

Clozapine reinitiation following a “red result” secondary to chemotherapy

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Abstract: We describe a case of a patient whose clozapine was discontinued after a “red result” following R-CHOP (rituximab with cyclophosphamide, hydroxydaunorubicin, Oncovin, and prednisolone) chemotherapy for large B-cell lymphoma. In some cases, manufacturers grant permission, on compassionate grounds, for clozapine to be continued or reinitiated following assessment by their consultant hematologist. Other than a recent case report, there is not much literature surrounding this medical issue. However, since the two leading causes of mortality in schizophrenia are cancer and cardiac disease, this is not an uncommon occurrence. Clinicians are reluctant to prescribe clozapine in view of its side-effect profile, despite its proven efficacy for managing treatment-resistant schizophrenia. The alternative is to prescribe two antipsychotics to manage symptoms. This approach may be associated with increased side effects, and evidence for actual benefits is scant. The consequences were disastrous in this case, as the individual not only relapsed following clozapine discontinuation, but the therapy for this treatable form of lymphoma had to be delayed. He was eventually admitted to an inpatient unit after having been stable for 15 years. We managed to stabilize him with olanzapine and aripiprazole which enabled the heme-oncology group to resume R-CHOP therapy with filgrastim (granulocyte colony-stimulating factor). Even so, he continued to exhibit severe psychotic symptoms, with religious delusions and auditory hallucinations. We therefore applied for permission to rechallenge him on clozapine. Permission was granted when protocol conditions were met, and reinitiation went without any adverse events. The patient’s symptoms showed improvement within a few weeks, and the other antipsychotics were discontinued once clozapine was titrated up to 300 mg. The decision to reinitiate clozapine following a red result is not to be taken lightly, but needs to be considered in terms of the risks versus benefits. More literature surrounding this issue would be of great benefit to clinicians, patients, and their families.

Keywords: clozapine agranulocytosis, clozapine discontinuation, red result, clozapine rechallenge, R-CHOP chemotherapy

Introduction

As most clinicians are aware, clozapine is clearly superior in the management of treatment-resistant schizophrenia. Unlike classic neuroleptic agents, clozapine does not cause parkinsonism, dystonia,¹ or tardive dyskinesia, nor does it elevate prolactin levels.²

A meta-analysis³ confirmed the efficacy of clozapine over conventional neuroleptics in reducing symptoms of patients with both treatment-resistant and nonresistant schizophrenia.

However there is reluctance regarding its usage due to its side effects, and more recently, in some clinicians’ opinions, in terms of its metabolic profile. The use of clozapine has been limited in view of the risk of agranulocytosis, despite clear evidence

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of its efficacy over other antipsychotics.⁴ Wheeler estimated that the mean duration between year of first contact with a clinician and starting clozapine in 2,796 individuals was 9.7 years, and Taylor et al calculated that the mean delay in using clozapine was 5 years in individuals admitted to London hospitals.^{5,6} Clozapine was superior to risperidone and quetiapine for patients who discontinued a second-generation antipsychotic in phase I.⁵

The risk of neutropenia/agranulocytosis is about 0.38% with monitoring and 2.5% without it.⁶ “Clozapine has been shown to substantially reduce the risk of suicide, such that the benefit gained in the reduction in all-cause mortality far outweighs the risk of death from agranulocytosis.”^{6,7}

The mechanisms implicated are immunologically mediated, and there are at least three of them. Immune complexes may selectively adhere to granulocytes or their immature precursor cells, the drug may bind to the granulocytes as carriers of the immunogenic drug, and finally the drug may induce antibodies directed to granulocyte-specific structures.^{8,9}

There was some suggestion that a metabolite could be responsible for clozapine-induced agranulocytosis, either by direct toxicity or through an immune-mediated mechanism. It has been found that several drugs associated with a relatively high incidence of drug-induced agranulocytosis are metabolized by activated neutrophils to chemically reactive metabolites. In preliminary experiments with clozapine, it was found that it was metabolized by neutrophils.^{10,11}

There have been attempts to identify genetic links in this area, eg, in a study carried out to examine the human leukocyte antigen-encoded genetic susceptibility to clozapine-induced agranulocytosis. The antigens did not reveal any relation to this hematotoxic reaction.¹²

In view of the speculations that agranulocytosis is possibly caused by the clozapine-mediated stimulation of cytokines and soluble cytokine receptors release, followed by induction of granulocyte proliferation and induction of myeloperoxidase (MPO) and NADPH-oxidase as NADPH-oxidase/MPO which may oxidize clozapine to highly reactive nitrenium ions, the authors in a research project investigated the role of hereditary polymorphisms in the NADPH oxidase/myeloperoxidase system in agranulocytosis patients who received clozapine ($n = 49$), ticlopidine ($n = 11$), and other drugs prior to the event. Sequencing the entire coding region of the NADPH subunit cytochrome b_{245} , beta polypeptide (CYBB; gpS1 phase) disclosed that *CYBB* is a highly conserved gene, which does not represent a risk factor for clozapine-induced agranulocytosis. The impact of polymorphic myeloperoxidase, however, needs further

verification to predict a patient's risk to develop drug-induced agranulocytosis.¹³

