Impact of Metronomic Chemotherapy on Quality of Life in Recurrent, Residual and Metastatic Head & Neck Cancers

Authors
Shilpa Kandipalli, Santhosh. V, Praveena Voonna
Department of Medical Oncology, Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati – 517507, India
Corresponding Author
Shilpa Kandipalli
Mobile no: 9440731463, 9490075199, Email: shilpakandipalli@gmail.com

Abstract
Background: Quality of life is significantly affected in both radically treated as well as palliative care patients of Head & Neck cancers. Both Surgery as well as Radiation with concurrent chemotherapy affect quality of life with long lasting disabilities. Hence the present study was done to evaluate the role of Metronomic Chemotherapy on Quality of life in Residual, Recurrent and Metastatic Head & Neck cancers.

Methods: All patients who met the inclusion criteria in our study were treated with Oral Metronomic Chemotherapy with Methotrexate and Capecitabine. Quality of Life assessment was done at month 0, month 3 and month 6.

Results: The predominant problematic domains identified by QOL H&N-35 scale were pain, difficulty in swallowing, dry mouth, mouth opening, sticky saliva, social eating, social contact and less sexuality. There is a significant improvement in QOL of most of the survivors in the present study at the end of 6 months. But there was no significance as far as illness, senses, coughing, feeding tube and weight gain are concerned

Conclusion: Oral Metronomic Chemotherapy with Methotrexate and Capecitabine significantly improves the Quality of life in patients with Residual, Recurrent and Metastatic Head & Neck cancers.

Keywords: Metronomic Chemotherapy, Quality of Life, Head & Neck cancers.

Introduction
Worldwide, head and neck cancer accounts for more than 550,000 cases and 380,000 deaths annually\(^1\). Head & Neck squamous cell carcinoma (HNSCC) is common in Asian countries\(^2\) with an annual incidence of approximately 9-10\%.

The WHO characterizes Quality Of Life (QOL) as “an individual’s perception of their position in life, in the context of the culture and value systems in their life and in relation to their goals, expectations, standards and concerns”\(^3\). Regardless of the significant advances in science and therapeutics, malignancy and its treatment keep on bringing terrible pain and suffering, not only for patients who do not survive, but at the same time for the individuals that are effectively treated. This is particularly valid for Head & Neck cancers that cause excessively extreme effect on the QOL of the patients\(^5\). Patients with Head & Neck cancers are helpless against extreme psychosocial issues in light of the fact that social communications and emotional expression depend
on the integrity of the function of neck and head region (6).

Studies on QOL in recurrent or metastatic head and neck cancers are meagre. Most of the trials were conducted in radically treated head and neck cancers either post surgery or post Radiotherapy.

With this background, the present study aimed to evaluate the effect of Oral Metronomic Chemotherapy on Quality of life in Recurrent, Residual and Metastatic Head & Neck Cancers

**Aim & Objective**

To study the impact of Oral Metronomic Chemotherapy on Quality of life in Recurrent, Residual and Metastatic Head & Neck Cancers

**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. ECOG Performance Status 0-2
3. Patients with Recurrent, Residual & Metastatic disease after primary Multimodality therapy
4. Patients with clinically measurable tumour

**Exclusion Criteria**

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

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.

**Quality of Life Assessment and Scoring**

The European Organisation of Research and Treatment of Cancer Quality of Life Core Questionnaire, version 3.0 (EORTC QLQC30) and EORTC head and neck module (EORTC QLQ-HN35) were used to measure the QOL. Scoring was done prior to start of metronomic therapy, i.e. at month 0, after completion of 3 months and 6 months post therapy.

Questionnaires were given in vernacular language of the patients. It took around 15-20 min for patients to answer the questionnaire.

The EORTC QLQC30 contains five functional scales (physical, role, emotional, cognitive and social functioning), symptom scales and a global health status scale. Functional Scales and Global health scale were mainly analysed in the present study. Symptom scales were not analysed.

