Principal Investigator

First Name: Shaji
Last Name: Kumar
Degree: MD
Primary Affiliation: Mayo Clinic
E-mail: Abdallah.Nadine@mayo.edu
State or Province: MN
Country: United States

General Information

Key Personnel (other than PI):
First Name: Nadine
Last name: Abdallah
Degree: MD
Primary Affiliation: Mayo Clinic
SCOPUS ID: Requires Data Access? Yes

First Name: Li
Last name: Yan
Degree: MD
Primary Affiliation: Mayo Clinic
SCOPUS ID: Requires Data Access? Yes

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Colleague

Conflict of Interest


Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT02252172 - 54767414MMY3008 - A Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects With Previously Untreated Multiple Myeloma Who Are Ineligible for High Dose Therapy

What type of data are you looking for?: Individual Participant-Level Data, which includes Full
Research Proposal

Project Title

Allostatic Load, Treatment Outcomes, and Mortality in Transplant-Ineligible Patients with Multiple Myeloma

Narrative Summary:

The allostatic load is a measure of cumulative burden of stressors throughout an individual’s life which has been associated with mortality in cancer patients. It is calculated using laboratory biomarkers of the endocrine, cardiovascular, and immune systems. There are limited studies evaluating the association between the allostatic load and outcomes in multiple myeloma patients. We are proposing a retrospective study to evaluate the association between the allostatic load and treatment toxicity and mortality among transplant-ineligible patients with newly diagnosed multiple myeloma. Interventions targeting patients with higher allostatic load may lead to improved outcomes.

Scientific Abstract:

Background: The allostatic load is a measure of cumulative burden of repeated stress responses on multiple biological systems calculated using a set of readily available laboratory biomarkers. Some studies have found associations between a higher allostatic load and cancer-related mortality. Objective: The objective of this study is to evaluate the association between the allostatic load and treatment toxicity and mortality in transplant ineligible patients with newly diagnosed multiple myeloma. Study design: This is a retrospective study that will utilize data on clinical and laboratory variables to calculate the allostatic load for each patient prior to starting treatment. These variables are: systolic blood pressure, diastolic blood pressure, heart rate, hemoglobin A1c, albumin, glomerular filtration rate, fasting blood glucose, alkaline phosphatase, blood urea nitrogen, and white blood cell count. The association between the allostatic load and treatment toxicity and mortality will be evaluated. Participants: Transplant-ineligible patients with newly diagnosed multiple myeloma enrolled on the Phase III MAIA Trial Outcome measures: The outcome measures of interest for this study are the rate of high-grade treatment-related adverse events, health-related quality of life, and overall survival. Statistical analysis: The association between allostatic load and development of high-grade treatment-related adverse events and will be estimated using multivariable logistic regression, adjusting for age, treatment arm, and ECOG performance status. Univariate and multivariate cox proportional hazards models will be used to evaluate the impact of allostatic load on overall survival adjusting for age, ECOG performance status, disease stage and treatment arm.

Brief Project Background and Statement of Project Significance:

Background: Multiple myeloma (MM) is the second most common hematologic malignancy accounting for 2% of all cancers in the United States. Patients with MM exhibit wide heterogeneity in baseline physiologic status and ability to tolerate various treatments. There is also wide variability in survival outcomes even among uniformly treated patient. Thus, the management of patients with MM demands a personalized treatment approach which starts by the identification of patients who are at increased risk of treatment-related complications and disease-related mortality. The allostatic load, a term that reflects the cumulative burden exerted by repeated stress responses on multiple biological systems, has been evaluated in several studies as a predictor of cancer-related outcomes using composite scores based on a set of readily available laboratory biomarkers. These include various combinations of neuroendocrine, cardiovascular, inflammatory, metabolic, and/or
immune biomarkers. There has been wide variability in the number, combination, and clinical cutoffs of the biomarkers used in various studies to measure the allostatic load. While some studies have found an association with cancer-related and all-cause mortality, this has not been consistent across studies.5-7 There are limited studies evaluating the association between the allostatic load and outcomes in patients with MM. A recent study used data from MM patients enrolled in the ECOG-ACRN E1A11 trial to measure the allostatic load and evaluated its association with baseline symptom burden, completion of treatment, and mortality. A composite score for the allostatic load was calculated using extreme values of 7 biomarkers: alkaline phosphatase, albumin, creatinine, creatinine clearance, C-reactive protein, white blood cell count, and BMI. Increased allostatic load was associated with baseline fatigue but such an association was not observed at 5.5-month from study entry. There was no association between a high allostatic load and pain, bother, or completion of induction chemotherapy. However, an elevated allostatic load at baseline was associated with worse overall survival after adjusting for sex, age, race, disease stage, performance status and type of treatment.8

Study rationale and significance: There are limited studies evaluating the association between the allostatic load and treatment outcomes in patients with MM, with existing studies focusing primarily on survival outcomes. We propose a retrospective study to evaluate the association between the allostatic load and treatment-related toxicity, health-related quality of life, and survival among transplant-ineligible patients with newly diagnosed MM enrolled on the Phase III MAIA Trial.9 The identification of patients at increased risk of treatment toxicity will allow personalization of treatment strategies which has the potential to improve outcomes of transplant-ineligible patients with MM.

