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RESEARCH ARTICLE

RADIOTHERAPY WITH HYPOXIC RADIOSENSITIZER IN LOCALLY ADVANCED HEAD AND NECK CANCER

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Abstract

Background: Bulky solid tumors contain oxygen-deficient hypoxic areas which cause tumors to become radioresistant. Modification of tumor hypoxia will result in improved outcomes.

Objective: To assess and compare the immediate loco regional response rates of locally advanced head and neck squamous cell carcinoma (LAHNSCC) treated with radiotherapy and Nimorazole, with radiotherapy alone; to assess the degree of symptom relief and acute toxicities.

Methods: 30 patients with LAHNSCC with performance status (PS) 3, ineligible to receive concurrent chemotherapy were treated with radiotherapy 50Gy/16# and Nimorazole. The response after 6 weeks was assessed using RECIST criteria. The symptoms present before and after treatment were registered using symptom assessment scale. The toxicities of radiation and nimorazole were documented.

Results: 14 among 21 patients with stage IV B showed partial while others had static response. Among the 9 in stage IV A, 6 had complete and 3 had partial response. Overall response rate was 77% compared to 51-73% in historical controls. Significant (>50%) improvement in symptoms was seen in 20 patients (80%). None of the patients developed severe toxicities specific to Nimorazole. 4 patients who developed grade 1 vomiting had dose reduction. None developed rashes or flushing.

Conclusion: Hypofractionated radiotherapy along with Nimorazole demonstrated a good response with better symptom control in LAHNSCC patients with poor performance status without added toxicities.

Introduction:-

Around the world, head and neck squamous cell carcinoma (HNSCC) accounts for >5 million new cancer cases every year. Globally it is the 5th common malignancy. About 300,000 head and neck cancer patients are dying annually, which is a very high burden on our community[1]. Majority of such cases (60%-80%) in India are presenting in advanced stage[2]. Radical chemo radiotherapy is not tolerated by these patients because many are in poor performance status (PS). Since there is no general consensus regarding RT schedule in poor PS, researchers have analysed conventionally fractionated radiotherapy and hypofractionated radio therapy schedules. Many have

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compared 60 Gy to 70 Gy over 6 to 7 weeks with 48 Gy to 50 Gy over 3 to 4 weeks in stage IV locally advanced HNSCC. They did not observe any significant difference in terms of tumor control, acute or chronic toxicity.

Most radiation oncologists believe that conventional fractions of radiotherapy will give poor response in larger tumors. Hence there prevails a general consensus of treating bulky solid tumors of the head and neck with hypofractionated regimens of radiotherapy. For such cases we have an institutional protocol of 50 Gy in 16 fractions. Another reason to choose such regimen was the high patient load, especiallly in government institutions, so that we get an advantage of completing treatment soon.

When we give only radiotherapy, even with the best possible modification of RT schedules, only a 50% to 70% local control rate and 30% to 40% Disease Free Survival (DFS) could be achieved[3]. Patients with weak PS are not fit to receive a radical schedule of concurrent chemotherapy. Even when we give reduced dose of weekly chemotherapy it will produce toxicities of mucositis and myelosuppression, which may further land up in increased treatment breaks and reduced outcomes in tumor response; more importantly reduced symptom control and unacceptable QoL. In patients with poor PS, personalised treatment should be considered. So in this study we avoided any chemotherapy to patients along with RT.

Hypoxia and neovascularisation are interlinked. The radiopharmaceuticals like 18F-Fluoromisonidazole selectively accumulate in the hypoxic tissue, with reduced uptake in well oxygenated tissues. 18F-Fluoromisonidazole gives us information on biological characterization of head and neck cancers prior to treatment, and finally we can get the prognostic information, which implies response to treatment[4].

Hypoxic modifications:
Researchers have found hypoxic modification of radiotherapy has yielded clinical benefit in the treatment of HNSCC and to some degree in uterine cervical cancer. Based on these findings and also due to the outcomes of the DAHANCA 2 and DAHANCA 5 studies, Nimorazole has been adapted for routine clinical use in Denmark since 1990 in head and neck cancer patients[5].

