ASH® CLINICAL PRACTICE GUIDELINES

Acute Lymphoblastic Leukemia in Adolescents and Young Adults – Frontline Management

An Educational Slide Set

American Society of Hematology 2026 guidelines for Frontline Management of Acute Lymphoblastic Leukemia in Adolescents and Young Adults (ALL in AYAs)

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American Society of Hematology 2026 guidelines for Frontline Management of Acute Lymphoblastic Leukemia in Adolescents and Young Adults (ALL in AYAs)

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ASH Clinical Practice Guidelines on ALL in AYAs

1. **Frontline Management of ALL in AYAs**
2. Relapsed/Refractory Management of ALL in AYAs

How were these guidelines generated?

PANEL FORMATION

Each guideline panel was formed following these key criteria:

- Balance of expertise (including disciplines beyond hematology, and patients)
- Close attention to minimization and management of conflicts of interest

CLINICAL QUESTIONS

11 **clinically-relevant questions** generated in **PICO format** (population, intervention, comparison, outcome)

Example: PICO question

For AYA with ALL receiving frontline therapy, what are the comparative benefits and harms of asparaginase vs. non-asparaginase-containing regimens?

EVIDENCE SYNTHESIS

Evidence summary generated for each PICO question via systematic review of health effects plus:

- Resource use
- Feasibility
- Acceptability
- Equity
- Patient values and preferences

MAKING RECOMMENDATIONS

Recommendations made by guideline panel members based on evidence for all factors.

ASH guidelines are reviewed annually by expert work groups convened by ASH. Resources, such as this slide set, derived from guidelines that require updating are removed from the ASH website.

How patients and clinicians should use these recommendations

	STRONG Recommendation		CONDITIONAL Recommendation	
	"The panel recommends…"	"The panel recommends against…"	"The panel suggests…"	"The panel suggests against…"
				
For patients	Most individuals would want the intervention.		A majority would want the intervention, but many would not.	
For clinicians	Most individuals should receive the intervention.		Different choices will be appropriate for different patients, depending on their values and preferences. Use **shared decision making**.	

Objectives

By the end of this session, you should be able to

1. Determine the recommended initial treatment regimen for AYAs with Ph- B-ALL
2. Consider dosing, pre-medication strategies, and management of drug-related toxicity of PEG-Asparaginase
3. Recognize limits of data for newer agents for up front therapy of T-ALL/LL
4. Recognize optimal upfront and post-remission therapy for Ph+ B-ALL in AYA, including the role of CNS prophylaxis and HSCT

CASE 1

Philadelphia chromosome negative (Ph-) B-ALL

Case 1: Ph$^-$ B-ALL

A 19-year-old female presents with fevers, increased fatigue, bruising, and petechiae. CBC is notable for hyperleukocytosis with a WBC 150K/uL, anemia with a Hb 7g/dL, thrombocytopenia with platelets 25K/uL, and 85% blasts on the differential. Peripheral blood flow is consistent with B-ALL.

After performing a diagnostic bone marrow aspirate and biopsy and lumbar puncture with intrathecal chemotherapy, how would you treat this patient?

a. Pediatric-inspired (asparaginase containing) chemotherapy regimen
b. Non-asparaginase containing (adult) chemotherapy regimen
c. CAR-T cells
d. Immunotherapy with inotuzumab and blinatumomab

Recommendation

Recommendation	Strength	Evidence Certainty
Recommends pediatric-inspired (asparaginase-containing) chemotherapy regimens for AYAs with B-cell or T-cell acute lymphoblastic leukemia (B-ALL/T-ALL)/T-cell acute lymphoblastic lymphoma (T-LBL/LLy) receiving frontline therapy	Strong	Moderate

Rationale:

- Potential for improved event-free survival (EFS) and overall survival (OS) with pediatric compared to adult regimens.
- Very low certainty of evidence for improved OS, but **moderate confidence** that estimated improvement represents true effects.
- Although RCT data are limited, consistent comparative evidence in AYA populations strongly favors pediatric-inspired regimens, leading the panel to upgrade the certainty in the EtD framework to moderate.
- Benefits of pediatric regimens likely outweigh harms, despite limited evidence about toxicities and complications.
- Reviewed studies do not include ongoing trials incorporating immunotherapies into either pediatric or adult regimens.

Evidence

For AYA patients treated with pediatric (v. adult) regimens, evidence showed:

Supported by Tier 1 evidence, with a median age in the AYA range, including one RCT and additional prospective and retrospective comparative studies.

Overall Survival	• 7yr OS - HR=0.53, 95%CI 0.37-0.77
Event Free Survival	• 7yr EFS – HR=0.45, 95% CI: 0.33-0.63
2-year Relapse	• HR=0.74, 95%CI 0.4-1.3

Case 1 Continued

Your patient is receiving asparaginase as part of their upfront chemotherapy. Upon reading the drug information sheet, they noticed mention of an increased risk of blood clots.

