Preoperative Chemotherapy and Metronomic Scheduling of Chemotherapy in Locally Advanced Oral Cancers

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Abstract
Locally advanced oral cavity cancers are treated with a multimodality approach. Surgery is the most efficient local modality in comparison to chemoradiation in oral cancers. Preoperative chemotherapy has failed its expectations to improve disease-free survival or overall survival in resectable oral cancers. Its use as an organ preservation tool is being studied. Induction chemotherapy followed by assessment for surgery is an appropriate option for borderline resectable or technically unresectable oral cancer. Metronomic chemotherapy is being studied as a bridge to surgery and as adjuvant chemotherapy in locally advanced oral cancers. The role of induction chemotherapy in unresectable oral cancers is unproven. Metronomic chemotherapy has shown improved progression-free survival and overall survival in oral cancers in comparison to intravenous cisplatin. A phase 3 study for confirmation of this finding has begun.

Introduction
Locally advanced oral cancers are generally treated with a multimodality approach [1–4]. This subset of head and neck tumors is a heterogeneous group with a varied spectrum of local involvement and regional nodal spread [5]. Though the TNM system has traditionally been used for staging, prognosis and treatment decisions, the complexity of anatomical structures in the head and neck region often leads to tumors being put in the same group despite differences in resectability and outcomes [6]. The present review is specifically focussed on locally advanced cancers which typically include stage III and IV disease. For illustrative purposes, consider 3 patients with locally advanced cancer. The first patient, Mr. X, with a buccal mucosa primary >4 cm in size (cT3) and a single 2-cm ipsilateral lymph node in level IB (cN1) will have cT3cN1 disease (stage III). The second patient, Mrs. Y, with a buccal mucosa primary >4 cm with involvement of the skin (cT4a) and a single 2-cm ipsilateral lymph node in level IB (cN1) will have cT4acN1 disease (stage IVa). At the other end of the spectrum is a patient, Mr. Z, with a buccal mucosa primary >10 cm in size with involvement of the masticator space and a single 5-cm ipsilateral lymph node (cN1), cT4b cN2a disease (stage IVb). It is quite ob-
vious that the first two patients would be candidates for resection, while the third patient would be planned for chemoradiation or palliative chemotherapy alone. Thus, we believe that locally advanced cancers should not be a basket case of tumors based only on TNM stage, but should rather be dealt with on an individualized basis. For the rest of the discussion, we will consider the management of locally advanced oral cancers under the following 3 groups: (1) resectable oral cancers; (2) borderline resectable/technically unresectable oral cancers (where R0 resection is doubtful), and (3) unresectable oral cancers (where R0 resection is not possible).

Surgery as the Treatment Option in Oral Cancer

Complete surgical resection with negative margins appears to be the most appropriate treatment option in oral cancers. In a recently reported randomized study by Iyer et al. [7], surgery with adjuvant treatment was compared against chemoradiation in locally advanced head and neck cancers. Results in the subset of patients with oral cancer showed that survival was significantly superior in patients treated with surgery and adjuvant treatment compared to chemoradiation. The reported 5-year disease-specific survival was 68% in the surgery arm versus 12% in the chemoradiation arm (p = 0.038) [7]. Similar conclusions have been reported in retrospective studies by Gore et al. [8].

Preoperative Chemotherapy in Resectable Oral Cancers

Preoperative chemotherapy has been tested in resectable oral cancers for improving the locoregional control or overall survival (OS) and, secondly, for organ preservation. Two large randomized studies have addressed these issues [9, 10]. The first study by Licitra et al. [9] in 2003 had 2 arms, the standard arm consisting of surgery followed by postoperative radiation to high-risk patients and the experimental arm including induction chemotherapy followed by the same sequence as in the standard arm. The induction chemotherapy used was three cycles of cisplatin 100 mg/m² and fluorouracil 1,000 mg/m² (120-hour infusion administered every 21 days) (CF regimen). 195 patients were randomized, 98 in the surgical arm and 97 in the induction chemotherapy arm. This was a negative study and there was no difference in the OS between the 2 arms (5-year OS in both arms was 55%) [9]. The long-term results of this study reported by Bossi et al. [11], after a median follow-up 11.5 years, confirmed the same results. Induction chemotherapy failed to have an impact on locoregional control, distant metastasis and OS [11]. Another study by Zhong et al. [10] with a similar chemotherapy regimen failed to show a benefit for induction therapy. In this study, locally advanced resectable oral cancer patients were randomized to either upfront surgery followed by postoperative radiation or 2 cycles of a docetaxel, cisplatin and 5FU (TPF) regimen followed by surgery and adjuvant radiation. 256 patients were enrolled, and after a median follow-up period of 2.5 years, there was no difference in either the OS (hazard ratio, 0.977; 95% CI, 0.634–1.507; p = 0.918) or the disease-specific survival (hazard ratio, 0.974; 95% CI, 0.654–1.45; p = 0.897) [10]. Thus, it can be concluded that induction chemotherapy did not result in improvement in OS or disease-specific survival in resectable oral cancers.

