Peripheral Blood T cell responses to immunotherapy related adverse events in NSCLC patients treated with Immunotherapy

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Background

There has been prospective and retrospective evidence for the onset of immunotherapy (IO) related adverse events (irAE) and efficacy of anti PD1 and PD L1 antibodies[1,2,3]. The incidence of irAE in these studies ranged anywhere from 30-44%. There have been attempts to cluster irAEs into distinct subtypes by T cell profiling before and after immunotherapy particularly anti PD1 and PDL1 antibodies[4] where T- cell markers showed a predictive value for the development of each subtype of irAEs. Our present observation, which is part of another project of investigating a biomarker of irAEs, is along the same lines of predictive capability of T cell markers for irAEs, which we consider as valid reporting in this context.

Aim

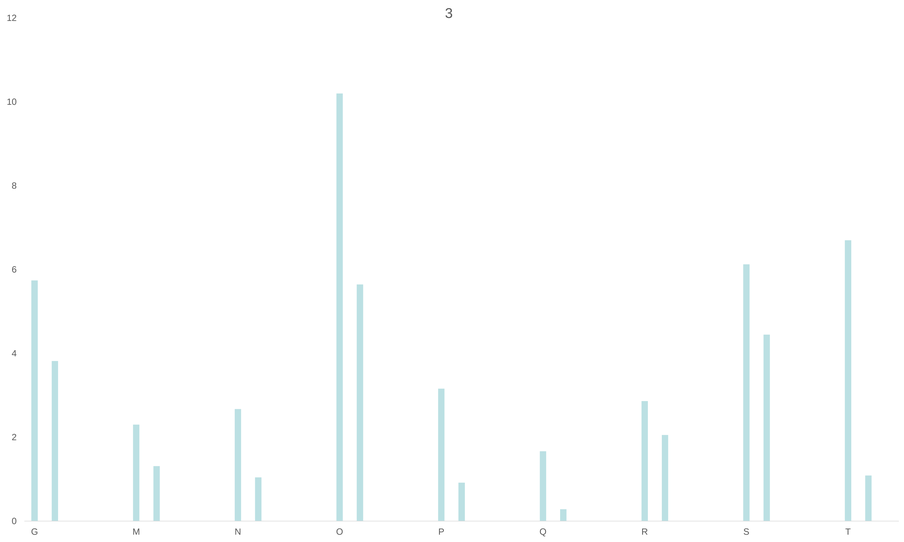
To observe the trend of CD4/CD8 changes during immunotherapy with PD1 and PDL1 monoclonal antibodies and the related adverse events to identify any predictive trend in order to find ways to mitigate the severe toxicities, so the benefits of immunotherapy can be extended to far more number of patients.

MATERIALS & METHODS

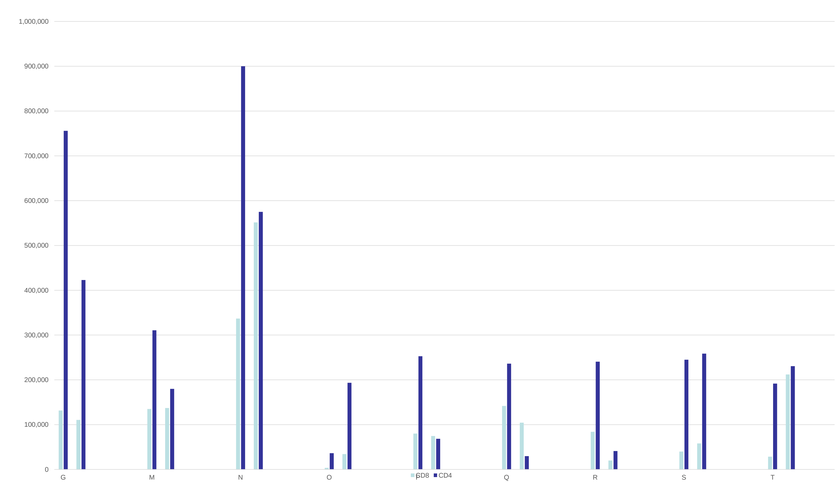
We have collected blood samples from 20 patients of Non Small Cell Lung Cancer patients (NSCLC) before each cycle of immunotherapy with informed consent as part of a related project after our institutional review board approval. We have isolated the different inflammatory markers such as IL6, IL10 using ELISA and cellular components such as CD4, CD8 along with others using magnetic bead technique, from these samples in our research laboratory at East Carolina University. We have also collected clinical information including the adverse events with their CTCAE 5.0 grading, different cell counts, CRP and many more needed for our other project. While we are still working on the details of the other project, interim analysis caught our attention even though this is from a small number of patients.

RESULTS

In the cohort of 20 patients that were treated with immunotherapy for NSCLC, 9 experienced irAE, out of which 6 had grade 2, including thyroiditis, pneumonitis, cytokine release syndrome (CRS), 1 had grade 3 pneumonitis, 1 had grade 3 dermatitis and 1 had grade 1 encephalopath. When we looked at the CD4/CD8 ratio before each cycle, the one prior to the incidence of the grade 2-3 irAE had atleast 30% drop in the ratio consistently although there were minor fluctuations in the ratio at other times in both directions. The two patients that had grade 1 irAE (R and S) did not quite reach the 30% threshold, but were close. However, it is unclear if grade correlates with the degree of this change as some grade 2 patients had more change than grade 3 irAE.



CD4/CD8 ratio (on Y-axis) in the patients (depicted on X- axis with letters), in the 2 cycles prior to irAE with the right most line indicating the one immediately prior to the irAE



Individual trend of CD4 and CD8 counts in cells/mL blood of the same patients, during the 2 cycles preceding irAE, the rightmost line indicating the one immediately prior to irAE

DISCUSSION

Although most irAEs can be treated and reversed with steroids and other immunosuppressive agents, prolonged immunosuppression can lead to reduced efficacy if IO and development of undue opportunistic infections[5]. Experience with IO has shown that there is association between the irAE and efficacy of PD1 and PDL1 antibodies [6] and earlier initiation of immunosuppression shortens the required treatment. However, given the challenge in the subtility of the earlier presentation, therapies are frequently delayed. Hence, biomarker to identify the early manifestations is of critical importance for early intervention. Studies suggest there is clonal expansion of CD8 T cells preceding grade 2-3 irAEs[7]. Studies also indicate that increased T cells in the tumor is indicative of response to immunotherapy[8]. Our observation suggests that increased CD8 in proportion to CD4 in the peripheral blood precedes the onset of irAE. It is unclear as to how this leads to increased toxicity when the immunotherapy treatment works by affecting T cell function. One possible explanation is that the T cell response in the tumor tissue is beneficial, however, T cell response in the peripheral blood may indicate response against self antigens leading to toxicities in the form of irAE.

Limitations

This observation by no means is a conclusive evidence of biomarker status given the small sample size, observational findings and the lack of standardization for grading. However, this could be considered as a potential area of investigation to identify predictable markers of irAE that are easy to obtain using readily available tests and are cost effective to the patient as well as informative enough that the treating physician can act upon to mitigate the adverse events without compromising the efficacy of immunotherapy in this patient population. It is to be noted that the measurement of T cells from the peripheral blood in this study is obtained by magnetic bead isolation technique in a research lab while the regular patient testing is done via flow cytometry (usually only total lymphocyte number without CD4 or CD8 T cell numbers) and therefore cross correlation is required before large scale studies are conducted.

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