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Case Report

Secondary B-Cell Acute Lymphoblastic Leukemia Following Multimodal Therapy for Diffuse Large B- Cell mphoma: A Case Report and Literature Review

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Abstract

Secondary acute lymphoblastic leukemia (s-ALL) is a rare but serious complication of cytotoxic therapy for primary malignancies. We report the case of a 51-year-old female who developed B-cell acute lymphoblastic leukemia 14 years after her initial diagnosis of diffuse large B-cell lymphoma (DLBCL), following multiple lines of treatment including chemotherapy, radiation, and immunomodulatory therapy. The patient demonstrated resistance to conventional ALL induction chemotherapy but achieved complete remission with a personalized regimen combining the FLT3 inhibitor sorafenib and the hypomethylating agent decitabine, guided by next-generation sequencing findings. This case highlights the distinct molecular landscape of therapy-related ALL, the importance of comprehensive genomic profiling in guiding treatment decisions, and the potential for targeted approaches in this traditionally poor-prognosis population.

Introduction

Secondary acute lymphoblastic leukemia (s-ALL) refers to ALL that arises after a prior malignant neoplasm, encompassing both therapy-related ALL (t-ALL) directly attributed to previous cytotoxic treatment and prior malignancy ALL (pm-ALL) where the association is less clearly defined. While therapy-related myeloid neoplasms are well- characterized, t-ALL remains relatively understudied, accounting for approximately 3-9% of all ALL cases. Emerging evidence suggests that t-ALL represents a distinct biologic entity with adverse genetic features and clinical outcomes compared to de novo ALL

The pathogenesis of t-ALL is attributed to the genotoxic effects of chemotherapy and radiation on hematopoietic stem cells, though the precise mechanisms are less understood than in therapy-related myeloid neoplasms. Alkylating agents, topoisomerase II inhibitors, and immunomodulatory drugs such as lenalidomide have all been implicated [citation:1, citation:3]. The median latency from primary malignancy to t-ALL diagnosis is approximately 6.8 years, with higher incidence reported in females, older adults, and patients with prior breast cancer or central nervous system tumors

Currently, no standardized treatment approach exists for t-ALL, and response rates to conventional ALL therapies are generally poor, with long-term survival largely dependent on allogeneic hematopoietic stem cell transplantation. Here, we present a case of secondary B-ALL arising in a patient with multiply relapsed DLBCL, in which molecular profiling guided a successful targeted treatment approach

Case Presentation

Patient History and Primary Malignancy

A 51-year-old female initially presented in 2009 with an upper abdominal mass. Surgical resection and pathological examination revealed diffuse large B-cell lymphoma (DLBCL), stage IA, with an International Prognostic Index (IPI) score of 1 (low-risk group). She received six cycles of CHOP chemotherapy (cyclophosphamide, pirarubicin, vindesine, dexamethasone) and achieved complete remission

In August 2019, she presented with CNS lymphoma. Bone marrow aspiration and flow cytometry confirmed DLBCL stage IV (IPI score 2, medium-low risk). She received craniospinal irradiation with significant radiographic response. From January 2020 onward, she received seven cycles of rituximab plus lenalidomide (R2) followed by lenalidomide maintenance therapy, with a total lenalidomide exposure of 27 months

Presentation of Secondary Leukemia

In April 2023, routine blood count monitoring revealed leukocytosis with circulating blasts. Complete blood count showed: white blood cell count 21.59 × 10^9/L, hemoglobin 108 g/L, platelet count 70 × 10^9/L, with lymphocyte percentage 44.4%, monocyte percentage 52.3%, and absolute neutrophil count 0.64 × 10^9/L. Peripheral blood smear demonstrated circulating abnormal lymphocytes.

Treatment and Clinical Course

Initial induction chemotherapy consisted of dexamethasone 10 mg and vindesine 4 mg, with imatinib added for BCR::ABL1 positivity. One week later, bone marrow examination demonstrated persistent disease with 70.5% blasts, indicating primary resistance Based on the NGS findings—particularly the presence of FLT3 and DNMT3A mutations—treatment was adjusted to a personalized regimen: decitabine 20 mg/m^2 on days 1-5, sorafenib 0.4 g twice daily, and dasatinib 70 mg once daily. Dasatinib was continued for BCR::ABL1 coverage while incorporating sorafenib for FLT3 inhibition and decitabine as a hypomethylating agent.

Risk Factors and Pathogenesis

The patient exhibited multiple risk factors for t-ALL development. Her treatment history included exposure to alkylating agents (cyclophosphamide), topoisomerase II inhibitors (pirarubicin), radiation therapy, and prolonged lenalidomide maintenance . Lenalidomide has been specifically implicated in secondary B-ALL, with proposed mechanisms including proteasomal degradation of IKZF1 (Ikaros), a transcription factor critical for lymphoid development

Differential Diagnosis

Given the patient's extensive treatment history, distinguishing t-ALL from relapse of DLBCL with aberrant immunophenotype or from a composite lymphoma/leukemia was essential. The immunophenotype (CD19+, CD34+, TdT+,cCD79a+) was definitive for B-lymphoblastic leukemia rather than mature B-cell neoplasm. The absence of mutations commonly associated with DLBCL on NGS further supported a new, therapy-related leukemia rather than disease transformation

Conclusion

We report a case of secondary B-ALL arising 14 years after initial DLBCL diagnosis, following multiple lines of chemotherapy, radiation, and immunomodulatory therapy. The patient achieved complete remission with a genotype-guided regimen incorporating sorafenib and decitabine after failing conventional ALL induction. This case adds to the growing literature characterizing t-ALL as a distinct biologic entity and illustrates the critical role of molecular profiling in personalizing therapy for this high-risk population. As targeted agents and immunotherapies continue to expand treatment options for ALL, prospective studies specifically addressing t-ALL are needed to establish evidence-based treatment algorithms.

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