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How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2017/08/sborov_coi_7-sep-2021.pdf

https://yoda.yale.edu/wp-content/uploads/2019/11/muhamed_coi.pdf
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https://yoda.yale.edu/wp-content/uploads/2021/04/COI_YODA_YXu.pdf

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
2. NCT02195479 - 54767414MMY3007 - A Phase 3, Randomized, Controlled, Open-label Study of VELCADE (Bortezomib) Melphalan-Prednisone (VMP) Compared to Daratumumab in Combination With VMP (D-VMP), in Subjects With Previously Untreated Multiple Myeloma Who Are Ineligible for High-dose Therapy

Research Proposal

Project Title

Thromboembolism Prophylaxis and the Incidence of Venous Thromboembolism in Newly Diagnosed Multiple Myeloma Patients Enrolled on the MAIA trial

Narrative Summary:

Multiple myeloma (MM) patients have a nine-fold increased risk of venous thromboembolism (VTE). VTE incidence is highest during the first 6 months following diagnosis and the optimal prophylaxis strategy is unknown, especially in patients treated with newer drugs like daratumumab. This retrospective study aims to investigate VTE risk and incidence for patients enrolled on the randomized phase 3 MAIA trial, correlate the baseline risk of VTE per SAVED score with overall VTE incidence, and examine the degree to which anti-thrombosis prophylaxis was administered. Ultimately, this data will provide key insights to inform the appropriate design of future prospective trials.

Scientific Abstract:

Background: Multiple myeloma (MM) is an incurable malignancy associated with an estimated 5-year survival of 54% and approximately 13,000 deaths in the US annually. Significant improvements in treatment options have significantly improved survival and while novel combination regimens lead to objective responses in > 90% of patients, disease and treatment-related morbidity persist. Venous thromboembolism (VTE) continues to be a significant issue for all patients with MM and VTE prophylaxis guidelines are outdated and not routinely utilized.
Objective: Ultimately, the optimal VTE prophylactic strategy is unknown and the overall objective of the present project is to determine the incidence of VTE and investigate the impact of various VTE prophylactic strategies on the rate of VTE based on SAVED risk stratification for patients with newly

diagnosed transplant ineligible MM enrolled on clinical trials including treatment with daratumumab.
Study design: The present study will retrospectively investigate the incidence of VTE and investigate the impact of various VTE prophylactic strategies on the rate of VTE based on SAVED risk stratification for patients with transplant ineligible newly diagnosed multiple myeloma.
Participants: All patients randomized on the phase 3 MAIA and ALCYONE trials.
Primary outcome: Rate of VTE for patients treated with 1) daratumumab, lenalidomide, and dexamethasone, 2) lenalidomide and dexamethasone, 3) velcade, melphalan, and prednisone, and 4) daratumumab, velcade, melphalan, and prednisone.
Secondary outcomes: Rates of VTE within SAVED and IMPEDE risk stratification models for patients treated with 1) daratumumab, lenalidomide, and dexamethasone, 2) lenalidomide and dexamethasone, 3) velcade, melphalan, and prednisone, and 4) daratumumab, velcade, melphalan, and prednisone. Additional secondary outcomes to be measured include time from treatment initiation to VTE onset, CTCAE grade of VTE events, type of thromboprophylaxis treatment, duration of thromboprophylaxis treatment, rate and grade of bleeding events, overall drug exposure, and rates of grade 3 or higher thrombocytopenia per treatment regimen.
Statistical analysis: A descriptive analysis describing disease clinical and biologic features, treatments, and outcomes is planned. Continuous variables will be summarized as means or medians including standard deviations and range, respectively. Differences between continuous variables will be examined using the t-test, and the Mann-Whitney test will be used to examine non-normally distributed measurements. Categorical variables will be summarized as frequencies and associations between these variables will be tested via the chi-squared test.
Incident VTE rates will be estimated overall, and separately within IMPEDE and SAVED risk strata, along with exact 95% confidence intervals. Comparisons of VTE rates across IMPEDE and SAVED risk strata will be conducted in the context of logistic regression models, in univariate analyses as well as multivariable analyses adjusted for patient characteristics. VTE rates will be estimated and compared across VTE prophylactic strategies, again based on logistic regression models, in univariate analyses separately within IMPEDE and SAVED risk strata as well as multivariable analyses adjusted for potential confounders. Patient characteristics will be also be considered as moderators of VTE prophylactic strategy comparisons.

