Sequential Analysis of Neutrophil-to-lymphocyte Ratio for Differentiated Thyroid Cancer Patients Treated With Lenvatinib

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Abstract. Background/Aim: Neutrophil-to-lymphocyte ratio (NLR) has been reported to be associated with poor prognosis for radioactive iodine ablation refractory differentiated thyroid cancer (RR-DTC). Little is known whether NLR can be a tumor marker for RR-DTC patients treated with lenvatinib. Patients and Methods: We retrospectively analyzed RR-DTC patients treated with lenvatinib. NLR was calculated at 4 points before and during lenvatinib treatment. Results: The median NLR value increased at the start of lenvatinib treatment, compared to 6 months prior to initiation of lenvatinib treatment. The median overall survival was significantly longer in patients with the lower NLR (<3) at the start of lenvatinib treatment. The median NLR values decreased when the patients achieved best tumor response, and increased again upon disease progression. Conclusion: NLR values vary before and during lenvatinib treatment, suggesting that this ratio can reflect disease activity of RR-DTC. NLR can supportively be used as a tumor marker of RR-DTC and an indicator for starting lenvatinib treatment.

According to a recent survey by the National Cancer Center Japan, it is estimated that 19,800 new patients will be newly diagnosed and 1,800 patients will die from thyroid cancer in Japan in 2019 (1). The treatment for metastatic or recurrent thyroid cancer depends on its histological subtype.
Statistical significance was defined as median age was 68 years (range=22-83 years), and 14 (42%) patients were male. The histological subtypes were PTC in 29 (88%) and FTC in 4 (12%) patients. All patients had measurable lesions and received surgery for the primary tumor. Six (18%) patients had previously received sorafenib. Three patients were enrolled in the phase III trial for lenvatinib. Six (18%) of the patients were anti-thyroglobulin antibody (TgAb)-positive.

**Efficacy of lenvatinib for all patients.** As of February 14th 2019, the median follow-up time was 15.4 months (range=0.6-69.0 months). The median PFS was 12.0 months (95%CI=6.9-34.4) and the median overall survival (OS) was 23.1 months (95%CI=12.0-NR) (Figure 1). Objective response rate (ORR) was 60.6% (95%CI=42.1-77.1).

**NLR values and treatment outcomes of lenvatinib for RR-DTC patients.** We compared the treatment outcomes of lenvatinib for RR-DTC patients, according to the NLR values at the start of lenvatinib treatment. ORR was 69.6% (95%CI=47.1-86.8) in the lower NLR (NLR<3) group and 40.0% (95%CI=12.2-73.8) in the higher NLR (NLR≥3) group (p=0.28). Disease control rate (DCR) was 95.7% (95%CI=78.1-99.9) in the lower NLR group and 60.0% (95%CI=26.2-87.8) in the higher NLR group (p=0.07) (Table II). The median PFS was 20.3 months (95%CI=6.9-34.7) in the lower NLR group and 12.0 months (95%CI=2.3-NR) in the higher NLR group (p=0.35). The median OS was significantly longer in the lower NLR group [35.0 months (95%CI=17.2-NR)] than in the higher NLR group [11.9 months (95%CI=4.0-NR)] (p<0.05) (Figure 2).

**Changes of NLR values before and during lenvatinib treatment.** We next evaluated the changes in NLR values before and...
during lenvatinib treatment for RR-DTC patients. The median NLR value significantly increased at the start of lenvatinib treatment [2.63 (range=1.35-24.35)] (p<0.01) compared to that at 6 months (median 5.8 months, range=3.5-9.7 months) before starting lenvatinib [2.17 (range=1.13-11.80)] (Table III). For patients who achieved partial response (N=20), the median NLR significantly decreased from 2.54 (range=1.35-5.92) to 1.73 (range=1.16-3.36) at the time patients achieved best tumor response (p<0.001). However, the median NLR values increased again up to 6.36 (range=1.12-54.58) upon disease progression (p<0.01). This trend was not observed in patients who did not respond to lenvatinib (N=13) (Table IV).