So a study has been designed to assess the effect of nimorazole with definitive hypofractionated radiotherapy in bulky and locally advanced head and neck cancer patients with poor PS.

Materials And Methods:-

30 consecutive patients presenting to our institute who were eligible to be included as per the study protocol were selected. Institutional Ethics Committee approval obtained. Information sheet on the study was given to patients and informed consents were obtained.

Inclusion Criteria:
Biopsy proven cases of squamous cell carcinoma of head and neck (SCCHN) from oropharynx, hypopharynx and larynx, Stage IV A and IV B (AJCC 7th e.) with PS 3, Age: 18-70, not fit for concurrent chemotherapy.

Exclusion criteria: severe medical comorbidities, disorders of connective tissue, Prior treatment with chemotherapy or radiotherapy, Second primary malignancies, relapsed or recurrent disease.

Pre-treatment work up and general measures: pan endoscopy, CECT neck, Chest X-ray, CBC, RFT, LFT, Viral markers, Dental prophylaxis, Smoking and alcohol cessation counseling, Swallowing and Speech evaluation, Nutrition assessment and feeding tube placement, if indicated, Screening for depression, symptom assessment using symptom assessment scale (SAS).

Study protocol included radiotherapy to the target volume, 50 Gy in 16 #, with Tab.Nimorazole 1.2 gm/m² daily (only on RT days), to be swallowed 90 min before radiation, if ≤1.5 m² Body Surface Area (BSA) – 3 tablets (1500mg), if >1.5 m² BSA - 4 tablets (2000mg).

Radiotherapy Technique: Radiotherapy was delivered in parallel opposed lateral portals with a telecobalt Theratron Phoenix machine in 2D technique, 5 #/ week, up to 16#. Treatment volume included the primary tumor and level I B to V B neck nodal regions and 5mm margin for setup error. A 0.5cm wet gauze cotton bolus was used in cases with skin infiltration. The dose was prescribed to the midline depth. In N3 nodes with clinically N0 on the other side, a 2:1

weightage was be given. Offcording was done after 10#. Off-cording was individualised to each patient as per the posterior location of the nodal mass.

Primary End point: To assess and compare the immediate response rates of treatment protocol with historical controls of radiotherapy alone.

Secondary End point: To assess the degree of symptom relief and acute toxicity of the treatment.

Symptom assessment: All major distressing symptoms experienced by the patients were assessed using the 11 point symptom assessment scale[14] (SAS) (Figure 3). Assessment was done at the baseline, during and 6 weeks after treatment.

Toxicity of radiotherapy: Mucositis, Laryngitis, Pharyngitis, Skin reactions, Xerostomia, Hb level and complete blood counts were assessed weekly and after treatment, using RTOG acute toxicity grading.

Toxicity of Nimorazole: Nausea, Vomiting, Flushing and Skin rashes were assessed during and after treatment, usingCTCAE version 4.03.

Response evaluation: After treatment patients were reviewed once in 2 weeks to assess and treat the toxicities, if any. After 6 weeks, patients were advised to take CT scan of the primary and neck with contrast. Response evaluation was done using RECIST criteria. Degree of symptomatic relief was assessed using symptom assessment scale. Based on this, patients were grouped into three viz., those having <25%, 25 - <50%, ≥50% relief. Those with ≥50% reduction of symptoms was said to have significant relief[14]. All outcomes were expressed in percentages.

Results:-

The patients were aged from 52 to 70 years. The median age was 65 years. 13 and 17 patients were in the age group of 51-60 and in 61-70, respectively (Table 1). All the 30 were males. This skewed distribution towards the male gender was probably due to increased carcinogen exposure in the males.

Oropharynx was the primary site of disease in 15 patients, hypopharynx in 9 and supraglottic larynx in 6; majority of the tumors were from oropharynx (Table 1). Majority had moderately differentiated tumors. Majority were in T3 and T4 stage and in N3 stage; 6 were with ulcerated nodes. Most were in stage group IV B (AJCC 7th e.) (Table 2). All were in PS 3. Based on BSA, 7 patients received 4 tablets of nimorazole while others got 3 (Table 3).

