Immune checkpoint inhibitors are becoming a cornerstone of cancer immunotherapy as a result of their clinical success in relieving immune suppression and driving durable antitumor T cell responses in certain subsets of patients. Unfortunately, checkpoint inhibition is also associated with treatment-related toxicities that result in a myriad of side effects, ranging from mild and manageable to severe and debilitating. In this issue of the JCI, Das and colleagues report an association between early therapy-induced changes in circulating B cells and an increased risk of high-grade immune-related adverse events (IRAEs) in patients treated with checkpoint inhibitors that target cytotoxic T lymphocyte–associated antigen-4 (CTLA4) and programmed cell death protein 1 (PD1). These findings identify potential predictive biomarkers for high-grade IRAEs that may be leveraged to improve patient monitoring and may prompt new treatment strategies to prevent IRAEs.

Find the latest version:
https://jci.me/99036/pdf
B cells as biomarkers: predicting immune checkpoint therapy adverse events

Shannon M. Liudahl and Lisa M. Coussens

Department of Cell, Developmental and Cancer Biology and the Knight Cancer Institute, Oregon Health and Science University (OHSU), Portland, Oregon, USA.

Checkpoint blockade therapy: the good, the bad, and the toxic

Immune checkpoint inhibitors are becoming a cornerstone of cancer immunotherapy as a result of their clinical success in relieving immune suppression and driving durable antitumor T cell responses in certain subsets of patients. Unfortunately, checkpoint inhibition is also associated with treatment-related toxicities that result in a myriad of side effects, ranging from mild and manageable to severe and debilitating. In this issue of the JCI, Das and colleagues report an association between early therapy-induced changes in circulating B cells and an increased risk of high-grade immune-related adverse events (IRAEs) in patients treated with checkpoint inhibitors that target cytotoxic T lymphocyte–associated antigen-4 (CTLA4) and programmed cell death protein 1 (PD1). These findings identify potential predictive biomarkers for high-grade IRAEs that may be leveraged to improve patient monitoring and may prompt new treatment strategies to prevent IRAEs.

Checkpoint therapy adverse events

Related Article: p. 715

Related Article


preceded the development of IRAEs (9, 10). While changes in T cell genomic signatures in patients undergoing anti-CTLA4 and anti-PD1 mAb treatment have also been identified (11), changes in B cells during checkpoint inhibition have not been previously reported.

In this issue, Das et al. analyzed circulating B cells in a small cohort of patients with advanced melanoma before and after treatment with anti-CTLA4 and anti-PD1 mAbs, administered as single agents or in combination (12). They found that a reduction in total peripheral B cells after a single cycle of combined checkpoint blockade (CCB) coincided with enrichment of plasmablasts and a proliferative CD21lo PD1+ memory B cell subset. Single-cell RNA sequencing of CD21lo PD1+ B cells collected from a patient prior to and after CCB revealed increased transcription of genes associated with cell activation and inflammatory cytokine production following treatment. CD21lo B cells also expressed lower levels of the lymphoid tissue-homing chemokine receptors CXCR4 and CXCR5 as compared with CD21hi B cells, indicating that CD21lo cells may have a greater capacity to traffic to nonlymphoid tissues and contribute to inflammatory processes that may mediate autoimmunity.

Given these findings, Das et al. developed a metric to evaluate whether changes in the frequency of circulating B cells in CCB-treated patients correlated with an increased risk or severity of IRAEs. Using this metric, the authors found that patients with a 30% or greater reduction in baseline levels of total circulating B cells and a two-fold or greater increase in CD21lo B cells or plasmablasts were significantly more likely to develop high-grade IRAEs than were patients without B cell changes (Figure 1). Moreover, early changes in circulating B cells after only one round of CCB correlated with a median time of three weeks to IRAE onset. Importantly, changes in the frequency of other circulating immune cell populations, including T cells, before and after therapy did not correlate with the development of IRAEs.

Given these findings, Das et al. developed a metric to evaluate whether changes in the frequency of circulating B cells in CCB-treated patients correlated with an increased risk or severity of IRAEs. Using this metric, the authors found that patients with a 30% or greater reduction in baseline levels of total circulating B cells and a two-fold or greater increase in CD21lo B cells or plasmablasts were significantly more likely to develop high-grade IRAEs than were patients without B cell changes (Figure 1). Moreover, early changes in circulating B cells after only one round of CCB correlated with a median time of three weeks to IRAE onset. Importantly, changes in the frequency of other circulating immune cell populations, including T cells, before and after therapy did not correlate with the development of IRAEs.

