Original Research Paper

Volume-8 | Issue-6 | June-2018 | PRINT ISSN No 2249-555X

Oncology

METRONOMIC CHEMOTHERAPY IN RECURRENT, RESIDUAL AND METASTATIC HEAD & NECK CANCERS

Shilpa Kandipalli	Department of Medical Oncology, Sri Venkateswara Institute Of Medical Sciences (SVIMS), TIRUPATI – 517507
T. Kannan *	Department of Medical Oncology, SVIMS, TIRUPATI – 517507. *Corresponding Author
Bhargavi D	Department of Medical Oncology, SVIMS, TIRUPATI – 517507.
Ravi Sankar. A	Department of Medical Oncology, SVIMS, TIRUPATI – 517507.
Praveena Voonna	Department of Medical Oncology, SVIMS, TIRUPATI – 517507.
V. Santosh	Department of Medical Oncology, SVIMS, TIRUPATI – 517507.

ABSTRACT

Background: Despite advances in multimodality therapy, options for patients with Recurrent Head & Neck cancers are desparately limited. Hence, the present study was done to evaluate the role of Metronomic Chemotherapy in Recurrent, Residual and Metastatic Head & Neck cancers with regard to Response and Progression Free Survival.

Methods: Oral Metronomic Chemotherapy with Methotrexate and Capecitabine was given to all patients who met the inclusion criteria in our study. Response assessment was done at end of 3 months and 6 months and compared to baseline imaging using RECIST 1.1 criteria. Toxicities and Progression Free Survival were also analysed.

Results: At 6 months follow up, Stable disease was observed in 34%, Partial response in 19.1% with an overall response rate of 53.1%. Progressive disease was seen in 40.4%, initial stable disease followed by progressive disease in 6.4% of the patients. Toxicities were minimal. The Overall Mean progression free survival (PFS) was 164 days (5.5months) + 36days (95% confidence interval)

Conclusion: Oral Metronomic Chemotherapy with Capecitabine and Methotrexate is a good alternative to conventional intravenous chemotherapy in patients with Recurrent, Residual and Metastatic Head & Neck cancers with good response rates, better toxicity profile and significant improvement in PFS especially in patients with good PS

KEYWORDS : Metronomic Chemotherapy, Head & Neck cancers, PFS

INTRODUCTION

Head & Neck squamous cell carcinoma (HNSCC) is common in Asian countries [1] with an annual incidence of approximately 9-10%. It is the third most common cancer in India and second commonest cancer in Indian males[2] mainly due to excessive use of chewable tobacco. Despite advances in surgery (S), radiotherapy (RT) and chemotherapy (CHT), the survival of patients with HNSCC has not improved significantly over the past decades. The main reason for treatment failure is the development of loco-regional recurrences and/or metastasis, especially in patients with locally advanced disease. Based on Extreme trial results, platinum-fluorouracil chemotherapy plus cetuximab is now-a-days considered the first-line standard treatment, due to the significant improvement in median overall survival (OS) and progression free survival (PFS) compared with CHT alone (10.1 and 5.6 months versus 7.4 and 3.3 months, respectively)[3]. However the response rates are still low (36 %).[3] Majority of the failures occur in first 1-2yrs after completion of treatment.[4,5]Palliative treatment remains an important option in such patients [6,7].

The need of hour in such a scenario would be to institute a therapy that would prevent progression of tumour, effect its regression, to be easily deliverable, minimally or totally non-toxic and economical.This would especially be important in low and middle income countries like India. A turning point in cancer chemotherapy started in 2000, to avoid problems caused by traditional chemotherapeutic agents through a new modality of treatment called "Metronomic Chemotherapy" (MC). [8]

Aim & Objective: To study the response of Oral Metronomic Chemotherapy in Recurrent, Residual and Metastatic Head & Neck Cancers and to assess the Progression Free Survival (PFS)

Materials and Methods: This is a Prospective Observational Study done at our institute. All patients who attended Medical Oncology services during the period May 2016 to May 2017 and fulfilled the inclusion criteria were enrolled and further followed up till December 2017.

INCLUSION CRITERIA

1. Biopsy proven Squamous Cell Carcinoma of Head & Neck region
2. Patients with clinically measurable tumour
3. Patients with Recurrent, Residual & Metastatic disease after primary Multimodality therapy
4. ECOG Performance Status 0-2

EXCLUSION CRITERIA

1. Histology other than Squamous Cell Carcinoma
2. Patients whose tumour size is clinically not measurable
3. ECOG Performance Status > 2
4. Patients who default before the first assessment.

