Preoperative chemotherapy in advanced resectable OCSCC: long-term results of a randomized phase III trial

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Received 31 July 2013; revised 5 November 2013; accepted 13 November 2013

Background: Data on preoperative chemotherapy in resectable oral cavity cancer are conflicting. We present the long-term results of a randomized trial of induction chemotherapy in resectable oral cavity cancer.

Patients and Methods: A randomized, parallel, multicentre trial evaluated the impact of three cycles of cisplatin 100 mg/m² and fluorouracil 1000 mg/m² (120-h infusion administered every 21 days) in stage T2–T4, N0–N2, previously untreated patients with advanced disease. Control group received upfront surgery. Postoperative radiation was offered to both arms when pathologic risk features were identified. The co-primary end points were the occurrence of locoregional or distant tumour relapse, and death.

Results: Among the 198 enrolled patients, with a median follow-up of 11.5 years, there was no difference in the incidence of locoregional relapse between chemotherapy and control group (P = 0.6337), nor in distant metastasis development (P = 0.1527). There was also no difference between groups in overall survival (P = 0.3402). Patients with a pathological complete response (pCR) had higher probability of survival than those without (10-year OS: 76.2% versus 41.3%, P = 0.0004).

Late toxicities in patients with a minimum follow-up of 60 months (42 in each group) were similar between arms, except for fibrosis (cumulative incidence 40% versus 22% in chemotherapy arm) and grade 2 dysphagia (14% versus 5%).

Conclusions: Long-term follow-up of this randomized trial confirmed the absence of survival benefit with preoperative chemotherapy in oral cavity cancer. Late toxicity was similar in the two arms except for fibrosis and dysphagia, which were less in the chemotherapy arm. The survival benefit for patients achieving a pCR was maintained.

Key words: resectable oral cavity cancer, randomised trial, induction chemotherapy, cisplatin, fluorouracil, pathological complete response

introduction

The mainstay of locally advanced oral cavity cancer treatment lies on surgery followed by radiotherapy and chemotherapy in case of high-risk pathological features [1]. On the other side, primary chemotherapy and radiation are considered for patients whose cancer is technically or functionally un-resectable [2].

Approximately half of the patients with locally advanced oral cavity cancer will not survive beyond 5 years from time of diagnosis, due to locoregional and/or distant metastases or a secondary primary tumour [3].

Moreover, surgery and radiation result in functional impairment, such as in eating, drinking and speaking difficulties, leading to a decrease in quality of life [4]. Therefore, investigation into ways to improve treatment and outcomes for patients with oral cavity cancer is warranted.

The original trial by Licitra et al. [5], on which this article is based, focused on the use of a preoperative chemotherapy regimen and was conducted in a highly selected patient population. At that time, it was the first trial to focus solely on advanced resectable oral cavity tumours. This multicentre, randomized trial investigated the effects of induction chemotherapy on overall survival (OS) and disease relapse. Although the trial showed no survival benefit or reduction in probability of tumour relapse, it did reveal that fewer patients required a mandibulectomy and/or radiation, both of which have the potential to negatively affect patient’s quality of life.

In line with the open debate about the role of induction chemotherapy, the long-term results of the above-mentioned trial of preoperative chemotherapy in patients with resectable oral cavity cancer are reported here.

patients and methods

The methodology of the original study has been fully published [5], therefore only a brief synopsis is provided here.
study design
The study was a randomized, parallel, multicentre trial, conducted by a multidisciplinary team and coordinated by the Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy.

patients
Eligible patients included those with biopsy-confirmed, stage T2–T4 (T2 tumours must be >3 cm), N0–N2, previously untreated oral cavity squamous cell carcinoma (OCSCC). Tumour spread to oropharynx was admitted if more than 50% of the lesion was confined within the oral cavity.

Before randomization, all patients underwent panendoscopy to exclude the presence of concurrent secondary primary tumours.

