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Journal of
Thyroid Disorders & Therapy

Research Article

Factors Influencing the Chemo-Sensitivity of Weekly Paclitaxel for Anaplastic Thyroid Cancer: A Clinico-Pathologic Analysis of Cases Enrolled in a Clinical Trial

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ABSTRACT

This study was conducted to identify the clinico-pathologic factors influencing the response to weekly paclitaxel treatment for Anaplastic Thyroid Cancer (ATC), a rare refractory disease. We investigated clinico-pathological factors as well as the expressions of Ki67, p53, MAD2, TLE3, ALDH1, β-tubulin, E-cadherin and vimentin among the subjects enrolled in a recent nationwide clinical trial of 56 patients with ATC in Japan. We compared the factors of eight responders and eight non-responders. The responders survived significantly longer than the non-responders (median 11.6 *vs.* 3.6 months, p=0.039). No significant between-group difference was found in histological subtype, TNM classification, or the expression of Ki67, p53, MAD2, TLE3, ALDH1, β-tubulin, E-cadherin or vimentin. When the patients' Prognostic Index (PI) was determined with the sum of four clinical factors, i.e., (1) Acute symptom within 1 month, (2) Tumor size >5 cm, (3) Distant metastasis, and (4) Leukocytosis ≥10,000/mm^3, a response in the target lesion was observed significantly more frequently in the patients with a low PI score (0 or 1 positive factor) (5/5, 100%) compared to those with a high PI score (more than two positive factors) (4/11, 36.4%) (p=0.034). In conclusion, ATC patients who responded to chemotherapy with weekly paclitaxel survived significantly longer than non-responders. Patients with a low PI commonly showed a response to this chemotherapy.

Keywords: Anaplastic thyroid carcinoma; Chemotherapy; Paclitaxel; Sensitivity; Prognostic index

INTRODUCTION

Anaplastic Thyroid Cancer (ATC) is a rare entity, well known for its aggressive nature, rapid progression, and extraordinal poor outcome. The median survival time from the diagnosis was reported to be <6 months, with frequent resistance to conventional therapeutic approaches by surgery, radiation, or chemotherapy [1-3]. No standardized effective therapeutic strategy has been documented for ATC in any guidelines due to the lack of objective data on the outcomes of practical treatment [4,5].

We demonstrated the feasibility and the efficacy of weekly Paclitaxel (wPAC) for patients with ATC in our recent clinical trial [6]. This systemic chemotherapy was effective in approximately one-fifth of the patients, showing partial responses. The adverse events were mild and manageable, and high dose intensity could be maintained for more than eight administrations of paclitaxel (80 mg/m^2). The effect of wPAC was clearly demonstrated when it was used as a pre-operative induction treatment as had been suggested in a case series [7]. However, the response was not satisfactory to all patient; the time to progression was short (median 1.6

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Received: February 26, 2019; **Accepted:** March 18, 2019; **Published:** March 25, 2019

Citation: Onoda N, Hirokawa M, Kakudo K, Sakamoto A, Sugino K, Nakashima N, et al. (2019) Factors influencing the chemo-sensitivity of weekly paclitaxel for anaplastic thyroid cancer: A clinico-pathologic analysis of cases enrolled in a clinical trial. J Thyroid Disord Ther 8:231. doi: 10.24105/2167-7948.8.231

months), and patients without tumor remission had to reconsider their therapeutic strategy within their limited lifetime. It is, thus, important to identify the patients who may have a high probability of manifesting a clinical benefit before conducting systemic induction therapy with wPAC.

Clinical prognostic factors that could be used to predict the survival time of ATC patients have been reported [1,2,8,9]. The expressions of several proteins were reported to indicate the effect of paclitaxel in some recent studies [10,11]. The aggressive growth of cancer cells, measurable by Ki-67 positivity, may influence the outcome of the chemotherapy. An insufficient mechanism of the cellular damage response causes resistance to cytotoxic chemotherapy, and p53, a gene that is frequently altered in ATC, is known to play a central role in this process [12]. Phenotypical features of the Epithelial to Mesenchymal Transition (EMT) and the stemness of the cancer cells also contribute to chemoresistance [12]. The expressions of some markers suggesting EMT and stemness are commonly found in ATC [13,14]. However, we still do not know the factors that could be used to predict the efficacy of systemic chemotherapy conducted to manage ATC.

In the present study, we attempted to identify factors that can predict the outcome of systemic chemotherapy with wPAC for this rare refractory disease by using the clinical information and tissue samples obtained before the initiation of the treatment during our recent clinical trial conducted by a nationwide research consortium [6,15].

MATERIALS AND METHODS

Patients

We evaluated the efficacy of wPAC for ATC in a total of 56 patients in our recent clinical trial conducted by a nationwide research consortium. The trial included pathologically-proven ATC patients of any stage, details were described previously [6,15]. Forty-two of these patients had a target lesion evaluable with the RECIST criteria. A final total of 38 patients was evaluated. No patient achieved a complete response, eight patients showed partial remission, 22 showed stable disease, and eight patients showed progressive disease. The aim of the present study was to clarify the factors that could be used to predict the effect of wPAC; therefore, we selected eight patients with partial remission (responders; 2 males and 6 females), and another eight patients with progressive disease (non-responders; 3 males and 5 females) for a comparison of their features. The cancer tissue before chemotherapy could not be obtained from one female non-responder. We thus collected 15 tissue samples of ATC to investigate.

The clinical factors of the patients had been recorded during the clinical trial. The Prognostic Index (PI) of each patient was also evaluated. The PI is determined as the sum of four risk factors: (1) Acute symptoms within 1 month, (2) Large tumor, i.e., >5 cm, (3) The presence of metastatic disease, and (4) Leukocytosis of >10,000 mm^3 white blood cells. A favorable prognosis can be expected if the sum of risk factors is ≤ 1 [16].

Determination of the histological subtypes of the ATC

ATC is known to show various histopathological features [17,18]. In the present series, the histopathological features of each tumor were identified by three pathologists (HM, SA, KK) independently, and a consensus was reached in cases when their assessments differed. All subtypes identified were listed, and predominant characteristics were also determined. Most of the samples were obtained by core needle biopsy, and the co-existence of differentiated cancer, necrosis, or fibrosis could not be evaluated in some specimens. The infiltration of neutrophils or lymphoid cells was also evaluated [19].

Immunohistochemistry

The immunohistochemical examination was performed using the following antibodies: anti-Ki-67 (MIB1, 1:200 dilution, Dako, Carpinteria, CA, USA), anti-p53 (DO7, 1:200 dilution, Dako), anti-E-cadherin (NCH-38, 1/400 dilution, Dako), anti-vimentin (V9, ready to use, Nichirei, Tokyo), anti-MAD2 (610678, 1/50 dilution, BD Bioscience Japan, Tokyo), anti-ALDH (44/ALDH, 1/100 dilution, BD Bioscience Japan), anti-TLE-3 (sc-9124, 1/100 dilution, Santa Cruz Biotechnology, Dallas, TX), anti-beta-tubulin isotope III (3D10, 1/100 dilution, Sigma, Saint Louis, MO). The staining was carried out using either the Leica Bondmax system (Leica Microsystems, Buffalo Grove, IL), and Bond refine kit (Leica Microsystems) for Ki-67, p53, E-cadherin, and vimentin, or the Histofine PO kit (Nichirei) for MAD2, ALDH-1, TLE3, and beta-tubulin according to the manufacturer's recommendations.

For p53 immunostaining, we defined cases as positive if >50% of the tumor cells were stained. To estimate the Ki-67 Labeling Index (LI), we counted ≥ 500 carcinoma cells in the hot-spot areas observed under ×400 magnification, and we calculated the percentage of positively stained nuclei. MAD2 staining was evaluated as described [20]. Immunoreaction for ALDH1, TLE3, and beta-tubulin was evaluated as described [21,22].

Statistics

The statistical analyses were performed using SPSS 13.0 statistical software (SPSS, Chicago, IL) Fisher's exact test was used to compare the prevalence or distribution of two variables. Survival data were estimated by the Kaplan-Meier method, and the log-rank test was used for the univariate survival analysis. Differences in the numeric values of the two groups were compared by Mann-Whitney's U-test. A p-value <0.05 was considered significant.