In countries with limited resources and, to an extent, even in western countries, there is another concern related to long waiting lists and delays of 1–2 months before surgery [12, 13]. Chemotherapy could theoretically be useful to prevent progression during the waiting period. While it has not been possible to have a randomized study in this setting until now, there is some evidence from a small retrospective matched-pair analysis reported by Pai et al. [14]. A cohort of patients undergoing upfront surgery followed by adjuvant treatment was compared against a cohort with delayed surgery dates receiving metronomic chemotherapy. Patients with delayed dates (3 weeks or more of delay in surgery) were given oral metronomic chemotherapy (methotrexate 15 mg/m² weekly and celecoxib 200 mg twice daily) until 1 day prior to surgery. Subsequently, the patients underwent surgery and adjuvant treatment similar to the other patients. Metronomic chemotherapy was then continued as adjuvant treatment for 18 months. The authors reported a 2-year disease-free survival of 86.5% in the metronomic cohort as opposed to 71.6% in the surgical cohort (p = 0.12) [14]. Based on these results, a larger multicentric study is currently underway in India and is actively recruiting patients. The trial should hopefully cast some light on the use of preoperative metronomic therapy. Until such time, the use of preoperative therapy should be considered experimental.

The role of induction chemoradiotherapy in laryngeal cancers for organ preservation has been extensively studied [6]. There is limited data, however, for organ preservation in oral cancers. In the study by Licitra et al. [9], it was seen that mandibular resection could be avoided in 21% of patients who received induction chemotherapy. Response
to induction chemotherapy also seems to be a favorable prognostic factor [9, 10]. Patients with pathological complete response had a 10-year OS of 76.2 compared to 41.3% in patients without pathological complete response (p = 0.0004) [9]. Preservation of the mandible during surgery could lead to an improved cosmesis and improved functional outcomes [15, 16]. The effect on OS is still to be determined. Induction chemotherapy for mandibular preservation is being studied in our institute by Chaukar and colleagues in a phase 2 study.

Thus, current data to support the use of induction chemotherapy in resectable oral cavity cancers is lacking. Metronomic chemotherapy before delayed surgery and mandibular preservation are areas under active research.

### Borderline Resectable/Technically Unresectable Oral Cancers

While R0 resection is the desired aim of surgery, R1 or R2 resections are often seen when surgery is attempted in locally advanced T4 lesions [17, 18]. At our center, though, the margin-positive rate is low (below 5%) in oral cancers. T4 tumors contribute 80% of this margin-positive rate [19]. Borderline resectable or technically unresectable oral cancers are gray zone tumors. Surgical resectability is an interplay between the surgeon’s skill and the extent of tumor spread. Objective criteria are difficult to generate in such areas; however, criteria defining such tumors are available in the literature [20]. These are:

1. in case of 'buccal mucosa primary', either if the extent of the tumor or peritumoral edema reaches up to or above the level of zygomatic arch, or extension of the tumor to the high infratemporal fossa;
2. in case of 'oral tongue primary' or 'floor of mouth primary', extending up to the vallecula or disease infiltrating or reaching up to the hyoid bone or up to the high infratemporal fossa;
3. in case of oral cancers with extensive skin infiltrations, making achievement of negative margins a rarity.
4. None of these tumors should have frank skull base invasion, prevertebral fascia involvement or carotid encasement.