Brief Project Background and Statement of Project Significance:

Patients with multiple myeloma (MM) have a nine-fold increased risk of developing venous thromboembolism (VTE) compared to the general population and have increased risk of mortality associated with these events. The incidence of VTE in MM is considered to be highest during the first 6 months after diagnosis. Given the progression to ?triplet? and ?quad? induction therapies, the incidence as well as the prevalence, of venous thromboembolism complications in MM are expected to rise.
Routine administration of VTE prophylaxis with anticoagulation is an effective way to decrease the burden of VTE in cancer patients and multiple trials have shown that low molecular weight heparin (LMWH) and various direct oral anticoagulants (DOAC) reduce VTE risk without increased risk of major bleeding. Despite the significant amount of data available for cancer patients, the applicability of these findings for patients with MM is limited due to the fact that very few MM patients were included in these trials (some < 2%).
The National Comprehensive Cancer Network (NCCN) guidelines recommend that decisions regarding thromboprophylaxis in MM patients be based on VTE risk assessment. Several risk stratification systems such as the International Myeloma Working Group (IMWG) VTE guidelines exist, but even with these guidelines available, only ~20% of patients receive the appropriate prophylaxis11. Additionally, the accuracy of these assessment tools has been shown to poorly correlate with the development of VTE. In fact, despite a protocol-stipulated thrombosis risk assessment using the IMWG guidelines coupled with a minimum recommended 3 months of thromboprophylaxis, rates of VTE remained greater than 10% on the Myeloma XI trial. To improve upon the prediction of VTE in patients with NDMM starting chemotherapy, the SAVED VTE model was developed. This scoring system allows adjustment for baseline use of dexamethasone, surgery within 90 days of starting treatment, history of VTE, age > 80, and Asian race.
There are a number of significant questions that exist in respect to VTE prophylaxis in patients with MM including the effect of modern multi-drug induction regimens on the incidence of VTE and optimal choice of VTE thromboprophylaxis regimen based on SAVED and other risk stratification

models. In the past 5 years, a number of landmark trials investigating novel multi-drug combinations for the treatment of patients with MM have been published, including ENDURANCE, GRIFFIN, CASSIOPEIA, MAIA, SWOG S0777, POLLUX, and CASTOR amongst other. In each of these trials, thromboprophylaxis per IMWG guidelines was recommended but the rates of VTE and bleeding based on type of anticoagulation has not been reported. Understanding modern practice patterns in patients with MM via retrospective analysis of these trials will determine the impact of various thromboprophylactic strategies on incidence of VTE, and ultimately, guide the design of prospective clinical trials aimed at minimizing VTE and optimizing patient safety.

Specific Aims of the Project:

Aim 1: Calculate the baseline SAVED risk scoring and stratification of newly diagnosed transplant ineligible multiple myeloma (NDMM) patients enrolled on the randomized phase 3 MAIA and ALCYONE trials.
Aim 2: Calculate the baseline IMPEDE risk scoring and stratification of newly diagnosed transplant ineligible multiple myeloma (NDMM) patients enrolled on the randomized phase 3 MAIA and ALCYONE trials.
Aim 3: Determine the incidence of venous and arterial thromboembolism and investigate the impact of various thromboembolism prophylaxis strategies [low vs high dose aspirin, prophylactic vs therapeutic dose anticoagulants [e.g. low molecular weight heparin, direct oral anticoagulants (DOACs), warfarin etc.] on the rate of thromboembolism based on SAVED risk stratification (low, intermediate or high risk) and IMPEDE if adequate data is available.

