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Neutrophil-to-Lymphocyte Ratio as a Prognostic Marker for Anaplastic Thyroid Cancer Treated With Lenvatinib

NAOKI FUKUDA[1], KAZUHISA TODA[2], YU FUJIWARA[1], XIAOFEI WANG[1], AKIHIRO OHMOTO[1], TETSUYA URASAKI[1], NAOMI HAYASHI[1], YASUYOSHI SATO[1], KENJI NAKANO[1], MAYU YUNOKAWA[1], MAKIKO ONO[1], JUNICHI TOMOMATSU[1], HIROKI MITANI[2] and SHUNJI TAKAHASHI[1]

[1]Department of Medical Oncology, The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan;
[2]Department of Head and Neck Oncology, The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan

Abstract. *Background/Aim: Lenvatinib is one of the few options for patients with anaplastic thyroid cancer (ATC). However, tumor markers for ATC treated with lenvatinib is lacking. The aim of this study was to explore whether the neutrophil-to-lymphocyte ratio (NLR) can be a tumor marker for ATC treated with lenvatinib. Patients and Methods: We retrospectively analyzed the prognostic significance of the NLR in 13 ATC patients treated with lenvatinib. Results: The disease control rate was better in patients with lower NLR (<8; 89%) than higher NLR (≥8; 25%) (p=0.05). Median progression-free survival and overall survival were longer in patients with lower NLR than higher NLR (4.0 vs. 1.6 months, p<0.05; and 10.2 vs. 3.8 months, p<0.05, respectively). Patients whose NLR on day 14 decreased compared to baseline had a slightly higher overall response rate than patients without NLR decrease (42.9% vs. 0%, p=0.19). Conclusion: The baseline NLR is a potential prognostic marker, and the change of NLR can be an early indicator of response for ATC patients treated with lenvatinib.*

According to the GLOBOCAN, it is estimated that 567,000 patients newly diagnosed with thyroid cancer worldwide, and 41,000 of these patients died from the disease in 2018 (1). Approximately 95% of thyroid cancer cases involve differentiated thyroid cancer (DTC), including papillary thyroid cancer and follicular thyroid cancer (2, 3). The majority of DTC cases tend to be of a slow-growing nature; however, the prognosis of anaplastic thyroid cancer (ATC) is extremely poor, with a disease-specific mortality >90% (4). Although ATC comprises only 1-2% of all thyroid cancers, ATC accounts for 14-39% of all thyroid cancer deaths (5, 6). Lenvatinib is an antiangiogenic multi-kinase inhibitor (MKI) that prevents ligand-induced receptor autophosphorylation of vascular endothelial growth factor receptor (VEGF-R) 1-3, fibroblast growth factor receptor 1-4, ret proto-oncogene (RET), stem cell factor receptor (KIT), and platelet-derived growth factor receptor-alpha (PDGFRα) (7-9). A phase 3 study of lenvatinib in patients with radioactive iodine ablation-refractory (RR)-DTC showed improvement in progression-free survival (PFS) compared to placebo (10). Moreover, lenvatinib exhibited efficacy and safety for patients with ATC [objective response rate (ORR)=24%] in a phase 2 trial (11, 12).

No tumor markers for ATC have been established. Thyroglobulin, a well-known tumor marker for RR-DTC, is widely used for post-operative follow-up and as a supportive indicator for starting MKIs (13). However, thyroglobulin is not suitable for use in ATC patients. In a large Japanese cohort of ATC patients, the presence of acute symptoms, leukocytosis [white blood cell (WBC) count ≥10,000/mm^3), large tumor size (≥5 cm), T stage (T4b), and presence of distant metastases were associated with a poor prognosis (14). These factors are used as a prognostic index to determine the appropriate treatment strategy for ATC, but their use in patients with recurrent or metastatic ATC receiving lenvatinib is not established.

