Induction Chemotherapy in Squamous Cell Carcinoma of Tongue—Still a Slippery Role?

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Background  Tongue cancers are more common in the Indian subcontinent and a leading cause of morbidity and mortality among oral cavity cancers. Induction chemotherapy has been considered an intriguing and smart option for many reasons, but even after years of studies and debates, its role has not been fully established in the management of tongue cancers.

Materials and Methods  In this study, we evaluated 17 patients with oral tongue carcinomas with locally advanced stage, enrolled into a protocol of three drug (docetaxel, cisplatin, 5-fluorouracil) induction chemotherapy for three cycles. After completion of the three cycles, patients were clinically and radiologically re-evaluated and surgery was done if locally operable.

Results  At the completion of three cycles, five patients were partial responders, four patients were complete responders, and five patients had progressive disease after three cycles. Those patients with response underwent surgery. There were no significant morbid intraoperative or postoperative complications observed in seven out of nine patients. At the end of treatment completion, five out of nine patients had tumor residue/high-risk features and were planned for adjuvant radiotherapy.

Conclusion  For locally advanced oral tongue carcinomas, the role of induction chemotherapy before surgery has been fruitful and its impact on function preservation with acceptable oncological clearance is an emerging alternative. Spacing chemotherapy and radiotherapy reduce the incidence of adverse effects of combined treatment.

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of the tumor at presentation at presentation, surgery, radiotherapy or chemoradiotherapy are validated options. The recommended choice in Squamous cell carcinomas of the oral cavity is surgery. When the aim of treatment is preservation of Speech and swallowing function, or when surgery is not feasible, an effective treatment consists of the combination of chemotherapy and radiotherapy, either in a sequential or concomitant modality.

After several years of clinical trials, concomitant chemotherapy is now regarded as the standard of care for fit patients affected by LAHNSCC. The chemotherapy agents are known to cause a lot of deleterious side effects in patients with Head and neck cancers because of the additive toxicity profile of co administered radiotherapy. One still unresolved question is, knowing what is the best timing for the administration of Chemotherapy?

The Meta-Analysis of Chemotherapy in squamous cell Head and Neck Cancer (MACH-NC) meta-analysis by Lacas et al. documented the superiority of chemoradiation over radiotherapy in terms of overall survival (OS). Although the concomitant approach demonstrated to be the most effective one, it is not evident how useful can be the delivery of chemotherapy before radiation. This modality, defined as induction chemotherapy (IC), has been considered an intriguing and smart option for many reasons but, after years of studies and debates, its role has not been fully established.

The main objectives of IC can be summarized as follows:

1. Tumor shrinkage and organ preservation.
2. Early treatment while waiting for the beginning of radiotherapy (a real problem for many centers).
3. The reduction rate of locoregional relapse and distant metastases.
4. The selection of chemosensitive patients to reduce the intensity of subsequent radiotherapy or chemoradiotherapy.

In a trial conducted by Tata Memorial Hospital (TMH), use of IC is safe and can achieve resectability in 30.9% of T4b oral cavity cancer patients. Those patients undergoing resection after IC have much better OS than those who underwent nonsurgical local treatment.

The trials comparing IC followed by radiotherapy alone or by concomitant chemoradiotherapy have been analyzed, with a special focus on the European trial TAX 323/EORTC 24971 and the American trial TAX 324, both published in 2007. The first study delivered four cycles of TPF (docetaxel, cisplatin, 5-fluorouracil (FU)) versus PF (cisplatin, 5-FU) followed by radiotherapy and demonstrated significant survival benefits for TPF in a population of patients with previously untreated, unresectable LAHNSCC. The second trial delivered three cycles of TPF versus PF followed by concomitant carboplatin during radiotherapy, in a population of patients either unresectable and of low surgical curability, or candidates for speech and swallowing function preservation. Again, the median OS was significantly higher in the TPF arm that is now considered the standard treatment when the choice falls on IC.

The Choice of IC

**Standard Regimen TPF**

For 50 years, IC has been proposed for LAHNSCC. Several regimens were used, mainly platinum-based polychemotherapy.

The combination of cisplatin and 5-FU was confirmed by a comparative phase III trial of 237 patients with operable and inoperable disease. Patients were randomized in two arms: IC with cisplatin (100 mg/m²) and 5-FU (1,000 mg/m²/days for 5 consecutive days) for four cycles 3 weeks apart (PF) followed by radiotherapy or radiotherapy alone. There was a significant benefit in the OS rate at 5 and 10 years in the subgroup of inoperable patients (21 and 16% with induction vs. 8 and 6% without induction, p = 0.04).

