



Concurrent Chemoradiotherapy with Hydroxyurea vs Cisplatin in locally advanced Head and Neck Cancers

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Abstract

Background: Head and neck cancers constitute 6% of cancers worldwide. The management requires a multidisciplinary approach. Concomitant CRT with cisplatin is the standard approach for locally advanced head and neck cancers. In developing countries, poor built and general condition of patients may allow use of other radio sensitizers like Hydroxyurea to enhance the effect of radiation.

Methods: Squamous cell carcinoma of stage III, IVA and IVB of oropharynx, hypopharynx and larynx were studied for one year. 90 patients were randomized in control and study arm, 45 patients in each arm. Total dose of radiation was 66Gy/33#/6 ½ weeks from Monday to Friday in both the arms with inj. Cisplatin 30mg/m²i.v. infusion weekly in control arm and oral Hydroxyurea 25mg/kg approx. 16-18 hours before radiation.

Results: The locoregional control was similar in both the arms at 1st follow up as well as at median follow up. However a trend towards better response was seen with cisplatin arm. The acute toxicities in Hydroxyurea arm were more but they were managed conservatively.

Conclusions: Hydroxyurea can be used in the patients of head and neck cancers as a radio sensitizer where the use of cisplatin is precluded like old age, comorbidities or patient is reluctant for weekly injectable chemotherapy or in developing countries like India, where infrastructure is lacking.

Keywords: HNC (Head and Neck cancer), Hydroxyurea (HU), EBRT (External Beam Radiotherapy), CRT (Concurrent chemoradiotherapy).

Introduction

Head and neck cancer (HNC) is the sixth most common type of cancer, accounting for approximately 550,000 patients¹. Nearly 60% of this population presents with locally advanced but nonmetastatic disease. According to Hospital Based

Cancer Registry, IGMC, Shimla 14.85% of patients were of head and neck cancers from 2014 to 2016.

Radiation therapy alone was initially used for inoperable locally advanced head and neck cancers. Over the time Concomitant Chemo radiotherapy evolved for organ preservation in locally advanced disease² but with increased toxicities & additional burden on patient & health care facilities. A meta-

analysis demonstrated that adding chemotherapy to RT in HNC correspond to an absolute benefit in OS of 4.5% at 5 years³ and has now become the standard of care in locally advanced head and neck cancers.

Due to differences in genetic, dietary, comorbidities and poor general condition of the patient in Indian setup as compared to western population, also, differences in availability of radiotherapy, chemotherapy facilities, work schedule and socioeconomic conditions, standardization of concomitant chemo-radiotherapy has not become possible. Thus, other strategies also need to be conceived to enhance the effects of radiation therapy in such situations. Also cisplatin is precluded in certain patient population like elderly patients, pre-existing medical problems - with abnormal renal, hepatic or bone-marrow function, few patients who might refuse weekly injectable chemotherapy. In these patients, other oral agents need to be studied as radio sensitizer.

HU (HU) is one among them (half-life= 2-4hours) and has two effects on the cell population. First, all cells in S phase take up the drug and are killed. Second, it blocks at the end of the G1 phase and synchronizes the cells. 16 – 20 hours removal of the drug from the system brings all the cells close to mitosis which are killed when exposed to radiation⁴. Here we aim to study the disease response and locoregional control in locally advanced HNC with CRT using cisplatin in control arm and HU in the other, also to find out the tolerability & toxicities of both the drugs. Based on the results of HU in squamous cell carcinoma cervix, we thought that oral HU may be given a trial of being used as single agent concurrent chemotherapy with EBRT in place of Inj. cisplatin.

Methods

This prospective randomized study was conducted in the Department of Radiation Oncology, Tertiary Cancer Centre, IGMC, Shimla, Himachal Pradesh after approval of Institutional Research and Ethical Committee for a period of one year (from 1st July, 2016 to 30th June 2017.)

Inclusion Criteria

Patients with age \leq 70yrs with squamous cell carcinoma Oropharynx, Hypopharynx, Larynx, Stage III, IV A and IV B (*AJCC Cancer Staging Manual 7th edition, 2010*) which are previously untreated with normal complete haemogram, renal and liver function tests and performance status $>$ 70.

Pretreatment Workup

- Complete History and Detailed Physical Examination
- Indirect and/or direct Laryngoscopy
- Biopsy
- Routine Hematological and Biochemical Profile
- Dental Prophylaxis
- Chest X-ray, X-ray STN, CECT Neck
- Staging by AJCC 7e (2010)
- Informed consent

Randomization

Randomization was carried out by stratification, and the treatment assignment stratified according to clinical stages of disease. Patients were randomized into study and control group based on treatment they received. 45 patients were assigned to each group.