Study Design:

Individual trial analysis

Research Methods

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

All patients enrolled on the randomized phase 3 MAIA and ALCYONE trials will be included in this analysis.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary: Rate of VTE for patients treated with 1) daratumumab, lenalidomide, and dexamethasone, 2) lenalidomide and dexamethasone, 3) velcade, melphalan, and prednisone, and 4) daratumumab, velcade, melphalan, and prednisone. Rates of VTE will be defined as any grade 1 - 5 arterial or venous thromboembolic event as defined by CTCAE v4 grading criteria.
Secondary: Rates of VTE within SAVED and IMPEDE risk stratification models for patients treated with 1) daratumumab, lenalidomide, and dexamethasone, 2) lenalidomide and dexamethasone, 3) velcade, melphalan, and prednisone, and 4) daratumumab, velcade, melphalan, and prednisone. Addition secondary outcomes include time from treatment initiation to VTE onset, CTCAE grade of VTE events, type of thromboprophylaxis treatment, duration of thromboprophylaxis treatment, rate and grade of bleeding events per CTCAE v4, overall drug exposure as defined as time of treatment initiation to end of study drug including dose holds and dose modifications, and rates of grade 3 or higher thrombocytopenia

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

NA

Other Variables of Interest that will be used in your analysis and how they will be

categorized/defined for your study:

Others variables of interest will include the following:
1) Demographics including age, race, myeloma subtype, R-ISS/ISS risk at diagnosis, tumor burden as measured by serum/urine biomarkers, bone marrow aspirate/biopsy, and diagnostic imaging
2) IMPEDE risk score calculation includes Patient BMI at screening, presence of absence of fracture (pelvis, hip, or femur), use of erythropoietin stimulating agents (ESA), race (Asian/Pacific Islander vs other), history of prior VTE, presence of absence of central venous catheter, pretreatment use of prophylactic or therapeutic anticoagulation
3) SAVED risk score calculation includes Surgery within 90 days, Asian race, VTE history, age > 80, treatment with dexamethasone (low (120-160 mg) vs high (> 160 mg) dose)

Statistical Analysis Plan:

A descriptive analysis describing disease clinical and biologic features, treatments, and outcomes is planned. Continuous variables will be summarized as means or medians including standard deviations and range, respectively. Differences between continuous variables will be examined using the t-test, and the Mann-Whitney test will be used to examine non-normally distributed measurements. Categorical variables will be summarized as frequencies and associations between these variables will be tested via the chi-squared test.
Incident VTE rates will be estimated overall, and separately within IMPEDE and SAVED risk strata, along with exact 95% confidence intervals. Comparisons of VTE rates across IMPEDE and SAVED risk strata will be conducted in the context of logistic regression models, in univariate analyses as well as multivariable analyses adjusted for patient characteristics. VTE rates will be estimated and compared across VTE prophylactic strategies, again based on logistic regression models, in univariate analyses separately within IMPEDE and SAVED risk strata as well as multivariable analyses adjusted for potential confounders. Patient characteristics will be also be considered as moderators of VTE prophylactic strategy comparisons, to assess evidence that particular VTE prophylactic strategies need to be tailored to particular types of patients.
In secondary analyses, VTE prophylactic strategies will be compared via matching weighted logistic regressions. Multinomial propensity models will be constructed based on potential confounders via random forest. Balancing of potential confounders across strategy comparison groups will be assessed in terms of standardized mean differences. Effect moderation and patient tailoring will be assessed in subgroup analyses, accompanied by tests of moderator by treatment interaction.

Project Timeline:

The proposed timeline for completion of this project including data retrieval, review, and analysis is 6 months. It is planned that this data will be submitted for presentation at the 2023 American Society of Hematology Annual Meeting (submission approximately 1-Aug-2023) and initial submission for publication by 1-Nov-2023.

Dissemination Plan:

The proposed plan for data dissemination is for submission to the 2023 American Society of Hematology (ASH) Annual Meeting in December 2023. In conjunction with presentation of this data at ASH, our group plans to submit for publication to Blood Advances, American Journal of Hematology, or British Journal of Hematology in November 2023.

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