In 2007, two trials showed a significant benefit of adding taxanes. The TAX 324 trial with 501 patients compared induction with PF to TPF (three cycles of 75 mg/m² docetaxel, 100 mg/m² cisplatin, both on day 1 and 1,000 mg/m²/day 5-FU by continuous intravenous infusion day 1–4), followed by concomitant chemoradiation with concurrent weekly carboplatin. With the addition of taxanes to the PF combination, the OS rate went up to 71 versus 30 months with PF (p = 0.006). Moreover, the triple-agent combination was well-tolerated, except for grade 3 and 4 neutropenia, which was more frequent in the TPF arm (83 vs. 56%). In total, fewer patients had treatment delays with the TPF regimen (29 vs. 65% for the PF scheme). The TAX 323/EORTC 24971 trial performed an assay with lower doses of 5-FU (750 mg/m²/day by continuous intravenous infusion for five consecutive days, without bolus) and cisplatin (75 mg/m² on day 1). The control arm consisted of cisplatin at the dose of 100/m², administered on day 1, followed by 5-FU at the dose of 1,000 mg/m²/day, administered by continuous intravenous infusion for 5 consecutive days. Three-hundred fifty-eight patients were randomly assigned, and median OS was higher in the TPF arm (18.8 vs. 14.5 months, p = 0.02). Tolerance was also better for TPF, with 24.3% of patients not able to complete the treatment in the TPF arm versus 35% in the PF arm. Mortality from IC was lower in the TPF arm, with 2.3% treatment-related deaths versus 5.5% in the PF arm. In other phase III trials, mortality of TPF ranged from 2 to 7%. In the TAX 324 trial, taxanes addition increased the risk of neutropenia.

In addition, quality of life was improved with TPF versus PF in the TAX 323 trial and the cost-utility analysis of both the TAX 323 and 324 studies showed benefit in quality-adjusted life-years in favor of TPF.

In conclusion, when IC has to be chosen, the strongest supported regimen is TPF. New options of radiation therapy have rapidly progressed in the recent years and now intensity-modulated radiotherapy is the preferred technique. An argument against IC is the burden of toxicity that is going to add up, whenever any chemotherapy is combined with radiotherapy.

In summary, for unresectable nonlaryngeal diseases, concomitant chemoradiotherapy is the standard, but IC prior to surgery or radiotherapy (± concurrent chemotherapy)
remains an option. For laryngeal and hypopharyngeal cancer, IC is strongly suggested, with the aim of maximizing functional preservation without compromising survival.

In this study, we will review the role of IC for oral tongue cancers and their role in less morbid and more organ conserving approaches.

Materials and Methods

In this study, we evaluated 17 patients with oral tongue carcinomas with locally advanced stage and enrolled them into a protocol of three drug (TPF) induction chemotherapy for three cycles. At the completion of the three cycles, the patients were clinically and radiologically re-evaluated and proceeded with surgery if resectable.

Following parameters were analyzed after IC:

- Rate of tumor shrinkage (anteroposterior, transverse axis, and Depth Of Invasion [DOI])
- Nodal burden after chemotherapy
- Type of surgery planned initially versus type of surgery done after IC
- Postoperative stage and tumor volume
- Adjuvant treatment given
- Early postoperative morbidity and recurrence pattern

Results

Eleven patients with squamous cell carcinoma of tongue who were in T3/T4 stage were enrolled in the study. Average age at the presentation was 38. The stage at presentation was initially T3 or T4 with nodal burden varying between N1 and 2. Ten out of the 17 patients had no chemotherapy-related toxicities with rest of the five patients having grade 1 toxicity and two patients having grade 2 toxicity during the second and third cycles of treatment. All these patients were initially planned for morbid extensive composite/compartmental excision initially as per the disease extent at presentation. At the completion of three cycles, five patients were partial responders (>30% volume shrinkage by Response Evaluation Criteria In Solid Tumors [RECIST] criteria), four patients were complete responders, and eight patients had progressive disease after three cycles. Those patients with response underwent hemiglossectomy (6/9) and compartmental excision (3/9) and Modified Radical Neck Dissection (MRND). Eight out of ten patients had nodal disease at the completion of chemotherapy both clinically and radiologically. There were no significant morbid intraoperative or early postoperative complications observed in seven out of nine patients with remaining two patients having minimal surgical site infection of neck wound. Rate of sterilization of the neck node was almost 80% in this study (8/9 patients) with variable response of around 40 to 60% for primary tumor status (5/9 patients). At the end of treatment completion, 5 out of 10 patients had tumor residue and/or high-risk features and were planned for adjuvant radiotherapy.

There was no notable early postoperative morbidity and all patients were in strict follow-up after completion of adjuvant radiation and they were found to have no recurrence until first 3 months of close follow-up. At each cycle, thorough clinical examination and 6 monthly magnetic resonance imaging of local part were done and no early or delayed locoregional recurrences were noted.

Conclusion

For oral tongue carcinomas, the role of IC before surgery has been fruitful and its impact on function preservation with acceptable oncological clearance. Spacing chemotherapy and radiotherapy reduce the incidence of adverse effects of combined treatment. Further investigation in phase III trials is warranted to determine the optimal treatment after induction TPF.

Conflict of Interest

None declared.

References

control with docetaxel, cisplatin, 5-fluorouracil and cisplatin (TPF), 5-fluorouracil (PF) for induction in unresectable locoregionally advanced head and neck cancer patients (EORTC 24971/TAX 323). Br J Cancer 2010;103(08):1173–1181