HODGKIN’S LYMPHOMA IN A PATIENT WITH RESISTANT SCHIZOPHRENIA ON CLOZAPINE THERAPY


ABSTRACT

We are reporting here a case of 31a year-old-male patient, with resistant schizophrenia, who was treated by clozapine. After three years of treatment, he developed Hodgkin’s lymphoma. Clozapine was discontinued and chemotherapy was initiated which led to complete remission. Unfortunately, his mental condition deteriorated, and Olanzapine was introduced to treat this relapse, which is his current prophylactic antipsychotic medication. Little is known about Clozapine and any potential relation with malignancy if any. We wish to report this to stimulate further research in this field.

Key words: Clozapine, agranulocytosis, Hodgkin's lymphoma

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Case Report

A 31-year-old male patient, known to have schizophrenia for the last ten years, was maintained on conventional antipsychotic agents (mainly Phenothiazines & Buterophynone) but without satisfactory improvement. Accordingly, he was reassessed and considered as a case of resistant schizophrenia; Clozapine was introduced in June 1998, which was gradually built up to 300mg per day (maximum Clozapine dose is 900mg/day)(1). Two weeks after commencing Clozapine he developed epileptic fits(1,2) and 900mg Sodium Valproate was started in divided doses to control his seizures. Clozapine treatment was monitored according to the British National Formulary.

The patient showed significant improvement and stability in his mental condition and global function which lasted for around three and half years until the 26th of December 2001, when he presented with a neck swelling and a stable mental status. Physical examination revealed multiple bilateral cervical lymph node enlargements but no other lymphadenopathy; liver and spleen were not palpable. Cervical lymph node biopsy was taken and was reported as Hodgkin's lymphoma of mixed cellularity type (CD15 negative, CD30 positive) (Fig. 1 & 2).

He was admitted to the Hematology and Oncology Department at King Hussein Medical Center for further management. Clozapine and Sodium Valproate were stopped, and 12 cycles of chemotherapy were given. Each cycle consisted of Adriamycin 25mg/m square, Bleomycin 15mg, Velban 10mg, and DTIC (Dacarbazin) 375mg/m square. Radiotherapy was planned for the patient however, it was not available.

Within four weeks of Clozapine and Sodium Valproate discontinuation, his mental condition deteriorated. Subsequently, Olanzapine (another antipsychotic) was used, which is safer regarding hematological side effect profile(3). The dose of Olanzapine was escalated to 15mg per day and Valproic acid was reintroduced as well with a dose of 500mg b.d(4). Despite his compliance for Olanzapine and Valproic acid, which are his current medications, he did not show a satisfactory improvement compared to Clozapine.

After completion of chemotherapy, he got complete remission and enjoyed good physical health.

Discussion

Can we reintroduce Clozapine for a patient with a history of Hodgkin's lymphoma in remission? Clozapine, a dibenzodiazepine derivative, is an atypical
antipsychotic indicated for patients with resistant schizophrenia or those who are unable to tolerate the side effects of the classical antipsychotic agents. The recommendations of weekly WBC monitoring for the first 6 months of treatment, and biweekly after 6 months is due to a higher risk of agranulocytosis compared to the traditional agents. The highest risk of agranulocytosis occurs in the first six months of therapy, but sudden late onset of such side effect had been reported in some cases(5).

There is a robust body of evidence and research done to prove the clinical efficacy and superiority of clozapine in treating resistant cases of schizophrenia, and to use it earlier on once a case appears to be refractory, in order to limit both social and personal morbidity of chronic psychosis(6,7). Data from a cohort of 223 patients whom were considered to be poor responders to the traditional agents were evaluated and it has been found that at least 60% responded to Clozapine therapy positively(8).

The most serious side effect of Clozapine is agranulocytosis, which might be fatal, and therefore it is considered to be the second line treatment in psychosis(5). The incidence of agranulocytosis ranges from 1%-2%(9) and it has been found that there is no correlation between WBC, Hb, and the dose of Clozapine(10). Several hypotheses have been generated to explain the mechanism of the hematological adverse effect, but the exact one is still unknown(9). Trials to find people at risk using HLA typing were performed and concluded that HLA-Cw*7 allele may represent an immunogenetic trait marker identifying patients at risk for hematotoxic idiosyncratic drug reaction(11). During our search of the literature (Pubmed 1988-2003, Medscape 1997-2003) we were able to trace two case reports regarding the reintroduction of Clozapine in patients with hematological malignancy, especially lymphoma, where Clozapine was introduced safely to patients with history Hodgkin's lymphoma(12,13). Miller stated that their case provides an alert but not a conclusion about the use of Clozapine for a patient with history of Hodgkin's lymphoma in remission(13).

Valproic acid and its derivatives do not induce agranulocytosis seriously as Carbamazepine might do, therefore they can be used safely to treat seizures which may occur as a side effects of Clozapine therapy(14).

Conclusions and Recommendations

The exact mechanism of how hematological side effects can happen is not yet known. A direct cytotoxic effect on bone marrow, an immune mechanism involving formation of antibodies, or an immune mediated hypersensitivity reaction which can be linked to the metabolic activation of the drug by peroxidases and consequently the formation of free radicals have been considered as possible mechanisms to how such side effects might occur(9). Even though there were two case reports regarding successful trials of Clozapine reintroduction to patients with Hodgkin's lymphoma, the authors were unable to generalize(13) and moreover therapeutic recommendation from reports and experience of respected authorities are considered level IV of evidence (meta-analysis of randomized controlled trials are on level I)(15).

We felt that it is very important to raise such an issue to stimulate further research and to alert colleagues, because it is highly possible that any psychiatrist might face such a dilemma. As a team we feel that it is worth trying to reintroduce Clozapine but the patient's family remains hesitant.

Fig. 1. Cervical lymph node biopsy 1 mixed cellularity type

Fig. 2. Cervical lymph node biopsy 2 mixed cellularity type

References
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