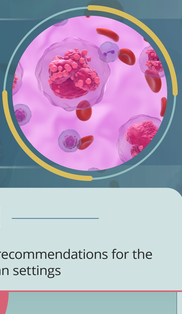
Choice of Therapy in R/R B-cell ALL: Optimal vs. Real-World Practice



Objective

To develop evidence-based practical consensus recommendations for the management of B cell ALL in Indian settings

Methodology

The Delphi method: A robust method to collect real-world knowledge from a small panel of experts to form a consensus

Panel selection
- 15 members, including a chairperson
- Based on academic and clinical track record

Evidence review
- Based on literature review (Jan 2001-Sept 2022)
- Panel surveyed on
  - diagnosis and risk assessment
  - Frontline therapy
  - Choice of therapy in R/R setting

Delphi consensus (round 1)
- Consensus categorized as
  - High (≥80%)
  - Moderate (60-79%)
  - No consensus (<60%)

Discussion rounds 2 & 3
- Any gaps or revisions to recommendations were addressed

Finalization of recommendations

Choosing the right therapy for R/R B-cell ALL

Consensus/recommendations on prognostic factors:

Early vs. late relapse

» Experts used the BFM study group definition of "early" and "late" relapse in their clinical practice (high consensus). The BFM group study categorized time to relapse or length of first CR as follows:
- Very early relapse (< 18 months from diagnosis)
- Early relapse (> 18 months from diagnosis and < 6 months after frontline therapy) and
- Late relapse (> 6 months after frontline therapy)

Key factors for CR and survival:

Response to salvage therapy (high consensus) and performance of allo-HCT (moderate consensus)

Other considerations

Age, time to relapse, pre-transplant MRD negativity, donor availability and type.

Important considerations

Choice of therapy for R/R Ph+ or Ph− B-ALL patients in the first relapse

Optimal choice

Recommendations

High Consensus

» Use of immunotherapy agents (InO or blinatumomab) followed by allo-HCT for R/R Ph+ or Ph- B-ALL patients in the first relapse.

» Addition of TKI should always be considered for Ph+ B-ALL patients.

» The treatment approach remains the same for early and late relapse (medullary and extramedullary).

» Important determinants for allo-HCT include:
- Donor availability
- Comorbidities
- Depth of remission
- Social support

» Immunotherapy, particularly InO, is the preferred therapy for best outcomes in the first salvage.

» In patients with residual disease, alternative treatment approaches such as immunotherapies can enhance treatment outcomes.

» MRD negativity has a significant impact on transplant outcomes.

» Choice of agents to achieve MDR negativity: InO or blinatumomab.

» Monitoring liver enzymes is essential during treatment with InO

» The ideal period from the last dose of InO before proceeding with a transplant can be between 4-6 weeks. It is important to achieve a balance between preventing VOD and the risk of relapse.

» Conventional maintenance therapy for two years, in patients with relapse, after six cycles of InO, if no transplant.

Moderate Consensus

» Treatment with InO before transplant is associated with both improved CR and MRD negativity.

» Concurrent use of InO with intrathecal chemotherapy for R/R B-ALL patients with systemic relapse and CNS disease.

Real-world choice

Recommendations

High Consensus

» Use of standard-intensive chemotherapy (with TKI for Ph+ patients) followed by transplant.

» For late relapse, risk stratification and considerations for transplant would depend upon the protocol.

Choice of therapy for R/R Ph+ or Ph− B-ALL patients in second and subsequent relapse

Optimal choice

Recommendations

High Consensus

» CAR-T therapy is preferred if available in clinical trial settings. Palliative care is to be considered in the absence of CAR-T therapy. This is assuming that immunotherapy has already been used in the first relapse.

» Treatment approach remains the same for early and late relapse (medullary and extramedullary).

Real-world choice

Recommendations

No Consensus

» Early isolated medullary relapse: responses split between palliative care and immunotherapy (InO/blinatumomab) followed by allo-HCT.

» Early isolated extramedullary relapse: responses split between palliative care and TKI (if Ph+) and/or chemotherapy followed by allo-HCT.

» Late relapse (isolated medullary and extramedullary): responses split among palliative care; TKI (if Ph+) and/or standard-intensive chemotherapy followed by allo-HCT; TKI (if Ph+) and/or standard-intensive chemotherapy; immunotherapy (InO/blinatumomab) followed by allo-HCT.

Isolated testicular relapse treatment

Recommendations

High Consensus

» Isolated testicular relapse is not treated differently from other relapse if it is an early relapse.

Choice of treatment for R/R B-ALL patients with high disease burden

Optimal choice

Recommendations

High Consensus

» InO in adult patients with BMB percentage ≥50%

Real-world choice

Recommendations

High Consensus

» Standard-intensive chemotherapy (with TKI if Ph+)

Key takeaways

- Use of immunotherapy agents followed by allo-HCT is the optimal choice of therapy for R/R Ph+ or Ph− B-ALL patients in the first relapse.
- The ideal period from the last dose of Inotuzumab before proceeding with a transplant can be between 4 and 6 weeks. It is important to achieve a balance between preventing VOD and the risk of relapse.
- In patients with persistent residual disease, alternative treatment approaches such as Inotuzumab can enhance treatment outcomes.
- Concurrent use of Inotuzumab with intrathecal chemotherapy is recommended for R/R B-ALL patients with systemic relapse and CNS disease.

Abbreviations:
ALL: Acute lymphoblastic leukemia; **Allo-HCT:** Allogeneic hematopoietic cell transplantation; **Blina:** Blinatumomab; **BMB:** Bone marrow blast; **CNS:** Central nervous system; **CAR-T:** Chimeric antigen receptor T-cell; **CR:** Complete remission; **InO:** Inotuzumab; **MRD:** Minimal residual disease; **Ph+:** Philadelphia chromosome positive; **Ph−:** Philadelphia chromosome negative; **R/R:** Relapsed/ refractory; **TKI:** Tyrosine kinase inhibitor; **VOD:** Veno-occlusive disease

Reference:
1. Mathews V, Konula A, Chokropani A, Bhurani D, Bhattacharyya J, Sengar M, Malhotra P, Boyalla PK, Singh PK, Ganesan P, Dhawan R. Management of B-cell lineage acute lymphoblastic leukemia: expert opinion from an Indian panel via Delphi consensus method. Frontiers in Oncology. 2023 Apr 24;13:1175858.e

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