**Specific Aims of the Project:**

Primary aim: To evaluate the association between a high allostatic load and the development of high-grade (grade ?3) treatment-related adverse events among transplant-ineligible patients with newly diagnosed MM. Hypothesis: An increased allostatic load score is associated with an increased risk of developing high-grade treatment-related adverse events.

Secondary aims:
To evaluate the association between a high allostatic load and health-related quality of life at baseline and after 3 months from starting treatment among transplant-ineligible patients with newly diagnosed MM. Hypothesis: An increased allostatic load score is associated with lower quality of life scores at baseline and after 3 months from starting treatment.
To evaluate the association between a high allostatic load and overall survival among transplant-ineligible patients with newly diagnosed MM. Hypothesis: An increased allostatic load score is associated with decreased overall survival.

**Study Design:**

Individual trial analysis

**Research Methods**

**Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:**

Inclusion Criteria:
Patients ? 18 years with newly diagnosed multiple myeloma.
Transplant ineligible

Have data available for the following variables: systolic blood pressure, diastolic blood pressure, heart rate, hemoglobin A1c, albumin, glomerular filtration rate, fasting blood glucose, alkaline phosphatase, blood urea nitrogen, and white blood cell count.

Exclusion criteria:
Have missing data for any of the following variables: systolic blood pressure, diastolic blood pressure, heart rate, hemoglobin A1c, albumin, glomerular filtration rate, fasting blood glucose, alkaline phosphatase, blood urea nitrogen, and white blood cell count.
Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary outcome measure:
High grade (grade ?3) treatment related adverse events defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0).11

Secondary Outcome measures:
Health-related quality of life measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item and the EuroQol 5-dimensional descriptive system at baseline and after 3 months from starting treatment.
Overall survival defined as the time from starting treatment until death from any cause.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
Allostatic load will be analyzed as a continuous variable except for log-rank tests, where it will be analyzed as a categorical variable split into 4 categories (scores of 0, 1-2, 3, and ?4).

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
None

Statistical Analysis Plan:
We propose a retrospective study using data from the MAIA phase III therapeutic clinical trial which was designed to evaluate daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone among transplant ineligible patients with newly diagnosed MM. We will collect data on allostatic load variables at the time of study enrollment selected based on their availability in the study data set and use in prior studies. The variables of interest are: systolic blood pressure, diastolic blood pressure, heart rate, hemoglobin A1c, albumin, glomerular filtration rate, fasting blood glucose, alkaline phosphatase, blood urea nitrogen, and white blood cell count. The allostatic load will be calculated as a composite score of these biomarkers. For each biomarker, a score of one will be assigned if the value was in the high-risk category corresponding to the highest sample quartile for systolic blood pressure, diastolic blood pressure, heart rate, total cholesterol, triglycerides, hemoglobin A1c, fasting blood glucose, alkaline phosphatase, blood urea nitrogen, and white blood cell count and the lowest sample quartile for albumin, creatinine clearance, glomerular filtration rate and HDL. The total allostatic load score is the sum of the biomarker scores. Patients who have missing values for any of the biomarkers will not receive a score. We will also calculate the allostatic load using an alternative approach where each variable will be categorized as high-risk, moderate-risk or high-risk using cutoffs defined in previous studies.10 One point will be assigned for the high-risk category, half a point for the moderate-risk categories, and zero points for the low-risk category. Half a point will be added to the total score for patients who report taking a medication for hypertension and diabetes, and have low-risk values for blood pressure and fasting glucose/hemoglobin A1c, respectively. The outcomes of interest are: 1) grade ?3 treatment related adverse events, 2) health-related quality of life at baseline and after 3 months from starting treatment, and 3) overall survival. The association between allostatic load and development of high-grade treatment-related adverse events and will be estimated using multivariable logistic regression, adjusting for age, treatment arm, and ECOG performance status. Overall survival will be analyzed using Kaplan-Meier method, and log-rank test will be used to test for differences between groups based on the allostatic load. Univariate and multivariate cox proportional hazards models will also be used to evaluate the impact of allostatic load on overall survival adjusting for age, ECOG performance status, disease stage and treatment arm. For all tests, 2-sided p values

Project Timeline:
Project start date: July 1st, 2023. Analysis completion date: September 30th, 2023. Date of first draft: November 30th, 2023. Date of final manuscript draft: December 30th, 2023. Date results
reported back to the YODA project: January 1st, 2024. Date of submission for publication: January 1st, 2024.

Dissemination Plan:

This study is expected to lead to an original research article. The target audience for this study is clinicians, trainees, and researchers interested in hematological disorders. Potentially suitable journals for submission include: Blood, American Journal of Hematology, Blood Cancer Journal, and Leukemia.

Bibliography: