Induction Chemotherapy Followed by Radiotherapy in Patients with Cervical Lymph Node Metastases from Unknown Primary Carcinoma

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Abstract Cervical metastases from unknown primary tumors are rare and no clear therapeutic options are available. This study was performed to assess the efficacy and safety profiles of induction chemotherapy followed by radiotherapy in patients with cervical lymph node metastases from unknown primary cancer. Patients with histological diagnosis of cervical lymph-node metastasis from carcinoma with an unknown primary cancer underwent induction chemotherapy followed by radiotherapy. All patients had squamous cell carcinoma. Induction chemotherapy consisted of 3–4 cycles every 3 weeks of docetaxel (day 1.70 mg/m²) and cisplatin (day 1.75 mg/m²). Radiation therapy (RT) was started with in 10 weeks of the last cycle of chemotherapy, and it was administered 5 days per week. It was given in daily fractions of (1.8) Grays (Gy) of 2 Gy and the total dose to the primary tumor was 70–74 Gy. Neck dissection was reserved for residual disease after definitive radiotherapy. Overall survival, recurrent free survival, and locoregional control were calculated using the Kaplan–Meier method. Twenty one patients with an unknown primary cancer underwent induction chemotherapy and radiotherapy. After induction chemotherapy, 6 patients achieved CR and 8 patients achieved PR. The overall response rate after radiation, was 90.4 % (19 of 21

patients). Neutropenia and infection were the most common grade 3–4 adverse event during induction chemotherapy. Mucositis and dermatitis were the most common grade 3–4 toxicities during radiotherapy. With a median follow-up of 50.6 months, the estimated 2 years OS rates were $71 \pm 6 \%$, respectively. The median OS was 42 months (95 % confidence interval CI 8–65 months). The recurrent-free survival rate at 2 years was 57 %, respectively. In the patients with responder to induction chemotherapy, superior relapse free survival and overall survival rate observed. No occurrence of primary cancer was observed during the follow-up period. Induction chemotherapy followed RT for unknown primary cancer has provided good overall and disease-free survival in all the patients with an acceptable rate of complications. The use of induction chemotherapy and radiation therapy for more advanced disease led to good clinical results with reasonable toxicities.

Keywords Head and neck cancer ·
Lymph node metastasis · Unknown primary ·
Induction chemotherapy

Introduction

Cervical lymph node metastases of squamous cell carcinoma from unknown primary (CUP) represent about 5 % of all head and neck cancers [1–3]. Because of the lack of evidence from randomized studies and the early closing of the only randomized study proposed by the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group, the standard therapy has not been identified yet. Historically, lymph node dissection with or without postoperative irradiation was the mainstay

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of therapy. Recently, combined-modality treatment with chemotherapy and radiation therapy (RT) has become the standard of care for advanced head-and-neck disease because of the greater survival rates [4], but most clinical trials of concurrent chemoradiotherapy (CCRT) have shown increased toxicities such as mucositis and dermatitis [5]. As a result, CCRT causes a greater reduction of dose intensity and more common interruption of treatment than that for sequential treatment. Moreover, induction chemotherapy (ICT) has shown benefit in locally advanced head and neck cancer by reducing tumour size and micrometastases before definitive RT [6]. Cisplatin-based ICT induces response rates of 80–90 %, with complete response (CR) rates of 20–40 % in locally advanced squamous cell head and neck cancer and decrease occult primary cancer [7].

This study was performed to determine the effectiveness of induction chemotherapy and radiotherapy and evaluate the toxicity of induction chemotherapy and radiotherapy in patients treated for neck lymph node metastases from an unknown primary cancer.

Materials and Methods

Patient Evaluation and Staging

We retrospectively identified and reviewed the medical records of all patients with cervical node squamous cell carcinoma (SCC) metastases from an unknown primary site who underwent induction chemotherapy and radiotherapy. The pretreatment evaluations consisted of a complete history and physical examination, including direct laryngoscopy with fiberoptic endoscope, panendoscopy under general anesthesia, and biopsy of the enlarged lymph node and suspicious pharyngeal mucosal sites. All the patients underwent diagnostic tonsillectomy, if the tonsils were still in place. The patients typically underwent a complete blood count, biochemical profile, chest radiography, computed tomography (CT) and/or magnetic resonance imaging, and positron emission tomography.