Among 30 patients, 23 (6 CR+ 17 PR) achieved some form of response in the tumor which yielded an overall response rate (ORR) of 77% (20+57) (Table 4).The complete response (CR) which was attained in 6 patients was from the stage group IV A. Most of the patients had response with this treatment protocol; about 17 had a partial response (PR), contributing to a good volume of 57% response. Most of the patients who attained partial response were from stage group IV B (Table 5).

The most common complaint was pain, which was reported by 83%. Dysphagia and otalgia were the next common presenting complaints, which accounted for in 60% and 50% of patients, respectively. Insomnia was found in 76%. Other symptoms were dyspnoea, cough and voice change. Few of the patients had all of the above mentioned symptoms, while others had many of these. Those with ≥50% improvement in their symptoms were considered significant and taken for analysis (Table 6). Local pain improved in 20 out of 25 (80%); Dysphagia improved in 12 out of 18 (66%); Otalgia improved in 12 out of 15 (80%).

Radiation related toxicities: 14 patients developed grade 3 mucositis / pharyngitis. None of the patients developed grade 2 or 3 skin reactions; most of them developed grade 1 reactions like dry desquamation which were treated with an ayurvedic preparation called Cansafe ointment. Grade 2 salivary gland reaction was seen in 10 patients; all others developed grade 1 toxicity. All patients had minimal hoarseness of voice; 8 developed grade 3 laryngitis and otalgia due to referred pain. None of the patients developed thrombocytopenia or grade 2 haematological or grade 4 acute radiation toxicities.

Toxicities specific to nimorazole: Skin rashes, flushing or grade 3 nausea were not seen in any of the patient. Grade 2 nausea was seen in 4 patients and had dose reduction in nimorazole (Table 7). They received 1000 mg instead of 1500 mg per day, for remaining treatment.

Discussion:-

The treatments aiming to improve the Quality of Life (QoL), target on better response in the tumor and hence better symptom control. Even by adding a minimal response in the tumor we can add up to improvement in symptom control, but it should not add up toxicities. Hence improvement in the response of the tumor should be one of our goals in any intent.

Tumour hypoxia in human cancers was shown with histologic evidence and was initially reported in 1955. Researchers have shown low oxygen concentration is associated with poor locoregional control with either RT or chemotherapy. These earlier findings together with the recent results from nuclear imaging studies using radiolabelled misonidazole, give us strong evidence for the presence of tumour hypoxia. These findings influence not only radiotherapy treatment but also any cancer treatment outcome. (Lee DJ et al. 1996)

Moulder JE et al., (1984)[6] had shown that radiobiologically hypoxic cells are present in most of the solid rodent tumors. Also as the tumor size increases the hypoxic fraction increases. It has been proved from many preclinical trials that solid tumors may contain oxygen-deficient areas called as hypoxic areas and because of these hypoxic cells, tumors may become resistant to treatment (Overgaard 2007)[7].

There are evidences to conclude that because of high level of hypoxia in solid tumors adverse prognosis occurs in the evolution of a malignant tumor, especially after treatment. The lack of oxygen in the blood was correlated with poor tumor response to any kind of treatment[8,9]. Hypoxia is proved to be a marker of aggressive tumor phenotype and it could be blamed for the resulting poor prognosis and high likelihood of further recurrences after surgery[10,11]. Furthermore, hypoxia might be responsible for tumor resistance to some oncological agents[12].

Based on the presence of necrotic tissue beyond 180µ radius from the capillary margin it was concluded that there existed diffusion-limited hypoxia in human lung cancer (Figure 1). Perfusion-limited hypoxia also plays a vital role in making the cancer cells more locally aggressive, metastatic, and most importantly resistant to therapy. Hence the hypoxic modification should be our prime thought, at least in large volume tumors.

The oxygen effect: Ionizing radiation can produce free radicals that lead to cell death by causing single and double strand DNA breaks. Oxidation is the process of fixing this damage with oxygen. Molecular oxygen has the ability to react with free radicals and can produce many downstream molecules that are highly lethal to the cell. But in the presence of hypoxia within the tumor cells this beneficial effect of free radical damage will not occur. It has been observed that oxygenated cells respond to ionizing radiation about 2.5 times more than the hypoxic cells (Figure 2).

