Prediction of Immune checkpoint inhibitors benefit from routinely measurable peripheral blood parameters

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Abstract: Immunotherapy of cancer has been the most remarkable advance in cancer therapy in the last several years with the successful introduction of monoclonal antibody drugs that block inhibitory immune receptors to invigorate immune attack against tumors. With the introduction of these drugs the parallel need of predictive markers of response has arisen. Beyond markers from the tumor and the tumor micro-environment, the peripheral blood supplies several biomarkers for response that have been reported individually or in combinations to provide valuable predictive information. These include the number of circulating cell subsets, various ratios of them and combinations of factors that also encompass biochemical measurements such as LDH. Peripheral blood biomarkers are usually obtained during the routine patient evaluations, methodology is well-calibrated for the routine practice and their acquisition does not require extra infrastructure or financial resources. This paper will review available data on predictive markers for immune checkpoint inhibitors (ICIs) from peripheral blood, including biomarkers that have been less extensively studied. In addition, it will discuss ways forward for the use of peripheral blood biomarkers in immunotherapy prognostication.

Keywords: Immune checkpoint inhibitors (ICIs); biomarkers response prediction; ipilimumab; nivolumab; pembrolizumab

Introduction

Immune blockade inhibitors (also called immune checkpoint inhibitors; ICIs) represent monoclonal antibody drugs that function through reactivation of immune system to elicit an anticancer response. As a class these drugs bind and inhibit the function of inhibitory immune receptors (1). Immune checkpoint molecules that are inhibited by ICIs in clinical use currently include Cytotoxic T lymphocyte Antigen 4 (CTLA-4) and Programmed Death 1 (PD-1) and its ligand PD-L1. Other immune inhibitory receptor blockers, such as the macrophage inhibitor Hu5F9-G4 blocking the eat-me-not receptor CD47, are in advanced development and will probably become available in the clinic, as data mature (2). ICIs holding approval for clinical use include CTLA-4

blockers ipilimumab and tremelimumab, PD-1 receptor blockers nivolumab, pembrolizumab and cemiplimab and PD-L1 blockers atezolizumab, avelumab and durvalumab. At least one checkpoint inhibitor has been approved for use alone or in combination with another checkpoint inhibitor or other drugs in a wide variety of malignancies. Examples are lung adenocarcinomas, squamous carcinomas and small cell lung cancers, urothelial and renal carcinomas, Hodgkin's lymphoma, melanoma and squamous carcinomas of the skin, head and neck cancers, triple negative breast cancers, as well as hepatocellular carcinoma and other gastrointestinal cancers (3-13). Moreover, the PD-1 inhibitor pembrolizumab has obtained a site-agnostic indication for treatment of any tumor with microsatellite instability (MSI), representing the first anti-neoplastic drug with approval not based on

tumor site (14). ICIs have shown remarkable activity in the treatment of malignancies notoriously resistant or refractory to chemotherapy such as metastatic melanoma and renal carcinomas. They also outperform chemotherapy in subsets of other cancers such as lung carcinomas and urothelial carcinomas, at later line treatment (3,5,15).

Immune blockade inhibitors have been studied in clinical trials for many common and less common cancers. In some occasions the observed activity was low and no regulatory approval for these drugs was obtained. In more responsive cancers, when non-selected populations are studied, the common pattern of response observed is a variable and many times low overall response rate while a long duration of response is obtained in a significant minority of responders. Rigorous research is underway in order to identify biomarkers predictive of response to ICIs. Some of those biomarkers have already been successfully incorporated into clinical practice. The best example is the target ligand of the PD-L1/PD-1 pair, PD-L1 which has been shown to predict higher responses with some of the ICIs blocking the pair and for some but not all tumor types. Another example is the presence of MSI or defects in Mismatch Repair proteins (dMMR) which forms the basis for a site-agnostic indication of pembrolizumab, as mentioned above. A significant minority of colorectal, endometrial and gastric cancers as well as rare cases of carcinomas from other locations harbor defects in MMR. Other biomarkers include the total number of mutations in the tumor referred to as tumor mutation burden (TMB) and the quantity and quality of immune cell infiltrates in the tumor micro-environment. These latter are not yet used in the clinic due to cost and standardization considerations. Related to the tumor immune infiltrates, subsets of circulating cells that may supply the tumor with immune infiltrates, guided by local cytokines have been studied and proposed to predict response to ICIs individually or in various combinations. Other measured indices such as Red cell Distribution Width or enzymes measured in the peripheral blood such as LDH have also been studied as predictors of response to ICIs.

