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ORIGINAL ARTICLE

Role of Single-Agent Methotrexate as a Neoadjuvant Chemotherapy in Oral Cavity Cancers

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Abstract

Oral cancers are the most common cancer in India due to tobacco abuse in the form of chewing, smoking, and inhalation. Majority of these patients present late at advanced disease stage. Such patients have significant morbidity irrespective of the intent of treatment; the survival rate is very poor. To improve loco-regional control and survival, neoadjuvant chemotherapy has been started in many centers all over the world. To study the effect of injecting methotrexate as a single agent in (1) down-staging and increasing operability of oral cancers, (2) need for reconstructive surgery, and (3) recurrence. A total of 50 patients with biopsy-proven oral malignancy were selected over a period of 2 years from August 2014 to August 2016 for the study. Patients were subjected to weekly dose of injecting methotrexate 1 mg/kg given intravenously for 6 weeks. All patients underwent surgery after completing 6 cycles of methotrexate. A total 50 patients were started on inj. methotrexate of which 9 patients did not complete neoadjuvant chemotherapy. 53.7% of patients showed more than 50% decrease in tumor size. 29.26% of patients showed complete disappearance of cervical lymph nodes and 31.7% of patients showed more than 50% decrease in size of cervical lymph nodes. 48.78% of patients were managed with wide local excision with primary closure, decreasing the need of reconstructive surgery. 94.74% of patients did not show any recurrence in follow-up period of 1 year. Single agent methotrexate is effective in down-staging oral cancers, improving operability and decreasing morbidity and recurrence among patients.

Keywords Oral cancer · Neoadjuvant chemotherapy · Methotrexate · Down-staging

Introduction

Oral cancer is the most common cancer and constitutes a major health problem in developing countries. Although representing 2–4% of the malignancies in the west, this carcinoma accounts for almost 40% of all the cancers in the Indian subcontinent [1]. They are of great significance, as they have a potential to jeopardize the health and longevity of the patient [2]. Over the years, the incidence of oral cancers in the population has increased manifold especially among younger generation, possibly related to the rising trend of pan masala and gutkha chewing, smoking, and alcohol consumption in the population. Though it is more common in males, the rate is increasing in females also [3].

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Although tumors of the oral cavity are readily accessible due to their anatomic location, most are diagnosed at an advanced stage. Oral squamous cell carcinoma (OSCC) is the most common type of tumor in the oral cavity [4]. Early-stage tumors account for about 30% of the tumors. The majority of the tumors are locally advanced and have relatively poor prognosis with 5-year survivals < 50–60% [5–7]. At present, the standard of care for resectable locally advanced OSCC is the surgical treatment of the primary tumor and neck followed by postoperative radiotherapy or chemo-radiotherapy, depending on the presence of intermediate- or high-risk features [8]. The pattern of failure for oral cancer is predominantly loco-regional [9]. Extensive procedures are required in these locally advanced cancers which are associated with a substantial amount of cosmetic deformity and functional morbidity.

Neoadjuvant chemotherapy (NACT) in the head and neck cancers has been investigated for long with an aim of reducing surgical margins, distant metastasis rates, and improving outcomes. The two most commonly used regimes are cisplatin and 5-fluorouracil and cisplatin and bleomycin [10]. Overall response rates of 80% are frequently achieved, complete

response rates are 30%. Toxicity is moderate to severe, though the rate of distant metastasis is decreased, survival rate is not constantly improved and only in 1 out of 10 studies it is found to be improved [11].

Low-dose injectable methotrexate at a dose of 40 mg/m^2 weekly is a standard palliative chemotherapy option in head and neck cancer [12]. Methotrexate was previously regarded as the standard chemotherapeutic agent for end-stage disease and its dosage and mode of administration have been extensively investigated in phase II studies. Weekly administration of 40–60 mg m^2 produces the best response rates; higher dosage and/or more frequent administration does not improve the rate or duration of response (Muggia et al. 1980).

Intramuscular methotrexate administration is desirable because there is better absorption than by the oral route, the peak concentrations are similar to the intravenous (IV) route, and there is slower drug absorption and more prolonged exposure to the drug than with IV administration [13]. Conversely, oral methotrexate may be associated with reduced gastrointestinal tolerance [14]. Previous studies have shown better efficacy of intramuscular than oral methotrexate, based on pharmacokinetic indices of absorption and bioavailability.

