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Effect of low dose of lithium carbonate on preventing chemotherapy-induced neutropenia: A pilot study

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Abstract
Purpose: To evaluate the effect of lithium carbonate (Li2CO3) on chemotherapy induced neutropenia (Absolute neutrophil count <1000/ml).
Patients and methods: This prospective pilot study was conducted on all patients referred to the Oncology department from February to march 2006 and who were to receive chemotherapy. Li2CO3 was given in the dose of 300 mg Bid for seven days from the first day following chemotherapy. Patients expected to experience severe neutropenia were assigned to the study group (Li2CO3) and all other patients were randomly entered to the study and the control group. A total of twenty five patients were enrolled for this study.
Results: The age range was from 15 to 69 years with the median age being 58 years. 46% of the subjects comprised of lung and breast cancer, 26% lymphomas and sarcomas and the remaining 28% having other malignancies. 18% of the patients received combination chemotherapy expected to cause severe neutropenia (more than two myelotoxic drugs), seventy percent received chemotherapy expected to cause moderate neutropenia (two myelotoxic drugs) and twelve percent received chemotherapy expected to cause mild neutropenia (one myelotoxic drug). All the patients had normal prechemotherapy complete blood picture. 73% percent had neutropenia in the second week of which 41% were from the control group and 32% percent from the study group.30% of the patients in the control group had neutropenia extending to the third week delaying the second cycle of chemotherapy. Only one patient had neutropenia at the end of the third week in the study group. All patients in the control group who had their second cycle delayed due to neutropenia were shifted to the study group with hundred percent doses given in the subsequent cycles. These patients continued to receive the full dose with no further delay in the chemotherapy schedule. Febrile neutropenia was seen in two patients of the control group and one in the study group. One patient developed mild nausea and tremors to lithium with no other toxicities observed.
Conclusions: Li2CO3 is a useful drug which helps to reduce the duration of neutropenia following chemotherapy thus enabling a planned dose and schedule to be administered. A large randomized trial is needed to clearly identify the role of Li2CO3 in reducing chemotherapy induced neutropenia, its appropriate dose and toxicities. The easy affordability and availability of this drug makes it an ideal choice for clinical trials in developing countries.

Keywords: Lithium carbonate, chemotherapy, Neutropenia

Introduction
In cancer treatment, the role of appropriate dose delivery and time schedule in chemotherapy is the cornerstone for a successful outcome. However, a chemotherapy-induced hematological side effect like leukopenia is a major problem as at times it can be life threatening and may lead to the death of the patient[1]. In clinics hematopoietic growth factors like G-CSF are administered to prevent the plummeting counts and revive the condition [1]. In the early 1980s lithium carbonate (Li2CO3), an inexpensive drug, widely used in psychiatry for mood instability and as an adjunct to antidepressants has been shown to attenuate the leukopenia associated with systemic chemotherapy [1]. Li2CO3 was investigated extensively in various cancers and found to be effective in chemotherapy induced neutropenia.
Lithium has been reported to stimulate murine pluripotential stem cell proliferation in the bone marrow, increase bone marrow organ cellularity and the peripheral WBC counts [2]. Li2CO3 is a very safe drug when used in the dose of 300 mg Bid.

The major hematological effect of Li2CO3 is stimulation of granulopoiesis, the most likely mode being enhancement of CSA (colony stimulating activity). However the advent of more effective colony stimulating factors enthused oncologists to opt for the biologicals over Li2CO3 [1, 2]. When the study was conducted (in 2009) growth factors was extremely expensive and was out of reach for most patients. Under these circumstances, considering the facts that Li2CO3 was a clinically used drug with known pharmacokinetic profile, was devoid of toxicity, cheap, orally administrable and above all was effective in chemotherapy induced neutropenia, encouraged the investigators to study the protective effects in Indian context.

Patients and methods

The study was carried out at Father Muller Medical Cancer Centre from January 2006 to June 2009 after obtaining the permission from the Institutional Ethics Committee. All the patients referred to the Oncology department who were planned for chemotherapy were selected to either receive Li2CO3 carbonate 300 mg bid for seven days post chemotherapy (study group) or chemotherapy only (control group). Their weekly haemoglobin, total neutrophil count and platelet counts were done starting from the first day (prechemotherapy). Exclusion criteria were any patient receiving cardiac medication. Chemotherapy regimes were classified according to the number of myelotoxic agents as those causing mild neutropenia (one myelotoxic drug), moderate neutropenia (two myelotoxic drugs) and severe neutropenia (three myelotoxic drugs). All patients expected to experience severe neutropenia were assigned to the study group and the rest of the patients were randomly selected. Patients in the control group whose second course had to be delayed due to prolonged neutropenia were shifted to the study group with a 100% dose. Patients who had febrile neutropenia received treatment according to the standard protocol.

Results

A total of 43 patients in the age range was from 15 to 69 years (median age 58 yrs) were the participants of the study. 46% of the patients comprised of lung and breast cancer with 26% percent having lymphomas and sarcomas with 28% having other malignancies. 18% of the patients received combination chemotherapy expected to cause severe neutropenia, 70% of the patients received chemotherapy expected to cause moderate neutropenia and 12% percent received chemotherapy causing mild neutropenia. All patients had normal prechemotherapy total WBC, haemoglobin above 9 gms% and normal platelet counts. 73% had neutropenia in the second week of which 41% were from the control group and 32% percent from the study group.

