Long-term survival of induction chemotherapy plus surgery and postoperative radiotherapy in patients with stage IV hypopharyngeal cancer

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This study was conducted to evaluate the safety, efficacy, and tolerability of induction chemotherapy plus surgery and postoperative radiotherapy in patients with stage IV hypopharyngeal cancer. The patients received two to three cycles of induction chemotherapy before surgery, with cisplatin (100 mg/m^2) by rapid intravenous (i.v.) infusion over 15–20 min on day 1, bleomycin (10 mg/m^2) on days 1 and 5, and 5-fluorouracil (800 mg/m^2/day) by continuous i.v. infusion on days 1 through 5, repeated every 21 days. Adjuvant radiotherapy was begun 4–6 weeks after surgery. From July 1999 to December 2004, a total of 52 patients were enrolled. After completion of two to three courses of induction chemotherapy, 22 cases of CR (complete response) and 16 cases of PR (partial response) in the primary site were confirmed, giving an overall response rate (ORR) of 73.1% [95% confidence interval (CI), 61.1–85.2%]. There were 17 CRs and 19 PRs in neck lymph nodes, giving an ORR of 69.2%. The combined primary tumor site and lymph node response was 17 CRs and 16 PRs, giving an ORR of 63.5% (95% CI, 50.4–76.6%). The median time to progression and overall survival for all the patients were 32 months (95% CI, 7.6–56.4 months) and 36 months (95% CI, 22.3–49.7 months), respectively. The estimate of time to progression and overall survival at 5 years was 24.5% (95% CI, 12.5–36.5%) and 35.9% (95% CI, 23.2–48.6%), respectively. In conclusion, induction chemotherapy plus surgery and postoperative radiotherapy is a treatment modality that is tolerated with encouraging activity and survival outcome in patients with stage IV hypopharyngeal cancer. *Anti-Cancer Drugs* 21:872–876 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Hypopharyngeal cancers are often presented at an advanced stage at diagnosis and are therefore associated with poor prognosis [1]. Tumors in the hypopharynx are often thought to pursue a particularly aggressive course. They are rarely found at the early stage when they are small and localized to the site of the primary lesion. More frequently, the patient is not aware of the problem until the tumor is large and obstructive symptoms or pain occurs. Submucosal spread is a characteristic feature, as is cervical lymph node metastasis and direct invasion of adjacent structures in the neck [2–4]. By the time the diagnosis is made, more than 50% of patients have cervical metastasis [2]. As diffuse lymphatic spread seems to be an early event, control of the disease is predictably low.

Surgery with postoperative adjuvant radiotherapy (RT) has long been the standard treatment for patients with advanced hypopharyngeal carcinoma, with 5-year survival reportedly varying between 18 and 50% [1,2,5–7]. For the purpose of improving survival and preserving organ function, a combination of neoadjuvant chemotherapy (CTx) and RT has been under study for the management of advanced head and neck cancer [7,8]. The rationale for the use of neoadjuvant CTx includes better drug delivery, improved tolerance and compliance with optimal doses of CTx, reduction of tumor size, and higher chances of cure [9]. On the basis of these favorable results, we conducted the present phase II study to evaluate the safety, efficacy, and tolerability of induction CTx plus surgery and postoperative RT in patients with stage IV hypopharyngeal cancer.

Patients and methods

Patient selection

Patients with histologically confirmed squamous cell carcinoma of the hypopharynx were eligible for this study. They were also required to have resectable stage IV disease without distant metastases according to the staging system of the American Joint Committee on Cancer 1997 [10], to have had no earlier treatment, to be below 80 years of age, to have an Eastern Cooperative Oncology Group performance status of 0–2, and to have adequate hematological function (white blood cell count 4000–12 000/mm^3; neutrophils $\geq$ 2000/mm^3; platelets

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$\geq 100\,000/mm^3$; hemoglobin ≥ 9.0 g/dl), adequate hepatic function (total bilirubin < 1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase < 60 IU/l), and adequate renal function (creatinine ≤ 1.2 mg/dl, creatinine clearance ≥ 60 ml/min). Patients with active infection, severe heart disease, uncontrollable hypertension or diabetes mellitus, active concomitant malignancy and pleural, and/or pericardial effusion requiring drainage were excluded. All patients were initially evaluated by a multidisciplinary team. The evaluation included medical history, clinical examination, flexible fiber-optic nasopharyngoscopy with photographic recording, complete blood cell count, complete blood chemistry, head and neck computed tomographic (CT) scan or magnetic resonance imaging, chest X-ray, bone scan, and liver echography. The institutional review board of the authors' institution approved the protocol, and written informed consent was obtained from all patients before enrollment.

