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CHRONOMODULATED CHEMOTHERAPY AND CONCOMITANT RADIOTHERAPY, FOR THE MANAGEMENT OF LOCALLY ADVANCED, HEAD AND NECK SQUAMOUS CELL CARCINOMA

Yashpal Verma *[1], Ashok K. Chauhan [1], Harmeet Singh [2], Ramesh Sabharwal [3], Mukesh Bharti [4], Paramjeet Kaur [1]

Department of Radiotherapy [1], PGIMS, Rohtak, Haryana, India
Clearmedi Healthcare Pvt. Ltd [2], New Delhi, India
LNJP Hospital, Kurukshetra [3], Haryana, India
DMCH [4], Darbhanga, Bihar, India

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Correspondence to Author:

Dr Yashpal Verma

Medical Officer, Department of Radiotherapy, Post-graduate Institute of Medical Sciences, Rohtak, Haryana, India

E-mail: yashpverma@gmail.com

ABSTRACT:

Purpose: To compare the efficacy and toxicity of chronomodulated concomitant chemotherapy using weekly Cisplatin at 0600 hour and 1800 hour along with radical external beam radiotherapy (EBRT) in the management of locally advanced head and neck carcinoma (LAHNC).

Material and method: Previously untreated, histopathologically proven 60 patients of LAHNC (stage III-IVB) were taken for definitive treatment by concurrent chemo-radiation. These patients were randomly assigned (by draw of lots) either of two groups; **group I**, the 0600 hour cisplatin administration and **group II**, the 1800 hour cisplatin administration group, each in dose of 30 mg/m^2. EBRT was given as 66Gy/ 33Fr/ 6.5 weeks on telecobalt machine. Night shift workers were excluded. Response to treatment and toxicity were investigated. Observations were made at the end of treatment and 6 months of follow up.

Results: At the end of treatment, complete tumor response (CR_T) in group II were better (40.0% versus 26.7%) and complete node response (CR_N) were comparable (34.8% versus 34.6%). Acute skin and mucosal reactions (grade 3) were 3.3% versus 10% each. Hematological toxicity: fall in hemoglobin (grade 3) was lesser in group II patients- 3.3% versus 10% in group I, fall in total leukocyte count was observed up to grade 1 only in two patients (6.7%) of each group. Upper gastro-intestinal toxicity was significantly lesser in group II (6.7% versus 26.7%; *p= 0.038*), also translating to weight loss, (3.3% versus 13.3%; p= 0.161). Disease status at last follows up was as follows: CR_T in group I and II- 70% versus 73.3% and CR_N 70.1% versus 78.3%. Late mucosal reactions were same in two groups (grade I+II, 73.3%). Skin reactions were lesser in group II. None of the patients experienced grade 3 or 4 toxicity.

Conclusion: Administration of cisplatin; in the evening is better compared to morning administration in terms of disease control and toxicity profile; given concurrent with EBRT, for management of LAHNC. A larger study with more groups receiving chemotherapy at frequent intervals (say 6 hours apart) may further establish the very right time of administration of chemotherapy.

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INTRODUCTION: Cancer is an alarmingly increasing health problem worldwide [1]. Out of all cancers, approximately one third occur in the head and neck region. Approximately 70-80% of these patients are diagnosed with locally advanced disease and 30-50% had lymph node involvement.

Radiotherapy with or without chemotherapy remains the mainstay of treatment. Meta-analysis has revealed the maximum benefit in survival with concomitant chemoradiation [2]. It has also been observed that the chemotherapeutic agents show differential efficacy as well as toxicity when administered at different times of day [3-6]. Based on the information and literature available so far; this study has been carried out in an effort to find out the differences in effects and side effects of administration of chemotherapeutic agent namely Cisplatin, at two different times of day - morning and evening (started around 0600 hr and 1800 hr), concomitant with radiotherapy in cases of LAHNC.