This paper will review peripheral blood cell numbers and other elements of peripheral blood as predictors of response to ICIs with a focus to parameters which may be of importance but have been less studied.

Lymphocytes, neutrophils, platelets and combinations

The most abundant components of leukocytes, neutrophils and lymphocytes as well as platelets have been extensively studied as prognostic factors in several common cancers (16-23). More recently their value as predictors of ICIs response has been proposed separately or in combinations.

In general, patients with higher neutrophil and platelet counts and lower lymphocyte counts tend to fare worse and derive lower benefits from ICIs. A study of 108 melanoma patients that received nivolumab or pembrolizumab examined the predictive value of neutrophils, platelets and lymphocytes for PFS (24). Authors divided patients in three groups for each measured hematologic parameter and found that the intermediate group had not statistically significant different PFS than the worse group (higher counts for neutrophils and platelets and lower counts for lymphocytes). However, the group with the lower neutrophil counts and lower platelets counts and the group with the higher lymphocyte counts had a statistically significant better PFS than the worst group in each hematologic parameter category (24).

Another study that examined melanoma patients who received ipilimumab reported that among responders 94% of patients had a baseline lymphocyte count above 1×10^9/L while among non-responders only 78% of patients had a baseline lymphocyte count above 1×10^9/L (25). A study that analyzed melanoma patients who participated in prospective trials showed that higher lymphocytes counts both at baseline and before the third cycle of ipilimumab but also in the control arms receiving alternative treatments were associated with better survival (26). These results suggest that the absolute lymphocyte count may not be predictive of ipilimumab response but prognostic in all melanoma patients independently of therapy received.

The most studied combination of markers is the ratio of neutrophils to lymphocytes (NLR) which has been already the subject of several studies and at least two meta-analyses (27,28). The most recent meta-analysis found higher NLR ratios to be associated with a hazard ratio (HR) for benefit from ICIs of 2.61 for OS (95% confidence interval: 1.77–3.86) and a HR of 1.74 (95% confidence interval: 1.34–2.27) for PFS compared with lower NLR ratios (28). Studies included in the meta-analysis used different cut-offs for classifying patients to the high or low ratio groups that ranged between 3 and 5.5. The ratio seems to predict benefit from ICIs in all cut-offs, although a higher cut-off (5 and higher) was associated with a higher HR suggesting that higher cut-offs were able to better separate the groups that benefited or did not benefit from ICIs. Studies included in the meta-analysis concerned patients treated

with ipilimumab or nivolumab. Similar HR for OS with the two drugs were observed in the high and low neutrophil to lymphocyte ratio groups. Moreover, similar HR were observed in the studies that concerned melanoma patients and NSCLC patients. A single study that referred to metastatic renal cell carcinoma patients showed a higher HR for the prediction of inferior OS in the high neutrophil to lymphocyte ratio group (HR for OS of 5.3 versus 2.5 in the studies of NSCLC and melanoma) (29). Another study in 42 patients with metastatic renal cell carcinoma that received ICIs (11 of them in combination with VEGF drugs), and was not included in the above meta-analysis, showed worse PFS and OS in patients with NLR above 3 (30). The evolution (change) of NLR between baseline and the fourth treatment with nivolumab rather than a static NLR in time was examined in a cohort of 59 advanced NSCLC patients (31). Patients with a change of NLR of 1 or more progressed earlier and had a shorter OS than patients in whom NLR changed less. Others have reported that NLR of 5 or above after 2 cycles of nivolumab in NSCLC patients was predictive of worse OS (32). Moreover, non-responders had more often an increase of NLR after 2 cycles of therapy compared to nivolumab responders. The same phenomenon was described in another small series of nivolumab treated NSCLC patients where NLR increases during therapy was more often observed in progressive disease (33).

The ratio of platelets to lymphocytes (PLR) was examined in a few further studies as an ICIs predictive marker. In a small study of 52 metastatic NSCLC patients receiving nivolumab both PLR and NLR were predictive of OS. Patients with ratios above the median had worse survival (34). A study of 54 NSCLC who were treated with nivolumab or pembrolizumab examined NLR, PLR and the product of NLR times platelets (which authors named Systemic Immune-Inflammation Index, SII) at baseline and at 6 weeks after initiation of treatment as predictors of response (35). None of the ratios was predictive at baseline. At 6 weeks after treatment initiation, NLR of less than 5 and SII of less than 730 were predictive of a higher response (35). In contrast PLR with a cut-off of 169 was not predictive even at 6 weeks. Another small study of 58 metastatic RCC receiving nivolumab examined NLR, PLR and monocyte to lymphocyte ratio (MLR) as predictive markers of survival and found higher MLR to be an independent factor for worse PFS and higher MLR as well as higher NLR to be independent factors for worse OS (36).