What would you tell your patient about prophylactic anticoagulation or product repletion?

a. Venous thromboembolism (VTE) prophylaxis with cryoprecipitate repletion
b. VTE prophylaxis with low molecular weight heparin (LMWH) or direct oral anticoagulants (DOACs)
c. VTE prophylaxis with unfractionated heparin (UFH)
d. No prophylaxis with either cryoprecipitate or UFH

Recommendation

Recommendation	Strength	Evidence Certainty
Recommends against routine use of cryoprecipitate replacement (or fibrinogen concentrate) outside the context of active bleeding for AYAs with ALL receiving asparaginase-containing regimens.	Strong ✗	Very Low
Recommends against the routine use of unfractionated heparin (UFH) for venous thromboembolism (VTE) prophylaxis.	Strong ✗	Very Low
Evidence *is insufficient* to issue a recommendation for or against routine VTE prophylaxis with LMWH or DOACs.	NA	NA
Evidence is *insufficient* to issue a recommendation for or against routine AT replacement.	NA	NA

Remark (for this group of VTE prophylaxis with asparaginase recommendations):

- Uncertainty in the timing and duration of VTE prophylaxis (induction, consolidation, intensification), LMWH dosing, and AT replacement targets. They also highlight the importance of risk models to identify patients at high-risk for developing VTE.

Rationale

- Pediatric (asparaginase-containing) regimens can result in antithrombin (AT) deficiency and increased risk for VTE.
- A number of VTE prophylaxis interventions were considered including:
  - AT replacement (to various target thresholds)
  - cryoprecipitate / fresh frozen plasma (FFP) infusions
  - apixaban (a factor Xa inhibitor)
  - LMWH, and
  - UFH

Evidence

Across 14 studies reviewed, only 3 were randomized controlled trials (RCTs).

AT Replacement

AT replacement reduced VTE
- Pooled data from 3 studies, RR 0.57 (95% CI: 0.35-0.92)

FFP Replacement

No difference in VTE with FFP replacement compared to no prophylaxis
- 3 studies, RR 0.62 (95% CI: 0.12-3.32)

Cryoprecipitate Repletion

No significant difference in VTE with cryoprecipitate repletion vs. no prophylaxis in induction

LMWH

Enoxaparin (LMWH) reduced VTE compared to no prophylaxis
- 2 pooled studies, RR: 0.54 (95% CI: 0.36-0.83).
  - In one RCT, enoxaparin was superior to unfractionated heparin (UFH) for VTE prophylaxis, RR 0.37 (95% CI: 0.14-0.96).

Apixaban

In one RCT there was a **trend towards reduced risk of VTE with apixaban,** but this did not reach statistical significance.

Case 1 Continued

Your patient is in an MRD-negative remission, consulting Dr. Google about the utility of adding targeted therapies to their chemotherapy regimen.

What do you advise based on the best available evidence to date?

a. Add the CD22 monoclonal antibody inotuzumab ozogamicin

b. Add the CD19/CD3 bispecific T-cell engager (BiTE) blinatumomab

c. Do not add the chimeric anti-CD20 antibody rituximab

d. Proceed with allo-HSCT

Recommendation regarding Blinatumomab

Recommendation	Strength	Evidence Certainty
Suggests the addition of blinatumomab for AYAs with B-ALL who achieve morphologic remission, regardless of MRD status	Conditional 	Very Low

- **Remarks:**
  - The panel recognizes there are limited data using blinatumomab within conventional pediatric-inspired (asparaginase-containing) chemotherapy backbones in AYAs.
  - The panel further recognizes the evolution of evidence in this space, and that the recommendation may change with the availability of more data.
  - Guidance for individuals with MRD persistence is addressed separately.

Rationale

Benefits/Desirable effects

Improvement in RFS and OS with blinatumomab + chemotherapy backbone.

Toxicities include cytokine release syndrome, neurotoxicity, and the development of hypogammaglobulinemia.

While toxicities are manageable, blinatumomab can be associated with increased cost, need for hospitalization for its initiation, requirement for a 4-week infusion, and potentially an increased overall duration of therapy.

Harms/Undesirable effects

Lack of prospective RCT data in AYAs with conventional pediatric chemotherapy backbones.

