Neutrophil to lymphocyte ratio in immunotherapy for malignancies

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ABSTRACT In the quest for a simple and effective biomarker for PD-1 antibody efficacy many candidates have emerged. The simplest one is the ratio between neutrophils and lymphocytes (NLR) in peripheral blood. Since 2012 the emergence of checkpoint inhibitor therapy has introduced a new paradigm in cancer therapy, adding a powerful tool in the oncology treatment armamentarium. The progress achieved in clinical trials has revealed efficacy in different tumor types and with different immunotherapy combinations. However optimal duration of therapy, optimal dose, optimal schedule, are for the most part unknown. In this review we will discuss the utility of information obtained from the peripheral blood CBC as a contributor to solving this question.

KEYWORDS pd1, pdl 1, checkpoint inhibitors, neutrophil to lymphocyte ratio

Since 2012 the emergence of checkpoint inhibitor therapy has introduced a new paradigm in cancer therapy, adding a powerful tool in the oncology treatment armamentarium. The progress achieved in clinical trials has revealed efficacy in different tumor types and with varying combinations of immunotherapy. However, the optimal duration of therapy, optimal dose, optimal schedule, are for the most part unknown. Current treatment recommendations are to treat until progression or for an arbitrary period such as 24 months.

The impact on cost, adverse events, quality of life and efficacy need to be considered. T-cell exhaustion needs to be taken into consideration and measured. The presence of brain metastases may be an essential variable in treatment planning.

One Phase I study of pembrolizumab looked at 1,3, or 10mg/kg doses and treated until progression, they concluded that robust clinical activity would be observed at doses equal to or greater than 2mg/kg.[1] The standard dose of pembrolizumab used today is a fixed dose of 200mg every three weeks.

Patients who have stopped early due to adverse events, seem to fare no worse than those that have continued treatment — especially those who have achieved a complete response.

One theory suggests that intermittent treatment may be more beneficial as it is less likely to cause t-cell exhaustion. Retreatment on recurrence may be just as, or more effective as continuing treatment until progression. However, a recent trial with nivolumab failed to show the benefit in progression-free survival using this strategy. [2] In the CheckMate-153 study, those who were treated continuously had significantly improved PFS compared with those who stopped nivolumab (hazard ratio [HR], 0.43; 95% CI, 0.25-0.76), according to a presentation of the findings at the 2017 ESMO Congress in Madrid.

Information on the optimal duration of checkpoint inhibitors is being explored in the design of a randomised phase III study of duration of anti-PD-1 therapy in metastatic melanoma (STOP-GAP): Canadian Clinical Trial Group study (CCTG) ME 13. The authors of this study state that during the development of phase I-II, I trial no optimal duration of treatment was identified. Clinical reports suggest that stopping treatment early due to toxicity does not affect efficacy.

Their hypothesis that treatment to maximum tumour response will result in non-inferior overall survival with better QoL, less toxicity and lower cost than continuous therapy. Retreatment at time of progression is part of the study design. Currently, 78 of 550 pts have been enrolled. An English study (DANTE) is testing the hypothesis that one year is as effective as two years of therapy in metastatic melanoma. The estimated overall trial end date is 31-5-2027.

Until we get the results of these melanoma studies and hope-
fully others in other malignancies, we will not know the answers to the question of duration, schedule, and efficacy of combining different immune-based therapies with chemo or radiotherapy.

The results of the (PURE-01) open-label, single-arm phase II study demonstrated an interesting finding. In this study patients with muscle-invasive bladder cancer (T2-3b, N0, M0) were treated with three cycles of neoadjuvant pembrolizumab before radical cystectomy. To be included, they had to be tested for PDL-1 using the combined positive score (CPS), and genomic sequencing (Foundation ONE assay). They were treated with only three cycles of pembrolizumab 200mg 3 weeks apart before surgery. Notably, 42% of patients were T0 at surgery, (54.3% of patients with PDL-1 CPS (combined positive score) greater than 10% and 13.3% of patients less than 10%). Besides, a significant association between T0 and TMB greater than 15 was observed. This reveals that it is possible to achieve a complete response in muscle-invasive bladder cancer patients using a relatively short course of pembrolizumab. [3]

The importance of detecting the patients who will respond and who will not be predicted using PDL-1 CPS and TMB. But real-time measurements using specific T-cell populations, and predicting treatment failure or futility remain to be defined. These predictors seem to be sensitive for some tumours and not for others and are not 100% predictive of response depth or duration.

The significance of immune markers that demonstrate immune sensitisation of T-cells to tumour antigens, or if further strategies in stimulating this sensitisation are needed. Markers and importance of t-cell exhaustion and tracking of the depth of response activity are required.

There are many different lab tests and markers being studied, some as complex as identifying specific monocyte and T-cell populations using flow cytometric or molecular techniques, others by evaluating the T-lymphocytes that are infiltrating the tumour.

