A Novel Chemo-radiotherapy with Low-dose Daily Cisplatin, 5-Fluorouracil and Doxorubicin for Anaplastic Thyroid Carcinoma: A Preliminary Report

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Objective: Although anaplastic thyroid carcinoma (ATC) has a dismal prognosis, some patients show favorable survival following multimodal treatment with surgery, external irradiation and chemotherapy. However, no regimen has yet been established. We reviewed outcomes for patients who underwent a unique chemoradiotherapy regimen between 1998 and 2007.

Methods: The regimen consists of external irradiation (40 Gy at 2 Gy/day) combined with concurrent low-dose cisplatin at 5 mg/m² on Days 1–5, 8–12, 15–19 and 22–26, 5-fluorouracil at 200 mg/m² on Days 1–26 and doxorubicin at 20 mg/m² on Days 1 and 15. This regimen was performed on 21 patients (13 men, 8 women) with anaplastic thyroid carcinoma. Median age at the time of treatment was 66 years (range, 54–81 years).

Results: The treatment regimen was completed in 19 patients (90%) and was interrupted in 2 (10%) due to progressive distant metastases. After excluding 10 patients who underwent complete resection before chemoradiotherapy, 1 patient (11%) showed partial response, 7 (78%) showed stable disease and 1 (11%) had progressive disease on the basis of Response Evaluation Criteria in Solid Tumors. Overall, 6-month survival rate for patients treated with chemoradiotherapy was 57%. With this novel chemoradiotherapy, death from loco-regional disease was seen in only two patients (11%). Grade 3–4 toxicities were observed in 12 patients (63%), but no treatment-related deaths were encountered.

Conclusions: Our new chemoradiotherapy is effective for loco-regional control of anaplastic thyroid carcinoma, particularly when combined with radical surgery. This regimen could not prevent distant metastases, but offers acceptable toxicity while maintaining patient quality of life.

Key words: anaplastic thyroid carcinoma – chemoradiation therapy – prognostic index

INTRODUCTION

Anaplastic thyroid carcinoma (ATC) is uncommon, but is one of the most lethal neoplasms in humans. The prognosis remains dismal even with aggressive surgical resection. Some investigators have thus attempted to improve survival by adding radiotherapy and chemotherapy to the treatment of this disease (1,2). Indeed, some patients survive for a fairly long time after such aggressive treatment (3–6). While most ATCs present as rapidly progressive disease (PD), elderly patients in poor general condition cannot tolerate an overly intensive approach. Aggressive treatment may occasionally worsen quality of life (QOL) and shorten survival.

At our institution, we have been using prognostic index (PI) to determine the appropriate strategies for the individual patient. As described previously, PI is based on the presence of four unfavorable prognostic factors: (i) presence of acute
symptoms; (ii) large tumor (>5 cm); (iii) distant metastasis and (iv) leucocytosis (white blood cell count ≥10 000/mm³) (7). We attempt aggressive multimodal therapy for patients with lower PI to obtain the best results in terms of survival. On the other hand, palliative therapy is recommended for patients with higher PI, in order to maintain patient QOL.

Recently in Japan, combined chemotherapy containing cisplatin, adriamycin and etoposide (EAP) or cisplatin and etoposide (EP) has often seen use as an aggressive chemotherapy for ATC (8). However, these chemotherapies can show severe adverse events and results have proven unsatisfactory when carried out in our division. Since 1998, we have been performing chemoradiotherapy (CRT) as a multimodal therapy mainly for patients with low PI to obtain the best results in terms of survival. On the other hand, palliative therapy is recommended for patients with higher PI, in order to maintain patient QOL.

This CRT was originally developed as a therapy for esophageal cancer and squamous cell carcinoma of the head and neck, utilizing the radiosensitizing and biochemistry-modulating effects of cisplatin and 5-fluorouracil (5-FU) (9,10). As CRT was well tolerated, we eventually extended the indications to patients with higher PI (inoperable patients). The present study reviewed the outcomes of 21 patients with ATC who underwent this CRT.

PATIENTS AND METHODS

We reviewed the medical records of 21 patients (13 men, 8 women) with ATC treated between 1998 and 2007 with CRT at the Cancer Institute Hospital, a tertiary oncology referral center in Tokyo, Japan. The ethics committee of the hospital approved the protocol in January 1998. Median age at the time of starting CRT was 66 years (range, 54–81 years). All patients were histologically confirmed as having ATC. Performance status was 0 in 6 patients, 1 in 13 patients and 2 in 2 patients. Eleven patients were inoperable, and 10 patients received surgery before CRT. All 10 operated patients underwent curative resections; that is, complete removal of gross disease. No patients underwent palliative surgery. CRT was interrupted in two patients (10%) because of progressive distant metastases. The remaining 19 patients (90%) completed the full course.