We previously reported that the neutrophil-to-lymphocyte ratio (NLR) can be a prognostic factor for RR-DTC patients treated with lenvatinib (15). The NLR is the absolute number of neutrophils divided by the absolute number of lymphocytes, as determined from a complete blood cell count. A systematic review and meta-analysis reported that

Correspondence to: Dr. Naoki Fukuda, The Cancer Institute Hospital of the Japanese Foundation for Cancer Research 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan. Tel: +81 335200111, Fax: +81 335200141, email: naoki.fukuda@jfcr.or.jp

Key Words: Anaplastic thyroid cancer, neutrophil-to-lymphocyte ratio, lenvatinib, prognostic factors.

Table I. *Patient characteristics (n=13).*

		Number	%
Age	Median (range)	68 (39-80)	
Gender	Male	4	31
	Female	9	69
ECOG PS	0	9	69
	1	4	31
Initial stage (AJCC 8th)	IVB	10	77
	IVC	3	23
Metastatic sites	Lung	10	77
	Lymph node	7	54
	Bone	1	8
Prior therapies	Surgery	10	77
	External beam radiotherapy	6	46
	Chemotherapy	4	31
Pretreatment WBC (/mm^3)	Median (range)	5900 (4300-31500)	
Pretreatment NLR	Median (range)	5.02 (1.34-30.56)	
Leukocytosis		3	23

ECOG PS: Eastern Cooperative Oncology Group performance status; AJCC: American Joint Committee on Cancer; WBC: white blood cell; NLR: neutrophil-to-lymphocyte ratio.

the NLR reflects the balance of systemic immunity while being associated with survival in patients with solid tumors (16). In a phase 2 trial of lenvatinib for treating thyroid cancer patients, including those with ATC, a non-significant trend suggested that pre-treatment NLR is associated with shorter PFS (12). Moreover, in a retrospective cohort study, ATC patients whose NLR increased during follow-up period showed worse prognosis than non-increased patients (17). We, therefore, performed an exploratory analysis of the NLR as a marker lenvatinib treatment for ATC in this study.

Patients and Methods

We retrospectively analyzed recurrent or metastatic ATC patients who were treated with lenvatinib from December 2012 to June 2019 at the Department of Medical Oncology of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research. For all patients, the treatment consisted of 24 mg of once-daily oral lenvatinib. Dose modifications or delays during the treatment schedules were allowed according to the physicians' discretion. Treatment was continued until disease progression, unacceptable toxicity despite appropriate dose reduction and interruption, or the patient's refusal of treatment.

Treatment response was evaluated by computed tomography scans according to Response Evaluation Criteria in Solid Tumors (RECIST) (ver. 1.1) criteria. PFS was defined as the time between the initiation of treatment and disease progression or death by any cause. We defined overall survival (OS) as the time between the initiation of treatment and death by any cause. NLR was defined as the absolute number of neutrophils divided by the absolute number of lymphocytes, as determined from a complete blood cell count.

Table II. *Efficacy of lenvatinib based on the NLR.*

Best overall response	NLR <8 (n=9)	NLR ≥8 (n=4)	*p*-Value
CR	0 (0.0%)	0 (0.0%)	
PR	3 (33.3%)	0 (0.0%)	
SD	5 (55.6%)	1 (25.0%)	
PD	1 (11.1%)	3 (75.0%)	
Objective response	3 (33.3%) (95%CI=7.5-70.1%)	0 (0.0%) (95%CI=0.0-52.7%)	0.50
Disease control	8 (88.9%) (95%CI=51.8-99.7%)	1 (25.0%) (95%CI=0.6-80.6%)	0.05

NLR: Neutrophil to lymphocyte ratio; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; CI: confidence interval.

We used EZR (R ver. 4.0.0) software to perform the statistical analyses (18). Categorical variables were compared by the 2-tailed Fisher's exact test. The PFS and OS were estimated by the Kaplan-Meier method. The HR and *p*-value for OS and PFS were evaluated using the Cox proportional hazard model. The survival results were expressed as the median value with a 95% CI. Statistical significance was defined as $p<0.05$.