Evidence

Very Low certainty of evidence supporting blinatumomab

Two comparative studies:

Overall Survival

3.5-year superior OS: HR=0.16, 95%CI, 0.05-0.47
- MRD-negative patients

Disease-Free Survival

3.5-year lower hazard of relapse/death; HR=0.53, 95%CI, 0.32-0.87
- MRD-negative patients

Relapse Free Survival

AYA subset (n=22, 18-39 years)
- 3-year RFS: 77%, OS: 86%
- MRD-negative and MRD-positive patients

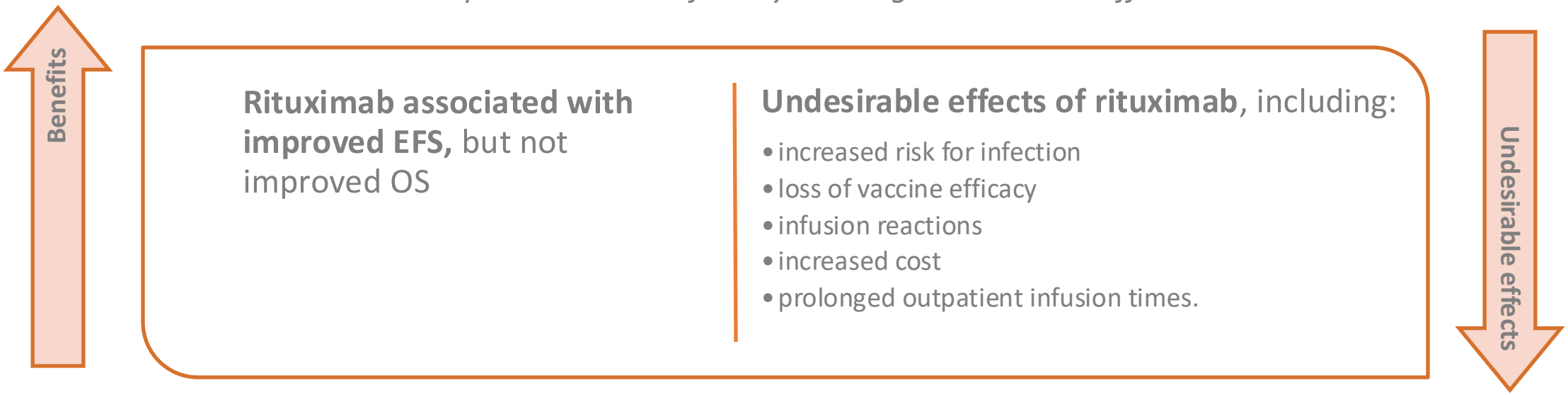
Recommendation regarding Rituximab

Recommendation	Strength	Evidence Certainty
Suggests the addition of rituximab to standard chemotherapy for AYAs with CD20-positive B-ALL receiving frontline therapy	Conditional 	Very Low

- **Remark:** Considerable uncertainty associated with rituximab dosing frequency and timing of administration, the minimum required level of CD20 expression, and the lack of data specific to younger AYA individuals.

Rationale

Potential improved EFS benefit may outweigh undesirable effects



Uncertainty of results due to differences in study designs of two clinical trials (UKALL14 and GRAALL-2005), including dosing and timing of rituximab administration and level of CD20 expression of enrolled patients

Evidence

Event Free Survival

One RCT showed improvement in EFS with addition of rituximab to chemotherapy in CD20-positive B-ALL patients

HR 0.66 (95% CI 0.45-0.98).

Second RCT did not show same benefit

HR 0.89 (95% CI 0.68-1.15).

Overall Survival

Neither study showed OS benefit

Lower hazard of death following allo-HSCT in CR1 in patients who received pre-HSCT rituximab

Differences in the study designs and patient population age (lack of data specific to younger AYAs) contribute to the uncertainty of the results.

Recommendation regarding Inotuzumab ozogamicin

Recommendation	Strength	Evidence Certainty
No recommendation Evidence is insufficient to issue a recommendation for or against the addition of inotuzumab ozogamicin for AYAs with B-ALL receiving frontline therapy.	NA	NA

Case 1 Continued

Now consider if the patient has achieved remission but remains MRD-positive after at least three cycles of intensive therapy.

What is the best strategy for patients on upfront treatment who are found to have measurable minimal disease after at least 3 cycles of therapy?

a. Change consolidation approach to include immunotherapy or HSCT
b. Complete all planned consolidation chemotherapy and check MRD again
c. Complete another 2 cycles of consolidation and check MRD again
d. Change consolidation from low intensity to high intensity chemotherapy

Recommendation

Recommendation	Strength	Evidence Certainty
For patients with B-ALL with persistent MRD after ≥3 months of frontline therapy (induction plus a minimum of one block of post-remission therapy), the panel ***recommends*** a change in approach to treatment.	Strong	Very low

Remarks:

- The change in therapy could include several approaches including immunotherapy or allogeneic transplant (allo-HSCT). The optimal timing, choice of intervention(s), order, or combination of these approaches has not been defined.
- While T-ALL has not been studied individually, patients with T-ALL were included in the studies demonstrating the benefit of transplant for patients with MRD-positivity.

Good Practice Statement. Measurement of disease response using MRD is considered standard of care in AYA ALL for both prognostic value and, in some cases, determination of treatment intensity.

Rationale

- In MRD-positive patients:

Blinatumomab	HSCT
Blinatumomab associated with improved RFS and attainment of HSCT compared to no blinatumomab (no statistically significant OS benefit)	HSCT is associated with improved OS and RFS compared to no transplant

- Need to escalate/change therapy from standard chemotherapy in MRD-positive
  - Duration of persistent MRD-positive to warrant escalation and optimal approach remain uncertain

Evidence

Studies stratified by MRD status; 4 focusing on MRD(+) included in meta-analysis

- 1 comparative study on blinatumomab (additional single arm studies)
- 3 comparative studies on HSCT (additional single arm studies)
- Certainty of evidence very low due minimal comparative evidence and indirectness

Outcome	Blinatumumab	No Blina	Absolute effect	Relative effect
Overall survival	49/79 (62%)	84/175 (48%)	127 more per 1,000	RR 0.68 (0.42 – 1.09)
Relapse free survival	41/79 (51.9%)	51/175 (29.1%)	269 more per 1,000	RR 0.47 (0.30 – 0.73)

Outcome	HSCT	No HSCT	Absolute effect	Relative effect
Overall survival	67/110 (60.9%)	62/162 (38.3%)	118 more per 1,000	RR 0.40 (0.25 – 0.64)
Relapse free survival	36/69 (52.2%)	11/58 (19.0%)	316 more per 1,000	RR 0.41 (0.26 – 0.66)

Other considerations

- Recommendations based on survival outcomes with very limited evidence of long-term impact of these therapies on QOL
- There are substantial costs and resources implications associated with access to frequent MRD assessment and subsequent therapies on the basis of MRD status

CASE 2

Frontline use of Asparaginase and toxicity management

Background

AYA individuals with B- and T- ALL are strongly recommended to be managed with frontline pediatric (asparaginase-containing) regimens

Asparaginase dosing, dose capping and dose adjustment are important clinical considerations given challenges posed with asparaginase use

The therapeutic efficacy of asparaginase needs to be balanced against the risks and asparaginase associated complications in a given individual

Case 2: Asparaginase

A 22 year-old male presents with mediastinal lymphadenopathy and circulating peripheral lymphoblasts. Diagnostic workup confirms T-cell acute lymphoblastic leukemia. He has no significant past medical history and normal baseline liver function tests. He is planned to commence a pediatric-inspired AYA ALL protocol. His body surface area is calculated at 2.3 m^2.

What is the most appropriate initial peg-asparaginase dosing strategy for this patient?

a. Standard dosing at 2500IU/m2

b. Reduced dosing at 2000IU/m2

c. Dose capping at 3750 IU

d. Monitor asparaginase activity and adjust

Recommendation

Recommendation	Strength	Evidence Certainty
Suggests that empiric dose capping and dose reductions are reasonable strategies to mitigate asparaginase-induced toxicities without evidence of adversely impacting disease outcomes.	Conditional	Very Low

Remarks:

Dose Capping

Maximum PEG-asparaginase dose of 3750 international units (IU)

Dose Reduction

Any weight-based dose:

-below 2500 IU/m2 for individuals <22 years of age, or

-below 2000 IU/m2 for individuals > 22 years of age

Good Practice Statement: Use therapeutic drug monitoring (TDM) to ensure adequate asparagine depletion when dose capping and dose reductions are undertaken. TDM should also be utilized in the context of pre-medication to determine if hypersensitivity reactions are associated with antibody-mediated inactivation (i.e., undetectable Nadir Serum Asparaginase Activity (NSAA) levels) or to identify silent inactivation.

Rationale

- Dose capping and dose reduction (as low as 1000 IU/m2) are reasonable strategies to mitigate asparaginase-induced toxicities in AYAs without evidence of adversely impacting disease outcomes.
  - May help mitigate toxicities in AYA patients, especially in older AYAs and those with obesity, diabetes or underlying liver disease
- Available data are sparse and complicated by historic controls with differences in adverse event reporting between studies.

Evidence

9 comparative studies identified, of which 5 directly related to AYAs

Survival

- Lower doses of PEG-asp achieve therapeutic asparaginase activity levels and asparagine depletion
- No significant difference in survival outcomes between...
  - Low dose PEG-asp (1000 IU/m2)
  - Dose capped PEG-asp (3750 IU) or
  - Uncapped dose PEG-asp (2500 IU/m2)

Toxicity

- Dose capping (median 3750 IU) associated with a trend towards less hepatotoxicity, pancreatitis, and thrombosis
- Direct impact of lower dosing and dose capping on reduction in toxicity was difficult to determine, given limitations of available studies.