Induction chemotherapy

The CTx regimen consisted of cisplatin (100 mg/m^2) by rapid intravenous infusion over 15–20 min on day 1, bleomycin (10 mg/m^2) on days 1 and 5, and 5-fluorouracil (5-FU) (800 mg/m^2/day) by continuous intravenous infusion on days 1 through 5, repeated every 21 days. Cisplatin infusion was preceded by hydration with 1000 ml of 0.9% sodium saline. Mannitol (40 g) was given concurrently with cisplatin infusion. After cisplatin infusion, 2000 ml of 0.9% sodium saline containing 40 mEq of potassium chloride was given. All the patients received antiemetic prophylaxis consisting of 5-hydroxytryptamine-3 receptor antagonists and 20 mg of dexamethasone.

CTx was delayed by a week in case of myelosuppression until leukocyte counts were greater than $3000/mm^3$ and platelet counts were greater than $100\,000/mm^3$. The dose of 5-FU was reduced by 25% if severe stomatitis or diarrhea developed. The dose of cisplatin was adjusted according to the value of creatinine after the last course. If serum creatinine was less than 1.5 mg/dl or if creatinine clearance was greater than or equal to 60 ml/min, no dose adjustment was required. If the serum creatinine increased from 1.5 to 2 mg/dl or creatinine clearance was between 40 and 59 ml/min, cisplatin was reduced by 50% for the next course. If the serum creatinine was greater than 2 mg/dl or creatinine clearance was less than 40 ml/min, no further cisplatin was given. No cisplatin was administered until complete recovery from renal toxicity occurred. In this trial, the criteria used for giving two or three cycles of CTx included the tumor response and the patient's tolerance. At the end of two cycles, patients who tolerated CTx well and had at least partial response (PR) were given one more cycle of CTx followed by surgery. Further CTx was omitted for patients who did not satisfy these criteria.

Surgery

Surgery consisted of total laryngectomy with partial or total pharyngectomy and esophagectomy with flap reconstruction as indicated. Unilateral or bilateral radical neck dissection was also performed. Pathology reports were reviewed for evidence of grade, surgical margins, perineural invasion, vascular space invasion, necrosis, lymph nodes involved, and extracapsule extension.

Postoperative radiotherapy

Adjuvant RT was begun 4–6 weeks after surgery. The radiation therapy technique consisted of three fields: two opposing lateral fields encompassing the primary tumor bed and upper cervical nodes, and one anterior lower neck field to treat the lower cervical nodes and/or tracheostomy stoma. Radiation therapy was given postoperatively to a total dose of 6120–7560 cGy according to pathological risk features (6120 cGy in patients with complete resection without nodal involvement, 6840 cGy in patients with complete resection with nodal involvement but without extracapsular extension, and 7560 cGy in patients with positive surgical margins or extracapsular extension of nodal disease). The initial dose (3960 cGy) was administered using a conventional three-field technique, followed by a boost of 2160–3600 cGy using a three-dimensional conformal treatment planning system (Clinac 600C; Varian Associates Inc., Palo Alto, California, USA). The spinal cord was shielded after the initial 40–43 Gy and posterior neck strips were irradiated with 9–12 MeV electron beams thereafter. RT was delivered at 1.8 Gy/day for 5 consecutive days by a linear accelerator (Clinac 1800; Varian Associates Inc), 6 MV at 320 cGy/min, with patients lying supine with a mask. The spinal cord dose was limited to 45 Gy.

Response to treatment and adverse effects

The primary endpoint of this study was response rate (RR) and secondary objectives were toxicity, time to progression (TTP), and overall survival (OS). After two cycles of induction CTx, response was evaluated by CT scans according to Response Evaluation Criteria in Solid tumors criteria. Of the lesions observed before treatment, a maximum of five measurable lesions from each metastasized organ up to a total of 10 lesions were selected as target lesions. In cases of PR or complete response (CR), a confirmative CT scan was performed 4 weeks later. Responses at the primary site and the regional nodes were scored separately, and the overall response was based on the worst of the two responses. Toxicity was reported using a National Cancer Institute–Common Toxicity Criteria version 2.0 toxicity scale. Radiation toxicity was graded according to the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group toxicity scale criteria. Tumor-related symptoms were assessed at baseline and before each cycle.