MATERIAL AND METHOD:

Patients: Between 2009 and 2012, sixty treatment naeve, histopathologically proven patients of LAHNC (stage III-IVB), attending the Department of Radiotherapy, Pt. B.D. Sharma Post Graduate Institute of Medical Sciences, Rohtak (India) were taken up for definitive treatment by concurrent chemo-radiation therapy. The patients had Karnofsky performance status >70, hemoglobin >10gm/dl. Neutrophil & platelet counts, liver function and renal function tests were within normal range. Chest x-ray and USG abdomen showed no apparent evidence of metastatic disease. Night shift workers and patients with co-morbid disease were excluded. The study was carried out only after the protocol was approved by the institution's ethics review board.

Radiation: All patients were planned for radical radiotherapy with Cobalt teletherapy machine and simulated on Simulator CT. Intended radiation treatment for all was 66Gy in 33 fractions over 6.5 weeks (one daily fraction of 200cGy, 5 fractions a week). Replanning with spinal cord sparing was done after 22 fractions.

Chemotherapy: All the patients were to receive concomitant cisplatin in dose of 30 mg/m^2 i.v. every week. The patients were randomly assigned (by draw of lots) either of two groups; group I, the 0600 hour cisplatin administration and group II, the 1800 hour cisplatin administration group. A complete hemogram, liver and kidney function tests were done before every cycle of cisplatin. Chemotherapy was withheld in cases of any grade 2 or more hematologic, hepatic or renal toxicity, till the normal values were recovered after specific management. Study design is shown in **Diagram 1**.

Observations: Observations were made at the end of treatment and 6 months of follow up. Response for the purpose was determined by clinical examination. Radiological examination, fine needle aspiration cytology or a biopsy was carried out in clinically suspicious cases. Patient characteristics are shown in **Table 1**.

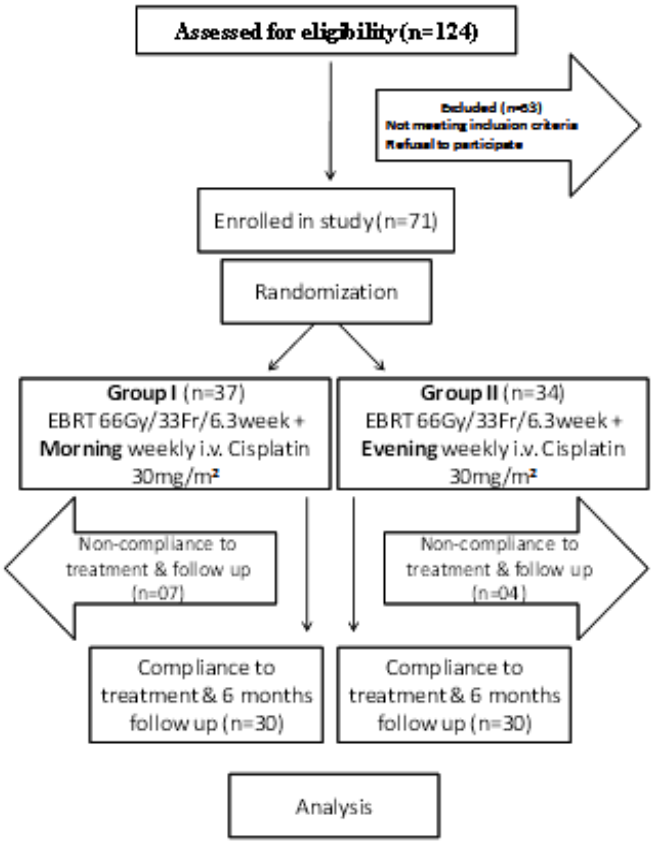


Diagram 1. Study Design

During & at the end of the treatment: Patients were monitored weekly for tumor & node response and for acute hematological, skin, mucosal & upper gastrointestinal toxicity. Patient's weight was also recorded weekly to assess nutritional status. The severity of acute toxicities was scored using RTOG criteria. Maximum response & toxicity was recorded at the end of treatment.

During & at the end of the follow up: Patients were monitored monthly for tumor & node response and for late skin & mucosal toxicity. Severity of toxicities was scored using RTOG criteria. Maximum response & toxicity was recorded at the end of follow up.

Quality assurance: Senior radiation oncologists in the department reviewed the records and also conducted examination of the patients at random to verify findings of response & toxicities.