This study was approved by the institutional review board of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (no. 2017-1052). The study was conducted in accordance with the Helsinki Declaration of 1964 and later versions. In light of the retrospective nature of this study, the requirement for patients' informed consent was waived by our hospital's institutional review board.

Results

Patient characteristics. Between December 2012 and June 2019, 13 ATC patients were treated with lenvatinib at our Hospital. Patient characteristics are shown in Table I. The median age was 68 years (range=39-80 years), and 4 (31%) patients were males. The initial stage of cancer was IVB in 10 (77%) and IVC in 3 (23%) patients. Ten (77%) patients had previously undergone surgery for primary tumor, 6 (46%) received external-beam radiotherapy, and 4 (31%) received chemotherapy with taxane (paclitaxel or docetaxel). The median size of the largest tumor was 30 mm (range=15-74 mm). The median pre-treatment WBC count and NLR were 5,900/mm^3 (range=4,300-31,500) and 5.02 (range=1.34-30.46), respectively. Leukocytosis (WBC ≥10,000/mm^3) was observed in 3 (23%) patients.

Efficacy of lenvatinib for all patients. Regarding the data cutoff (December 23, 2019), the median follow-up time was 7.3 months (range=1.9-47.5 months). The median PFS was 3.8 months (95%CI=1.8-6.4 months), and the median OS was 10.2 months (95% CI=3.7-17.6 months) (Figure 1A and B). The ORR was 23.1% (95% CI=5.0-53.8), and the disease control rate (DCR) was 69.2% (95% CI=38.6-90.9%).

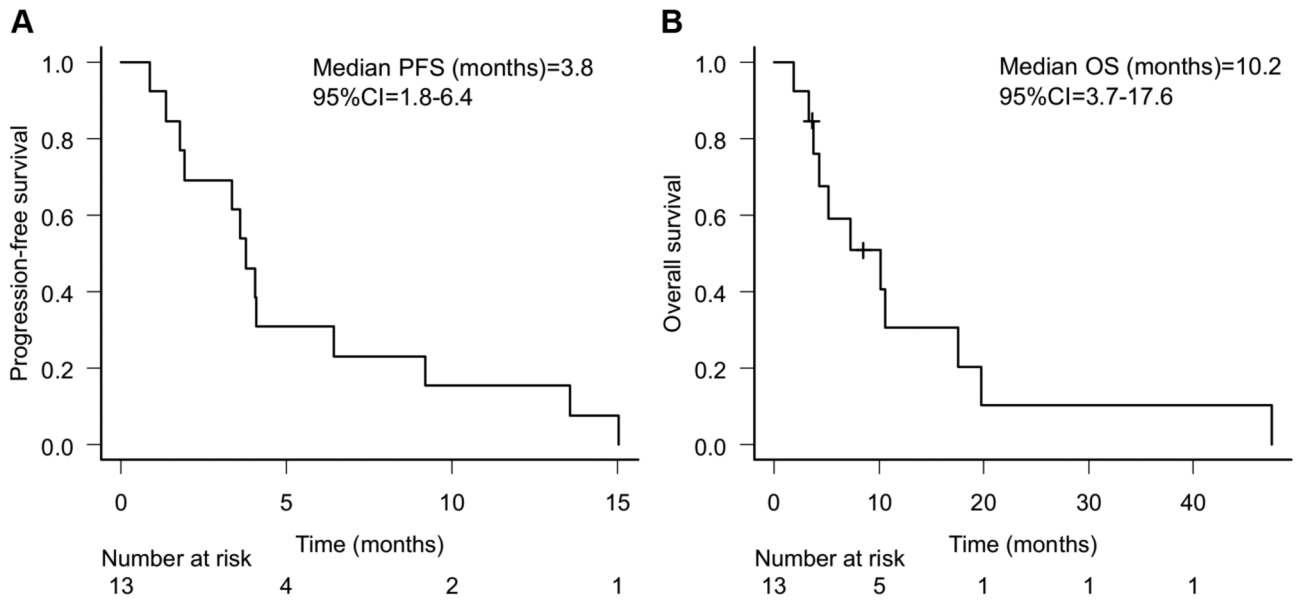

Figure 1. *Kaplan-Meier curves for progression-free survival (PFS) (A) and overall survival (OS) (B).*