**Discussion**

To the best of our knowledge, no other study has evaluated the NLR values sequentially before and during lenvatinib treatment in RR-DTC patients.

Between 6 months before starting lenvatinib and at the start of lenvatinib treatment, the NLR values significantly increased in patients with RR-DTC. During these 6 months, disease progression was observed and it became necessary to start lenvatinib in all of the patients. In the previous large surgical cohort of thyroid cancer patients, the median NLR value was 1.57, which was lower than the value observed in our study at the start of lenvatinib treatment (13). This may be explained by the differences in patient characteristics. In the surgical cohort, few patients had recurrent or metastatic disease, whereas all of the patients had recurrent or metastatic disease in our study. During lenvatinib treatment, the NLR values significantly decreased in RR-DTC patients who responded to lenvatinib, whereas NLR did not decrease in patients who did not respond to lenvatinib. The patients

**Table II. Efficacy of lenvatinib according to neutrophil to lymphocyte ratio (NLR) value.**

| Best overall response | NLR <3 (n=20) | NLR ≥3 (n=13) | p-Value* |
|-----------------------|--------------|--------------|---------|
| CR                    | 0            | 0            |         |
| PR                    | 14 (70%)     | 6 (46%)      |         |
| SD                    | 5 (25%)      | 3 (23%)      |         |
| PD/NE                 | 1 (5%)       | 4 (31%)      |         |
| Objective response    |              |              |         |
| (95%CI=46-88)         |              |              |         |
| Disease control       | 19 (95%)     | 9 (69%)      | 0.28    |
| (95%CI=75-100)        |              |              |         |

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluated; CI: confidence interval.
with lower baseline NLR values demonstrated better OS. The PFS, ORR, and DCR were also slightly better in patients with lower baseline NLR. In the phase II trial of lenvatinib, a similar non-significant trend was observed in PFS (baseline NLR ≥3 vs <3, HR=1.67, 95%CI=0.78-3.55, p=0.18), as shown by the multivariate analysis (7). Consequently, NLR values correlate with tumor activity in RR-DTC patients, and can supportively be used as a prognostic and predictive marker for RR-DTC patients treated with lenvatinib.

Although RR-DTC is originally an indolent malignancy with slow progression, it sometimes becomes an aggressive and life-threatening disease in metastatic or recurrent patients. Therefore, it is an important and difficult question when to start systemic therapy including lenvatinib. The phase III trials of multi-kinase inhibitors for RR-DTC, enrolled patients who had confirmed disease progression by the RECIST criteria within 12-14 months (6, 15). This can be one of the indicators for deciding to start lenvatinib treatment. Thyroglobulin levels have also been studied as a tumor marker for DTC (16). In the SELECT trial, baseline thyroglobulin levels were associated with poorer PFS in RR-DTC (17). It has been reported that a shorter thyroglobulin doubling time (<1 year) is associated with a poor prognosis (18). Therefore, in clinical practice, a shorter thyroglobulin doubling time (<1 year) is also one of the indicators to start lenvatinib treatment. However, these indicators are not always available. It is often difficult to measure diffuse pulmonary metastases or bone metastases using the RECIST criteria. The measurement of thyroglobulin is affected by anti-thyroglobulin antibodies (TgAb) (19). It has been reported that 17-29% of DTC patients have anti-thyroglobulin antibodies, which makes it difficult to use thyroglobulin as a universal tumor marker for RR-DTC (20, 21). In fact, 18% of the patients were TgAb-positive in our

| Table III. Change of neutrophil to lymphocyte ratio (NLR) for radioactive iodine ablation refractory differentiated thyroid cancer (RR-DTC) patients before treatment. |
|---------------------------------------------|
| At 6 months before starting lenvatinib | At the start of lenvatinib | p-Value |
| Median NLR (range) | 2.17 (1.13-11.80) | 2.63 (1.25-24.36) | <0.01 |

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluated; CI: confidence interval.
study. Our results suggested that NLR can be supportively used as an indicator to start lenvatinib treatment, in combination with tumor size and thyroglobulin doubling time.

Our study has several limitations. First, this was a retrospective analysis of a small number of patients at a single institute. Second, the value of NLR is easily affected not only by tumor progression but also by infection, corticosteroids, radiotherapy, or other physiological stresses. Though we used a cutoff value of 3 for NLR according to the previous report, the appropriate cutoff value is still controversial. We are now planning a prospective cohort study to resolve these limitations.

In conclusion, our study suggested that the NLR values may reflect tumor activity in RR-DTC patients before and during lenvatinib treatment. NLR can supportively be used as a tumor marker and an indicator for starting lenvatinib treatment.

Conflicts of Interest

Takahashi S received grants and personal fees from Eisai, Novartis, Taiho, MSD, Chugai, Daiichi-Sankyo, Bayer and AstraZeneca. Fukuda N and Tomomatsu J received personal fees from Eisai. The Authors declare no other conflicts of interest associated with this manuscript.

Authors’ Contributions

Fukuda N wrote the manuscript; Wang X, Omoto A, Urasaki T, Sato Y, Nakano K, Nishizawa M, Yunokawa M, Ono M, Tomomatsu J, and Takahashi S contributed to the critical revision of the manuscript.

References

1 N.C.C.I. Japan, Projected Cancer Statistics (2018). Available at: http://ganjoho.jp/en/public/statistics/short_pred.html

2 Pacini F, Ito Y, Luster M, Pitoia F, Robinson B and Wirth L: Radioactive iodine-refractory differentiated thyroid cancer: unmet needs and future directions. Expert Rev Endocrinol Metab 7(5): 541-554, 2012. PMID: 30780891. DOI: 10.1586/een.12.36

3 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

4 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

5 Okamoto K, Kodama K, Takase K, Sugi NH, Yamamoto Y, Iwata M and Tsuura 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

6 Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brouse MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, Giannoukakis AG, Kiyota N, Taylor MH, Kim SB, Krzyzanowska MK, Duthe 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

7 Takahashi S, Kiyota N, Yamazaki T, Chayahara N, Nakano K, Usaki T, Sato Y, Nakano K, Nishizawa M, Yunokawa M, Ono M, Tomomatsu J, and Takahashi S contributed to the critical revision of the manuscript.

8 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

Table IV. Neutrophil to lymphocyte ratio (NLR) change during lenvatinib treatment for radioactive iodine ablation refractory differentiated thyroid cancer (RR-DTC) patients according to tumor response.

| Tumor response | At the start of lenvatinib | At the best tumor response | At disease progression |
|----------------|----------------------------|----------------------------|------------------------|
|                | p-value (start to best)    | p-value (best to PD)       |                        |
| All patients (n=33) | 2.63 (1.25-24.36)          | 1.94 (1.00-16.39)          | 5.69 (1.12-54.58)       |
| NLR (median, range) | p=0.03                     | p=0.03                     |                        |
| Responder (PR) (n=20) | 2.54 (1.35-5.92)           | 1.73 (1.16-3.36)           | 6.36 (1.12-54.58)       |
| NLR (median, range) | p<0.001                    | p<0.01                     |                        |
| Non-responder (SD+PD+NE) (n=13) | 2.29 (1.86-11.13)       | 2.63 (2.05-16.39)          | 2.91 (2.11-3.41)        |
| NLR (median, range) | p=0.58                     | p=0.81                     |                        |

PR: Partial response; SD: stable disease; PD: progressive disease; NE: not evaluated; CI: confidence interval.
9 Rosenberg SA: Progress in human tumour immunology and immunotherapy. Nature 411(6835): 380-384, 2001. PMID: 11357146. DOI: 10.1038/35077246

