Gilteritinib-Based Salvage and Donor Lymphocyte Infusions in Multiply Relapsed APL with *FLT3-ITD*: A Case-Based Strategy for Post-Transplant Relapse

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Introduction

- Acute promyelocytic leukemia (APL) is defined by the **PML-RARA fusion** and is highly curable with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO).
- **FLT3-ITD mutations** are uncommon in APL but confer a higher risk of relapse.
- Relapse after hematopoietic cell transplantation (HCT) is rare and lacks well-defined management strategies.
- **Donor lymphocyte infusion (DLI)** is infrequently employed in APL due to low tumor immunogenicity and rarity of the disease.
- Use of **FLT3 inhibitors** in APL relapse has not been systematically described.

Objectives

- To describe a case of multiply relapsed FLT3-ITD APL refractory to standard salvage approaches.
- To report the use of **DLI in combination with gilteritinib** following allogeneic HCT.
- To discuss potential therapeutic implications of combining **FLT3 inhibition with immunotherapeutic augmentation**.

Case Presentation

- **Patient:** 51-year-old female diagnosed in November 2021 with APL and two FLT3-ITD mutations (variant allele frequencies: 8.8% and 12.5%).
- **Initial therapy:** ATRA/ATO per Lo-Coco protocol; achieved complete molecular remission (CMR); consolidation completed August 2022.
- **Relapse #1 (March 2023):** Treated with ATRA/ATO and idarubicin; underwent autologous HCT in August 2023 in CMR2.
- **Relapse #2 (January 2024, Day +154 post-auto):** Bone marrow with 30% blasts and 52% donor chimerism; treated with ATRA/ATO and gemtuzumab ozogamicin (GO); underwent mismatched unrelated allogeneic HCT in August 2024.
- **Relapse #3 (December 2024, Day +95 post-allo):** Salvaged again with ATRA/ATO and GO.
- **January 2025:** Initiated DLI with concurrent low-dose ATRA, 6-mercaptopurine, and methotrexate.
- **February 2025:** Gilteritinib introduced and later dose-adjusted for hepatotoxicity.
- Patient subsequently received three DLIs, maintained full donor chimerism, and developed no graft-versus-host disease (GVHD).

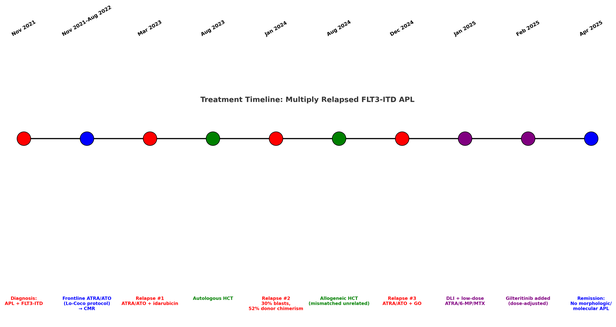


Figure 2. Treatment timeline.
Course of multiply relapsed FLT3-ITD APL showing diagnosis, frontline ATRA/ATO, three relapses with autologous and allogeneic HCT, and sustained molecular remission after DLI plus gilteritinib.

Results

- Achieved and sustained **molecular remission** on combined therapy.
- **Serial molecular monitoring:** PCR and next-generation sequencing demonstrated absence of PML-RARA.
- **Bone marrow (April 24, 2025):** No morphologic or molecular evidence of APL; confirmed full donor chimerism.
- **Safety:** Therapy was well tolerated; hepatotoxicity was manageable; no GVHD flare.

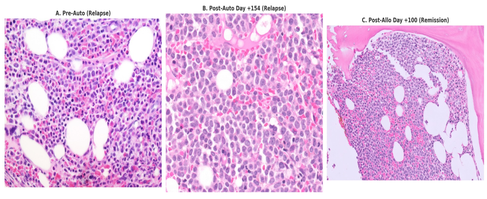


Figure 1. Bone marrow histopathology at key disease stages.
(A) Pre-autologous HCT relapse: hypercellular marrow with sheets of abnormal promyelocytes consistent with recurrent APL.
(B) Day +154 post-autologous HCT: marrow with ~30% blasts and partial donor chimerism, confirming relapsed APL.
(C) Day +100 post-allogeneic HCT following DLI and gilteritinib: normocellular marrow with trilineage hematopoiesis and no morphologic evidence of APL.

Discussion

- **FLT3-ITD APL** may be associated with increased relapse risk and adverse outcomes.
- Relapse following allogeneic HCT in APL is rare and associated with poor prognosis.
- **DLI alone** is typically ineffective due to limited graft-versus-leukemia effect in APL.
- **FLT3 inhibition with gilteritinib** is FDA approved for relapsed FLT3-mutated AML
- The combination of DLI and gilteritinib in this case:
  - Produced complete molecular remission.
  - Was well tolerated, without GVHD.
  - Suggests a synergistic effect between targeted inhibition and immune augmentation.
- This strategy may provide a rational salvage pathway for patients with high-risk, relapsed APL.

Conclusion

- This is the **first reported case** of multiply relapsed FLT3-ITD APL salvaged with DLI and gilteritinib.
- Therapy achieved **molecular remission** with excellent tolerability and no GVHD.
- Findings suggest feasibility of integrating **FLT3 inhibition with DLI** as a novel salvage approach.
- Further investigation and longer-term follow-up are needed to evaluate durability and broader applicability.

References

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