1910 (224 adults aged 30–70 in MRD-negative CR, 57% with high-risk features) blinatumomab raised 3-year survival from 68% to 85% (hazard ratio 0.41); grade ≥ 3 neuropsychiatric events 23% vs 5% ([Litzow 2024](#)^[1]). UpToDate applies this to all patients in CR, whatever the MRD.
- **High risk, MRD-negative:** chemo-immunotherapy plus maintenance or allogeneic HCT are both acceptable; many favour HCT for t(4;11), complex karyotype, low hypodiploidy/near-triploidy, TP53 or WBC $>70,000/\mu\text{L}$.
- **MRD-positive ($\geq 10^{-4}$):** one or two cycles of blinatumomab (78% of 113 patients became MRD-negative; responders lived longer, 39 vs 13 months) and then allogeneic HCT if eligible ([BLAST](#)^[2]). In GRAALL, transplant helped patients with MRD $\geq 10^{-3}$ (survival HR 0.43) but not those below ([Dhédin 2015](#)^[18]).
- **Maintenance:** low-intensity treatment for at least 2 years (daily 6-mercaptopurine, weekly methotrexate, often vincristine-steroid pulses); test TPMT and NUDT15 when counts fall on standard doses; better outcomes when counts are kept suppressed.

Allogeneic transplant

Allogeneic transplant in first remission: fewer relapses, more treatment deaths

Donors: only about a quarter have a matched sibling; matched unrelated, haploidentical (post-transplant cyclophosphamide) and cord grafts give comparable results. Reduced-intensity conditioning for older or less fit patients; most centres limit HCT to fit patients under about 70–75 years. Survival benefit of HCT in the meta-analysis was confined to patients under 35.

India: transplant beds are limited and waiting lists long; JIPMER offers first-remission HCT mainly for Ph+, KMT2A-rearranged and persistently MRD-positive disease, guided by donor, cost and the family's ability to stay near the centre (Ganesan 2021).

Figure 12. Transplant evidence (Goldstone 2008; Gupta 2013; Seftel 2016; UpToDate post-remission reviews; Ganesan 2021).

- **Evidence:** in UKALL XII/ECOG 2993, sibling-donor HCT improved 5-year survival in standard-risk disease (62% vs 52%) at the cost of more non-relapse deaths (20% vs 7%); in high-risk disease fewer relapses (37% vs 63%) were offset by non-relapse mortality (36% vs 14%) ([Goldstone 2008](#)^[19]). The survival gain was confined to patients under 35 in a meta-analysis ([Gupta 2013](#)^[20]), and paediatric-inspired chemotherapy outperformed matched allografts in a CIBMTR comparison (4-year survival 73% vs 45%; [Seftel 2016](#)^[21]).
- **Donors and grafts:** matched sibling or unrelated donor preferred; haploidentical (post-transplant cyclophosphamide) and cord grafts give comparable results; peripheral blood grafts for most adults; reduced-intensity conditioning for older or less fit patients.

Older or unfit adults

- **B-ALL:** inotuzumab plus dexamethasone in patients over 55 (CR in all 43, 3-year survival 73%; [Stelljes 2024](#)^[22]); mini-hyper-CVD plus inotuzumab (median age 68: CR 85%, 3-year survival 56%, liver VOD 8%, treatment deaths 12%; [Kantarjian 2018](#)^[23]); mini-hyper-CVD plus venetoclax ([Luskin 2025](#)^[24]).
- **T-ALL:** mini-hyper-CVD plus venetoclax (expert opinion; inotuzumab does not work without CD22).
- **Frail:** vincristine with prednisone, or POMP, can control the disease for a time. Talk honestly: in India, curative attempts in older patients with comorbidities often end in intensive-care admissions and early relapse ([Ganesan 2021](#)^[5]).

T-ALL and lymphoblastic lymphoma

- **T-ALL** is treated with the same induction as B-ALL (no B-cell antibodies). Nelarabine improved 5-year DFS (88% vs 82%) and cut CNS relapse (1% vs 7%) in children and young adults up to 31 ([COG AALLO434](#)^[25]) but has not improved outcomes in adults; adding it to hyper-CVAD gave no benefit over historical controls.
- **Lymphoblastic lymphoma** (mostly T-LBL with a mediastinal mass): stage with marrow and lumbar puncture, then treat on the ALL protocol of that lineage with full CNS prophylaxis; COG AALLO434 included T-LBL. About 60% of T-LBL later infiltrate the marrow. Whether a residual mediastinal mass needs RT is not settled by the supplied sources (see section 05).

- **Testes and CNS:** both are involved more often in T-ALL; examine and grade at diagnosis.
- **India:** a low-cost protocol at CMC Vellore gave 51% 5-year survival in 113 adults with T-ALL ([Abraham 2014^{\[26\]}](#)).

Ph-positive ALL

Ph-positive ALL: a TKI from day 1 to the end, with gentle partners

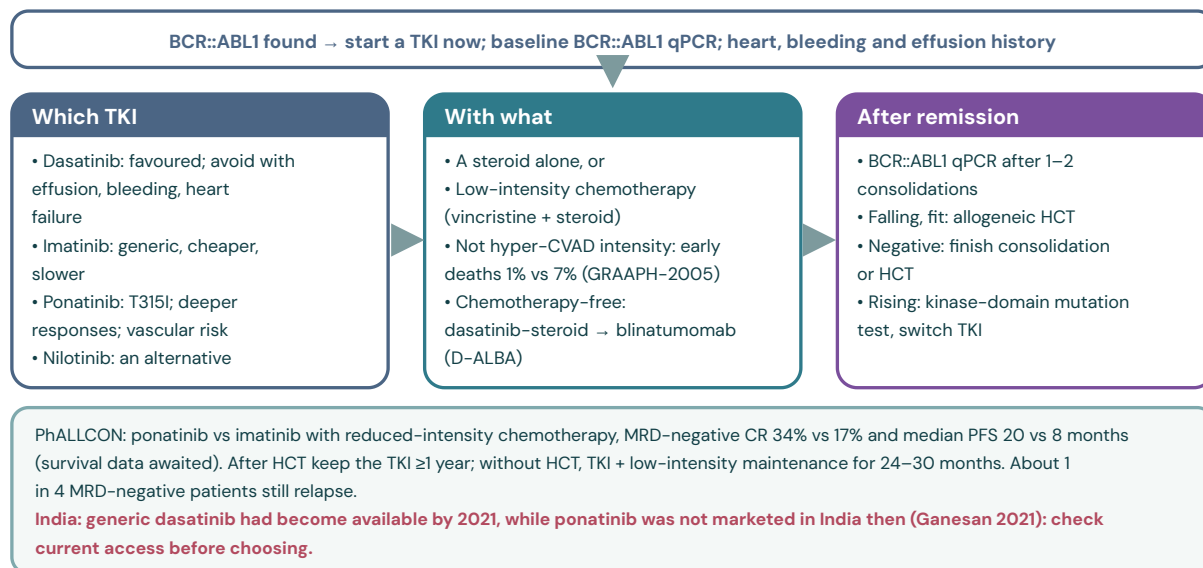


Figure 13. Ph-positive ALL (UpToDate Ph+ induction and post-remission reviews; Chalandon 2015; Foà 2020; Jabbour 2024; Ganesan 2021). No doses.

- **A TKI is essential but not enough:** TKI-based induction gives CR above 90% and long-term survival around 50%, against ≤20% with chemotherapy alone; pair it with a steroid or chemotherapy, and continue it through every phase.
- **Gentle partners:** in GRAAPH-2005 (268 adults) imatinib with vincristine–dexamethasone gave more CRs (98% vs 91%) and fewer early deaths (1% vs 7%) than imatinib with hyper-CVAD, with equal 5-year survival ([Chalandon 2015^{\[3\]}](#)). Older patients: dasatinib with low-intensity chemotherapy (median age 69: CR 96%, 5-year survival 36%; [EWALL-PH-01^{\[27\]}](#)).
- **Chemotherapy-free:** dasatinib plus a steroid gave CR in 98% ([LAL1205^{\[28\]}](#)); followed by blinatumomab, MRD negativity rose from 29% to 60% ([D-ALBA^{\[4\]}](#)). Relapses on dasatinib often carry T315I.
- **Which TKI:** dasatinib is favoured (some CNS penetration; avoid with effusions, bleeding, heart failure); imatinib is generic and cheaper but slower; ponatinib covers T315I and gave more MRD-negative CRs than imatinib (34% vs 17%; [PhALLCON^{\[29\]}](#); with hyper-CVAD 3-year EFS 70%, [Jabbour 2018^{\[30\]}](#)) at a cost of arterial events.
- **After remission:** one or two consolidations, then BCR::ABL1 MRD. Falling MRD and fit → allogeneic HCT; MRD-negative → finish consolidation or transplant (no survival difference in a retrospective study of 230 patients; [Ghobadi 2022^{\[31\]}](#)); rising MRD → kinase-domain mutation test and a TKI switch. TKI for ≥1 year after HCT; without HCT, TKI plus low-intensity maintenance for 24–30 months.

