PET/CT Quantitative Assessment of Myocardial Blood Flow Changes in Oncologic Patients Receiving Checkpoint Inhibitor Therapy

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Abstract (150 words or less with hypothesis)

Immune checkpoint inhibitors (ICI) are novel chemotherapeutic agents which disinhibit T-cell activity, thereby enhancing autoimmune response[1] and ushering in a new era of treatment for patients with both solid and hematologic malignancies.[2] Unfortunately, resultant side effects of ICI use, termed immune-related adverse events (IRAE), are difficult to both diagnose and treat resulting in high fatality rates.[3] The ability to accurately detect subclinical decline in myocardial performance and the resultant initiation of targeted therapy has markedly improved the outcomes of patients prescribed the more traditional cardiotoxic chemotherapeutic agents such as anthracyclines.[4] Consequently, means by which to detect subclinical myocardial injury is garnering increasing interest and now includes the assessment of endothelial function.[5-7] Quantitative positron emission tomography computed tomography (PET-CT) is a highly accurate, reproducible and repeatable technique by which to assess myocardial blood flow (MBF) and endothelial function. [8, 9] For instance, recent studies have demonstrated a decrease in myocardial flow reserve (MFR) in patients receiving doxorubicin.[7] We hypothesize that PET/CT MFR will decrease in some patients receiving ICI thereby representing early, subclinical myocardial injury and potentially serving as an early indicator of patients who might be predisposed to IRAEs.

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A. Rationale: Brief paragraph establishing rationale

Established chemotherapeutic agents such as anthracyclines, trastuzumab and bevacizumab have proven cardiotoxic effects.[10] Historically, some of these sequelae have been severe enough to render a patient's prognosis poorer than that of a patient with ischemic heart failure.[11] Consequently monitoring protocols designed to detect decline in cardiovascular function were initiated in the 1970s and have continued to evolve to include mutligated acquisition scan (MUGA), strain echocardiography and high sensitivity troponin.[12, 13] Early detection of chemotherapeutic cardiotoxicity paired with institution of therapy has markedly improved the prognosis of oncologic patients.[4, 14]

Immune checkpoint inhibitors (ICI) disinhibit T-cell activity thereby allowing for a heightened antitumor immunologic response.[1,15] Resultant outcomes for patients with both solid and hematologic malignancies have been promising.[2, 16, 17] However, immune-related adverse events (IRAE) have been reported secondary to administration of these agents including myocarditis (odds ratio of 11.21), cardiomyopathy and conduction abnormalities.[18, 19] Furthermore, a fatality rate as high as 39 percent has been reported for patients who develop IRAE myocarditis. [3] Approximately 75 percent of patients who develop myocarditis have normal myocardial function prior to therapy and no known preexisting cardiovascular conditions.[3] When myocarditis does occur as an IRAE it typically does so in the first month.[3] Unfortunately IRAEs have thus far been difficult to diagnose and to treat with leaders in the field calling for "development of guidelines for early diagnosis."[3]

Endothelial dysfunction has been demonstrated with the use of other multiple chemotherapeutic agents [3, 5, 20] and is likely due either to endothelial cell death or reduced nitric oxide availability. Quantitative positron emission tomography computed tomography (PET-CT) is an emerging modality which provides a highly accurate, reproducible, repeatability, noninvasive means by which to assess total myocardial blood flow, specifically myocardial flow reserve (MFR,) including assessment of the endothelium.[8, 9] Recently, PET-CT MFR was utilized to demonstrated a decrease in MFR in some patients after expose to doxorubicin but not others thereby labeling them as more likely to develop cardiotoxicity.[3] The current proposal seeks to utilized PET-CT MFR to assess dynamic changes in MFR that occur pre and post

initiation of ICI and thereby potentially identify early cardiotoxicity in patients who might be more prone to more devastating IRAEs such as myocarditis.

There is also considerable interest in identifying unique immune cell phenotypes in the peripheral blood that can predict which patients are most at risk for developing checkpoint inhibitor-mediated IRAEs.[21] [i]In the long-term, this would serve as a less invasive means of monitoring patients both before and during treatment. Thus, this proposal will also collect and analyze peripheral blood from the patients who undergo PET-CT MFR to determine if a particular T cell phenotype prior to therapy may correlate with imaging changes and cardiotoxicity of ICI.