Case 2 continued

Following the decision to use lower PEG-asparaginase dosing, the pharmacist next asks the team for their choice of premedication prior to each PEG-asparaginase dose.

Which premedication approach is recommended?

a. No premedication
b. Antihistamines alone
c. Acetaminophen with antihistamines
d. IV steroids plus antihistamines plus acetaminophen

Recommendation

Recommendation	Strength	Evidence Certainty
Recommends the use of prophylactic premedication to prevent hypersensitivity reactions.	Strong	Very Low

Rationale

- IV steroid premedication is well tolerated
- Prevents hypersensitivity reactions to PEG-asparaginase
- Low risk of harm
- potential significant clinical and economic benefit, including potentially mitigating the need to switch to alternate formulations

Remark:

IV steroid at a minimum and may also include antihistamines and/or acetaminophen

Evidence

6 comparative, mostly retrospective, non-randomized studies of premedication with steroids

Hypersensitivity Reactions

Meta-analysis including all studies showed **reduced risk of hypersensitivity reactions** (overall RR=0.24, 95%CI, 0.10-0.58).

Drug Cost Savings

Reduces need to switch to Erwinia-based asparaginase (RR=0.40, 95%CI, 0.27-0.59)

- Results in drug cost savings

Silent Inactivation

Limited data addressing risk of silent inactivation and effect on serum asparaginase activity levels

Case 2 continued: Managing toxicity

After the third PEG-asparaginase dose, the patient develops hyperlipidemia and elevated serum lipase (3 X ULN), although no clinical pancreatitis was evident. Other than these recent derangements, they had been tolerating the pediatric PEG-asparaginase containing regimen including supportive measures.

After treatment of the hyperlipidemia and normalization of the serum lipase, what is the appropriate next step in the patient's management with regard to PEG-asparaginase?

a. Permanently discontinue asparaginase
b. Hold PEG-asparaginase for one dose and rechallenge
c. Continue PEG-asparaginase at a reduced dose
d. Switch to a different formulation of asparaginase
e. Individual risk stratification and patient informed decision given lack of clear evidence

Recommendation

Recommendation	Strength	Evidence Certainty
No recommendation For non-hypersensitivity asparaginase related toxicity there was insufficient evidence to make a formal recommendation on the optimal strategy for resumption of asparaginase therapy	NA	NA

- Insufficient evidence to guide resumption of asparaginase following non-hypersensitivity complications

- Decision for continuation/resumption of asparaginase of must be individualized based on:
  - severity of toxicity
  - risk-benefit assessment, and
  - alternate therapy options

Case 2 continued: Alternate asaparaginase formulations

Two minutes into the fourth PEG-asparaginase dose, the patient develops hives, coughing, and vomits. He improves after one dose of sub-cutaneous epinephrine.

What is the appropriate next step in the patient's management with regard to PEG-asparaginase?

a. Permanently discontinue asparaginase
b. Hold PEG-asparaginase for one dose and rechallenge with a desensitization protoc
c. Continue PEG-asparaginase at a reduced dose
d. Switch to an erwinia asparaginase formulation
e. Individual risk stratification and patient informed decision given lack of clear evidence

Recommendation

Recommendation	Strength	Evidence Certainty
Recommends that patients switch to an Erwinia-based asparaginase formulation over discontinuation of asparaginase therapy	Strong	Very Low

Remarks

- The panel was unable to provide a recommendation related to desensitization due to the lack of evidence comparing effects of desensitization versus alternative asparaginase products.
- The ASH guideline panel concluded that the benefits, such as improved survival and disease control, outweighed the drawbacks, including the high costs and resources for Erwinia-based treatments.

No recommendation related to desensitization due to the lack of evidence comparing effects of desensitization versus alternative asparaginase products

Evidence

Reviewed seven studies:

Survival

- Failure to receive all peg-asparaginase doses associated with inferior DFS (HR=1.5, 95%CI, 1.1-1.9, p=0.002)
- Substitution with Erwinia mitigates inferior DFS (HR=1.1, 95% 0.8-1.7)

CASE 3

T-cell acute lymphoblastic leukemia (T-ALL)/lymphoma (T-LBL/LLy)

Case 3a: T-LBL/LLy

A 31-year old male presented with increased shortness of breath and mediastinal mass. Subsequent work up confirmed T-cell lymphoblastic lymphoma. Bone marrow was not involved by T-LBL. Lumbar puncture prior to start of treatment did not demonstrate any evidence for malignancy. He is planned to start a pediatric-inspired AYA ALL protocol.

