An audit of the results of a triplet metronomic chemotherapy regimen incorporating a tyrosine kinase inhibitor in recurrent/metastatic head and neck cancers patients

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Abstract

Background: Addition of erlotinib to metronomic chemotherapy (MCT) may lead to further improvement in progression-free survival (PFS) and overall survival in head and neck cancers. The aim of this study was to study the PFS with MCT + erlotinib combination in our setting. **Methods:** A single-arm prospective observational study conducted at Malabar Cancer Center. Patients warranting palliative chemotherapy for head and neck cancers, having adequate organ function, not-affording cetuximab and not willing for intravenous chemotherapy were included in this study. Oral methotrexate (15 mg/m^2/week), oral celecoxib (200 mg twice daily), and erlotinib (150 mg once daily) were administered till the progression of the disease or till intolerable side-effects. Patients underwent toxicity (CTCAE version 4.02) and response (RECIST version 1.1) assessment every 30 days. Statistical analysis was performed using SPSS version 16 (IBM, New York, USA). Descriptive statistics and Kaplan–Meier analysis have been performed. **Results:** A total of 15 patients received MCT. The median age of these patients was 65 years (range: 48–80). The Eastern Cooperative Oncology Group Performance Status was 0–1 in seven patients (46.7%), while it was 2 in eight patients (53.3%). The primary sites of tumor were predominantly oral cavity, 11 (73.4%). Prior to MCT, treatment with palliative radiation therapy was given in 11 patients and curative treatment in two patients. The best response post-MCT was complete remission in two patients, partial remission in seven patients, stable disease in four patients, and progressive disease in two patients. The median estimated PFS was 148 days (95% confidence interval 95.47–200.52 days). For a median follow-up of 181 days, there were only three deaths. Grade 3–4 toxicity was seen in six patients (40%). Dose reduction was required in four patients (26.7%). **Conclusion:** The addition of erlotinib to an MCT schedule of methotrexate and celecoxib resulted in a promising PFS and should be tested in future studies.

Key words: Erlotinib, head and neck cancer, metronomic administration, palliative chemotherapy

Introduction

Head and neck cancer is one of the most common cancers seen in India and it contributes to nearly one-fifth (22.1%) of the cancer-related mortality in the country.[1] The estimated mortality rates per 1000 patients in head and neck cancers are higher in a rural population (31.8 vs. 14).[1] Age-standardized cancer mortality rate is also higher in illiterate patients as opposed to inpatients educated above secondary level (24.7 vs. 9.0/100,000) in head and neck cancers.[1] This reflects that this disease is not only common in patients in a rural population and in those with the low socioeconomic condition but also is more fatal.[1-3] The lack of adequate treatment facilities and manpower coupled with the lack of social security may be responsible for this disparity.[4] Metronomic chemotherapy (MCT) was developed to overcome such challenges.[5] Outcomes of patients receiving oral MCT results have been published previously from Mumbai.[6,7] The MCT schedule used in these studies was of methotrexate (15 mg/m^2/week) and daily oral celecoxib 200 mg twice daily. However, the reported progression-free survival (PFS) with this schedule in an ASCO abstract of 2014 was around 3 months.[8] A considerable proportion of these patients had subsequently received erlotinib on progression. With erlotinib, these patients had a response rate of 15.4%. In addition, high-response rates of around 29% have been reported with erlotinib in neoadjuvant chemotherapy setting.[9]

The combination of a cyclooxygenase-2 (COX-2) inhibitor and epidermal growth factor receptor (EGFR) pathway blocker has a biological rationale as a COX-2 pathway, and EGFR pathway has significant cross-talk.[10-12] Resistance to EGFR tyrosine kinase inhibitor may be inhibited by COX-2 inhibitor.[11] Hence, combined inhibition upfront can target the tumor angiogenesis, apoptosis, and tumor growth suppression and decrease the metastatic potential.[11]

The mechanism of action of erlotinib and MCT are complementary and both have nonoverlapping toxicity hence we thought of combining these drugs. The aim of this study was to study the efficacy of this MCT in our setting. It was hypothesized that this MCT schedule can be considered for further studies at our center if it leads to an estimated PFS of 120 days or more.

