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Original Article

A phase II randomized trial comparing neoadjuvant chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in advanced squamous cell carcinoma of the pharynx or larynx

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ABSTRACT

Background: To clarify the effect of induction chemotherapy (ICT) in patients with advanced pharyngeal and laryngeal squamous cell carcinoma (PLSCC) treated with concurrent chemoradiotherapy (CCRT).

Methods: Patients with treatment-naïve nonmetastatic advanced PLSCC were stratified according to disease stage (III or IV) and resectability before being randomized to either a ICT/CCRT or CCRT arm. A cisplatin/tegafur-uracil/leucovorin regimen was administered during ICT and CCRT. The primary end point was overall survival (OS).

Results: We enrolled 151 patients during December 2006 to February 2011. The median follow-up of surviving patients was 54.5 months. The ICT/CCRT arm included more patients with hypopharynx cancer (57.1% vs 40.5%, $p = 0.09$) and N2 or N3 diseases (85.7% vs 74.4%, $p = 0.02$). In the ICT/CCRT and CCRT arms, the 5-year OS was 48.1% and 53.2%

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($p = 0.45$); progression-free survival (PFS) was 31.8% and 55.6% ($p = 0.015$); and locoregional control (LRC) was 37.7% and 56.2% ($p = 0.026$), respectively. The adverse events and compliance to radiotherapy were similar. However, the proportion of patients receiving a total dose of cisplatin during CCRT <150 mg/m^2 was higher in the ICT/CCRT arm (46.8% vs 16.2%; $p = 0.000$) and independently predicted poorer PFS and LRC in multivariate analysis. *Conclusion:* OS did not vary between the ICT/CCRT and CCRT arms. However, poorer compliance to CCRT and inferior LRC and PFS were observed in the ICT/CCRT arm. Optimizing the therapeutic ratio in both ICT and CCRT settings are necessary for developing a sequential strategy for patients with advanced-stage PLSCC.

At a glance commentary

Scientific background on the subject

The role of induction chemotherapy (ICT) in patients of advanced pharyngeal and laryngeal squamous cell carcinoma (PLSCC) treated with concurrent chemoradiotherapy (CCRT) remains to be clarified.

What this study adds to the field

This study showed that ICT/CCRT and CCRT provides similar overall survival, but poorer compliance to CCRT and inferior locoregional control and progression-free survival were observed in the ICT/CCRT arm. Optimizing the therapeutic ratio in both ICT and CCRT settings are necessary for developing a sequential strategy for advanced PLSCC.

Numerous attempts have been made to improve the outcomes in patients with head and neck squamous cell carcinoma (HNSCC) by combing radiotherapy (RT) with chemotherapy (CT) since the data of the Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) revealed a 6.5% 5-year absolute survival benefit of concurrent chemoradiotherapy (CCRT) [1]. CCRT has been proposed to be the ideal approach to incorporate CT into RT for treating advanced HNSCC. Generally, no overall survival (OS) benefit of induction CT (ICT) schedules has been identified. Only a marginal improvement in the OS was observed in ICT trials using a cisplatin and 5-fluorouracil (PF) combination [1]. Although phase III ICT trials for HNSCC have demonstrated a stronger overall response and survival rate for a docetaxel, cisplatin, and fluorouracil (TPF) combination compared with a PF combination [2–4], randomized trials of CCRT preceded or not preceded by ICT TPF have not yet supported the use of ICT [5,6].

Although the role of ICT in managing HNSCC is still being explored and debated, it is used as a common clinical treatment for HNSCC. The potential clinical advantages of ICT in addition to organ-function preservation [7,8] are to provide early symptom and function improvement before RT, rapidly shrink tumors and, thus, reduce the requirement for urgent interventions (e.g., tracheostomy for airway obstruction, feeding tube for swallowing dysfunction), bridge definitive treatment when immediate RT initiation is not possible, eradicate micrometastasis, and in vivo assess the treatment response to provide prognostic information for subsequent treatment. These potential advantages are commonly required for treating patients with advanced HNSCC, and ICT is reported to render a survival benefit in patients with unresectable HNSCC [9]. However, according to the preceding considerations, patients with advanced tumors or a compromised health status for CCRT may be treated with ICT during daily practice. The 3-year OS of our patients with advanced-stage pharyngeal or laryngeal squamous cell carcinoma (PLSCC) treated with CCRT and ICT was 60% and 45%, respectively. Whether the inferior outcome of ICT in daily practice is attributable to treatment selection bias requires clarification.

In Taiwan, 80%–90% of HNSCC patients are betel quid chewers, and >40% of our patients experienced ≥ grade 3 stomatitis following ICT PF [10]. The high incidence of severe stomatitis was due to betel quid-chewing related oral mucosa change [11]. Severe mucositis, poor compliance, and reduced dose intensity worsened the therapeutic outcomes for ICT PF [10]. We have developed cisplatin (P)/tegafur (T) or tegafur-uracil (U)/leucovorin (L) combined regimens since 2002. To ameliorate emesis and nephrotoxicity, cisplatin at 100 mg/m^2 triweekly was modified to 50 mg/m^2 biweekly, and to ameliorate stomatitis and maintain efficacy, 5-fluorouracil (5-FU) at 1000 mg/m^2/d through 120-h infusion was replaced with daily oral 5-FU prodrugs (tegafur 800 mg/d or tegafur-uracil at 300 mg/m^2/d) [12]. According to a dose-finding study investigating toxicity, oral leucovorin at 60 mg/d was used in combination with tegafur for protracted treatment [13]. PUL and PTL combinations had lesser toxicity, particularly for severe stomatitis (5%–7%), and stronger efficacy compared with PF in our patients [14,15]. Moreover, oral 5-FU prodrugs can be easily administered as radiosensitizers during CCRT. CCRT with PTL in patients of advanced PLSCC yielded a 5-year OS of 59.7% [16].

This randomized study examining PUL during ICT and CCRT was designed to clarify the effect of ICT on CCRT.

Materials and methods

Patients

Patients with measurable nonmetastatic histologically proven stage III or IV PLSCC were eligible if either their tumors were declared unresectable by a multidisciplinary team consensus or they were candidates for organ preservation. The American Joint Committee on Cancer criteria (2002) were used for disease staging [17]. The included patients were aged 18–70 years, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate bone marrow function (leukocyte count ≥ 4000/L; platelets ≥ 100,000/L),