Clinical implications and future directions
Together, findings from Das and colleagues indicate that changes in circulating B cells may be useful predictors of IRAE risk (12). Clinical application of B cell monitoring could lead to earlier IRAE intervention and reduced IRAE severity, both of which would ideally translate to a reduced discontinuation of checkpoint therapy. The sample size in this study was limited, thus, a critical next step will be to determine the robustness of the proposed B cell signature in expanded patient cohorts. Significant changes in both total B cell frequency and the frequency of CD21lo B cells and plasmablasts were only observed in the CCB group, indicating that patients undergoing combination therapy may preferentially benefit from B cell monitoring. However, future evaluation of larger cohorts will reveal whether subsets of patients receiving monotherapy undergo similar B cell changes equally predictive of IRAE risk. It will also be necessary to determine whether changes in circulating B cells occur specifically in melanoma, or whether this signature is also detectable in patients with other tumor types.

The mechanistic contribution of B cells to IRAEs also remains unclear. While changes in T cell genomic signatures in patients undergoing anti-CTLA4 and anti-PD1 mAb treatment have also been identified (11), changes in B cells during checkpoint inhibition have not been previously reported.

In this issue, Das et al. analyzed circulating B cells in a small cohort of patients with advanced melanoma before and after treatment with anti-CTLA4 and anti-PD1 mAbs, administered as single agents or in combination (12). They found that a reduction in total peripheral B cells after a single cycle of combined checkpoint blockade (CCB) coincided with enrichment of plasmablasts and a proliferative CD21lo PD1+ memory B cell subset. Single-cell RNA sequencing of CD21lo PD1+ B cells collected from a patient prior to and after CCB revealed increased transcription of genes associated with cell activation and inflammatory cytokine production following treatment. CD21lo B cells also expressed lower levels of the lymphoid tissue-homing chemokine receptors CXCR4 and CXCR5 as compared with CD21hi B cells, indicating that CD21lo cells may have a greater capacity to traffic to nonlymphoid tissues and contribute to inflammatory processes that may mediate autoimmunity.

Given these findings, Das et al. developed a metric to evaluate whether changes in the frequency of circulating B cells in CCB-treated patients correlated with an increased risk or severity of IRAEs. Using this metric, the authors found that patients with a 30% or greater reduction in baseline levels of total circulating B cells and a two-fold or greater increase in CD21lo B cells or plasmablasts were significantly more likely to develop high-grade IRAEs than were patients without B cell changes (Figure 1). Moreover, early changes in circulating B cells after only one round of CCB correlated with a median time of three weeks to IRAE onset. Importantly, changes in the frequency of other circulating immune cell populations, including T cells, before and after therapy did not correlate with the development of IRAEs.

Clinical implications and future directions
Together, findings from Das and colleagues indicate that changes in circulating B cells may be useful predictors of IRAE risk (12). Clinical application of B cell monitoring could lead to earlier IRAE intervention and reduced IRAE severity, both of which would ideally translate to a reduced discontinuation of checkpoint therapy. The sample size in this study was limited, thus, a critical next step will be to determine the robustness of the proposed B cell signature in expanded patient cohorts. Significant changes in both total B cell frequency and the frequency of CD21lo B cells or plasmablasts were only observed in the CCB group, indicating that patients undergoing combination therapy may preferentially benefit from B cell monitoring. However, future evaluation of larger cohorts will reveal whether subsets of patients receiving monotherapy undergo similar B cell changes equally predictive of IRAE risk. It will also be necessary to determine whether changes in circulating B cells occur specifically in melanoma, or whether this signature is also detectable in patients with other tumor types.

The mechanistic contribution of B cells to IRAEs also remains unclear. While changes in T cell genomic signatures in patients undergoing anti-CTLA4 and anti-PD1 mAb treatment have also been identified (11), changes in B cells during checkpoint inhibition have not been previously reported.