Relapsed or refractory ALL

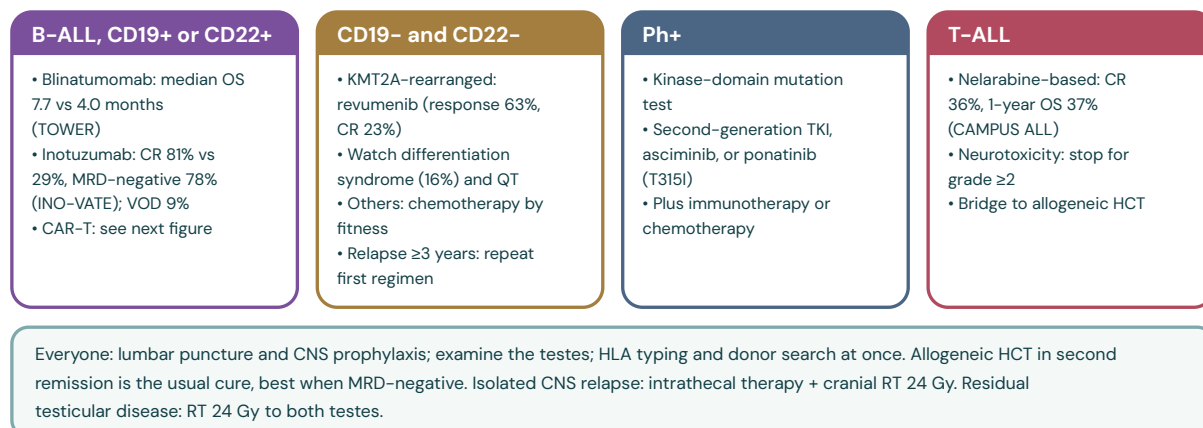
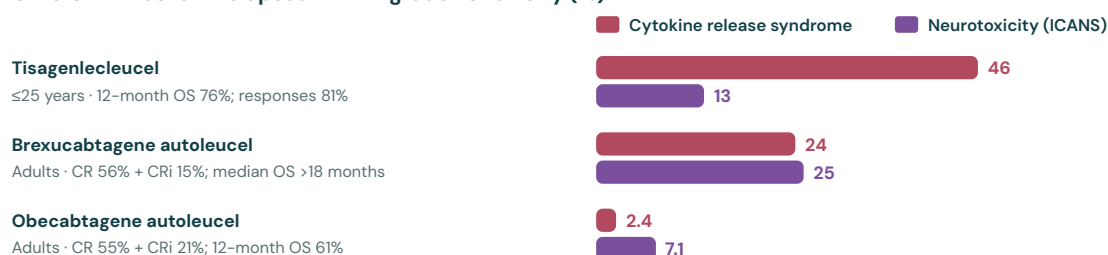
Relapsed or refractory ALL: choose by antigen, genetics and lineage, then transplant

Figure 14. Relapse (UpToDate adult relapsed/refractory review; Kantarjian 2017; Kantarjian 2016; Issa 2025; Candoni 2020).

CD19 CAR-T cells in relapsed B-ALL: grade ≥3 toxicity (%)

Obecabtagene uses a lower-affinity CD19 binder: much less severe CRS and ICANS. All CAR-T products also cause prolonged cytopenias, low immunoglobulins and infections; tocilizumab must be on hand. CRS and ICANS grading and treatment: see the Aggressive B-cell Lymphomas module.

India: NexCAR19 (ImmunoACT with IIT Bombay and Tata Memorial) received CDSCO approval on 13 October 2023 for relapsed or refractory B-cell lymphoma and leukaemia.

Figure 15. CAR-T (Maude 2018; Shah 2021; Roddie 2024; UpToDate adult relapsed/refractory review; NexCAR19 pivotal trial, verified 16 Oct 2026). Trials differ: do not rank products from this chart.

- **Blinatumomab** (CD19×CD3): median survival 7.7 vs 4.0 months over chemotherapy in 405 adults with relapsed Ph-negative ALL, with better quality of life; grade ≥3 CRS 5% ([TOWER](#)^[32]).
- **Inotuzumab ozogamicin** (CD22 conjugate): CR 81% vs 29% and MRD negativity 78% vs 28%, 2-year survival 23% vs 10%; hepatic VOD 9% vs 1%, and 10 of 48 transplanted patients developed VOD ([INO-VATE](#)^[33]). Avoid giving it immediately before HCT if possible.
- **CD19 CAR-T**: tisagenlecleucel up to 25 years ([ELIANA](#)^[34]), brexucabtagene in adults ([ZUMA-3](#)^[35]), obecabtagene with much less severe CRS and ICANS ([FELIX](#)^[36]). CRS and ICANS management is described in the [Aggressive B-cell Lymphomas module](#). India: NexCAR19 is approved for relapsed B-cell lymphoma and leukaemia ([NexCAR19 trial](#)^[37]).
- **CD19- and CD22-negative**: these relapses are increasing after frontline antibodies. KMT2A-rearranged → revumenib (57 patients: response 63%, CR 23%; differentiation syndrome 16%; [AUGMENT-101](#)^[38]); others → chemotherapy by fitness; relapse ≥3 years after diagnosis → the first regimen again.
- **T-ALL**: nelarabine-based chemotherapy (118 adults: CR 36%, 1-year survival 37%; 38% 5-year survival after HCT; [Candoni 2020](#)^[39]), then HCT. **Ph+**: a TKI chosen by mutation testing plus immunotherapy or chemotherapy.

- **After second remission:** allogeneic HCT for the fit, best when MRD-negative; CNS prophylaxis for everyone. In India, salvage is usually offered only when transplant is realistic ([Ganesan 2021](#)^[5]).

ALL-specific supportive care and toxicity

Asparaginase: the drug that makes paediatric-style regimens work, and how to keep it safe

Allergy and silent inactivation

- Give only where anaphylaxis can be treated
- Pegylated form: less immunogenic
- Check activity: day 7 <0.1 IU/mL or nil at day 14 = inactivation
- Switch to an Erwinia product

Liver, pancreas, metabolism

- Raised transaminases common (two-thirds on some regimens)
- Pancreatitis
- High glucose and triglycerides
- Worse with BMI >30 or fatty liver
- Avoid other liver toxins while active

Clots and bleeding

- Low antithrombin, protein C/S, fibrinogen
- Thrombosis in 14% of adults (half catheter-related)
- Cerebral sinus thrombosis
- Fibrinogen often <100 mg/dL

ISTH guidance: consider prophylactic LMW heparin while platelets are $\geq 30,000/\mu\text{L}$ (data are retrospective and mixed: 14% vs 27% VTE in one study, no difference in another); weekly antithrombin with replacement below 50–60%. Treat VTE with LMW heparin (anti-Xa monitoring) for ≥ 6 months; hold asparaginase for cerebral sinus thrombosis, large PE, proximal DVT or arterial clots, and consider resuming after about 4 weeks.

India: pegylated asparaginase from Indian manufacturers has lowered cost but remains dearer than native asparaginase; JIPMER limits asparaginase above 50–60 years (Ganesan 2021).

Figure 16. Asparaginase (UpToDate Ph-negative induction and antithrombin deficiency reviews; Zwicker 2020; Sibai 2020; Mort 2025; Wetzler 2007; Ganesan 2021). No doses.