Methods

A review of a prospective database maintained of all patients undergoing MCT in the time period of August 2013 to February 2014 was conducted. The audit protocol was the Institutional Review Board approved. Patients were considered eligible for MCT subject to their fulfilling the following criteria.

Inclusion criteria

1. Age >18 years
2. Pathologically proved squamous cell carcinoma
3. without uncontrolled severe comorbidity
4. Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–2
5. Not-affording cetuximab and unwilling for intravenous chemotherapy
6. QTc interval below 450 ms.

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Exclusion criteria

1. Patients with HIV positivity and hepatitis B virus or hepatitis C virus-related hepatitis
2. Patients not willing for close follow-up
3. Primary in nasopharynx.

Intervention

These patients were discussed in the multidisciplinary clinic and option for MCT was given. The MCT schedule comprised of tablet methotrexate (2.5 mg tablet) 15 mg/m^2 administered once in a week PO, capsule celecoxib 200 mg twice daily PO given daily, and tablet erlotinib 150 mg PO once daily without food.

Rationale for selection of doses

Phase 1 study dose finding study of celecoxib with erlotinib (fixed dose 150 mg) and reradiation in recurrent head and neck cancers recommended a dose of 400 mg of celecoxib.[13] We selected these same doses of erlotinib and celecoxib for our study. In addition, we decided to use a dose of 15 mg/m^2 of methotrexate weekly as this dose with celecoxib dose of 400 mg/day was well tolerated in the MCT published literature.[6-8]

Follow-up schedule

The patients were called at regular follow-up at monthly intervals for the first 4 months and then 2 monthly intervals. Compliance was confirmed verbally. At each visit, the patients were assessed clinically for disease status and toxicity was chartered in accordance with CTCAE version 4.02. Radiological response assessment was done at 2-month intervals if the patient did not have gross clinically documented progression.

Data collection

The details of the basic demographic profile, staging details, MCT details, toxicity details (CTCAE version 4.02), response (RECIST version 1.1), date of progression, death of last follow-up, and date of death were noted from the prospective database of these patients maintained in the outpatient department.

Statistical analysis

SPSS version 16 (IBM, New York, USA) was used for analysis. The database was closed for analysis on April 14, 2014. Descriptive statistics in the form of median and interquartile range are presented for continuous variables, while frequencies for categorical variables. Kaplan–Meier survival analysis was done for estimation of PFS and overall survival (OS). PFS was defined as time duration in days from the date of start of MCT till the date of progression. Patients were censored at the date of death or last follow-up if no progression was documented. OS was defined as time duration in days from the date of start of MCT till the date of death. Patients were censored at the date of the last follow-up.

Results

Baseline characteristics

There were 15 patients who received MCT within the stipulated time period. The median age of these patients was 65 years (range: 48–80). There were ten males (66.6%) and five females (33.4%). The ECOG PS was 0–1 in seven patients (46.7%), whereas it was 2 in eight patients (53.3%). Details about baseline characteristics of the patient are shown in Table 1.

Tumor and previous treatment details

The primary sites of tumor were an oral cavity in 11 (73.4%), oropharynx in 3 (20%), and hypopharynx in 1 (6.6%) patient. The indication for palliative chemotherapy was metastatic disease in 1 (6.7%) patient, while 14 (93.3%) patients had unresectable locally advanced disease or recurrent disease not amenable to local therapy. The details of previous treatment are shown in Table 2.

Prior to MCT palliative treatment with palliative RT was delivered in 11 patients. In two patients treated curatively, both had undergone surgery, followed by adjuvant RT. The median time interval between initiation of MCT and primary treatment in patients treated with palliative intent was 2 months (interquartile range: 1.5–2 months).

