Use of clozapine alongside chemotherapy in a treatment-resistant bipolar disorder patient with ovarian carcinoma: A case report and brief review

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ABSTRACT

Regular monitoring of blood counts ensures the safety of clozapine use; however, certain clinical situations may pose a dilemma for management such as use of clozapine in the presence of myelosuppressive chemotherapy. Further, there is very limited literature to guide such decisions. We report a case of a clozapine-stabilized, treatment-resistant bipolar disorder patient with ovarian carcinoma requiring chemotherapy. The clinical challenges are discussed in light of a brief review of the available reports.

Key words: Bipolar disorder, carboplatin, chemotherapy, clozapine

INTRODUCTION

Clozapine has demonstrated superior efficacy in the management of treatment-resistant schizophrenia and bipolar disorder.[1] Regular monitoring of blood counts ensures the safety of clozapine use; however, certain situations may pose a dilemma.[2,3] One such difficult scenario is decision about clozapine use with myelosuppressive chemotherapy. No controlled studies are feasible in this context for obvious reasons and it is not a common encounter in psychiatric settings, with just a few cases reported worldwide.

We report a case of a clozapine-stabilized, treatment-resistant bipolar disorder patient with ovarian carcinoma requiring chemotherapy. The clinical challenges are discussed in light of a brief review of the available reports.

CASE REPORT

Ms. A, 38-year-old, unmarried female, educated till 9th standard, is a known case of obsessive-compulsive disorder[4] since 8 years of age, and bipolar affective disorder[4] since 22 years of age. She has been on regular treatment, with highly inadequate control of illness, multiple hospitalizations, and modified electroconvulsive therapies (MECTs) since adolescence. Following a failure to respond to several psychotropic medications/combinations thereof, the patient was finally initiated on clozapine (200–300 mg/day) in addition to lithium (900 mg/day; adequate serum levels) in the year 2002, with a remarkable decrease in the frequency and duration of episodes. Improvement continued with a further addition of lamotrigine since 2007 (to control intermittent mild depressive episodes). On these medications, course was stabilized. There was no need of any further hospitalization between 2002 and 2014. She continued to have brief hypomanic episodes twice or thrice a year. In addition,
the patient had hypertension, hypothyroidism (possibly, lithium-induced), and obesity (body mass index: 33.8). The medical illnesses were under control on regular treatment.

In July 2014, the patient was diagnosed to have ovarian carcinoma (papillary adenocarcinoma Stage IIIIC). In the same month, she underwent operative surgery (total abdominal hysterectomy with bilateral salpingo-oophorectomy and debulking), with a plan to initiate chemotherapy with carboplatin. A review of psychiatric management was warranted since carboplatin is known to be associated with a significant drop in blood counts in the course of treatment. Due to high likelihood of developing cytopenia with chemotherapy and difficulty in identifying the culprit drug, after several discussions, it was planned that clozapine may be tapered off gradually (at least during chemotherapy). Lithium and lamotrigine were continued as before.

Chemotherapy cycles were started at a dose of 200 mg in 5% dextrose on a weekly basis (one full cycle of chemotherapy involved three sessions of weekly carboplatin followed by 3 weeks gap, i.e., 6 weeks in total). Before each chemotherapy, complete blood counts and renal function test were checked.

Around 2 weeks after the cessation of clozapine, the patient started to have manic symptoms with irritable mood, increase in goal-directed activity, demandingness, reduced sleep, and occasional aggression. Lithium levels were within therapeutic range (0.87–1.1 mEq/L) and thyroid function tests were within normal limits. Haloperidol was added and increased to 20 mg/day with only a mild improvement in her symptoms. The patient was discharged after three full cycles of chemotherapy, with a plan to continue the rest three cycles from her hometown. The manic symptoms increased in ensuing weeks, posing difficulty in managing her at home.

The patient received the 4th chemotherapy in her hometown, which was associated with a drop in blood counts within 3 weeks (Hemoglobin: 7 g/dL, total lymphocyte count: 1800 cells/µL, neutrophils: 600 cells/µL, platelet: 38,000/µL, and dipping further to 18,000/µL), after which they again presented. After consulting a hematologist and a medical oncologist, it was considered to be postchemotherapy drop, with advice to manage it conservatively (and a plan to initiate granulocyte colony-stimulating factor [G-CSF] in case of further decline/complications). The patient was readmitted for monitoring. Repeat counts over the next week came out to be trending upward.