Overall, most, but not all, studies that examined circulating neutrophils, platelets and lymphocytes as predictive factors for ICIs efficacy confirm the positive predictive value of higher lymphocytes counts and the adverse predictive influence of higher neutrophil and platelet counts. Ratios that include these cells may improve their prognostic strength. However, defining the optimal cut-offs would be critical for improvement of predictive performance.

Lymphocyte and monocyte subsets and activation status

Peripheral lymphocyte sub-sets have been examined as prognosticators of PD-1 blockade response. In a study of melanoma patients that received pembrolizumab, baseline peripheral blood CD8+/PD-1+ cells that expressed a level of Ki67 proliferation marker above 6.5% were associated with systemic inflammation and lower OS (37). Interestingly, higher baseline aggregate tumor burden as measured from the total number of metastatic tumors present in patients was also associated with worse OS. The ratio of post-treatment level of Ki67 (3 weeks after starting pembrolizumab) in peripheral blood CD8+/PD-1+ cells to baseline tumor burden tended to correlate with response to therapy and OS.

CD4 cell sub-sets are also relevant for response to ICIs. Both an increase of CD8+ and of CD4+ lymphocytes after 4 and 8 weeks of ipilimumab treatment in melanoma were associated with better responses than patients that showed decreases in those lymphocytes at the same time period (38). CD4+/Foxp3−/PD-1^{high} cells accumulate in tumor sites and may have a suppressive immune effect (39). In addition, these cells tend to increase in peripheral blood of patients treated with CTLA-4 inhibitors. When a PD-1 inhibitor is added in the treatment, responding patients display a decrease of CD4+/Foxp3−/PD-1^{high} cells in periphery while non-responders do not show such a decrease. Authors suggest that in combination treatments PD-1 blockers should be administered in excess of CTLA-4 drugs in order to maintain their capability to suppress CD4+/Foxp3−/PD-1^{high} cells (39).

An additional signature for lack of response to ICIs may include a phenotype of senescence in peripheral T cells with higher expression of TIM3 inhibitory receptor and lower CD28 co-stimulatory molecule (40). The activatory receptor ICOS was found to be commonly increasing in CD4+ T cells of patients treated with ipilimumab but whether this increase influences response to treatment

remains unknown (41).

The monocytic subset of myeloid-derived suppressor cells (moMDSCs) a sub-set of MDSCs with the phenotype CD14$^+$/HLA-DR$^{low/negative}$ tends to be higher in melanoma patients than in healthy donors (42). moMDSCs were examined in patients with metastatic melanomas treated with ipilimumab (43,44). Patients with lower CD14$^+$/HLA-DR$^{low/negative}$ cell numbers in their peripheral blood at baseline and at 6 weeks of ipilimumab treatment had a longer OS than patients with higher CD14$^+$/HLA-DR$^{low/negative}$ cell numbers (43). Patients that obtained a clinical benefit from therapy tended to have a decrease in circulating moMDSCs compared with patients with progressive disease that showed no decrease. Patients with moMDSCs that were less than 13.05% of the total circulating CD4+ lymphoid cells at 6 weeks of treatment had a better OS than counterparts with moMDSCs above the cut-off (HR 2.89, 95% confidence interval: 1.59–6.99). Similarly, patients with a higher effector memory CD8+ phenotype (CD8+/CD45RA–/CCR7–) at 9 weeks of treatment had better OS than patients with lower circulating effector memory CD8 cells (44). A subset of CD8+ effector memory (CD8+/CD45RA–/CCR7–) cells characterized by positivity to CD27 and CD28 were also associated with response of melanoma patients to ipilimumab (45). Patients with this subset of CD8+ cells representing more than 13% of the CD8+ compartment had better Response Rate (RR) and OS than counterparts with lower CD8+/CD45RA–/CCR7–/CD27+/CD28+ cells. In contrast, higher levels of terminally differentiated cells with the phenotype CD8+/CD45RA+/CCR7–/CD27–/CD28– (representing more than 23.8% of the CD8 compartment) were associated with worse OS and RR outcomes (45). Another study, though, suggested that the baseline ratio of central memory (CD45–/CCR7+) T cells to effector (CCR7–) T cells was associated with PFS in NSCLC patients receiving nivolumab (46). Patients with a higher ratio had better PFS. Authors suggested that this may be due to the association of higher central memory T cell to effector T cell ratios with an inflammatory signature and higher expression of PD-L1 in tumor.

