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A comprehensive case study on successful multimodal therapy in philadelphia chromosome-positive acute myeloid leukemia with *NPM1* and *IDH2* mutations

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ABSTRACT

A 67-year-old female came to Tampa General Hospital with Philadelphia chromosome-positive (Ph+) acute myeloid leukemia (AML) featuring an intriguing combination of mutations, including *NPM1* and *IDH2* mutations. Novel combination therapy with azacitidine, venetoclax and ponatinib allowed her to successfully achieve a complete response (CR) and undergo an allogeneic hematopoietic stem cell transplant (HSCT). This case report provides an overview of her clinical course, emphasizing the significance of integrated therapy and the challenges associated with balancing treatment for AML. It also underscores the importance of a multidisciplinary approach and careful monitoring of patients with complex hematologic conditions.

1. Introduction

The Philadelphia chromosome, resulting from the translocation of chromosomes 9 and 22 (t[9;22][q34;q11]) and characterized by the BCR/ABL fusion gene, is a hallmark of chronic myeloid leukemia (CML). It is also frequently observed in mixed-phenotype acute leukemia and acute lymphoblastic leukemia [1]. Despite being provisionally classified in the 2016 WHO revision under myeloid neoplasms and acute leukemia, Philadelphia chromosome-positive acute myeloid leukemia (Ph+ AML) remains a rare entity, representing only 1 % of cases with the Philadelphia chromosome [2]. This report details an unusual case of Ph+ AML harboring *NPM1* and *IDH2* mutations and highlights the complexities in managing such cases, emphasizing the successful application of combined chemotherapy and targeted therapy, and allogeneic hematopoietic stem cell transplant (HSCT). As shown in previous studies, combination regimens involving venetoclax and tyrosine kinase inhibitors (TKIs) represent a viable strategy for addressing advanced Ph+ myeloid leukemia [3].

2. Case presentation

A 67-year-old female initially presented with an extremely elevated white blood cell count (WBC) of 200.000/µl. AML was confirmed by flow cytometry showing CD33, CD13, CD123, CD11b and partial MPO positive blasts. CD34, CD117, HLA-DR, CD19, CD20, CD10, TdT were negative. Patient underwent leukapheresis and treatment with hydroxyurea in order to decrease her WBC count prior to transfer to Tampa General Hospital (TGH). On arrival, bone marrow biopsy performed showing hypercellular marrow (100 %) with 60 % myeloblasts. MDS FISH, t(8:21), and inv16 were negative. Next Generation Sequencing showing NPM1 p.W288CFs*12 VAF 13.5 %, IDH2 p.R140Q VAF 19.6 % and *BCOR* p. L1612Pfs*6 VAF 37.6 %. The patient was started on induction chemotherapy with 7 + 3 (cytarabine 200 mg/m2 for 7 days and 3 days of daunorubicin 60 mg/m2) plus gemtuzumab ozogamicin (GO) 3 mg/m2 × 1 dose. D14 bone marrow biopsy showed hypocellular (30–40 %) marrow with residual leukemic blasts (40 % by flow cytometry). Around the same time, identification of the Philadelphia chromosome occurred via cytogenetic analysis (46,XX,t(9;22)(q34.1;q11.2)[11]/46, XX[2]) and was confirmed by PCR showing BCR/ABL p210 at 0.4622. Given her NPM1 and IDH2 mutations as well as Ph+ disease, the