Statistical analysis: This was a randomized trial with 1:1 allocation ratio by means draw of lots randomization. Frequency tables with counts and percentages were used to describe pre-treatment and treatment characteristics for each group. The categorical clinical characteristics between the two treatments were compared. For continuous variables, mean and median values were compared between the groups. Endpoints included tumor & node response and acute & late toxicities. Subgroup analysis was carried out on various prognostic variables. Data were analyzed using the statistical software La Morte. A p-value of <0.05 was taken as significant.

TABLE 1: PATIENT CHARACTERISTICS

Characteristics		Group I	Group II
Age (years)	31-40	03 (10.0%)	07 (23.3%)
	41-50	06 (20.0%)	09 (30.0%)
	51-60	12 (40.0%)	09 (30.0%)
	61-70	09 (30.0%)	05 (16.7%)
Gender	Males	29 (96.7%)	28 (93.3%)
	Females	01 (3.3%)	02 (6.7%)
Social background	Rural	22 (77.3 %)	24 (80.0 %)
	Urban	08 (22.7 %)	06 (20.0 %)
Smoking habit	Smoker	29 (96.7 %)	26 (86.7 %)
	Non-smoker	01 (3.3 %)	04 (13.3 %)
Chief complaints	Difficulty in swallowing	10 (33.3%)	12 (40.0%)
	Pain in swallowing	06 (20.0%)	06 (20.0%)
	Neck mass	08 (26.7%)	08 (26.7%)
	Non-healing ulcer	02 (6.7%)	01 (3.3%)
	Earache	03 (10.0%)	01 (3.3%)
	Altered voice	01 (3.3%)	02 (6.7%)
Site of primary tumor	Ant. Tongue	01 (3.3%)	00
	Floor of Mouth	01 (3.3%)	00
	Hard palate	01 (3.3%)	00
	Tonsil	07 (23.3%)	13 (43.3%)
	Base of Tongue	13 (43.3%)	12 (40.0%)
	Soft Palate	02 (6.7%)	01 (3.3%)
	Hypopharynx	03 (10.0%)	02 (6.7%)
	Larynx	02 (6.7%)	02 (6.7%)
Stage (AJCC 2010)	III	10 (33.3%)	13 (43.3%)
	IV	20 (66.7%)	17 (56.7%)
Histopathology	Well Differentiated SCC	03 (10.0%)	02 (6.6%)
	Moderately Differentiated SCC	24 (80.0%)	24 (80.0%)
	Poorly differentiated SCC	02 (6.7%)	02 (6.7%)
	SCC, not otherwise specified (NOS)	01 (3.3%)	02 (6.7%)
Tumor Morphology	Ulcerative	06 (20.0%)	05 (16.7%)
	Indurative	03 (10.0%)	06 (20.0%)
	Proliferative	21 (70.0%)	19 (63.3%)
KPS	80	11 (36.7%)	12 (40.0%)
	90	19 (63.3%)	18 (60.0%)

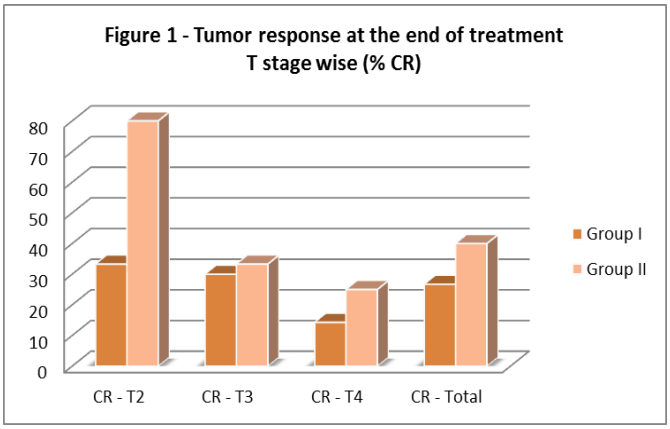
RESULTS:

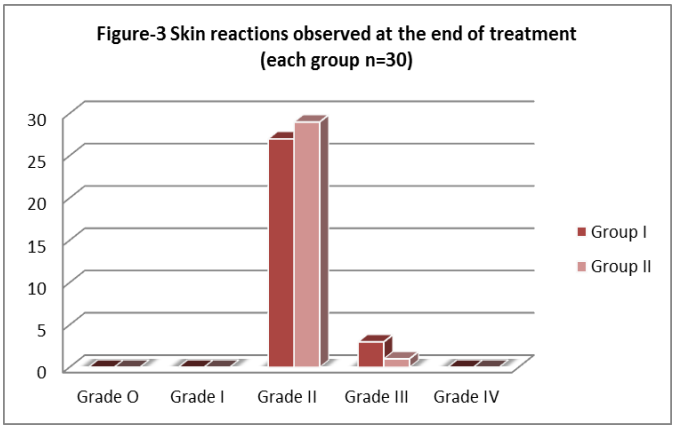
At the end of treatment: Complete tumor response (CR_T) in group II was better than group I, 40.0% vs 26.7% (p=0.273 NS). On subgroup analysis, corresponding CR_T was 80% vs 33.3% for T2 subgroup, 33.3% vs 30% for T3 subgroup and 25% vs 14.3% for T4 subgroups.

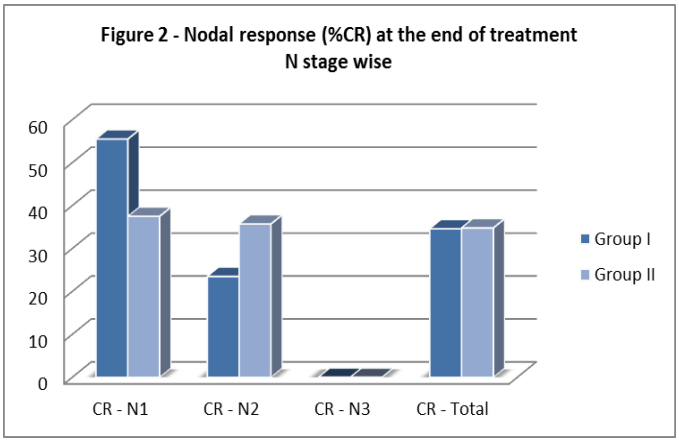
Complete node response (CR_N) was comparable in group II and group I (34.8% vs 34.6%, *p*=0.990 NS). On subgroup analysis, corresponding CR_N was 37.5% vs 55.5% for N1 subgroup and 35.7% vs 23.5% for N2 subgroup. The only case of N3 in group II showed partial response.

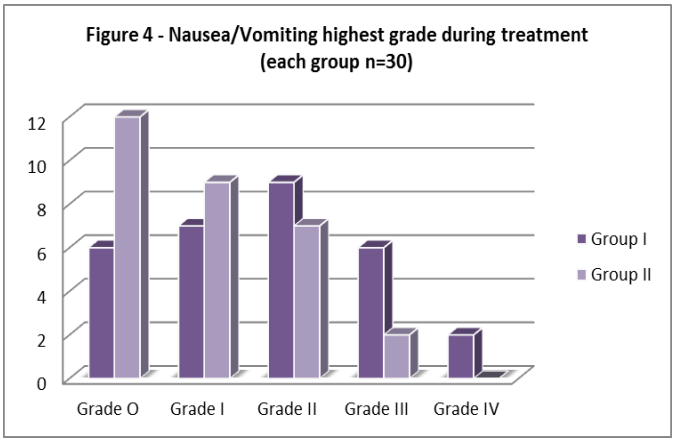
Overall disease complete response (CR_T + CR_N) for all stages was better in group II – 26.7% versus 13.3% in group I (*p*= 0.197 NS). On subset analysis, CR_T + CR_N were 30.8% versus 20% in stage III and 23.5% versus 10% in stage IV patients, all in favour of group II.

Overall severe (grade 3 + 4) toxicity was 26.7% versus 6.7%, significantly lesser in group II (***p= 0.038* SS**). Four patients (13.3%) in group I experienced more than 10% weight loss over the course of treatment compared to just one patient (3.3%) in group II (p= 0.161 NS).