Despite manufacturing companies' advertised willingness to allow a continued supply of medication on compassionate grounds for individuals undergoing chemotherapy, there are notable cases in which clozapine has been stopped when proper liaison had not been carried out between the services. This can lead to disastrous consequences, with the patient becoming so unwell that the actual cancer treatment cannot be carried out. The following case report is of a similar nature, where a patient who had been stable for 15 years was taken off clozapine by the community psychiatrist following chemotherapy for lymphoma, which caused the white blood cells and neutrophils to fall, even though this was a predictable consequence of R-CHOP (rituximab with cyclophosphamide, hydroxydaunorubicin, Oncovin, and prednisolone) chemotherapy. There have been few case reports or expert reviews on this topic, although a recent case report was published in 2012.¹⁴ A manuscript in the *British Journal of Psychiatry* serves as good guidance for clinicians embarking on rechallenging patients on clozapine.¹⁵ Patients were required to have a break for at least a week in order to qualify as a rechallenge patient. In addition, communication with the monitoring division of the company is extremely important in order to obtain permission on compassionate grounds. As there are other stakeholders involved in such cases (ie, the oncology/hematology team administering the treatment), they would also have to be on board with it.

Case report

In the next part of this document, we discuss the case of CE, a 58-year-old male with chronic paranoid schizophrenia. Institutional Research Ethics Board approval (PSIY-380-12) and patient consent were obtained for the presentation of the current case. CE had been placed on clozapine after several trials of other antipsychotics in 1998, following a prolonged admission at a chronic care facility. He had been stable from that time onwards with clozapine at 500 mg in divided doses, and was residing at a group home under the care of the local assertive community team (ACT). ACTs are multidisciplinary mental health teams that manage individuals with severe mental illness in the community. They originated in North America in the 1980s as part of the planning to deinstitutionalize the chronic inpatient population and transition them in the community. It is an intense form of support in the community in most places in North America to manage severely mentally ill patients with multiple needs

who would otherwise be unable to stay outside tertiary care hospitals. This community mental health team offers support in various domains, like medication compliance, maintenance of accommodation, employment, adhering to probation if required, managing addictions, and offering interventions to improve physical health. At some point, the team was considering discharging him to a step-down service in the community. He developed a swelling in the jaw (4 cm mass in the right preauricular region extending down into the sub-mandibular region) and a right axillary mass (6 cm), which was on examination a lymph-node swelling as noted by the family physician. In addition to this, there were bilateral posterior sternocleidomastoid nodes (measuring 1–2 cm). This prompted a referral to an ear, nose, and throat specialist, who diagnosed him with a large B-cell lymphoma. An emergency referral to the hematologist was set in motion. The lymphoma was graded at clinical stage 3A.

This being a treatable form of lymphoma, the hematologist started the CHOP therapy with additional rituximab, now popularly known as the R-CHOP therapy, used for B-cell lymphomas. The plan was set in place for a 21-day cycle with six treatments. The first chemotherapy cycle was well tolerated by the patient, and showed a good response in shrinking of the mass. However, his white cell and neutrophil count went quite low (1.1 and 0.8, respectively) on the 13th day of the cycle, though this was as predicted. The white cell count climbed to 7.0 on the 19th day of the cycle. The local lab alerted the community psychiatrist when CE went for his monitoring blood work. As a consequence of being in the "red zone," the Clozapine Monitoring Network was promptly informed and a discontinuation protocol initiated.

This had an adverse effect on his mental state: he became extremely agitated and restless, and was unable to sleep for days. He was placed on quetiapine in order to manage his psychiatric symptoms. This proved to be inadequate, and he relapsed; his usual relapse signature symptoms of religious delusions exacerbated, and he seemed to be clearly responding to auditory hallucinations. Unfortunately, this meant the hematology team could not give him his second treatment of the R-CHOP cycle. This led to various issues between the ACT service, the hematology team, and the family, who were extremely unhappy with the situation.

He ended up in the acute psychiatric unit in view of his psychotic relapse. In an attempt to stabilize him, he was initiated on olanzapine 20 mg in divided doses. Later on, aripiprazole was added to the regimen, which was titrated to 15 mg once daily. He was much calmer and able to sleep, though

still tormented by his active psychotic symptoms (ie, religious delusions and auditory hallucinations). The chemotherapy was resumed with the cover of filgrastim (granulocyte colony-stimulating factor) by the heme oncology team.

