Clinical trial of weekly paclitaxel chemotherapy for papillary thyroid carcinoma with squamous cell carcinoma component

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Abstract. Papillary thyroid carcinoma (PC) can occasionally include a squamous cell carcinoma (SCC) component. In this study, we evaluated the effect of weekly paclitaxel chemotherapy in 3 patients with PC including an SCC component. None of these patients had lesions of anaplastic carcinoma on pathological examination. Weekly paclitaxel chemotherapy was performed as an induction chemotherapy for 2 patients. All 3 patients underwent locally curative surgery and weekly paclitaxel chemotherapy after surgery as an adjuvant therapy. The response to the chemotherapy was evaluated based on the RECIST guideline (version 1.1). Two patients had partial responses (PRs) and the remaining 1 had stable disease (SD). The response rate was 67% and the clinical benefit rate (PR+SD) was 100%. One patient died of the growth of lung metastases that had been detected before surgery 22 months after the diagnosis. The remaining 2 are still alive, 14 and 22 months after the diagnosis, respectively. Taken together, weekly paclitaxel may be one of the effective adjuvant therapies for PC with an SCC component.

Key words: Squamous cell carcinoma component, Weekly paclitaxel, Chemotherapy

SQUAMOUS CELL CARCINOMA (SCC) of the thyroid is a very rare tumor and has a very aggressive behavior, resembling anaplastic thyroid carcinoma (AC) [1]. In the latest edition of the World Heath Organization’s histologic classification of thyroid tumors [2], tumors can be diagnosed as SCC of the thyroid only when tumor lesions are comprised entirely of squamous differentiation. However, squamous differentiation is generally detected as a component in papillary carcinoma (PC), especially in the tall cell variant [3-8]. Treatment for PC with an SCC component has not yet been established. Similar to AC, combined modality therapy is usually performed, but very few effective cases of chemotherapy have been reported [9-15].

Paclitaxel is the first member of the taxane family which exerts its cytotoxic effect by arresting mitosis through microtubule stabilization, resulting in cellular apoptosis. The use of paclitaxel as a chemotherapeutic agent has become broadly accepted [16]. We previously reported the effect of induction chemotherapy by weekly paclitaxel for AC of the thyroid [17], of which response rates were 33% for Stage IVB and 25% for Stage IVC patients.

We then also applied it for PC with an SCC component. To date, we have performed weekly paclitaxel chemotherapy in 3 patients with evaluable target lesions and, in this study, we demonstrate its effectiveness in these 3 patients.

Patients

Between 2006 and 2010, 10 patients diagnosed with PC including SCC components with or without anaplastic lesions on pathological examinations were treated in Kuma Hospital [18]. Of these patients, 3 did not include AC components and had target lesions to evaluate the response to chemotherapy, and they were enrolled in this study. All patients gave informed consent prior to participation. Weekly paclitaxel che-
Chemo-therapy was performed along with the protocol as previously described [17]. The response to the chemotherapy was evaluated based on the RECIST guideline (version 1.1) [19].

Results

Clinical Histories

Case 1

A 70-year-old woman was referred to Kuma hospital with the complaint of hard neck mass. Ultrasound examination detected a solitary 5.9-cm tumor in the right lobe of the thyroid and multiple node metastases in the right lateral compartment (maximal diameter: 1.6 cm). She had incomplete recurrent laryngeal nerve paralysis of the right side, probably due to tumor invasion. SCC was suspected on fine needle aspiration biopsy (FNAB) of the primary tumor. On CT scan, multiple lung metastases were detected. Induction chemotherapy involving weekly paclitaxel was performed with 80 mg/m² for 3 cycles. The tumor size decreased by 45%, evaluated as partial response (PR) (Fig. 1a, b). Lung metastasis disappeared after induction chemotherapy and was evaluated as a complete response (CR) (Fig. 1c, d). Total thyroidectomy and modified radical neck dissection were then performed, which was a locally curative surgery. Histopathological examination revealed SCC with PC (Fig. 2a, b) and the SCC lesion was extensively necrotic (Fig. 2c). In the lymph nodes, metastatic lesions only of PC were detected. Two additional cycles of weekly paclitaxel were performed but, thereafter, it was suspended because of pretibial edema. For local control, extrabeam radiation therapy (EBRT) (60 Gy in total) was also performed. Lung metastases were identified again 6 months after surgery, and we restarted weekly paclitaxel chemotherapy at the same dose. Thirteen cycles of chemotherapy were performed in total, but lung metastases enlarged gradually. She was died 21 months after the diagnosis (18 months after surgery).