Sub-sets of immune cells could vary in their ability to serve as predictive biomarkers of different ICIs treatment efficacy. This may be expected given that the mechanisms of anti-tumor invigoration and the sub-sets of immune cells expanded following therapy is distinct between CTLA-4 blockers and inhibitors of the PD-1/PD-L1 pair (47). Thus, memory T cell subsets seem to be more important for prediction in CTLA-4 blockade while NK cell expression of CD69 and MIP-1β could play a key role in PD-1 inhibition (48).

Use of immune cells sub-sets as described in this section has the drawback that they are not routinely used in practice and their validation would have to include analytical steps in clinical laboratories. This is important to consider in measurements that concern surface expression of proteins in circulating cells as these could be significantly influenced by *ex vivo* factors such as time from venipuncture to sample processing (42). Moreover, the optimal subset for prediction of ICIs effectiveness is unclear from the available data and may depend on the specific drugs. For these reasons, it is unlikely that lymphocyte and monocyte subsets will become useful clinical markers, despite their interest from a pathophysiologic point of view.

Other hematologic parameters

Other hematologic parameters, beyond neutrophils, lymphocytes and platelets, have been studied as predictors of ICIs response in cancer patients less frequently. The red cell distribution width (RDW), a measure of variability of red cell size (anisocytosis), has been proposed as a predictive marker in a study of 47 patients treated with nivolumab for stage III or metastatic NSCLC (49). In multivariate analysis, patients with RDW of 16% or above had a worse OS than patients with lower RDW. Authors examined also RDW in combination with NLR and reported that patients that had both high RDW and high NLR of 5 or above had the worse OS followed by patients that had only one of the two parameters elevated, while the group with both RDW below 16% and NLR below 5 had the best OS (49).

Monocytes were examined as prognostic markers for outcomes in a study of 32 metastatic NSCLC patients receiving nivolumab or pembrolizumab (50). Neither baseline monocytes nor neutrophils, that were examined in parallel, were predictive for response rate. However, responding patients with a higher level of peripheral monocytes above 0.7×10^9/L had a shorter time to response. In addition, patients with lower neutrophils below 4.2×10^9/L after the first dose of therapy had a higher response rate (50). Monocytes were also used together with lymphocytes for prognostication in melanoma patients treated with pembrolizumab (51). Patients with a lymphocyte to monocyte ratio above 1.7 had a better PFS and OS than counterparts with lymphocyte to monocyte ratio below 1.7 (51). As discussed in a previous section, lymphocytes together with monocytes were also predictive

of PFS and OS in RCC patients treated with nivolumab (36).

Eosinophilia was observed more often in melanoma patients that received ICIs than in patients that were treated with other medications (52). An increase in eosinophilic count by at least 0.1×10^9/L between the first and second infusion of ipilimumab was noticed to be associated with improved OS in metastatic melanoma patients (53). This phenomenon was also observed in another melanoma cohort treated with ipilimumab where responders had a significant increase in eosinophil counts as opposed to non-responding patients that had a less prominent increase in eosinophil counts (54). A higher than 1.1% relative eosinophilic count was also predictive of favorable OS in patients with advanced melanoma receiving ipilimumab and nivolumab combination therapy (55). In this cohort absolute monocyte counts below 0.8×10^9/L, relative basophil count above 0.6%, lower LDH (below 246) and lower NLR (below 4.73) were also associated with better OS. Another study on melanoma patients treated with ipilimumab showed higher absolute eosinophil counts, above 0.05×10^9/L, to predict improved OS (56).