Statistical analysis

This trial used a two-stage optimal design, as proposed by Simon [11], with an 80% power to accept the hypothesis and 5% significance to reject the hypothesis. This trial was designed to detect a RR of 60% compared with a minimal, clinically meaningful RR of 40%. Allowing for a follow-up loss rate of 10%, the total sample size was 52 patients with a measurable disease. All the patients who were enrolled were included in the intention-to-treat analysis of efficacy. TTP and survival analyses were all estimated using the Kaplan–Meier method. The TTP was calculated from the initiation of treatment to the date of disease progression, whereas OS was measured from the initiation of treatment to the date of the last follow-up or death. The statistical data were obtained using an SPSS Software package (SPSS 11.5 Inc., Chicago, Illinois, USA).

Results

Patient characteristics

From July 1999 to December 2004, a total of 52 patients were enrolled in this study. The characteristics of the patients are summarized in Table 1. The median age was 57 (range, 34–78) years, with 42 male and 10 female patients. The site of origin was sinus piriformis in 38 (73.1%), postcricoid area in 5 (9.6%), and postpharyngeal area in 9 patients (17.3%).

Tumor response to induction chemotherapy

The responses to induction CTx are listed in Table 2. Of the 52 patients, 50 (96.2%) were assessable for response, of the two patients not assessable, both were lost to follow-up after the first cycle of treatment. All efficacy data are reported using the intent-to-treat patient population. After the completion of two to three courses of induction CTx, 22 cases of CR and 16 cases of PR in the primary site were confirmed, giving an ORR of 73.1% [95% confidence interval (CI), 61.1–85.2%]. There were 17 CRs and 19 PRs in the neck lymph nodes, giving an ORR of 69.2%. The combined primary tumor site and lymph node response was 17 CRs and 16 PRs, giving an ORR of 63.5% (95% CI, 50.4–76.6%).

Table 1 Patient characteristics

Characteristics	Number of patients, *n* (%)
Patients enrolled	52
Sex	
Male	42 (80.7)
Female	10 (19.2)
Age at diagnosis (years)	
Median (range)	57 (34–78)
ECOG performance status	
0	40 (76.9)
1	10 (19.2)
2	2 (3.8)
Primary tumor site	
Sinus piriformis	38 (73.1)
Postcricoid area	5 (9.6)
Postpharyngeal area	9 (17.3)
Tumor stage	
1	6 (11.5)
2	10 (19.2)
3	11 (21.2)
4	25 (48.1)
Node stage	
1	9 (17.3)
2	19 (36.5)
3	24 (46.2)

ECOG, Eastern Cooperative Oncology Group.

Table 2 Tumor response to induction chemotherapy (intention-to-treat analysis, *n*=52)

Response	Primary tumor site, *n* (%)	Neck lymph nodes, *n* (%)	Primary tumor site + neck lymph nodes, *n* (%)
Overall response rate	38 (73.1)[a]	36 (69.2)[b]	33 (63.5)[c]
Complete response	22 (42.3)	17 (32.7)	17 (32.7)
Partial response	16 (30.8)	19 (36.5)	16 (30.8)
Stable disease	8 (15.4)	9 (17.3)	8 (15.4)
Progressive disease	4 (7.7)	5 (9.6)	9 (17.3)
Not assessable	2 (3.8)	2 (3.8)	2 (3.8)

[a]95% confidence interval (CI)=61.1–85.2%.
[b]95% CI=56.7–81.8%.
[c]95% CI=50.4–76.6%.

Induction chemotherapy toxicity

A total of 139 cycles were administered in 49 patients assessable for toxicity. The occurrence and the incidence of the hematological and nonhematological toxicities are shown in Table 3. The most severe hematological adverse event was anemia, which occurred with grade 3 intensity in two (4.1%) patients and grade 4 in one (2.0%) patient. Neutropenia occurred with grade 3 intensity in two (4.1%) patients. However, no grade 4 neutropenia was observed. Nausea/vomiting, diarrhea, and hair loss were the most common nonhematological toxicities. Grade 1/2 nausea/vomiting, diarrhea, and asthenia were observed in 23 (46.9%), 17 (34.7%), and 15 (30.6%) patients, respectively. In addition, grade 3 nausea/vomiting and diarrhea were observed in five (10.2%) and one (2.0%) patients. Yet, no grade 4 nonhematological toxicity was observed. There were no treatment-related deaths during this study.