All patients with Biopsy confirmed Recurrent, Residual and Metastatic Head & Neck cancers were counselled regarding option of Metronomic chemotherapy and were included in the study for treatment after obtaining informed consent.

Regimen given is:

Oral Methotrexate : 2.5mg twice weekly
Oral Capecitabine : 500mg twice daily

continuously for at least 6 months or until progression.

Response to treatment was assessed clinically at every visit. Radiological assessment for response is done with CT scans after 3months and 6months of treatment and compared with baseline imaging done at month 0. Response assessment was based on RECIST criteria version 1.1 PFS is defined as the time period between initiation of Metronomic Chemotherapy till progression of disease or death of the patient.

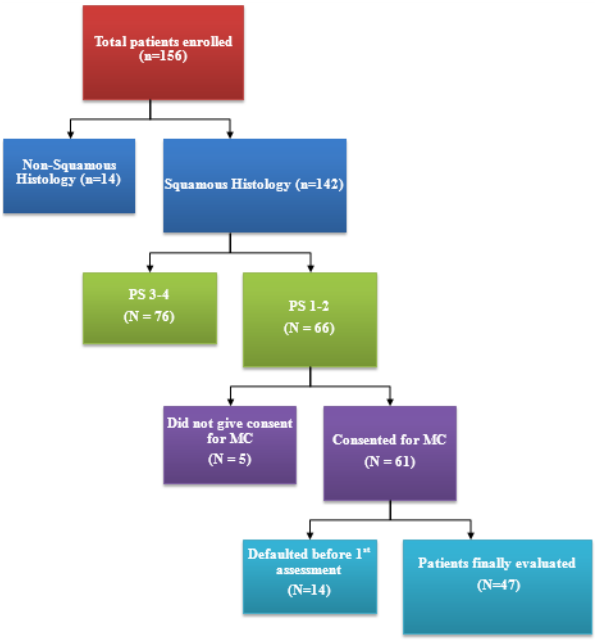
Patients who have progressed at the end of 3 months (i.e. 1st assessment) were excluded for the next assessment (i.e. at end of 6months) as they were either advised best supportive care or shifted to alternate therapy.

STATISTICS: Data was recorded on a pre-designed proforma using Microsoft excel spread sheet. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) software version 20.

For continuous variables, mean ± standard deviation (SD) was calculated. Categorical data was expressed in percentages. For

Survival analysis Kaplan Meier curves were used. P-value of ≤ 0.05 is considered significant.

Figure-1: CONSORT Flow Diagram



RESULTS

Table - 1

S. No	Category	Subset	Number (N)	Percentage (%)
1	**Age**	31-40 yrs	2	4.3
		41-50	15	31.9
		51-60	16	34.0
		61-70	6	12.8
		71-80	8	17
2	**Sex**	Male	25	53.2
		Female	22	46.8
3	**Habits**	Smoking	25	48
		Smoking + Alcohol	5	10
		Smoking + Betelnut	7	14
		Betelnut	14	29
		No habits	9	19
4	**Performance Status**	1	9	19.1
		2	38	80.9
5	**Site of Primary**	Hypopharynx	9	19.1
		Nasopharynx	3	6.4
		Oral Cavity	30	63.8
		Oropharynx	5	10.6
6	**Initial Stage**	III	4	8.5
		IV A	28	60
		IV B	15	32
7	**Disease Status**	Recurrence	28	60
		Residual	15	32
		Metastatic	4	8
8	**Prior Therapy**	RT	32	68
		RT+Surgery	10	21
		Surgery	4	9
		Nil	1	2
9	**Response at Month 3**	Partial Response	8	17
		Stable Disease	20	43
		Progressive Disease	19	40
10	**Response at Month 6**	Partial Response	9	19
		Stable Disease	16	34
		Progressive Disease	19	41
		Initial Stable,later Progression	3	6
11	**Overall Response**	Partial Response	8	17
		Stable disease	9	19
		Progressive disease	22	47
		Death	8	17
11	**Toxicities**	Anemia – grade 1	2	4
		Anemia – grade 2	1	2
		Neutropenia	2	4
		Pancytopenia	1	2
		Mucositis – grade 1	3	6
		Mucositis – grade 3	1	2