These tumors are classically treated with either radical chemoradiation or palliative radiation [6]. The outcomes of such large tumors with nonsurgical treatments are dismal. The reported median survivals in such studies are uniformly under 1 year [21–24]. The use of induction chemotherapy and assessment for surgery in such tumors seemed a logical option.

A recent large retrospective analysis by Patil et al. [20] confirms the benefit of such an approach. 721 patients fitting the abovementioned criteria were selected. They received 2 cycles of induction chemotherapy after which they were assessed for surgery. 310 patients (43%) underwent surgery after induction chemotherapy. It was a R0 resection in all patients. The locoregional control rate at 2 years was 20.6% for the whole cohort, 32% in patients undergoing surgery and 15% in patients undergoing nonsurgical treatment (p = 0.0001). The median OS was 19.6 months in patients undergoing surgery (95% CI, 9.59–25.21 months) and 8.16 months (95% CI, 7.57–8.76) in patients treated with nonsurgical treatment (p = 0.0001). Thus, it seems that in borderline resectable/technically unresectable oral cancers, induction chemotherapy followed by reassessment for surgery can be an appropriate alternative to concurrent chemoradiation.

### Unresectable Oral Cancers

Oral cancers with frank skull base invasion, prevertebral fascia involvement or carotid encasement are included. These groups have been addressed as subsets in the PARADIGM study and the DeCIDE study [25, 26]. As these cancers are not going to become resectable, the management of this group is beyond the scope of this chapter. However, in both these studies, patients with unresectable cancers were randomized to either concurrent chemoradiation or induction chemotherapy followed by concurrent chemoradiation. Induction chemotherapy failed to improve the disease-specific survival or OS.

### Regimen for Preoperative Chemotherapy in Oral Cancer

The 3-drug combination of TPF seems to be the most appropriate regimen for preoperative chemotherapy. Noronha et al. [27] retrospectively compared various chemotherapy regimens. Patients had received either a 2-drug combination using taxane (either paclitaxel or docetaxel) and platinum (either cisplatin or carboplatin) or a 3-drug combination of TPF. The response rate was significantly higher with the 3-drug combination: 50% versus 22% with the 2-drug regimen (p = 0.004). Comparing the taxane-based regimens, docetaxel had a 30.3% response rate, while paclitaxel had a response rate of 17.2% (p = 0.018). There was no statistically significant differ-
ence in the response rate between patients receiving either carboplatin or cisplatin [27].

A comparison of a cisplatin and 5FU-based combination versus a 3-drug TPF regimen has not been studied in oral cancers in the preoperative setting. However, corollaries can be drawn from the TAX 323 and 324 studies, where these 2 regimens were compared in locally advanced head and neck cancers as induction chemotherapy before definitive radiotherapy and chemoradiation [28, 29]. In both studies (TAX 323 and 324), the use of a 3-drug combination (TPF) showed a better response rate and better OS. In TAX 323, the median OS was 18.8 months in the TPF arm, while it was 14.5 months in the PF arm (p = 0.02) [28]. Similarly, in the TAX 324 study, the median OS was 71 months in the TPF arm, while it was 30 months in the PF arm (p = 0.006) [29]. An individual patient data meta-analysis done by Blanchard et al. [30] confirmed these findings. In both TAX 323 and 324, oral cancer patients were included, though the proportion was below 20% [28, 29]. From these two studies and an earlier study from our center [27], it can be generalized that the TPF regimen may be the preferred regimen of choice for preoperative chemotherapy [27].

**Number of Cycles of Preoperative Chemotherapy**

How many cycles should be given before preoperative surgery is an open question. In the era of cisplatin and 5FU, Paccagnella et al. [31] showed that the response to induction chemotherapy improves until the fourth cycle. So it could be said that when CF is used as the induction chemotherapy, 4 cycles are required. However, the number of cycles required with the TPF regimen is not known. To the best of our knowledge, there is no study comparing 2 cycles of TPF with a higher number of cycles. In TAX 323 and 324, 4 cycles of TPF were used [28, 29]. In the PARADIGM study, 3 cycles of TPF were used [25]. In DeCIDE, 2 cycles of TPF were used [26]. Similarly, 2 cycles of TPF were used by Zhong et al. [10]. So it seems that at least 2 cycles and a maximum of 4 cycles can be used when TPF is administered as preoperative chemotherapy.

