Walking the fine line between risk and benefit in managing clozapine-induced agranulocytosis

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Background

Clozapine is limited in practice for treatment-resistant schizophrenia because of its unique adverse effect profile.[1] Occurring more commonly in the first 18 weeks of treatment, clozapine is reported to cause neutropenia in 2% to 3% of patients and agranulocytosis in 1% of patients.[1,2] Due to these life-threatening adverse effects, close monitoring of white blood cell (WBC) and neutrophil count is mandatory and distribution is restricted to registered prescribers and pharmacists.[1,2] Clozapine is contraindicated in patients with new onset and prior drug-induced neutropenia or agranulocytosis, and protocol dictates patients must immediately cease treatment and avoid re-exposure to clozapine.[2] There is limited evidence to support the continuation of clozapine therapy and the use of concomitant granulocyte colony stimulating factor (G-CSF) in clozapine-induced agranulocytosis.

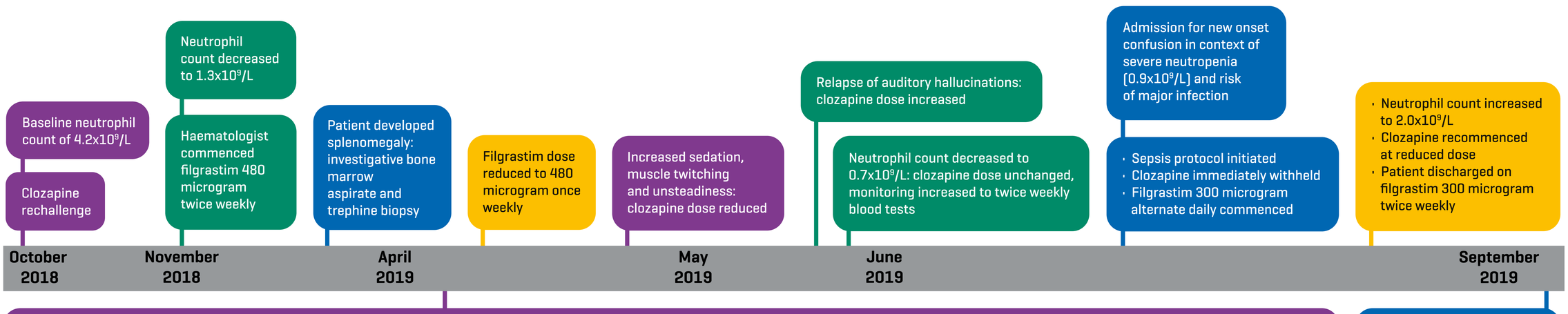
Objective

To present a case on the use of filgrastim (G-CSF) for the management of clozapine-induced agranulocytosis in a patient with treatment-resistant schizophrenia.