Figure – 2: Response at Month 3

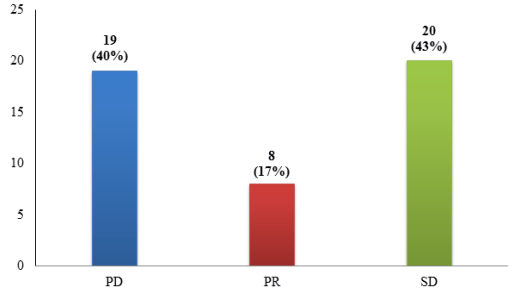


Figure – 3: Response at Month 6

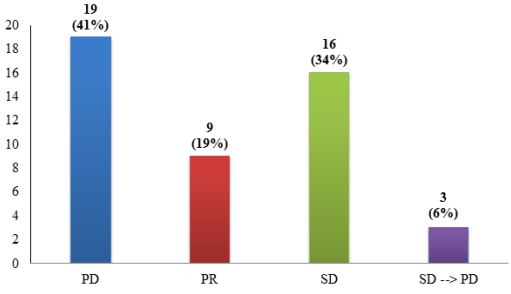


Figure-4: Kaplan-Meier curve showing PFS in relation to Performance Status

P=0.001

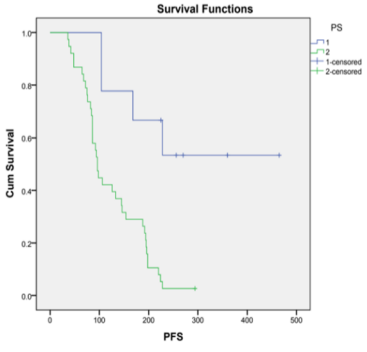
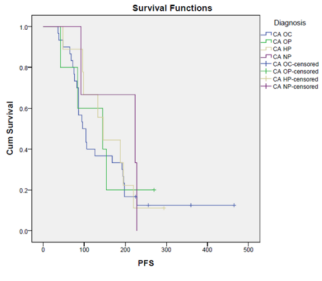


Figure-5: Kaplan-Meier curve showing PFS in relation to Primary Site of malignancy

P=0.459



OC – Oral cavity OP – Oropharynx
HP – Hypopharynx NP- Nasopharynx

Total of 156 Recurrent, Residual and Metastatic Head and Neck cancer patients attended Medical Oncology OPD during the period May 2016 to May 2017. Out of which 14 patients had histology other than Squamous and were excluded. In the remaining 132, 76 patients had poor Performance Status and were excluded. Out of the remaining 66 patients, 5 did not give consent for Metronomic Chemotherapy and were excluded. The remaining 61 patients were started on Metronomic Therapy as per the protocol. However, 14 patients defaulted prior to first response assessment i.e before 3 months period and were excluded. The remaining 47 patients were taken up for the final analysis.

Majority (31) of patients in the present study were between the age group 41-60yrs (65.9%).

Majority (80.9%) of the patients were in PS 2.
Habits were present in 39 (81%) of the patients. Only Smoking was the habit in 12 (25%), both smoking and alcohol in 5 (10%) patients, combined smoking and betelnut chewing in 7 (14%) patients and exclusive betelnut chewing in 14 (29%) patients.

Majority (30) had Oral cavity carcinoma (63.8%), 9 patients (19.1%) had carcinoma Hypopharynx, 5 patients (10.6%) had carcinoma Oropharynx and the remaining 3 (6.4%) had Nasopharyngeal carcinoma.

Response assessment at the end of 3 months showed Stable disease in 20 (42.6%) patients, Partial Response in 8 (17%) patients with an Overall Response Rate of 49.6% (42.6+17) and Progressive disease in 19 (40.4%) patients.

At 6 months follow up, the Overall response was Stable disease in 16 (34%), Partial response in 9 (19.1%) with an overall response rate of 53.1%. Progressive disease in 19 (40.4%), initial Stable disease followed by progressive disease in 3 (6.4%) patient.

The Overall Mean progression free survival (PFS) was 164 days (5.5months) ± 36days (95% confidence interval).

Anemia of grade-1 was seen in 4%, grade-2 in 2%, Neutropenia in 4%, Pancytopenia in 2%, Mucositis of grade-1 in 6% and grade-3 in 2%

DISCUSSION

Majority (31) of patients in the present study were between the age group 41-60yrs (65.9%). This is consistent with the Epidemiological Studies of Head and Neck cancer in South Indian population conducted by Rekha et al.[9]

In the present study the Overall response rate is relatively better compared to ORR in a phase III trial conducted by Jacobs et al[10] using either single agent cisplatin (18%) or cisplatin, methotrexate and leucovorin (33%) [10].