The relative eosinophilic count was found to be predictive of PFS and OS in patients with advanced head and neck cancers treated with nivolumab (57). The cut-off used was 1.5% and the group of patients with values above this cut-off had better PFS and OS compared with counterparts with values below the cut-off. In the same study, the relative neutrophil count and the relative lymphocyte count were significant for survival outcomes in the univariate analysis but lost significance in multivariate analysis. LDH was not predictive of outcomes in these patients (57). In NSCLC patients treated with nivolumab, absolute eosinophil counts above 0.15×10^9/L together with absolute lymphocyte counts above 1×10^9/L and absolute neutrophil counts below 7.5×10^9/L were predictive of better PFS and OS (58). Patients with two or three of these factors faired significantly better than counterparts with only one factor. This may have been due to the association of favorable factors with expression of PD-L1 in tumor. All patients with PD-L1 expression above 50% had two or three factors present (58).

Incorporation of biochemical measurements

LDH is an enzyme that has been examined as a predictor of response to ICIs. In a study of advanced NSCLC patients, high LDH in combination with high (above 3) derived NLR (dNLR, defined as the ratio of neutrophils to white cells minus neutrophils) were predictive of worse PFS and OS in patients receiving PD-1 or PD-L1 blockers but not in patients receiving chemotherapy (59). In another study of NSCLC patients treated with nivolumab, high LDH was associated with absence of response to therapy (60). In melanoma patients receiving nivolumab, LDH values above 454 were associated with worse PFS and OS in multivariate analysis (61). Higher NLR was also predictive of worse outcomes in this cohort. In another melanoma cohort treated with ipilimumab, patients with LDH 2.3 times or more above normal had worse OS than patients with LDH between 1.2 to 2.3 times above normal or below 1.2 times above normal (56). In metastatic clear cell renal cell carcinoma treated with nivolumab, elevated serum LDH levels were associated with worse PFS compared with patients with normal LDH levels (62).

A study that used an index comprised of albumin, LDH and NLR (initially proposed as stratifying predictor for inclusion in phase I studies at the Institut Gustave-Roussy, France) as predictor of response to pembrolizumab, nivolumab or atezolizumab in 76 metastatic NSCLC patients found the index to be a predictor for OS but not PFS (63). In contrast, another index comprised of albumin, LDH and number of metastatic sites (The Royal Marsden Hospital Index) was predictive of PFS but not OS. When parameters were evaluated separately to find the most influential predictor, albumin and NLR but not LDH or number of metastatic sites were associated with OS (63). An index combining LDH with age and sex of the patient, previous ipilimumab treatment and presence of liver metastases was studied in melanoma patients for prediction of response to PD-1 targeted therapy (64). The index was confirmed to be predictive for response to treatment.

An index named ALI (Advanced Lung cancer Inflammation index) calculated as the product of albumin times BMI (Body Mass Index) divided by the NLR was investigated as prognostic factor in a series of 201 advanced NSCLC patients treated with nivolumab (65). Patients with an ALI below 18 had a significantly worse PFS and early progression on treatment. The same study confirmed that higher NLR was also associated with worse PFS.

A retrospective multicenter analysis of 616 metastatic melanoma patients who received pembrolizumab identified four peripheral blood parameters as being associated with longer OS (66). These included a baseline LDH value below 2.5 times the upper limit of normal, a relative eosinophil count above 1.5%, a relative lymphocyte count above 17.5% and the absence of metastases in other organs

beyond soft tissue and lung. Patients with all four factors had OS at 1 year of 83.9%, while the 1-year OS of patients with none of these factors present was 14.7% (66).

Discussion

Abnormalities of peripheral blood cell counts such as anemia, neutrophilia or thrombocytosis have been recognized as prognostic in cancer. In some cancers such as RCC these factors have been incorporated in widely used prognostic systems (67,68). Cells of peripheral blood and other markers that may be measured in the blood could reflect aspects of the tumor immune microenvironment. The immune system receives clues from the tumor and responds by mobilizing immune cells of the innate and adaptive arms. Lymphocytes, neutrophils monocytes and NK cells are all mobilized by cytokines produced directly by cancer cells or indirectly by other cells that respond to signals from the tumor microenvironment. Moreover, other cells such as platelets and red cells are affected by signals emanating from the tumor or produced by the systemic inflammatory reaction that the tumor creates and their changes in number or size variability reflect this environment. Elevation of platelets may be a marker of immunosuppressive tumor micro-environment. Cancer Associated Fibroblasts (CAFs) secrete IL-6 which recruits myeloid derived suppressive cells and in addition promotes thrombopoiesis (69). Red cell anisocytosis as measured by RDW is also a marker of chronic inflammation and immune exhaustion. In HIV+ patients RDW correlates with high PD-1 expression in peripheral CD4+ lymphocytes (70).