Exploratory analysis of the NLR and leukocytosis as prognostic factors. We compared the treatment outcomes of lenvatinib for ATC patients according to baseline leukocytosis and NLR. We set the NLR cutoff value at 8 using receiver operating characteristic (ROC) curve analysis of the DCR. Higher NLR (≥8) and leukocytosis (WBC ≥10,000 mm^3) coexisted in 2 (15%) patients. The ORR was 33.3% (95% CI=7.5-70.1%) in the lower NLR group and 0% (95% CI=0.0-52.7%) in the higher NLR group (p=0.50). The DCR was slightly better in the lower NLR group [88.9% (95% CI=51.8-99.7%)] than in the higher NLR group [25.0% (95% CI=0.6-80.6%)] (HR=3.6, p=0.05) (Table II). The median PFS was significantly longer in the lower NLR group [4.0 months (95% CI=1.8-13.5 months)] compared to the higher NLR group [1.6 months (95% CI=2.3 months–not available)] (HR=3.8, p<0.05). The median OS was also significantly longer in the lower NLR group [10.2 months (95% CI=3.7-19.8 months)] than the higher NLR group [3.8 months (95% CI=1.9 months –not available)] (p<0.05) (Figure 2A and B).

Median OS was significantly longer in patients without leukocytosis (10.6 months *vs*. 4.3 months, p<0.05), similar to patients with a lower NLR. However, there was no significant difference between patients with and without leukocytosis (3.9 months *vs*. 3.4 months, p=0.37) (Figure 2C and D). The DCR was similar regardless of baseline WBC count (70% in patients with leukocytosis and 66% in patients without leukocytosis).

The median NLR value on day 14 (±7) after starting lenvatinib 3.5 (range=1.1-12.5). Patients whose NLR value decreased compared to baseline showed a non-significant trend for higher ORR than patients without NLR decrease (42.9% *vs*. 0%, p=0.19).

Discussion

To date, there are no available tumor markers for ATC patients treated with lenvatinib, such as thyroglobulin for patients with RR-DTC. The results of this exploratory analysis suggest that the NLR is a potential tumor marker that can be readily evaluated in a low-cost manner in ATC patients treated with lenvatinib.

The NLR is reportedly higher in ATC patients than RR-DTC patients (19). Indeed, in our previous report, the median NLR at start of lenvatinib was 2.63 (range=1.35-24.35) in RR-DTC patients, which was lower than the value in the present ATC cohort (15). These results suggest that the NLR is a diagnostic marker that discriminates ATC from RR-DTC. A previous genetic analysis indicated that a portion of ATC cases arise from DTC (20), whereas another study reported that anaplastic transformation accounts for 15% of all ATC cases (21). Moreover, both DTC and ATC can be simultaneously present in a single surgical specimen (22). An increase in NLR may reflect either anaplastic transformation or the coexistence of DTC and ATC. The results of our cohort analysis indicate that the NLR can be useful for detecting these phenomena during active surveillance of RR-DTC and as an indicator of when to initiate lenvatinib therapy.

The presence of leukocytosis was reported as an independent prognostic factor for ATC patients in a Japanese multicenter cohort (14). That cohort was not designed only