The benefits of neoadjuvant chemotherapy, according to studies, are tumor reduction, local control, decreased recurrence, decreased distant metastasis, organ preservation in resectable tumors, less need of postoperative radiotherapy, less need for mandibulectomy, and 4–6% increase in survival rate [15].

Materials and Methods

This clinical study was carried out at the Department of General Surgery in a tertiary care hospital after approval of local institutional ethical committee. First 50 cases of histopathologically confirmed cases of oral cancer were included. This study is a prospective interventional time-based study conducted at this institution over a period of 2 years from August 2014 to August 2016.

Inclusion Criteria

- Biopsy-proven cases of locally advanced oral malignancy (T3, T4 lesions)
- Patients with no medical contraindication for methotrexate
- No distant metastasis at time of presentation

Exclusion Criteria

- Early lesions (T1, T2 lesions)
- Contraindication to methotrexate therapy
- Intolerance to first dose of methotrexate
- Previously exposed to chemotherapy or radiotherapy
- Patients with distant metastasis.

Thorough clinical history and physical assessment were done and biopsy was taken for confirming diagnosis. Patient underwent relevant investigations for staging of disease and fitness. Patients were given intramuscular methotrexate in a dose of 50 mg/m^2 along with proper hydration and antiemetics and cycle repeated at weekly intervals for 6 weeks. Before every cycle, patient was reassessed in terms of reduction in size of tumor and lymph nodes and loco-regional control. At the end of 6 weeks, patients were reassessed and then posted for surgery. Standard surgical and oncology protocols were followed and patient was managed accordingly and discharged. Patients were followed-up for a period of 1 year for any complications arising from treatment and recurrence of disease.

Results and Discussion

A total 50 patients were enrolled for the study of which 41 patients completed full 6 cycles of weekly methotrexate injections followed by surgery. Nine patients had not completed full neoadjuvant chemotherapy; they had 2 or 3 cycles of neoadjuvant chemotherapy and lost follow-up may be due to regression of tumor size and palliation of symptoms; this was the fallacy of neoadjuvant chemotherapy. Out of the 41 operated patients after neoadjuvant chemotherapy in this study, 38 patients had regular follow-up to 1 year after surgery, 3 patients were lost in follow-up after surgery.

Maximum patients in our study were in 51–60 years age group with 62% of patients being males. Tobacco chewing being the most common (70%) etiologic factor for oral malignancies in our study with maximum number of patients belonging to lower socio-economic groups like laborers and workers.

Buccal mucosa and bucco-alveolus groove being the most common site of malignancy. 92.68% of patients had squamous cell carcinoma on FNAC and histopathology.

Of the total 41 patients, after single agent neoadjuvant therapy, out of 29 patients who had tumor size of more than 4 cm (T3) downgraded to 18 patients having tumor size less than 2 cm (T1), 10 patients having tumor size less than 4 cm (T2), and 1 patient having no change in size of tumor. Out of the 12 patients who had resectable growth stage T4A, downgraded to 9 patients having tumour size less than 4 cm (T2) and 3 patients having tumour size of more than 4 cm (T3) (Table 1).

After single agent neoadjuvant therapy, 17 patients who had N1 palpable cervical lymph nodes downgraded to 11 patients who had no palpable lymph node (N0) and 6 patients who had N1 palpable cervical lymph nodes. Seventeen patients who had N2A palpable cervical lymph nodes

Table 1 T stage before and after neoadjuvant chemotherapy

T staging on admission		T staging after neoadjuvant			
		T1	T2	T3	Total
T3	No. of patients	18	10	1	29
	Percent	100.00%	52.60%	25.00%	70.70%
T4A	No. of patients	0	9	3	12
	Percent	0.00%	47.40%	75.00%	29.30%
Total	No. of patients	18	19	4	41
	Percent	100.00%	100.00%	100.00%	100.00%

downgraded to 1 patient who had no palpable lymph nodes (N0), 15 patients who had N1 palpable cervical lymph nodes, and 1 patient had N2A lymph nodes. Seven patients who had N2B palpable cervical lymph nodes downgraded to 6 patients who had N1 palpable cervical lymph nodes and 1 patient who had N2A cervical lymph nodes (Table 2).

Complete response (*CR*) was defined as the disappearance of all clinical evidence of tumor for a minimum of 4 weeks. *Partial response* (*PR*) was defined as a 50% or more decrease in the sum of the products of all diameters of measured lesions for a minimum of 4 weeks without the appearance of any new lesions. *Stable disease* (*SD*) was defined as a steady state or a decrease in measurable lesions less than that would qualify for a PR without the worsening of symptoms or without appearance of new lesions for a minimum of 4 weeks. *Progression* was defined as the unequivocal increase of at least 25% in the size of any measurable lesion, appearance of new lesions, or uncontrolled hypercalcemia.