The EORTC QLQ HN-35 module incorporates seven multiple-item scales that assess the symptoms of pain, swallowing ability, senses (taste/smell), speech, social eating, social contact and sexuality. It also includes eleven other single-items which relate to teeth, mouth opening, dry mouth, mouth opening, sticky saliva, coughing, and feeling of illness, weight loss, and weight gain, use of pain killers, nutritional supplements and feeding tube. All of them were analysed.

Scoring was done according to the instructions in EORTC QLQ scoring manual. The scores for all scales range from 0 to 100. A high score for functional scale or global health status scale indicates a high quality of life. Conversely, a high score for a symptom scale indicates low quality of life.

**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. The normality test was applied to the quality of life scores and the scores showed a non-normal distribution. So, non-parametric tests were used to do the analysis. The QOL scores were calculated at various time points and compared to baseline values using Friedman test. To compare paired data Wilcoxon Signed Ranks Test was used. P-value of $\leq 0.05$ is considered significant.

**Results**

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.

Most (31) of the patients were between the age group 41-60yrs (65.9%). Only 2 were below 40yrs (4.3%). 6 patients (12.8%) were between 61-70yrs and 8 patients (17%) were between 71-80yrs.

Out of 47, 25 patients (53.2%) were male and 22 (46.8%) were female.

PS was 1 in 9 (19.1%) and 2 in 38 (80.9%) patients.

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 betel nut 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.

Initial stage of the disease was IV A in 28 (59.6%), IV B in 15 (31.9%) and III in 4 (8.5%) patients.

**Figure-1: CONSORT Flow Diagram**
Table 1: Clinical Characteristics of Our Patients

| 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              |

Functional Score (FS) evaluation at the end of 6 months compared to baseline was statistically significant (p=0.004). Whereas there was no difference in FS between baseline to 3 months (P=0.5450) and between 3months to 6months (P=0.055).

Global Score (GS) evaluation showed statistical significance between baseline to 3 months (p=0.008), 3months to 6 months (p=0.045) as well as between baseline to 6 months (p=0.0005).

Pain Score (PS) evaluation at the end of 6 months showed statistical significance (p=0.0005) compared to baseline. Between 3months to 6months also there was statistical significance (p=0.003) but there was no significance between baseline to 3 months (p=0.122).

Swallowing Score (SS) evaluation at the end of 6 months showed statistical significance (p=0.01) when compared to baseline. Between 3months to 6months also there was statistical significance (p=0.004) but there was no significance between baseline to 3 months (p=0.705).

Teeth (T) evaluation at the end of 6 months compared to baseline showed statistical significance (0.018). Between 3months to 6months also there was statistical significance (p=0.046) but there was no significance between baseline to 3months (p=0.106).

Mouth Opening (MO) evaluation at the end of 6 months compared to baseline showed statistical significance (p=0.001). Between 3months to 6months also there was statistical significance (p=0.008) but there was no significance between baseline to 3 months (p=0.499).

Dry Mouth (DM) evaluation at the end of 6 months compared to baseline showed statistical significance (p=0.0005)
significance also there was statistical significance (p=0.001). Between 3months to 6months also there was statistical significance (p=0.005) but there was no significance between baseline to 3months (p=0.058).

Sticky Saliva (SS) evaluation at the end of 6 months compared to baseline showed statistical significance (p=0.001). But there was no significant difference in SS between baseline to 3 months (0.130) and between 3months to 6 months (0.132).

Senses (S) evaluation at the end of 6 months compared to baseline did not show statistical significance (p=0.409). Between baseline to 3 months also there was no significance statistically (0.339) But between 3 to 6 months there was a significance(p=0.03)

Cough (C) evaluation at the end of 6 months compared to baseline did not show statistical significance (p=0.712). Between baseline to 3months also there was no significance statistically (0.334). But between 3 to 6 months there was a significance(p=0.034)

Speech (SP) evaluation at the end of 6 months compared to baseline showed statistical significance (p=0.015). Between 3months to 6months also there was statistical significance (p=0.005) but there was no significance between baseline to 3months (p=0.203).

Illness (I) evaluation did not show any statistical significance either between baseline to 3 months (p=0.632) or between 3 months to 6 months (p=0.180) or between baseline to 6 months (p=0.107).

Trouble with Social Contact (SC) evaluation at the end of 6 months compared to baseline showed statistical significance (p=0.0005). Between 3months to 6months also there was statistical significance (p=0.003) but there was no significance between baseline to 3months (p=0.337).

Trouble with Social Eating (SE) evaluation at the end of 6 months compared to baseline showed statistical significance (p=0.012). Between 3 months to 6 months and from baseline to 3months were also significance (p=0.003 and p=0.009 respectively).

Less Sexuality (Sex) evaluation was significant statistically at the end of 3 months compared to baseline (p=0.023), also between 3 months to 6 months (p=0.023) and between baseline to 6 months (0.003).

Pain Killer (PK) usage evaluation at the end of 6 months compared to baseline showed statistical significance (p=0.0005). Between 3months to 6months also there was statistical significance (p=0.005) but there was no significance between baseline to 3months (p=1.000).

Nutritional Supplements (N) evaluation at the end of 3 months and 6months compared to baseline showed statistical significance(p=0.0005 and p=0.005 respectively). But between 3 to 6 months also there not much significance (p=0.564).

Feeding Tube (FT) usage at the end of 3 months showed statistical significanc (p=0.014). But between 3 to 6 months (p=1.000) and baseline to 6 months there was no significance(p= 0.564).

Weight Loss (WL) evaluation at the end of 6 months compared to baseline was statistically significant (p=0.014). Whereas there was no difference in WL between baseline to 3 months (p=0.285) and between 3 months to 6 months (p=0.137)

Weight Gain (WG) evaluation did not show any statistical significance either between baseline to 3 months (p=0.083) or between 3months to 6 months (p=0.317) or between baseline to 6 months(p=0.083).
### Table 2: QOL Evaluation

| S.No | Item                  | Month 0 mean rank | Month 3 mean rank | Month 6 mean rank | Chi-square | p-value |
|------|-----------------------|-------------------|-------------------|-------------------|------------|---------|
| 1    | Functional Score      | 1.11              | 2.17              | 2.72              | 24.8       | 0.0005  |
| 2    | Global Score          | 1.08              | 2.25              | 2.67              | 39.76      | 0.0005  |
| 3    | Pain Score            | 2.78              | 1.91              | 1.30              | 29.94      | 0.0005  |
| 4    | Swallowing Score      | 2.35              | 2.26              | 1.39              | 16.67      | 0.0005  |
| 5    | Teeth                 | 2.26              | 1.98              | 1.76              | 9.172      | 0.010   |
| 6    | Mouth Opening         | 2.43              | 2.00              | 1.57              | 20.0       | 0.0005  |
| 7    | Dry Mouth             | 2.50              | 1.98              | 1.52              | 22.53      | 0.0005  |
| 8    | Sticky Saliva         | 2.41              | 1.98              | 1.61              | 17.15      | 0.0005  |
| 9    | Senses                | 2.13              | 2.11              | 1.76              | 5.200      | 0.074   |
| 10   | Cough                 | 2.00              | 2.20              | 1.80              | 4.154      | 0.125   |
| 11   | Speech                | 2.39              | 2.22              | 1.39              | 18.87      | 0.0005  |
| 12   | Illness               | 2.33              | 1.91              | 1.76              | 8.829      | 0.012   |
| 13   | Social Contact        | 2.59              | 2.09              | 1.33              | 24.72      | 0.0005  |
| 14   | Social Eating         | 2.41              | 2.26              | 1.33              | 20.36      | 0.0005  |
| 15   | Sex                   | 2.35              | 2.09              | 1.57              | 16.00      | 0.0005  |
| 16   | Pain Killer           | 2.17              | 2.17              | 1.65              | 16.00      | 0.0005  |
| 17   | Nutrition             | 1.33              | 2.37              | 2.30              | 28.3       | 0.0005  |
| 18   | Feeding Tube          | 1.96              | 2.02              | 2.02              | 0.667      | 0.717   |
| 19   | Weight loss           | 2.28              | 1.83              | 1.89              | 12.28      | 0.002   |
| 20   | Weight gain           | 1.87              | 2.07              | 2.07              | 6.000      | 0.050   |