The CRT regimen consisted of external irradiation (40 Gy at 2 Gy/day) combined with concurrent low-dose cisplatin (CDDP) at 5 mg/m² on Days 1–5, 8–12, 15–19 and 22–26, 5-FU at 200 mg/m² on Days 1–26 and doxorubicin (ADM) at 20 mg/m² on Days 1 and 15. Therapeutic effects were evaluated by imaging studies.

Two patients received additional radiotherapy (58.8 and 10 Gy, both on lung metastases), and another two patients received five courses of additional chemotherapy (CDDP at 40 mg/m², 5-FU at 1200 mg/m² and ADM at 20 mg/m² every 2–4 weeks) in the outpatient unit.

In earlier cases, we used CRT as an adjuvant therapy after curative surgical resection of the tumor. In more recent cases, we have applied CRT even for patients with higher PI, and used CRT both with surgery and alone.

Effects and adverse events of CRT were analyzed according to Response Evaluation Criteria in Solid Tumors version 1.1 definitions and Common Terminology Criteria for Adverse Events version 4.0, respectively (11,12).

Duration of survival was calculated from whichever occurred earlier, the date of tissue diagnosis or start of treatment, until the date of death or last follow-up examination. Survival curves were determined using the Kaplan–Meier method and were compared for statistical significance using the log-rank test.

RESULTS

Clinical characteristics of the 21 patients are shown in Table 1. PI was ≤1 in 10 patients and ≥3 in 7 patients (mean PI, 1.8). Seven of the 10 patients (70%) with PI ≤1 underwent curative surgical resection of the tumor, while 5 of 7 patients (71%) with PI ≥3 did not receive any operations.

Curative surgical resection of the tumor was performed for 10 patients (48%) before CRT therapy, and CRT was not completed in 2 patients. Excluding these 12 patients, response to CRT was partial response (PR) in one case (11%), stable disease (SD) in seven cases (78%) and PD in one case (11%) (Table 2).

Table 1. Patient and tumor characteristics

<table>
<thead>
<tr>
<th>Factor</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) (range)</td>
<td>66 (54–81)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>13/8</td>
</tr>
<tr>
<td>Tumors &gt;5 cm in maximum diameter</td>
<td>18</td>
</tr>
<tr>
<td>White blood cell count &gt;10 000/mm³</td>
<td>5</td>
</tr>
<tr>
<td>Extrathyroid invasion</td>
<td>14</td>
</tr>
<tr>
<td>Prognostic index (PI)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>1</td>
<td>6 (28%)</td>
</tr>
<tr>
<td>2</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>3</td>
<td>5 (24%)</td>
</tr>
<tr>
<td>4</td>
<td>2 (10%)</td>
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</tbody>
</table>

Figure 1 shows findings from computed tomography before and after CRT in a patient who survived 2 years and 9 months. PI was estimated as zero in this 60-year-old man, and surgery was not indicated due to the presence of unresectable mediastinal lymph node metastasis. As he experienced bilateral recurrent laryngeal nerve paralysis, tracheotomy was performed. He received one course of CRT plus CDDP, 5-FU and ADM chemotherapy. Therapeutic effect was judged as PR. He eventually died of tracheo-esophageal fistula.

Table 1. Patient and tumor characteristics
Overall, two patients in the CRT group died of suffocation caused by loco-regional disease. Seventeen patients died of distant disease or general symptoms due to cachexia. To date, two patients remain alive (16 and 43 months after initial treatment). Mean survival time was 11 months (range, 1–43 months). Survival rate was 57% at 6 months and 33% at 1 year. Only seven patients (33%) survived more than 1 year.

Adverse events for CRT were mainly grade 2–3 (Table 3). Leucocytopenia was observed in 11 patients (52%), nausea and vomiting in 7 (33%), hyperkalemia in 2 (10%), hypotension in 1 (5%), dyspnea in 1 (5%) and diarrhea in 1 patient (5%).

DISCUSSION

ATC accounts for 1–2% of all thyroid carcinomas in iodine intake-sufficient countries such as Japan and the USA (13). Although no therapeutic regimens have yet been established, some patients show improved survival with multimodal treatment combining surgery, external irradiation and chemotherapy. Our institution has been using PI to select patients likely to benefit from such aggressive treatment (7).

Various chemotherapy regimens for ATC have been reported in the past. Shimaoka et al. (14) noted that therapeutic results for the combination of ADM (60 mg/m²) and CDDP (40 mg/m²) were far superior to those for single-agent chemotherapy, providing a 33% response rate and achieving complete response (CR) in 3 of 18 patients.

Tsutsui (8) reported the surprisingly high efficacy of a combination of CDDP at 80 mg/m², ADM at 30 mg/m² on Day 1 and etoposide at 60 mg/m² on Days 1–5, every 3 weeks (EAP regimen). In that series of 19 patients, 4 patients achieved complete remission and 8 showed PR, yielding an overall response rate of 63.2% (5). EAP and EP are now popular regimens in Japan.

