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ORIGINAL ARTICLE

Induction chemotherapy with dose-modified docetaxel, cisplatin, and 5-fluorouracil in Asian patients with borderline resectable or unresectable head and neck cancer

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Background/purpose: Significant ethnic differences in susceptibility to the effects of chemotherapy exist. Here, we retrospectively analyzed the safety and efficacy of induction chemotherapy (ICT) with dose-modified docetaxel, cisplatin, and 5-fluorouracil (TPF) in Asian patients with borderline resectable or unresectable head and neck squamous cell carcinoma (HNSCC).
Methods: Based on the incidence of adverse events that occurred during daily practice, TPF_{90} (90% of the original TPF dosage; docetaxel 67.5 mg/m^2 on Day 1, cisplatin 67.5 mg/m^2 on Day 1, and 5-fluorouracil 675 mg/m^2 on Days 1–5) was used for HNSCC patients who were scheduled to receive ICT TPF.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Results: Between March 2011 and May 2014, 52 consecutive patients with borderline resectable or unresectable HNSCC were treated with ICT TPF_{90} followed by concurrent chemoradiotherapy. Forty-four patients (84.6%) received at least three cycles of ICT TPF_{90}. The most commonly observed Grade 3–4 adverse events included neutropenia (35%), anemia (25%), stomatitis (35%), diarrhea (16%), and infections (13.5%). In an intention-to-treat analysis, the complete and partial response rates after ICT TPF_{90} were 13.5% and 59.6%, respectively. The complete and partial response rates following radiotherapy and salvage surgery were 42.3% and 25.0%, respectively. The estimated 3-year overall survival and progression-free survival rates were 41% [95% confidence interval (CI): 25–56%] and 23% (95% CI: 10–39%), respectively. The observed median overall survival and progression-free survival were 21.0 months (95% CI: 13.3–28.7 months) and 16.0 months (95% CI: 10.7–21.3 months), respectively.

Conclusion: TPF_{90} is a suitable option for Asian patients with borderline resectable or unresectable HNSCC who are scheduled for ICT.

Introduction

The combination of radiotherapy (RT) and chemotherapy (CT) may improve the clinical outcomes of patients with head and neck squamous cell carcinoma (HNSCC). In this regard, the meta-analysis of CT in head and neck cancer demonstrated that concomitant chemoradiotherapy (CCRT) confers an absolute benefit of 6.5% [hazard ratio, 0.81; 95% confidence interval (CI), 0.78–0.86; $p < 0.001$] at 5 years.[1] In contrast, induction CT (ICT) schedules do not generally show any positive impact on overall survival (OS), the only exception being the combination of cisplatin and 5-fluorouracil (PF).[1] Although Phase III ICT trials in HNSCC patients reported that a triple regimen comprising docetaxel, cisplatin, and 5-fluorouracil (TPF) is superior to PF in terms of clinical response and survival rates,[2–4] randomized trials do not provide strong support for the use of ICT.[5,6] In this scenario, the potential benefits of ICT in the clinical management of HNSCC patients remain a matter of debate. These observations notwithstanding, ICT continues to be commonly used for HNSCC patients.

In the era of organ-function preservation, the long-term results of the RTOG 91–11 and GORTEC 2000–01 studies demonstrated the clinical usefulness of ICT followed by RT in patients with advanced larynx or hypopharynx squamous cell carcinomas.[7,8] Other potential clinical advantages of ICT include the following: (1) reduction in symptoms and functional improvement before RT; (2) accelerated tumor shrinkage that can reduce the need for urgent maneuvers (e.g., tracheostomy for airway obstruction, tube feeding for swallowing problems); (3) acting as an effective bridge before definitive treatment when RT cannot be initiated immediately; (4) clearance of micrometastases; and (5) *in vivo* assessment of treatment response that may guide subsequent therapeutic interventions. Such potential advantages are paramount in the clinical management of patients with unresectable HNSCC, for whom ICT may confer a survival benefit.[9] In light of these findings, the Taiwanese National Health Insurance implemented (as of 2011) a reimbursement program for ICT TPF performed in patients with unresectable HNSCC.

Unfortunately, ICT TPF can be associated with serious side effects, including subsequent inability to undergo definitive therapy and deaths, in a substantial proportion of patients with advanced HNSCC (especially in those with a low socioeconomic status and poor general conditions).[10] Significant ethnic differences in susceptibility to the effects of docetaxel exist, with Asian patients having a 19-fold increased risk of docetaxel-induced severe neutropenia compared with non-Asian individuals.[11] Consequently, docetaxel dose reduction has been proposed in Asian HNSCC patients.[12,13] Another point that merits consideration is the high prevalence of betel quid chewing in the Taiwanese population, with > 80% of HNSCC patients being betel quid chewers. Notably, the incidence of severe (≥ Grade 3) mucositis in Taiwanese patients treated with ICT PF is significantly higher (approx. 40%) than that observed in Western populations (8–11%),[14] possibly because of betel quid chewing-related mucosa damage.[14,15] In this scenario, a dosage adjustment optimization that can protect against toxicity without reducing the efficacy of treatment would be of paramount importance. We therefore presented the safety and efficacy of dose-modified ICT TPF in Asian patients with borderline resectable or unresectable HNSCC.

Materials and methods

Patients

TPF was reimbursed for unresectable HNSCC by the Taiwan National Health Insurance since January 2011. Since then, patients with biopsy-proven HNSCC judged to be borderline resectable or unresectable by a multidisciplinary tumor board were enrolled if their consent to ICT TPF was obtained. All patients were staged according to the American Joint Committee on Cancer 2010 staging criteria.[16] Patients had to meet the following criteria to receive ICT TPF: (1) age ≤ 70 years; (2) Eastern Cooperative Oncology Group performance status between 0 and 2; (3) adequate bone marrow function (leukocyte count ≥ 4000/L; platelet count ≥ 100,000/L); and (4) acceptable renal (serum creatinine < 2.0 mg/dL) and liver (total bilirubin ≤ 1.5 × the upper limit of normal; serum glutamic