Surgery and postoperative radiotherapy

After induction CTx, there were 38 (77.6%) patients who underwent total laryngectomy and 11 (22.4%) patients who underwent partial laryngectomy. Eleven patients needed to undergo reconstruction because of local extensive invasion, eight patients needed reconstruction with a pectoralis major myocutaneous flap, two patients were reconstructed with a forearm flap, and one was reconstructed with a anterolateral thigh flap. All patients underwent radical neck dissection. Of the 22 patients, seven with clinical CR after induction CTx were confirmed to have residual cancer cells, another 15 had pathological CR. Postoperative complications included local wound infection in 10 (20.4%) patients, aspiration pneumonia in one (2.0%), and fistula in one (2.0%).

Table 3 Toxicity with induction chemotherapy (by patients, $n=49$)

	Grade[a], *n* (%)			
	1	2	3	4
Hematologic				
Anemia	11 (22.4)	8 (16.3)	2 (4.1)	1 (2.0)
Neutropenia	9 (18.4)	7 (14.3)	2 (4.1)	0 (0)
Thrombocytopenia	5 (10.2)	3 (6.1)	0	0
Nonhematologic				
Nausea/vomiting	14 (28.6)	9 (18.4)	5 (10.2)	0
Diarrhea	12 (22.5)	5 (10.2)	1 (2.0)	0
Hair loss	11 (22.4)	4 (8.2)	0	0
Asthenia	5 (10.2)	3 (6.1)	0	0
Edema	3 (6.1)	1 (2.0)	0	0
Neuropathy	6 (12.2)	2 (4.1)	0	0
Skin reaction	3 (6.1)	1 (2.0)	0	0
Pneumonia	3 (6.1)	1 (2.0)	0	0

[a]National Cancer Institute-Common Toxicity Criteria version 2.0 toxicity scale.

Final histological analysis showed positive margins in four (8.2%) patients. Postoperative radiation was used in 49 patients. The median postoperative dose was 6450 cGy (range, 5800–7200 cGy); only four patients received less than 6000 cGy.

Patterns of failure and survival

The median follow-up period was 70.5 months (range, 61.5–110.5 months). At the time of evaluation, the rates of local and regional failures were 28.6% (14 of 49) and 20.4% (10 of 49), respectively. Seven (12.3%) patients developed distant metastasis. Relapses were treated with surgery, RT, CTx, or combined treatment. The median TTP for all patients was 32 months (95% CI, 7.6–56.4 months). The estimated median OS was 36 months (95% CI, 22.3–49.7 months; Fig. 1). The estimate of TTP and OS at 5 years was 24.5% (95% CI, 12.5–36.5%) and 35.9% (95% CI, 23.2–48.6%), respectively.

Late toxicity

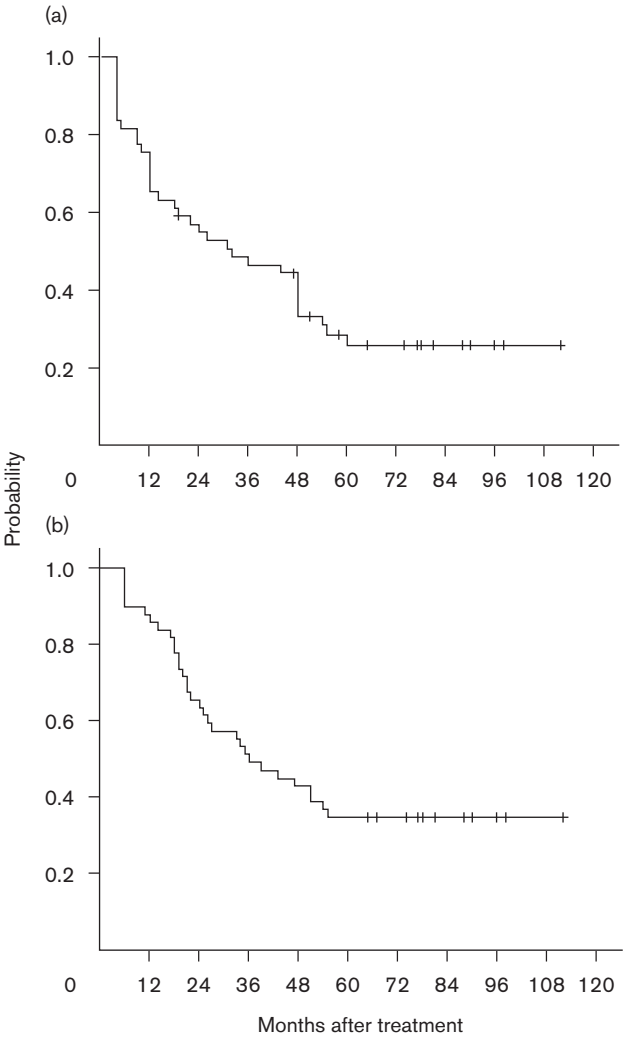
The most commonly observed late effect was xerostomia. A total of 69.2% patients had grade 1/2 xerostomia, at 3 months, but the severity diminished over time, and the detectable xerostomia at 24 months was 11.5%. No grade 3/4 xerostomia was detected. No patients were discontinued from the study because of toxic effects.