In this issue, Das et al. analyzed circulating B cells in a small cohort of patients with advanced melanoma before and after treatment with anti-CTLA4 and anti-PD1 mAbs, administered as single agents or in combination (12). They found that a reduction in total peripheral B cells after a single cycle of combined checkpoint blockade (CCB) coincided with enrichment of plasmablasts and a proliferative CD21lo PD1+ memory B cell subset. Single-cell RNA sequencing of CD21lo PD1+ B cells collected from a patient prior to and after CCB revealed increased transcription of genes associated with cell activation and inflammatory cytokine production following treatment. CD21lo B cells also expressed lower levels of the lymphoid tissue-homing chemokine receptors CXCR4 and CXCR5 as compared with CD21hi B cells, indicating that CD21lo cells may have a greater capacity to traffic to nonlymphoid tissues and contribute to inflammatory processes that may mediate autoimmunity.

Given these findings, Das et al. developed a metric to evaluate whether changes in the frequency of circulating B cells in CCB-treated patients correlated with an increased risk or severity of IRAEs. Using this metric, the authors found that patients with a 30% or greater reduction in baseline levels of total circulating B cells and a two-fold or greater increase in CD21lo B cells or plasmablasts were significantly more likely to develop high-grade IRAEs than were patients without B cell changes (Figure 1). Moreover, early changes in circulating B cells after only one round of CCB correlated with a median time of three weeks to IRAE onset. Importantly, changes in the frequency of other circulating immune cell populations, including T cells, before and after therapy did not correlate with the development of IRAEs.
CD21<sup>+</sup> memory B cells and plasmablasts in IRAE pathogenesis.

Despite the outstanding questions regarding specific B cell mechanisms in IRAEs, B cell monitoring represents a relatively simple, noninvasive clinical biomarker assessment strategy that could also yield preventative benefits. Circulating biomarkers for treatment-related toxicities in other forms of immunotherapy have recently been identified and are poised to have clinical impact. For example, in cancer patients receiving chimeric antigen receptor T cell (CAR-T cell) therapy, early elevation of specific serum cytokines and other soluble factors, including IFN-γ, MIP1α, IL-6, and soluble gp130 (sgp130), precedes the development of severe cytokine release syndrome (CRS) (13, 14). Use of the IL-6 receptor (IL-6R) inhibitor tocilizumab is now approved for the treatment of severe CRS in CAR-T cell recipients, and the identification of circulating biomarkers that predict CRS may lead to prophylactic administration of tocilizumab or other cytokine inhibitors in patients who have markers associated with increased risk. Similarly, B cell changes as a biomarker for IRAEs in checkpoint inhibition therapy could lead to new preventative strategies. Along these lines, Das and colleagues suggest the potential utility of B cell–targeted therapies as a preventative measure against IRAEs. This idea is compelling, especially given the clinical success of B cell–depleting antibodies and inhibitors of Bruton’s tyrosine kinase (BTK), an essential kinase for B cell maturation and signaling, for treating autoimmune diseases (15) and graft-versus-host disease (16).

It is likely that, in addition to reducing the risk of IRAEs, B cell depletion or BTK inhibition may also enhance the antitumor efficacy of checkpoint inhibitors, at least in some settings. The role of B cells in melanoma progression is controversial, as both pro- and antitumor B cell functions have been reported (17); however, the results from the use of B cell depletion in a small cohort of melanoma patients appear promising (18). Recent studies of other solid tumors have identified various B cell subsets as critical protumoral mediators of malignancy (19–25), and the enriched B cell populations identified by Das and colleagues may share similar functional properties. If so, these findings would support B cell depletion or BTK inhibition along with checkpoint inhibition as an appealing strategy to further explore. In fact, a clinical trial involving patients with head and neck squamous cell carcinoma is currently evaluating this approach (ClinicalTrials.gov NCT02454179). Time will tell whether such combinations simultaneously enhance antitumor immunity, limit IRAEs, and improve clinical outcomes. What is clear for now is that, although T cell responses are often the main focus of immunotherapy, B cells should not be overlooked.

Acknowledgments

The authors acknowledge support from a Department of Defense (DOD) Breast Cancer Research Program (BCRP) Era of Hope Scholar Expansion Award (W81XWH-08-PRMRP-IIRA); the Susan G. Komen Foundation (KG110560); the Breast Cancer Research Foundation; a Stand Up To Cancer – Lustgarten Foundation Pancreatic Cancer Convergence Dream Team Translational Research Award; the OHsu Benson-Colson Center for Pancreatic Care; and the OHsu Knight Cancer Institute.

Address correspondence to: Lisa M. Cousens, Department of Cell, Developmental & Cancer Biology, Knight Cancer Institute, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, Oregon 97239-3098, USA. Phone: 503.494.7811; Email: cousensl@ohsu.edu.