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CASE REPORT

High-Dose Chemotherapy and Stem Cell Transplantation in *ZBTB16::RARA* Acute Promyelocytic Leukemia: A Case Report

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A small proportion of patients with acute promyelocytic leukemia (APL) harbor variant chromosomal translocations that lead to fusion of *RARA* to one of several alternative partner genes. The most frequently reported of variant is the t(11;17)(q23;q21), which generates the fusion of the zinc finger gene *ZBTB16* (formerly PLZF) to the *RARA* locus (*ZBTB16::RARA* fusion). This APL subtype is typically resistant to standard APL-directed therapies and most patients with this translocation relapse within one year with limited subsequent treatment options. Here, we report on a patient with *ZBTB16::RARA* APL who achieved durable molecular complete remission lasting more than two years after high-dose chemotherapy with busulfan and cyclophosphamide followed by autologous stem cell transplantation. This therapeutic approach has not previously been described for this rare APL variant and may represent a promising consolidation strategy in selected patients.

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Introduction

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML) characterized by the accumulation of abnormal promyelocytes and balanced translocation t(15;17)(q24;q21), which results in the formation of the *PML::RARA* oncogene. A small proportion of patients harbor variant translocations that lead to fusion of RARA with one of several alternative partner genes.[1,2] The most frequently reported variant is the t(11;17)(q23;q21), resulting in fusion of the zinc finger gene *ZBTB16* (formerly *PLZF*) with the *RARA* locus *(ZBTB16::RARA).*[3]

Typical APL is morphologically characterized by abnormal promyelocytes with irregular and highly variable nuclei, which are often kidney-shaped or bilobed in variant APL, and densely packed cytoplasm with large granules and single or bundled ("faggots") Auer rods. In contrast, cases with the variant *RARA* translocation t(11;17)(q23.2;q21.2) resulting in *ZBTB16::RARA* show distinct cytomorphological features, including a predominance of cells with regular nuclei, abundant granulations, frequent absence of Auer rods and an increased number of pelgeroid neutrophils.[2,4] However, a review of the literature indicates that the absence of Auer rods or faggot cells, previously described as a characteristic morphologic feature of t(11;17)(q23;q21) APL,[2,4,5] cannot be confirmed in all published cases. Granularity is also highly variable and therefore not a reliable distinguishing feature from classic or variant APL with t(15;17)/*PML::RARA*.

When the hypercoagulable status is controlled by supportive therapy, typical APL has a good prognosis and responds well to retinoid-based therapy with all-trans retinoic acid (ATRA) in combination with either anthracyclines or arsenic trioxide (ATO), which yields high rates of complete remission and overall survival.[6,7] Therefore, it is essential to recognize variants of *RARA* translocations, as the fusion partner considerably impacts disease biology, particularly with regard to ATRA sensitivity.

APL can be divided into two disease subtypes: an ATRA-responsive subtype, which includes APL with *RARA* fused to *PML*, *NPM1*, *NuMA*, and possibly *BCOR, PRKAR1A* or *FIP1L1*; and ATRA- and ATO-resistant subtype characterized by the presence of the *ZBTB16::RARA* and *STAT5B::RARA* fusions.[1,5,8] Although ATRA induces degradation of the ZBTB16–RARA fusion protein at the molecular level, oncoprotein loss is insufficient to induce differentiation or clinical response.[9] Resistance to ATRA has been attributed to the reciprocal RARA–ZBTB16 proteins which upregulates CRABPI, a retinoic acid-binding protein involved in retinoid catabolism.[10]

Most variant *RARA* rearrangements, including *RARA::ZBTB16,* are resistant to anthracyclines and ATO, and combinations of ATRA with anthracycline have generally not been successful.[11] Prolonged exposure to higher-dose

ATRA (60 mg/m^2 instead of 45 mg/m^2) has shown limited differentiation effects, suggesting that response to ATRA was not completely lost.[11] Some clinical benefit has been observed when combining ATRA and other agents, such as granulocyte colony-stimulating factor (G-CSF) or histone deacetylase inhibitors.[11-14] Nevertheless, most patients relapse within one year and subsequently show refractoriness to further therapy. Standardized treatment recommendations are lacking due to the rarity of these variants.