Discussion

Cancer of the hypopharynx carries with it one of the worst prognoses of all the cancers of the head and neck [12]. Neither earlier single treatment nor combined treatments within the recent 10 years had good-enough therapeutic effects on advanced stage hypopharyngeal cancer, with the reported survival rate of less than 40% [5,13,14].

This phase II trial using cisplatin, bleomycin, and 5-FU as induction CTx in stage IV hypopharyngeal cancer showed that it is generally well tolerated. The most common toxicities were anemia, neutropenia, and nausea/vomiting.

Fig. 1



Time to disease progression (a) and overall survival (b) for all patients.

A 6.1% incidence of anemia grade greater than or equal to 3 was comparable with rates in the literature in which cisplatin, bleomycin, and 5-FU were used [15,16]. The ORR of 63.5% with induction CTx in this study was not as good as the rates achieved in the earlier published studies of 68–77.1% [17–19]. However, our study enrolled a higher proportion of patients with stage IV (100%) than in the other studies (51.4–83%) [17–19]. This may account for the lower RR seen in our study.

Induction CTx is one of the commonly adopted chemotherapy methods to treat head and neck carcinoma. It is used to improve local control rate, decrease distant metastasis rate, and thus improve the OS rate. Induction CTx can kill potential preclinical tumor including distant metastases. In advanced stage hypopharyngeal carcinoma cases, although the obvious local infiltration is considered to have safe excise edge by doctors, minor submucous

infiltration may exist. Kraus *et al.* [5] reported that 18% of hypopharyngeal carcinoma patients with a negative excised edge had minor submucous infiltration leading to local recurrence, compared with 20% as reported by Ho *et al.* [14]. On the basis of published data, most researchers believe that induction CTx cannot improve the local restriction rate of late-stage hypopharyngeal carcinoma [20–22]. However, a few researchers believe that induction CTx can reduce distant metastasis rate to some small extent [23,24]. Besides local control, the survival rate for hypopharyngeal cancer is quite poor because of distant metastasis. The reported frequency of distant metastases in patients with locally advanced hypopharyngeal carcinoma is more than 40% [12]. The incidence of distant metastases was 12.3% in this study, suggesting that this may be an effective strategy. However, it needs to be confirmed by a large-scale, prospective randomized trial in further study.

Another purpose of the application of induction CTx is to improve organ preservation rate. The rate of laryngeal preservation is considered to be one of the most important aspects when treating advanced hypopharyngeal carcinoma. Induction CTx can retain the preservation of larynx function by decreasing the size of the primary tumor and lowering clinical stage, while sustaining the survival rate [7,8]. Kraus *et al.* [5] retrospectively reviewed 132 patients who underwent surgery and postoperative RT for squamous cell carcinoma of the hypopharynx. They reported 5-year OS rates and disease-free survival rates of 30 and 41%, respectively. In our study, 5-year overall survival rates were 35.9%, which shows comparable results, considering that all cases with stage IV hypopharyngeal cancer were in this study, whereas patients with stage III were also enrolled in most of the other studies [5,25].

In conclusion, induction CTx plus surgery and postoperative RT is a treatment modality that is tolerated with encouraging activity and survival outcome in patients with stage IV hypopharyngeal cancer.

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