Response Rate in Terms of Tumor Size

In this study of locally advanced oral cancer, out of 41 patients, 22 (53.7%) patients showed more than 50% decrease in size of tumor (partial response), 18 (43.9%) patients showed less than 50% decrease in size of tumor, 1 (2.4%) patient showed no change in size of tumor, and no patient showed complete disappearance of tumor or increase in size of tumor so we can say methotrexate showed a response rate of 53.7% (CR+PR).

Table 2 N stage before and after neoadjuvant chemotherapy

N Staging on admission		N staging after neoadjuvant			
		N0	N1	N2A	Total
N1	No. of patients	11	6	0	17
	Percent	91.70%	22.20%	0.00%	41.50%
N2A	No. of patients	1	15	1	17
	Percent	8.30%	55.60%	50.00%	41.50%
N2B	No. of patients	0	6	1	7
	Percent	0.00%	22.20%	50.00%	17.10%
Total	No. of patients	12	27	2	41
	Percent	100.00%	100.00%	100.00%	100.00%

Response Rate in Terms of Lymph Node Size

In this study of locally advanced oral cancer, out of 41 patients, 13 (31.7%) patients showed more than 50% decrease in size of cervical lymph node size, 12 (29.26%) patients showed complete disappearance of cervical lymph node, 9 (21.95%) patients showed less than 50% decrease in size of cervical lymph nodes, and 7 (17.07%) patients showed no change in size of cervical lymph node. We can say that methotrexate showed a response rate of 60.97% (CR+PR).

P value is < 0.05 which is statically significant which signifies that methotrexate downgraded the tumor size and decreased regional lymph node metastasis and overall increased outcome (Table 3).

De Conti et al. [16] conducted a randomized prospective clinical trial involving 259 cases of advanced recurrent stage III and IV epidermoid cancers of the head and neck. The treatments consisted of weekly methotrexate, biweekly methotrexate with leucovorin rescue (ML), and biweekly ML combined with cyclophosphamide and cytosine arabinoside (MLCC). Complete and partial objective responses were achieved in 26%, 24%, and 18% by each treatment. Methotrexate alone produced a median duration of response of 105 days compared with 42 and 49 days from the other treatments. Duration of response was significantly longer and survival was better in the methotrexate-alone group.

In the present study, at the end of neoadjuvant chemotherapy, methotrexate showed a response rate (complete + partial) of 53% for tumor size and 60% for lymph node size. Hence, we can say that our study has good response rate as compared to above study.

Wide local excision with modified radical neck dissection type 3 was the primary procedure done in maximum number of 20 patients (48.78%). In the present study out of 41 patients, reconstruction was done in 18 (43.90%) patients with pectoralis major myocutaneous flap.

Out of the 41 operated patients after neoadjuvant chemotherapy, 38 patients (92.68%) had regular follow-up for 1 year after surgery, 3 (7.38%) patients were lost to follow-up after surgery, and 2 patients had recurrence of malignancy. The remaining 36 patients had no recurrence in the follow-up period. Those patients who had recurrence were sent to a higher center for further treatment (Table 4).

Forty-one patients had completed neoadjuvant chemotherapy; methotrexate had less side effect which could be managed easily without life-threatening complications. Intramuscular methotrexate resulted in significantly more skin

Table 3 Response rate for tumor size and lymph node status

	Percentage decrease in tumor size		Percentage decrease in lymph node status	
Response	No. of patients	Percent	No. of patients	Percent
Less than 50%	18	43.9	9	21.95
More than 50% (PR)	22	53.7	13	31.71
No change (stable)	1	2.4	7	17.07
Complete response (CR)	0	0	12	29.27
Progression	0	0	0	0
Total	41	100	41	100

and mucosal toxicity than hematological and gastrointestinal toxicity. 14.62% of patients experienced mucosal and skin toxicity. 9.75% of patients had hematological side effect. No patients experienced gastrointestinal side effect. Hence, we can say that intramuscular methotrexate is safe with less side effect and with good clinical activity.