RESULTS

The median overall survival of the eight responders was 10.2 (95% CI: 1.1–19.2) months, and was significantly longer compared to the 3.4 (95% CI: 2.8–4.0) months of the eight non-responders (Figure 1). The clinical characteristics of the patient are summarized in (Table 1). There was no significant difference in age, gender, performance status, tumor size, T-category, or N-category between the responders and non-responders. The responder group had four patients (50.0%) with a low PI score (PI=0 or 1, suggesting a favorable prognosis). In contrast, only one patient (14.3%) in the non-responder group had a low PI. This patient demonstrated partial remission of the target lesion. However, the final response of this patient was determined as PD due to the appearance of new lesions at distant organs. Therefore, all five patients scored a low PI as demonstrated by the response at the target lesion. The frequency of the response at the target lesion was significantly more common in the patients whose PI was low compared to those with high PIs (4 of 11; 36.4%, p=0.034).

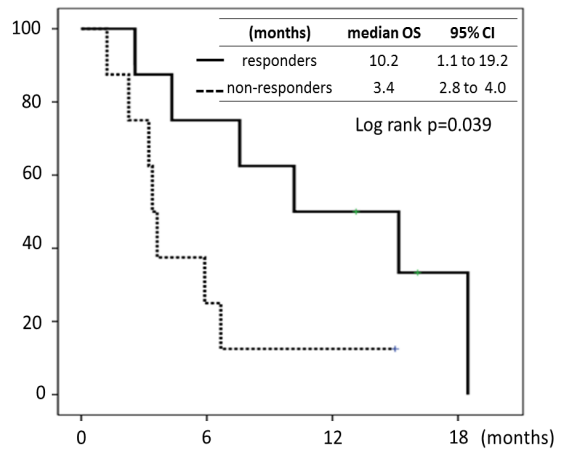

Figure 1: Overall survival of the patients plotted by Kaplan-Meier method. The survivals of the responders (solid line) and non-responders (dotted line) showed a significant difference (p=0.039, log-rank test).

Table 1: Characteristics of the patients according to the response.

Factors	Responders (8 patients)	Non-responders (7 patients)	p
Age (median)	60–78 (65.9)	67–77 (73.2)	0.674
Gender Male Female	 2 6	 3 4	0.61
BMI[a] (median)	15.7–24.4 (22.3)	18.0–30.6 (22.7)	0.345
PS[b] 0 1	 7 1	 6 1	1.00
PI[c] 0, 1 2–4	 4 4	 1 6	0.28[e]
Target lesion	7 primary, 1 metastatic	3 primary, 2 metastatic, 2 recurrent	0.11
Tumor size (median)	19–86 (44.1) mm	15–63 (41.9) mm	0.834
T classification 4b x	 8 0	 4 3	0.08
N classification 0 1	 2 6	 3 4	0.61
M classification 0 1 x	 5 3 0	 1 4 2	0.27
Stage[d] IVB IVC x	 5 3 0	 1 3 3	0.55
Adverse events grade 0–2 grade≥ 3)	 7 1	 6 1	1.00

[a]BMI: Body Mass Index before treatment; [b]PS: Performance Status according to Eastern Cooperative Oncology Group; [c]PI: Prognostic Index; [d]Stage was stratified according to the UICC 7th edition. [e]p-value: when compared the number of patients scored PI 0/1.

Comparison of the pathological characters between responders and non-responders was demonstrated in (Table 2). The histological subtypes of the tumor varied. The most common type was pleomorphic (giant cell) type, found in 12 of the 15 tumors investigated. Spindle (sarcomatoid) type was identified in six tumors. Four tumors consisted partly of the epithelioid (epithelial) subtype, and all four of these patients responded to the chemotherapy. Infiltration of neutrophils was more commonly found in tumors of the responders (5 of 8; 67.5%) compared to the non-responders (3 of 7; 42.9%). In contrast, infiltration of lymphocytes was more often found in the non-responders (5 of 7; 71.4%) compared to the responders (3 of 8; 32.5%). Necrosis and fibrosis were often found in the two groups' tumors (11 of 15, 73.3% and 8 of 15, 53.3%, respectively) irrespective of the response.

Table 2: Comparison of the pathological characters between responders and non-responders.