To date, high-dose chemotherapy consisting of busulfan and cyclophosphamide followed by autologous stem cell transplantation has not been described as a consolidation strategy in this setting. Here, we present a case of a patient with *ZBTB16::RARA*-positive APL who achieved a durable molecular complete remission lasting more than two years following high-dose chemotherapy with busulfan and cyclophosphamide and subsequent autologous stem cell transplantation.

Clinical presentation

Initial presentation and diagnosis

A 68-year-old patient initially presented with slowly progressive pancytopenia over a six-month period. Peripheral blood counts at diagnosis showed neutrophils 0.42 Gpt/L, hemoglobin 8.7 g/dL and platelets 88 Gpt/L). He was in very good general health without signs of bleeding. The only relevant comorbidity was hereditary hemochromatosis.

Peripheral blood smear revealed 12% hypergranulated promyelocytes, including one containing faggots of Auer rods, contrary to what is reported in the literature.[4,15] Bone marrow aspirate showed predominantly hypergranulated promyelocytes with mostly round, non-lobated nuclei (**Figures 1A-E**). Auer rods and faggots were present. Few neutrophilic granulocytes showed pseudo-Pelger-Huët anomalies and occasional cytoplasmic inclusions.

Molecular testing did not confirm the suspected *PML::RARA*-transcript. Cytogenetic analysis revealed a reciprocal translocation between the long arm of chromosome 11 and the long arm of chromosome 17 in 10 of 20 metaphases, corresponding to a *ZBTB16::RARA* rearrangement. The remaining metaphases showed a normal male karyotype. Interphase fluorescence *in situ* hybridization (FISH) detected the *RARA* rearrangement in 92 of 100 cells.

Therapeutic interventions and outcomes

Given the known resistance of *ZBTB16::RARA* APL to ATRA, ATO[1,7] and standard-dose cytarabine and daunorubicin chemotherapy, we initiated induction therapy consisting of intermediate-dose cytarabine (1,000 mg/m^2 twice daily on days 1–3), mitoxantrone (10 mg/m^2 on days 3–5), ATRA

