

CLOZAPINE, CANCER CHEMOTHERAPY AND NEUTROPENIA - DILEMMAS IN MANAGEMENT

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INTRODUCTION

Clozapine is the antipsychotic of choice in the management of treatment resistant schizophrenia. Neutropenia is a rare but serious adverse effect of clozapine. The risk for neutropenia with clozapine is highest in the first 18 weeks of treatment and decreases with time though a few cases were reported after several years of continued therapy. Different protocols that guide the monitoring for neutropenia have been developed; in Australia we follow the protocol implemented through the Clopine® Alert Programme.

Despite an increased risk of poor physical health and shortened life span in patients with schizophrenia, the overall incidence of cancer in schizophrenia is not significantly increased. This suggests a discrepancy between cancer risk exposure (e.g., smoking) and cancer incidence in schizophrenia (Goldacre et al. 2005), an association that has been described paradoxical (Hodgson et al, 2010). Nevertheless, these two conditions co-occur (Goldacre et al. 2005). It can create difficulties in management when the patient is clinically stable on clozapine and require chemotherapeutic agents that can frequently cause myelosuppression and neutropenia as it can pose several dilemmas for the clinicians. A systematic literature search identified 11 case-reports (Avnon & Stolerman 1993, Bareggi et al. 2002, Frieri et al. 2008, Goulet & Grignon 2008, Haut 1995, Hundertmark and Campbell 2001, Kolli et al. 2012, McKenna et al. 1994, Rosenberg et al. 2007, Rosenstock 2004, Wesson et al. 1996). The results are summarized in Table 1. Interestingly, Clozapine was successfully continued during chemotherapy treatment regime in most of these cases despite neutropenia (Bareggi et al. 2002, Goulet & Grignon 2008, Kolli et al. 2012, Rosenberg et al. 2007, Rosenstock 2004, Wesson et al. 1996). There is however little guidance to appropriately manage the potential risks under these circumstances (Rosenstock 2004). We present here three cases and discuss three of the dilemmas that clinicians can face under such circumstances- identifying the offending agent, decision to continue clozapine treatment and use of human granulocyte colony stimulating factor (G-CSF).

SUBJECTS

These were patients of the Hunter New England Mental Health Service; we received the Hunter New England Ethics Committee approval to present de-identified case reports.

CASE REPORTS

Case 1 was a 53-year-old male with stable chronic paranoid schizophrenia taking clozapine monotherapy for about 5 years. In early 2010, he was diagnosed with stage 2c Seminoma and received three cycles of chemotherapy using cisplatin, bleomycin and etoposide. During the first cycle of chemotherapy, the patient developed leukopenia (count = $1.4 \times 10^9/L$) and neutropenia (count = $0.3 \times 10^9/L$). The leukocyte and neutrophil counts became normal after administration of G-CSF, which was used till the completion of chemotherapy with no further incidents of blood dyscrasia. Clozapine was continued throughout the period and his mental status remained stable during the entire course.

Case 2 was a 41-year-old female with stable chronic schizo-affective disorder taking clozapine and sodium valproate for more than 10 years. She was diagnosed with carcinoma in the left breast in 2008. This was managed with radical mastectomy and chemotherapy with 3 cycles of chemotherapy using docetaxel. Following the first cycle of chemotherapy leukopenia (count = $2.1 \times 10^9/L$) and neutropenia (count = $0.2 \times 10^9/L$) was detected. Following discussion with the haematologist and the oncology team, clozapine, valproate and chemotherapy were continued without interruption with weekly monitoring of total blood counts. G-CSF was not used. The blood indices returned to normal in four weeks, coinciding approximately with completion of chemotherapy. The mental status remained in stable remission.

Case 3 was a 32 year old woman with a diagnosis of schizophrenia. She was started on clozapine monotherapy in 2006. She remained in stable residual state and was living independently with minimal community support. She was diagnosed with large bowel cancer in 2010. She received 22 fractions of adjunct radio therapy

Table 1. Clozapine and chemotherapy: Summary of literature review

Author	Patient Age	Sex	Diag.	Type of cancer	Chemotherapy	Clozapine maintained or not during chemotherapy	Leucopenia Yes or no
Avnon & Stolerman	44	F	Sch	Moderately differentiated carcinoma of uteral endometrium and type II B well differenetiated papillary serous carcinoma of ovary	N/A	Yes	Yes
Bareggi et al. 2002	37	M	Sch	Undifferentiated nasopharyngeal carcinoma	Cisplatin plus radiotherapy	Yes	Lowest count neutrophils 1.5×10^9
Frieri et al. 2008	44	M	Sch	Follicular non-Hodgkin's lymphoma	Chlorambucil 6 cycles followed by Fludarabine and Mitoxantrone 4 cycles Followed by combination of Cyclophosphamide, Vincristine and Prednisolone	Clozapine discontinued during Chlorambucil therapy, but was recommened due to worsening in clinical state	Yes and G-CSF was administered
Goulet & Grignon 2008	51	M	Sch	Small cell lung carcinoma	Cisplatin and Etoposide	Yes	No
Haut et al. 1995	41	M	Sch	High grade non-Hodgkin's lymphoma	Cyclophosphamide Hydrozydaunorubicin Oncovin Prednisolone	Discontinued but reinstated following psychotic relapse	No
Hundertmark & Campbell 2001	N/A	F	Sch	Diffuse large B-cell lymphoma	N/A	Clozapine was commenced to stabilize the patient	Yes
Kolli et al. 2012	46	M	Sch	Diffuse large B-cell lymphoma with Central Nervous System	CHOP regimen that consists of Cyclophosphamide, Vincristine Doxorubicin, and Prednisone, followed by Rituximab and Methotrexate	Yes	Yes; patient given G-CSF
McKenna et al. 1994	49	M	Sch	Small cell lung cancer	Cisplatinum Etoposide	Yes	N/A
Rosenberg et al. 2007	39	M	BA D	Hodgkin's lymphoma	Ablation chemotherapy and stem cell transplant	Clozapine was discontinued for fear of agranulocytosis and then recommened due to poor response and decompensation in mental state	Yes
Rosenstock 2004	46	F	Sch	Breast cancer	Doxorubicin Cyclophosphamide Radiotherapy	Yes	Yes
Wesson 1996	40	M	Sch	Testicular teratoma	Bleomycine Etoposide Cisplatin	Yes	Yes