As his psychotic symptoms persisted, a decision was made to reinitiate him on clozapine, and the Clozapine Support Network was contacted. The directive given by them was as follows:

1. Patient is deemed to be capable of consenting and signs the consent form.
2. Letter to be submitted by the prescribing physician outlining the details of the treatment with chemotherapy regimen.
3. Monitoring criteria to be set by the prescribing physician in consensus with the hematologist.
4. The consultant hematologist would review the submissions and if in agreement, the patient would be registered with the Novartis Special Program on a compassionate basis.
5. The monitoring service would be informed of the start and end dates of the chemotherapy.
6. If the chemotherapy had ended, the regular monitoring protocols would be put in place upon informing the monitoring service.

These requirements were fulfilled, and the patient was allowed to be reregistered on clozapine. He continued to stay as an inpatient, and received all six cycles of the R-CHOP therapy with filgrastim cover. His white blood cell counts remained within the range of 3.5–11.6, with his neutrophils in the vicinity of 3–5. His lymphoma went onto clinical remission; there was one remaining 2.5 cm right axillary node that was attributed to fibrotic tissue.

The patient's mental state gradually improved with upward titration of clozapine to achieve a suitable therapeutic response at 375 mg daily in divided doses. The achievement of adequate efficacy at a lower dose than previously was attributable to his substantial reduction in smoking while an inpatient. His religious delusions went into the background, and the auditory hallucinations lessened in intensity and frequency to a great extent. He was finally discharged to the care of the ACT after being an inpatient for approximately 4 months. The monitoring service was subsequently informed a few months later after review by the cancer (heme oncology) specialists that his treatment for the malignant lymphoma had been completed.

Discussion

In this case, liaison between the cancer team, inpatient, and the community mental health team was successful in

achieving a good outcome eventually, though unfortunately the patient suffered for a prolonged length of time. However, in hindsight this could have been done in a more effective and less painful manner. Such events might possibly become actionable in the future, as in this case there was a clearly identifiable cause for the agranulocytosis.

In a published case report in the *British Journal of Psychiatry*, a patient was continued on clozapine despite a red-alert status; this was an individual who required chemotherapy for a testicular carcinoma with pulmonary metastases. It probably needs to be mentioned, though, that the treatment was initially delayed due to refusal to consent.¹⁴

In a manuscript published in the *American Journal of Psychiatry*,¹⁵ a comment was: “discontinuation of clozapine in a treatment resistant patient often results in relapse, and this may be prevented if the clinician is able to identify a causative agent other than clozapine.” The authors proposed that polypharmacy may have contributed to the initial episode of neutropenia as well as the failed rechallenge. There are other similar case reports in which the patients were taking additional psychotropic medications that carry a risk for blood dyscrasia, namely valproic acid, haloperidol, or risperidone.^{16,17}

In a letter to the editor in the *American Journal of Psychiatry*, the authors gave their opinion on drug interactions: benign ethnic neutropenia and medical comorbidity can often contribute to clozapine-induced agranulocytosis.¹⁷ Most patients who develop neutropenia and agranulocytosis do not restart clozapine after its discontinuation.¹⁸

In terms of the risk of clozapine-induced agranulocytosis, there is reduced incidence after the first 6 months; moreover, it is higher in women and increases with age.¹⁹ In the future, we might be able to identify individuals at higher risk of developing agranulocytosis/neutropenia by genetic linkage and hereditary polymorphism. The risk of clozapine-induced leucopenia or agranulocytosis decreases exponentially over time, and after 1 year of treatment the incidence is nearly equivalent to that observed in phenothiazines.²⁰ A systematic review published in 2012 examined patients who were rechallenged with clozapine after potentially life-threatening adverse events. It showed that the rechallenge was successful in 69.6% patients and none of them died. This systematic review in addition to the Dunk et al¹⁵ study can possibly serve as some assurance and guidance to clinicians who are considering the possibility of a rechallenge. These research papers have reliable data that indicates that rechallenges for neutropenia are successful in two-thirds of cases.^{15,21–23}

A high level of commitment on the part of the treating team is crucial to implementation of clozapine treatment in these circumstances, and after the treatment begins, the team must be able to contain their own and everybody else's anxiety. These processes become easier with practice.²⁴

Conclusion

In conclusion, this was an event that could have been avoided with some due diligence and close liaison between the various services with planning for the actual chemotherapy. It would be beneficial if there were more data available in this area to guide clinicians in weighing the risks and benefits in making a decision as to whether to rechallenge patients on clozapine or with respect to how to avoid such a scenario arising by being prepared for the situation. It could be worth suggesting that a descriptive column be added in the form from the clozapine-monitoring service to the discontinuation section in order to obtain useful clinical data. As we are well aware with the patient population with schizophrenia, malignancy is not an uncommon occurrence. In fact, it is a leading cause of death in addition to cardiac diseases in such patients. In a recent study in Western Australia, the findings were that more than 77% of “excess deaths” were attributed to physical health conditions, including cardiovascular diseases (29.9%) and cancer (13.5%), and 13.9% of “excess deaths” were attributed to suicide.²⁵

Disclosure

The authors have no conflicts of interests associated with presentation of this case report.

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