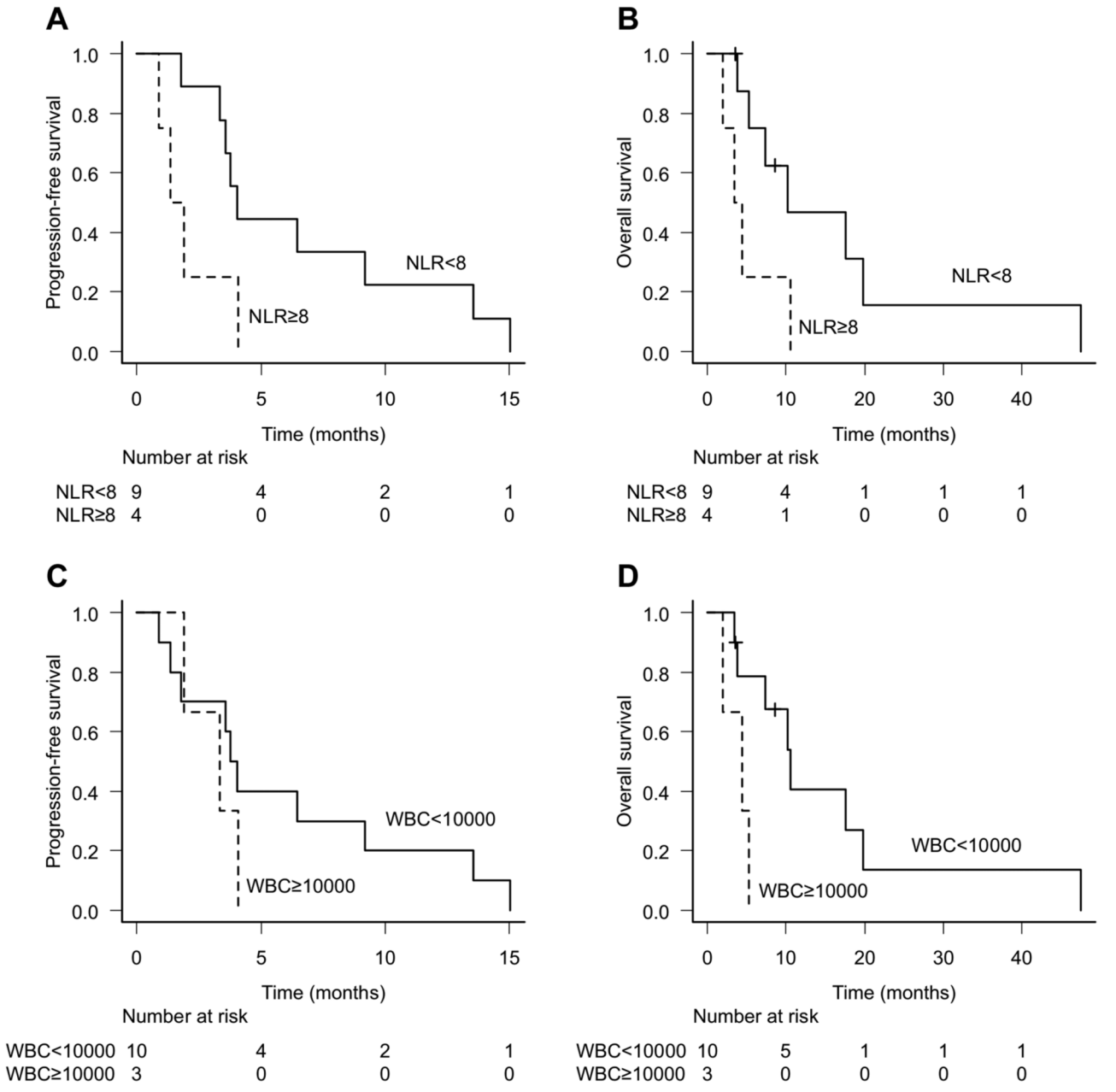

Figure 2. *Kaplan-Meier curves for progression-free survival and overall survival according to the NLR (A, B) and presence of leukocytosis (C, D).*

for metastatic or recurrent setting, as only 50% of the patients received chemotherapy. Moreover, even though all of patients in our cohort were in an unresectable or metastatic setting, only 23% of patients had leukocytosis. Both the PFS and OS were better in the lower-NLR group in our cohort, suggesting that a higher NLR can predict poor prognosis before starting lenvatinib even if leukocytosis is absent.