Fig. 1 CT images of Case 1 before and after induction chemotherapy

a. Primary lesion before induction chemotherapy.  b. Primary lesion with tumor shrinkage after induction chemotherapy.  c. Lung metastatic lesion before induction chemotherapy.  d. Lung metastatic lesion disappeared after induction chemotherapy.
Case 2

A 68-year-old woman presented with neck swelling. She had a 4.4-cm tumor in the right lobe of the thyroid and node metastasis measuring 2.7 cm in the right lateral compartment. FNAB findings led to a suspicion of SCC or AC for the primary lesion and PC metastasis for the lymph node. The primary lesion was diagnosed as SCC on core needle biopsy. Chest and abdominal CT scan showed no distant metastasis. Induction chemotherapy involving weekly paclitaxel (80 mg/m²) was performed for 2 cycles. The tumor size decreased by 15%, and the response was evaluated as SD. Total thyroidectomy and modified neck dissection were performed, and the tumor was completely resected. Histopathological examination revealed SCC with the tall cell variant of PC (Fig. 3a). No SCC lesions were detected in metastatic nodes. Four additional cycles of chemotherapy were performed after surgery. EBRT of 50 Gy in total was also performed. She is alive 29 months after the diagnosis (27 months after surgery), with no evidence of carcinoma recurrence.

Fig. 2 H & E sections of Case 1
Lesion of PC. Viable lesion of SCC. Necrotic lesion of SCC.

Fig. 3 H & E sections of SCC lesion of Case 2 (a) and Case 3 (b)
Case 3

An 82-year-old woman presented with a 5.8-cm neck mass in the right lobe of her thyroid. She had lymph node metastasis measuring 1.7 cm detected on ultrasonography in the right lateral compartment. No distant metastasis was detected by chest and abdominal CT scan. FNAB suggested PC or poorly differentiated carcinoma. Total thyroidectomy and modified radical neck dissection were then performed, and the tumor was completely resected. Histopathological evaluation revealed the tall cell variant of PC with an SCC component both in the primary lesion and lymph node metastasis (Fig. 3b). A total of 50 Gy of EBRT was administered, thereafter. However, recurrent tumors in front of her right common carotid artery (CCA) and in the skin were detected during EBRT (Fig. 4a, c). Core needle biopsy of the tumor in front of the CCA was performed and its histopathologic examination revealed SCC. Then, weekly paclitaxel chemotherapy with 60 mg/m² was performed for 3 cycles. The tumor in front of the CCA disappeared based on CT and ultrasound (US) evaluation (Fig. 4b), but the skin tumor showed no change (Fig. 4d). Therefore, the response to chemotherapy was judged as PR. The skin tumor was resected under local anesthesia and was histologically diagnosed as SCC. Additional paclitaxel chemotherapy was performed for 2 cycles, but it was suspended due to general fatigue thereafter. She is still alive and disease-free 23 months after the diagnosis (22 months after initial surgery).

Response to weekly paclitaxel chemotherapy

Clinical courses of the patients are summarized in Table 1. The follow-up period was counted from the diagnosis. Two patients had PRs (Cases 1 and 3) and 1 patient had SD (Case 2). So, the response rate was 67% and clinical benefit rate (PR+SD) was 100%.