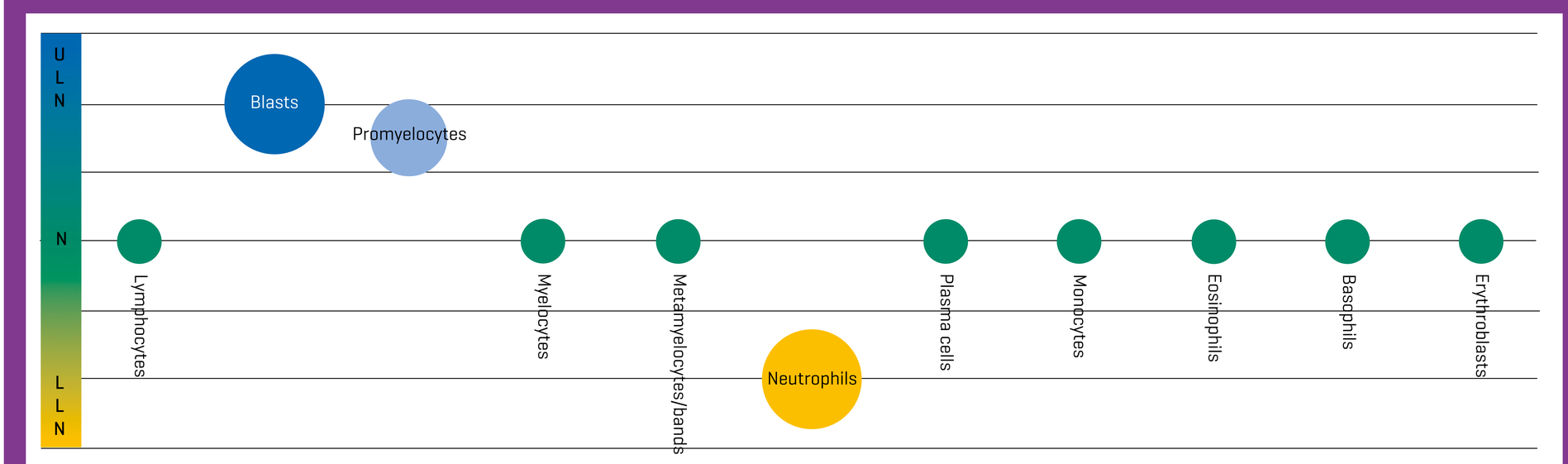
Clinical Features

In October 2018, a 41-year-old Caucasian male was rechallenged with clozapine, after treatment cessation two years prior due to clozapine-induced agranulocytosis. Patient had a longstanding history of treatment-resistant schizophrenia, controlled with clozapine for 10 years. Rechallenge was based on poor response to other antipsychotics, despite maximal doses and trials of various drug combinations. The patient was under the care of the psychiatrist at a rural hospital. A haematologist, practicing at the neighbouring regional hospital 50 kilometres away, consulted on the case to guide management.

Case Progress and Outcomes



Bone Marrow Aspirate and Trephine Biopsy Results: identified normal overall cellularity, with several abnormalities and a marked reduction in mature neutrophils. This may reflect a response to long-term routine administration of G-CSF, or alternatively be an early indicator of underlying neoplastic disorder of the bone marrow.



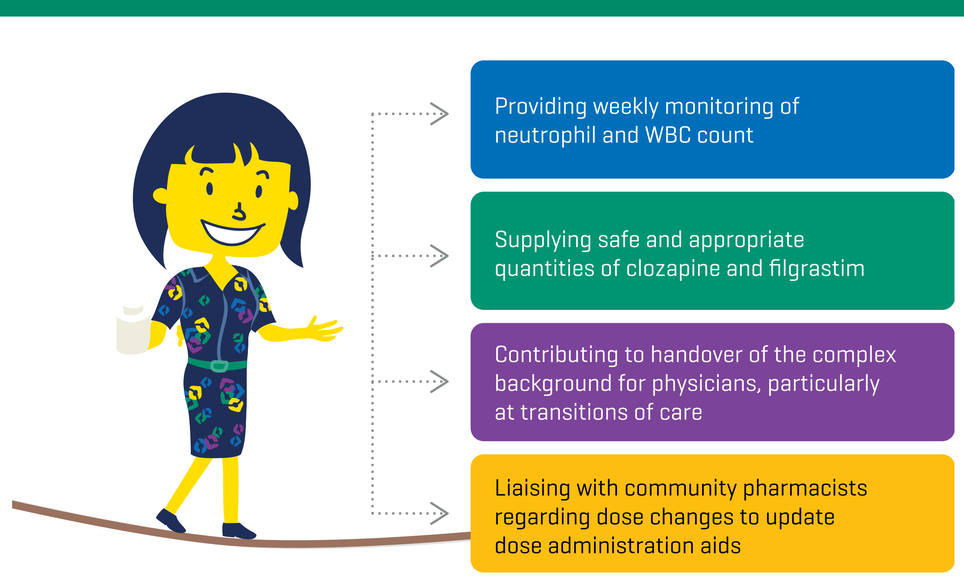
*ULN: Upper Limit of Normal; N: Normal; LLN: Lower Limit of Normal

Repeat bone marrow aspirate and trephine biopsy, using novel testing platform, Next Generation Sequencing, to assist with distinguishing between a clonal or reactive (G-CSF) cause (results pending)

Pharmacist Interventions

This case presented challenges relating to the continuity of care, often stemming from rural hospital limitations. The hospital is susceptible to a high rotation of locum physicians, no on-site haematologist or capacity to complete high risk bone marrow biopsy procedures, and a sole clinical pharmacist to review and supply clozapine weekly.

The pharmacist improved consistency and continuity of care for the patient by:



- Providing weekly monitoring of neutrophil and WBC count
- Supplying safe and appropriate quantities of clozapine and filgrastim
- Contributing to handover of the complex background for physicians, particularly at transitions of care
- Liaising with community pharmacists regarding dose changes to update dose administration aids

Conclusion

This case demonstrates the challenges faced by a multi-disciplinary team within a rural setting in managing treatment-resistant schizophrenia patients with a history of clozapine-induced agranulocytosis. Specialist care was essential to balance the mental health benefits of clozapine, against the significant risks associated with concomitant long-term G-CSF to manage clozapine-induced agranulocytosis. Pharmacist consultation remained consistent throughout the case to uphold strict monitoring requirements, medication safety, and maintain communication between the multi-disciplinary team.

References

1. Psychotropic 7[1] Expert Group. Therapeutic guidelines: Schizophrenia and related psychoses. Melbourne: Therapeutic Guidelines Limited; 2014.
2. Therapeutic Goods Administration. Australian Product Information – Clopine (Clozapine). Canberra: Therapeutic Goods Administration; 2019. Available from <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-01813-1&d=201910161016933>.