Study Design

Control arm (Cisplatin): Patients were subjected to standard cisplatin based CRT. Inj. cisplatin 30 mg/m² (max. 50mg) iv infusion weekly on D1 of every week for seven doses.

Study arm (HU arm): HU per oral at a dose of 25mg/kg, not more than 1500mg, given approx. 16 – 18 hours prior to the delivery of radiation i.e. Sunday to Thursday at 8 to 10 pm throughout the treatment.

Administration of Radiation Therapy

External beam radiation therapy was given by Theratron® 780e or Equinox™ Cobalt-60 machines using either two parallel and opposed fields or three field technique using Thermoplastic cast for immobilization. Dose of 66Gy were given in 6½ weeks in 33# @ 2Gy per fraction, 5 fractions from Monday to Friday were administered per week in both the arms.

Acute reactions were carefully monitored during radiotherapy and symptomatic treatment was given accordingly.

Assessment of Disease Status and Toxicity

Locoregional Status was recorded during each follow up clinically. The response was considered to be complete if there was no visible or palpable disease, partial if there was more than 50% regression, stable if lesion regressed less than 50% in maximal diameter and progressive if lesion increased by 25% or appearance of new lesion or secondary metastatic disease.

Toxicity (RTOG Criteria) was recorded every week during treatment, at the end of treatment and on subsequent follow ups

Follow Up

First follow-up was done at 6 weeks with complete history and a thorough clinical examination for assessment of disease and toxicity status and subsequent follow ups every two months. Side effects of treatment occurring within 90 days of start of radiotherapy were considered acute and those occurring or persisting more than 90 days were considered as late effects.

Statistical Analysis: Response rate were the primary end point for analysis. The data obtained from both arms were analysed by student “t”-test and chi-square test.

The statistical significance was defined as:

- ❖ P > 0.05 Non significant
- ❖ P 0.05 - 0.01 Significant
- ❖ P < 0.01 Highly significant

Results

Patient characteristics included in study were comparable in both the groups on the basis of age, sex, stage, site and subsite of the disease. (Table 1)

Table 1: Patient characteristics

		Group			
		HU arm		CISPLATIN arm	
		Number	% age	Number	% age
AGE	31-40	2	4.4%	1	2.2%
	41-50	6	13.3%	4	8.9%
	51-60	17	37.8%	23	51.1%
	61-70	20	44.5%	17	37.8%

SEX	MALE	43	95.6%	41	91.1%
	FEMALE	2	4.4%	4	8.9%
SITE	HYPOPHARYNX	8	17.7%	7	15.6%
	OROPHARYNX	20	44.4%	15	33.3%
	LARYNX	17	37.7%	23	51.1%
Stage	III	26	57.8%	20	44.5%
	IVA	18	40.0%	24	53.3%
	IVB	1	2.2%	1	2.2%

Over 120 patients were assessed for eligibility & 90 of them were enrolled. Of the 90 patients, 45 patients were randomized to study arm i.e. HU based CRT and 45 patients were randomized to the control arm i.e. radiotherapy with cisplatin weekly.

Response at First Follow-Up

Overall 67 patients (74%) were with no evidence of disease at primary site. In the HU CRT arm, 35 patients (78%) and in Cisplatin CRT arm 32 patients (71%) were with no evidence of disease. There was no statistical significant difference in the disease response at primary site in both the arms (p =0.468).

Response at Median Follow Up (Table 2): The difference in locoregional response was not significant at median follow up (p=0.323), but a trend towards better response was seen with cisplatin arm.

Table 2: Locoregional Response at Median Follow Up

Locoregional Control	HU Arm	CISPLATIN Arm
Complete response	60%	75%
Progressive disease	8%	6%
Recurrence/Residual Disease	32%	19%

Acute Toxicities during Treatment

Skin Toxicity (G1 to G3) (Figure 1) were seen in both the arms and Grade 3 toxicity was higher in HU CRT arm but difference was not statistically significant (24% vs 20%, p=0.612).

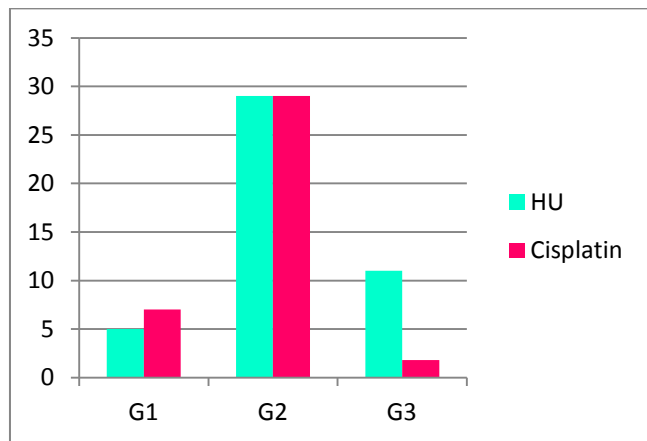


Figure 1: Skin toxicity during treatment

Mucosal Toxicity (Figure 2) Grade 2 was more common in cisplatin arm ($p = 0.001$) and grade 3 toxicity was more common in HU arm ($p= 0.017$).

