Does a simple hematological examination predict the response and side effects in patients undergoing induction chemotherapy and/or neoadjuvant chemotherapy?

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Locally advanced cancers or advanced-stage cancers, regardless of which organs are related, are still a biggest challenge in the modern cancer treatment, because of therapeutic difficulty, poor compliance, or intolerability of the patients.[1–3] Systematic treatment, such as chemotherapy, especially prior to the definite curative therapy (called neoadjuvant chemotherapy-NACT), such as radiation therapy or surgical intervention, has been generally accepted in the management of various kinds of cancers and also has remarkably improved the outcome of these patients. However, it remains uncertain who will benefit from this treatment, although the following recommendations are suggested for the use of NACT or induction chemotherapy for patients with locally advanced cancers, large-size tumor, tumor involving the regional lymph node, or patients who prefer primary tumor reduction to achieve a better cosmetic result or have a better chance of total eradication of tumors, or patients who require the postponements of surgeries due to physical inability.[4–6] Therefore, significant efforts to determine patients who would most likely benefit from NACT and/or induction chemotherapy have consistently been made by physicians and researchers. However, only a few parameters are suggested as predictors of tumor response after NACT treatment.[4] Additionally, there are also few parameters available to predict the adverse events of patients who undergo this treatment.

We are happy to introduce the study by Liu and Lin,[7] published in the last November issue of the *Journal of the Chinese Medical Association*, on the investigation of predictive factors associated with good response and incidence of acute toxicity of patients with advanced-stage head and neck cancers after docetaxel-combined induction chemotherapy. The authors performed a retrospective study to evaluate the value of hematological parameters on the aforementioned aims. The authors found that low platelet-lymphocyte ratio (PLR) (<8.5) and higher white cell counts (WBC ≥ 10.3 × 10^3/μL) could be used as independent predicting factors of better overall response after induction chemotherapy and additionally, higher neutrophil-lymphocyte ratio-NLR (≥ 3.5) and serum potassium ≥ 3.9 mEq/L were an independent predictive factors of acute toxicities more than grade III after induction chemotherapy.[7] This study is interesting and worthy of discussion.

At first, is it strong enough to use peripheral hematological parameters as a prognostic factor? Cancer development and progression seemed to be associated with local (tumor microenvironment) and systemic inflammation as well as alternation in antitumor immunity, various kinds of cytokines, such as interleukin, as well as immune cells and others, including tumor infiltrating lymphocytes, tumor-associated neutrophils, M2 polarized macrophages, FOXP3 positive regulatory T cells, and platelets.[8,9] Among these, the role of neutrophils, platelets, and lymphocytes attracts the researchers' interest, because they can be easily obtained by simple blood test. Neutrophils can exist in distinct and dynamically changing phenotypic states that can be shaped by the primary tumor as well as other host cells.[10] Neutrophils mediated by CCL2 can inhibit metastases, but it only works in certain instances. It is reported that neutrophils exert immunosuppressive function by inhibiting cytotoxic $CD8^+$ T cell response and the intraluminal clearance of carcinoma cells by natural killer cells and accelerate the metastatic process, mediated by neutrophil extracellular traps, which capture tumor cells in the circulation with prolonged survival intraluminally, adherence to endothelial cells, and extravasation.[10] The assistance of tumor metastases is also mediated by platelets. Cancer cells rapidly associate with platelets, and interaction that is triggered by tissue factor displayed on the surface of the cancer cells, leading to not only imbalances in the normal homeostatic control on coagulation, for example, formation of microthrombi, disseminated intravascular coagulation, and pulmonary emboli, but also protection from elimination by cellular arms of the immune system. For example, adhered platelets can prevent cancer cell recognition and lysis by natural killer cells.[10] Based on aforementioned observation, it is rationale to suppose the close correlation between these peripheral blood parameters and outcome of tumors. However, all focus on their action in circulation (circulating cancer cells and metastases), but does the phenomenon

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fit the head and neck cancer? The morbidity and mortality of the head and neck cancer is often the result from extensive local destruction, such as direct invasion to the main vital organs or main blood vessels, and distant metastases seemed to be rare in patients with head and neck tumors. Therefore, the immune response might be more similar to the wound healing in head and neck cancers with extensive and local destruction, which all involve the immune system and local reaction.[11–13]

Second, the cutoff value of the ratio, such as NLR, and PLR, seems to be varied greatly. Of most importance, the thresholds of NLR or PLR are also changed when they are applied for the different purpose. In Liu and Lin's study, we found that the authors used the NLR of 4.4, and PLR as 8.5 to predict the overall response after treatment, and by contrast, NLR of 3.5 and PLR of 15 were applied to evaluate the grade III acute toxicity after treatment. We are wondering how can be used in clinical routine practice. No standard cutoff value could be followed, suggesting that every institute should be establish their own standard reference. In fact, we do not neglect the potential value of using these simple parameters for our patients. By contrast, we totally agree with its value, because there are many studies to show the association of NLR greater than the cutoff with worse overall survival in several cancers, and this observation is also apparent in the higher PLR associated with poor outcomes in cancers.[8,9,14,15] In addition, the response rate of treatment and toxicity after treatment is also reported to be closely correlated with NLR and PLR.[7,14,16] However, we should be concerned about the reproducibility and easy use, since it may be relatively difficult to follow if physicians would like to apply this simple examination into the clinical routine practice without their own standard reference.

Taken together, systematic inflammatory response might be easily evaluated and the predictor value is widely accepted. Since a lot of uncertainties, such as the cutoff value of these hematological parameters are present, we welcome more and more studies to explore this topic.

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