Factors	Responders (8 patients)	Non-responders (7 patients)	p
Histological subtype (P/S/E/R)[a]	5/4/4/1	6/2/0/0	0.28[e]
Infiltrate cells (Neu/Lym/Mul)[b]	5/3/1	3/5/1	0.62
Necrosis	6 (75.0%)	5 (71.4%)	1.00
Fibrosis	6 (75.0%)	2 (28.6%)	0.13
Ki67-LI[c] high (>50%)	4 (57.1%)	5 (71.4%)	0.61
P53-positive (>50%)	5 (62.5%)	3 (42.9%)	0.62
E-cadherin-positive	0 (0%)	0 (0%)	1.00
Vimentin-positive	8 (100%)	8 (100%)	1.00
MAD-1positive	4 (50.0%)	5 (71.4%)	0.61
TLE3-positive (>10%)	4 (50.0%)	6 (100%)[d]	0.08
ALDH-1-positive (>10%)	6 (75.0%)	4 (66.7%)[d]	0.61
Beta-tubulin-positive	8 (100%)	7 (100%)	1.00

[a]P: Pleomorphic type, S: Spindle type, E, Epithelial type, R: Rhabdoid type, contained overlapping; [b]Neu: Neutrophil, Lym: Lymphocyte, Mul: Multinucleated giant cell; [c]Ki67-LI: Ki67 labelling index; [d]Not informative in 1 case; [e]When compared cases including epithelial type or not.

All tumors but one demonstrated a high rate of Ki67-positive cancer cells (>25%), and 10 of 14 evaluable tumors (71.4%) had a Ki67-LI >50%. There was no correlation between the Ki67-LI or the positivity and the response to the therapy. P53-positive cells were also frequently found; eight of the 15 tumors (53.3%) showed >50% p53-positive cells in the tumor; five in responders and three in non-responders. No tendency was found in p53 positivity to indicate the response. Only scant reactivity of E-cadherin was noted in two tumors, and it was not correlated with the histological diagnosis of epithelioid subtype. Vimentin was expressed strongly and universally in all tumors. MAD2-positivity was found in nine of the 15 tumors (60.0%) regardless of the response. TLE3-positive tumors were more commonly found in the non-responder group (6 of 6 evaluable specimens; 100%) than in the responder group (4 of 8; 50%) without significance. ALDH-1 expression was observed only in the limited small stromal part in 10 tumors (66.7%) without any correlation to the response. Beta-tubulin was universally found in all tumors.

DISCUSSION

According to the reports based on a large database, <20% of the patients with ATC underwent a curative operation. At the same time, >40% already had distant disease. Thus, systemic therapy is one of the important treatment strategies to treat patients with ATC at present. Still, no effective chemotherapeutic agent has yet been identified. We recently conducted a clinical trial of systemic chemotherapy in ATC patients to examine the efficacy and feasibility of weekly paclitaxel, and we observed the effect in >20% of the patients with the high feasibility of the regimen [6]. In the present study we investigated factors that could be used to predict chemosensitivity to wPAC by using the information and tissue samples obtained in the clinical trial.

Our present findings showed that all five patients with a low PI score (0 or 1) responded to wPAC at the primary target. In contrast, four of the eight patients (50.0%) with the PI of 2 and both of the two patients with a PI >3 did not respond to wPAC. The response at the target lesion was significantly more frequent in the patients with a low PI score compared to those with a high score. The PI was originally devised to predict the overall survival of patients with ATC [16], and a favorable prognosis can be expected when the sum of four poor prognostic factors is <1. The PI has the advantage of being applicable in all ATC patients instantly without any invasive examination before initiating therapeutic attempts, e.g., at the time of initial presentation. This simple method was prospectively confirmed [23] and is listed in the 2018 Japanese guidelines for the treatment of thyroid tumors [24]. According to our present observations, the PI might also be used to predict the response to wPAC as well as the overall prognosis of ATC patients.

In our previous investigation of the significance of histology in the prognosis of ATC patients, we found that long-term survival after chemotherapy was significantly more likely when the tumor showed epithelial growth [19]. In the present study, all four tumors that consisted partly of the epithelial (Epithelioid) subtype showed a response. The existence of an epithelial part in the tumor suggested the phenotypical features of more differentiated characters. The resistance to chemotherapy might be due in part to the phenotypical acquisition of mesenchymal characters by an EMT [25]. We therefore investigated some markers involved in the EMT process, i.e., E-cadherin, vimentin, p53, Ki67, and ALDH-1. Our analyses did not demonstrate any significant difference in the expression of these markers regarding response. ATC is well known for the frequent expression of EMT markers [13,14]. Unique markers might be necessary to determine the histological differences in ATC other than conventional EMT markers.

