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A CHRONOPHARMACOLOGICAL STUDY RELATED TO DOXORUBICIN BASED BONE MARROW SUPPRESSION

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Abstract

Myelosuppression is the most common toxicity of anti-neoplastic therapy due to inhibition of cell replication in bone marrow. This can be minimized by administering drugs on the basis of circadian time basis. Hence the aim is to study circadian time cycle related bone marrow suppression variation resulting from doxorubicin based cancer chemo therapy regimen. A prospective observational clinical study based on circadian time Cycle was done for a period of six months at a tertiary care hospital. Standard doxorubicin Regimen was given in the dose of 60 mg/m as iv infusion. Each cycle is repeated every 21 Days. Complete hemogram was done on day 0 and day 10 of both day and night cycle. Results were analyzed using students paired t test .It was found that during Night cycle therapy bone marrow suppression was minimal and statistically significant ($p<0.001$). Chronotherapy is useful in minimizing bone marrow toxicity.

Key words

Myelosuppression, Doxorubicin, Chemotherapy, circadian cycle, Bone marrow cells.

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Introduction

Myelosuppression is the most common toxicity of antineoplastic therapy due to inhibition of cell replication in bone marrow often results in leukopenia and thrombocytopenia although anemia can occur. [1] Bone marrow suppression by cancer chemotherapy will predispose to bacterial and fungal infections. Treatment with haemopoietic growth factors had WBC transfusion will reduce high risk complications. But the treatment with blood and blood products are costly and side effect prone.

Myelosuppression can be minimized by administering drugs on basis of circadian time cycle. But cancer cells do not follow circadian rhythm as multiply continuously and fastly throughout 24 hrs cycle period. [2] So administering anti cancer drugs at any part of the day will not affect cytotoxic effect on tumor. Human bone marrow shows highest DNA synthesis at midday than at mid night. [3]

Doxorubicin is one among the anticancer drugs showing circadian variations in pharmacokinetic and pharmacodynamic actions [4]. Since human bone marrow is less active around midnight, administration of anticancer drugs around midnight will minimize bone marrow suppression without affecting cancer cell cytotoxicity. Hence this study was undertaken to find out whether circadian rhythm influences bone marrow suppression produced by doxorubicin in cancer patients.

Materials and Method

This chronopharmacological study was done on patients of oncology department, Government Rajaji Hospital, Madurai in collaboration with Institute of Pharmacology for a period of six months after getting institutional ethical clearance and informed consent. Twenty (20) cancer patients on standard single agent doxorubicin were included. Patients with other myelosupprssive agents were excluded for this prospective nonrandomized comparative clinical study on the basis of circadian time cycle.

Patients were subjected alternatively to day and night cycle with an interval of 21 days. Blood sample was collected on day 0 of day cycle and doxorubicin was given in the dose of 60 mg/ sq mt [5] as iv infusion in 500 ml of normal saline for one hour at 10.00 am to 11.00 am. On day 10 complete hemogram was repeated. Same patient was subjected to night cycle after 21 days at 10.00 pm to 11.00 pm and on day 10 complete hemogram was repeated. Results were analyzed statistically using Students paired t test.

Results

In present study 20 patients were included and were given doxorubicin in dose of 60 mg/sq.mt as iv infusion. Complete automated hemogram was repeated on day 0 and day 10 of both day and night cycles.WBC count was tabulated for analysis (Table 1). Range of WBC suppression during day cycle was between2600 to 8200 and night cycle was between 0 to 1200. Results were analyzed using Students paired t test. During night cycle therapy bone marrow suppression is minimal which is statistically significant.

Discussion

Bone marrow suppression is the challenging adverse effect of anticancer chemotherapeutic agents. During Myelo suppression the first cell to be suppressed is white blood cells.

In the present study, out of 20 patients studied range of WBC suppression during day cycle was between 2600 to 8200 and night cycle was between 0 to 1200. From this observation bone marrow suppression was minimal with the night cycle therapy of doxorubicin which is clinically beneficial for patients. Circulating neutrophil counts have traditionally been one of the clinical criteria used to determine whether a patient has recovered sufficiently from a previous cycle of cytotoxic chemotherapy and ready to tolerate the next planned cycle.