10 Chen ZY, Raghav K, Lieu CH, Jiang QZ, Eng C, Vauthey JN, Chang GJ, Qiao W, Morris J, Hong D, Hoff P, Tran H, Menter DG, Heymach J, Overman M and Kopetz S: Cytokine profile and prognostic significance of high neutrophil-lymphocyte ratio in colorectal cancer. Br J Cancer 112(6): 1088-1097, 2015. PMID: 25688736. DOI: 10.1038/bjc.2015.61

11 Kim JY, Park T, Jeong SH, Jeong CY, Ju YT, Lee YJ, Hong SC, Ha WS, Choi SK and Jung EJ: Prognostic importance of baseline neutrophil to lymphocyte ratio in patients with advanced papillary thyroid carcinomas. Endocrine 46(3): 526-531, 2014. PMID: 24272600. DOI: 10.1007/s12020-013-0089-6

12 Manatakis DK, Tseleni-Balafouta S, Balalis D, Soulou VN, Korkolis DP, Sakorafas GH, Plataniotis G and Gontikakis E: Association of baseline neutrophil-to-lymphocyte ratio with clinicopathological characteristics of papillary thyroid carcinoma. Int J Endocrinol 2017: 8471235, 2017. PMID: 28572821. DOI: 10.1155/2017/8471235

13 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

14 Kanda Y: Investigation of the freely-available easy-to-use software “EZR” (Easy R) for medical statistics. Bone Marrow Transplant 48: 452-458, 2013. PMID: 23208313. DOI: 10.1038/bmt.2012.244

15 Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, de la Fouchardiere C, Facini F, Paschke R, Shong YK, Sherman SI, Smit JW, Chung J, Kappeler C, Peña C, Molnár I and Schlumberger MJ; DECISION investigators: Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet 384(9940): 319-328, 2014. PMID: 24768112. DOI: 10.1016/S0140-6736(14)60421-9

16 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

17 Tahara M, Schlumberger M, Elisei R, Habra MA, Kiyota N, Paschke R, Dutcus CE, Hihara T, McGrath S, Matijevic M, Kadowaki T, Funahashi Y and Sherman SI: Exploratory analysis of biomarkers associated with clinical outcomes from the study of lenvatinib in differentiated cancer of the thyroid. Eur J Cancer 75: 213-221, 2017. PMID: 28237867. DOI: 10.1016/j.ejca.2017.01.013

18 Miyauchi A, Kudo T, Miya A, Kobayashi K, Ito Y, Takamura Y, Higashiyama Y, Fukushima M, Kihara M, Inoue H, Tomoda C, Yabuta T and Masuoka H: Prognostic Impact of serum thyroglobulin doubling-time under thyrotrpin suppression in patients with papillary thyroid carcinoma who underwent total thyroidectomy. Thyroid 21(7): 707-716, 2011. PMID: 21649472. DOI: 10.1089/thy.2010.0355

19 Rosário PW, Maia FF, Fagundes TA, Vasconcelos FP, Cardoso LD and Purisch S: Antithyroglobulin antibodies in patients with differentiated thyroid carcinoma: methods of detection, interference with serum thyroglobulin measurement and clinical significance. Arq Bras Endocrinol Metabol 48(4): 487-492, 2004. PMID: 15761511. DOI: 10.1590/s0004-2730200400000008

20 Kumar A, Shah DH, Shrihari U, Dandekar SR, Vijayan U and Sharma SM: Significance of antithyroglobulin autoantibodies in differentiated thyroid carcinoma: methods of detection, interference with serum thyroglobulin measurement and clinical significance. Endocrine 11:257-262, 2004. PMID: 15761511. DOI: 10.1089/end.2004.11.257

21 Görges R, Maniecki M, Jentzen W, Shew SN, Mann K, Bockisch A and Janssen OE: Development and clinical impact of thyroglobulin antibodies in patients with differentiated thyroid carcinoma during the first 3 years after thyroidectomy. Eur J Endocrinol 153(1): 49-55, 2005. PMID: 15994745. DOI: 10.1530/eje.1.01940

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