As the patient had not shown response to haloperidol for optimum dose and duration, the reintroduction of clozapine was considered in addition to on-going lithium and lamotrigine. At this point, both clozapine versus MECT were considered as possible options, however it was decided first to go in favor of clozapine in view of excellent response to clozapine in the past few years stabilizing the course of illness and a definite requirement of long-term prophylaxis in her case. Risk benefits of clozapine were reassessed and the decision was finalized only after discussion with the patient’s family members. Close monitoring and interdepartmental liaison were kept. Clozapine was initiated and built up more gradually, 12.5–25 mg for every 3–4 days. When the weekly chemotherapy dose was due, the dose of clozapine was kept static for additional 2–3 days. A final dose of 275 mg/day was reached with regular monitoring of blood counts. She continued to receive two further chemotherapy cycles over coming weeks. Steady improvement in her mood and behavioral symptoms paralleled the buildup of clozapine dosage. The patient was subsequently discharged in early 2015 with no further drop in blood counts at any other point.

For the past 1 year, the patient continues to be in active follow-up with no recurrence of carcinoma and largely stabilized on previous medications (viz., clozapine, lithium, and lamotrigine).

**DISCUSSION**

This report contributes to a very limited literature on the concurrent use of clozapine with chemotherapy, which is expected to cause a significant drop in blood counts in the usual course. The initial options involve discontinuing clozapine or replacing it with another antipsychotic drug/s, or concurrent administration of clozapine and chemotherapy with careful monitoring. On one hand, the circuitous path of withdrawing a medication on which a treatment-resistant patient is stabilized may compromise psychiatric stability, yet there is a valid argument that such inconvenience would pale in the face of serious hematological risks. Such difficult decisions could also be better informed if the evidence support becomes more robust and elaborates on the various clinical considerations.

A PubMed-based literature search (1995–2015), followed by cross-references search, using relevant keywords found only 16 case reports worldwide (one from India) reporting clozapine use during chemotherapy. These have been summarized in Table 1. In some cases, initially, it was decided to discontinue clozapine, but it had to be reintroduced after a failed trial with another antipsychotic drug/s. Leukopenia/neutropenia was observed in a large majority (all except three) of these reports, it was attributed to consequent drop of chemotherapy. Usually, it normalized over the next few days on its own. A precaution which has been taken in several reports is the modified white blood cell monitoring protocol, i.e., for every 2 days as opposed to weekly in the presence of leukopenia. It is important to discuss with oncologists whether the clinical presentation is consistent with chemotherapy-induced...
leukopenia. In some case reports, G-CSF administration was required after the drop in blood counts.\textsuperscript{[14]}

Some studies have suggested the concurrent use of G-CSF along with clozapine, when the counts are low. Although the G-CSF guidelines restrict its use as a primary prophylaxis (to patients with \( \geq 20\% \) risk for febrile neutropenia based on patient-, disease- and treatment-related factors),\textsuperscript{[21]} it has been given along with chemotherapy and clozapine in few case reports.\textsuperscript{[12,16]} Lithium may also promote leukocytosis\textsuperscript{[22]} and it is suggested to be potentially beneficial in patients with leukopenia. In this patient, lithium was continued for her psychiatric condition, but may have contributed beneficially to blood counts.

Clinicians from western countries have to apply for a “waiver” from manufacturer to use clozapine in such exceptional circumstances. Even then, clozapine has to be stopped in the event of severe reduction in blood counts. Till date, there is no nationwide clozapine registry in

| Study reference | Age/gender/ psychiatric diagnosis and treatment | Type of carcinoma and its treatment | Clozapine-decision to continue (yes/no) | Leukopenia (yes/ no) | Reintroduction of clozapine (for psychiatric worsening) | Special considerations/ outcome |
|-----------------|-----------------------------------------------|-----------------------------------|----------------------------------------|---------------------|------------------------------------------------|--------------------------------------------------|
| Wesson et al.\textsuperscript{[5]} | 40 years, male Schizophrenia Clozapine | Testicular carcinoma Orchiectomy and chemotherapy | Yes | Yes | -na- | Clozapine continued with rigorous monitoring despite neutropenia and “red alert” status on full blood count |
| Bareggi et al.\textsuperscript{[6]} | 37 years, male Schizophrenia Clozapine | Nasopharyngeal carcinoma | Yes | No | -na- | Cautious administration with concomitant chemoradiation |
| Rosenstock\textsuperscript{[7]} | 46 years, female Schizophrenia Clozapine (700 mg/day) for 13 years | Breast cancer Surgical treatment, chemotherapy (doxorubicin and cyclophosphamide) and radiotherapy | Yes | Yes | TCL as low as 1300/mm\(^3\) and ANC 300/mm\(^3\) | Patient stable Neutropenia persisted for 6 months after chemoradiation |
| Rosenberg et al.\textsuperscript{[8]} | 39 years, male Bipolar I disorder Clozapine (600 mg/day) and Lithium (1800 mg/day) for 10 years | Hodgkin’s lymphoma Ablation chemotherapy and an autologous stem cell transplant | No | Replaced with olanzapine (30 mg/day) | Yes | Waiver granted by manufacturer for clozapine use in the presence of leukopenia; rigorous monitoring |
| Frieri et al.\textsuperscript{[9]} | 44 years, male Schizophrenia Clozapine (300 mg/day) for 10 years | Non-Hodgkin’s lymphoma Chlorambucil/fludarabine and mitoxantrone/ cyclophosphamide, vincristine, and prednisolone | No | Replaced with haloperidol (15 mg/day) | Yes | G-CSF administered twice after blood counts fell (as low as TLC 630/mm\(^3\), ANC 70/mm\(^3\)) |
| Goulet and Grignon\textsuperscript{[10]} | 51 years, male Schizophrenia Clozapine (300 mg/day) for 10 years | Small cell lung carcinoma with metastasis Palliative chemotherapy (cisplatin and etoposide) | Yes | Yes | -na- | Fluctuations in TLC coincided with the nadir of chemotherapy Blood counts monitored for every 2 days in case there was “yellow code” Lymphocytes elevated secondary to leukemia, therefore neutrophils ANC monitored instead of TLC |
| Liu et al.\textsuperscript{[11]} | Age NA, female Schizophrenia Clozapine (500 mg/day) for several years | CLL on chemotherapy | Yes | No | -na- | In remission during months of follow-up |
| Munshi et al.\textsuperscript{[12]} | 58 years, male Schizophrenia Clozapine (500 mg/day) for 15 years | B-cell lymphoma R-CHOP therapy | Yes But later replaced with olanzapine and aripiprazole after leukopenia | Yes Day 13\textsuperscript{th} TLC: 1100/mm\(^3\) ANC: 800/mm\(^3\) | Yes, up to 375 mg/day Along with G-CSF |

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### Table 1: Contd...

| Study reference | Age/gender/psychiatric diagnosis and treatment | Type of carcinoma and its treatment | Clozapine-decision to continue (yes/no) | Leukopenia (yes/no) | Reintroduction of clozapine (for psychiatric worsening) | Special considerations/outcome |
|-----------------|---------------------------------------------|-----------------------------------|-----------------------------------------|-------------------|------------------------------------------------|--------------------------------|
| Sankaranarayanan et al. [13] (3 cases) | 53 years, male Schizophrenia Clozapine for 5 years | Seminoma Cisplatin, bleomycin, and etoposide | Yes | Yes | Managed with G-CSF | -na- |
| | 41 years, female Schizoaffecive disorder Clozapine for 5 years | Carcinoma breast Surgery and docetaxil | Yes | -na- | Close monitoring |
| | 32 years, female Schizoaffecive disorder Clozapine for 5 years | Large bowel cancer 5-fluorouracil with adjunct radiotherapy | Yes | Yes | Occurred 4-week postchemotherapy (Possibly due to clozapine) | Neutropenia with zero granulocytes 4 weeks postchemotherapy, so clozapine was stopped and G-CSF was administered. Neutropenia reappeared after clozapine rechallenge. |
| Kolli et al. [14] | 46 years, male Schizophrenia Clozapine (700 mg/day) for 6 years and citalopram | B-cell lymphoma CHOP regimen, rituximab, and methotrexate | Yes | Yes | Managed with G-CSF | -na- |
| Deodhar et al. [15] (India) | 39 years, male Schizophrenia Clozapine (300 mg/day) for past 7 years | Carcinoma tongue Platinum- and taxane-based neoadjuvant chemotherapy and radiotherapy | Yes (dose reduction to 250 mg/day) | -na- | Counts as low as 1000/mm³, managed with G-CSF/antibiotics Prophylactic G-CSF administration in subsequent cycles | Pancytopenia managed with the addition of G-CSF |
| Usta et al. [16] | 53 years, male Schizophrenia Clozapine (600 mg/day) for 7 years | CLL on chlorambucil Chemotherapy with fludarabine, cyclophosphamide, and rituximab for aggressive lymphoma (Richter transformation) | Yes | But replaced with risperidone (8 mg/day) due to leukopenia after 4th cycle | Yes | Given with G-CSF |
| Cunningham et al. [17] | 56 years, male Schizophrenia Clozapine (500 mg/day) for 8 years | Squamous cell lung carcinoma with metastasis Radiotherapy and chemotherapy (carboplatin + etoposide/paclitaxel) | Yes | ANC: As low as 250/mm³ | -na- | Veterans Affairs National Clozapine Coordination Center was consulted. Patient died due to metastatic disease 14 months later |
| Barreto et al. [18] | 55 years, male Schizoaffecive disorder Clozapine and ziprasidone for 7 years, with partially controlled symptoms | High-grade lymphoma (Burkitt’s) combination chemotherapy (R-CODOX-M) + (G-CSF) support | Yes | But had to be stopped on day 11 of chemotherapy after leukopenia | Yes | No |
| Chamberlain et al. [19] | Age/gender NA Schizophrenia Clozapine for several years | Hodgkin’s lymphoma Doxorubicin, bleomycin, vinblastine, and dacarbazone | Yes | No | -na- | Patient had impaired capacity to consent Court of Protection granted permission Patient was good till 6-month follow-up |

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India. Nonetheless, clinicians need to clearly document the reasons favoring the continuation of clozapine and consent of family members.