What additional agents or dosing strategies should NOT be used as part of the pediatric inspired backbone?

a. Capizzi methotrexate

b. Bortezomib

c. Prophylactic intrathecal therapy

d. Nelarabine

Case 3b: T-ALL

A 31-year old male presented with increased shortness of breath and mediastinal mass. Subsequent work up confirmed T-cell lymphoblastic leukemia with bone marrow involvement of ~50%. Lumbar puncture prior to start of treatment did not demonstrate any evidence for malignancy and he was started on an intensive pediatric inspired regimen containing asparaginase and unfortunately developed severe pancreatitis. It was decided that he could no longer receive asparaginase and interim maintenance was planned with high dose methotrexate.

What additional agents should be strongly considered with a pediatric inspired backbone when high dose methotrexate is used?

a. Nelarabine

b. Bortezomib

c. Prophylactic intrathecal therapy

d. Venetoclax

Recommendation for AYAs with T-Acute Lymphoblastic Leukemia (ALL)

Recommendation	Strength	Evidence Certainty
Suggests against the addition of bortezomib for AYAs with T-ALL, due to insufficient evidence demonstrating efficacy for bortezomib in these patients.	Conditional 	Very low
Evidence was insufficient to make a recommendation for or against the addition of nelarabine for AYAs with T-ALL receiving frontline therapy with all planned doses of asparaginase (including Capizzi methotrexate based interim maintenance)	NA	NA

- Excellent outcomes were demonstrated when using a pediatric regimen with Capizzi methotrexate was used as interim maintenance with/without nelarabine.
- A recommendation was not made for or against the addition of nelarabine. Incorporating nelarabine may provide benefit among subgroups of AYAs including those with non-ETP subtype, CNS3 disease, and/or others who receive a high-dose methotrexate-based interim maintenance regimen.
- Nelarabine appeared to be of greatest benefit for those who received high dose methotrexate as interim maintenance. Available data are very limited.

Recommendation for AYAs with T-Lymphoblastic Lymphoma (T-LBL/LLy)

Recommendation	Strength	Evidence Certainty
Suggests against the addition of nelarabine for AYAs with T-LBL/LLy, due to insufficient evidence demonstrating efficacy for nelarabine in these patients.	Conditional 	Very low
Evidence was insufficient to make a recommendation for or against the addition of bortezomib for AYAs with T-LBL/LLy.	NA	NA

- Excellent outcomes were demonstrated with CMTX and no routine use of prophylactic cranial radiation for most T-LBL/LLy.
- A recommendation was not made for or against the addition of bortezomib. The panel noted that incorporating bortezomib may provide benefit amongst the youngest adolescents of the AYA population. Available data are limited.

Evidence - Nelarabine

T-ALL

- Significant 5y DFS benefit for those randomized to nelarabine (RR=1.07, 95%CI, 1.01-1.15)
  - No OS benefit
  - AYA group DFS benefit not maintained (survival ratio 0.96, 95%CI, 0.67-1.39, p=0.81)
- The benefit of nelarabine for CNS3 disease was hard to distinguish.
  - Those receiving Interim maintenance with HD-MTX may benefit from the addition of nelarabine

T-LBL/LLy

- No OS or DFS benefit with addition of nelarabine

Evidence - Bortezomib

T-ALL

- No statistically significant OS or DFS benefit with addition of bortezomib
- Suggest against addition of bortezomib in T-ALL

T-LBL/LLy

- Improved EFS (RR=1.12, 95C%CI, 1.01-1.27) and OS (RR=1.13, 95%CI, 1.03-1.24) with bortezomib
- No panel recommendation for or against bortezomib for AYAs
  - Only ~20% of patients >16 years.
  - Possible benefit in the youngest adolescents.

CASE 4

Philadelphia chromosome-positive (Ph-pos) ALL

Case 4: Ph-positive B-Cell ALL

A 32-year-old male with no PMH presents to the ER with 1-week exertional dyspnea and fatigue. WBC 6.1 K/uL, Hgb 9.5 g/dL, platelets 89 K/uL. Peripheral smear shows ~50% blasts. Peripheral blood flow cytometry confirms 53% blasts, which are CD34+, CD10+, CD19+, TdT+; sCD22+(dim), CD20-negative. FISH positive for t(9;22) and negative for KMT2A. Bone marrow exam confirms diagnosis of precursor B-cell ALL and RT-PCR of aspirate was positive for the presence of BCR::ABL, coding a 210-kDa protein. There were no other cytogenetic alterations. You are called to guide the patient's therapy.