In the present study, patients whose NLR value on day 14 decreased compared to baseline had better ORR (42.9% *vs.* 0%), although not statistically significant. A previous study described that the patients whose NLR value increased during the follow-up period had a worse OS than patients with whose NLR value did not increase (17). It is also reported that the dynamic changes of the NLR value before and during lenvatinib treatment for patients RR-DTC were associated with disease progression or treatment response (15). Taking together these results, it is suggested that the decrease of NLR value from baseline to day 14 might reflect

disease activity of ATC, and it may enable to estimate the treatment effect of lenvatinib before 1st radiological evaluation.

The median PFS and OS were extremely short (1.6 and 3.8 months, respectively), and the ORR was 0% in patients with higher NLR; therefore, the benefit of lenvatinib for these patients is considered limited. The development of a more effective salvage therapy for these patients is, thus, urgently needed. The addition of pembrolizumab, an anti-programmed cell death 1 (PD-1) antibody, to lenvatinib appears to be a candidate for the next treatment development, although it is still under investigation (22, 23). At present, there are no more-effective options than lenvatinib for ATC patients. As such, we should consider quality of life (QOL) due to the limited efficacy of lenvatinib in ATC patients with a higher NLR. The toxicity of lenvatinib is not always mild, and some of its side-effects, such as appetite loss, diarrhea, fatigue, and palmar-plantar erythrodysesthesia, directly affect patient QOL. Indeed, 76% of the RR-DTC patients in the SELECT trial experienced adverse events of grade ≥3 (10). Therefore, intensive palliative care without chemotherapy may be preferable in some patients. Physicians should carefully consider the balance between risks and benefits when administrating lenvatinib to ATC patients with a higher NLR.

Our study has several limitations. First, this was a retrospective analysis of a small number of patients at a single institute. We could not perform multivariate analyses due to the small number of patients. It is challenging to prospectively analyze a sufficient number of ATC patients, as ATC is an orphan cancer with an extremely high mortality rate. Indeed, although only 17 ATC patients were enrolled in the Japanese phase 2 trial of lenvatinib, it was approved by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan (11). Second, the NLR can be affected by not only tumor progression but also infection, corticosteroids, radiotherapy, or other physiological stresses. Although we used an NLR cutoff value of 8 based on ROC curve analysis, the appropriate cutoff value for ATC patients has not been reported. To resolve these issues and validate our results, a further prospective study will be needed.

In conclusion, we propose that the NLR is a potential prognostic marker for ATC patients treated with lenvatinib. ATC is a rare and extremely fatal disease, and lenvatinib is one of the few therapeutic options for recurrent or metastatic disease. Due to the limited efficacy of lenvatinib, physicians should carefully consider the balance between QOL and expected prognosis when starting patients on lenvatinib for ATC.

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Conflicts of Interest

NF, JT, KT, and ST received personal fees from Eisai. The other Authors have no commercial associations or competing financial interests, either actual or potential, which might create a conflict of interest in connection with the submitted article.

Authors' Contributions

NF wrote the manuscript; YF, KT, XW, AO, TU, NH, YS, KN, MY, MO, JT, HM, and ST contributed critical revisions of the manuscript.

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References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin *68(6)*: 394-424, 2018. PMID: 30207593. DOI:10.3322/caac.21492

2 Ezaki H, Ebihara S, Fujimoto Y, Iida F, Ito K, Kuma K, Izuo M, Makiuchi M, Oyamada H, Matoba N and Yagawa K: Analysis of thyroid carcinoma based on material registered in Japan during 1977-1986 with special reference to predominance of papillary type. Cancer *70(4)*: 808-814, 1992. PMID: 1643612. DOI: 10.1002/1097-0142(19920815)70:4<808::aid-cncr2820700415>3.0.co;2-l

3 Aschebrook-Kilfoy B, Ward MH, Sabra MM and Devesa SS: Thyroid cancer incidence patterns in the United States by histologic type, 1992-2006. Thyroid *21(2)*: 125-134, 2011. PMID: 21186939. DOI: 10.1089/thy.2010.0021