Our institution tried EAP from 1995 to 2007 for nine patients. However, the 6-month survival rate was 22%, and adverse events from EAP were often grade 3 or more, including two chemotherapy-related deaths (Table 3).

The CRT used in our institution, a combination of CDDP, 5-FU and ADM, has been developed as an effective treatment modality for patients with both operable and inoperable esophageal cancer (8,15). For patients with head and neck squamous cell cancer, this CRT showed much better effectiveness for loco-regional control and overall survival than radiotherapy alone (16). The rationale for the CRT is based on the radiosensitizing and biochemistry-modulating effects of chemotherapeutic agents, and maximum effects are achieved by daily CDDP administration before each fraction of radiation (17). We have adopted this CRT for patients with ATC since 1998. In our series, CRT offered better survival time and rate, and less severe adverse events than EAP. Also, CRT had a better therapy accomplish rate (90%) than EAP (78%), and less deaths from loco-regional causes (11% of all deaths) compared with EAP (33% of all deaths), and no deaths for CRT caused by adverse events. There was one death caused by adverse events for EAP.

The indications for radiotherapy now range from palliation to pre- and/or postoperative therapy to prolong survival. Current protocols use doses between 30 and 60 Gy. At our institution, 13 of 67 ATC patients (19%) treated between

Table 2. Outcome of chemoradiotherapy (CRT)

<table>
<thead>
<tr>
<th>Outcome of CRT</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>SD</td>
<td>7 (78%)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (11%)</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

The indications for radiotherapy now range from palliation to pre- and/or postoperative therapy to prolong survival. Current protocols use doses between 30 and 60 Gy. At our institution, 13 of 67 ATC patients (19%) treated between

Figure 1. A good responder to chemoradiotherapy (CRT). A 60-year-old male patient, Prognostic index (PI) = 0. Computed tomography before (A) and after (B) CRT. Therapeutic effect was judged as partial response (PR). The patient survived 2 years 9 months and died of tracheo-esophageal fistula.
1985 and 2007 received simple radiotherapy of >40 Gy as an initial treatment for ATC. Some patients also received additional surgery.

Simple radiotherapy showed the following effects: two patients (17%) who received 60 Gy of radiation showed PR; one patient (8%) who received 40 Gy showed SD. No significant difference was identified between therapeutic effects of CRT and those of simple radiotherapy (Student’s t-distribution, \( P = 0.57 \)).

Adverse events of radiotherapy were as follows: grade 2 leukocytopenia in two patients; grade 2 anemia and grade 3 dermatitis in one patient; grade 1 skin induration in one patient; and grade 2 laryngeal edema in one patient. To achieve the same effect, CRT would reduce the doses, and consequently reduce the adverse effects of radiation.

CRT tends to be useful for loco-regional control. The surgery plus CRT group tended to show longer survival compared with the surgery-only group (log-rank test, \( P = 0.06 \)). Six-month and 1-year survival rates were as good as 70 and 50% for patients with both surgery and CRT, while survival rates were 28 and 11% for surgery only.

CRT is thought to be useful for loco-regional control, even in patients with \( PI \geq 3 \), while allowing QOL to be maintained. CRT used to be performed as an aggressive multimodal therapy mainly for patients with \( PI \leq 1 \). In such patients, the 6-month survival rate was as good as 57%, and the rate of grade 3–4 adverse events was 57%. As CRT was well tolerated, we eventually extended the indications to patients with \( PI \geq 3 \) to maintain QOL. Among patients with \( PI \geq 3 \), the CRT group showed significantly longer survival than the non-CRT group (log-rank test, \( P = 0.011 \)). Moreover, no difference was seen in the rate of patients who could be discharged from hospital (Mann–Whitney U-test, \( P = 0.43 \)), which is one of the barometers of QOL. Consequently, CRT provides good local control rate, and is effective for patients with \( PI \leq 1 \) as a part of aggressive therapy, and also for patients with \( PI \geq 3 \) to maintain QOL.

The problem with this CRT is the poor control of distant metastases. The rate of distant failures was higher than the rate of local failures. Another problem with this CRT is the fact that 24-h infusion of 5-FU requires hospitalization.

Given the lack of efficacy of existing treatment modalities for ATC, attention is turning to new chemotherapeutic agents and molecular treatment strategies. Taxanes appear to represent a good candidate for the treatment of ATC. Induction chemotherapy with weekly paclitaxel offers an effective therapeutic strategy for stage IVB ATC patients (18). However, clinically useful and effective therapies among the new therapies are few. CRT appears capable of reducing death from loco-regional factors and maintaining patient QOL.

**Conflict of interest statement**

None declared.

**References**


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Table 3. Adverse effects of CRT and cisplatin, adriamycin and etoposide (EAP)

<table>
<thead>
<tr>
<th>Grade</th>
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<th>EAP (%)</th>
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<tr>
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