Several strategies[13] have been introduced by the researchers to modify and specifically target hypoxia related therapeutic resistance:

1. Oxygen delivery can be enhanced, by using carbogen breathing or hyperbaric oxygen or ARCON (accelerated radiotherapy with carbogen and nicotinamide) treatment,
2. Hypoxic radiosensitizers, such as misonidazole or nimorazole and
3. Hypoxic cytotoxin, for eg. tirapazamine.

Hypoxic modification using nitroimidazole group of drugs such as misonidazole, metronidazole, benznidazole, desmethylmisonidazole, etanidazole, pimonidazole, nimorazole, ornidazole, and RSU 1069, have been proved fit enough for clinical evaluation as hypoxic radiosensitizers. There had been a significant relationship between the drug tolerance and resulting hypoxic modification. So we need to choose the most tolerable drug group, which were found to be 5-nitroimidazoles, but they had smallest activity. Still, due to higher tumor/plasma concentrations they may be more clinically effective than others.

Nimorazole: Nimorazole is a 5-nitroimidazole drug having same structural class as metronidazole. It has high electron affinity which makes the drug mimic the effect of oxygen thereby it makes the tumor more radiosensitive. It is found to be less potent than misonidazole still it has a high tumor/plasma ratio which brings a similar or better radiosensitization; and added advantage is that it lacks neurological toxicity. It is available in 500mg tablet

formulation. Recommended dose in trials was 1.2 gm/m^2 BSA and in DAHANCA trial they used three, four or five tablets for patients with ≤ 1.6, >1.6 – ≤ 1.9, > 1.9 m^2 BSA, respectively. The main advantages with nimorazole are its ease of administration through oral route, very less and still easily manageable toxicities and hence good patient compliance, easy titration of the dose when toxicities occur and finally cost effectiveness,.

The report published by Danish Head and Neck Cancer Study (DAHANCA) Protocol 5-85, was a major breakthrough in the treatment using hypoxic radiosensitizer. Jens Overgaard et al. (1997)[5,7]assessed in a phase 3 trial the efficacy and tolerance of nimorazole given concurrently with radiotherapy in invasive cancer of the supraglottic larynx and pharynx. They observed that the nimorazole group had a significantly better loco-regional control rate compared to the placebo group (49 versus 33%) and it was also observed that it did not produce any major side-effects; and better 10-yr overall survival, but was not significant.

In the DAHANCA-5 study only 51% of the patients completed the planned drug regimen with radiotherapy. The present study shows that 87% of the patients completed full prescribed dose (4 patients had dose reduction). While adding cisplatin with nimorazole and RT, as in few trials it was difficult to assess whether the nausea / vomiting were really due to nimorazole. But many studies have already demonstrated it to be a fairly tolerable drug.

Historically, the patients under 'Christie Scheme' hypofractionated radiotherapy were treated using the same dose used in this study. The BED value of this schedule was 65.6 Gy_{10} and the EQD_2 was 54.7 Gy. Most of the patients were in stage IV. They observed an overall response rate ranging from 51 to 73% (Table 8); in the present study it was 77% and in addition none of the patients had progressive disease (PD), which could be attributed to the addition of hypoxic radiosensitizer.

Further dose escalation can be tried in those patients with good tolerance to achieve a BEDvalue of at least 70 Gy, with the intent of increasing the response in the tumor, so that we can achieve better symptom control and hence better QoL.

In this present study only very few patients developed significant side effects of nimorazole; they were neither severe nor long lasting. Most patients tolerated the treatment regimen well. Along with the good symptom control, partial to complete response was attained in the tumor in many patients. All together the treatment protocol resulted in good symptom relief and hence a better QoL in a good proportion of patients.

Tables:

Table 1:- Profile of the study participants.

S.No.	Variable	Frequency	Proportion
1	**Age**		
	51-60	13	43
	61-70	17	57
2	**Gender**		
	Male	30	100
3	**Smoking**		
	Yes	27	90
	No	3	10
4	**Tobacco**		
	Yes	22	73
	No	8	27
5	**Subsite**		
	Oropharynx	15	50
	Tonsillar fossa -9		
	Posterior 1/3rd tongue -4		
	Soft palate -2		
	Hypopharynx		
	Pyriform fossa -5	9	30
	Posterior pharyngeal wall -3		
	Post cricoid region -1 Supraglottic**Larynx**		
		6	20

Table 2:- Distribution of study participants according to grade and stage of tumour.