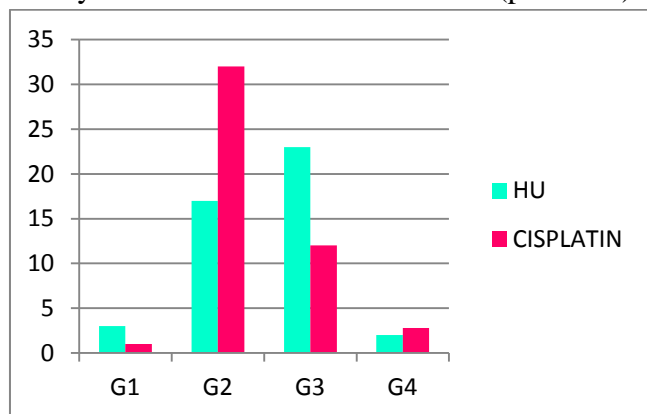


Figure 2: Mucosal toxicity during treatment

Late Toxicities

Chronic Salivary Toxicity at Median Follow Up (Figure 3): Majority of patients (73%) had G1 salivary gland toxicity which was not statistically significant

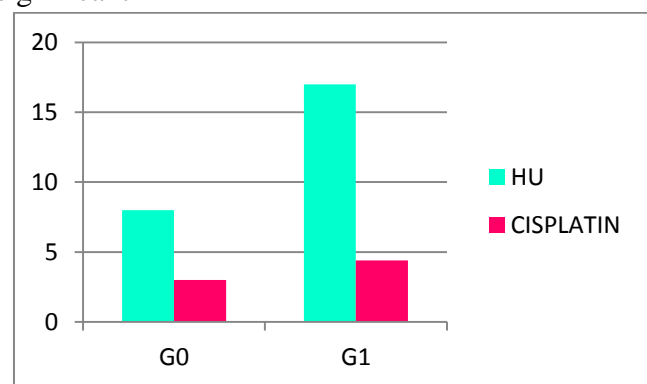


Figure 3: Salivary toxicity at median follow up

Subcutaneous Fibrosis at Median Follow Up (Figure 4) was present in 92% of patients in HU

arm and 69% of patients in CISPLATIN CRT arm ($p =0.064$) which was not statistically significant.

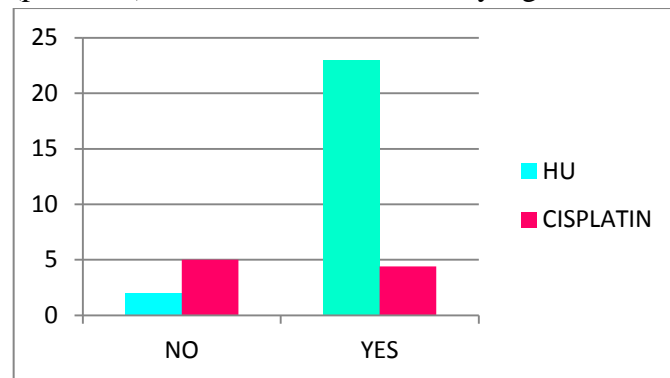


Figure 4: Subcutaneous fibrosis at median follow up

Discussion

The HU was chosen for the reason that it kills all the cells in S-phase and put a block at the end of G1-phase. So we presumed that all the cells will be collected at the end of G1-phase and as the concentration of drug will go down, the block will be removed. As a result all the cells will pass on the different phases of cell cycle simultaneously and as they reach to the most sensitive phase of the cell cycle like G2M, the radiation will kill maximum number of the tumour cells⁴.

Response

On the first follow up, 78% had complete response at primary site in HU arm and 71% in cisplatin CRT arm. This difference was not statistically significant. In a study⁵ using paclitaxel, 5FU and HU with concurrent radiotherapy in HNC out of 17 patients without prior local therapy 70% had CR. Overall 71.4% achieved complete response using weekly cisplatin in HNC in another study⁶. The median follow up period in our study was 5.5 months. During median follow up the complete response was seen in 60% in HU arm and 75% in cisplatin arm.