The acute skin reactions in group I and group II respectively were observed as follows; Grade 2- 90% versus 96.7% and Grade 3 reactions 10% versus 3.3% (*p*= 0.301 NS). Same were the acute mucosal reactions, favoring evening group schedule.

Maximum level of hematological toxicity as fall in hemoglobin was observed lesser in group II patients- grade 3 toxicity: 3.3% versus 10% in group I (*p*= 0.301 NS). Fall in total leukocyte count (TLC) was observed up to grade 1 only, in two patients (6.7%) of each group, which was persistent in one patient of group I.

Upper gastro-intestinal grade 3 toxicity was observed in six patients (20.0%) in group I and two patients (6.7%) in group II. Grade 4 toxicity was observed in two patients (6.7%) in group I and none in group II.

At the end of follow up: Complete tumor response (CR_T) was – 73.3% in group II versus 70.0% in group I (*p*= 0.774), slightly better in evening. Corresponding complete node response (CR_N) was better in evening group, 78.3% versus 70.1% (*p*= 0.674). Overall disease complete response (CR_T + CR_N) was comparable, 60.0% versus 63.3% (*p*= 0.791).

There were total of eleven recurrences- five in group I and six in group II. In group I, three recurrences were at primary site and two were nodal. In group II, all the recurrences were at primary site, most cases being those of stage IV. Earliest recurrences were noted in fourth follow up.

Late radiation toxicity as observed at 6th follow up, were graded according to RTOG criteria. Mucosal reactions were same in two groups (grade 1+2, 73.3%).

Though not statistically significant (p = 0.067), skin reactions were lesser in group II. None of the patients experienced grade 3 or 4 toxicity.

Figure 5 - Tumor response at the end of follow up T stage wise (% CR)

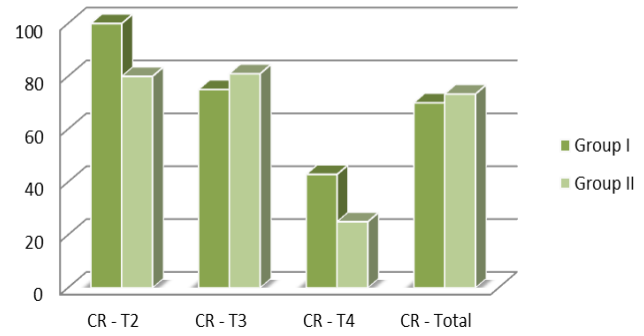


Figure 6: Node response (% CR) at the end of Follow up N stage wise

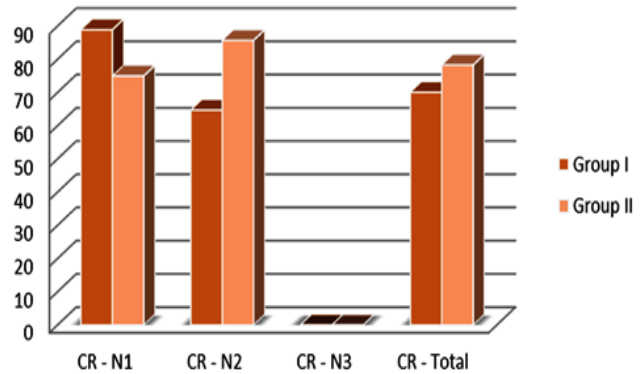
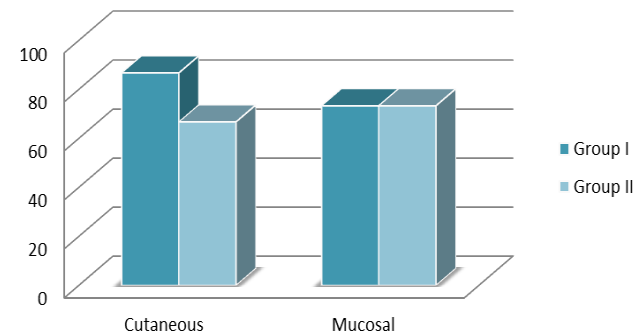


Figure 7 - Skin and mucosal reactions at the end of follow-up



Results are shown in figures 1-7.