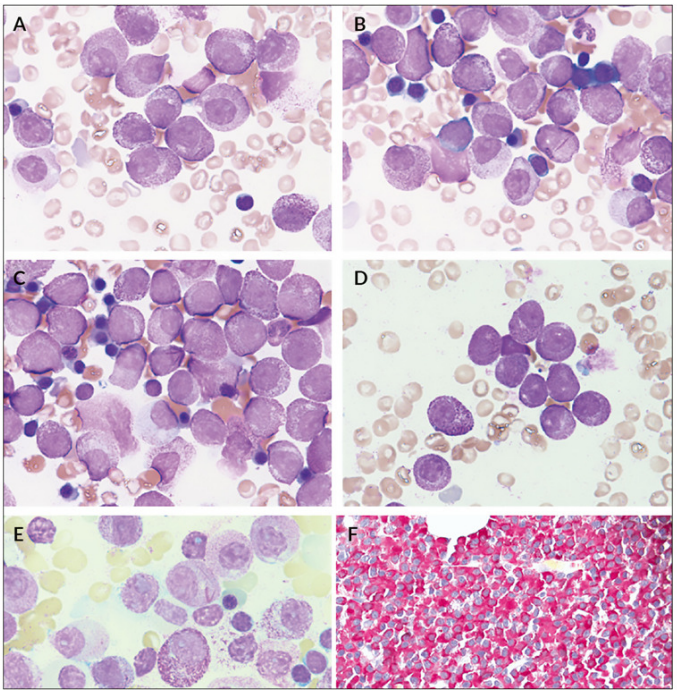


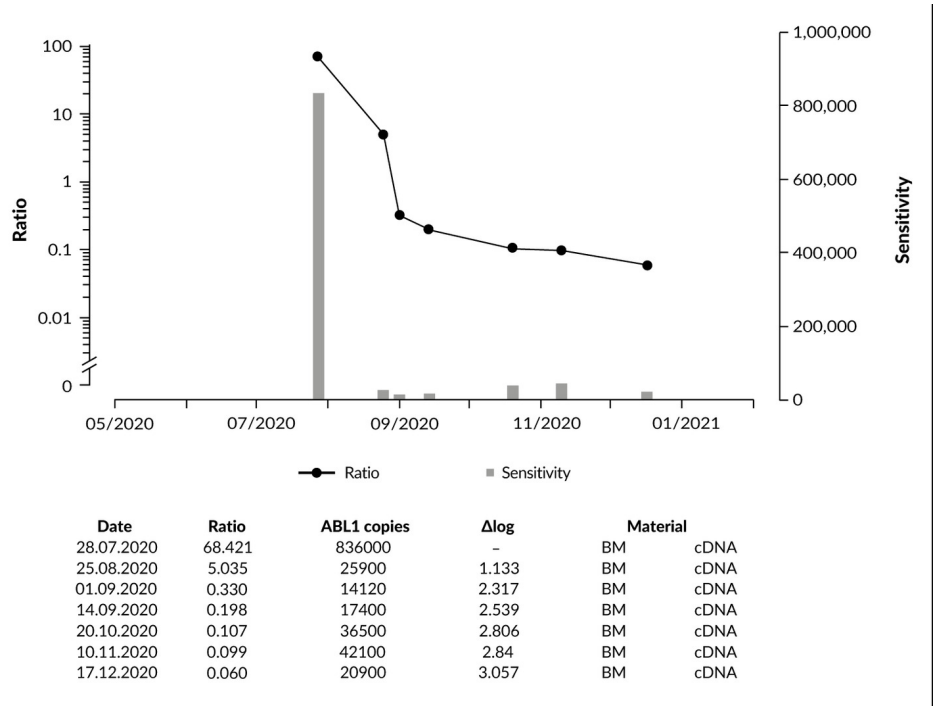
Figure 1. Cytomorphology and histopathology of the bone marrow at initial presentation.

A-E) Wright-stained marrow aspirate smear with hypergranular and non-lobated promyelocytes, some with Auer rods and one faggot cell (x100; Nikon Digital Sight DS-Fi2). F) Bone marrow trephine biopsy shows a markedly hypercellular bone marrow with sheets of abnormal hypergranular promyelocytes with non-lobated nuclei (stained by NAPH, × 400; Leica DM4000B).

(45 mg/m^2 on day 1 up to day 60) and G-CSF (5 µg/kg). G-CSF was included based on reports suggesting partial reversal of ATRA resistance.[1, 13] Dexamethasone (10 mg/m^2) was administered prophylactically during the first two weeks to prevent differentiation syndrome, followed by slow dose tapering.

Bone marrow evaluation on day +28 showed a good molecular response, with quantitative PCR for *ZBTB16::RARA* decreasing from an initial percentage of 68.421% to 5.035% (**Figure 2**). Following induction therapy, autologous stem cell apheresis from peripheral blood was successfully performed. The apheresis product was negative for *ZBTB16::RARA*.

Relevant side effects included a generalized maculopapular rash, which required continuous treatment with prednisolone and antihistaminic drugs, as well as severe bone pain predominately affecting the hips and lumbar spine. Infectious or extramedullary disease was excluded by computed tomography (CT) and magnetic resonance tomography (MRT) imaging and laboratory evaluation. These symptoms were considered potentially related to the combination of twice-daily G-CSF and concomitant ATRA. After completion of G-CSF and ATRA therapy, the rash resolved, while bone pain persisted for several weeks at reduced intensity.



Date	Ratio	ABL1 copies	Δlog	Material	
28.07.2020	68.421	836000	-	BM	cDNA
25.08.2020	5.035	25900	1.133	BM	cDNA
01.09.2020	0.330	14120	2.317	BM	cDNA
14.09.2020	0.198	17400	2.539	BM	cDNA
20.10.2020	0.107	36500	2.806	BM	cDNA
10.11.2020	0.099	42100	2.84	BM	cDNA
17.12.2020	0.060	20900	3.057	BM	cDNA

Figure 2. Quantitative real-time polymerase chain reaction (qPCR) monitoring of *ZBTB16::RARA* transcript levels during therapy.

The *ZBTB16::RARA* level changed from an initial percentage of 68.421% to 0.330% during therapy. In the last control, the minimal residual disease (MRD) was negative in peripheral blood. qPCR was performed using the LightCycler system (Roche). Expression of *ZBTB16::RARA* was normalized to *ABL1*. Values below 0.074 were classified as negative. The method-specific background threshold of 0.074 was established from a cohort of 59 negative samples.

