Oral Oncology 73 (2017) 118–123

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Long-term results of a phase II study of gemcitabine and cisplatin chemotherapy combined with intensity-modulated radiotherapy in locoregionally advanced nasopharyngeal carcinoma

Mingyao Wu, Dan Ou, Xiayun He*, Chaosu Hu

Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China
Department of Oncology, Shanghai Medical College, Shanghai, China

ARTICLE INFO

Keywords:
Gemcitabine
Cisplatin
Intensity-modulated radiotherapy
Nasopharyngeal carcinoma
Chemotherapy

Introduction

Two-thirds of nasopharyngeal carcinoma (NPC) patients who present with stage III-IVA-B are potentially eligible for curative chemoradiotherapy. In the 2DRT era, concurrent chemoradiotherapy (CCRT) was the standard treatment in locoregionally advanced NPC since the publication of the landmark Intergroup 0099 study [1]. Several subsequential clinical trials also confirmed the effectiveness of this treatment modality [2–4]. The current NCCN guidelines recommend that CCRT followed by adjuvant chemotherapy (AC) for locoregionally advanced NPC, originate from the results of these studies. However, the main concern about concurrent chemoradiotherapy is the unsatisfactory tolerance of the scheduled cycles of chemotherapy due to severe acute toxicities. Our previous phase III trials of comparing induction chemotherapy (IC) with CCRT combined with radiotherapy did not show improvements in overall survival at a median follow-up of 60 months; the 5-year overall survival (OS) rates were 75.5% and 79.4% in the CCRT + AC and IC + AC groups, respectively (P = 0.47, hazard ratio (HR) = 0.84, 95%CI 0.53–1.33). Higher rates of acute toxicities, including mucositis and vomiting, were noted in the C-CRT + AC group [5].

Intensity-modulated radiotherapy (IMRT) is a technique that facilitates the delivery of high radiation doses to the target while sparing the adjacent organs. All studies concerning the use of IMRT for the treatment of locoregionally advanced NPC demonstrated relatively better survivals and mild toxicities. The predominant cause of failure is distant metastasis after IMRT [6–8]. To the best of our knowledge, no published results of randomized trials are available to confirm the value of CCRT for locoregionally advanced NPC in the IMRT era. Wu et al. reported a prospective, multicentric clinical study in 249 patients with locoregionally advanced NPC who were treated by IMRT combined with concurrent chemotherapy. With a mean follow-up of 54.1 months, 52 patients developed distant metastases. Distant metastasis remained the main cause of treatment failures. Du et al. evaluated the efficacy and toxicity of induction-adjuvant chemotherapy using cisplatin, fluorouracil, plus docetaxel (TPF) combined with IMRT for locoregionally advanced NPC. The regime obtained promising outcomes with good compliance and well-tolerated toxicities [9]. Therefore, with the advent of IMRT, it is essential to determine the optimum chemotherapeutic modality to decrease distant metastasis and improve overall survival.

Gemcitabine is an analog of deoxycytidine, which inhibits DNA synthesis. The efficacy results and tolerable toxicity profiles of gemcitabine-containing regimens have been encouraging for metastatic and recurrent NPC treatment [10–12]. A head-to-head, randomized, phase III trial by Zhang et al. showed that gemcitabine plus cisplatin prolonged progression-free survival in patients with recurrent or metastatic nasopharyngeal carcinoma, compared with fluorouracil plus cisplatin [13]. Thus, the aim of our study was to evaluate the long-term outcome and late toxicities of combining a regime of cisplatin-gemcitabine chemotherapy with IMRT for locoregionally advanced NPC.

* Corresponding author at: Dongan Road 270, Fudan University Shanghai Cancer Center, Shanghai, China.
E-mail address: donganlu270hao@gmail.com (X. He).

http://dx.doi.org/10.1016/j.oraloncology.2017.08.016
Received 10 May 2017; Received in revised form 16 August 2017; Accepted 27 August 2017
Available online 01 September 2017
1368-8375/

Materials and methods

Patient selection

This phase II trial was conducted in our institution from September 2005 to October 2012 to evaluate the efficacy and tolerability of cisplatin-gemcitabine combination with IMRT for locoregionally advanced NPC. The study was approved by the ethical review board. Written informed consents were obtained from all of the participating patients prior to treatment.

Eligibility criteria included: WHO 2/3 pathology type, stage III, and IVA-IVB according to the 2002 American Joint Cancer Committee (AJCC) staging criteria, previously untreated NPC, 18–70 years old, Karnofsky Performance Status (KPS) ≥ 70, and adequate hematological, renal and hepatic functions.

Details of the staging workup, radiotherapy technique, modification of the chemotherapy dose, and follow-up assessment were described in our previous report [14]. The initial evaluation included chest X-ray or computed tomography (CT), liver ultrasonography or CT, magnetic resonance imaging (MRI) scans of the nasopharynx and upper neck, bone scintigram and nasopharyngoscopy. Additional investigations were performed only on those patients with suspicious findings. If deemed necessary, dental extractions were performed before radiation therapy. Patients were excluded if they had a history of other past or current neoplasms, previous chemotherapy or radiotherapy, uncontrolled infection, or a positive pregnancy test for women.

