Checkpoint blockade therapy

IMMUNOTHERAPY TRIALS LACK A BIOMARKER FOR INCLUSION: IMPLICATIONS FOR DRUG DEVELOPMENT

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Background Next-generation sequencing and other biomarkers have demonstrated the capability to identify potentially pathogenic molecular aberrancies. Immune checkpoint inhibitors (ICI) have benefited patients in almost every oncologic histologic. Combining these innovations has transformed how oncologists treat previously untreatable diseases.

Methods The 413 trials from clinicaltrials.gov website were reviewed using the terms ‘nivolumab’ or ‘pembrolizumab’ between January 1, 2019 and December 31, 2019. Additionally, all 33 interventional therapeutic trials for ‘glioblastoma multiforme’ and 79 for ‘pancreatic cancer’ that were either recruiting, not yet recruiting, or active not recruiting trials between January 1, 2019 and December 31, 2019 were analyzed.

Results In total of 413 trials, 57,853 were planned for enrollment with 37 (8.96%) trials requiring a biomarker for entry (n = 5,602 [9.7%]). Overall, there were 41 trials with single-agent immunotherapy planned to enroll 6222 patients and of those trials 7 (17.1%) required a biomarker for enrollment (n = 285 [4.6%]). There were 193 trials with >2 immunotherapies combined planned to enroll 21,360 patients and of those trials 7 (8.8%) required a biomarker for enrollment (n = 1254 [9.9%]). There were 69 trials with immunotherapy and chemotherapy combined planned to enroll 12,354 patients and of those trials 3 (4.3%) required a biomarker for enrollment (n = 83 [0.67%]). There were 58 trials with immunotherapy and targeted therapy combined planned to enroll 11,967 patients and of those trials 6 (10.3%) required a biomarker for enrollment (n = 3244 [27.1%]). There were 52 trials with other immunotherapy combinations (e.g. vaccine) planned to enroll 5950 patients and of those trials 4 (7.7%) required a biomarker for enrollment (736 [12.4%]). Within pancreatic cancer, 31 trials were planned to use immunotherapy (monotherapy, combination, with chemotherapy, with targeted therapy) including 4493 patients total; 5 (16%) of those trials required biomarkers enrolling 309 (7%) patients. Within glioblastoma multiforme, 13 trials were planned to use immunotherapy (monotherapy, combination, with chemotherapy, with targeted therapy) including 730 patients total; 7 (8%) of those trials required biomarkers enrolling 309 (1%) patients.

Conclusions For immunotherapy-based trials in 2019, <10% of patients expected to be enrolled would be selected by a biomarker for inclusion. Precision oncology continues to struggle in the era of ICI with an all-comers approach to patient selection and trial initiation. Selecting patients for trials based on biomarkers may help better identify responders to ICI.

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180 THE EFFECT OF PACKED RED BLOOD CELL TRANSFUSIONS ON THE CLINICAL EFFICACY OF IMMUNOTHERAPY

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Background Transfusions of packed red blood cells (PRBC) have been postulated to be immunosuppressive, an effect known as transfusion-related immunomodulation (TRIM). TRIM is thought to be a result of the immunosuppressive and pro-inflammatory effects of residual leukocytes, apoptotic cells, inflammatory mediators, micro particles and free hemoglobin. Prior studies have shown a negative association between peroperative PRBC transfusions and overall mortality in multiple malignancies. To date there are no studies addressing the impact of transfusions on survival in patients undergoing treatment with checkpoint inhibitor (CPI) immunotherapy. We conducted a retrospective study to investigate the clinical outcomes associated with PRBC transfusions in patients with non-small cell lung cancer (NSCLC), urothelial carcinoma (UC) and renal cell carcinoma (RCC) who received immunotherapy for advanced/metastatic disease.

Methods From January 2010 - June 2019, patients at Fox Chase Cancer Center who received a PRBC transfusion within 120 days of treatment with a CPI and with advanced NSCLC, UC and RCC were included. Patient demographics including age, sex, ethnicity, race, tobacco use and ECOG performance status (PS) were abstracted. We also assessed previous chemotherapy, radiation and targeted therapy utilization among all patients. The primary endpoints were progression free survival (PFS) and overall survival (OS) in those who have and have not received PRBCs. We then evaluated PFS and OS via a cox proportional hazards model that was adjusted for cancer type, age, PS, previous therapies and tobacco use.

Results 304 patients including 272 NSCLC, 24 UC and 8 RCC subjects were evaluated. 54 patients underwent a mini-invasive resection within 120 days of treatment with a CPI and with advanced NSCLC, UC and RCC were included. Patient demographics including age, sex, ethnicity, race, tobacco use and ECOG performance status (PS) were abstracted. We also assessed previous chemotherapy, radiation and targeted therapy utilization among all patients. The primary endpoints were progression free survival (PFS) and overall survival (OS) in those who have and have not received PRBCs. We then evaluated PFS and OS via a cox proportional hazards model that was adjusted for cancer type, age, PS, previous therapies and tobacco use.

Conclusions For immunotherapy-based trials in 2019, <10% of patients expected to be enrolled would be selected by a biomarker for inclusion. Precision oncology continues to struggle in the era of ICI with an all-comers approach to patient selection and trial initiation. Selecting patients for trials based on biomarkers may help better identify responders to ICI.

survival (26.1 months versus 13.8) were shorter in patients who underwent transfusion. After multivariable adjustment, the negative associations between transfusion and PFS (HR: 1.53, p=0.03) and overall survival (HR: 1.40, p=0.09) were preserved (figure 1–2). A sub-analysis of the NSCLC patients was conducted and shorter PFS (HR:1.58, p=0.03) and overall survival (HR:1.56, P=0.03) were again seen in the transfusion cohort (figure 3–4).

Conclusions PRBC transfusions led to an inferior PFS and OS in advanced cancer patients receiving checkpoint inhibitors even after adjustments for multiple prognostic variables. These results suggest a possible attenuation of the effectiveness of immunotherapy as a result of the immunosuppressive effects of PRBC transfusions. The findings require prospective and mechanistic confirmation as inherent bias may exist in this retrospective analysis.

Ethics Approval This study was approved the institutional review board at Fox Chase Cancer Center, approval number 19-9006.

Consent N/A

REFERENCES

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