Following stratification by institution and nodal stage, eligible patients were randomized to one of two groups: either induction chemotherapy followed by surgery (chemotherapy group, N = 99) or standard surgery alone (surgery group, N = 99). Radiation therapy was offered to both groups after surgery if pathological exam showed high-risk characteristics (positive surgical margins and/or invasion of soft tissues and/or more than three node metastases and/or extra-capsular tumour spread).

consent and ethics
All patients provided an informed consent, and the study was approved by the local Ethical Committee and conducted in accordance with the Declaration of Helsinki.

treatment
chemotherapy. Patients randomized to the chemotherapy group received three cycles of cisplatin 100 mg/m² and fluorouracil 1000 mg/m², as a 120-h infusion administered every 21 days. Patients received the third chemotherapy cycle only if a partial response was observed.

surgery. Resection was planned after 21 days and up to 40 days from chemotherapy last cycle, and it was defined only after clinical evaluation and determination of a mandatory macroscopic safe margin of 1.5 cm. Standard surgical approaches were adopted, and in all cases were associated with ipsilateral neck dissection.

radiation. Only high-risk patients received postoperative radiation therapy, which was administered 4–5 weeks following surgery. Concurrent chemotherapy was not a standard at that time.

efficacy evaluation
Tumour responses were evaluated using the World Health Organization scale [6]. After two cycles, those patients with either stable or progressive disease were referred for surgical resection. Postoperatively, surgical specimens were assessed pathologically for tumour response. A complete pathologic remission was defined as the absence of any tumour cell. Microscopic residual tumour was assessed in the presence of scattered foci of a few tumour cells.

follow-up
Patients were examined every 3 months for the first 2 years and every 6 months thereafter; after the fifth year, the patients were followed yearly. Chest X-ray was carried out every 6 months for the first 5 years. Radiological examinations were carried out whenever signs and/or symptoms possibly related to either the disease, distant spread and/or second primary were suspected.

toxicity
Late toxicities were assessed according to National Cancer Institute Common Toxicity Criteria, NCI/CTC [7].

depend points
The co-primary end points of the study were the occurrence of locoregional or distant tumour relapse (in terms of crude cumulative incidence, CCI as well as disease-free survival, DFS) and the occurrence of any-cause death. Of note, the diagnosis of second tumours was not considered as an efficacy end point. Time to occurrence of tumour events and death were calculated from the randomization date.

statistical methods
Incidence curves for neoplastic relapse events were created according to the methodology described by Kay and Schumacher [8] and compared with the Gray test. Survival curves were obtained with the Kaplan–Meier methodology and compared with the log-rank test. Second tumours incidence curves in particular were obtained considering distinct time horizons (over 10 years from randomization, with 0–60 and 60–120 months intervals).

Hazard ratios (HRs) were calculated using the Cox proportional hazards model.

The planned sample size of 258 patients guaranteed 90% power to detect a 20% absolute risk reduction in the chemotherapy group. However, only 198 patients were finally enrolled due to the difficulty in accruing patients. For this reason, the power of the study was reduced to 78%.

results
In July 2000, mature results were published and reported no added benefit in terms of survival or locoregional and distant tumour relapse [5].

The present analysis is based on a 11.5-year median follow-up. This update yielded similar results to those assessed in the original trial after a median follow-up period of 76 months [5] in terms of the incidence of locoregional relapse (5 and 10-year CCI: 29.6% in the chemotherapy arm versus 32.0% in the control arm) and distant metastases occurrence (4.1% versus 9.3%); these differences between arms were not significant (P = 0.6336 and P = 0.1527, respectively) (Figure 1). There was also no significant difference between arms either in 10-year OS (46.5% versus 37.7%; P = 0.3402; HR = 0.837) (supplementary Figure 1, available at Annals of Oncology online), or in 10-year DFS (48.5% versus 36.0%; P = 0.1771; HR = 0.775) (supplementary Figure 2, available at Annals of Oncology online). The incidence of second tumours occurring after 60 months followed a similar pattern, with the two groups displaying no significant differences (CCI: 10.6% versus 22.1%; P = 0.6050) (Figure 2).

However, patients with a pathological complete response (pCR) had a significant survival improvement when compared with those without a pCR (10-year OS: 76.2% versus 41.3%, P = 0.0004; HR 0.230) (Figure 3).

The benefit in survival mainly depended on better loco-regional control of disease: local–regional recurrence CCI at 10 years was 11.1% for patients achieving a pCR, while was 32.7% for patients with residual disease after chemotherapy (P = 0.0289).

Patients achieving a pCR (22 of 82 patients operated) had a relatively less advanced stage at diagnosis, with 41% stage II, 50% stage III and 9% stage IV; subsite of disease was floor of the
mouth in nine cases, tongue in six cases, retromolar trigone in four cases, alveolar ridge in two cases and buccal mucosa in one case.

We carried out an exploratory analysis of DFS and OS according to baseline node characteristics, without finding any benefit in selected subgroups. In particular, we did not find any survival improvement in clinical N2 patients subgroup ($P = 0.96; HR = 0.98$).

Globally, there were 54 deaths in chemotherapy arm and 61 in control group. Causes of death are reported in supplementary table. Table 1 reports late toxicities assessment according to treatment in all the patients with a minimum follow-up of 60 months (42 in each group).

In control group, a higher incidence of fibrosis (CI 40% with respect to 22% in chemotherapy arm) and grade 2 dysphagia (14% versus 5%) were detected. Mucositis and xerostomia were negligible in both groups.

**Table 1.** Late toxicities in patients with a minimum follow-up of 60 months

<table>
<thead>
<tr>
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<th>Chemotherapy arm (%)</th>
<th>Control arm (%)</th>
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<tbody>
<tr>
<td>Dysphagia</td>
<td>Grade 1 29</td>
<td>Grade 2 5</td>
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<tr>
<td></td>
<td></td>
<td>Grade 1 29</td>
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<td></td>
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<td>Grade 2 14</td>
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<tr>
<td>Fibrosis</td>
<td>Grade 1 10</td>
<td>Grade 2 12</td>
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<td></td>
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<td>Grade 1 33</td>
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<td>Grade 2 7</td>
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<tr>
<td>Xerostomia</td>
<td>Grade 1 5</td>
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<td>Grade 1 5</td>
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<td>Grade 2 /</td>
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<tr>
<td>Mucositis</td>
<td>Grade 1 2</td>
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**Figure 1.** Incidence of locoregional relapse (A) and distant metastases (B) in the induction chemotherapy arm and in the control group.

**Figure 2.** Incidence of second tumour occurrence in the induction chemotherapy arm and in the control group.

**Figure 3.** Disease-free survival in the induction chemotherapy arm according to pathological complete response (pCR) achievement.

**Discussion**

Although a positive trend was shown for almost all the end points, the long-term follow-up of this randomized trial confirmed the absence of significant survival benefit with preoperative chemotheraphy in oral cavity cancer, as well as the lack of any advantage with regard to locoregional relapse, distant metastases or second tumour. Current data underline the
importance of obtaining a pCR to induction chemotherapy as a surrogate end point of survival.

The role of induction therapy in head and neck cancer has long been debated, with mixed results. Earliest data did not support the efficacy of adding chemotherapy to the locoregional curative treatment approach, possibly because of sub-optimal chemotherapy, underpowered statistics and heterogeneous patient populations in terms of selection criteria, tumour site and stage and locoregional treatment [9, 10]. On the contrary, more recent evidence from three meta-analyses concluded that a small (4%–6%) but statistically significant survival benefit was observed with the use of chemotherapy, especially in concomitant setting [11–13]. Indeed, when the trials adopting full-dose induction cisplatin and 5-fluorouracil were analysed, there was a statistically significant OS benefit of 5% at 5 years [13]. In a comprehensive analysis by tumour site, chemotherapy was confirmed to reduce risk of death in oral cavity cancer (HR = 0.87), irrespective of chemotherapy timing [14].

Data with newer chemotherapy regimens (taxane added to cisplatin and 5-fluorouracil) have renewed interest in induction approaches [15, 16], even if its role before curative chemoradiation has been questioned again by the most recent results from two randomized trials [17, 18].

When analysing different trials, inclusion criteria of tumour resectability may offer a key for results interpretation. In particular, some evidence revealed benefits for induction therapy mainly in patients with unresectable head and neck squamous cell cancer. The long-term follow-up of a randomized study conducted in Italy showed that induction chemotherapy was an improving outcome in a group of patients for whom surgery was not an option [19]. These findings were supported by another study showing some benefit for patients with unresectable disease who received an intensified induction chemotherapy regimen [20].

