Peer Review File

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Reviewer A

This is an interesting study about NLR and prognosis of lenvatinib treatment for anaplastic thyroid carcinoma. Unfortunately, there was no correlation, but anyway the study seems interesting for publication.

Comment 1: What do you mean by stable condition?

Reply 1: We intended that a stable condition had no other inflammatory factor such as infection. We modified text as advised (see Page 7, line 12).

Change in the text: Baseline CBC data were obtained while the patients were in a stable condition, which had no other inflammatory factor such as infection, before undergoing surgery or core needle biopsy for ATC.

Comment 2: Did you measure any other inflammatory marker?

Reply 2: We did not measure other inflammatory markers such as CRP and pre-albumin. This study is a retrospective study, and those items were not measured necessarily before starting the treatment of lenvatinib.

Change in the text: No change.

Comment 3: May NLR vary by underlying disease (comorbidities)?

Reply 3: All patients had no comorbidities which could influence the baseline inflammatory values. We modified text as advised (see Page 7, line 6-7).

Change in the text: All patients had no comorbidities such as autoimmune disease, and did not take a medicine such as steroid and other immunosuppressant.

Comment 4: May NLR vary dependent on if the patient got surgery or not? Patient who did not receive surgery may have more advanced tumor stage (resectable vs unresectable).

Reply 4: No significant differences in baseline inflammatory biomarkers were observed between ATC patients whose primary thyroid tumor was resectable and unresectable. We added some data (see Page 9, line 13-18).

Change in the text: No significant differences in baseline inflammatory biomarkers were observed between ATC patients whose primary thyroid tumor was resectable (n = 6) and unresectable (n = 14) [median NLR: resectable, 4.9 (range, 1.8–19.7) vs. unresectable, 4.4 (range, 1.4–16.7); p = 0.509, median PLR: resectable, 230.3 (range, 66.–671.1) vs. unresectable, 164.4 (range, 68.2–377.6); p = 0.547, median LMR: resectable, 2.7 (range, 0.5–4.1) vs. unresectable, 2.6 (range, 1.6–5.5); p = 0.901].

Reviewer B

This is a negative result from a retrospective small-sampled study, which concluded that there is no association between prognosis or treatment efficacy of lenvatinib and baseline inflammatory biomarker values (NPL, PLR) in cases with anaplastic thyroid carcinoma. If authors could discuss more issues in manuscript, it still could provide some information for clinical practice.

The following issues are suggested to address more in content:

Comment 1: 1. The mechanism of cancer-related inflammatory or immune response correlated to the proliferation and survival of tumor cells, angiogenesis and prognosis should be reinforced in introduction.

Reply 1: We modified text as advised (see Page 5, line 17-18, Page 6, line 1).

Change in the text: Inflammatory responses play decisive roles at different stages of tumor development, including initiation, promotion, malignant conversion, invasion, and metastasis. Inflammation also affects immune surveillance and responses to

therapy [6].

Comment 2: A comprehensive review and discussion of the previously positive and negative roles of NLR, PLR in predicting the anti-cancer treatment or prognosis for different cancers, especially thyroid cancer.

Reply 2: We discussed about this and modified text as advised (see Page 12, line 4-9).

Change in the text: The NLR, which can be determined inexpensively and routinely measured in daily oncological practice, may be useful for identifying high-risk patients. The NLR has been indicated as the factor associated with recurrent risk, treatment resistance, and metastasis prediction among patients with differentiated thyroid carcinoma (DTC) and medullary thyroid carcinoma (MTC) [7, 22]. Additionally, it is suggested that preoperative PLR was associated with advanced stage in DTC and MTC [23, 24]. This is the first study, as far as we know, that refer to PLR in lenvatinib treatment for ATC.

Comment 3: Discuss the potential physio-pathologic mechanisms for the negative results from this study.

Reply 3: We thought the possibility that lenvatinib efficacy might be correlated with the expression of its target receptors in tumor tissue. We modified text as advised (see Page 13, line 6-16).

Change in the text: We have previously examined the association between the treatment efficacy of lenvatinib and the expression of target receptors in ATC tissues, and reported that the fibroblast growth factor receptor 4 expression was associated with treatment efficacy [29, 30]. Additionally, the same association has also been shown in hepatocellular carcinoma (HCC) [31]. Therefore, the response to lenvatinib might be influenced not only by baseline inflammatory biomarkers but also the expression of target receptors.

Comment 4: Discuss the potential negative predictive effect of PLR by lenvatinib treatment, which could inhibit platelet-derived growth factor receptor a (PGDFRa).

Reply 4: We discussed about this and modified text as advised (see Page 13, line 11-16).

Change in the text: In this study, there was no association between baseline PLR value and treatment efficacy though lenvatinib inhibits PDGFR. One possible reason is that lenvatinib shows antitumor effect by mainly inhibiting vascular endothelial growth factor 2 [29]. Another possible reason is that the expression of PDGFRa in tumor tissue may be more correlated with efficacy than PLR value. There is no report on the expression of PDGFRa and lenvatinib treatment, and further study is needed to investigate this association.

Comment 5: It could present a dynamic change of the NLR and PLR because of many interference factors. The appropriate time period to assess NLR or PLR is also an important issue to discuss more.

Reply 5: We discussed about this and modified text as advised (see Page 14, line 10-16).

Change in the text: Nakano et al. evaluated the changes in the NLR before and one month after molecular-targeted treatment which included lenvatinib and reported that HCC patients with decreased neutrophil-to-lymphocyte ratio survived significantly longer than patients with increased neutrophil-to-lymphocyte ratio [32]. In our study, we collected NLR data of the first two months after initiation of lenvatinib based on SELECT trial, but the trial included only DTCs. Since ATCs progress rapidly compared with DTC, we may need to evaluate the change of NLR at shorter interval like HCC. Further prospective study is needed to determine the appropriate evaluation interval.