and chemotherapy (5-fluorouracil). Following the start of chemotherapy she developed neutropenia (count= $1.4 \times 10^9/L$) but total leukocyte count was normal ($3.6 \times 10^9/L$). Clozapine was continued after considering the possibility that the neutropenia could be chemotherapy-

related. Subsequent blood counts were not consistently in the abnormal range as the total leukocyte counts ranged between $3.7 \times 10^9/L$ and $2.4 \times 10^9/L$ and neutrophil count between $2.7 \times 10^9/L$ and $1.4 \times 10^9/L$ and. But four weeks after completion of chemotherapy, she developed

febrile neutropenia with zero granulocyte count and total leucocytes $=0.5 \times 10^9/L$. At this juncture it was determined that clozapine, rather than the chemotherapy may be the likely offending agent and clozapine was ceased abruptly in view of her clinical condition. G-CSF was used and the patient received intensive treatment with broad spectrum antibiotics. The abrupt cessation of clozapine was associated with deterioration in her mental status and relapse of psychotic symptoms. Use of risperidone and quetiapine did not lead to any improvement. Clozapine was restarted but neutropenia (count $= 0.6 \times 10^9/L$) recurred after 3 weeks of therapy that needed further treatment with G-CSF. Clozapine was ceased and Ms C was commenced on olanzapine with only partial control of psychotic symptoms (Table 1).

DISCUSSION

We faced three dilemmas in managing these patient situations.

Dilemma 1. What is the offending agent?

The first clinical dilemma was to clarify if the neutropenia was secondary to chemotherapy or clozapine; answering this question would help in defining the resulting course of action- to continue clozapine or to stop it. In all the three cases, the temporal relationship between incidence of the blood dyscrasia and the initiation of chemotherapy led us to consider the possibility that neutropenia in these cases was related to chemotherapy and not clozapine. But in Case 3 we were temporarily misled by this reasoning. The development of febrile neutropenia four weeks after completion of chemotherapy and the recurrence of neutropenia on rechallenge with clozapine established its origins. In all the three cases we considered that both drugs could have contributed to neutropenia though there were no references that establish a synergistic effect of clozapine and chemotherapy on blood counts (Goulet & Grignon 2008). The role of sodium valproate in case 2 remains unclear as there are reports of occurrence of neutropenia with its use (Stoner et al. 2008). Unfortunately clinical rules such as the Naranjo algorithm are not suitable to identify drug-drug interactions.

Dilemma 2. To continue or discontinue clozapine therapy

Clozapine has the best evidence base for patients with treatment resistant schizophrenia. All our three patients had prolonged course of unstable and severe psychosis before their symptoms resolved with clozapine allowing them to live independently in the community. The knowledge that neutropenia, which may have been chemotherapy related in these cases, still required cessation of clozapine by strict adherence to the protocol (@Clopine Connect placing them at risk of disastrous consequence to their mental status created both clinical and an ethical dilemma. Cases 1 and 2 continued to maintain their mental status as they were also continued on clozapine while Case 3 showed

deterioration as we were compelled to withdraw clozapine. This is in keeping with available evidence. In three reports (Haut et al. 1995, Rosenberg et al. 2007, Frieri et al. 2008) clozapine was ceased and later recommenced following deterioration in mental state. Recurrence of neutropenia on restarting clozapine is not rare. An analysis reported that 38% of 53 patients (not on cancer chemotherapy) who previously experienced neutropenia, when rechallenged with clozapine, experienced recurrence of neutropenia, most of them occurring more quickly on rechallenge (Dunk et al. 2006). Our experience with case 3 was in keeping with this finding.

Dilemma 3. When to use of Granulocyte Colony Stimulating Factor (G-CSF)

Our third dilemma was to decide whether to use G-CSF or to closely monitor for risks through the period of chemotherapy, which would mean an increased risk of serious infection due to neutropenia. G-CSF is recommended for management of treatment-emergent neutropenia and as a prophylaxis to reduce risk of severe neutropenia. Although use of CSF in clozapine induced neutropenia has been reported (Hagg et al. 2003), its use in the context of chemotherapy is less well-studied (Kolli et al. 2012). Cost however is a major limiting factor in the widespread use of G-CSF (Dale 2002). The use of G-CSF in cancer chemotherapy is guided by the risk for Febrile Neutropenia (Aapro et al. 2006). In Australia, G-CSF is available under the Highly Specialised Drugs Program. In the three cases described here, the oncology team made this decision as they were in a better position to assess risk for Febrile Neutropenia.

CONCLUSION

There is very little clinical evidence to draw any general conclusion as to the safety of maintaining clozapine administration during chemotherapy (Goulet & Grignon 2008). While clozapine could activate common apoptotic pathways shared with anticancer drugs, the mechanisms of neutropenia secondary to clozapine is different from those of the antineoplastic drugs induced neutropenia. The predictable course of chemotherapy-induced myelosuppression also contrasts with the idiosyncratic occurrence of agranulocytosis due to clozapine. The management of neutropenia in patients treated with clozapine and cancer chemotherapy is a complex one and needs to be individually tailored with involvement of the respective medical teams in the decision-making.

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