Treatment

Docetaxel was administered at a dose of 70 mg/m² over 1 h, followed by hydration with a 2 h infusion of 1,000 ml normal saline. Afterward, cisplatin was given at 75 mg/m². Prophylactic corticosteroids were given with each dose of docetaxel to minimize the hypersensitivity reaction and peripheral edema. The induction chemotherapy consisted of two cycles. If a response was recognized (complete response, CR or partial response, PR),

then they received one more course of chemotherapy before undergoing the radiotherapy. Dose adjustments were permitted for both drugs according to the specific toxicities as noted in previous studies [7–9]. Colony stimulating factor was given for treating patients with grade 4 neutropenia or febrile neutropenia, for which there was a 25 % subsequent dose reduction of both drugs. Complete blood counts were performed weekly and follow-up physical examinations, serum biochemistry, urine analysis and evaluation of the local findings were performed before each cycle of chemotherapy. CT or MRI scan and laryngoscopy were performed after the second cycle. Toxicity was graded according to the NCI-CTC version 4.0 criteria and the treatment response was assessed by the RECIST criteria. The radiation dose administered to the involved lymph nodes received 70–74 Gy (2 Gy per day, 5 days per week). Uninvolved lymph nodes were treated with at least 50 Gy. After completion of definitive RT, a planned neck dissection was offered to the patient if residual disease was confirmed either clinically or radiologically.

The patients with locoregional failure or death resulting from cancer were excluded from the assessment of toxicities. Early and late toxicities were evaluated according to the common terminology criteria of adverse events, version 4.0. Statistical analysis was performed using the statistical package for social sciences, version 17.0.1 (SPSS, Chicago, IL). Disease free survival, overall survival (OS), and locoregional control, distant relapse were calculated using the Kaplan–Meier method. Survival was calculated from the date of the last day of RT to the date of death from any cause for OS and from the date of the first event (local, regional, or distant relapse, second primary, or death from any cause) for disease-free survival.

Results

Patients and Staging Evaluation

All patients had squamous cell carcinoma. Of the 21 patients who underwent treatment, most patients had Karnofsky performance score 100, most lymph node stage N2, N3. Of the 21 patients, 16 were men and 5 were women, with a median age of 65 years old. The patient characteristics are listed in Table 1.

Efficacy and Survival

After two cycles of induction chemotherapy, 6 patients achieved CR and 8 patients achieved PR. The overall response rate after radiation was 90.4 % (19 of 21 patients). Neck surgery was performed in 2 patients with

Table 1 Patients characteristics

Characteristic	Value
Gender	
Male	16
Female	5
Age	
Median	65
Range	42–76
KPS at presentation	
100	13
90	6
80	2
70	0
N stage	
N2a	5
N2b	5
N2c	6
N3	5
Smoking history	
Yes	18
No	3

KPS Karnofsky performance score

persistent disease: 1 remained tumor-free, whereas the other experienced disease recurrence in the neck and lungs 7 months after neck dissection. With a median follow-up of 50.6 months, the estimated 2 years OS rates were $71 \pm 6\%$, respectively. The median OS was 42 months (95 % confidence interval CI 8–65 months). The recurrent-free survival (RFS) rate at 2 years was 57 %, respectively. In the patients with responder to induction chemotherapy, superior relapse free survival and overall survival rate observed (Fig. 1). Among 11 patients who showed recurrence, 7 patients presented locoregional recurrence, 4 patients developed distant metastasis. No occurrence of primary cancer was observed during the follow-up period.

Toxicity of Chemotherapy and Radiotherapy

The toxicities are listed in Tables 2 and 3. A total of 59 cycles of chemotherapy were analyzed. Five patients required a delay of their scheduled chemotherapy by a mean of 1 week due to myelosuppression ($n = 3$), fatigue ($n = 2$) and a dose reduction of docetaxel by 25 % was done for 8 patients. The median dose intensity of docetaxel was $25.1 \text{ mg/m}^2/\text{week}$ and the median dose of cisplatin was $23.8 \text{ mg/m}^2/\text{week}$. The mean relative dose intensity for docetaxel and cisplatin was 0.94 (range 0.7–1.0) and 0.95 (range 0.7–1.0), respectively. Granulocyte-colony stimulating factor was administered to 6 patients. The main adverse events were hematologic toxicity. The most common toxicity of $\geq$ grade 3 was neutropenia,

Fig. 1 Survival of patients according to response of induction chemotherapy (ICT)

which occurred in 6 patients and 4 of these patients had febrile neutropenia. The neutropenia was reversible. The median time to the nadir of neutropenia was 9 days (range 5–15 days). The median recovery time to grade 0 was 8 days (range 4–15 days). There was no treatment-related death.