Table 1: Baseline details of patients

Variable	Value (%)
Age	Median 65 years (range: 48-80)
Sex	
Male	10 (66.7)
Female	05 (33.3)
ECOG PS	
0-1	07 (46.7)
2	08 (53.3)
Comorbidity	
Diabetes mellitus	02 (13.3)
Hypertension	03 (20.0)
COPD	01 (6.7)
None	09 (60.0)
Habits	
Nonaddict	04 (26.7)
Smoker	09 (60.0)
Tobacco chewer	09 (60.0)
Alcohol	05 (33.3)
Education level	
Illiterate	05 (33.3)
Till primary education	09 (60.0)
Till secondary education	01 (6.7)
Median monthly income	10 USD (range: 3-80 USD)

ECOG PS=Eastern Cooperative Oncology Group Performance Status, COPD=Chronic obstructive pulmonary disease

Table 2: Previous treatment details

Variable	Value (%)
Previous treatment received	
Yes	13 (86.7)
No	02 (13.3)
Previous surgery received	
Yes	02 (13.3)
No	13 (86.7)
Previous RT received	
Yes	13 (86.7)
No	02 (13.3)
Previous chemotherapy received	
Yes	04 (26.7)
No	11 (73.3)
Event-free period from last treatment	Median: 2 months (0-33 months)
Best response to last treatment	
CR	03
PR	01
SD	08
PD	01

RT=Radiation therapy, CR=Complete remission, PR=Partial remission, SD=Stable disease, PD=Progressive disease

Efficacy of metronomic chemotherapy

The best response post-MCT was complete remission in two patients, partial remission in seven patients, stable disease in four patients, and progressive disease (PD) in two patients. Thus, the response rate was 60% (nine patients). The benefit in terms of reduction in pain grade was seen in eight patients (53.3%), while the requirement for analgesics (a decrement in WHO step of analgesic) decreased in four patients (26.7%).

By the time of analysis, MCT was stopped in nine patients. The causes of stoppage of MCT were PD in eight patients, and patients desire to discontinue treatment in one.

Progression was seen in nine patients. The median estimated PFS was 148 days (95% confidence interval 95.47–200.52 days) [Figure 1]. For a median follow-up of 181 days, there were only three deaths; hence, median OS cannot be calculated.

Metronomic chemotherapy toxicity

The details of the maximum grade of toxicity during MCT have been shown in Table 3. No Grade 5 toxic events were seen.

Thus, Grade 3–4 toxicity was seen in six patients (40%). Indoor admission for the management of toxicity was required in 1 (6.7%) patient. This patient had a hypopharyngeal primary. He had a partial response but got admitted with aspiration pneumonia without neutropenia, with type 1 respiratory failure. The patient succumbed to this complication.

Dose delays were required in three patients (20%). The reasons for dose delays were toxicity in all patients. It was erlotinib-induced rash in one patient, transaminitis in one patient, and Grade 3 neutropenia in one patient. In these three patients, one patient required break once for neutropenia. The other two required breaks twice for rash and transaminitis. The maximum duration of break required for the decrement in an erlotinib-induced rash was 30 days.

Dose reduction was required in four patients (26.7%). Three were the above-mentioned patients with delays and breaks. The other patient required it in view of mucositis. Mortality due to toxicity was seen in no patient. Thus, 11 patients (73.3%) could receive the schedule without dose modifications or delays.

Discussion

The median OS even with the use of cetuximab-based EXTREME like chemotherapy in head neck cancers treated palliative is far from satisfactory. In such scenario, there is an urgent felt need for developing new regimens which may either improve survival or would provide similar survival with less toxicity. Access to care is an important issue in low- and middle-income countries, and cetuximab unfortunately is not an easily affordable drug.[5,14-16] In such scenario, having a cheaper chemotherapy with equivalent survival is also important.