B. Hypothesis:

PET-CT MFR will identify a certain proportion of oncologic patients being prescribed ICIs who develop microvascular damage/endothelial dysfunction. This initial study could serve as the foundation for larger evaluations of this population in determining whether or not routine surveillance can identify patients early who are at higher risk of IRAE and potentially improve outcomes.

C. Aims:

The aims of the current study are two-fold. First is to determine if ICI administration causes microvascular damage/endothelial function. If so, the second aim is to serve as a pilot study for larger trials to determine the prevalence of ICI-induced microvascular damage/endothelial dysfunction and specifically if it identifies patients who are at increased risk of IRAEs.

D. Innovation:

What is known:

1) Traditional chemotherapeutic agents can cause microvascular damage/endothelial dysfunction[3, 5, 20]
2) Early detection of chemotherapeutic toxicity can improve outcomes[4]
3) PET-CT MFR can be used to detect chemotherapeutic reduction in MFR in patients receiving traditional agents such as doxorubicin[3]
4) ICI induced IRAE can cause significant morbidity and mortality

5) Increased lymphocyte counts and clonal expansion of $CD8^+$ T cells in the peripheral blood can precede development of ICI-induced IRAE. [22,23]

What remains to be discovered:

1) Do ICIs cause microvascular disease/endothelial dysfunction?
2) If ICIs do cause microvascular disease/endothelial dysfunction how common is this occurrence and what is its bearing on patient prognosis?
3) Is there any correlation between T cell phenotypes in the peripheral blood and microvascular disease/endothelial dysfunction that occurs on ICI therapy?

E. Significance: How will this change our practice, increase our national standing, attract patients or advance our knowledge about CV disease. What is Mayo unique? (numbered list).

1) Cardio-oncology is a rapidly expanding field and Mayo Clinic has several clinicians at the forefront[10]
2) Oncologic patients are attracted to Mayo Clinic already for our expertise and this will further enhance the practice
3) Mayo Clinic is a leading center for cardiac PET and specifically PET-CT MFR[6]

E. Brief Synopsis of Methods: Very brief summary – numbered list acceptable – of what will actually be done.

1) Collaboration between Cardiology, Oncology and Cardiac PET to recruit 6 consecutive patients beginning ICI therapy
2) Screening labs, including troponin, high sensitivity CRP, and **NT-proBNP**; peripheral blood draw sent to research lab (Dr. Haidong Dong) for T cell phenotyping.
3) Complete PET-CT MFR[6] immediately before and 4-6 weeks after initiation of ICIs
4) Assess change in MFR (per literature 20% or more decreased indicates significant change)[7]
5) Continue long-term follow-up of the patients in charts to determine if any develop IRAEs
6) For patients who develop myocarditis a FDG PET-CT would be performed to assess for inflammation

E.1 Detailed Methods

1) Recruitment: Investigator JPB has met with hematology team (Konstantinos Leventakos MD PhD) who will work with his PA team to identify eligible patients for recruitment. Those deemed eligible will be approached during their initial visits with oncology (prior to initiation of ICI.

2): PET-CT MFR methodology (performed during two sessions-one before and one 4-6 weeks after administration of ICI):

A GE Discovery 690XT, Discovery Molecular Insights (DMI) or 710 PET/CT system (GE Healthcare, Waukesha, WI) will be utilized in performing the studies. The imaging system consists of full ring Cerium-doped Lutetium Yttrium Orthosilicate (LYSO) crystals. 128x128 PET matrix size with zoomed 41.9 cm field of view centered over the heart will be used to obtain the PET images. Furthermore, three-dimensional list mode acquisition will be employed. Three-dimensional iterative reconstruction algorithm with time-of-flight correction, CT attenuation, scatter, randoms, normalization, decay and dead time correction will be utilized. Three-dimensional Hanning post-filter with a 10 mm cut-off will also be used.

A 64 slice-spiral CT will be employed with auto exposure control with modulated current in order to maintain consistent noise index (noise index set at 33 with mA range 10-180). For our CT attenuation imaging tube ration is 0.5 s, kV is 120 and pitch is 0.98. Slice thickness is 3.75 mm and slice increment is 3.27 mm. Matrix size is 512 x 21.

