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Role of Metronomic Chemotherapy in Head and Neck Malignancies

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Abstract
Head and neck cancer describes malignant tumor arising in or around the throat, larynx, nose, sinuses, and mouth.Pathologiclallymost of them are squamous cell carcinoma.Magnitude of problem in India Overall, 57.5% of global head and neck cancers occur in Asia especially in India. Head and neck cancers in India accounted for 30% of all cancers. In India, 60 to 80% of patients present with advanced disease as compared to 40% in developed countries. The incidence of HNSCC continues to rise and is anticipated to increase by 30% (that is, 1.08 million new cases annually) by 2030.Loco-regional recurrence is seen within two years in almost 60% of patients. These patients suffer with severe painThese patients are treated commonly with Platinum agents. Recently we have Pembrolizumab and Cetuximab introduced in the management of recurrent head and neck malignancy. These are not affordable by 95% of our population.We are in search of an effective ,affordable and accessible chemotherapeutic agent for such patients. We conducted a study on Metronomic chemotherapy in Head and Neck cancer patients.

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I. Materials And Methods

Study Details
We had 92 patients of recurrent head and neck who were enrolled in our study.

Inclusion Criteria
Histologically confirmed Squamous cell carcinoma of Head and Neck
Had received definitive Radiation
Had residual or recurrent disease after radiation
Perfomance status of ECOG 0 to 3

Exclusion Criteria
Patients with viral disease HIV,HBV HCV
Patients with ECOG below 3

Treatment Protocol
All the selected patients were prescribed oral MCT consisting of oral methotrexate at a dose of 20 mg/m^2 once a week . All these patients were assessed fortnightly clinically,They werecontinued treatment until disease progression or unacceptable toxicities or death.

Patient Characteristics

		NUMBER OF PATIENTS	PERCENTAGE
AGE	Less than 50	34	36
	More than 50	58	64
PS SCORE	0 TO 1	75	81
	More than 1	17	20
REGION	Oral cavity	36	39
	Pharyngeal	56	61
Time from Previous treatment	Less than 6months	28	30
	More than 6 months	64	70

Previous Treatment Details

	NUMBER OF PATIENTS	PERCENTAGE
Neo adjuvant chemo followed by RT	56	68
CCRT	82	82
Chemo alone	10	11

II. Results

Response Assesment

Response assessment was done on based on clinical and symptomatic relief. They were also assessed with CTimaging, [1] The disease response was graded as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

	NUMBER OF PATIENTS	PERCENTAGE
Complete Response	1	1
Partial Response	58	63
Stable Disease	17	18
Progressive Disease	16	17

Toxicity

	NUMBER OF PATIENTS	PERCENTAGE
Mucositis	28	30
Hypertransaminasemia	10	10
Neutropenia	14	15

Our patients were followed up for 10 months. Median survival was around 6.8 months. Fifteen patients had discontinued treatment after 6months. Sixteen patients had died during the study period due to advanced stage of the disease . Almost all our patients initially had pain relief for about four months ,pain progressed after that and patients were given Morphine simultaneously.

III. Discussion

Head and neck cancer is increasing in incidence tremendously during the past years and is expected to increase by 30% in 2030'.[1]The five main types of head and neck cancers are:Laryngeal and hypopharyngeal cancer. Nasal cavity and paranasal sinus cancer.Nasopharyngeal cancer.Oral and oropharyngeal cancer.Salivary gland cancer. Current standard of care depends on the site,stage and performance status of the patient.However most patients relapse within two years of treatment.The treatment of these patients remains as a challenge to most oncologists as there is no affordable treatment which is going to increase the overall survival**.** The survival for HNSCC has improved modestly over the past three decades[2].The treatment approach is individualized to each patient and depends on anatomical subsite, stage, disease characteristics, patient wishes and functional involvement.Surgery is usually done for oral cavity cancers and radiation for pharyngeal and laryngeal cancers. Moderately hypofractionated radiation schedule results in better locoregional control and survival in laryngeal cancers. Advances in minimally invasive resection, robotic or laser resection , larynx-preserving partial laryngectomy and improved reconstructive techniques, have extended the indications for primary surgical management.Tri modality therapy increases the late toxicities of radiation, including chronic dysphagia and aspiration, and might increase the risk of non-cancer-related mortality in survivors.[3] Concurrent cisplatin-radiation therapy is now the standard of care in patients with pathologic high-risk HNSCC.[4] Incorporation of molecular targeting agents, such as cetuximab, an IgG1 human-murine monoclonal antibody against the epidermal growth factor receptor (EGFR) gives promising results. For patients with recurrent or residual head and neck cancers single agent chemotherapy with Taxols,Methotrexate, AfatinibKey factors that need to be considered in choosing a treatment include the following: Exposure to previous chemotherapy,its response,whether patient received concurrent chemoradiation,time to disease progression, perfomance status and comorbidities of the patient. Patients with severe comorbidities and/or a poor performance status may be best treated with supportive care.For stage iv head and neck cancers survival is less than one year. [5]

