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Induction chemotherapy with docetaxel, cisplatin and fluorouracil followed by concurrent chemoradiotherapy or chemoradiotherapy alone in locally advanced non-endemic nasopharyngeal carcinoma

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ABSTRACT

Objectives: To evaluate the efficacy of induction chemotherapy with docetaxel, cisplatin and fluorouracil (TPF) followed by concurrent chemoradiotherapy (IC + CCRT) or CCRT alone in non-endemic locally advanced nasopharyngeal carcinoma (NPC) patients.
Materials and methods: Data of 106 patients with NPC treated from January 1999 to June 2012 with IC + CCRT (n = 58) or CCRT alone (n = 48) were retrospectively reviewed.
Results: Median follow-up was 6.4 years. Distribution of age, performance status, stage and concurrent chemotherapy regimen were imbalanced between the two groups. The 5-year overall survival (OS) and progression-free survival (PFS) were not significantly different between IC + CCRT and CCRT groups (OS: 78.3% vs. 82.7%, p = 0.77; PFS: 72.5% vs. 68.2%, p = 0.81, respectively). There were less total cumulative incidence of grade 3–4 late radiation morbidity in the IC + CCRT group (44.8% vs. 70.8%, p = 0.01). Five-year OS for patients with post-IC complete response (CR), partial response (PR) and stable disease (SD) sub-groups were 100%, 79.4% and 60%, respectively.
Conclusion: Compared with CCRT alone, IC (TPF regimen) + CCRT did not improve OS or PFS in patients with NPC, but less grade 3–4 late toxicities were observed. Responsiveness of IC may provide additional prognostic information.

Introduction

Nasopharyngeal carcinoma (NPC) has a distinct epidemiology and natural behavior [1]. It is relatively rare among the indigenous French population, but is more common in migrants from Southeast Asia and North Africa.

Incorporation of chemotherapy with radiotherapy (RT) has improved the therapeutic outcome of patients with locally advanced NPC [2–6]. In the updated MAC-NPC meta-analysis [6,7], an absolute benefit of 6.3% of overall survival (OS) at 5 years was demonstrated with the addition of chemotherapy to RT. The interaction between treatment effect on OS and the timing of chemotherapy was significant in favor of concurrent chemoradiotherapy (CCRT). One of the main questions debated currently is the role of induction chemotherapy (IC) in addition to CCRT. Theoretically, IC may debulk the tumor, eradicate early micrometastases, and the tolerance in chemo-naive patients is better compared with that of AC [8]. In both TAX-323 and TAX-324 studies, the docetaxel/cisplatin/5-fluorouracil (TPF) regimen has been demonstrated to significantly improve response rates and long term outcomes compared to the 2-drug regimen (cisplatin plus 5-FU, PF) in patients with head and neck squamous cell carcinoma (HNSCC) [9,10]. The superiority of taxane-cisplatin-fluorouracil over PF as IC in HNSCC was also demonstrated in the meta-analysis MACHNC [11]. Therefore, this combination in the IC setting is attractive and is being actively investigated.

To compare induction TPF chemotherapy plus concurrent chemoradiotherapy (IC + CCRT) with CCRT alone in locally advanced NPC, we retrospectively analyzed the outcomes of a non-endemic cohort of such patients.

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Materials and methods

Patients

From January, 1999 to July 2012, 216 consecutive patients with newly diagnosed NPC treated definitively with radiotherapy with or without chemotherapy at Gustave Roussy were reviewed. All cases were restaged according to the American Joint Cancer Committee (AJCC) staging classification 7th edition. Approval for the study was obtained from the institutional head and neck clinical research and ethics committee. Patients were excluded for the following reasons: Stage I (n = 8); no concurrent chemotherapy (n = 58); non-TPF IC (n = 43); second cancer (n = 1). This left 106 biopsy-proven NPC patients treated with definitive IC (TPF) + CCRT (n = 58) or CCRT alone (n = 48). Pretreatment evaluation included patient history, physical and neurological examination, hematological and biochemical profiles, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the head and neck, fiberoptic nasopharyngoscopy, chest CT, ultrasound or CT of the abdomen, and bone scintigraphy. Other examinations and studies such as position emission tomography (PET) scans were performed at the treating physician's discretion. Comorbidity was assessed retrospectively by thoroughly reviewing patients' pre-treatment medical history. Patients with presence of one or more following conditions existing simultaneously were graded as 1: cardiovascular disease, diabetes mellitus, renal or hepatic insufficiency, previous malignant tumor; patients with none of the above comorbidities were graded as 0.