**Compliance and Tolerability of Induction Chemotherapy**

In our experience, compliance with preoperative chemotherapy is an issue that needs to be considered. In a routine practice report by Patil et al. [20], 15.8% of patients discontinued induction chemotherapy after the first cycle. The reasons for discontinuation were mainly logistic issues, but toxicity was an issue in 0.7% patients [20]. In a prospective study by Zhong et al. [10], only 1.7% of patients would tolerate 1 cycle of the TPF regimen. Overall, it seems that TPF is well tolerated as preoperative chemotherapy and only 1–2% of patients cannot sustain a second cycle due to toxicity. However, in routine practice, discontinuation due to other reasons seems an issue especially in the developing world.

Hence, it may be useful if in such patients receiving TPF, detailed counselling is followed by an assessment of adherence-related factors especially in the developing world [32].

Selection of patients for TPF is important. The low mortality rate in randomized trials is due to the stringent inclusion and exclusion criteria. Not surprisingly, TPF is associated with high mortalities in routine practice. A mortality rate associated with TPF as high as 15.3% has been reported from California [33].

**Metronomic Chemotherapy in Oral Cancers**

Necessity is the mother of invention. This has been the story of metronomic chemotherapy in head and neck cancers so far. Metronomic scheduling of chemotherapy has been used in oral cancers mainly in two situations. First, as palliative chemotherapy, and second as a bridge to surgery and then continued as adjuvant. The issues related to the second indication have already been discussed above. In this section, we will be concentrating on issues related to the use of metronomic scheduling as palliative chemotherapy in oral cancers.

Metronomic chemotherapy has been postulated to have effects on tumor vasculature, tumor immunity and a direct anticancer effect [34, 35]. Celecoxib and methotrexate are both active agents in head and neck cancers [36–38]. Celecoxib at a dose of 200 mg twice daily and oral methotrexate at a dose of 15 mg/m² weekly has been the most commonly reported metronomic schedule in head and neck cancers. The selected dose of methotrexate was 15 mg/m² as it saturates head and neck squamous cell cancer tumor dihydrofolate reductase [39].

The EXTREME study used a combination of cetuximab, cisplatin and 5FU [40]. In 30 years, it was the first time that a regimen improved OS compared to platinum-based chemotherapy [41]. However, the high cost associated with cetuximab precludes the routine use of such a regimen in patients in the developing world [42]. At a
rural outreach centre near Mumbai, we explored the metronomic schedule of oral methotrexate and celecoxib [43]. It produced promising results with low toxicity. Encouraged by these results, we are doing a prospective study. In the first study in 18 patients with advanced oral cancers, this schedule was administered for palliation. The estimated median progression-free survival in the subgroup of patients was 5.2 months [44]. Following these results, the cohort was extended to 57 patients, and the median progression-free survival observed was 153 days and OS was 186 days [45]. Considering these results, a prospective randomized study was conducted to compare the efficacy of the metronomic schedule with that of intravenous chemotherapy (single-agent platinum). 110 patients were enrolled in this study. Patients in the metronomic arm had a median progression-free survival of 3.67 months compared to median a progression-free survival of 2.2 months in the cisplatin arm (p = 0.014). The median OS was 8.3 months (95% CI, 222.5–275.5 days) in the metronomic arm compared to a median of 5.07 months (95% CI, 104.2–199.8 days) in the cisplatin arm (p = 0.02) [46]. Though in comparison to the EXTREMEx study, the OS in the chemotherapy arm is lower. The subgroup analysis of the EXTREME study showed that in oral cancers, the median OS was 4.0 months in the standard chemotherapy arm, while it was 11.0 months in the cetuximab arm [40]. In this metronomic study, 84 of 110 patients had oral cancers. In addition to the benefit in efficacy, there were fewer grade 3/4 adverse effects in the metronomic arm (18.9 vs. 31.4%, p = 0.14). The number of hospital visits required was also lower. These results are now being confirmed in a large phase 3 multicentric study.

Thus, a metronomic schedule of oral methotrexate and celecoxib seems to be a reasonable option in patients not willing to undergo intravenous chemotherapy or in those who cannot afford cetuximab.

Disclosure Statement
The authors declare no conflicts of interest.

References