Some patients who relapse may be candidates for salvage therapy with curative intent, using either surgery or reirradiation. However most patients who recur ultimately require palliative systematic therapy. The optimal regimen for these patients has not been defined. chemotherapy demonstrates progress in treatment outcomes, including better local control, lower incidence of systemic recurrences, improved disease-free survival, and most importantly, improved overall survival. The quality of life has improved for many of these patients, especially when the larynx and voice function is preserved in cancers of the larynx or hypopharynx. Improvement in the overall survival was demonstrated by prospective randomized phase III studies and meta-

analyses, and more significantly, by population-wide statistics The current standard for palliative systematic therapy for recurrent head and cancer recommends cisplatin, fluorouracil, cetuximab and pembrolizumab with or without cisplatin and fluorouracil. The exact choice and line of treatment is evolving.[6] Decisions are driven by patient characteristics, including age, performance status, comorbidities, and expected toxicities. patients not eligible for surgical resection, previous exposure to chemotherapy,response to it and time to relapse.

Recently Immunotherapy has become the standard in the first line setting.[7] If patient has progressed following initial treatment with systemic platinum- based chemotherapy(with or without ceutuximab) and who are ineligible for immunotherapy, options include single agent or combination therapy with a taxane, a platinum (preferably carboplatin if prior cisplatin exposure), fluorouracil or methotrexate. The other options for patients without prior exposure. drugs used in recurrence are Bleomycin,5fu. Methotrexate, Hydroxyurea and Cyclophosphamide. Metronomic chemotherapy is one which can be tried in most patients with recurrent head and neck cancer.It has been constantly developing since This therapy is administered orally and does not require cold chain maintenance and is affordable . . There are three mechanisms of cancer dormancy include angiogenic dormancy, whereby tumor cellsare unable to recruit blood vessels, arrests tumor cells in G0-G1 arrest and prevents residual tumor cells expansion by way of immune survelliance Therefore, by inhibiting angiogenesis and controlling immune system, MC can promote tumor dormancy.. There are three mechanisms of cancer dormancy including angiogenic dormancy (inability of tumor cells to immune system, MC can promote tumor dormancy.[8]

Patients receiving Immunotherapy survived for more than 2 years. Globally 75% of population of head and neck patients are within low to middle income countries and cannot afford Immunotherapy. 70% of all deaths due to cancer occurring in these countries.[9] Immunotherapy is possible only in 3% of recurrent head and neck cancer patients. Hence there is a need to develop a more accessible and less toxic alternative therapy for patients with head and neck cancer who require palliative systematic therapy. We need to choose a chemotherapy regimen which will be well tolerated, provides pain control and improves Quality of life with least toxicity profile. [10]

Most of the centers use Methotrexate as metronomic chemotherapy.We also randomized recurrent head and neck cancer patients to receive Methotrexate .We did follow up for 10 months. Median overall survival was 6.8months in our patients which is in par with literature,Most of our patients had excellent pain relief.

IV. Conclusion

Patients with recurrent Head and Neck cancer can be safely given Metronomic chemotherapy.This helps in improving the disease free survival, provides pain relief ,improves quality of life and thereby gives excellent palliation. Our patients also had a median survival of 7 months with metronomic chemotherapy. However oral metronomic chemotherapy is not and alternative if patient can afford immunotherapy or monoclonals. Modern reirradiation with intensity-modulated radiation therapy or stereotactic body radiation therapy widens the therapeutic option in recurrent head and neck cancer patients.

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