A bone marrow aspirate performed before the first consolidation therapy with intermediate-dose cytarabine (1 g/m^2 twice daily on days 1,3 and 5) in combination with ATRA (45 mg/m^2 daily) showed further molecular response, with the *ZBTB16::RARA* ratio declining to 0.330% (**Figure 2**). During this phase, the patient again developed generalized rash, fever and pain. G-CSF was discontinued and ATRA was continued until day +21.

Further evaluation suggested that a macrophage-activating syndrome (MAS) may have contributed to recurrent fever, pain and rash. Sweet syndrome and relevant infectious complications were repeatedly excluded.

The second consolidation therapy consisted of high-dose chemotherapy with busulfan (4 × 0.8 mg/kg/day on days -7 to -4) and cyclophosphamide (60 mg/kg on days -3 to -2), followed by autologous stem cell transplantation (3.88 × 10^6 CD34$^+$ cells/kg) on day 0. Before transplantation, the absence of leukemic contamination in the stem cell apheresis product was confirmed by PCR.

The therapy was well tolerated. Serial assessments of minimal residual disease (MRD) showed complete molecular remission. **Figure 2** illustrates further progressive decline of *ZBTB16::RARA* expression following consolidation

therapy and high-dose chemotherapy with autologous stem cell transplantation. The patient remains in sustained complete remission for nearly two years after transplantation.

Discussion and conclusions

A genetic variant of APL which does not involve the *PML::RARA* gene fusion is very rare and constitutes <2% of all APL cases. Currently, 17 distinct gene fusion partners of *RARA* have been described that resulted in the development of an APL or APL-like disease.[1,16] Within the group of genetic APL variants, APL caused by the *ZBTB16::RARA* gene fusion is the most prevalent, accounting for approximately 1% of all APL cases.[3,17] This genetic APL variant is resistant to treatment with ATRA. In *ZBTB16::RARA* APL, the function of the lineage-determining transcription factor CCAAT/enhancer-binding protein alpha (CEBPa) appears to be strongly impaired.[18] Guidez et al. demonstrated that the reciprocal translocation product *RARA-ZBTB16* leads to increased expression of cellular retinoic acid-binding protein I (CRABPI), a receptor involved in the catabolism of retinoids,[10] which might explain the strongly reduced susceptibility to ATRA and why the application of higher ATRA doses in these cases may at least partially overcome resistance to therapy.

Given the scarcity of prospective data on *ZBTB16::RARA* APL, the reported management has largely relied on AML-like induction and intensified consolidation rather than differentiation-based regimens. A large series of X-*RARA* cases indicate that the outcomes for *ZBTB16::RARA* are substantially inferior to those for *PML::RARA* APL treated with ATRA/ATO, supporting the early consideration of treatment intensification and transplant-based strategies in selected patients.[19,20] In this context, achieving a deep molecular response prior to consolidation is clinically relevant because transplant outcomes, particularly with autologous approaches, appear best when performed in molecular remission,[21] providing a rationale for the durable remission observed in our patient.

If allogeneic stem cell transplantation is not an option, this case report suggests high-dose chemotherapy with autologous stem cell transplantation as an effective consolidation therapy for patients with *ZBTB16::RARA* variant APL. The acceptable safety profile and durable molecular remission observed in our patient suggest that this therapeutic approach may help overcome treatment resistance in this rare APL variant. Future studies incorporating molecular profiling of additional mutations may further refine risk stratification and enable individualized therapeutic management for patients with *ZBTB16::RARA* variant APL. In 2025, the patient remained alive and in remission.

Ethics approval and consent to participate

Written consent for the further use of patient data was obtained.

Consent for publication

Consent for publication was obtained.

Availability of data and materials

All patient data that support this case report are included in anonymized form in the published article.

Conflict of interest

The authors declared that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author contributions

All authors contributed substantially to this work. The specific contributions are as follows: SP and MS wrote the manuscript. GO, TH and KSK contributed to the diagnostic course and drafting the manuscript and commented on the manuscript. All authors approved the final manuscript.

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