4 Denaro N, Nigro CL, Russi EG and Merlano MC: The role of chemotherapy and latest emerging target therapies in anaplastic thyroid cancer. Onco Targets Ther *9*: 1231-1241, 2013. PMID: 24092989. DOI: 10.2147/OTT.S46545

5 Hundahl SA, Fleming ID, Fremgen AM and Menck HR: A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995. Cancer *83(12)*: 2638-2648, 1998. PMID: 9874472. DOI: 10.1002/(sici)1097-0142(19981215)83:12<2638::aid-cncr31>3.0.co;2-1

6 Kitamura Y, Shimizu K, Nagahama M, Sugino K, Ozaki O, Mimura T, Ito K, Ito K and Tanaka S: Immediate causes of death in thyroid carcinoma: clinicopathological analysis of 161 fatal cases. J Clin Endocrinol Metab *84(11)*: 4043-4049, 1999. PMID: 10566647. DOI: 10.1210/jcem.84.11.6115

7 Matsui J, Funahashi Y, Uenaka T, Watanabe T, Tsuruoka A and Asada M: Multi-kinase inhibitor E7080 suppresses lymph node and lung metastases of human mammary breast tumor MDA-MB-231 *via* inhibition of vascular endothelial growth factor-receptor (VEGF-R) 2 and VEGF-R3 kinase. Clin Cancer Res *14(17)*: 5459-5465, 2008. PMID: 18765537. DOI: 10.1158/1078-0432.CCR-07-5270

8 Matsui J, Yamamoto Y, Funahashi Y, Tsuruoka A, Watanabe T, Wakabayashi T, Uenaka T and Asada M: E7080, a novel inhibitor

that targets multiple kinases, has potent antitumor activities against stem cell factor producing human small cell lung cancer H146, based on angiogenesis inhibition. Int J Cancer *122(3)*: 664-671, 2008. PMID: 17943726. DOI: 10.1002/ijc.23131

9 Okamoto K, Kodama K, Takase K, Sugi NH, Yamamoto Y, Iwata M and Tsuruoka A: Antitumor activities of the targeted multi-tyrosine kinase inhibitor lenvatinib (E7080) against RET gene fusion-driven tumor models. Cancer Lett *340(1)*: 97-103, 2013. PMID: 23856031. DOI: 10.1016/j.canlet.2013.07.007

10 Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, Gianoukakis AG, Kiyota N, Taylor MH, Kim SB, Krzyzanowska MK, Dutcus CE, de las Heras B, Zhu J and Sherman SI: Lenvatinib *versus* placebo in radioiodine-refractory thyroid cancer. N Engl J Med *372(7)*: 621-630, 2015. PMID: 25671254. DOI: 10.1056/NEJMoa1406470

11 Tahara M, Kiyota N, Yamazaki T, Chayahara N, Nakano K, Inagaki L, Toda K, Enokida T, Minami H, Imamura Y, Sasaki T, Suzuki T, Fujino K, Dutcus CE and Takahashi S: Lenvatinib for anaplastic thyroid cancer. Front Oncol *7*: 25, 2017. PMID: 28299283. DOI: 10.3389/fonc.2017.00025

12 Takahashi S, Kiyota N, Yamazaki T, Chayahara N, Nakano K, Inagaki L, Toda K, Enokida T, Minami H, Imamura Y, Fukuda N, Sasaki T, Suzuki T, Ikezawa H, Dutcus CE and Tahara M: A Phase II study of the safety and efficacy of lenvatinib in patients with advanced thyroid cancer. Future Oncol *15(7)*: 717-726, 2019. PMID: 30638399. DOI: 10.2217/fon-2018-0557