Radiotherapy

All patients had been referred to a multidisciplinary head and neck tumor board prior to treatment initiation. Patients received radiotherapy using three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT) techniques delivered at a median dose of 70 Gy (range 54–70 Gy) to the gross tumor volume of the primary site (GTV-T) and involved lymph nodes (GTV-N) in 35 fractions (range 27–35 fractions) at 5 fractions per week with a median overall treatment time of 50 days (range 39–81 days). A dose of 60 Gy and 50–54 Gy were delivered to the intermediate- and low-risk clinical target volume (CTV). The CTVs were each expanded using 3–5 mm margins to generate their respective planned target volumes.

Chemotherapy

IC with TPF regimen included docetaxel (75 mg/m^2 day 1) + cisplatin (75 mg/m^2 day 1) + 5-FU (750 mg/m^2/d day 1–5) every 3 weeks up to a total of 3 cycles.

For concurrent chemotherapy, carboplatin was used instead of cisplatin in patients with evidence of hearing impairment or reduced glomerular filtration rate. Forty-two (39.6%) patients were treated with 3-week cisplatin regimen: cisplatin (100 mg/m^2)/on days 1, 22, and 43 of radiotherapy, with a maximum of 3 cycles. Twenty-one (19.8%) patients were treated with weekly cisplatin regimen: cisplatin (40 mg/m^2) on day 1, repeated every week, with a maximum of 7 cycles. Thirty-seven (34.9%) patients were treated with weekly carboplatin regimen: carboplatin (AUC2) on day 1, repeated every week, with a maximum of 7 cycles. Four (3.8%) patients received concurrent cisplatin, detailed regimens unavailable. Two (1.9%) patients received concurrent carboplatin after 1 cycle of initial cisplatin due to increased creatinine and loss of hearing, respectively.

Follow-up

Patients were assessed 3 months after completion of treatment with physical examination and imaging studies and then every 3 months for 2 years, every 6 months until 5 years, and every year after 5 years. Evaluation at each follow-up visit included medical history, physical examination and nasopharyngoscopy. Head and neck MRI and cervico-thoracic CT were repeated alternatively every 6 months for 5 years. Further tests were done whenever there was any clinical indication.

Statistical analysis

Categorical variables between groups were compared using $\chi 2$ test or Fisher exact test, and continuous variables were analyzed using Student's *t*-test. Follow-up was estimated using the reverse Kaplan–Meier method. The survival rates were calculated using the Kaplan–Meier method and were compared using the log-rank test. Survival rates were defined as the time between the date of diagnosis and the first event. Events were death from any cause for OS, death or tumor progression for PFS, locoregional recurrence for loco-regional control (LRC), and distant metastasis for distant control (DC). Univariate analysis (UVA) was performed using a Cox proportional hazards model. Variables with a p value < 0.2 on UVA entered the multivariate backward elimination Cox regression for the multivariate analysis (MVA). T and N classification which were clinically highly relevant were included in MVA as well despite their p value > 0.2 on UVA. In the Cox model, continuous variables (PS, T, N, and age) were dichotomized. The age cut-off value for patient OS by receiver operating characteristic (ROC) curve was 51.5 years old (the sensitivity was 71.4% and the specificity was 66.7%), with an area of 0.72 (p = 0.003). Statistical analyses were performed using SPSS software, version 19 (SPSS Inc., Chicago, IL, USA). A two-tailed p values <0.05 were considered statistically significant.

Results

Patients

Patients' demographic and clinical characteristics are detailed in Table 1. Patients receiving IC + CCRT were younger (p = 0.01), had better performance status (p = 0.045) and more advanced disease (overall stage, p < 0.001) than the CCRT group. More patients in the IC + CCRT group received concurrent carboplatin instead of cisplatin (p = 0.01).

Treatment compliance

Fifty-four (93.1%) patients in the IC + CCRT group (n = 58) completed 3 cycles of IC. Three (5.2%) patients received 2 cycles instead of 3 because the planned RT time was due. One (1.7%) patient received 1 cycle because of cardio-vascular comorbidity.

For patients with concurrent chemotherapy details available, in the IC + CCRT group (n = 53), 49 (92.5%) patients completed 2–3 cycles of 3-weekly cisplatin or 6–7 cycles of weekly-cisplatin or carboplatin during CCRT. The corresponding numbers for the CCRT group (n = 47) was 42 (89.4%) patients (p = 0.73).

All but 1 patient in the IC + CCRT group completed RT to the prescribed dose. The remaining patient moved to another city despite doctor's suggestions when he received 54 Gy and did not complete the planned treatment. The mean RT duration was 49 days (range, 39–71) in the IC + CCRT group and 50 days (range, 39–81) in the CCRT group.