Response rate is also better compared to intergroup E1395 trial done by ECOG in recurrent/metastatic head & neck cancers which showed ORR of 27% vs 26% with Paclitaxel+Cisplatin vs classic PF (cisplatin,5-FU) regimen respectively. [11]However, the response rate was slightly lower compared to the study done by Shin et al comparing TIP vs TIC with an ORR of 58% and 59% respectively.[12,13] but it is comparable with the study done by Jannis et al with TPF regimen showing the ORR 44%.[14]

Table 2: Comparison of Response rates with other Studies

STUDY	DRUGS	RESPONSE RATE
Present Study	Oral Capecitabine + Methotrexate	53.1%
Jacobs et al	i.v. Cisplatin	18%
	i.v.Cisplatin, methotrexate and leucovorin	33%
Intergroup E1395	Paclitaxel+Cisplatin	27%
	Paclitaxel+5-FU	26%
Shin et al	Paclitaxel+Ifosfamide+Cisplatin	58%
	Paclitaxel+Ifosfamide+Carboplatin	59%
Jannis et al	Paclitaxel+Cisplatin+5-FU(TPF)	44%

Toxicities observed in the present study were grade-1 anemia in 2(4%) and grade-3 anemia in 1(2%), neutropenia in 2(4%), pancytopenia in only 1(2%) patient. and grade 1 mucositis in 3(6%) patients. Grade 3 mucositis was seen in only 1 patient (2%). This therapy related toxicities were very low compared to the above studies with i.v chemotherapy.

Table 3: Comparison of Toxicities with other Studies:

TOXICITY	STUDY	PERCENTAGE
Febrile Neutropenia	Present study	0%
	Shin et al	27-30%
	Jannis et al	15%
Grade-3 mucositis	Present study	2%
	Intergroup E1395	31%

Other complications unrelated to therapy were secondary infections in 7(14%) patients (including 2 tracheostomy tube infections), multiple cranial nerve palsies in 3(6%), upfront internal jugular vein(IJV) thrombosis in 3(6%) and retrobulbar neuritis in 1(2%) , which have accounted for early progression or mortality compared to others.

The Overall Mean progression free survival (PFS) was 164 days (5.5months) + 36days (95% confidence interval). This is better compared to the phase 2 study done by Martinez-Trufero et al (4.8 months PFS) using single agent Capecitabine orally in patients with recurrent and metastatic head and cancers.(15)

Comparision of PFS and ORR is also comparable or even better than some studies as shown below:

Table 4: Comparison of PFS and ORR with other Studies

Author/Study	Phase	Regimen	ORR(%)	PFS (months)
Burtness et al (2005) [16]	III	CDDP+Cetuximab CDDP+Placebo	26 10	4.2 2.7
Bourhis et al(2006) [17]	I/II	PF + Cetuximab	36	5.1
Vermorken et al(2008) [18]	III	PF + Cetuximab PF	36 20	5.6 3.3
Hitt et al (2007)[19]	II	Paclitaxel+Cetuximab	60	5.0
Buentzel et al(2007) [20]	II	Pacli/carbo+cetuximab	56	5.0
PRESENT STUDY	-	Capecitabine+Methotrexate	53	5.2

CDDP – Cisplatin; PF – Platinum + 5-fluorouracil

Performance Status (PS) of the patients showed statistical significance (p=0.001) in relation to PFS.

Mean PFS was 320 days(10.6months) + 107days for patients with PS 1. For patients with PS 2, the Mean PFS was 123 days(4.1months) + 20 days.

Primary site of malignancy did not show any statistical significance (p=0.459) in relation to PFS. Mean PFS for Oral Cavity cancers was 156 days (5.2 months) + 44 days, for Oropharyngeal cancers was 139 days (4.6 months) + 68 days, for Hypopharynx cancers was 157 days (5.2 months) + 46 days and that of Nasopharyngeal cancers was 181 days (6 months) + 88 days

CONCLUSIONS

- Oral Metronomic Chemotherapy with Capecitabine and Methotrexate is a good alternative to conventional intravenous chemotherapy in patients with Recurrent, Residual and Metastatic Head & Neck cancers.
- Response rates are comparable with conventional chemotherapy.
- Better Toxicity profile compared to conventional chemotherapy
- Significant improvement in PFS especially in patients with good PS

Limitations of the Study

- The drawback of the present study is sample size. Further studies with larger patient population might be necessary to validate these findings.

Acknowledgements:

- Department of Radiology, Department of Radiotherapy and Department of Surgical Oncology, Sri Venkateswara Institute of Medical Sciences, Tirupati.