It is therefore possible that only the unresectable population profits from induction systemic therapy. Whether this is related to the intensification treatment opportunity offered by induction chemotherapy of more aggressive tumours is left to be demonstrated.

However, long-term data from our trial showed that at least a sub-population of operable patients experiencing a pCR to induction chemotherapy had a significant survival improvement. This result is in line with the observation made in two, non-randomized trials in oral cavity cancer evaluating different induction schedules and in a recent randomized trial adopting induction docetaxel, cisplatin and 5-fluorouracil (TPF): these studies showed that pathological complete or major responses were prognostic factors for survival [21–23]. The improved survival of patients obtaining pCR could be due to the beneficial effect of chemotherapy or it could also be due to an intrinsic favourable outcome of responding patients.

However, pCR represents an accepted surrogate end point for survival; recently, in high-risk, early-stage breast cancer, the Food and Drug Administration released a draft guidance to support marketing approval of drugs in preoperative setting using pCR as a surrogate end point [24].

In our trial, the favourable prognostic effect achieved by patients showing a pCR did not reflect into a survival benefit for the whole group of induction chemotherapy-treated patients. This could be due to the relatively low number of pCR that could have diluted the survival benefit.

Future studies should concentrate on the identification of biomarkers predictive of response to induction chemotherapy, in order to fully exploit the role of preoperative drugs in chemosensitive patients and to spare toxicities in unresponsive ones.

We previously reported that tumours maintaining p53 functionality had a higher probability to achieve pCR [25]. The validation of predictive biomarker in a prospective model could offer a strategy to select the most chemo-sensitive population. In this regard, a prospective clinical trial has been promoted by our institution with preoperative TPF chemotherapy in an enriched population of oral cavity cancer patients, selected according to a favourable molecular profile in terms of response to induction treatment (clinicaltrials.gov identifier: NCT01914900).

From another point of view, new insights are requested before being able to ‘deintensify’ the locoregional treatment based on major response to induction therapy. Strategies aimed to reduce the amount of surgical resection or to employ (chemo)radiation strategies in place of surgery in case of favourable response to chemotherapy deserves further investigations.

Our long-term follow-up showed that the induction chemotherapy is not associated with more late toxicity; instead, fibrosis and dysphagia were less frequent in patients receiving chemotherapy before surgery. This observation can be ascribed to less extensive surgery carried out in the chemotherapy group (31% versus 52% in control group) and less patients receiving post-operative radiotherapy (33% versus 46% in control group). No grade 3–4 events were reported in our series.

There are very few data about late toxicities after surgical curative treatment in oral or oropharyngeal cancer. Long-term evaluation of the RTOG 9501 trial comparing postoperative radiotherapy with or without concurrent chemotherapy in head and neck squamous cell cancer (with about 30% of the cases composed by oral cavity cancer), showed a limited prevalence of late toxicities in patients with a follow-up of more than 5 years [26]. In fact, only 9% of the patients in radiation arm and 4% in combined chemoradiation group displayed grade 3–4 late toxicities.

In conclusion, our results should encourage to persist in trying to identify subgroup of patients for whom induction chemotherapy is beneficial both in terms of treatment ‘deintensification’ and/or survival improvement, knowing that this approach, unlike to concomitant chemoradiation, seems not to be associated with severe late effects.

However, induction chemotherapy in advanced oral cavity cancer should be employed only in the context of clinical trials.

acknowledgements

We thank Luca Giacomelli and Silvana Pileggi for the assistance in medical writing and Mr Vittorio Poletti for the enthusiastic support to our work.

funding

She also received research funds from Eisai, Eli-Lilly, Merck Serono, Amgen, Boheringer Ingelheim and Pfizer.
**disclosure**

LL served as a consultant for BMS, GSK, Eli-Lily, Merck Serono, Amgen, Boheringer Ingelheim, Debiopharm and Ventrx. The other authors declare no conflicts of interest.

**references**