Attempt for Salvage Therapy: In patients with residual disease, recurrence, or progression of disease, salvage surgery, chemotherapy or palliative treatment was offered, depending on the status of the individual patient, their symptoms and previous treatment.

DISCUSSION: To the best of our knowledge, this is first published randomised prospective study, comparing time scheduling (chronomodulation) of a chemotherapeutic agent, in concomitant setting, for the management of locally advanced head & neck squamous carcinoma.

As per World health organization's project on cancer incidence, mortality and prevalence - GLOBOCAN 2008; worldwide there were approximately 12.66 million new cancer cases (excluding non-melanoma skin cancers) and 7.56 million deaths accounting for approximately 13% of all deaths, thereby ranking second as a non-communicable cause of death after heart diseases [1]. Even if current global cancer rates remain unchanged, by 2030 the estimated new cancer cases will rise to 20-26 million and deaths due to cancer between 13-17 million [7].

In India, GLOBOCAN 2008 reported 9, 48, 858 new cancer cases and 6, 33, 455 deaths (excluding non-melanoma skin cancers). Female cases outnumber, with male to female ratio of 1:1.2. Out of all cancers approximately one third occur in the head and neck region [8].

Majority of head and neck neoplasms are squamous cell carcinomas (approximately 80%). Other less common types of malignant neoplasms are adenocarcinomas, sarcomas, melanomas, and lymphomas. Most of the head & neck cancers are triggered by alcohol and tobacco, which together account for approximately three-quarters of cases. The risk among cigarette smokers may be 10 times or more than that for non-smokers [9].

Clinical manifestations may be difficulty in swallowing, breathing or speech, altered voice, earache, headache, decreased tongue mobility, nasal obstruction, bleeding per nose or mouth, mucosal ulceration, neck mass and so on, depending upon the anatomical location of the disease. Approximately 70-80% of these patients are diagnosed with locally advanced disease and 30-50% has lymph node involvement.

Over the past decades, the treatment in oncology has progressed promisingly. The patients can be treated by surgery, radiotherapy (RT), chemotherapy (CT) or combination of these.

After diagnosis, it is also determined which treatment modality or a combination of these modalities would be most suitable in a particular case. Surgery or radiotherapy alone has equally good results for early stage cancers. Factors like the patient's performance status, the expected degree of functional impairment with surgery, and patient and physician preferences guide the decision between RT and surgery [10-12].

In locally advanced cases of head & neck carcinoma, surgery without adjuvant radiotherapy is associated with very poor cure rates. Compared with surgery alone, adjuvant radiotherapy resulted in an approximately 10% absolute increase in 5-year cancer-specific survival and overall survival for patients with lymph node-positive head and neck squamous cell carcinoma (HNSCC) [13].

Moreover, many locally advanced cases may even not be amenable to surgery either because of complications or sequelae of surgery. Radiotherapy with or without chemotherapy remains the mainstay of treatment [14]. Because, even the most effective radiotherapy regimen for advanced head and neck cancer results in local control rates of 50% to 70% and disease-free survivals of 30% to 40% only, chemotherapy/ cytotoxic agents have been advocated to improve the effect of radiation i.e. therapeutic ratio.

Depending on the aim of the therapy, chemotherapy can be administered as neo-adjuvant, concomitant or adjuvant to radiotherapy.A variety of anti-neoplastic agents have shown activity against the head & neck squamous cell carcinomas, which include; Cisplatin, Bleomycin, Methotrexate, Carboplatin, 5-flurouracil, Hydroxurea, Vinblastin, Doxorubicin, Ifosofamide, Paclitaxel, Docetaxel, Topotecan and Vinorelbine. Cisplatin is among the most extensively studied cytotoxic drug in HNSCC. Renal toxicity, being the toxicity of concern, can be ameliorated by mannitol diueresis.