With the introduction of ICIs of CTLA-4 and the PD-L1/PD-1 pair as active cancer immunotherapy, measurement of the tumor inflammation state has become an important element in prediction of cancers that will respond to these treatments. Tumors have been divided to cold or non-inflamed and hot or inflamed depending on their infiltration with cells of the immune system (71). Inflamed tumors have a better prognosis and respond better to ICIs therapy, especially if they produce a high number of neo-antigens, while most non-inflamed tumors do not respond to ICIs (72,73). Immune presentation machinery may shape the quality of immune infiltrates in a tumor (74). Immune presentation machinery is also crucial for presenting neo-antigens that could be recognized by incoming immune effectors in order to mount an immune anti-tumor attack (75). Thus, tumor cells and immune cells are engaged in a two-way inter-relationship that eventually shapes the effectiveness of the anti-tumor immunity.

It is plausible that alterations in numbers of circulating blood cells are predictive of response to ICIs because they are associated or even produced by alterations of cytokines that have influence on the overall activity of immune system and on the number and function of effector lymphocytes. The previously mentioned association of thrombocytosis with IL-6, a well-described immunosuppressive cytokine, is a relevant example. However, a role of platelets in protecting tumor cells in transit and facilitating their homing by interaction with endothelial cells has been described (76). Cytokines producing eosinophilia such as IL-5 and eotaxin-1 (CCL11) may have tumor suppressive effects, hence the association of eosinophilia with tumor responses to ICIs (77). Nevertheless, IL-4, another cytokine associated with eosinophil production has pro-tumorigenic effects (78). Administration of IL-2, used as immunotherapy in melanoma patients, results in elevation of IL-5 levels and eosinophilia (79). However, eosinophils may have anti-tumoral effects in the tumor micro-environment by promoting NK cells and T cells recruitment and direct cytotoxicity by production of granzymes and other cytotoxic proteins (80). Thus, both direct and indirect correlations of peripheral blood cells in tumor immunity may relate to their being prognostic and predictive factors in cancer. It is worth noticing that most of the data available on ICIs effectiveness prediction through peripheral blood elements lack comparative data on patients that received other therapies and strictly speaking represent arguments for these biomarkers being prognostic of the respective disease outcomes rather than solely predictive of immunotherapy outcomes. This fact is also supported by the known prognostic value of the biomarkers as studied in settings independent of therapy and by limited data from studies that included patients treated with other therapies (18-23,25). However, being concomitant cancer prognostic factors does not subtract from the clinical utility of peripheral blood biomarkers as predictive of immunotherapy response.

Currently several studies suggest that indices that consist of several types of cells and additional elements such as LDH or albumin may be more valuable than individual peripheral blood elements. However, the optimal number of elements that provide additive predictive value is not clear from the available data. The optimal manner to combine data and specifically whether indices that calculate ratios as opposed to predictive tools that use addition of abnormal findings in their calculations of risk

is also unclear. An additional element in the predictive associations from certain studies has been the timing of evaluation and specifically the value of baseline as opposed to later measurements or even the value of dynamic evaluations of changes between baseline and later time points in predicting outcomes. Of course, the preferable time point of a biomarker would be at baseline where the prediction information is obtained before use of the drug. Alternatively, a dynamic time point using, for example, in addition to the baseline measurements, biomarker measurements before the second drug administration could constitute a quite relevant clinical tool if prediction obtained by the addition of the later measurement is robust.

The ultimate point to consider in further advancing the field of immunotherapy prediction by peripheral blood biomarkers and indeed of any other biomarkers is whether it is preferable to study and develop predictors of specific drugs or inhibitors of specific checkpoint molecules or a more generic approach could offer useful prediction for all ICIs. Most of the peripheral blood biomarkers examined appear to predict outcomes in diverse type of cancers and their predictive value does not seem to depend on the specific tumor.

Measurement of cell numbers and other relevant data from peripheral blood appear to add information on inflammation and mobilization of immune effectors in a systemic level and could contribute to a better prognostication of ICIs possibly serving as an adjunct to other currently used biomarkers such as PD-L1 expression in tumors and presence of MSI. A combination of those established biomarkers with other markers from the tumor and its micro-environment, such as total mutation burden and tumor infiltrating lymphocytes, as well as biomarkers from the peripheral blood may eventually become the optimal means of ICIs prognostication.

Acknowledgments

Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/cco.2020.03.03). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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