Oral Oncology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

A prospective randomized phase II study comparing metronomic chemotherapy with chemotherapy (single agent cisplatin), in patients with metastatic, relapsed or inoperable squamous cell carcinoma of head and neck

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ARTICLE INFO

Article history:
Received 25 September 2014
Received in revised form 1 December 2014
Accepted 3 December 2014
Available online xxxx

Keywords:
Head and neck cancer
Metronomic administration
Palliative
Chemotherapy
Cisplatin
Oral cancer

ABSTRACT

Background: Cetuximab based treatment is the recommended chemotherapy for head and neck squamous cell cancers in the palliative setting. However, due to financial constraints, intravenous (IV) chemotherapy without cetuximab is commonly used in lesser developed countries. We believe that oral metronomic chemotherapy may be safer and more effective in this setting.
Methods: We conducted an open label, superiority, parallel design, randomized phase II trial comparing oral MCT [daily celecoxib (200 mg twice daily) and weekly methotrexate (15 mg/m^2)] to intravenous single agent cisplatin (IP) (75 mg/m^2) given 3 weekly. Eligible patients had head and neck cancers requiring palliative chemotherapy with ECOG PS 0–2 and adequate organ functions who could not afford cetuximab. The primary end point was progression-free survival.
Results: 110 Patients were recruited between July 2011 to May 2013, 57 randomized to the MCT arm and 53 to the IP arm. Patients in the MCT arm had significantly longer PFS (median 101 days, 95% CI: 58.2–143.7 days) compared to the IP arm (median 66 days, 95% CI; 55.8–76.1 days) ($p = 0.014$). The overall survival (OS) was also increased significantly in the MCT arm (median 249 days, 95% CI: 222.5–275.5 days) compared to the IP arm (median 152 days, 95% CI: 104.2–199.8 days) ($p = 0.02$). There were fewer grade 3/4 adverse effects with MCT, which was not significant. (18.9% vs. 31.4%, $P = 0.14$).
Conclusion: Oral metronomic chemotherapy has significantly better PFS and OS than single agent platinum in the palliative setting.

Background

Head and neck cancer, particularly oral cancer, constitutes more than 30% of all cancers in India [1,2]. According to the recently published Million deaths study, it is one of the commonest malignancies in India and is responsible for 22.9% of cancer related mortality [3]. Unfortunately, only 10–30% of these tumours are seen in an early operable state [4,5]. A substantial number of patients have an advanced T and/or N stage and have recurrent disease [6,7]. At recurrence, these patients are frequently suitable only for palliative chemotherapy [8].

Palliative chemotherapy consisting of cetuximab, cisplatin and infusional 5 FU is regarded as the standard of care in head and neck cancers [8,9]. However, in lesser developed, countries, head and neck squamous cell carcinoma (HNSCC) is frequently seen in the lower socioeconomic strata of the society. Consequently, cetuximab-based combination chemotherapy is received by less than 1% of the eligible patients [10]. Even conventional palliative chemotherapy is out of reach for many patients [10–12]. We have previously published a report highlighting such problems at our rural

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http://dx.doi.org/10.1016/j.oraloncology.2014.12.002
1368-8375/

outreach centre [13]. These factors, in addition to the aggressive nature of the disease, leads to decreased survival in patients with advanced and recurrent HNSCC in the developing world [11].

We have previously reported on our experience with a metronomic schedule of oral chemotherapy consisting of celecoxib and methotrexate in our rural outreach centre [13]. Celecoxib is known to inhibit ERK and MAPK in head and neck cancer cell lines leading to an antiproliferative action [14]. Methotrexate when administered in a metronomic dosing schedule has antiangiogenic effects. The use of a combination of celecoxib and methotrexate has been previously published in clinical and in vitro studies [15–17]. These retrospective studies showed promising efficacy and low toxicity profile for the combination in head and neck cancers [18,19]. Though there are no randomized trials, the combination was administered at our outreach centre on compassionate grounds to patients, mainly belonging to the lower socioeconomic strata who were unable to take intravenous chemotherapy (financial reason or geographical access). Following initial encouraging results, we started using the same schedule with palliative intent at our hospital for patients who were not willing or could not afford the standard intravenous chemotherapy. The combination is inexpensive (around 10 USD/month), universally available and can be administered as an outpatient therapy for patients residing in rural and far-flung areas [13,18,19].

The results from a retrospective study of our patients and data from Glück et al. suggested that the metronomic chemotherapy provided results which were comparable to or even better than intravenous platinum based chemotherapy [17–19]. Therefore, we decided to conduct a phase 2 study to compare the efficacy of oral metronomic chemotherapy vs. intravenous single agent cisplatin in patients who could not afford cetuximab based chemotherapy.

Methods

Eligibility criteria

We included patients who had metastatic, recurrent or locally advanced head and neck squamous cell cancers that were unsuitable for loco-regional treatment and were eligible for palliative chemotherapy. The patients were all offered cetuximab-based therapy and only patients who could not afford cetuximab were included in the study. The inclusion criteria were:

1. Age between 18 and 70 years.
2. KPS of 70 or more.
3. Histological proven squamous cell carcinoma.
4. Normal pre-treatment haematological and biochemical parameters.
5. Without any uncontrolled medical co morbidity.

Patients with thyroid, salivary gland or nasopharynx cancers or patients who had received cisplatin within the preceding 3 months or those having a Sero positive status either of HIV, HCV and HBV were excluded.

Study conduct and design

This was a single centre, open label, parallel design, superiority, randomized controlled trial. The trial was investigator initiated after inputs from all the investigators. The trial was reviewed by the institutional scientific review committee and the institutional ethics committee. The final approval of the study was granted on 7th June 2011. All patients had to provide written informed consent. The trial was conducted in accordance with the Good Clinical Practice guidelines (Declaration of Helsinki and the International Conference on Harmonization).The data was censored for analysis on August 2013. The trial was registered with clinical trial registry of India. (CTRI/2014/07/004791).

The trial underwent a review by an independent data monitoring committee on 29th January 2014. All the investigators had complete access to the data and helped in the interpretation and preparation of the manuscript.

Randomization and treatment arms

Patients were enrolled and randomized between the 2 study arms. The patients were stratified on the basis of site of primary (oral cavity or oropharynx and laryngo-pharynx) and the previous treatment received [with or without previous chemotherapy or radiation exposure]. Patients in arm A received 3-weekly cisplatin 75 mg/m^2 for a maximum of 6 cycles. We selected a dose of 75 mg/m^2 (not 100 mg/m^2) as almost all of the patients would have been exposed to a platinum agent as part of their previous multimodality treatment. Patents in arm B received daily oral celecoxib 200 mg twice daily and oral low dose methotrexate 15 mg/m^2 weekly. The dose of methotrexate selected here is the same dose which we have reported in our previous retrospective studies [17,18].

In arm A, starting the next cycle would require an ANC count above 1.5×10^9/L, a platelet count above 100×10^9/L , a creatinine clearance rate above 60 ml/min, and resolution of all non haematological toxicities (except alopecia and fatigue) to baseline or less than grade 1. In case of deranged creatinine clearance as calculated by the Cockcroft-Gault formula, the dose of cisplatin was modified. For creatine clearance between 50–59.99 ml/min a 25% dose reduction was done and for creatinine clearance between 45–49.99 ml/min a 50% dose reduction was done. In case of a delay longer than 14 days, the patient treatment was stopped. Other dose adjustments and reductions were done in accordance with standard guidelines.

In arm B commencement of the next cycle on day 31 required an ANC count above 1.5×10^9/L, a platelet count above 100×10^9/L , creatinine clearance rate above 45 ml/min, and resolution of all non haematological toxicities (except alopecia and fatigue) to baseline or less than grade 1. Treatment was discontinued in patients with progression of disease, intolerable side effects or life threatening grade 4 complications.

In arm A, the patients were followed up 3 weekly till completion of 6 cycles and thereafter at two month intervals. In arm B, the patients were followed up at an interval of 1 month for 4 months and then once every 2 month. At each visit, the toxicity was recorded in accordance with CTCAE version 4.02 and the clinical response was noted. In both arms the patients underwent radiological assessment once every 2 months from the start of the treatment if they did not have obvious clinical progression.

Endpoint assessment

The primary endpoint was progression free survival (PFS). The PFS was calculated in days from the date of randomization to the date of progression. The patients who had not progressed were censored at the last date of assessment. The secondary endpoints were overall survival, and comparison of toxicity. The overall survival was calculated in days from the date of randomization to the date of death or at the last date of known contact.

Sample size calculation

The PFS in the standard arm was proposed to be 2.7 months on the basis of previous studies. For arm B the PFS predicted on the

Please cite this article in press as: Patil VM et al. A prospective randomized phase II study comparing metronomic chemotherapy with chemotherapy (single agent cisplatin), in patients with metastatic, relapsed or inoperable squamous cell carcinoma of head and neck. Oral Oncol (2015), http://dx.doi.org/10.1016/j.oraloncology.2014.12.002