In the quest for a useful and straightforward biomarker for PD-1 antibody efficacy, many candidates have emerged. The simplest one is the ratio between neutrophils and lymphocytes (NLR) in peripheral blood. On April 25th 2019 this title was put into the PubMed database and only 11 citations appeared, of these ten were related to our subject. Only one study was related to anti-PD-1 inhibitor therapy in general, and the others were almost evenly divided into three cancers (melanoma, renal cell carcinoma, and lung cancer). This paucity of studies may be an indication that further research on this subject is needed. These studies are reviewed below. The meta-analysis: Pretreatment haematological markers predict clinical outcome in cancer patients receiving immune checkpoint inhibitors, was done by conducting a thorough literature search of PubMed, Embase, and Cochrane databases for studies dealing with the prognostic impact of pretreatment NLR and Platelet to Lymphocyte ratios (PLR) levels patients treated with immune checkpoint inhibitors (ICI). The clinical outcomes were progression-free survival (PFS) and overall survival (OS). Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated, and sensitivity and subgroup analyses were performed to investigate heterogeneity. Seventeen articles involving 2092 patients were included in the final analysis. The pooled HRs of PFS and OS for NLR were 1.81(95% CI 1.36-2.41) and 2.26 (95% CI 1.68-3.03), respectively, suggesting that patients with higher baseline NLRs had significantly poorer PFS and OS. Similar results were detected in sensitivity and subgroup analyses. However, no significant relevance was found between PLR and clinical endpoints in patients treated with ICIs (HR = 1.14, 95% CI 0.88-1.48 for PFS; HR = 1.35, 95% CI 0.86-2.12 for OS).

The studies on Renal cell carcinoma were reviewed. [5,6,7] These revealed that a high baseline NLR predicts a worse outcome in metastatic renal cell carcinoma.

The first study concluded from 313 evaluable patients and using univariate analysis, age, performance status, BMI, SII, NLR and PLR were able to predict the outcome. In multivariate analyses, SII ≥1375, BMI <25 and age ≥70 years independently predicted OS (HR, 2.96; 95% CI, 2.05-4.27; HR, 1.59; 95% CI, 1.10-2.30 and HR, 1.65; 95% CI, 1.07-2.55, respectively). A patient with both SII ≥1375 and BMI <25 was estimated to have a much worse OS (HR, 3.37; 95% CI, 2.29-4.95, P <0.0001) than a patient with neither or only one risk factor. SII changes at three months predicted OS (P <0.0001).

In the second study using a retrospective chart review, 38 patients with mRCC treated with nivolumab were evaluated. NLR was determined from complete blood count collected before starting treatment, and imaging was performed to assess progression. The median PFS was 2.6 months in the high NLR group but not reached in the low NLR group. Low NLR was strongly associated with increased PFS with a hazard ratio of 0.20 (95% confidence interval, 0.07-0.64; P = .006). The median OS was 2.7 months in the high NLR group but not reached in the low NLR group. Low NLR was significantly associated with a prolonged OS with a hazard ratio of 0.06 (95% confidence interval, 0.01-0.55; P = .012).

In the third study NLR and duration of prior anti-vascular endothelial growth factor (VEGF) inhibitors, as predictors of response rate, progression-free survival (PFS) and overall survival (OS) in mRCC patients treated with an immune checkpoint inhibitor (ICI), 42 patients were evaluated. Multivariable analysis showed pretherapy NLR ≥3 was predictive of shorter PFS and OS when treated with immune checkpoint inhibition with median 3.08 months and 13.50 months, respectively, versus 15.57 months and not reached for NLR <3 (adjusted p-values = 0.003 and 0.025, respectively). Prior anti-VEGF therapy <6 months was predictive of the increased likelihood of benefit from ICI therapies (adjusted p = 0.028). The median PFS was 3.72 months and 14.33 months, respectively, in cases with prior anti-VEGF treatment for ≥six months and <6 months.

The three lung cancer studies were also reviewed. [9,10] The first took a relatively large NLR of 5 as a cutoff and concluded in 18/54 patients that older age absence of brain metastasis and low post-treatment NLR had significantly lower progression-free survival 1.3 vs 6.1 months with a p less than 0.001. The second studied 88 patients, and the cutoff was an NLR of 4 at baseline. They concluded that a baseline NLR less than four was associated with a superior disease control rate (74% vs 50%) and overall survival, independent of PDL-1 tumour expression.

The clinical importance of these observations impacts decisions on duration of therapy, the threshold for imaging frequency, etc. Jeffrey S. Weber, MD, PhD A prominent researcher in anti-PD-1 therapy recommends: “at least 1 to 1.5 years therapy or best response plus one cycle, whichever is longer, and not more than two years of checkpoint inhibition.” These recommendations were based on several observations from several large studies. For example the checkmate 067 study which compared ipilimumab/nivolumab in the frontline setting found that 90% of patients achieving a complete response at two years remained in remission. It was also noted that in the same study, responders
who stopped treatment early because of adverse events, about 70% had ongoing responses. [11] The survival curve included a significant plateau at two years which is continuing to plateau at four years. Another notable observation is made in the keynote-006 study where 26/28 complete responders and 56/65, as well as 4/7 stable disease patients, remained in remission after two years of follow up. [12]

In conclusion, the optimal duration of immune checkpoint inhibitors is probably not the same for every patient; in addition, there are no set guidelines for follow up or frequency of imaging studies. The neutrophil to lymphocyte ratio seems to be a widely available and relatively significant indicator of response. However, the cutoff point of the NLR and the dynamic interaction with tumour response and re-occurrence over time is not clear yet, and it may prove to be an essential tool in the follow-up and treatment design in patients treated with immune checkpoint inhibition.

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