Lymphocytic infiltration but not neutrophilic infiltration in the tumor was suggested as one of the markers for response to chemotherapy [26]. We obtained similar findings in our previous study [19]. However, we obtained the opposite results in the present study. Most of the histological samples were small tissue obtained by needle from the center of the tumor. This may cause inadequacy in evaluating infiltrated lymphocytes and neutrophils. ATC often shows an inflammatory reaction around tumor. The secretion of several cytokines to induce an inflammatory reaction is a common feature of ATC [27]. This aggressive nature and common local inflammatory reaction might have affected our present findings. Infiltrations of lymphatic cells are thought to reflect the immune reactivity between the host and the tumor. A subset analysis of the infiltrated lymphocytes is necessary to identify the accurate local immune reaction in ATC.

MAD2 correlated with the response to paclitaxel due to its involvement in the spindle assembly checkpoint [10]. In the present study, no correlation was found between MAD2 expression and the response to wPAC. A similar negative observation was demonstrated in the case of TLE3. TLE3 was identified as a molecular marker associated with sensitivity to taxane chemotherapy in breast and ovarian cancer [11], but in the present study it was not shown to be a predictive factor. A recent study denied the usefulness of TLE3 to predict the efficacy of taxane chemotherapy [20-28]. According to our observations, both MAD2 and TLE3 could not show clear benefits in predicting the effect of wPAC treatment for ATC.

CONCLUSION

In conclusion, wPAC demonstrated a significant benefit in prolonging survival when the tumor responded to the therapy. A low PI was suggested to have significance for a higher possibility of a response to wPAC therapy in ATC patients. We, thus, found that PI is a useful marker for considering the therapeutic strategy of this aggressive disease. The existence of the histological subtype of epithelial feature might also indicate the response to wPAC. The size of our present sample is too small to enable conclusions, but this was the first study to investigate the factors involved in the chemotherapeutic response of ATC patients, a rare refractory malignancy. It is necessary to identify objective factors to predict the chemotherapeutic effect of treatment by using novel strategies to investigate previously unknown molecules, such as comprehensive analyses of genomic, epigenomic, and proteomic profiles.

ACKNOWLEDGEMENTS

We thank all the participants in the clinical trial and the members of the ATCCJ for supporting the clinical trial. Part of this study was presented at the 50th Annual Meeting of the Japanese Society of Thyroid Surgery (Fukushima, Japan)

FUNDING

This study was supported in part by a research grant from the Japan Agency for Medical Research and Development (#17ck0106377h0001).

AUTHORS' CONTRIBUTION

Naoyoshi Onoda designed the study, obtained and accumulated samples, performed immunohistochemistry, analyzed the data and wrote the manuscript. Mitsuyoshi Hirokawa, Kennichi Kakudo and Atsuhiko Sakamoto performed pathological evaluation. Kiminori Sugino and Noriaki Nakashima obtained clinical sample. Nobuyasu Suganuma obtained clinical sample, performed immunohistochemistry. Shinichi Suzuki and Ken-ichi Ito designed the study and obtained clinical sample. Iwao Sugitani designed the study, obtained and accumulated samples, analyzed the data and edited the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was reviewed and approved by the Institutional Review Board of Osaka City University (#2248) and each of the

participating institutions. Written informed consent was obtained from each patient.

PATIENT CONSENT FOR PUBLICATION

Written informed consent was obtained from each patient.

COMPETING INTERESTS

Naoyoshi Onoda received a research grant from Bayer, and honoraria from Eisai, Bayer, and Sanofi. IS received a research grant from Eisai, and speakers bureau and consultant fees from Bayer, Eisai, and Sanofi. Mitsuyoshi Hirokawa, Kennichi Kakudo, Atsuhiko Sakamoto, Kiminori Sugino, Noriaki Nakashima, Nobuyasu Suganuma, Shinichi Suzuki, Ken-ichi Ito and Iwao Sugitani have nothing to disclose.

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