In this study, we evaluated the efficacy of additional erlotinib with MCT. It was proposed that this combination may be considered for future testing if it showed a median PFS of 120 days or more. This figure of 120 days matches the results obtained in such a setting in the EXTREME trial.[17] In this respect, this study met its primary endpoint. This improvement in PFS is even more exciting considering the cohort of patient in which this combination was tested. The majority patients had a treatment-free interval of below 3 months. Treatment-free interval is considered to be an important prognostic factor in this setting and a lower period is associated with worse survival.[18] Most of the recently published trials did not accrue patients with treatment-free interval postchemotherapy of <6 months.[17,19] Therefore, the magnitude of benefit in such patients from EXTREME like or SPECTRUM like chemotherapy schedules remains unknown. Most of these patients had also failed after receiving palliative radiotherapy. The reported OS in literature postprogression on palliative radiotherapy[20-22] is in the range of 3–6 months. Finally, majority had oral cavity primaries, a site not associated with human papillomavirus[23] and having traditionally lower response rates[24,25] and having poorer OS,[26] than stage-matched nonoral cavity primaries in head and neck cancers. With these selection issues in mind, it seems reasonable to say that this regimen has activity in this setting.

The results of MCT have been presented at ASCO 2014. The median PFS and OS in patients who received MCT were 101 days and 249 days, respectively, while the median PFS and OS in patients who received cisplatin chemotherapy were 66 days and 249 days, respectively.[8] Numerically, the median PFS reported in this study seems better than that reported with MCT or single-agent cisplatin. This indicates a possible synergistic effect of erlotinib with MCT in this setting.

This combination though efficacious was not without toxicity. It contradicts the traditional belief that MCT is nontoxic. A Grade 3–4 adverse event rate of 40% and dose reduction in

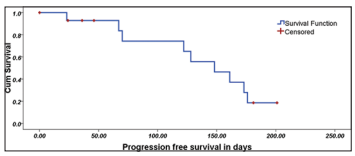

Figure 1: Kaplan–Meier estimated progression-free survival

Table 3: Toxicity details

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Upper GI				
Nausea	0	0	0	0
Vomiting	0	0	0	0
Mucositis	0	6	1	0
Dysphagia	0	4	0	1
Dysgeusia	1	2	NA	NA
Lower GI				
Diarrhea	1	2	0	0
Constipation	0	0	0	0
Systemic				
Fatigue	0	8	0	NA
Insomnia	0	0	0	0
Hematological				
Anemia	7	3	3	0
Neutropenia	0	1	1	0
Thrombocytopenia	0	1	1	0
Biochemical				
Renal dysfunction	0	0	0	0
Transaminitis	1	0	1	0
Hypernatremia	0	0	0	0
Hyponatremia	1	NA	0	0
Hyperkalemia	0	0	0	0
Hypokalemia	0	0	0	0
Dermatological				
Rash	1	3	1	0
Paronychia	0	2	1	NA

Numbers shown are an actual number of patients. NA=Not applicable, GI=Gastrointestinal

25% of population makes it necessary to modify this regimen. Hence, we do not recommend the use of this schedule in the present dosage for routine use outside a clinical trial.

The toxicity seen in this study was mainly of related to mucositis, transaminitis, and rash; these may be attributed mainly to erlotinib, but methotrexate is also known to cause similar side effects. Hence, in near future, we plan to conduct a Phase 2 study with two arms. In one arm dose of erlotinib would be escalated, while in another the dose of methotrexate. Postdose finding the cohorts in both arms would be expanded to compare the efficacy of both schedules for picking off the schedule for future studies.

Conclusion

The addition of erlotinib to an MCT schedule of methotrexate and celecoxib in metastatic/recurrent head and neck cancers resulted in a promising PFS and should be tested in future studies.

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Conflicts of interest

There are no conflicts of interest.

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