High Efficacy of Chemoradiation Therapy Sensitized by Weekly Docetaxel for Anaplastic Thyroid Cancer

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Abstract. *Background: Although rare, treatment of anaplastic thyroid carcinoma (ATC) is very difficult due to its aggressiveness and resistance to therapeutic efforts. Patients and Methods: We reviewed outcomes for six patients who underwent a unique chemoradiotherapy regimen consisting of external irradiation (45 to 60 Gy) combined with concurrent low-dose weekly docetaxel administration at 10 mg/m^2. Results: The scheduled treatment was completed and showed local disease control in all patients. Two patients showed complete response lasting for 166 and 257 days, three patients showed partial response for 58, 107 and 194 days, and one showed stable disease for 382 days. Overall, patients treated with this chemoradiotherapy survived from 86 to 1,901 days with additional systemic chemotherapy. No toxicities over grade 3 were observed. Conclusion: This chemoradiotherapy is useful for locoregional control of ATC, while offering acceptable toxicity. The effect lasted temporally but long enough to maintain patients' quality of life for this highly aggressive malignancy.*

Although uncommon, anaplastic thyroid carcinoma (ATC) is one of the most aggressive malignancies in humans. The prognosis remains very poor even after multimodal therapy, and the median overall survival has been reported to be less than six months (1, 2). Most cases exhibit resistance to these exploratory therapeutic efforts. Although several guidelines have been published, there is no clear scientific evidence indicating appropriate therapy for this disease, nor is there any effective management strategy available (3-6). Several clinical trials have investigated novel therapeutic regimens or newly- established drugs to control metastatic disease (1, 7). Effective management for local control, to avoid suffocation and dysphagia, is still an open question (8, 9).

Since 2002, we have been using chemoradiotherapy (CRT) utilizing the radiosensitizing and biochemistry-modulating effects of docetaxel (10), as a part of multimodal therapy for patients with ATC with incomplete local control after surgery, and found considerably high efficacy without severe adverse events. The present report reviewed the outcomes of six patients with ATC who underwent this CRT.

Patients and Methods

We reviewed the medical records of six patients (five men, one woman) with ATC treated with CRT at the Osaka City University Hospital between 2002 and 2012. Clinical characteristics of the six patients are shown in Table I. The present study was approved by the Institutional Ethics Committee (#2444). The median age at the time of CRT was 69 years (range=60-74 years). All patients were histologically confirmed as having ATC. Performance status was 0 in four patients and 1 in two patients. Disease in five patients was considered inoperable. Scheduled CRT was completed in all patients.

The CRT regimen consisted of external-beam radiation therapy (EBRT; total dose of 45-60 Gy at 2 Gy/once a day; the dose was determined by the skilled radiologist according to the characteristics of the tumor and the patient) combined with concurrent low-dose docetaxel administration at 10 mg/m^2 on day 1 each week during the course of EBRT (10). Therapeutic effects were evaluated by computed tomography within two weeks of CRT, and at an interval of for to six weeks thereafter.

One patient (case 4) received additional CRT to a metastatic tumor of the right thigh, and another four patients received one to 13 courses of additional chemotherapy (weekly docetaxel 25 mg/m^2 for one course in case 6, for five course in case 2 and 5, bi-weekly docetaxel 25-40 mg/m^2 for 13 courses in case 1) in the outpatient unit.

Effects and adverse events of CRT were analyzed according to the Response Evaluation Criteria in Solid Tumors version 1.1 definitions and Common Terminology Criteria for Adverse Events version 4.1, respectively (11, 12). Duration of the effect was calculated from the date of CRT termination until that of disease progression, confirmed either clinically or imaging. Duration of survival was calculated from the date of diagnosis of ATC until the date of death.