S.No.	Variable	Frequency	Proportion
1	**Grade**		
	Well differentiated	2	7
	Moderately differentiated		
	Poorly differentiated	24	80
		4	13
2	**T stage**		
	T1	3	10
	T2	4	13
	T3	10	33
	T4a	10	33
	T4b	3	10
3	**N stage**		
	N2b	6	20
	N2c	4	13
	N3	20	67
4	**Stage group**		
	IV A with PS 3	9	30
	IV B with PS 3	21	70

Table 3:- BSA of patients and Nimorazole dosage.

S. No.	Weight (kg)	Height (cm)	BSA	Nimorazole dose (500 mg tablets)
1.	40	162	1.34	3
2.	46	160	1.43	3
3.	37	170	1.32	3
4.	36	170	1.30	3
5.	39	162	1.31	3
6.	40	168	1.36	3
7.	48	170	1.51	4
8.	39	172	1.36	3
9.	45	170	1.46	3
10.	42	168	1.40	3
11	42	172	1.42	3
12.	45	160	1.41	3
13.	47	170	1.49	4
14.	44	167	1.43	3
15.	45	167	1.45	3
17.	47	170	1.49	4
18.	39	170	1.36	3
19.	40	165	1.35	3
20.	40	163	1.35	3
21.	47	172	1.50	4
22.	42	176	1.43	3
23.	46	170	1.47	3
24.	49	168	1.51	4
25.	39	168	1.35	3
26.	42	165	1.39	3
27.	50	170	1.54	4

28.	47	170	1.49	4
29.	42	168	1.40	3
30.	37	168	1.31	3

Table 4:- Overall response assessment.

Response	**Frequency**	**Proportion**
Complete response (CR)	6	20
Partial response (PR)	17	57
Stable Disease (SD)	7	23

Table 5:- Stage group wise tumor response assessment.

Stage group	**CR**	**PR**	**SD**
IV A	6	3	0
IV B	0	14	7

Table 6:- Symptoms assessment.

Symptoms	**At presentation**		**After treatment** (significant improvement)	
	Frequency	Proportion (out of total 30)	Frequency	Proportion (out of those who had that symptom)
Local pain	25	83	20	80
Dysphagia	18	60	12	66
Otalgia	15	50	12	80
Insomnia	23	76	15	65

Table 7:- Nimorazole specific toxicity.

Nausea	**Frequency**	**Proportion**
Grade 1	12	40
Grade 2	4	13
Grade 3	0	0

Table 8:- Comparison of response with historical groups.

Study	CR (%)	PR (%)	ORR (%)	SD (%)	PD (%)
Al mamgani et al[15]	45	28	73	6	21
Srivastava et al[16]	19	32.7	51.7	29.1	3.6
Madras medical college	21	46	67	28	5
Present study	**20**	**57**	**77**	**23**	**0**

Figures:

Figure 1:- Range of oxygen diffusion Vs necrosis inside tumor mass (vasculature at periphery).

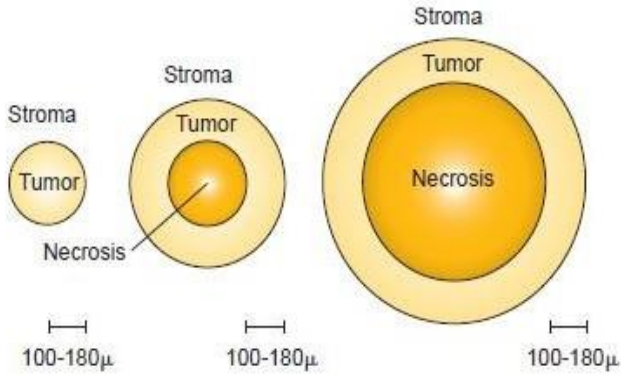


Figure 2:- Oxygen enhancement ratio of various radiation beams.