The non-hematologic toxicities were generally tolerable. In all patients who underwent radiotherapy, we observed mucositis and dermatitis as the two most frequent early complications, respectively. Five patients required hospitalization for an average of 16 days, in most cases for

Table 2 Toxicity of chemotherapy

Toxicity	G1	G2	G3	G4
Hematologic				
Neutropenia	5	2	6	1
Anemia	8	3	0	0
Thrombocytopenia	8	3	1	0
Non-hematologic				
Nausea/vomiting	8	2	3	0
Fatigue	9	2	3	0
Anorexia	9	4	1	0
Neurotoxicity	10	4	0	0
Stomatitis	7	3	1	0
Diarrhea	8	3	1	1
Renal toxicity	6	3	1	0

Table 3 Early complications of radiotherapy

Complication	Value
Mucositis	
Grade 1–2	8
Grade 3	5
Grade 4	0
Dermatitis	
Grade 1–2	9
Grade 3	2
Grade 4	0
Nausea	
Grade 1–2	10
Grade 3	2
Grade 4	0
Hospitalization	8
Mean duration (days)	16
Death (<30 days after treatment)	0 (0)
Weight loss	
Mean (kg)	6.88
Relative (%)	8.4
Range (kg)	1.5–15.2

radiation-induced toxicities (i.e., dehydration, neutropenia, pneumonia, and acute renal failure). The mean weight loss was 6.88 kg (range 1.5–15.2), which represented a mean decrease of 8.4 % compared with their weight at the beginning of RT.

Discussion

To date, no clear consensus has been reached on the management of cervical lymph node metastasis from UPC. The main goal of the present study, therefore, was to

review the outcomes and toxicities of induction chemotherapy and radiotherapy for patients with UPC treated with curative intent at our center. For UPC patients with the unfavorable factors include higher neck stage, extracapsular invasion, advanced stage and the presence of recurrent or residual disease after primary treatment, advanced stage, chemotherapy and radiotherapy plays a major role [8, 9]. Combined modality treatment with concurrent chemotherapy and RT was shown to significantly improve the outcomes of those with locally advanced head-and-neck cancer [10–13]. CCRT improves survival over RT, generally attributed to improved locoregional control (LRC). However, little impact of CCRT on distant metastases has been observed [14]. ICT can reduce metastases incidence [15], and cisplatin-based ICT decreases the incidence of occult primary disease compared with RT [16, 17]. There are other advantages of induction chemotherapy, particularly valued in the setting of unresectable disease. The likelihood that a high-dose RT volume would embrace all viable tumor cells is increased after marked gross tumor shrinkage often achieved by induction chemotherapy. This could be of critical importance in high-volume tumors, in which the margin added to the gross target volume to cover microscopic tumor extensions is often compromised in an attempt to reduce the risk of excessive RT toxicity. Also, a rapid reduction in tumor mass during induction chemotherapy can diminish airway obstruction, dysphagia, and pain, thus effectively reducing the need for tracheostomy and improving the nutritional status before the patient enters a more aggressive concomitant phase of the treatment protocol [18]. Finally, tumor response to induction chemotherapy was recognized as the most reliable in vivo assay of chemo/Radiosensitivity [19]. In this study showed overall survival of responder to ICT is better than non-responder to ICT. The survival rates of patients with oropharyngeal cancer who are HPV-positive have been reported to be greater than those who do not have HPV [20]. To determine whether the improvement in outcomes was more closely linked to HPV-positive disease, we are obtaining the pathologic specimens of all patients in the present study for an analysis of HPV status in a future report.

In the setting of UPC, limited experience with induction chemotherapy and RT is available in published studies [21]. In published study group, fifteen patients received three cycles of induction chemotherapy with the combination of docetaxel and cisplatin. Patients were subsequently treated with extended-field radiotherapy. Three complete responses were observed after induction chemotherapy and 13 after the chemoradiation treatment. The overall response rate after radiation, was 93.3 % (14 of 15 evaluable patients). One year disease-free-survival was 83.3 % (10 of 12 evaluable patients). Treatment was well-

tolerated. In the present study, no life-threatening complications were observed. However, grade 3 neutropenia during induction chemotherapy and grade 3 mucositis and dermatitis toxicities were present by the end of treatment. In terms of chemotherapy or radiation induced toxicities, we did not observe any grade 4 acute or chronic toxicities.

The limited number of patients and limited time of follow-up requires additional validation with prospective studies and a larger population. However, the present series has contributed to the small number of published patients with UPC treated with induction chemotherapy and radiotherapy.

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