Clozapine treatment of refractory schizophrenia during essential chemotherapy: a case study and mini review of a clinical dilemma

Nazife Gamze Usta, Cana Aksoy Poyraz, Melih Aktan and Alaattin Duran

Abstract

Background: Clozapine remains the antipsychotic of choice for refractory schizophrenia. Given the particular side effects of clozapine including neutropenia and myelosuppression, safety and efficacy of add-on chemotherapy for patients who are already under clozapine treatment remain unknown.

Objective: We present evidence from a patient with a diagnosis of refractory schizophrenia on clozapine medication, who required essential chemotherapy for chronic lymphocytic leukemia (CLL). We have also reviewed literature regarding this challenging clinical dilemma.

Method: We report details about a patient with treatment-resistant schizophrenia who was given chemotherapy (fludarabine, cyclophosphamide and rituximab) for CLL in the course of concomitant treatment with clozapine and granulocyte-colony stimulating factor (G-CSFs). In addition, we have reviewed literature using the PUBMED data base.

Results: Current evidence remains insufficient to provide authoritative guide to clinicians regarding the efficacy and safety of the combined use of clozapine and chemotherapy. However, general conclusion from our case and of the published evidence is that a combination of clozapine use and chemotherapeutic agents do not cause additional hematological worsening with no decreasing efficacy concerns raised.

Conclusion: Continuing with clozapine in the course of chemotherapy may be relatively safer for patients who responded well to clozapine concomitant with G-CSF treatment.

Keywords: clozapine, schizophrenia, chemotherapy, agranulocytosis

Introduction

Clozapine remains the most efficacious and in most cases a life-saving antipsychotic in patients with refractory schizophrenia [Munshi *et al.* 2013]. Unfortunately, agranulocytosis (revealed by a decline in peripheral neutrophil granulocytes below the level of $0.5 \times 10^9/l$) is a rare but potentially fatal adverse drug reaction. At least 0.8% [Pirmohamed and Park, 1997] of patients treated with clozapine develop agranulocytosis. There are no clinical or other parameters to predict this adverse reaction in a given patient and over 80% of the cases occur within the first 18 weeks of treatment [Munro *et al.* 1999]. Precise pathophysiological origins of agranulocytosis remain unclear.

Such patients who develop malignancy and require life-saving chemotherapy frequently develop myelosuppression and neutropenia. Therefore, we are presenting a case in which a patient was given diagnosis of schizophrenia (refractory) and required chemotherapy for chronic lymphocytic leukemia (CLL). In addition, we have reviewed and discussed evidence regarding patients presenting such clinical therapeutic challenge. A summary of the literature review is given in Table 1.

Case report

The report the case of a 53-year-old male patient with schizophrenia diagnosed according to the

Ther Adv Psychopharmacol

2014, Vol. 4(6) 276–281

DOI: 10.1177/

2045125314553610

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Correspondence to:

Cana Aksoy Poyraz, MD

Department of Psychiatry,

Cerrahpaşa Medical

School, Istanbul,

Turkey, Halaskargazi

cad. No:81 Çiçek apt.

daire:8,Osmanbey

Istanbul/Turkey

canaaksoy@yahoo.com

Nazife Gamze Usta, MD

Alaattin Duran, MD, Prof

Department of Psychiatry,

Cerrahpaşa Medical School,

University of Istanbul,

Turkey

Melih Aktan, MD, Prof

Department of Internal

Medicine, Division of

Hematology, Istanbul

Medical School, University

of Istanbul, Turkey

Table 1. Clozapine use during chemotherapy: summary of literature review.

Reference	Age, sex, diagnosis	Type of cancer	Chemotherapeutic agent	Leucopenia	G-CSF	Clozapine discontinuation	Prognosis/ comments
Avnon and Stolerman [1993]	44, F, S	Moderately differentiated carcinoma of uterine endometrium+ type II B well-differentiated papillary serous adenoma of ovary	N/A	Yes	No	No	Not much detail about case
Liu <i>et al.</i> [2010]	N/A, F, SA	Chronic lymphocytic leukemia	N/A	No	No	Yes	With the concern of agranulocytosis clozapine was stopped. After two cycles of chemotherapy, clozapine restarted due to decompensation.
Wesson <i>et al.</i> [1996]	40, M, S	Testicular Teratoma	Bleomycin, Etoposide, Cisplatin	Yes	No	No	
Bareggi <i>et al.</i> [2002]	37, M, S	Undifferentiated nasopharyngeal carcinoma	Cisplatin plus radiotherapy	Lowest neutrophil count: $1.5 \times 10^9/L$	No	No	
McKenna <i>et al.</i> [1994]	49, M, S	Small cell lung cancer	Cisplatinum, Etoposide	N/A	N/A	No	After first cycle of chemotherapy, patient decided against further chemotherapy
Hundertmark and Campbell [2001]	N/A, F, S	Diffuse large B-cell lymphoma	N/A	Yes	After clozapine discontinuation	Yes	Reintroduction of clozapine during chemotherapy
Rosenberg <i>et al.</i> [2007]	39, M, B	Hodgkin's lymphoma, nodular sclerosing type	Ablation chemotherapy and stem cell transplantation	Yes	No	Yes	Clozapine reinitiated due to decompensation despite treatment with olanzapine
van Gool <i>et al.</i> [2008]	37, F, S	Cervical cancer	N/A	N/A	N/A	Yes	In Dutch, Information gathered from abstract in English
Frieri <i>et al.</i> [2008]	44, M, S	Follicular non-Hodgkin's lymphoma	Chlorambucil 6 cycles Fludarabine and Mitoxantrone 4 cycles Rituximab 4 cycles Cyclophosphamide, Vincristine, Prednisolone	Yes	During clozapine treatment	Yes	Reintroduction of clozapine after chlorambucil therapy due to exacerbation of psychotic symptoms