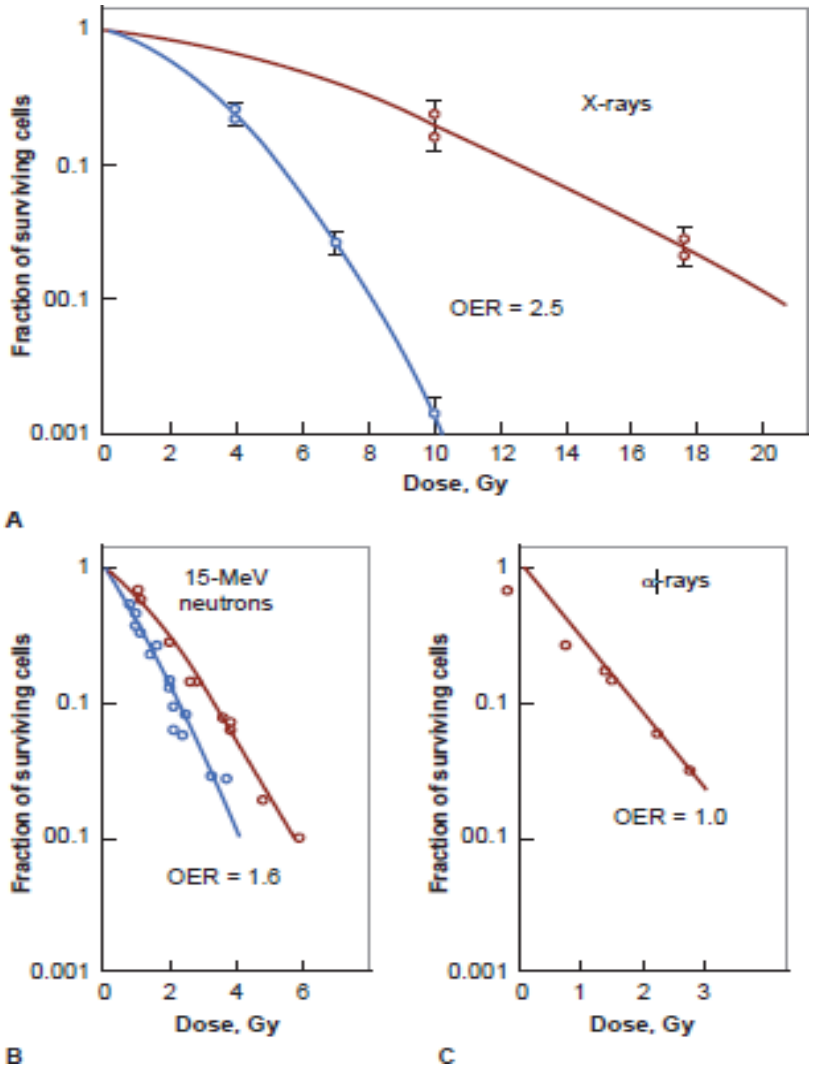
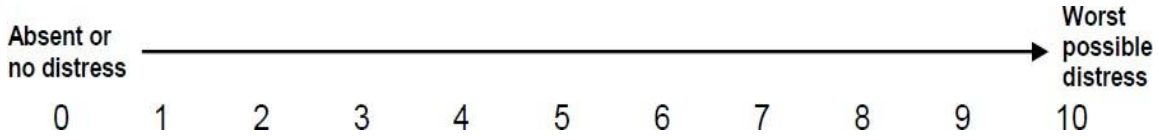


Figure 3:- Symptom assessment scale.



Conclusion:-

In patients with locally advanced HNSCC, hypofractionated radiotherapy along with nimorazole effectively restrained the growth of tumor, resulted in cure in few, achieved good palliation of symptoms and thereby increased the QoL of patients without any added toxicities, in the short run. Also, this study is trying to strike a balance between economic burden, treatment duration and hospital stays, and patient load on the radiotherapy machines. We recommend the hypoxic radiosensitizers to be considered for all eligible patients of head and neck cancer with bulky disease. Still larger sample size with longer follow up of patients is needed to arrive at a definitive conclusion on survival analysis and for calculating statistical significance.

Conflicts of interest:

Nil.

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