Other drugs, other dangers: what ALL treatment does beyond the marrow

Vincristine

- Neuropathy in nearly all; constipation, colic, ileus
- Azoles and other CYP3A4 inhibitors make it worse
- Avoid in Charcot-Marie-Tooth

High-dose methotrexate

- Hydrate; keep urine pH ≥ 7 ; drain effusions and ascites first
- Stop NSAIDs, PPIs, penicillins, ciprofloxacin and TKIs if possible
- Leucovorin until the level is $<0.05\text{--}0.1\mu\text{M}$
- Kidney injury: glucarpidase within 48–60 h

Steroids, cytarabine, nelarabine

- Dexamethasone: osteonecrosis (adolescents), infection, mood, high glucose
- High-dose cytarabine: cerebellar syndrome (10–25%)
- Nelarabine: neuropathy; stop for grade ≥ 2

Antibodies and CAR-T

- Blinatumomab: CRS; grade ≥ 3 neurotoxicity 7–14%
- Inotuzumab: liver VOD, especially before HCT
- CAR-T: CRS, ICANS, cytopenias, low IgG

Methotrexate neurotoxicity: acute somnolence or seizures within 24 hours of high doses; a subacute stroke-like episode 2–14 days after intrathecal or high-dose treatment that usually resolves (3.8% of 369 children); later leukoencephalopathy, especially after cranial RT. Rechallenge is usually possible after a transient episode.

Figure 17. Toxicity (UpToDate neurotoxicity, high-dose methotrexate, relapsed/refractory and SOS reviews; Ramsey 2018). No doses.

- **Tumour lysis:** ALL with WBC $\geq 100,000/\mu\text{L}$ or LDH $\geq 2\times$ the upper limit is high risk (IV fluids plus rasburicase, not in G6PD deficiency; monitor closely, ICU if kidney function is poor); all other ALL is intermediate risk (fluids plus allopurinol) ([Perissinotti 2023](#)^[40]; [Coiffier 2008](#)^[41]). With steroid-based induction, hypotonic dextrose-saline is favoured because steroids retain sodium.
- **Asparaginase:** give only where anaphylaxis can be treated; check activity (silent inactivation) and switch preparation if needed; asparagine depletion predicts better outcome ([Wetzler 2007](#)^[42]). Thrombosis in 14%

of adults; ISTH suggests LMW-heparin prophylaxis while platelets are $\geq 30,000/\mu\text{L}$ and antithrombin replacement below 50–60% ([Zwicker 2020](#)^[43]); evidence is mixed ([Sibai 2020](#)^[44]; [Mort 2025](#)^[11]).

- **High-dose methotrexate:** hydrate, alkalinise, drain third spaces, stop interacting drugs (NSAIDs, proton-pump inhibitors, penicillins, ciprofloxacin, TKIs), monitor levels, rescue with leucovorin, and use glucarpidase within 48–60 hours when levels stay high with kidney injury ([Ramsey 2018](#)^[45]). Acute kidney injury still occurs in about 2%.
- **Vincristine:** avoid azole antifungals around doses where possible (severe neuropathy, ileus); some Indian centres stop voriconazole for 24 hours before each dose ([Ganesan 2021](#)^[5]).
- **Liver VOD/SOS:** think of it after inotuzumab or HCT (weight gain, ascites, tender liver, rising bilirubin, platelet refractoriness); diagnose with EBMT criteria ([Mohty 2016](#)^[46]); ursodeoxycholic acid prophylaxis around HCT; defibrotide for severe disease.
- **Blood products and infection:** keep haemoglobin around 8–9 g/dL; prophylactic platelets below $10,000/\mu\text{L}$; leukodepleted products, irradiated for transplant candidates, CMV-negative for CMV-negative candidates; Pneumocystis prophylaxis; no live vaccines; influenza vaccine for patient and family.

Emergencies shared with AML

- **Leukostasis, DIC, neutropenic fever and antibacterial/antifungal prophylaxis** are covered once, in the [AML module, emergencies section](#).
- **Specific to ALL:** the mediastinal mass (airway, SVC, pericardial tamponade), high-risk tumour lysis, asparaginase thrombosis and bleeding, methotrexate kidney injury, and CRS or neurotoxicity with blinatumomab and CAR-T.

India: check availability and cost before planning

- Generic imatinib and dasatinib are used widely; ponatinib was not marketed in India in 2021 ([Ganesan 2021](#)^[5]). Check current access to ponatinib, asciminib, blinatumomab, inotuzumab, revumenib, nelarabine, Erwinia asparaginase and rituximab, and their cost, at the start of treatment.
- NexCAR19 (CDSCO approval 13 October 2023) is an Indian CD19 CAR-T option for relapsed B-ALL; eligibility, centres and cost should be checked case by case.
- MRD testing (flow at 10^{-4} or PCR) and transplant beds are concentrated in a few centres: plan referrals at diagnosis, not at relapse.
- Abandonment (11–15%) and interruptions are major causes of failure: involve social workers and counsellors, and agree a written plan for the 2–3 years of treatment.

Quick reference (also as a printable PDF on the Printable Teaching Resources page)

Table A. Diagnosis and work-up tests and what they change

Test	When	What it changes	Pitfalls
CBC + smear review	Every suspected case	Lymphoblasts; cytopenias	White count may be low, normal or very high
PT, aPTT, fibrinogen, D-dimer	At diagnosis; during asparaginase	Bleeding and clot risk	Asparaginase lowers fibrinogen and antithrombin

Test	When	What it changes	Pitfalls
Potassium, phosphate, calcium, urate, creatinine, LDH	Before and during induction	TLS risk: high if WBC $\geq 100,000/\mu\text{L}$ or LDH $\geq 2\times$ upper limit	ALL is never low risk for TLS
Flow cytometry (blood or marrow)	All	B vs T lineage; CD19, CD20, CD22 for antibody choice; MRD baseline	Only surface CD3 is T-lineage specific; MPO+ = AML
Karyotype + FISH; RT-PCR BCR::ABL1	All, within days	Ph+ $\rightarrow$ TKI at once; KMT2A, hypodiploidy = high risk	ETV6::RUNX1 is cryptic on banding
Ph-like screen (CRLF2 flow, fusion panel, RNA sequencing); NGS for TP53	B-ALL, where available	High-risk group; trials of ABL/JAK inhibitors	Not standard everywhere
Lumbar puncture	When blasts clear from blood, with first intrathecal dose	CNS-1/2/3 $\rightarrow$ intensity of CNS therapy	Traumatic tap with blasts: compare WBC:RBC ratios
CT chest; biopsy of mass	Mediastinal mass or LBL	LBL if marrow blasts $<20\%$; airway and SVC risk	Diagnose from blood, marrow or effusion if possible
ECG, echo; HBV, HCV, HSV, CMV; pregnancy test	Before induction	Anthracycline and TKI choice; antiviral prophylaxis	Dasatinib/ponatinib: QT, effusions, vascular risk
HLA typing (patient and siblings)	Transplant-eligible patients, at diagnosis	Donor search for high-risk or MRD-positive disease	Only about a quarter have a matched sibling

Table B. Treatment by setting

Setting	Usual approach	Alternatives	Key points
Ph-, fit, ≤ 40 years	Paediatric-inspired asparaginase regimen (CALGB 10403, DFCI)	Hyper-CVAD	+ rituximab if CD20+; cure 60–80%
Ph-, fit, 40–65 years	Asparaginase regimen (E1910, GRAALL-2005) or hyper-CVAD	—	Choose by toxicity, comorbidity and experience
Ph-, older or unfit B-ALL	Inotuzumab-based or mini-hyper-CVD-based	Mini-hyper-CVD + venetoclax; vincristine + steroid; POMP	Watch liver VOD with inotuzumab
Ph-, older or unfit T-ALL	Mini-hyper-CVD + venetoclax	Vincristine + steroid	No inotuzumab (no CD22)
Ph-, CR, standard risk	Consolidation chemotherapy + blinatumomab, then maintenance ≥ 2 years	Allogeneic HCT (some experts, persistent MRD)	E1910: 3-year OS 85% vs 68%
Ph-, CR, high risk, MRD-negative	Chemo-immunotherapy + maintenance, or allogeneic HCT	—	Favour HCT for KMT2A, complex, low hypodiploid, TP53
Ph-, MRD-positive	Blinatumomab 1–2 cycles $\rightarrow$ allogeneic HCT	Chemo-immunotherapy + maintenance if not eligible	MRD cleared in about 78%
Ph+, any fitness	TKI + steroid or TKI + low-intensity chemotherapy	TKI + blinatumomab (chemotherapy-free)	TKI in every phase; avoid high-intensity chemotherapy
Ph+, in CR	MRD-guided: allogeneic HCT if fit and MRD falling	Consolidation if MRD-negative	TKI ≥ 1 year after HCT; 24–30 months if no HCT

Setting	Usual approach	Alternatives	Key points
Relapsed B-ALL, CD19+/CD22+	Blinatumomab, inotuzumab or CAR-T	Chemotherapy	Then allogeneic HCT if eligible
Relapsed KMT2A-r; relapsed T-ALL	Revumenib; nelarabine-based chemotherapy	Trial	Then allogeneic HCT
Lymphoblastic lymphoma	Same protocol as ALL of that lineage	—	CNS prophylaxis; marrow and LP at staging

Table C. Treatment options: evidence and best fit

Option	Best fit	Evidence	Watch for
Asparaginase-rich paediatric-inspired regimen	Fit adults, especially ≤40	CALGB 10403 ^[12] : 3-year OS 73%	Liver, pancreatitis, thrombosis, allergy
Hyper-CVAD ± rituximab	Fit adults 40–65	Thomas 2010 ^[15] : 3-year OS 50%	Neutropenia, infections, admissions
Rituximab	CD20+ (>10–20% of blasts), under 65	GRAALL-2005/R ^[16] : 4-year EFS 55% vs 43%	Infusion reactions; HBV reactivation
Blinatumomab (CD19×CD3)	Consolidation; MRD-positive; relapse	E1910 ^[1] ; BLAST ^[2] ; TOWER ^[32]	CRS, neurotoxicity; continuous infusion
Inotuzumab ozogamicin (CD22)	Relapse; older adults in first line	INO-VATE ^[33] : CR 81% vs 29%	Liver VOD (9%), especially before HCT
Dasatinib / imatinib / ponatinib	Ph+ ALL, all phases	PhALLCON ^[29] ; D-ALBA ^[4]	Effusions, QT, bleeding; ponatinib: arterial events
Nelarabine	Relapsed T-ALL; children/young adults first line	Candoni 2020 ^[39] ; AALLO434 ^[25]	Neuropathy, Guillain-Barré-like weakness
CD19 CAR-T	Relapsed/refractory B-ALL	ELIANA ^[34] ; ZUMA-3 ^[35] ; FELIX ^[36]	CRS, ICANS, cytopenias, low IgG
Revumenib (menin inhibitor)	Relapsed KMT2A-rearranged ALL	AUGMENT-101 ^[38] : response 63%	Differentiation syndrome, QT
Allogeneic HCT	High risk/MRD-positive CR1; Ph+; second remission	UKALL XII/ECOG 2993 ^[19] ; Dhédin 2015 ^[18]	Non-relapse mortality 15–35%; GVHD

Table D. Managing problems during treatment

Problem	Clues	First steps	Then
Tumour lysis	K, phosphate, urate up; calcium down; creatinine rising	Fluids; rasburicase if high risk (check G6PD)	Do not give calcium for asymptomatic low calcium while phosphate is high
Neutropenic fever	Fever ≥38 °C, neutrophils low	Cultures; broad antibiotics within the hour	See the AML module, emergencies section
Asparaginase thrombosis	Swollen limb; headache, seizure (sinus thrombosis)	Imaging; LMW heparin (anti-Xa); antithrombin if high-risk clot	Hold asparaginase; resume after about 4 weeks if judged safe
Asparaginase pancreatitis or allergy	Abdominal pain, lipase; rash, wheeze	Stop the dose; treat anaphylaxis	Allergy or silent inactivation → Erwinia product

Problem	Clues	First steps	Then
Delayed methotrexate clearance	Rising creatinine, high level	More fluids, alkalinise, more leucovorin; stop interacting drugs	Glucarpidase within 48–60 hours
Vincristine neuropathy, ileus	Tingling, constipation, cramps	Avoid azoles near doses; bowel care	Dose changes per protocol
Blinatumomab or CAR-T reactions	Fever, low BP; confusion, tremor, speech change	Grade CRS and ICANS; tocilizumab, steroids	See the Aggressive B-cell Lymphomas module
Liver VOD/SOS (inotuzumab, HCT)	Weight gain, ascites, tender liver, bilirubin	EBMT criteria; fluid balance; avoid liver toxins	Defibrotide if severe
Myelosuppression on maintenance	Low counts on standard 6-mercaptopurine	Check TPMT and NUDT15	Adjust per protocol
Steroid effects	Hip or shoulder pain; high glucose; mood change	Look for osteonecrosis; control glucose	Discuss steroid schedule with the protocol team

SHARE WITH PATIENTS: TREATMENT AND HOPE

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

[Every leukaemia patient needs a bone marrow transplant?](#)

[Leukaemia can never be cured?](#)

[Chemotherapy is the only treatment for leukaemia?](#)

[If leukaemia returns after treatment, nothing can be done?](#)

[Blood transfusions can cure leukaemia?](#)

07 Management algorithms

Six decision paths pull together sections 02–06.

ALGORITHM 1

Suspected ALL: the first 24–48 hours

Lymphoblasts on the smear, cytopenias, bone pain, nodes or a mediastinal mass → CBC and smear, PT/aPTT/fibrinogen, chemistry with urate, phosphate, LDH; chest X-ray

EMERGENCIES NOW

Mass → airway, SVC, pericardium before any sedation

TLS: WBC $\geq 100,000$ or LDH $\geq 2 \times$ ULN → rasburicase

Fever + neutropenia → antibiotics now

Leukostasis, DIC, infection: AML module

CONFIRM AND CLASSIFY

Flow: TdT+, MPO–

B → CD19, CD79a, CD22

T → CD3, CD7

BCR::ABL1 within days; karyotype, FISH

Mass + <20% marrow blasts = LBL

PLAN

Age, fitness, comorbidity

Ph+ → Algorithm 4

Ph– → Algorithm 2

LP with the first intrathecal dose

HLA-type patient and siblings; fertility

All: central line · echo and ECG · HBV/HCV/HSV/CMV · leukodepleted, irradiated products for transplant candidates · referral to a leukaemia centre.

ALGORITHM 2

Ph-negative ALL: induction by age, fitness and lineage

Ph-negative → fitness and comorbidity; CD20, CD22, T markers; CNS grade

FIT, ≤ 40 YEARS

Paediatric-inspired, asparaginase-rich

CALGB 10403 or DFCL

+ rituximab if CD20+

Cure 60–80%

FIT, 40–65 YEARS

Asparaginase regimen or hyper-CVAD

Asparaginase → liver, pancreas, clots

Hyper-CVAD → neutropenia

+ rituximab if CD20+

E1910 · GRAALL-2005

OLDER OR UNFIT

B-ALL → inotuzumab-based or mini-hyper-CVD

T-ALL → mini-hyper-CVD + venetoclax

Frail → vincristine + steroid, POMP

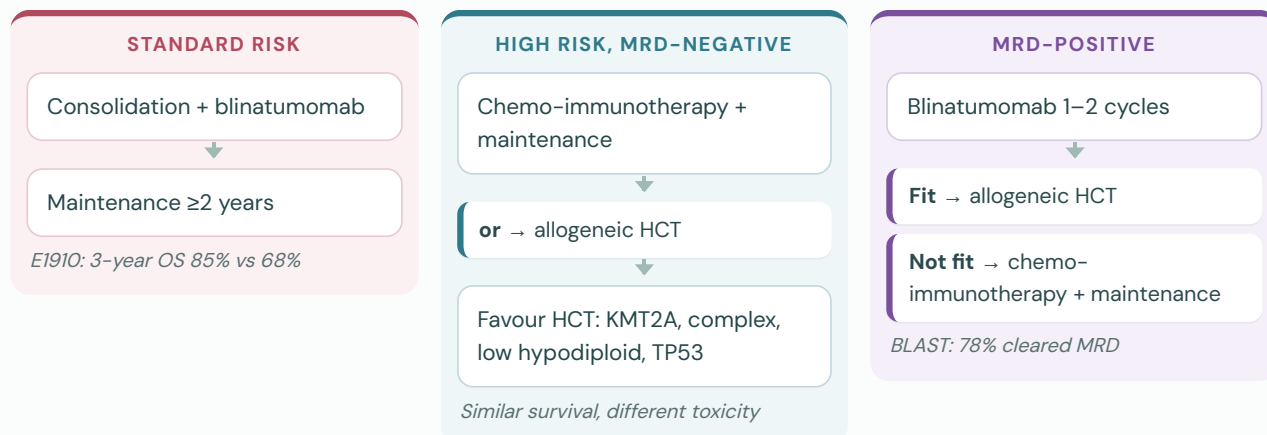
Inotuzumab: watch liver VOD

All: CNS prophylaxis from the first lumbar puncture · marrow and MRD at count recovery · no CR → Algorithm 5.

ALGORITHM 3

Ph-negative ALL in first remission

CR → risk group (age, WBC, genetics, time to CR) and MRD (assay $\leq 10^{-4}$); donor; fitness

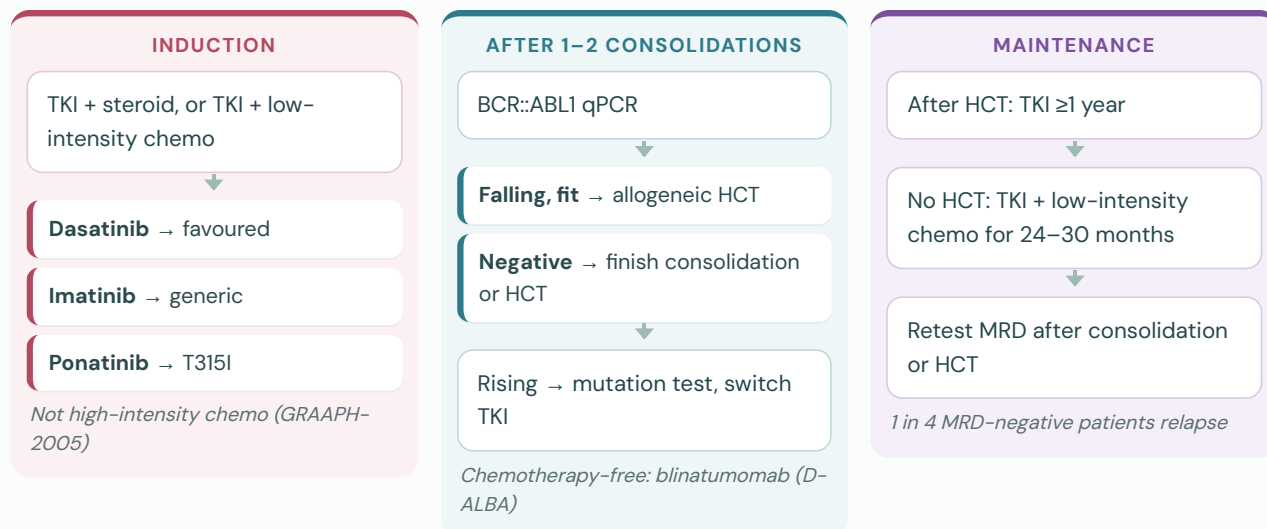


Maintenance: daily 6-mercaptopurine + weekly methotrexate $\pm$ vincristine-steroid pulses · TPMT/NUDT15 if counts fall ·
Pneumocystis prophylaxis · no live vaccines.

ALGORITHM 4

Ph-positive ALL

BCR::ABL1 positive → TKI today; baseline BCR::ABL1 qPCR; heart, bleeding and effusion history guide TKI choice

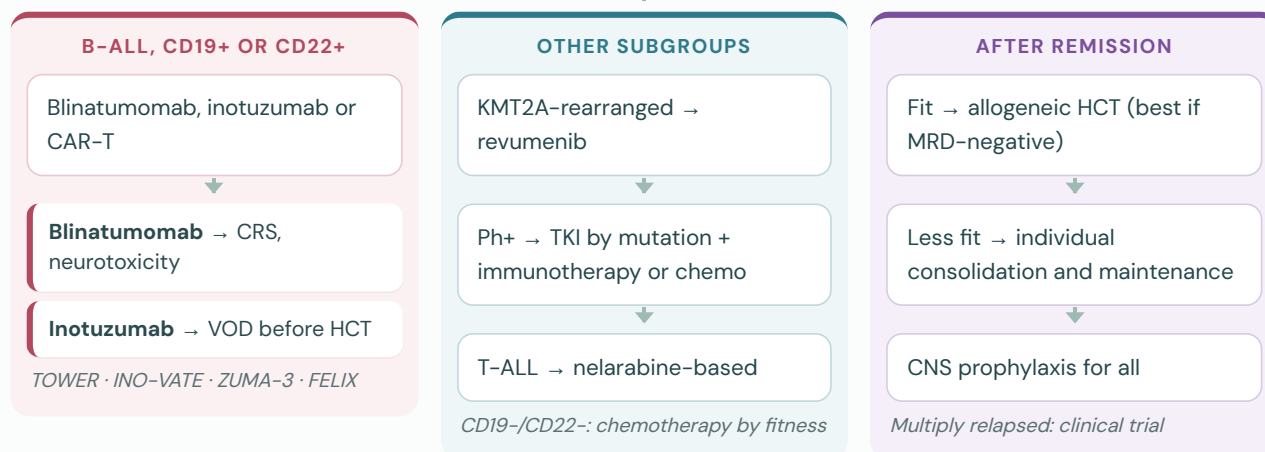


Frail: TKI + steroid · weak heart: avoid dasatinib, nilotinib and ponatinib where possible; no anthracycline if EF $< 30\%$.

ALGORITHM 5

Relapsed or refractory ALL

Relapse or no CR → marrow flow (CD19, CD22, CD20), cytogenetics, KMT2A, BCR::ABL1 mutations; LP; testes; fitness; donor search now

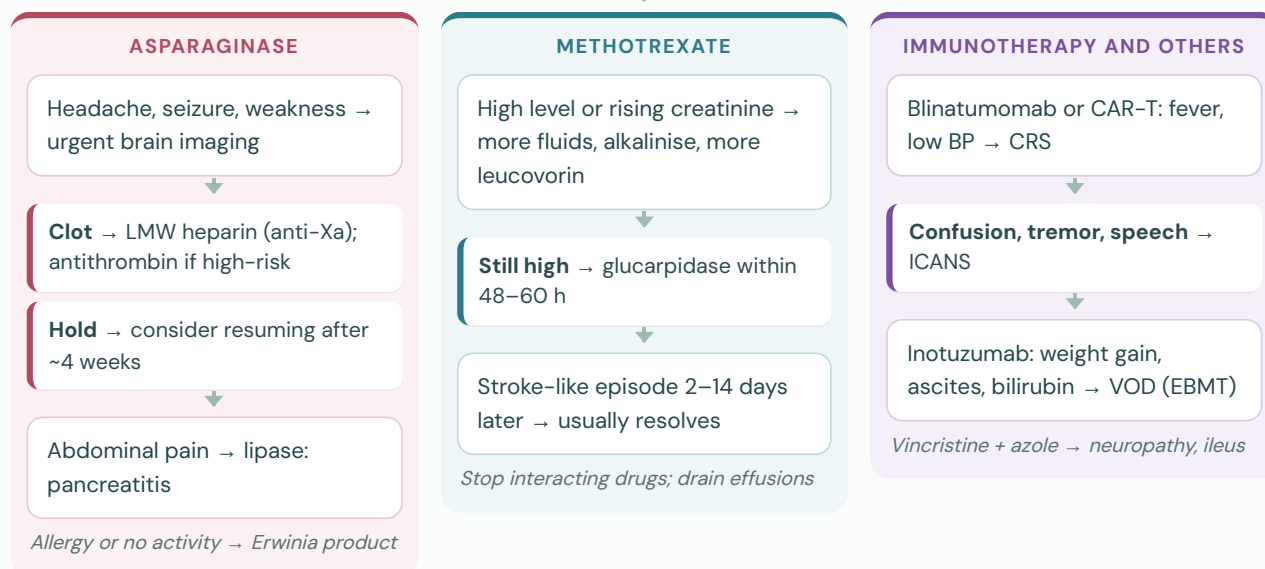


Isolated CNS relapse: intrathecal + cranial RT 24 Gy · residual testicular disease: RT 24 Gy to both testes · relapse ≥3 years: first regimen again.