Which of the following upfront regimen would you recommend in combination with a TKI to induce remission?

a. ASNase-containing intensive regimen

b. Intensive chemotherapy regimen without ASNase

c. Lower (reduced) intensity chemotherapy regimen

d. Steroids only

Recommendation

Recommendation	Strength	Evidence Certainty
Suggests reduced-intensity therapy with TKI for remission induction over intensive chemotherapy with TKI. This should be followed by post-remission therapy which could include intensive chemotherapy with TKI or immunotherapy with TKI, either of which be consolidated by allogeneic hematopoietic stem cell transplant (allo-HSCT) in first complete remission (CR1).	Conditional	Very low

- All patients must receive CNS prophylaxis with concurrent IT chemotherapy
- Post-remission therapies, including allo-HSCT, are evolving given emerging data with next-generation TKIs and novel/targeted immunotherapy
- May not be as applicable to the youngest AYA subgroup in which pediatric-inspired (asparaginase-containing) regimens would be applied; studies of pediatric-inspired backbones were not captured within the available dataset.

Rationale

- Evidence suggests that, compared to intensive chemotherapy with TKI, reduced intensity therapy regimens with TKI are:
  - Not inferior to induce remission
  - Not associated with increased early relapse
  - Associated with improved survival and decreased early mortality
  - Linked to reduced high-grade adverse events, including fewer infections

Evidence

- 25 studies (3 comparative studies and 22 non-comparative single group)
  - 3 studies* directly compared reduced intensity chemo + TKI vs. intense chemo + TKI and were included in the meta-analysis (only 1 was an RCT)
  - No studies included asparaginase-containing pediatric-inspired regimens
  - Certainty was very low and evidence was indirect

Outcome	Difference (TKI + Reduced vs. Intense)	Relative effect (95% CI)
Death during induction	60 fewer per 1,000	RR 0.11 (0.01 – 0.85)
Death up to 60 days	68 fewer per 1,000	RR 0.25 (0.07 – 0.85)
Event free survival	253 more per 1,000	RR 1.69 (1.14 – 2.51)

Other considerations

- The recommendation focuses on induction with TKIs and consolidation with novel targeted immunotherapies and transplant
  - There are cost/resource implications associated with specific TKI generations, access to optimal post-remission therapies (including immunotherapy), and access to allogeneic HSCT when required
- Patient acceptance and adherence to TKI therapy is multifactorial, potentially affecting decisions about complexity of chemotherapy treatment protocols

Case 4 continues: Ph-positive B-Cell ALL

The patient's treatment regimen is changed and he received consolidation therapy with blinatumomab. After 2 cycles, an MRD(-) status is achieved with no detectable measurable residual disease analysis in bone marrow aspirate by multiparameter flow cytometry (0.0000%), BCR::ABL1 RT-PCR (0/10,000), or DNA sequencing of the dominant clone (10^{-6}). You are asked about future steps in his treatment.

The patient has a 10/10 matched sibling donor available. What is the best next step in the treatment course?

a. Immediate HSCT in CR1

b. Stop all therapy and monitor with sequential MRD assessment

c. Complete appropriate consolidation therapy and continue TKI

d. Stop consolidation and switch to maintenance regimen

Recommendation

Recommendation	Strength	Evidence Certainty
For patients receiving appropriate frontline therapy and in first complete remission (CR1), the panel ***suggests against*** routinely proceeding with allogeneic hematopoietic stem cell transplantation (allo-HSCT) as consolidation.	Conditional 	Very low

Rationale

Potential improved RFS does not outweigh associated decrease in OS stemming from transplant related mortality

- Little data on subgroups that could benefit from upfront HSCT, including MRD(+) and high-risk biology patients
- Relative effects favor no HSCT for most AYA ALL patients

Remark: For specific high-risk subgroups (especially those with minimal residual disease [MRD] persistence, induction failure, high-risk biologic subsets), there may be a survival benefit from allo-HSCT in CR1.

Evidence

- The panel included 6 comparative studies of upfront HSCT vs. chemotherapy alone in the meta-analysis
  - 3 comparative study based on registry data
  - Most comparative studies focused on pediatric-inspired regimens
  - Certainty of evidence was very low due to the paucity of studies, some of which included registry data

Outcome	HSCT	No HSCT	Absolute effect	Relative effect (95% CI)
Overall survival	115/217 (53.0%)	203/263 (77.2%)	239 fewer per 1,000	RR 0.69 (0.60 – 0.79)
Relapse free survival	836 per 1,000	193 per 1,000	193 more per 1,000	RR 1.30 (1.15 – 1.46)
Cumulative relapse	320 per 1,000	237 per 1,000	83 fewer per 1,000	RR 0.74 (0.40 – 1.35)

CASE 5

CNS Prophylaxis

Case 5: CNS Prophylaxis

A 21yo patient with Ph-negative B-ALL undergoes an initial lumbar puncture which shows clear and colorless CSF, normal opening pressure, 42 mg/100 ml of protein, 80 mg/100 ml glucose, WBC of 4 cells/uL and no RBCs. CSF cytology shows absence of identifiable B lymphoblasts and flow cytometry does not yield results (hypocellular). CNS 1 status is determined. You are asked to guide the CNS prophylaxis.