(continued)

Table 1. Continued

Reference	Age, sex, diagnosis	Type of cancer	Chemotherapeutic agent	Leucopenia	G-CSF	Clozapine discontinuation	Prognosis/ comments
Rosenstock [2004]	46, F, S	Breast cancer	Doxorubicin, Cyclophosphamide, Radiotherapy	Yes	No	No	
Koli et al. [2013]	46, M, S	Diffuse large B-cell lymphoma with central nervous system	Cyclophosphamide, vincristine, doxorubicin, prednisone followed by rituximab and methotrexate	Yes	During clozapine treatment	No	
Munshi et al. [2013]	58, M, S	Large B-cell Lymphoma	R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisolone)	Yes	After clozapine discontinuation	Yes	Clozapine was reintroduced after psychotic relapse with G-CSF
FA [1995]	41, M, S	High-grade non-Hodgkin lymphoma	Cyclophosphamide hydroxydaunorubicin oncovin prednisolone	No	No	Yes	Clozapine was reintroduced after psychotic relapse
Goulet and Grignon [2008]	51, M, S	Small cell lung carcinoma	Cisplatin, etoposide	No	No	No	
De Berardis et al. [2013]	37, M, S	Behçet's disease	Azathioprine	No	No	No	
Sankaranarayanan et al. [2013]	Case 1: 53, M, S Case 2: 41, F, SA Case 3: 32, F, S	Stage 2c seminoma Breast cancer Large bowel cancer	Cisplatin, bleomycin, etoposide Radical mastectomy+ Docetaxel Adjuvant radiotherapy+ 5-fluorouracil	Yes Yes Neutropenia	During clozapine treatment No After clozapine discontinuation and after clozapine reinitiation	No No Yes	After completion of chemotherapy, patient developed febrile neutropenia. At this point clozapine was ceased. Despite combination of risperidone and quetiapine, psychotic symptoms relapsed. Clozapine was started with G-CSF but neutropenia reoccurred.

S, schizophrenia; SA, schizoaffective disorder; BD, bipolar disorder; F, female; M, male; N/A, not available; G-CSF, granulocyte colony-stimulating factor.

Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [APA, 2000], who has had a history of multiple hospitalizations since he was 19. He had been on several antipsychotic regimens until 1997, when he was started on clozapine with a daily dosage of 600 mg. Since then, he has been clinically stable with no hospitalization and his blood counts being in the normal range for about 7 years. In 2005 the patient was diagnosed with CLL and was commenced on chlorambucil by his hematology team. His total leukocyte counts have remained between 30 and $180 \times 10^3/\mu\text{l}$ and the absolute neutrophil counts were within normal limits. However, in 2012, he developed Richter transformation which is revealed through the development of aggressive lymphoma during the course of CLL. Then fludarabine, cyclophosphamide and rituximab (FCR) combination was started. After the fourth cycle, his neutrophil count decreased to 0.1 – $1.2 \times 10^3/\mu\text{l}$ and total leukocyte to 1.6 – $5.7 \times 10^3/\mu\text{l}$. With concern that the clozapine might have been responsible for neutropenia, we replaced clozapine treatment with 8 mg/day of risperidone. As soon as clozapine treatment discontinued, the patient became agitated with delusions and hallucinations. With the consent of his wife and support by the hematological team, clozapine was reintroduced and titrated to the previous dose. In addition, he was given granulocyte-colony stimulating factor (G-CSF) injection twice to stimulate the reproduction of white blood cells. His mental status improved rapidly and he has been stable since then. He was able to complete two other cycles of FCR chemotherapy with no further incident of neutropenia. CLL was remitted and the patient was mentally stable in the most recent follow up, about a year after chemotherapy was completed, under clozapine treatment.