The mechanism of clozapine-induced agranulocytosis remains controversial. The pathophysiological mechanisms may involve genetic susceptibility or immune-mediated toxicity. A possible activation of common apoptotic pathways by clozapine, similar to anticancer drugs, has also been hypothesized, but no concrete evidence points to such a synergistic effect. Clozapine-induced leukopenia usually occurs within the first year of initiation, and it is non-dose dependent and idiosyncratic, which contrasts with its predictable occurrence at the nadir of chemotherapy. There is a need for further research on the underlying mechanisms causing agranulocytosis.

To resolve the dilemma, we considered three points of utmost importance in guiding the decision/s, namely, (1) a careful risk-benefits assessment, depending on the patient’s oncological status and psychiatric condition, (2) detailed discussion with patient/family members and their consent, and (3) availability of strong consultation-liaison services, with support from medical oncology, hematology, and emergency medicine.

At times, there is a need to make calculated decisions and take "acceptable" risks, along with watchful monitoring and high level of preparedness. This case highlights one such instance and adds to very limited reports worldwide with the concurrent use of clozapine and chemotherapy.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Li XB, Tang YL, Wang CY, de Leon J. Clozapine for treatment-resistant bipolar disorder: A systematic review. Bipolar Disord 2015;17:235-47.

2. Joober R, Boks P, Clozapine: A distinct, poorly understood and under-used molecule. J Psychiatry Neurosci 2010;35:147-9.

3. Atkin K, Kendall F, Gould D, Freeman H, Liberman J, O’Sullivan D. Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. Br J Psychiatry 1996;169:483-8.

4. World Health Organization. International Statistical Classification of Diseases and Related Health Problem, 10th Edition (ICD-10). Geneva: WHO; 1992.

5. Wesson ML, Finnegan DM, Clark PI. Continuing clozapine despite neutropenia. Br J Psychiatry 1996;168:217-20.

6. Bareggi C, Palazzi M, Locati LD, Cerrotta A, Licitrà L. Clozapine and full-dose concomitant chemoradiation therapy in a schizophrenic patient with nasopharyngeal cancer. Tumori 2002;88:59-60.

7. Rosenstock J. Clozapine therapy throughout myelosuppressive chemotherapy: A case report and review of literature. Psychosomatics 2014;55:673-9.

8. Munshi T, Mazhar M, Hassan T. Clozapine reinstatement following a "red result" secondary to chemotherapy. Neuropsychiatr Dis Treat 2013;9:1267-71.

9. Sankaranarayanan A, Mulchandani M, Tirupati S. Clozapine, cancer chemotherapy and neutropenia – Dilemmas in management. Psychiatr Danub 2013;25:419-22.

10. Kolli V, Denton K, Borra D, Pulluri M, Sharma A. Treating chemotherapy induced agranulocytosis with granulocyte colony-stimulating factors in a patient on clozapine. Psychooncology 2013;22:1674-5.

11. Deodhar JK, Prabhakar K, Agarwal JP, Chaturvedi P. Clozapine and cancer treatment: Adding to the experience and evidence. Indian J Psychiatry 2014;56:191-3.

12. Cunningham NT, Dennis N, Dattilo W, Hunt M, Bradford DW. Continuation of clozapine during chemotherapy: A case study and review of a clinical dilemma. Ther Adv Psychopharmacol 2014;4:276-81.

13. Chamberlain FE, Walsh N, Faikowski J. Chemotherapy for Hodgkin’s lymphoma in a patient receiving clozapine for treatment-resistant schizophrenia: Use of the Mental Capacity Act 2005. BJPsych Bull 2015;39:305-7.

14. Barreto JN, Leung JG, Philbrick KL, Rasmussen KG, Thompson CA. Clozapine therapy throughout myelosuppressive chemotherapy: Regulations without standardization. Psychooncology 2015;24:1581-5.

15. Chamberlain FE, Walsh N, Faikowski J. Chemotherapy for Hodgkin’s lymphoma in a patient receiving clozapine for treatment-resistant schizophrenia: Use of the Mental Capacity Act 2005. BJPsych Bull 2015;39:305-7.

16. Monga V, Broucek M, Amapi M, Ramaswamy S. Concomitant chemotherapy and clozapine therapy: A case report. J Clin Oncol 2015;33:3199-212.

17. Suraweera C, Hanwell R, de Silva V. Use of lithium in clozapine-induced neutropenia: A case report. BMC Res Notes 2014;7:635.