Should clozapine be discontinued in a patient receiving chemotherapy?

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Mr. A is diagnosed with leukemia. He has schizophrenia and has long been stable on clozapine. Can this medication be continued, or is the risk of agranulocytosis too high?

CASE Schizophrenia, leukemia, and chemotherapy

Mr. A, age 30, has schizophrenia but has been stable on clozapine 600 mg/d. He presents to the emergency department with generalized pain that started in his right scapula, arm, elbow, and back. Laboratory tests and a diagnostic examination reveal severe leukocytosis, thrombocytopenia, and anemia, and clinicians diagnose Mr. A with B-cell acute lymphocytic leukemia (B-ALL). Upon admission, Mr. A is neutropenic with an absolute neutrophil count (ANC) of 1,420 µL (reference range 2,500 to 6,000 µL). The hematology team recommends chemotherapy. The treating clinicians also consult the psychiatry team for recommendations on how to best manage Mr. A's schizophrenia during chemotherapy, including whether clozapine should be discontinued.

HISTORY Stable on clozapine for >10 years

Mr. A was diagnosed with schizophrenia at age 15 after developing paranoia and auditory hallucinations of people talking to him and to each other. He had been hospitalized multiple times for worsened auditory hallucinations and paranoia that led to significant agitation and violence. Previous treatment with multiple antipsychotics, including haloperidol, quetiapine, aripiprazole, olanzapine, risperidone, and ziprasidone, was not successful. Mr. A began clozapine >10 years ago, and his symptoms have been stable since, without any further psychiatric hospitalizations. Mr. A takes clozapine 600 mg/d and divalproex sodium 1,500 mg/d, which he tolerates well and without significant adverse effects. Though he continues to have intermittent auditory hallucinations, they are mild and manageable. Mr. A lives with his mother, who reports he occasionally talks to himself but when he does not take clozapine, the auditory hallucinations worsen and cause him to become paranoid and aggressive. His ANC is monitored monthly and had been normal for several years until he was diagnosed with B-ALL.

What is the next step in managing Mr. A's schizophrenia?

a) Maintain clozapine as prescribed and continue monthly ANC monitoring

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Disclosures

The authors report no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

doi: 10.12788/cp.0254

b) Maintain clozapine as prescribed and more frequently monitor ANC
c) Decrease clozapine and continue monthly ANC monitoring
d) Discontinue clozapine and start another antipsychotic

The authors' observations

The decision to continue clozapine during chemotherapy is challenging and should weigh the risk of agranulocytosis against that of psychiatric destabilization. Because clozapine and chemotherapy are both associated with agranulocytosis, there is concern that concurrent treatment could increase this risk in an additive or synergistic manner. To the best of our knowledge, there are currently no controlled studies investigating the interactions between clozapine and chemotherapeutic agents. Evidence on the hematopoietic consequences of concurrent clozapine and chemotherapy treatment has been limited to case reports because the topic does not lend itself well to randomized controlled trials.

A recent systematic review found no adverse outcomes among the 27 published cases in which clozapine was continued during myelosuppressive chemotherapy.[1] The most notable finding was an association between clozapine discontinuation and psychiatric decompensation, which was reported in 12 of 13 cases in which clozapine was prophylactically discontinued to minimize the risk of agranulocytosis.

Patient-specific factors must also be considered, such as the likelihood that psychotic symptoms will recur or worsen if clozapine is discontinued, as well as the extent to which symptom recurrence would interfere with cancer treatment. Clinicians should evaluate the feasibility of switching to another antipsychotic by obtaining a thorough history of the patient's previous antipsychotics, doses, treatment duration, and response. However, many patients are treated with clozapine because their psychotic symptoms did not improve with other treatments. The character and severity of the patient's psychotic symptoms when untreated or prior to clozapine treatment can provide a clearer understanding of how a recurrence of symptoms may interfere with cancer treatment. To formulate an accurate assessment of risks and benefits, it is necessary to consider both available evidence and patient-specific factors. The significant agitation and paranoia that Mr. A experienced when not taking clozapine was likely to disrupt chemotherapy. Thus, the adverse consequences of discontinuing clozapine were both severe and likely.