![Fig. 4](image-url) CT images of recurrent tumors of Case 3 before and after chemotherapy

a. Local recurrence in front of the CCA before chemotherapy (see arrow).  
b. Disappearance of local recurrence after chemotherapy (see arrow).  
c. Skin recurrence before chemotherapy (see arrow).  
d. Skin recurrence did not change after chemotherapy (see arrow).
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SD, indicating that the response rate (RR) and clinical benefit rate (PR+SD) were 67 and 100%, respectively. There incidences were much more favorable than those in AC: clinical benefit rate of 56% in Stage IVB and 75% in Stage IVC [17]. Therefore, weekly paclitaxel may be more effective for SCC of the thyroid and PC with an SCC component than AC.

In our series, induction chemotherapy of weekly paclitaxel was performed for 2 patients who were preoperatively suspected of having SCC or AC in order to make the initial surgery easier. Cook et al. studied 16 patients with SCC of the thyroid, and demonstrated that long-term survival was expected only when complete resection was possible [15]. This is similar to the results of our study regarding AC [22]. Indeed, 2 patients who received induction therapy showed tumor reduction, indicating that induction therapy of weekly paclitaxel is a useful adjuvant therapy for locally curative surgery. Furthermore, lung metastasis of one patient (Case 1) also disappeared on chemotherapy before surgery, indicating that weekly paclitaxel can also be effective for distant metastasis. Although this patient eventually died of lung metastasis, it is possible that micrometastasis to distant organs or local lesions disappear on weekly paclitaxel chemotherapy. Indeed, small metastasis to the local lesion of Case 3 detected during EBRT disappeared on weekly paclitaxel, which may support our hypothesis.

In conclusion, we demonstrated that weekly paclitaxel chemotherapy may be one of the effective adjuvant therapies for PC with an SCC component in order to make locally curative surgery easier and resolve small recurrences and metastases of SCC.

Discussion

In this study, we demonstrated our treatment results using weekly paclitaxel chemotherapy for 3 patients with PTC having an SCC component. All patients in our series were of advanced age (68-83 years), had large primary lesions (larger than 4 cm), and significant extrathyroid extension, which are signs of aggressive features and indicate a poor prognosis [20]. It is therefore suggested that squamous cell differentiation is a phenomenon detected in PC with aggressive characteristics.

Previous studies demonstrated that SCC of the thyroid and PC with an SCC component shows an adverse prognosis [3-9]. Booya et al. showed that the mean survival period was 8.6 months, which was similar to other reports [9]. Therefore, multimodal therapy including surgery, chemotherapy, and EBRT is recommended, but, to date, no established protocols for chemotherapy effective for SCC of the thyroid and PC with an SCC component are available. Various chemotherapeutic agents like bleomycin, ariamycin, vincristine, and doxorubicin were used, but they were reported not to be beneficial [21].

In this study, we demonstrated that weekly paclitaxel chemotherapy is effective for PC with an SCC component. Two patients had PRs and the remaining 1 had SD, indicating that the response rate (RR) and clinical benefit rate (PR+SD) were 67 and 100%, respectively. There incidences were much more favorable than those in AC: clinical benefit rate of 56% in Stage IVB and 75% in Stage IVC [17]. Therefore, weekly paclitaxel may be more effective for SCC of the thyroid and PC with an SCC component than AC.

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References


Table 1 Clinical response to weekly paclitaxel in the 3 patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Clinical response</th>
<th>Reduction ratio</th>
<th>Follow-up period</th>
<th>Dead or alive</th>
<th>Time to recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>PR</td>
<td>45%</td>
<td>21 months</td>
<td>dead</td>
<td>6 months</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>SD</td>
<td>15%</td>
<td>29 months</td>
<td>alive</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>82</td>
<td>PR</td>
<td>43%</td>
<td>23 months</td>
<td>alive</td>
<td>-</td>
</tr>
</tbody>
</table>

PR, partial response; SD, stable disease