During night cycle therapy patients' sense of well-being was better. Incidence of mucositis, nausea and vomiting were less severe. Cytotoxic response to doxorubicin was similar in both day and night cycles.

Conclusion

The present study showed that night cycle therapy with doxorubicin has less myelotoxic compared to day cycle without compromising cytotoxic efficacy on tumours [6]. So Chronotherapy is useful in minimizing bone marrow toxicity.

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TABLE I

Table showing WBC count in day cycle and night cycle on day 0 and day 10

S. No	WBC COUNT : CELLS / µL					
	Day Cycle			Night Cycle		
	Day-0	Day 10	Difference	Day-0	Day 10	Difference
1	6300	2800	3500	4700	4500	200
2	7500	4400	3100	6400	5800	600
3	6800	3400	3400	5400	5100	300
4	10500	5000	5500	7500	7300	200
5	6200	3200	3000	4900	4800	100
6	9400	4100	5300	6800	6100	700
7	9100	4400	4700	8600	7900	700
8	6800	4200	2600	5800	5100	700
9	7500	4300	3200	6000	5900	100
10	10500	4100	6400	7600	7300	300
11	6100	3500	2600	4900	4900	0
12	6700	3700	3000	5300	5100	200
13	20400	13200	7200	20400	19200	1200
14	6000	2800	3200	3800	3600	200
15	6600	3700	2900	6000	5700	300
16	12100	3900	8200	9000	9000	0
17	7300	3800	3500	6200	6000	200
18	6500	3200	3300	5600	5100	500
19	6400	2800	3600	5800	5500	300
20	6800	3000	3800	5700	5300	400

FIGURE I

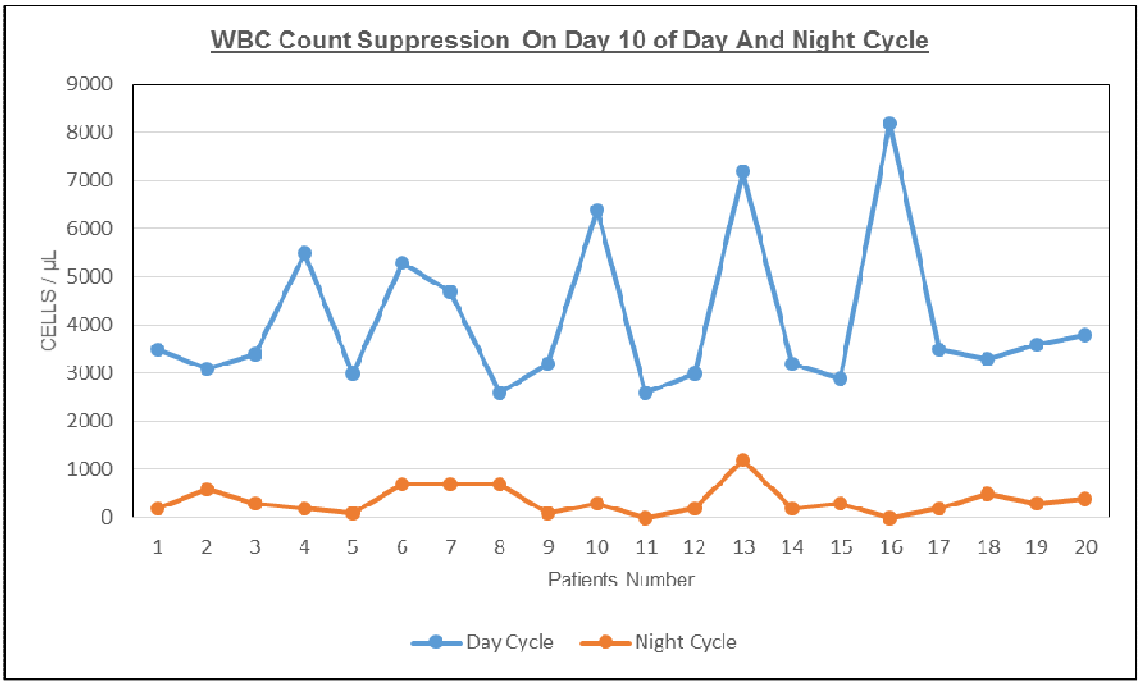

FIGURE II