Those patients expected to develop severe neutropenia were put in the study group. Two patients received BEP regime for mixed germ cell tumor, one patient received VAdrC alternating with ifosfamide /etoposside for Ewing's sarcoma of the scapula. All the three patients received full dose of chemotherapy but there was a delay of one week for the patient with Ewing's due to febrile neutropenia after the third cycle. The patient has completed seven cycles of chemotherapy without any complications and the Li2CO3 was given for ten days instead of seven days. 32% of the patients in the study group had neutropenia in the second week but only one developed febrile neutropenia in the third week and was treated with antibiotics. In the control group 41% percent of the patients had neutropenia in the second week and 30% had neutropenia extending to the third week delaying the second cycle of chemotherapy.

All patients in the control group who had their second cycle delayed due to neutropenia were shifted to the study group and given the full dose of chemotherapy. One patient who was on ABVD for Hodgkin's lymphoma developed severe neutropenia (ANC was 300/ml) after the second cycle. He received 100% dose with no further delay after being shifted to the study group. These patients continued to receive the full dose with no further delay in the planned schedule. Febrile neutropenia was seen in two patients in the control group and one in the study group. One patient developed mild nausea and tremors to lithium.

Discussion

Lithium, is a trace element and is found in variable amounts in food; the primary food sources are grains and vegetables; in some areas, the drinking water also provides some amount of the element [1]. The available experimental evidence now appears to be sufficient to accept lithium as essential; a provisional suggested RDA for an adult with seventy kilogram weight is 1000 microgm/day [1].

The role of Li2CO3 in chemotherapy induced neutropenia is well documented [1, 3-7]. Lyman *et al* [7] conducted a randomized trial on 45 patients with small cell carcinoma of the lung who were receiving combination chemotherapy. Patients randomized to receive Li2CO3 were started on 300mg tid for 18 days of every 21 day chemotherapy cycle. They found that lithium reduced the period of neutropenia and the febrile episodes resulting in adequate chemotherapy dosage and reduced hospital stay. Unfortunately, Oncology departments failed to use it or adequately study the drug for no clear reasons, except the availability of G-CSF. The study conducted in our hospital suggest that patients on Li2CO3 were able to receive the full chemotherapy dose with no delay in the planned schedule as confirmed in a study by Richman C M et al [4]. Earlier reports of lithium carbonate has been on various aspects of neutropenia and thrombocytopenia including mean absolute PMN nadir which was 26-40% higher than the control arm [5], nadir platelet count, interval between cycles and dose reduction [4].

In the present study 30% of the patients where shifted from the control to the study group and were able to receive 100% dose without delay in the subsequent cycles. The other options for these patients are a reduction in the dose or a delay in the planned schedule which will have a direct impact on the response and survival. This indicates the benefits of lithium car Li2CO3 in reducing the period of neutropenia. The use of Li2CO3 in acute myeloid luekemia after standard cytosine arabinoside and daunarubicin suggested that the median duration of neutropenia (<1000/ml) was 16 days in the study group as compared to 24.6 days in the control group [6]. Although the study was conducted on a small number of patients the results clearly state the need to evaluate the role of Li2CO3 in chemotherapy induced neutropenia considering the low cost and negligible toxicities in the present study as well as the earlier reports.

From a mechanistic perspective, the administration of lithium salts to hematologically normal subjects is

associated with increased marrow neutrophil production and release of hematopoietic growth factors (CSF) which are responsible for the proliferation of neutrophil granulocytes. Lithium salts selectively increase the number of neutrophil granulocytes quite significantly and to a lesser extent the eosinophil granulocytes and Lymphocytes; while the average number of erythrocytes is unaltered [8, 9]. The physiological effect of Li2CO3 on CSA is not clearly understood. The neutropenic status most likely to benefit from lithium treatment is those where impaired CSA is demonstrable. Hence lithium had no effect on patients with severe aplastic anaemia where stem cell failure is almost total [3].

As for as the authors are aware of this was the first study to assess for its myeloprotective effects of Li2CO3 against the chemotherapy-induced neutropenia in India. The other important aspect worth considering is that the dose used in this study is far by the lowest used (300 mg bid) and for a shorter duration of time of seven days. The normally recommended Li2CO3 dose in clinics for people with bipolar disorder is 900 mg bid and the dose used 300 mg bid is very low and comparatively non toxic. Multiple studies have shown that the short-term treatment with lithium is usually free of any complications or side-effects as long as serum levels of lithium are kept below 1 mM. Lithium toxicity is usually subtle in onset and a large variety of signs and symptoms is possible, but the most common are tremor and diarrhea. Symptoms vary from mild lethargy to seizures and coma. In the current context, recombinant CSF is only administered when there are indications of severe neutropenia. However the high cost of it is still a major hurdle for many patients in the developing countries. In such scenario the use of Lithium carbonate therapy for treating patients with chronic leucopenia following chemotherapy or radiotherapy is extremely cost-effectively if judiciously used.

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