Meta-analysis of chemotherapy on Head and Neck cancer prior to 1993 demonstrated that adding chemotherapy to radiation therapy resulted in 12% reduction in risk of death and an absolute improvement of 4% in 5-year survival. Recent updates of meta-analysis of chemotherapy on Head and Neck cancer in 2009, based on 93 randomized trials and 17,346 patients has revealed an absolute survival benefit of 4.5% at 5-year by addition of chemotherapy to radiotherapy (RT+CT) compared to radiotherapy (RT) alone ($p<0.0001$). Out of the three groups studied (adjuvant, induction and concomitant); the maximum benefit of 6.5% in 5-year survival was observed with concomitant chemotherapy [2].

The Radiation Therapy Oncology Group (RTOG) three-arm trial of radiation alone versus concurrent cisplatin versus induction cisplatin followed by irradiation in carcinoma larynx also revealed that concurrent therapy provides the best disease control, albeit without a statistically significant survival benefit [15].

Most biological phenomenon show rhythmic relationship that may be diurnal, fortnightly, seasonal or annual and alike. The most frequently observed and easily appreciable is the diurnal (day-night) or 'circadian' rhythm. This circadian rhythm persists and is reasonably uniform in most human including those suffering from cancer, until just before death.

It has also been observed that the chemotherapeutic agents show differential efficacy as well as toxicity profile when administered at different times of day [3-6]. This rhythm though casually observed, has not been fully explained. Many mechanisms have been proposed including 'clock' gene, supra-chiasmatic nucleus control, environmental synchronizers, chronopharmaco-kinetics and chronopharmaco-dynamics.

A study suggests that DNA synthesis and repair is intimately linked to circadian rhythm. Since the repair of DNA lesions contributes to the resistance of chemotherapy with DNA damaging agents such as cisplatin, understanding the fundamental molecular mechanism regulating DNA repair pathways is important for cancer therapy [4].

This 'circadian rhythm' might determine the 'best time of day' that can be utilized to treat cancer patient with cytotoxic agent(s), though this 'best time' may be quite short (of the range of couple of hours). This fact has been established by extrapolation of preclinical experiments, murine trials and also by multi-armed clinical studies.

Now optimal times of administration of more than 20 cytotoxic agents have been proposed for treatment of various cancers and studies are going on. The optimal time has been justified either in terms of better effects or in terms of reduced side effects [4-6].

Recent study in mouse liver tissue extract regarding repair of cisplatin induced damage has shown circadian pattern with repair zenith around 5 pm and nadir around 5 am, meaning thereby that cisplatin is more effective in morning in mouse. Since the mammalian circadian rhythm is out of phase with that of mice by about 12 hours, it was concluded that the findings may be used to guide timing of cisplatin chemotherapy [16].

Overall, we observed that disease response is better in evening cisplatin administration (group II). The results corroborate with earlier publication by Yang JO et al, in a pilot randomised study of chronotherapy, using cisplatin and 5-FU (in induction setting) in patients of nasopharyngeal carcinoma (NPC) [17]. We could not find detailed & subset analysis of tumor and node responses, despite an extensive search of literature. Another study in advanced ovarian carcinoma using cisplatin along with doxorubicin showed better outcomes with late afternoon cisplatin administration [18].

Upper gastrointestinal toxicity (nausea/ vomiting) observed is significantly lesser in evening cisplatin administration group. May be this was because patients used to go to sleep just after administration of chemotherapy in evening and had little per oral as compared to the other group patients. Also the skin & mucosal reactions were lesser in evening group.

Despite an exhaustive search of literature, we could not find a single study with comments or explanation of this kind of variation in upper gastrointestinal, skin and toxicity. But, the significant difference definitely warrants an explanation on molecular level or a larger study.

Difference in hematological toxicity in two schedules also corroborates with findings of earlier studies, in favour of evening cisplatin administration [17, 18].

Although we observed benefits with evening cisplatin administration in concomitant setting, in terms of better disease local control and favourable toxicity profile; implementation of such practice as routine needs to be established by larger studies and authentication by scientific explanation.

Limitation of this study is that it is a small study with only two timings of the day. May be some other time of the day is the very right time of administration of chemotherapy!

Nevertheless, taking into consideration the ease, feasibility, simplicity and cost effectiveness, this study has brought forth the relevance of conducting such a trial and has shown that existing standard of care may further be explored to get better without adding cost, especially when infrastructure constraints are there.

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