ALGORITHM 6

Problems during treatment: what to do first

New symptom on ALL treatment → which drug, which day, counts and clotting



Neutropenic fever, DIC, leukostasis: AML module emergencies section · CRS and ICANS grading: Aggressive B-cell Lymphomas module.

o8 Survivorship, follow-up & late effects

After treatment: remission, MRD, follow-up and late effects

Complete remission

- Marrow blasts <5%; cellularity >25%
- Normal blood counts; no extramedullary disease
- Marrow when neutrophils >1,000 and platelets >100,000/ μ L

Follow-up

- Examination, CBC, liver tests every 1–2 months in year 1
- Every 3–6 months in year 2
- Every 6–12 months after that
- Final marrow + MRD at end of maintenance

Late effects

- Neuropathy, cognition, osteonecrosis
- Endocrine and fertility problems
- Heart (anthracyclines)
- Second cancers
- After HCT: GVHD, infections, eyes, lungs

In German long-term survivors of adult ALL, two-thirds had a comorbidity: neurological (27%), endocrine (17% of men, 24% of women) or skin problems; transplanted survivors had more late effects. Adherence matters: in Indian series 11–15% abandon or interrupt therapy, and treatment delays cut relapse-free survival from 69% to 43% (Ganesan 2021).

Figure 18. Response and survivorship (UpToDate induction and post-remission reviews; childhood late-effects review; Ganesan 2021).

- **Adherence is treatment:** maintenance runs for 2–3 years at home; non-adherence and abandonment occur in 11–15% of Indian ALL patients, and treatment delays lowered relapse-free survival from 69% to 43% in one Indian series ([Ganesan 2021](#)^[5]).
- **Follow-up:** physical examination, CBC and liver tests every 1–2 months in the first year after therapy, every 3–6 months in the second, then every 6–12 months; a final marrow with MRD at the end of maintenance and further marrows only if indicated.
- **Late effects:** neuropathy (vincristine), cognitive and endocrine effects (especially after cranial RT), osteonecrosis (dexamethasone, adolescents), cardiomyopathy (anthracyclines), infertility, obesity and abnormal glucose metabolism, and second cancers. Transplanted survivors have more: chronic GVHD, infections, eye, lung, kidney and endocrine problems.
- **Prevention during and after treatment:** Pneumocystis prophylaxis during therapy; influenza vaccine for patient and household; no live vaccines while on chemotherapy; revaccination after HCT per transplant protocols.
- **MRD in follow-up:** a single positive MRD result does not by itself mean relapse (levels fluctuate), but persistent or rising MRD should trigger a donor search and closer monitoring.

SHARE WITH PATIENTS: LIFE DURING AND AFTER TREATMENT

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

[A normal blood count means leukaemia has completely disappeared?](#)

[Leukaemia patients must avoid all physical activity and social contact?](#)

[Children cured of leukaemia can't lead normal adult lives?](#)

09 Landmark trials

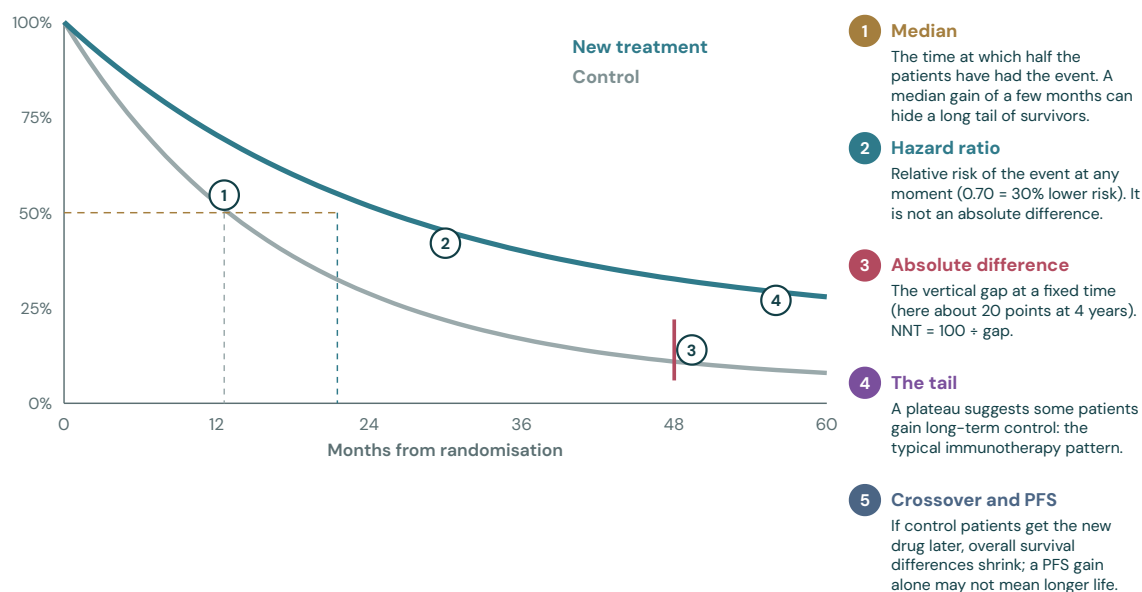


Figure 19. How to read a survival curve (illustrative). Use the absolute gap at a fixed time and overall survival, not the median or PFS alone, when weighing benefit against toxicity and cost.

The trials behind today's choices

E1910 · MRD-negative CR, 30–70 years

Chemo + blinatumomab vs chemo · 3-year OS (%)



GRAALL-2005/R · CD20+ B-ALL

Rituximab vs none · 4-year EFS (%)



COG AALL0434 · T-ALL, 1–31 years

Nelarabine vs none · 5-year DFS (%)



GRAAPH-2005 · Ph+ ALL

Low- vs high-intensity chemo + imatinib · CR (%)



PhALLCON · Ph+ ALL

Ponatinib vs imatinib · MRD-negative CR (%)



TOWER · relapsed B-ALL

Blinatumomab vs chemo · median OS (months)



INO-VATE · relapsed B-ALL

Inotuzumab vs chemo · CR (%)



Grey = comparator. Endpoints differ (months or %): compare within a trial, not across trials.

Figure 20. Landmark results as reported in the UpToDate induction, post-remission, Ph-positive, relapsed and childhood treatment reviews.

ALL in India: what published series show

Common threads: many young patients, multidrug-resistant infections during intensive therapy, limited transplant access, cost limiting rituximab, pegylated asparaginase and new antibodies, and 11–15% abandonment. At KGMU Lucknow, 10.6% of 75 AYA patients on BFM-95 did not complete induction (Shukla 2025).

Figure 21. Indian data (Ganesan 2021, Table 2, citing INWARD [Ganesan 2021], Rajendra 2021, Abraham 2014 and others; Shukla 2025). Different eras, ages and protocols: not comparable with each other.

- **CALGB 10403** showed that young adults can safely receive a paediatric regimen delivered by adult oncologists ([Stock 2019](#)^[12]).
- **E1910** moved blinatumomab into first-line consolidation for MRD-negative adults ([Litzow 2024](#)^[1]).
- **GRAALL-2005/R** established rituximab for CD20+ B-ALL ([Maury 2016](#)^[16]).
- **GRAAPH-2005 and D-ALBA** showed that Ph+ ALL needs a TKI more than intensive chemotherapy ([Chalandon 2015](#)^[3]; [Foà 2020](#)^[4]); PhALLCON showed deeper responses with ponatinib ([Jabbour 2024](#)^[29]).
- **TOWER and INO-VATE** made antibodies the standard first salvage for B-ALL ([Kantarjian 2017](#)^[32]; [Kantarjian 2016](#)^[33]).
- **MRD**: across 39 studies, MRD negativity predicted better survival in adults and children alike (hazard ratio 0.28; [Berry 2017](#)^[47]); in GMALL 07/2003, 5-year survival was 80% with MRD negativity by week 16 vs 42% without ([Gökbuget 2012](#)^[48]).
- **Indian evidence**: multicentre INWARD AYA data ([INWARD](#)^[49]), Tata Memorial AYA on modified BFM-90 ([Rajendra 2021](#)^[50]) and KGMU Lucknow on BFM-95, where 10.6% of 75 patients did not complete induction ([Shukla 2025](#)^[51]).

10 Practice pearls & pitfalls

- **Send BCR::ABL1 on day 1:** the result changes induction within days.
- **Never sedate or lay flat a patient with a big mediastinal mass** before the airway and SVC have been assessed.
- **ALL is never low risk for tumour lysis;** WBC $\geq 100,000/\mu\text{L}$ or LDH $\geq 2\times$ normal makes it high risk.
- **Keep the first diagnostic sample:** PCR-based MRD needs the leukaemia's own fingerprint.
- **"MRD-negative" needs a number:** ask the laboratory for the sensitivity ($\leq 10^{-4}$) and send the first pull of the aspirate.
- **Asparaginase activity, not just dose:** silent inactivation is common; check levels where possible.
- **Azoles and vincristine do not mix well;** plan antifungal cover around vincristine doses.
- **Before high-dose methotrexate:** stop proton-pump inhibitors, NSAIDs and other interacting drugs, and drain effusions.
- **Inotuzumab just before transplant raises liver VOD risk:** plan the sequence with the transplant team.
- **Re-check CD19, CD22 and CD20 at relapse:** antigen-negative relapses follow antibody and CAR-T therapy.
- **Maintenance is long and at home:** adherence, social support and a written plan matter as much as the drugs.

11 Case vignettes: lines of management

Nine cases from the clinic.

CASE 1 T-ALL · mediastinal mass · tumour lysis

Breathless when lying flat

19 years, man

WBC 142,000/ μ L

Anterior mediastinal mass

A 19-year-old college student from Nellore has had 3 weeks of cough and 4 days of breathlessness lying flat, with a puffy face. Chest X-ray shows a wide mediastinum; CT shows a 10 cm anterior mass with a pleural effusion and a narrowed trachea. WBC 142,000/ μ L with blasts; LDH 4 $\times$ normal; potassium and urate high.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

PROTECT THE AIRWAY

No sedation or lying flat; ICU review. The diagnosis can come from blood flow cytometry (and pleural fluid) without a mediastinal biopsy.

2

DIAGNOSE

Blasts TdT+, cytoplasmic CD3+, CD7+, CD1a+: T-ALL. BCR::ABL1 negative. Lumbar puncture later, when blasts have cleared from the blood.

3

TUMOUR LYSIS

High risk (WBC $\geq$ 100,000 and LDH $\geq$ 2 $\times$): IV fluids and rasburicase after a G6PD check; close electrolyte monitoring; steroid prephase begins debulking.

4

TREAT

Paediatric-inspired asparaginase-rich regimen with CNS prophylaxis; MRD at count recovery; T-ALL MRD in blood and marrow agree, but follow the protocol.

TEACHING POINTS

- Mediastinal mass: the airway comes before the biopsy.
- ALL with a very high count is high risk for tumour lysis.
- In adults nelarabine has not improved first-line outcomes; in young adults the COG data are the reference.

See: Sections O2, O3 and O6, Algorithm 1.

CASE 2 B-ALL · AYA · standard risk

A young mother with fever and pallor

26 years, woman

WBC 18,000/ μ L

CD20 positive

A 26-year-old woman from Kavali has had fever and weakness for 6 weeks. Haemoglobin 6.2 g/dL, platelets 34,000/ μ L, WBC 18,000/ μ L with 60% blasts. Marrow: B-ALL, CD19+, CD10+, CD20 on 40% of blasts; normal karyotype; BCR::ABL1 negative; spinal fluid CNS-1.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

CLASSIFY

Ph-negative B-ALL, standard risk (age <60, WBC <30,000, no adverse genetics). Ph-like screen if available.

2 INDUCTION

Paediatric-inspired asparaginase-rich regimen plus rituximab (CD20+); CNS prophylaxis; watch liver, pancreas and clotting with asparaginase.

3 AFTER REMISSION

CR with MRD negative at 10^{-4} : consolidation chemotherapy with blinatumomab, then maintenance for 2–3 years.

4 KEEP HER ON TRACK

Social worker and family meeting at the start: abandonment and interruptions are common in India and lower relapse-free survival.

TEACHING POINTS

- Rituximab for CD20+ B-ALL under 65 improves EFS.
- Blinatumomab in consolidation raised 3-year survival from 68% to 85% (E1910).
- Adherence is part of the treatment.

See: Sections O6 and O8, Algorithms 2 and 3.

CASE 3 B-ALL · MRD-positive · transplant**In remission, but not deep enough**

33 years, man

MRD 0.2%

Sibling donor

A 33-year-old teacher with B-ALL (WBC 52,000/ μ L at diagnosis) is in morphological CR after induction, but flow MRD is 2×10^{-3} . His younger sister is an HLA match.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1 RISK

High risk on two counts: WBC $>30,000$ and MRD $\geq 10^{-4}$.

2 CLEAR THE MRD

One or two cycles of blinatumomab (in hospital at the start; watch CRS and neurotoxicity). About three-quarters become MRD-negative.

3 CONSOLIDATE WITH TRANSPLANT

Allogeneic HCT from his sister; GRAALL data show benefit from HCT when MRD is $\geq 10^{-3}$.

4 IF MRD PERSISTS

More blinatumomab is unlikely to help; consider inotuzumab or a trial, and plan transplant timing to limit VOD risk.

TEACHING POINTS

- MRD after induction is the strongest single predictor in adult ALL.
- Blinatumomab is the bridge from MRD-positive to transplant.
- Use an assay that reaches 10^{-4} .

See: Sections O4 and O6, Algorithm 3.

CASE 4 Ph+ ALL · TKI · transplant**The fusion that changes everything**

52 years, woman

BCR::ABL1 p190

Diabetic

A 52-year-old woman from Gudur with diabetes presents with tiredness and bruising: WBC 64,000/ μ L, platelets 22,000/ μ L. Flow shows B-ALL; RT-PCR on day 2 shows BCR::ABL1 (p190). Echo normal; no

effusion or bleeding history.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

START THE TKI

Dasatinib at once (generic available; no effusion or bleeding history); baseline BCR::ABL1 qPCR.

2

PARTNER GENTLY

A steroid alone or vincristine–steroid, not hyper–CVAD: fewer early deaths with equal survival (GRAAPH–2005). Control glucose closely on steroids.

3

MONITOR

BCR::ABL1 qPCR after 1–2 consolidations: falling. Her brother is a match → allogeneic HCT (reduced intensity considered for age and diabetes).

4

AFTER TRANSPLANT

Restart the TKI when counts recover and continue ≥1 year; repeat MRD. Rising MRD → kinase–domain mutation testing (T315I → ponatinib, if obtainable).

TEACHING POINTS

- Ph+ ALL needs a TKI more than intensive chemotherapy.
- BCR::ABL1 qPCR is the MRD test.
- Check ponatinib access early in India.

See: Section O6, Algorithm 4.

CASE 5 Older adult · inotuzumab · VOD

Seventy, and keen to be treated

68 years, man

Ph–negative B–ALL

Ischaemic heart disease

A 68–year–old retired clerk with treated ischaemic heart disease has B–ALL, CD22 on 95% of blasts, BCR::ABL1 negative, performance status 1. He wants treatment that keeps him at home as much as possible.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

GOALS

Honest talk: cure is possible but less likely than in younger adults; intensive regimens carry high treatment mortality at his age.

2

CHOOSE

Inotuzumab–based moderate–intensity treatment (with dexamethasone, or with mini–hyper–CVD), avoiding an anthracycline–heavy regimen.

3

WATCH

Weight, abdominal girth and bilirubin for liver VOD (EBMT criteria); infections; prolonged low platelets.

4

IF FRAIL LATER

Vincristine–steroid or POMP maintenance for disease control; palliative care alongside.

TEACHING POINTS

- Inotuzumab is not for T-ALL (no CD22).
- Older adults need gentler, antibody-based regimens.
- Talk about goals before choosing intensity.

See: Section O6 (older or unfit), Algorithm 2.

CASE 6 Asparaginase · cerebral sinus thrombosis**Headache and a seizure on day 20**

22 years, man

On pegylated asparaginase

Platelets 60,000/ μ L

A 22-year-old on induction with pegylated asparaginase develops a severe headache and a generalised seizure on day 20. Platelets 60,000/ μ L; fibrinogen 90 mg/dL; antithrombin 45%.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

IMAGE

Urgent brain imaging: superior sagittal sinus thrombosis. Differentials: bleeding, methotrexate encephalopathy, asparaginase encephalopathy.

2

ANTICOAGULATE

LMW heparin with anti-Xa monitoring (antithrombin is low); antithrombin replacement for this high-risk clot; support fibrinogen and platelets to allow anticoagulation.

3

ASPARAGINASE

Hold it; after stabilisation (about 4 weeks) decide with a thrombosis expert whether to resume, because asparaginase intensity matters for cure.

4

DURATION

Anticoagulation for at least 6 months.

TEACHING POINTS

- Asparaginase lowers antithrombin and fibrinogen: clots and bleeds together.
- Cerebral sinus thrombosis typically appears after several weeks.
- Thrombosis affects about 14% of adults on asparaginase.

See: Section O6 (toxicity), Algorithm 6.

CASE 7 High-dose methotrexate · delayed clearance**The level that would not fall**

35 years, woman

Consolidation

Creatinine doubled

A 35-year-old in consolidation receives high-dose methotrexate. At 42 hours her creatinine has doubled and the methotrexate level is far above the expected curve. She has a small pleural effusion and has been taking a proton-pump inhibitor and ciprofloxacin.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

STOP THE CULPRITS

Stop the proton-pump inhibitor and ciprofloxacin; avoid NSAIDs.

2

SUPPORT CLEARANCE

Increase IV fluids and urinary alkalisation (urine pH ≥ 7) while urine output allows; increase leucovorin according to the measured levels.

3

GLUCARPIDASE

Levels stay high with kidney injury → glucarpidase, ideally within 48–60 hours of the start of the infusion; dialysis is only a temporary bridge.

4

NEXT CYCLE

Drain the effusion and review drugs before the next dose.

TEACHING POINTS

- Methotrexate is cleared by the kidney: acid urine and dehydration cause delay.
- Effusions are a reservoir.
- Glucarpidase works best early.

See: Section O6 (toxicity), Algorithm 6.

CASE 8 Relapsed B-ALL · antibodies · CAR-T**Back after 14 months**

30 years, man

CD19+, CD22+

On maintenance

A 30-year-old man treated for Ph-negative B-ALL relapses in the marrow 14 months after diagnosis, while on maintenance. Blasts CD19+ and CD22+; spinal fluid clear; testes normal. He has a matched sibling.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

RE-EVALUATE

Marrow flow for CD19, CD22 and CD20; cytogenetics (KMT2A?); lumbar puncture; donor work-up now.

2

RE-INDUCE

Blinatumomab (survival advantage over chemotherapy in TOWER) or inotuzumab (higher CR rate in INO-VATE); because HCT is planned, blinatumomab avoids the VOD risk of inotuzumab before transplant.

3

CONSOLIDATE

MRD-negative second remission → allogeneic HCT from his sibling; CNS prophylaxis continues.

4

IF IT FAILS

CD19 CAR-T: in India NexCAR19 is approved for relapsed B-cell leukaemia; check eligibility and cost.

TEACHING POINTS

- Early relapse needs transplant for cure.
- Choose the antibody with the transplant in mind.
- Antigen loss can follow antibody or CAR-T therapy: re-test at each relapse.

See: Section O6 (relapse), Algorithm 5.

CASE 9 T-lymphoblastic lymphoma**A mass, but a "normal" marrow**

21 years, man

Marrow blasts 8%

Stage IV

A 21-year-old has neck nodes and a large anterior mediastinal mass. Node core biopsy: TdT+, CD3+, CD7+, CD1a+ lymphoblasts. Marrow shows 8% lymphoblasts; spinal fluid CNS-1; LDH twice normal.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

NAME IT

Mass with <20% marrow blasts = T-lymphoblastic lymphoma: the same disease as T-ALL.

2

TREAT

An ALL protocol of T lineage with full CNS prophylaxis, tumour-lysis prevention and airway care; not a CHOP-type lymphoma regimen.

3

FOLLOW

Marrow and blood MRD as per protocol; about 60% of T-LBL later become leukaemic without effective therapy.

4

OPEN QUESTION

Residual mediastinal mass at the end of treatment: the supplied sources do not settle the role of RT; decide with the protocol and tumour board.

TEACHING POINTS

- LBL is treated as ALL.
- Thymoma is the key mimic: keratin and polyclonal thymocytes.
- CNS involvement is frequent: always do the lumbar puncture.

See: Sections 03, 05 and 06.

12 References & guidelines

- European LeukemiaNet 2024 recommendations for ALL in adults; NCCN Guidelines: Acute Lymphoblastic Leukemia (current version); ASH 2026 guideline for ALL in adolescents and young adults; WHO Classification 5th edition and International Consensus Classification (2022); ISTH guidance on asparaginase-related thrombosis; EBMT criteria for hepatic SOS/VOD.
- Cross-checked in October 2026 against 20 UpToDate topic reviews: clinical manifestations, pathologic features and diagnosis of B cell ALL/LBL; of precursor T cell ALL/LBL; classification, cytogenetics and molecular genetics of ALL/LBL; detection of measurable residual disease in ALL/LBL; clinical use of MRD detection in ALL; induction therapy for Ph-negative ALL in adults; Ph-negative ALL in adults: post-remission management; induction therapy for Ph-positive ALL in adults; Ph-positive ALL in adults: post-remission management; treatment of relapsed or refractory ALL in adults; tumor lysis syndrome: prevention and treatment; hepatic sinusoidal obstruction syndrome (veno-occlusive disease) in adults; antithrombin deficiency (section on asparaginase); overview of neurologic complications of conventional non-platinum cancer chemotherapy; therapeutic use and toxicity of high-dose methotrexate; and, for contrast only, the overview of presentation and diagnosis of ALL/LBL in children, prognostic factors and risk groups, treatment, relapsed or refractory disease, and outcomes and late effects in children and adolescents. All trial citations below come from the reference lists of these reviews, except the JIPMER review and the KGMU Lucknow series (found and verified by web search on 17 October 2026), the three Indian series cited from the JIPMER review's reference list, and the NexCAR19 trial (verified 16 October 2026).
- Reviewed and approved by Dr. Haritha Chiramana, 17 October 2026.

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FURTHER READING (NOT CITED IN THE TEXT ABOVE)

- **ELN 2024 adult ALL (Gökbuget 2024)**: Gökbuget N, Boissel N, Chiaretti S, et al. Management of ALL in adults: 2024 ELN recommendations from a European expert panel. *Blood* 2024;143:1903. [PubMed](#) **Diagnosis, genetics, risk and MRD**
- **Standard-risk MRD, GMALL (Brüggemann 2006)**: Brüggemann M, Raff T, Flohr T, et al. Clinical significance of minimal residual disease quantification in adult patients with standard-risk acute lymphoblastic leukemia. *Blood* 2006;107:1116. [PubMed](#) **Diagnosis, genetics, risk and MRD**
- **ASH AYA ALL guideline (DuVall 2026)**: DuVall AS, McNeer J, Cheung MC, et al. American Society of Hematology 2026 guidelines for frontline management of acute lymphoblastic leukemia in adolescents and young adults. *Blood Adv* 2026;10:4671. [PubMed](#) **Ph-negative ALL: induction, post-remission therapy and transplant**

Educational summary for health professionals, written in our own words from current guidelines and primary trials. No drug doses are given. Hodgkin, aggressive B-cell, indolent B-cell, T-cell and cutaneous lymphomas are parts 1–5, multiple myeloma is part 6 and acute myeloid leukaemia is part 7; chronic myeloid leukaemia is part 9; CLL is covered in the indolent B-cell module; childhood ALL appears here only as a contrast. Verify current guidelines, Indian regulatory approvals and individual patient factors before treatment decisions.