Chemotherapy

Patients received 2 cycles of IC: gemcitabine (1000 mg/m^2) administered intravenously for 30 min on days 1 and 8, and cisplatin (25 mg/m^2) infusion on days 1–3, repeated every 3 weeks. Two cycles of adjuvant chemotherapy (AC) was administered 28 days after completion of radiotherapy. The dosages of cisplatin and gemcitabine were reduced by 20% if grade 4 hematological toxicity appeared after the former cycle. Complete blood counts and liver and renal functions were assessed before each chemotherapy cycle.

Radiotherapy

IMRT with 6 MV X-ray began within 21 days after the start of the second cycle of IC. Contiguous slices 3–5 mm thick were obtained from the vertex to 2 cm below the clavicle. The gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV) and normal organs were outlined on all appropriate CT slices. GTV was defined as all known gross disease determined from imaging and clinical examinations. CTV included the whole nasopharyngeal cavity, anterior one-third of the clivus, pterygoid plates, parapharyngeal space, inferior sphenoid sinus, posterior one-third of the nasal cavity and the maxillary sinus, and drainage of the upper neck (levels II, III and Va) in N0 patients. In N1–N3 patients, levels IV and Vb were included. For T3 and T4 patients, the whole clivus and sphenoid sinus were covered. Normal tissues to be contoured included the spinal cord, brain stem, temporal lobe, eyes, lens, optic nerves, chiasm, parotid glands and larynx. The total dose to the PTVg (GTV with 0.5 cm margin) was 66–70.4 Gy in 30–32 fractions of 2.2 Gy each 5 days a week. The PTV60 (high-risk clinical target volume) covering the CTV and a 0.5 cm margin was prescribed 60 Gy. The PTV54 (low-risk clinical target volume with 0.5 cm margin) was prescribed 54 Gy.

Patient assessments and follow-up

Toxicities were assessed after each cycle of chemotherapy and weekly during radiotherapy. Tumor response assessment was performed after two cycles of IC. The size of the neck nodes was recorded clinically by palpation. After radiotherapy, response evaluation included physical examination, nasopharyngoscopy, and MRI scan of the nasopharynx and neck.

Response Evaluation Criteria In Solid Tumors (RECIST) was used for response evaluation of short-term treatment outcomes. National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Version 3.0 was used to evaluate chemotherapy-related toxicities. Radiotherapy-related acute and late toxicities were graded according to the Radiation Therapy Oncology Group (RTOG). Late toxicities were defined as those noted beyond 90 days from the start of radiotherapy.

After completing treatment, the patients were followed up every three months for 2 years, every 6 months for 3–5 years, and annually thereafter. Clinical and endoscopic assessments of the nasopharynx were performed during each follow-up visit, and X-ray or CT of the chest, ultrasonography of the abdomen and MRI scans of the nasopharynx and upper neck were performed once annually. Further investigations using CT/MRI or other tests were used whenever there was any clinical indication. Patients who developed recurrence or distant metastasis were recommended salvage re-irradiation, chemotherapy, or surgery.

Statistics

The results, including survival rates, locoregional failure-free rates and metastasis-free rates, were calculated from the start of treatment until the dates of death, recurrence, or metastasis. Survival rates were estimated using the Kaplan-Meier method. Differences in survival curves were calculated with log-rank tests. Statistical analyses were performed using SPSS software, version 20.0 (SPSS Inc., Chicago, IL, USA).

The 5-year overall survival (OS) rates for patients with stage III and IVA-IVB NPC treated with 2-dimensional radiotherapy were 60% and 45%, respectively [15,16]. We assumed that our treatment regimen would increase 5-year OS to 80% and 75% in stage III and IVA-IVB. For a significance level of 0.05 (one-side) with 80% statistical power for 5-year OS, 55 patients with stage III and 41 patients with stage IVA-IVB disease were required. Assuming a 10% drop-out or loss of follow-up, 61 patients with stage III and 46 patients with stage IVA-IVB disease were required.

Results

Patient characteristics

Between September 2005 and October 2012, a total of 112 patients with newly diagnosed, biopsy-proven, non-metastatic stage III and IVA-B NPC according to the AJCC 2002 staging system were eligible for enrollment in this study. All of the patients were treated in our institution. The patient characteristics are described in Table 1.

Compliance of chemotherapy

Of 112 patients treated with IC, 109 patients completed 2 cycles, 2 patients discontinued the regimen due to skin reactions (grade 3) and were treated with cisplatin and fluorouracil. One patient discontinued chemotherapy after 1 cycle due to liver function damage (grade 2) and was treated with radiotherapy after a 3-week rest period. Ninety-four patients finished 2 cycles of adjuvant chemotherapy, and ten patients completed only 1 cycle because of bone marrow suppression (7 patients), patients' refusal of chemotherapy (2 patients), and accidental bone fracture (1 patient). Eight patients were not administered adjuvant chemotherapy due to bone marrow suppression (3 patients), liver function damage (grade 2) (1 patient), skin reactions (2 patients), and other acute diseases, including gout or pancreatic diseases (2 patients).