Review of evidence

To make a decision whether to stop or to carry on with clozapine during cancer chemotherapy is a rather difficult case. For several reasons it is hard to terminate or to interrupt clozapine treatment. Abrupt cessation of clozapine may cause serious problems such as rapid deterioration of mental status, relapse of psychotic symptoms and/or delayed response to other psychotic drugs [Frieri *et al.* 2008] which could disrupt patients' adherence to chemotherapy. Therefore, proper liaison between hematology and psychiatry team should be established when dealing with such patients.

Determining the causes of neutropenia, whether associated with clozapine or a chemotherapeutic agent, is not always easy. The temporal relationship between the onset of neutropenia and initiation of cancer chemotherapy may guide physicians. Depending on the type or dose of chemotherapy, neutrophil counts generally start to drop about a week after each cycle of chemotherapy and usually drop to the lowest level about 7–14 days after treatment. This period is called nadir, the drop in neutrophil counts at the nadir of chemotherapy should not lead clinicians to stop clozapine. The risk of clozapine-induced agranulocytosis reduces substantially after the first 6 months of its use [Munshi *et al.* 2013]. Other risk factors defined are older age (often over 50 years of age) and those peculiar to the Asian race [Munro *et al.* 1999]. The risk of clozapine-induced agranulocytosis is not dose related.

Although there is no consensus about the mechanism of clozapine-induced agranulocytosis, it seems it can be best explained by genetic and immunotoxic factors [Guzelcan and Scholte, 2006]. Of the genetic basis of this adverse effect, there are some studies suggesting that specific human leukocyte antigen (HLA) subtypes are related to patients' susceptibility to develop clozapine-induced agranulocytosis [Lieberman *et al.* 1990; Dettling *et al.* 2001]. These findings emphasize that this adverse effect is an idiosyncratic drug reaction [Utrecht, 1989], which contrasts with the predictable course of chemotherapy-induced myelosuppression. No information is reported for direct toxic effect of clozapine on neutrophils. Yet there is some evidence about binding reactive metabolites might disrupt the neutrophil function or this may lead to the haptenization and cause immunity-mediated destruction [Pirmohamed and Park, 1997]. It has been shown that clozapine could activate common apoptotic pathways shared with chemotherapeutic drugs [Fehsel *et al.* 2005], but no evidence suggests a synergistic effect of concomitant use on neutrophil counts. These theories about the mechanisms of clozapine-induced agranulocytosis are to be separated from those of antineoplastic drugs and this difference leads us to the idea that continuing clozapine in the course of chemotherapy may be relatively a safe treatment method for patients already stabilized on clozapine.

Whatever the cause of agranulocytosis, clozapine or chemotherapy, G-CSFs may be useful to replenish white cell counts. G-CSFs have been

given in the treatment of clozapine-induced agranulocytosis [Sperner-Unterweger *et al.* 1998; Hagg *et al.* 2003]. Furthermore, clinicians have reported successful use of G-CSFs despite severe neutropenia in order to hold clozapine treatment [Sperner-Unterweger *et al.* 1998; Conus *et al.* 2001; Hagg *et al.* 2003]. Yet one should not underestimate the dangers of this combination, as the absolute neutrophil counts may continue to drop despite starting G-CSFs [Majczenko and Stewart, 2008]. There have been few reports concerning the use of G-CSFs in conjunction with clozapine and cancer chemotherapy [Kolli *et al.* 2013; Sankaranarayanan *et al.* 2013]. In our patient we also found the use of G-CSFs beneficial. However, guidelines limit the use of G-CSFs in the course of cancer chemotherapy according to the risk of febrile neutropenia, considering the cost of this treatment [Aapro *et al.* 2010]. In our case the oncology team decided to give G-CSFs which probably reduced the severity and duration of chemotherapy-induced neutropenia.

Conclusion

Current data are insufficient to guide clinicians about the combined use of clozapine and chemotherapy and it seems difficult to expand it with controlled randomized studies. A general conclusion drawn from the reported cases is that a combination of clozapine use and chemotherapeutic agents does not cause additional hematological worsening. Our case also supports the safe use of clozapine during chemotherapy.

Patients stabilized on clozapine are generally treatment resistant and discontinuing clozapine is often followed by the emergence of more symptoms, the consequences of discontinuing clozapine may even be more disastrous such as rapid deterioration of mental status and refusing chemotherapy in these very difficult patients generally resistant to multiple combination of antipsychotics. Therefore, clinicians should not discontinue clozapine during chemotherapy unless certain predictors such as the occurrence of neutropenia many weeks after completion of chemotherapy, indicate strongly that clozapine, rather than the chemotherapy, may be the likely the cause of neutropenia. For the management of such patients a multidisciplinary approach, especially a proper liaison between hematology and psychiatry teams, should be established, and patients should be monitored closely.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Patient consent

We confirm that guidelines on patient consent have been met and informed consent was obtained from the patient reported here. We certify that formal approval to report the case has been obtained from the patient described here. We are able to verify the validity of the results reported, all data related to the case reported here is preserved in the archives of inpatient unit of Cerrahpaşa Medical School, Department of Psychiatry.

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