What is the CNS prophylaxis regimen you recommend for this patient?

a. Cranial irradiation
b. High dose IV methotrexate
c. IT methotrexate +/- hydrocortisone
d. Triple IT therapy
e. C or D

Recommendation

Recommendation	Strength	Evidence Certainty
Suggests the use of either intrathecal (IT) methotrexate or triple intrathecal therapy (TIT) for CNS prophylaxis for AYA patients receiving frontline therapy.	Conditional	Very low

Rationale

- No demonstrated improvement in OS or EFS with triple IT therapy vs. single IT dosing
- Decrease in CNS relapse with triple therapy in older and heterogeneous studies, but with higher mortality from systemic relapses
- No significant difference in encephalopathy, neurotoxicity, or CNS toxicity outcomes (though minimal data on neurocognitive function)
- While no clear advantage, there is no evidence of risks and AEs
- Available data did not favor either intervention

Remark:
Hydrocortisone can be used (in conjunction with IT methotrexate) for prevention of chemical arachnoiditis

Evidence

- Of all reviewed studies, only 2 RCTs and one secondary analysis were included in the meta-analysis:
  - Very few data exist on long term neurocognitive outcomes
  - Certainty was very low or low due to indirectness and imprecision

Outcome	Triple IT therapy	Single IT Methotrexate	Absolute effect	Relative effect (95% CI)
Overall survival	1748/1875 (93.2%)	1797/1886 (95.3%)	19 fewer per 1,000	RR 0.98 (0.94 – 1.03)
Disease free survival	785/866 (90.6%)	809/868 (93.2%)	28 fewer per 1,000	RR 0.97 (0.71 – 1.33)
Isolated CNS relapse	43/1875 (2.3%)	75/1886 (4.0%)	17 fewer per 1,000	RR 0.58 (0.40 – 0.83)

Recommendation

Recommendation	Strength	Evidence Certainty
Suggests against the routine use of cranial radiation for CNS prophylaxis for patients treated on a pediatric-inspired (asparaginase-containing) backbone.	Conditional ⊗	Very low

Rationale

- Evidence did not demonstrate improvement in OS or EFS with cranial radiation for CNS prophylaxis compared to no radiation
- Several studies with longer follow-up terms identified worse cognitive outcomes with radiation
  - Perceptual processing, neuromotor abilities, vocabulary, visual learning, attention, visuomotor accuracy, visuospatial memory, academic impairment

Remark:
There is uncertainty with respect to the use of cranial radiation for CNS prophylaxis for AYA individuals with T-ALL who are unable to receive nelarabine.

Evidence

- 14 comparatives studies were reviewed, with 2 RCTs included in meta-analysis:
  - Certainty was very low or low due to risk of bias, indirectness and imprecision

Outcome	Triple IT therapy	Single IT Methotrexate	Absolute effect	Relative effect (95% CI)
Overall survival	853/1296 (65.8%)	477/867 (69.4%)	12 more per 1,000	RR 1.01 (0.97 – 1.07)
Event free survival	783/1296 (60.4%)	399/867 (58.1%)	13 fewer per 1,000	RR 0.98 (0.88 – 1.01)

Other considerations

Neurocognitive Function	Neurocognitive function was not found to be meaningfully different between treatment arms in triple vs. single IT therapy comparison
Sedation/Anesthesia	The consequences of sedation/anesthesia needed for CNS prophylaxis in younger AYAs were not captured
Arachnoiditis	Arachnoiditis as an AE of IT therapy is recognized, and addition of hydrocortisone is a reasonable long-standing practice
Toxicity	Current radiation doses and protocols may result in different toxicity rates than documented in older studies

Most studies on prophylactic cranial radiation have been conducted in children

Other considerations

- Access to care, cost, and system resource implications play an important role, posing a realistic challenge to the optimal care of AYAs with ALL across all practice settings.
- Treating AYAs with ALL involves consideration of their unique vulnerabilities, developmental stage and needs, and interface with the health system.
  - Delivering AYA cancer care requires a comprehensive approach.

In Summary: Back to our Objectives

1. Determine the recommended initial treatment regimen for AYAs with Ph- B-ALL
2. Consider dosing, pre-medication strategies, and management of drug-related toxicity of PEG-Asparaginase
3. Recognize limits of data for newer agents for up front therapy of T-ALL/LL
4. Recognize optimal upfront and post-remission therapy for Ph+ B-ALL in AYA, including the role of CNS prophylaxis and HSCT

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- See more about the **ASH ALL in AYAs** guidelines: hematology.org/ALLguidelines