Table 4 Distribution of patients according to reconstruction and recurrence

Reconstruction	No. of patients	Percent
Not done	23	56.09%
Done	18	43.90%
Recurrence	No. of patients	Percent
No	36	94.74%
Yes	2	5.26%
Total	38	100

In the study by De Conti et al. [16], equivalent overall drug-related toxicity was produced with a 5% drug-related fatality rate. The most common toxicities encountered were vomiting, mucositis, and blood count suppression. Weekly methotrexate alone resulted in significantly more skin and mucosal toxicity than the other treatments. The three-drug combination with leucovorin produced an excess of vomiting and significantly more myelosuppression in the patients receiving it; 39% experienced greater than moderate hematologic toxicity, as opposed to 17% and 15%, respectively, in the other two treatments (Fig. 1).

Methotrexate had less side effects which could be managed easily without life threatening complication. Hence, we can say that intramuscular methotrexate is safe with less side effect which can be easily managed.

Intramuscular injection of methotrexate is preferable because it has better absorption than the oral route and the peak concentrations in blood are similar to that of intravenous route and also there is slower drug absorption and increased drug

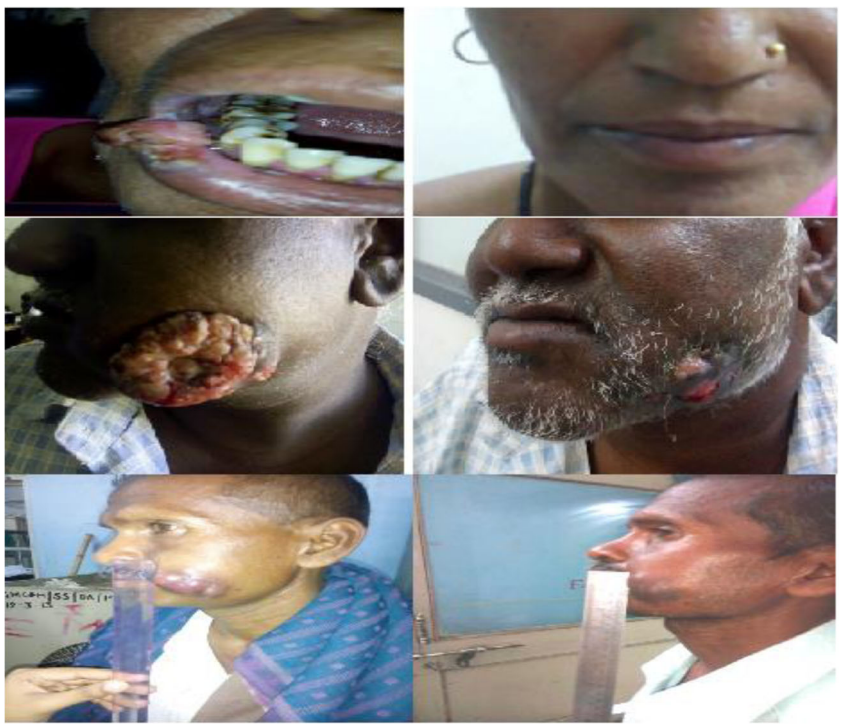

Fig. 1 Results of weekly single-agent methotrexate at the end of 6 cycles of weekly methotrexate in our study

exposure time than IV administration route [13]. Also gastrointestinal intolerance associated with oral methotrexate is reduced. Previous studies have shown better efficacy of intramuscular route than oral route, based on pharmacokinetic indices and absorption and bioavailability.

Though DCF (DCF: docetaxel, cisplatin, fluorouracil) has emerged as the new standard regimen when NACT is indicated [17], its use has been associated with an increased incidence of stomatitis, diarrhea, neutropenia, and febrile neutropenia (76%), and even toxic deaths (2.3%) [18]. Additionally, a substantial number of patients who received DCF chemotherapy did not receive radiation therapy or concurrent chemoradiotherapy as specified in the protocol in both TAX 323 and TAX 324 trials [19]. The cost of DCF chemotherapy along with the supportive care required is 1000–12,000 thousand/cycle beyond the reach of many patients. The most important advantage of this intramuscular methotrexate regimen lies in its economy. Each 50 mg methotrexate injection costs approximately only 60 rupees which is very low, anybody can afford this.

Conclusion

At the end of the present study, we concluded that methotrexate, a cost-effective, easily available, well-tolerated, and easily administrable single-agent neoadjuvant drug in locally advanced oral cancer in a dose of 1 mg/kg intramuscular weekly for 4–6 weeks, shows downgrading of tumor and lymph node size, increases operability, decreases need of reconstructive surgery, decreases loco-regional recurrence, and decreases cosmetic deformity and functional morbidity with low toxicity profile in patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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