TREATMENT Continuing clozapine

After an extensive discussion of risks, benefits, and alternative treatments with the hematology and psychiatry teams, Mr. A and his family decide to continue clozapine with increased ANC monitoring during chemotherapy. Concurrent treatment was pursued with close collaboration among the patient, the patient's family, and the hematology and pharmacy teams, and in careful consideration of the clozapine risk evaluation and mitigation strategy. Mr. A's ANC was monitored daily during chemotherapy treatments and weekly in the intervals between treatments.

As expected, chemotherapy resulted in bone marrow suppression and pancytopenia. Mr. A's ANC steadily decreased during the next 10 days until it reached 0 µL. This was consistent with the predicted ANC nadir between Day 10 and Day 14, after which recovery was expected. However, Mr. A's ANC remained at 0 µL on Day 15.

How can you determine if prolonged neutropenia is a result of clozapine-induced agranulocytosis or chemotherapy?

a) Review timing of treatments and clinical course of hematologic responses, including level of other blood cell lines such as lymphocytes, red blood cells, and platelets
b) Perform bone marrow biopsy

Clinical Point

Both clozapine and chemotherapy are associated with agranulocytosis

Table

Bone marrow characteristics in patients with nonchemotherapy drug-induced agranulocytosis

Category	Description
Type I	Hypercellular with adequate neutrophil precursors but an arrested neutrophil maturation, with few or no mature forms of neutrophils beyond myelocytes
Type II	Severe reduction or complete absence of granulocytic precursors with normal or increased erythropoiesis and megakaryocytes

Source: References 8,9

Clinical Point

Timing, clinical course, and hematologic monitoring can provide insight into whether clozapine may be responsible for neutropenia

c) Stop chemotherapy and monitor ANC
d) Stop clozapine and monitor ANC

The authors' observations

Temporary decreases in ANC are expected during chemotherapy, and the timing of onset and recovery is often well characterized. Prior to Day 15, the observed progressive marrow suppression was solely due to chemotherapy. However, because Mr. A's ANC remained 0 µL longer than anticipated, reevaluation of clozapine's effects was warranted.

Timing, clinical course, and comprehensive hematologic monitoring can provide important clues as to whether clozapine may be responsible for prolonged neutropenia. Though a prolonged ANC of 0 µL raised concern for clozapine-induced agranulocytosis (CIAG), comprehensive monitoring of hematologic cell lines was reassuring because CIAG selectively targets granulocytic cells (neutrophils).[2] In contrast, chemotherapy can affect other cell lineages, including lymphocytes, red blood cells, and platelets, which causes pancytopenia.[3] For Mr. A, though the clinical presentation of pancytopenia was significant and concerning, it was inconsistent with CIAG.

Additionally, the patient's baseline risk of CIAG should be considered. After 18 weeks of clozapine treatment, the risk of CIAG decreases to a level similar to that associated with other antipsychotics.[4,5] Therefore, CIAG would be unlikely in a patient treated with clozapine for more than 1 year and who did not have a history of neutropenia, as was the case with Mr. A.

While bone marrow biopsy can help differentiate between the causes of agranulocytosis,[6] it is highly invasive and may not be necessary if laboratory evidence is sufficient. However, if a treatment team is strongly considering discontinuing clozapine and there are no suitable alternatives, a biopsy may provide additional clarification.

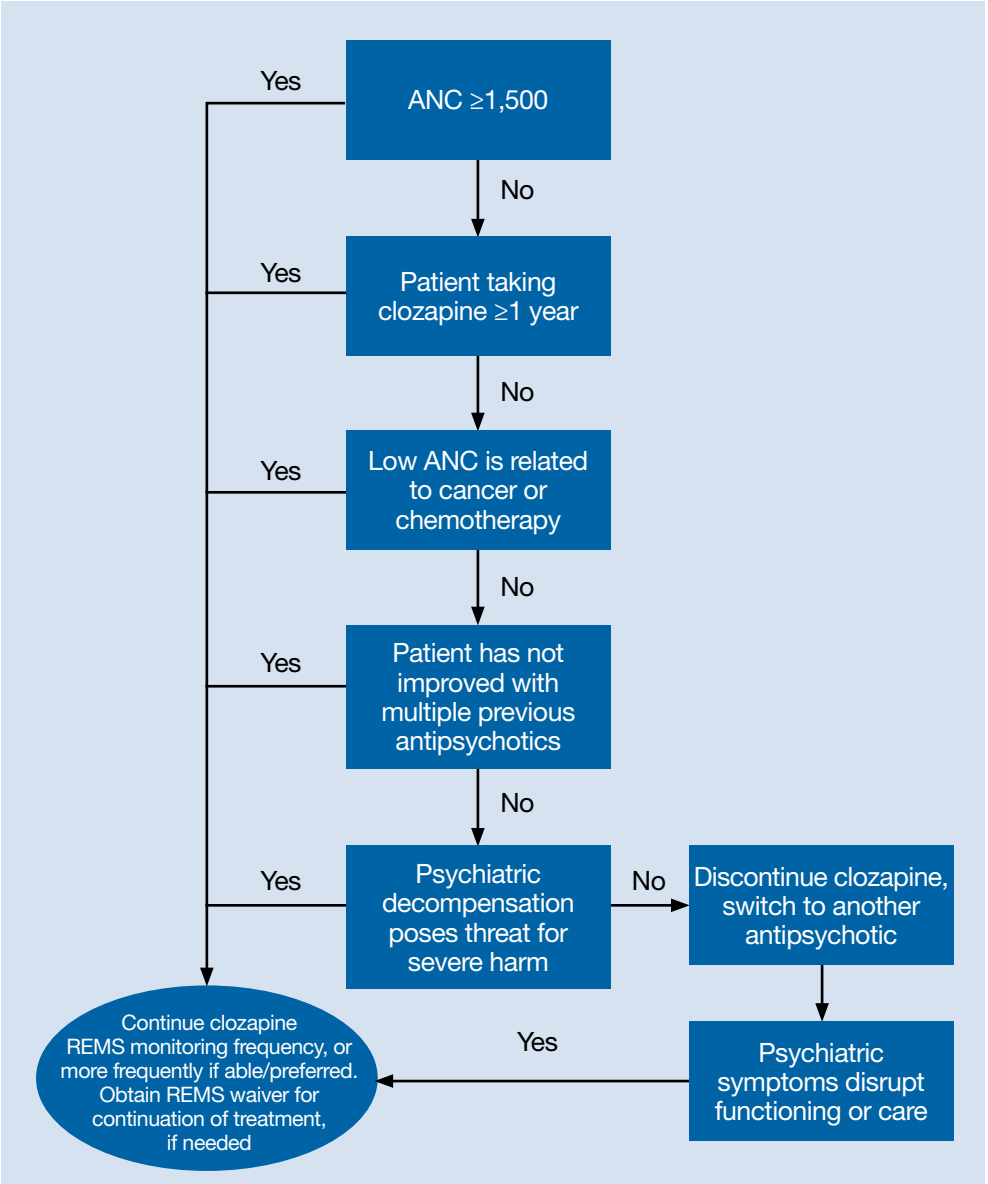
TREATMENT CAR T-cell therapy and cancer remission

Clozapine is continued with daily monitoring. On Day 19, Mr. A's ANC increases, reaching 2,600 µL by discharge on Day 40. Mr. A remains psychiatrically stable throughout his hospitalization and does not experience any complications associated with neutropenia, despite its prolonged duration.

Unfortunately, multiple cycles of chemotherapy fail to induce remission. Mr. A is referred for CD19/CD22 chimeric antigen receptor (CAR) T-cell therapy, which helps achieve remission. Allogeneic hematopoietic stem cell transplant (HSCT) is recommended to maximize the likelihood of sustained remission.[7] As with chemotherapy, Mr. A and his family agree with the multidisciplinary treatment recommendation to continue clozapine during both CAR T-cell therapy and HSCT, because the risks associated with psychiatric decompensa-

Figure

Continuing clozapine during cancer treatment: An algorithm



ANC: absolute neutrophil count; REMS: risk evaluation and mitigation strategy

tion were greater than a potential increased risk of agranulocytosis. Clozapine treatment is continued throughout both therapies without issue.

Four months after HSCT, Mr. A is admitted for neutropenic fever and left face cellulitis. Upon admission, his ANC is 30 µL and subsequently decreases to 0 µL. In addition to neutropenia, Mr. A is also anemic and thrombocytopenic. He undergoes a bone marrow biopsy.

What findings on bone marrow biopsy would indicate the neutropenia was not clozapine-induced?

a) Markedly hypocellular bone marrow with signs of regeneration

Clinical Point

Although invasive, a bone marrow biopsy can help differentiate between the causes of agranulocytosis if additional clarification is needed

Related Resources

- Grainger BT, Arcasoy MO, Kenedi CA. Feasibility of myelosuppressive chemotherapy in psychiatric patients on clozapine: a systematic review of the literature. Eur J Haematol. 2019;103(4):277-286. doi:10.1111/ejh.13285
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Drug Brand Names

Aripiprazole • Abilify
Clozapine • Clozaril
Divalproex sodium • Depakote
Epoetin alfa • Epogen
Haloperidol • Haldol
Olanzapine • Zyprexa
Quetiapine • Seroquel
Risperidone • Risperdal
Ziprasidone • Geodon

Clinical Point

Because Mr. A's neutropenia was unlikely due to clozapine, this agent was continued throughout his cancer treatment

b) Hypercellular bone marrow with adequate neutrophil precursors but an arrested neutrophil maturation, with few or no mature forms of neutrophils beyond myelocytes

c) Severe reduction or complete absence of granulocytic precursors with normal or increased erythropoiesis and megakaryocytes

The authors' observations

While no published cases have examined the bone marrow of patients experiencing CIAG, 2 retrospective studies have characterized 2 classes of bone marrow findings associated with drug-induced agranulocytosis resulting from nonchemotherapeutic agents (***Table, page 46***).[8,9] Type I marrow appears hypercellular with adequate neutrophil precursors but an arrested neutrophil maturation, with few or no mature forms of neutrophils beyond myelocytes.[8,9] Type II demonstrates a severe reduction or complete absence of granulocytic precursors with normal or increased erythropoiesis and megakaryocytes.[8,9] These findings have been used to accurately differentiate between chemotherapy and nonchemotherapy drug-induced agranulocytosis,[6] resulting in successful identification and discontinuation of the responsible agent.

Mr. A's bone marrow biopsy showed severe pancytopenia with profound neutropenia and normocytic anemia, without evidence of residual leukemia, inconsistent with Type I or Type II. Findings were suggestive of a myelodysplastic syndrome, consistent with secondary graft failure. Symptoms resolved after treatment with antibiotics, granulocyte colony-stimulating factor, epoetin alfa, and thrombopoietin. Mr. A's ANC remained 0 µL for 22 days before returning to normal (>1,500 µL) by Day 29. He had no secondary complications resulting from neutropenia. As the clinical evidence suggested, Mr. A's neutropenia was unlikely to be due to clozapine. Clozapine was continued throughout his cancer treatment, and he remained psychiatrically stable.

Clozapine, cancer treatments, and agranulocytosis

This case demonstrates that clozapine can be safely continued during a variety of cancer treatments (ie, chemotherapy, CAR T-cell therapy, HSCT), even with the development of agranulocytosis and prolonged neutropenia. Evidence to guide psychiatric clinicians to evaluate the likelihood that agranulocytosis is clozapine-induced is limited.

Bottom Line

Clozapine can be safely continued during a variety of cancer treatments (ie, chemotherapy, CAR T-cell therapy, HSCT), even in patients who develop agranulocytosis and prolonged neutropenia. Based on our experience and limited evidence, we offer an algorithm to assist clinicians faced with this challenging clinical dilemma.

We offer an algorithm to assist clinicians faced with this challenging clinical dilemma (***Figure, page 47***). Based on our experience and limited current evidence, we recommend continuing clozapine during cancer treatment unless there is clear evidence to suggest otherwise. Presently, no evidence in published literature suggests worsened outcomes in patients treated concurrently with clozapine and cancer therapies.

OUTCOME Cancer-free and psychiatrically stable

Mr. A continues clozapine therapy throughout all phases of treatment, without interruption. No adverse effects are determined to be secondary to clozapine. He remains psychiatrically stable throughout treatment, and able to participate and engage in his oncologic therapy. Mr. A is now more than 1 year in remission with no recurrence of graft failure, and his psychiatric symptoms continue to be well controlled with clozapine.

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Clinical Point

We recommend continuing clozapine during cancer treatment unless there is clear evidence to suggest otherwise