Neutrophil to lymphocyte ratio: another drop in the ocean of CRPC biomarkers?

This issue of Annals of Oncology reports on the results of two retrospective studies addressing the prognostic role of neutrophil to lymphocyte ratio (NLR), an easily derived circulating biomarker that could be obtained from a routine blood test. During the last decade, several new agents for castration-resistant prostate cancer (CRPC), including cabazitaxel, sipuleucel-T, abiraterone acetate, enzalutamide and radium-223, have shown an impact on overall survival (OS), which led to their regulatory approval. However, the best sequence of these therapies remains unclear in some settings as definitive data are lacking and no expert consensus has been reached. Thus, such decisions largely depend on available options and the physician’s experience, which could be assisted in stratifying the progression/death risk of metastatic CRPC (mCRPC) patients through the use of classical prognostic makers and/or nomograms.

A previous retrospective analysis of the TAX327 trial [1] identified several factors associated with OS, including performance status (PS), site of metastasis, pain level, alkaline phosphatase (ALP), haemoglobin, PSA, albumin, lactate dehydrogenase (LDH), and time since diagnosis [2-4]. In addition to these variables, in the post-docetaxel setting, the duration of first-line chemotherapy, whether progression occurred during chemotherapy, and the time from diagnosis to second-line chemotherapy can be used to predict survival [5]. Prognostic nomograms using these variables have also been developed and validated in men receiving first- and second-line chemotherapy. Nonetheless, an update of these nomograms’ ability to predict survival in CRPC is required since the advent of highly effective novel therapies that have an impact on survival [6].

A biomarker is defined as ‘a characteristic that is objectively measured and evaluated as an indicator of normal biological or pathogenic processes, or of pharmacological responses to a therapeutic intervention’ [7]. In the current mCRPC scenario, there are several drugs with diverse mechanisms, showing activity in a subset of patients while others remain primarily resistant. The efficient ‘a priori’ discrimination between both populations is still required. The development of novel biomarkers, which are truly indicative of tumour biology and/or tumour-host interaction, should enable individual patient risk stratification and improve treatment benefit prediction. Tumour biopsies are a technical and ethical challenge in the mCRPC setting, and circulating biomarkers have been suggested as an approach that is both less harmful and simpler to repeat.

An NLR is a measure of the proportion of systemic neutrophils and lymphocytes, and therefore serves as a potential circulating biomarker of cancer-related host inflammation, which in recent years has been recognized as one of the hallmarks of cancer progression [8]. Utilizing NLR is not a completely new method, as it has been shown to be associated with adverse outcomes in a large variety of tumour types (mesothelioma, bladder cancer, renal cancer, colon cancer, ovarian cancer, and gastric cancer) [9]. Although the studies reported by van Soest et al. [10] and Lorente et al. [11] in this issue are not the first to analyse the role of this biomarker in mCRPC, they add solid evidence to the independent value of NLR as a prognostic biomarker for mCRPC. All the same, is NLR really adding to the field compared with other biomarkers?

In the first study, van Soest et al. [10] began by testing the prognostic value of derived (d)NLR (as a lymphocyte count was not always available, they estimated the number of lymphocytes from subtracting the number of neutrophils to the total white cell count) in the VENICE trial [12] database using a ratio of <2 versus ≥2 as cut-off. They then confirmed that a dNLR of <2 was significantly associated with improved OS in the TAX327 [11] patients. Lorente et al. [11] used the TROPIC trial [13] database to find that a dNLR of <3 (median NLR distribution was 3.1) was independently associated with improved OS in mCRPC patients receiving second-line chemotherapy. Furthermore, Lorente et al. [11] have shown that conversion from unfavourable (NLR ≥3) to favourable (NLR <3) NLR during the first 12 weeks of treatment was associated with higher rates of PSA response and with improved OS. Of note, multivariable analyses in both studies confirmed the independent prognostic value of NLR (or dNLR), even though some prognostic factors were not included (i.e. LDH which was not collected in the TROPIC trial nor in the TAX327 trial). Finally, both authors explored, although ultimately unsuccessfully, whether NLR has any predictive value for the response to first-line or second-line taxanes (docetaxel versus mitoxantrone; cabazitaxel versus mitoxantrone).

Based on the results described above and the simplicity of the routine blood test required to measure NLR, physicians treating mCRPC may be tempted to implement it in daily clinical practice together with the other analytical biomarkers currently used. However, the optimal cut-off to consider NLR count favourable or unfavourable is still unclear, as it varies from one study to another [10, 11, 14-16]. Furthermore, there is still the possibility that NLR should be considered as a continuous variable. In either case, we must ask how much would it improve the prognostic ability of currently available biomarkers. Although both studies have proved that the prognostic value of baseline NLR is independent of other well-established prognostic variables (i.e. PSA levels, PS, metastatic site, presence of pain, and ALP) Lorente et al. have shown that the addition of NLR to Halabi’s nomogram for second-line chemotherapy [5] did not improve its prognostic ability.

The recent demonstration of improved survival with immunotherapy in men with mCRPC suggests the prognostic importance of immune function in this setting [17]. In contrast with targeted therapy, in which a majority of patients achieve an objective response, the main limitation of immunotherapy to date is that only a minority of patients will respond, although responses that do occur tend to be more durable. Immune biomarkers that are easy to implement in clinical practice are needed to identify patients who may benefit from those therapies, as well as to
monitor their response to these treatments. Since NRL may be an indicator of the inflammatory and immune state of the host and of his response to prostate cancer, studies assessing its role in immunotherapy strategies should be considered.

In this context, we should not ignore the potential biological interactions between NLR and the use of corticosteroids, as they are commonly used long term in CRPC. Corticosteroids cause an accelerated release of neutrophils from the bone marrow into the circulation and reduce the number of neutrophils moving out of the circulation, by impairing the ability of neutrophils to adhere to vessels walls and migrating from the circulation into the tissue. Besides, corticosteroids induce lymphocytopenia as a result of redistribution of circulating lymphocytes into other lymphoid compartments (e.g. spleen, lymph nodes, and bone marrow) [18, 19]. Consequently, one would expect that those patients on corticosteroids would present a higher NLR. Lorente et al. are the first to assess the impact of corticosteroids on baseline NLR. As expected, a median NLR was higher in patients receiving corticosteroids at baseline compared with those who did not (3.9 versus 2.9). When baseline corticosteroid use was included in the prognostic model, a baseline NLR remained significant; however, dose and duration of corticosteroid treatment were not analysed in this model.

In conclusion, the NLR adds evidence to the implication of white cell subsets in mCRPC prognosis and current results confirm its independent, albeit limited, prognostic value in first- and second-line chemotherapy. Nonetheless, its role as a prognostic and/or predictive factor for immunotherapy in mCRPC would need to be evaluated in further studies.

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references