References

1. Sankaranarayanan R, Masuyer E, Swaminathan R, Ferlay J, Whelan S. Head and neck cancer. A global perspective on epidemiology and prognosis. Anticancer Res 1998;18;4779-86
2. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001;94:153-6
3. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al.Platinum-based chemotherapy plus cetuximab in head and neck cancer. NEngl J Med. 2008;359(11):1116–27.
4. Patil VM, Prabhash K, Noronha V, Joshi A, Muddu V, Dhumal S, et al. Neoadjuvant chemotherapy followed by surgery in very locally advanced technically unresectable oral cavity cancers. Oral Oncol.2014;50:1000-4.
5. Ghadjar P, Simcock M, Simcock M, Studer G, Allal AS, Ozsahin M, Bernier J, et al. Concomitant cisplatin and hyperfractionated radiotherapy in locally advanced head and neck cancer: 10-yr follow-up of a randomised phase 111 trial (SAKK 10/94) Int J Radiat Oncol Biol Phys.2012;82:524-31
6. Parikh P, Patil V, Agarwal JP, Chaturvedi P, Vaidya A, Rathod S, et al. Guidelines for treatment of recurrent or metastatic head and neck cancer. Indian J Cancer. 2014;51:89-94.
7. Vermorken JB, Specenier P. Optimal treatment for recurrent/metastatic head and neck cancer. Ann Oncol.2010;21 9Suppl 7):vii252-61
8. Baselga J, Trigo JM, Bourhis J, Tortochaux J, Cortes-Funes H, Hitt R, et al. Phase 11 multicenter study of antiepidermal growth factor receptor monoclonal antibody Cetuximab in combination with platinum- based chemotherapy in patients with platinum-refractory metastatic and/or recurrent squamous cell carcinoma of head and neck. J Clin Oncol.2005;23:5568-77
9. R.Rekha, M. Vishnu Vardhan Reddy, P. Pardhananda Reddy. Epidemiological Studies of Head and Neck Cancer in South Indian Population. Journal of Research In Cancer and Tumor 2013, 2(2): 38-44
10. Jacobs C, Meyers F, Hendrickson C, Kohler M, Carter S. A randomized phase III study of cisplatin with or without methotrexate for recurrent and squamous cell carcinoma of head and neck: A North California Oncology group study. Cancer 1983;52:1563-9.
11. Gibson MK, Li Y, Murphy B, Hussain MH, DeConti RC, Ensley J, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): An intergroup trial of the Eastern Cooperative Oncology Group.JClinOncol2005;23:3562-7.
12. Shin DM, Glisson BS, Khuri FR, Ginsberg L, Papadimitrakopoulou V, Lee JJ, et al. Phase II trial of paclitaxel, ifosfamide, and cisplatin in patients with recurrent head and neck squamous cell carcinoma. J Clin Oncol 1998;16:1325-30.
13. Shin DM, Khuri FR, Glisson BS, Ginsberg L, Papadimitrakopoulou VM, Clayman G, et al. Phase II study of paclitaxel, ifosfamide, and carboplatin in patients with recurrent or metastatic head and neck squamous cell carcinoma. Cancer 2001;91:1316-23
14. Janinis J, Papadakou M, Xidakis E, Boukis H, Poulis A, Panagos G, et al. Combination chemotherapy with docetaxel, cisplatin, and 5-fluorouracil in previously treated patients with advanced/recurrent head and neck cancer: A phase II feasibility study. Am J Clin Oncol 2000;23:128-31.
15. J Martinez-Trufero, D Isla, JC Adansa et al, Phase II study of capecitabine as palliative treatment for patients with recurrent and metastatic squamous head and cancer after previous platinum based treatment. British Journal of Cancer (2010) 102, 1687-1691
16. Burtness B, Goldwasse MA, Flood W, et al. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer:an Eastern Cooperative Oncology Group study, J Clin Oncol ,2005, vol. 23 (pg. 8646-8654)
17. Bourhis J,Rivera , Mesia R, et al. Phase I/II study of cetuximab in combination with cisplatin or carboplatin and fluorouracil in patients with recurrent or metastatic squamous cell carcinoma of the head and neck, JClinOncol , 200, vol. 24(pg. 2866-2872)
18. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer, N Engl J Med , 2008, vol. 359 (pg. 1116-1127
19. Hitt R, Irigoyen A, Nuñez J, et al. Phase II study of combination cetuximab and weekly paclitaxel in patients with metastatic/recurrent squamous cell carcinoma of head and neck (SCCHN): Spanish Head and Neck cancer group (TTCC), J Clin Oncol , 2007, vol. 25 18 Suppl302s (Abstr 6012)
20. BuentzelJ, deVries A, Micke O. Experience with cetuximab plus paclitaxel/ carboplati num in primary platinum-resistant recurrent head and neck cancer, J Clin Oncol , 2007, vol. 25 18 Suppl318s (Abstr 6077)