As compared with radiotherapy alone, treatment with HU and radiotherapy significantly increased complete response in carcinoma cervix⁷. However treatment with cisplatin, 5- FU and radiotherapy resulted in greater improvement in Progression free survival and overall survival than did treatment with HU and radiotherapy. Similarly, Rose et al⁸

comparing weekly cisplatin vs cisplatin, 5FU and HU vs HU alone concurrent with radiotherapy in IIB to IVA cervical cancers. Both the groups that received cisplatin had higher rates of PFS and OS than HU alone. In our study, 78% had complete response at in HU arm and 71% in cisplatin CRT arm where we have used the dose of 25mg/m², not more than 1500 mg. But in the above studies, it was seen that the dose of HU used was very high (2-3gm/m² in Rose et al and 80mg/kg in Whitney et al) which lead to more acute and late toxicities. Moreover, HU was given only two days in a week 2 hours before EBRT due to which the plasma peak level and thus action of HU in cell cycle could not be achieved. These factors may be responsible for the inferior results of concurrent HU in these studies.

Acute Toxicity

The acute toxicities were seen more in HU arm. The mucosal grade 3 toxicities were common in HU arm with statistical significance. A trend towards higher severe acute reactions were seen in the HU CRT arm as compared to Cisplatin CRT arm but were short term and manageable with symptomatic treatment. In a study by Spencer et al⁹ in case of re-irradiation with HU and 5 FU, grade 3 mucositis occurred in 14% of patients & grade 4 in 5% of patients. In our study, Grade 3 mucositis was seen in 51% of patients with HU and 27% with Cisplatin. Acute radiation related morbidity in HU arm in the present study is comparable to Inter-group trial by Aldelstein et al¹⁰ in which Grade 3 and 4 mucositis was seen in 84% of patients treated with HU, paclitaxel and 5 FU.

Late Toxicities

All acute toxicities in patients of both the arms were completely healed after 6 weeks of completion of treatment. Regarding late toxicities in our study, we observed xerostomia and subcutaneous fibrosis at anterior aspect of neck, which did not differ significantly in both groups. In the HU RT arm 92% patients had G1 subcutaneous fibrosis and 69% had salivary toxicity as compared to 69 % had G1 subcutaneous fibrosis and 80% salivary toxicity in cisplatin CRT at median follow-up. However this difference was not statistically significant.

Conclusion

1. There was comparable loco-regional disease control with the use of HU CRT compared to cisplatin based concomitant chemoradiation with conventional fractionation.
2. On long term follow up, similar incidence of toxicities were seen in HU RT arm and cisplatin CRT arm.

Hence, based on our study (though it is small), it can be seen that HU can be an attractive approach where cisplatin is precluded from concomitant CRT. Since the loco regional control is comparable with cisplatin based CRT but with added advantage of oral chemotherapy with HU which is more compliant and can be given on out-patient basis. So in countries where most of the patients are from low socioeconomic status and there is a scarcity of infrastructure, this may be a good alternative. This may also be an option in patients with chronic renal disease or other co-morbidities which preclude the administration of cisplatin. Overall acute toxicities were observed to be more in the HU arm as compared to concomitant cisplatin arm but they were manageable conservatively.

Declarations

Funding: No funding sources

Conflict of interest: None

Ethical approval: Institutional Ethical Committee

References

1. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, et al. Global, Regional and National cancer incidence, Mortality, Years of life lost, years lived with disability & Disability Adjusted Life Years for 32 Cancer Groups, 1990-2015: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol* 2017;3:524
2. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med* 2003;349:2091-2098.

3. Pignon JP, Bourhis J, Domenge C, et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: Three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet* 2000;355:949-955.
4. Hall EJ, Brown JM, Cavanagh J. Radiosensitivity and the oxygen effect measured at different phases of the mitotic cycle using synchronously dividing cells of the root meristem of *Vicia faba*. *Radiat Res.* 1968;35:622-634.
5. Vokes EE, Haraf DJ, Brockstein BE, Weichselbaum RR. Paclitaxel, 5 FU, hydroxyurea and concomitant radiation therapy for poor prognosis head and neck cancer. *Semin Radiat Oncol.* 1999 Apr;9(2 Suppl 1);70-6
6. Kang MH, Kang JH, Song HN. Concurrent chemoradiation with low dose weekly cisplatin in locally advanced stage IV head and neck squamous cell carcinoma. *Cancer Res Treat.* 2015 Jul;47(3):441-447.
7. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIBIVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol* 1999;17: 1339-1348
8. Rose PG, Ali S, Watkins E, et al. Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a Gynecologic Oncology Group Study. *J Clin Oncol* 2007;25:2804-2810
9. Spencer SA, Harris J, Wheeler RH, et al. RTOG 96-10: re-irradiation with concurrent hydroxyurea and 5-fluorouracil in patients with squamous cell cancer of the head and neck. *Int J Radiat Oncol Biol Phys* 2001
10. Adelstein D, Li Ym Adams G, et al. An Intergroup Phase III Comparison of Standard Radiation Therapy and Two Schedules of Concurrent Chemoradiotherapy in Patients With Unresectable Squamous Cell Head and Neck Cancer. *Journal of Clinical Oncology* 2003; 21 : 92-98.