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Table I. *Characteristics of the patients, and the results of chemoradiation therapy (CRT).*

Case no.	Age (years), gender	T	N	M	Primary/ anaplastic change	Treatment before CRT	PS	Radiation dose (Gy)	Maximal local response	Days to progression	Survival (days)	Cause of death
1	74 M	4b	1b	0	Primary	Total Tx, EP	0	60	CR	257	1901	Cachexia
2	68 M	4b	1b	0	Primary	EP, biopsy (LN)	0	56	SD	382*	483	Cachexia
3	60 M	4b	0	1 (Lung)	Anaplastic change at the locally recurrent tumor around the tracheotomy	Laryngectomy for PTC 2 years earlier	1	60	PR	107*	128	Cachexia
4	74 M	4b	1b	0	Anaplastic change at the locally recurrent tumor at the contralateral lobe	Lobectomy for PTC 5 years earlier	0	45	CR	166*	188	Cachexia
5	70 F	4b	1b	0	Primary	None	1	45	PR	142	320	Bleeding
6	64 M	4b	1b	0	Primary	None	0	60	PR	58	86	Cachexia

*Maximal effect lasted until the time the patient died. M: Male, F: Female, Tx: Thyroidectomy, EP: A combination chemotherapy with etoposide and CDDP, LN: Lymph node, PTC: Papillary thyroid carcinoma, CR: Complete remission, SD: Stable disease, PR: Partial remission.

Results

Local response to CRT was judged as complete remission (CR) in two cases, partial remission (PR) in three, and stable disease (SD) in one case. Progressive disease (PD) was not observed (Table I). The duration to progression was a median of 154 days (range=58 to 382 days).

Figure 1 shows the tumor before and after CRT demonstrates tumor regression in case 4. This patient had initially undergone left lobectomy for differentiated thyroid cancer at another institute five years earlier. He noticed a painful mass in his right neck, and the pain worsened gradually until the time of initial presentation. An open biopsy revealed ATC, but surgery was not indicated because the invasive growth surrounded the carotid artery. He received CRT with 45 Gy of EBRT concomitant with 10 mg/m^2 of docetaxel for four weeks. The local tumor continued to shrink after CRT, with dramatic relief of the local symptoms. However, metastatic disease appeared in the right thigh, and CRT was conducted using the same regimen against this new lesion. Unfortunately, no response was found at the metastatic site, and multiple lung metastases also developed. The local tumor of the neck did not show any regrowth. The effect was judged as CR locally which lasted until he died of cachexia 166 days after initial CRT.

Case 1 underwent laryngectomy 355 days after CRT for locally recurrent tumor invading the larynx. Case 5 underwent tracheotomy for tumor regrowth into the trachea, and eventually died of bleeding. One case (case 4) had initially undergone laryngectomy, for differentiated thyroid cancer. Therefore, the remaining three cases did not require for tracheotomy. In all cases patients were able to maintain oral intake of food and medication without tubing until disease became of terminal stage. The overall survival was a median of 250 days (range=86 to 1,901 days) from the day of the diagnosis of ATC. The survival rate was 67% at six months and 33% at one year. Two patients survived more than one year.

Adverse events for CRT were mainly grade 2 sore throat, esophagitis, appetite loss, and dermatitis. These symptoms were managed with medications and temporal fluid infusion. No adverse effect over grade 3 was observed.

Discussion

Total eradication of the disease with curative surgery is the most preferable treatment to manage ATC, showing satisfactory long-term prognosis (13). However, these operable cases are rarely encountered, and most cases demonstrated inoperably advanced disease with local invasion to the adjacent organs and distant metastasis (1, 2, 13, 14). The importance of multimodal therapy has, thus, been emphasized.

Radiation therapy might be a useful modality to control for local disease. EBRT to the neck after grossly curative resection for ATC was found to be effective to avoid local recurrence (15). Hyperfractionated-accelerated radiotherapy has been introduced as an alternative method to maximize the efficacy (16). However, the incidence of severe toxicity was very high in the population, resulting in poor tolerance and failure to complete the planned dose of radiation (17).