### Table 3: Significance (p-values) of various items in QOL questionnaires

| S.No | Item                | Month 0-3 | Month 3-6 | Month 0-6 |
|------|---------------------|-----------|-----------|-----------|
| 1    | Functional Score    | 0.545     | 0.055     | 0.004     |
| 2    | Global Score        | 0.008     | 0.045     | 0.0005    |
| 3    | Pain Score          | 0.705     | 0.009     | 0.0005    |
| 4    | Swallowing Score    | 0.122     | 0.003     | 0.010     |
| 5    | Teeth               | 0.106     | 0.046     | 0.018     |
| 6    | Mouth Opening       | 0.499     | 0.008     | 0.001     |
| 7    | Dry Mouth           | 0.058     | 0.005     | 0.001     |
| 8    | Sticky Saliva       | 0.130     | 0.132     | 0.001     |
| 9    | Senses              | 0.339     | 0.034     | 0.409     |
| 10   | Cough               | 0.334     | 0.034     | 0.712     |
| 11   | Speech              | 0.203     | 0.005     | 0.015     |
| 12   | Illness             | 0.632     | 0.180     | 0.107     |
| 13   | Social Contact      | 0.337     | 0.003     | 0.0005    |
| 14   | Social Eating       | 0.009     | 0.003     | 0.012     |
| 15   | Sex                 | 0.023     | 0.033     | 0.003     |
| 16   | Pain killer         | 1.000     | 0.005     | 0.005     |
| 17   | Nutrition           | 0.0005    | 0.564     | 0.0005    |
| 18   | Feeding Tube        | 0.014     | 1.000     | 0.564     |
| 19   | Weight loss         | 0.285     | 0.317     | 0.014     |
| 20   | Weight gain         | 0.083     | 1.00      | 0.083     |
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.\(^{(7)}\).

Studies on QOL in recurrent or metastatic head and neck cancers are meagre. Most of the trials were conducted in radically treated head and neck cancers either post Surgery or post Radiotherapy. Krupa Palan et al evaluated QOL in radically treated Head & Neck cancers and the problematic domains identified by QLQ H&N-35 scale were sexual problems, trouble with social contact, symptoms of dry mouth, problem related to senses, difficulty in mouth opening and speech problems. About 70.8% of the respondents used painkillers for their pain management\(^{(8)}\). Stephen Wan Leung et al evaluated QOL in head and neck cancer survivors after radiotherapy and observed that tooth problems, dry mouth and sticky saliva were prominent worst symptoms.\(^{(9)}\)

Prima J Jyothi et al evaluated QOL in head and neck cancer patients receiving cancer specific treatments and found a positive correlation between QOL and performance status of the patients.\(^{(10)}\)
The predominant problematic domains identified by QOL H&N-35 scale were pain, difficulty in swallowing, dry mouth, mouth opening, sticky saliva, social eating, social contact and less sexuality. These findings are consistent with the studies done by Krupa Palan et al (8) and Stephen Wan Leung et al (9) on head and neck cancer survivors. Overall, there is a significant improvement in QOL of most of the survivors in the present study at the end of 6 months. But there was no significance as far as illness, senses, coughing, feeding tube and weight gain are concerned

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 significant improvement in QOL in responders.

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.

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