$^{13}NH_3$ will be administered at rest to allow qualitative and quantitative (rest myocardial blood flow) assessment of myocardial perfusion. Regadenoson will be administered as a stress agent followed by a $^{13}NH_3$ with subsequent qualitative and quantitative (myocardial blood flow) assessment of myocardial perfusion. MFR will then be determined by assessing the ratio of stress to rest myocardial blood flow.

For those patients who are suspected to have developed myocarditis they will undergo a FDG-PET CT inflammatory protocol. PET/CT parameters will be similar as noted above. However, no stress agent will be used. Furthermore, FDG will be administered per the inflammatory myocardial protocol for assessment of inflammation.

3) Analysis of T lymphocytes in peripheral blood for phenotypic markers via flow cytometry:

Peripheral blood mononuclear cells (PBMC's) will be isolated from whole blood using a Ficoll gradient, counted, and frozen in liquid nitrogen. For analysis, PBMC's will be thawed and plated overnight in complete RPMI media with IL-2 (10u/mL). The following day, cells will be counted and stained with fluorophore-labeled antibodies suitable for flow cytometry, which may include (but are not limited to): CD45 (clone HI30, catalog 304006), CD3 (clone OKT3, catalog 317344), CX3CR1 (clone 2A9-1, catalog 341616), CD11a (clone HI111, catalog 301212), and PD-1 (clone EH12.2H7, catalog 329904) antibodies from BioLegend; CD8 (clone RPA-T8, catalog 557746) and Ki67(clone B56, catalog 562899) antibodies from BD Biosciences; and anti–human granzyme B (clone GB11, catalog NBP1-50071PCP) from Novus. Cells will then be assayed using a Beckman Coulter Cytoflex LX flow cytometer and data analyzed using FlowJo software (BD Biosciences).

3): Statistical Analysis

General Considerations

Continuous data (e.g., age) will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, median, minimum value (min), and maximum value (max). For each continuous variable, the corresponding mean, median, minimum and maximum will be presented to 1 decimal place and the SD to 2 decimal places, unless otherwise specified.

Categorical variables (e.g., qualitative presence or absence of perfusion defecit) will be summarized using counts and percentages. Percentages will be presented to 1 decimal place. Summaries of continuous and categorical data will be presented, as appropriate.

Incomplete/Missing data: Missing data (e.g., dates, post-baseline values) will not be imputed, unless otherwise specified; i.e., all missing values and missing post-baseline values will remain as missing in all statistical analyses and listings, unless otherwise specified.

Outliers: No formal statistical analyses will be performed to detect and/or remedy the presence of statistical outliers.

Additionally, all subject data, including derived variables, will be presented in subject data listings; listings will display all subjects who were randomized or enrolled in the study.

Background Characteristics

Demographics and Baseline Characteristics

Demographics and baseline characteristics (age, sex, race, ethnicity, weight, height and body mass index [BMI]) will be summarized.

Efficacy Analysis

Analysis of Primary Efficacy Endpoint

Nominal continuous variables will be represented as the mean +/- SD and categorical variables will be noted as the number and percentage of total. Pearson chi-square test will be utilized to determine statistical significance for continuous variables whereas a Student's two-sample t-test will be implemented to determine statistical significance for continuous variables. Univariate and multivariate analyses will be performed when relevant. Statistical significance will be set a priori as a p-value less than 0.05. Given that this is a pilot study no power calculation will be performed. All statistical analyses will be performed using JMP Pro 9 (SAS Institute INC. Cary, North Carolina).

Adverse Events Collection:
Adverse Events will be collected only for activities done for research.

The selection of study subjects will be based upon the following inclusion and <u>exclusion criteria</u>:

Inclusion

1. First time administration of ICI
2. Willing and able to return in 4-6 weeks for follow-up study
3. Patients with previous heart conditions included (while this may impact MFR the delta MFR is what we are assessing)

Exclusion

1. Age < 18 years
2. Women who are pregnant, or breast-feeding.
3. Unable or unwilling to give consent to undergo PET/CT.

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