CRT, a simultaneous combination of EBRT and chemotherapy, has been attempted with the aim to demonstrate more effective disease control with fewer adverse events than EBRT alone (18, 19). A unique CRT was attempted by Troch *et al.*, using 100 mg of docetaxel administration every three weeks, concomitant with 60 Gy of EBRT. Although the

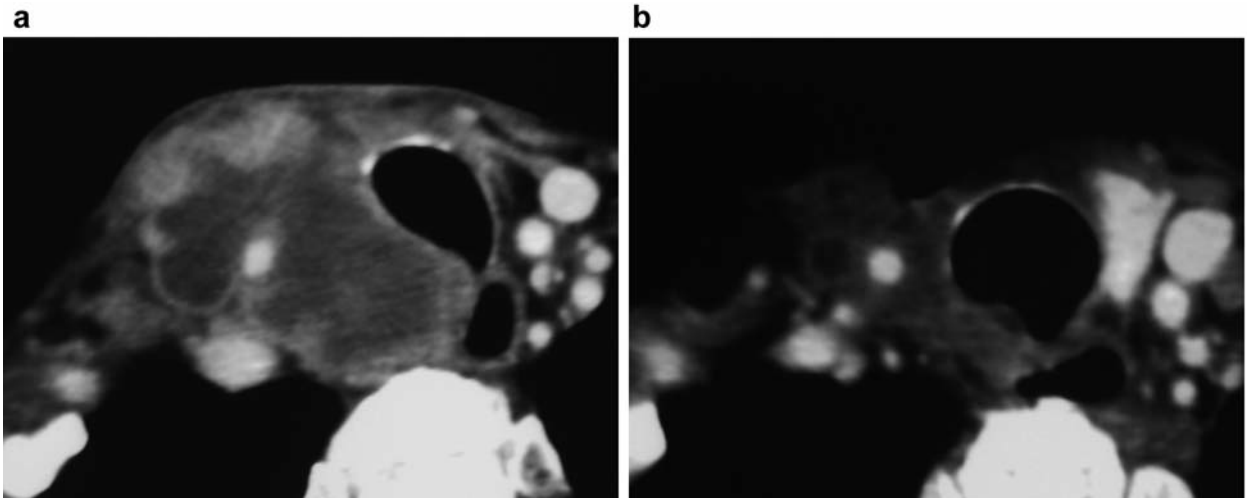

Figure 1. *A responder to chemoradiotherapy (CRT). Computed tomography of a 74-year-old male patient, before (A) and after (B) CRT are shown. The therapeutic effect was judged as complete response, and the effect lasted until the patient died of cachexia. The patient survived for 188 days from the initial diagnosis of anaplastic thyroid cancer with stable local control.*

protocol included a rather additional EBRT onto the scheduled six cycles of chemotherapy with docetaxel, all cases showed favorable response to the therapy (four CRs and two PRs). However, patients again suffered severe adverse events requiring hospitalization in all cases, and EBRT had to be terminated at 40-50 Gy in three cases (20). Recently, Tanaka *et al*. reported a new regimen for CRT with less severe adverse events and similar efficacy in cases with inoperable and post-operated ATC. They also mentioned the use of taxanes as a new strategy (26). The aim of CRT is local control rather than systemic therapy (9), and to maintain the quality of life of the patients by means of avoiding prolonged hospital stay, tracheotomy, and dysphagia. Therefore, it is of the utmost importance not to cause severe adverse events because of the palliative nature of this therapy.

In our series, we demonstrated similar efficacy by CRT with EBRT and weekly administration of docetaxel (10) with less toxicity than former reports (20, 21). This CRT also had a better therapy accomplishment rate (100%) than others, and no deaths from locoregional causes, and fewer/ less severe adverse events. The results are promising, although the size of the study is small and further prospective evaluation is needed.

As shown in every report, the rate of distant failure was higher than the rate of local failure with CRT (15, 20, 21). Several new chemotherapeutic approaches using taxanes (22, 23), molecular-targeted agents (24) have been introduced as an alternative way to treat ATC. Some new agents are orally available drugs. Therefore, indisputable local control with CRT in ATC might become more important in the new era of treatment to maintain not only the quality of life, but also continue anticancer treatment.

Conflicts of Interest

None declared.

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