13 Malandrino P, Latina A, Marescalco S, Spadaro A, Regalbuto C, Fulco RA, Scollo C, Vigneri R and Pellegriti G: Risk-adapted management of differentiated thyroid cancer assessed by a sensitive measurement of basal serum thyroglobulin. J Clin Endocrinol Metab *96(6)*: 1703-1709, 2011. PMID: 21450986. DOI: 10.1210/jc.2010-2695

14 Sugitani I, Miyauchi A, Sugino K, Okamoto T, Yoshida A and Suzuki S: Prognostic factors and treatment outcomes for anaplastic thyroid carcinoma: ATC Research Consortium of Japan cohort study of 677 patients. World J Surg *36(6)*: 1247-1254, 2012. PMID: 22311136. DOI: 10.1007/s00268-012-1437-z

15 Fukuda N, Wang X, Ohmoto A, Urasaki T, Sato Y, Nakano K, Nishizawa M, Yunokawa M, Ono M, Tomomatsu J and Takahashi S: Sequential analysis of neutrophil-to-lymphocyte ratio for differentiated thyroid cancer patients treated with lenvatinib. In Vivo *34(2)*: 709-714, 2020. PMID: 32111774. DOI: 10.21873/invivo.11828

16 Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, Leibowitz-Amit R, Sonpavde G, Knox JJ, Tran B, Tannock IF and Amir E: Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst *106(6)*: dju124, 2014. PMID: 24875653. DOI: 10.1093/jnci/dju124

17 Yamazaki H, Sugino K, Matsuzu K, Masaki C, Akaishi J, Hames K, Tomoda C, Suzuki A, Uruno T, Ohkuwa K, Kitagawa W, Nagahama M, Masuda M and Ito K: Inflammatory biomarkers and dynamics of neutrophil-to-lymphocyte ratio in anaplastic thyroid carcinoma. Endocrine, 2020. PMID: 32307657. DOI: 10.1007/s12020-020-02313-5

18 Kanda Y: Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant *48(3)*: 452-458, 2013. PMID: 23208313. DOI: 10.1038/bmt.2012.244

19 Cho JS, Park MH, Ryu YJ and Yoon JH: The neutrophil to lymphocyte ratio can discriminate anaplastic thyroid cancer against poorly or well differentiated cancer. Ann Surg Treat Res *88(4)*: 187-192, 2015. PMID: 25844352. DOI: 10.4174/astr.2015.88.4.187

20 Pozdeyev N, Gay LM, Sokol ES, Hartmaier R, Deaver KE, Davis S, French JD, Borre PV, LaBarbera DV, Tan AC, Schweppe RE, Fishbein L, Ross JS, Haugen BR and Bowles DW: Genetic analysis of 779 advanced differentiated and anaplastic thyroid cancers. Clin Cancer Res *24(13)*: 3059-3068, 2018. PMID: 29615459. DOI: 10.1158/1078-0432.CCR-18-0373

21 Pacheco-Ojeda LA, Martínez AL and Alvarez M: Anaplastic thyroid carcinoma in ecuador: analysis of prognostic factors. Int Surg *86(2)*: 117-121, 2001. PMID: 11918236.

22 Bastman JJ, Serracino HS, Zhu Y, Koenig MR, Mateescu V, Sams SB, Davies KD, Raeburn CD, McIntyre RC Jr, Haugen BR and French JD: Tumor-infiltrating T cells and the PD-1 checkpoint pathway in advanced differentiated and anaplastic thyroid cancer. J Clin Endocrinol Metab *101(7)*: 2863-2873, 2016. PMID: 27045886. DOI: 10.1210/jc.2015-4227

23 Iyer PC, Dadu R, Gule-Monroe M, Busaidy NL, Ferrarotto R, Habra MA, Zafereo M, Williams MD, Gunn GB, Grosu H, Skinner HD, Sturgis EM, Gross N and Cabanillas ME: Salvage pembrolizumab added to kinase inhibitor therapy for the treatment of anaplastic thyroid carcinoma. J Immunother Cancer *6(1)*: 68, 2018. PMID: 29996921. DOI: 10.1186/s40425-018-0378-y

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