

Continuation of clozapine during chemotherapy and a stem cell transplant

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Cancer incidence rates in the UK have increased by more than a third over the last four decades, so the likelihood of requiring concurrent chemotherapy and clozapine is increasing. In this situation clinicians are faced with a clinical conundrum: to stop clozapine and risk a psychotic relapse, or to continue clozapine and risk a potentially fatal agranulocytosis. This case report describes how a multidisciplinary team (MDT) worked together to balance the mental and physical health needs of a patient.



Around a quarter to a third of patients with schizophrenia are thought to be treatment resistant,¹ and it is in these cases that clozapine is recommended. Evidence has shown a number of benefits of clozapine use, including reduced suicidality and less sensitivity to extrapyramidal side effects.² Conversely, the drug is associated with serious adverse effects such as agranulocytosis.²

Due to the fact that cancer incidence rates in the UK have increased by more than a third since the mid-70s,³ the likelihood of requiring concurrent chemotherapy and clozapine is increasing. In these circumstances clinicians are faced with a dilemma: to stop clozapine and risk a psychotic relapse, potentially affecting compliance with life-saving treatment, or to continue clozapine and risk what could be a fatal agranulocytosis.

Our patient was diagnosed with amyloid light-chain (AL) amyloidosis and was successfully treated with ablation chemotherapy and an autologous stem cell transplant. Due to the limited evidence and guidance regarding the management of these cases, we completed

a literature review. To our knowledge, there is only one other case that reports clozapine use during a stem cell transplant.⁴

Psychiatric history

The patient is a 63-year-old Afro-Caribbean lady who has a long-standing history of treatment-resistant schizophrenia. She first presented to the services in 1987 with auditory hallucinations and persecutory delusions. Following a diagnosis of paranoid schizophrenia, she has been prescribed six different antipsychotics over the years, both typical and atypical, and has required six hospital admissions, both informally and under the Mental Health Act. There was no real stability in her mental state until 2001, when clozapine was initiated and amisulpride was augmented due to residual symptoms. She has been well maintained on these medications since, receiving clozapine 200mg in the morning and 300mg at night and amisulpride 200mg twice a day.

Medical history

In 2011, the patient presented to her GP with nephrotic syndrome. Following extensive investigations, a renal biopsy confirmed a diagnosis of AL amyloidosis, confined to the kidneys. This is a rare, incurable condition where misfolded

proteins, known as amyloid, accumulate in tissues and thus disrupt organ function.⁵ If untreated the average life expectancy is approximately 12 months from diagnosis.⁵ Fortunately, this has improved with the use of chemotherapy and stem cell transplantation.

The patient's initial chemotherapy regimen included cyclophosphamide, dexamethasone and thalidomide (CTD). In 2012, her cyclophosphamide was withheld due to concerns regarding interaction with clozapine, despite no recorded incidents of neutropenia. She then received bortezomib and dexamethasone (as Vel-dex), and was considered suitable for an autologous stem cell transplant. In December 2014 her stem cells were harvested and in May 2015 she was admitted to hospital for ablation chemotherapy and stem cell transplantation.

Stem cell transplantation

The patient had been maintained on clozapine leading up to the autologous stem cell transplant, with no recorded incidents of neutropenia. However, the issue faced was whether to continue clozapine during such an intensive procedure where ablation therapy would inevitably lead to neutropenia. A multidisciplinary meeting was held between psychiatry, haematology,

pharmacy, and the clozapine monitoring service – Zaponex Treatment Access System (ZTAS). Consequently, it was considered in the patient's best interests to continue the clozapine. An off-licence agreement was signed with ZTAS, agreeing a cut-off value of 0 for white blood cell count (WBC), and an absolute neutrophil count of 0.

Following admission to hospital she received melphalan conditioning at a dose of 200mg/m². Five days later her WBC had dropped to 2.5x10⁹/L, neutrophils were 2.3x10⁹/L, and she was thrombocytopenic. Her harvested stem cells were re-implanted, and it was expected that she would remain cytopenic for two to three weeks. Her WBC and neutrophil count decreased further and were recorded as 0.1x10⁹/L and 0x10⁹/L respectively. Subsequently, she spiked a temperature and required treatment with antibiotics for coagulase-negative staphylococci.

