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Case Report

Olaparib-induced myelodysplasia – A case report

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ABSTRACT

Olaparib is an antineoplastic agent that is a poly ADP ribose polymerase (PARP) inhibitor and is Food and Drug Administration-approved for the treatment of ovarian, breast, pancreatic, and prostate cancer. PARP inhibitors can cause DNA damage and epigenetic changes, leading to hematological transformations and increasing the risk of myelodysplasia. We present a case of a 58-year-old female with malignant breast cancer initiated on Olaparib after failing multiple treatment lines. The patient had persistent declining blood cell counts, and a bone marrow biopsy revealed hypercellular bone marrow with predominant myeloid cells with increasing number of blasts and promyelocytes. Olaparib was stopped. The patient elected for supportive care and hospice.

Keywords: Myelodysplasia, Olaparib, Pancytopenia, Poly ADP ribose polymerase inhibitors

INTRODUCTION

Olaparib is known to cause therapy-related pancytopenia and hematological side effects. In some patients, pancytopenia improves after decreasing the dose or switching the agent, while in others, it can cause genetic mutations leading to secondary hematological malignancies. Keeping this dreadful side effect in mind leads to timely management of Olaparib-induced pancytopenia.

CASE REPORT

A 58-year-old female with a past medical history of hypothyroidism presented with a lump in her breast and was diagnosed with stage IIIA left breast cancer, T2N2aM0, estrogen receptor (ER) positive, progesterone receptor (PR) negative, and human epidermal growth factor receptor 2 (Her2)-neu negative. Genetic testing was negative for BRCA1, BRCA 2, and CHEK 2 mutations. The patient underwent a left breast mastectomy and was started on a combination of Adriamycin and Cytoxan × 4 and Taxol × 12. The patient subsequently underwent radiation therapy. The patient was started on maintenance Arimidex, but unfortunately, after 2 years, the patient was found to have metastatic disease with bony metastasis. The patient was seen to have ER-positive, PR-negative, and Her2-neu-negative tumor. Foundation one showed BRCA 2, PIK3CA genomic findings, and high tumor mutational burden (TMB). As per foundation one testing and after a second opinion, the decision was made to start Faslodex and Ibrance. After around 5–6 months of therapy, the patient was noted to have a progression of disease in the thoracic area on bone scan and magnetic resonance imaging. The treatment was changed to Faslodex and Piqray, but the patient could not tolerate Piqray. She was then started on Olaparib/Keytruda combination. The patient was then noticed to have a drop in her hemoglobin, platelet counts, and white blood cell counts [Table 1]. There was

Table 1: Lab trend and time periods after initiation of Olaparib.

	Month 0	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7
WBC (4–11×10^9/L)	6.9	4.5	3	4.6	4.1	2.6	2.9
HB (11.7–15.5 g/dL)	10.2	11.9	9.5	11.3	9.8	8.2	7.5
MCV (80–100 fl)	100	106	107	115	115	112	111
PC (150–400×10^9/L)	538	319	227	259	116	48	39

Significant pancytopenia noted in 5–6 months. Month 0 is the initiation of Olaparib therapy. WBC: White blood cell, Hb: Hemoglobin, MCV: Mean corpuscular volume, PC: Platelet count

concern for Olaparib-induced pancytopenia. The patient was taken for a bone marrow biopsy. Bone marrow was noted to be hypercellular and demonstrates predominant myeloid cells with increased number of blasts and promyelocytes representing 21% of marrow cells. Chromosome analysis, acute myeloid leukemia (AML) panel fluorescence *in situ* hybridization study demonstrated tp53 deletion, monosomy 5, trisomy 11, and tetrasomy 8.

Unfortunately, the patient elected to go to hospice, and all treatments were stopped.

DISCUSSION

Olaparib is an antineoplastic agent which induces synthetic lethality by poly ADP ribose polymerase (PARP) inhibition. The PARP enzyme-inhibitor complex "locks" onto damaged DNA and prevents replication and repair, causing cell death.[1] Olaparib can commonly cause hematological toxicity which is dose dependent and reversible.[2] Therapy-related myeloid neoplasms have been reported to have an incidence of 1–3%.[3] Median duration of Olaparib-related secondary malignancy is 2 years and can vary from 6 months to 2 years. Olaparib is considered a double-edged sword as recent studies are evaluating its use to treat myeloid neoplasms despite known concern for causing secondary hematological malignancies.[4] Meta-analysis from Morice *et al.* demonstrated that the combination of PARP inhibitors increased the risk of myelodysplastic syndromes and AML.[5] Olaparib appeared to have a stronger association with myelodysplastic syndrome (MDS) and AML than did other PARP inhibitors based on a post-marketing study.[6] The increased PARP trapping has been proven to be associated with high myelosuppression.[7]

CONCLUSION

Pancytopenia is a common side effect from Olaparib but keeping in mind, the possibility of secondary hematological malignancies is very critical. This case study emphasizes keeping myelodysplastic syndrome in the differential diagnosis while evaluating therapy-related pancytopenia.

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