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decision was made to change therapy to azacitidine, venetoclax and, ponatinib. The first cycle included azacitidine 75 mg/m2 for 7 days and venetoclax 200 mg for 14 days (due to drug interaction with isavuconazole) and ponatinib 45 mg daily. A subsequent bone marrow biopsy 1 month after the first cycle demonstrated no residual AML with BCR/ABL PCR not detected. Ponatinib was reduced to 30 mg daily for cycle 2 with a further reduction to 15 mg daily 2 weeks later after confirmation of complete molecular remission by PCR. Over course of therapy, she needed continued dose reductions of venetoclax to allow for count recovery prior to subsequent cycles. Post cycle 4 bone marrow biopsy showed continued complete remission with BCR/ABL undetectable by PCR (assay sensitivity 0.002 %) and NPM1 measure residual disease (MRD) not detected (assay sensitivity of 0.005 %). Four additional cycles were given prior to HSCT due to social circumstances delaying ability to take patient directly to transplant. The patient then underwent an allogeneic haploidentical HSCT (remained MRD negative on vital organ testing) with conditioning with FluMelTBI. GVHD prophylaxis with Post-transplantation cyclophosphamide/mycophenolate mofetil/sirolimus were done. Day 30 and Day 90 post-transplant bone marrow biopsies demonstrated 100 % donor cells and no signs of leukemia. Maintenance ponatinib 15 mg daily started D100 post-HSCT with transaminitis led to its temporary discontinuation. She resumed after a 6-week interruption and is currently on ponatinib 15 mg daily. She remains with full donor chimerism and MRD negative on subsequent testing to date.

2.1. Discussion

The presented case encapsulates a complex clinical scenario, where a comprehensive understanding of the molecular landscape facilitated tailored therapeutic interventions in a disease historically associated with poor outcomes. The presence of the *NPM1* mutation, a recognized favorable prognostic factor in AML [4], likely contributed significantly to the positive treatment outcome observed in this case. Conversely, the Philadelphia mutation, typically considered an adverse prognostic factor in AML [2], may not have exerted a similarly negative impact due to the application of newer tyrosine kinase inhibitors such as dasatinib and ponatinib [5], as well as innovative combination therapies employed in this instance. The emergence of therapies centered around venetoclax has markedly influenced the paradigm of leukemia treatment. Azacitidine/venetoclax is now standard of care for front-line acute myeloid leukemia in elderly or unfit patients [6]. There is ongoing discussion on whether azacitidine/venetoclax could be as good or better than induction chemotherapy for certain molecular subsets regardless of fitness. *IDH2* mutations, for example, are particularly sensitive to venetoclax based strategies which is another likely contributor for this outcome of rapid molecular clearance and sustained response [7]. The incorporation of venetoclax alongside azacitidine and ponatinib, we believe, was pivotal in achieving deep molecular remission in this clinical scenario. While ongoing clinical trials are actively investigating the broader applicability of this regimen [8], the efficacy observed in this case underscores its potential efficacy.

The long-term prognosis of similar cases remains a topic of ongoing investigation. Many researchers believe that achieving minimal residual disease (MRD) negativity, particularly in Ph+ ALL, might obviate the necessity for allogeneic hematopoietic stem cell transplant (allo-HSCT) [9]. Similarly, *NPM1*-mutant AML patients that achieve MRD negativity after 2 cycles of intensive chemotherapy can often avoid allo-SCT [10]. However, whether these principles could be applied to cases like the one described above requires further exploration as prior to development of these novels therapies outcomes where very poor and HSCT has been unanimously recommended.

3. Conclusion

This case report illustrates a complex yet successful treatment course for a patient with Ph+ AML with *NPM1* and *IDH2* mutations. The integrated approach, combining chemotherapy, targeted therapy, and allogeneic HSCT, led to a favorable clinical outcome. This report serves as a valuable reference demonstrating the potential for long-term remission and improved outcomes with a well-coordinated and tailored approach using state of the art molecular data to drive treatment decisions.

Informed consent

Informed consent was obtained by patient prior to submission of this case report.

CRediT authorship contribution statement

Syed Muhammad Waqar Haider: . **Mehwish Zehra:** Writing – review & editing, Data curation. **Nikesh N Shah:** Writing – review & editing. **Eduardo M Sotomayor:** Writing – review & editing. **David M Swoboda:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

Drs. Swoboda, Haider, Zehra, Shah and Sotomayor declare no relevant conflicts of interest.

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