She had to remain an inpatient until her blood count sufficiently recovered. During this time psychotic symptoms started to emerge and she became more distracted, responding to only single words. Loneliness is known to precipitate the patient's psychiatric symptoms, and given the fact that she required isolation in a side room, the concern was that she would deteriorate further. Fortunately, she has an excellent rapport with her community psychiatric nurse, who supported her well.

Progress

Due to the ongoing involvement of the MDT, clozapine was continued despite repeated red alerts, and the patient was successfully discharged in June 2015. There was a further red alert in July 2015, but daily blood tests showed that her neutrophils and WBC stabilised.

She was followed up at the National Amyloidosis Centre in

London, in September 2015, where she reported that she felt back to normal. The centre reported that she tolerated the stem cell transplant well and maintained a complete light-chain response.

She has continued to take clozapine and her schizophrenia has remained stable.

Discussion

A literature review of available evidence, using the keywords clozapine and chemotherapy, was completed using Medline and a cross-database search. This generated 69 results, but a number of these were duplicates. As stated, there appeared to be only one other reported case on the use of stem cell transplantation during clozapine treatment, reported by Rosenberg *et al.*⁴ In this case clozapine was discontinued due to concerns about agranulocytosis, but recommenced because of deterioration in the patient's mental state.

Case reports imply that cessation of clozapine generally leads to a psychotic relapse and the need to reinstate clozapine.^{4,6–10}

Munshi *et al.*⁶ report a case of a patient who had been mentally stable for 15 years before developing B-cell lymphoma. As a predictable consequence of the R-CHOP chemotherapy regimen, the patient developed a red result and the community psychiatrist stopped the clozapine. The patient subsequently had a psychotic relapse, with an inadequate response to quetiapine, olanzapine or aripiprazole. Due to the nature of his relapse he was unable to receive his second cycle of R-CHOP. Following an MDT discussion clozapine was reintroduced; the patient received a further six cycles of chemotherapy and went into remission.

If a patient has been stable on clozapine for a number of years then the risk of blood dyscrasia is

low. The risk of clozapine-induced agranulocytosis or neutropenia after one year of treatment is less than 1%.⁷ In our case report the patient's cytopenia was almost certainly secondary to the ablation chemotherapy. However, one study has shown that of 53 patients rechallenged with clozapine following an initial blood dyscrasia, 38% developed a further leucopenia or neutropenia.¹¹ Clozapine has been shown to activate some of the same apoptic pathways as chemotherapy,¹² but it is not clear if concurrent use has an additional harmful effect.¹³

In many of the available case reports where neutropenia did occur, granulocyte-colony stimulating factor (G-CSF) was used to help increase white cell counts.^{6,9–10,13} As a result, clozapine could be continued and the severity and duration of chemotherapy-induced neutropenia was probably reduced.¹⁴ Our case differs in that G-CSF is contraindicated in amyloidosis. In patients with AL amyloidosis, G-CSF-induced stem cell mobilisation is associated with volume overload, arrhythmias, and capillary leak syndrome.¹⁵ The risk is therefore significant and can occur in patients without amyloidosis with cardiac involvement.

Conclusion

There is limited literature on the use of chemotherapy, stem cell transplantation and clozapine. The evidence that is available consists only of case reports and case series. Due to the nature of these cases, randomised control trials are not an option and thus no standardised guidelines are available.

The available evidence suggests that clozapine in combination with chemotherapy does not lead to an increased risk of life-threatening blood dyscrasias and this risk is lowest in those that have received clozapine for over a year.

This case highlights the importance of a multidisciplinary approach and it is fundamental that all relevant specialties are involved in an individual's care.

Dr Burlingham is a CT2 Psychiatry, Dr Anandakumar is an Associate Specialist and Dr Lisa Brownell is a Consultant Psychiatrist, all at Birmingham and Solihull Mental Health NHS Foundation Trust.

Declaration of interest

No conflicts of interest were declared.

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