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General Information

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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

https://yoda.yale.edu/wp-content/uploads/2024/07/SB-conflict-of-interest-form.pdf
https://yoda.yale.edu/wp-content/uploads/2024/07/FM-conflict-of-interest-form.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. 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
2. 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 CSR and all supporting documentation

Research Proposal

Project Title

Analysis of mutiple myeloma cell dynamics in response to different treatments.

Narrative Summary:

Since the pioneering work of Salmon and Durie, quantitative measures of tumor burden in multiple myeloma have been used to make clinical predictions and model tumor growth. However, such quantitative analyses have not yet been performed on large datasets from trials using modern treatments.

We would like to collect large datasets of tumor response data for different treatments to establish and validate a novel mathematical model of multiple myeloma cell dynamics.

Scientific Abstract:

Background:
Multiple myeloma is a cancer of plasma cells that is characterized by complex clonal evolution and hierarchical differentiation. Understanding the dynamics of myeloma cells in response to treatment is crucial for improving therapeutic strategies.

Objective:
The objective of this study is to investigate the dynamics of myeloma cells in response to treatment using new datasets, which will provide a more comprehensive understanding of the hierarchical differentiation and clonal evolution in multiple myeloma.

Study Design:
This study will use a longitudinal cohort design, analyzing data from multiple clinical trials, with replication and extension of methodologies from prior research.

Participants:
Participants will include patients diagnosed with multiple myeloma who have been treated with different regimens.

Primary and Secondary Outcome Measure(s):
Primary outcomes will include a model of M protein dynamics and the effect of each treatment of it. Secondary outcomes will include a comparison of the effectiveness of different treatment regimes for different patients.

Statistical Analysis:
We will first start with developing a mathematical model for M protein dynamics. Then, statistical analysis will involve survival analysis using Kaplan-Meier curves, Cox proportional hazards models, and hierarchical clustering to identify patterns of clonal evolution. Comparative analysis will be conducted to assess the consistency of findings with previous studies.

Brief Project Background and Statement of Project Significance:

Project Background:
Multiple myeloma (MM) remains an incurable malignancy despite advancements in treatment. Clonal heterogeneity and the hierarchical nature of myeloma cells complicate treatment outcomes, necessitating a deeper understanding of these dynamics. Previous research highlighted the importance of hierarchical differentiation and clonal evolution in MM. As an example, Matsui and colleagues provided experimental evidence for the existence of clonogenic myeloma progenitor

cells, which contribute to the hierarchical structure of MM [1]. Some mathematical models describing tumor growth and the dynamics of treatment response in MM patients have been developed, such as the pioneering work of Sullivan et al. [2] and Hokanson et al. [3]. However, more quantitative analyses on large datasets from trials using modern chemotherapy

Statement of Project Significance:
This project aims to investigate the dynamics of myeloma cells in response to treatment using new datasets, which will provide a more comprehensive understanding of the hierarchical differentiation and clonal evolution in multiple myeloma. The information gained will enhance our understanding of MM pathogenesis, potentially leading to improved therapeutic strategies and personalized medicine approaches. The findings will be instrumental in informing public health strategies and advancing generalizable scientific knowledge in oncology.

Specific Aims of the Project:

Objective 1: To develop and validate the hierarchical differentiation and clonal evolution model of myeloma cells using new datasets.
Hypothesis to evaluate: Myeloma cell dynamics observed in new datasets will corroborate the hierarchical differentiation and clonal evolution dynamics identified in previous studies.

Objective 2: to compare the effectiveness of different treatment regimens on patient outcomes in multiple myeloma and identify patient subgroups that benefit most from specific treatments based on clonal evolution patterns.
Hypothesis to evaluate: Different treatment regimens will have distinct effects on clonal evolution, influencing the evolution of MM in patients

Study Design:

Meta-analysis (analysis of multiple trials together)

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Confirm or validate previously conducted research on treatment effectiveness

Research on clinical prediction or risk prediction

Research Methods

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

Data Source:
The study will utilize datasets from multiple clinical trials available through the YODA Project, including but not limited to studies on myeloma treatments. Additional datasets will be sourced from institutional databases and public repositories, if needed.

Inclusion Criteria:
1) Patients diagnosed with multiple myeloma.
2) Patients who have received at least one line of therapy.

Exclusion Criteria:
1) Patients with incomplete data or who have not received standard first-line treatments.

Platform for Analysis:

Data will be pooled and analyzed using the R statistical software and the Stan platform for hierarchical modeling and Bayesian inference

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

Primary Outcome Measures:
Development of M protein dynamics model

Secondary Outcome Measures:
Comparative effectiveness of various treatment regimens across different patient groups. This measure will assess how one treatment performs relative to another in terms of effectiveness, allowing us to identify which treatments are superior or inferior for specific patient demographics or disease characteristics.

When applicable, any changes to the primary and/or secondary outcome measures in the final analysis will be described in the publication.

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

The primary independent variable is the type of treatment regimen administered, categorized by therapeutic agent combinations (e.g., immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies). Treatment regimens will be analyzed for their impact on both M protein dynamics and patient outcomes

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Other variables of interest will include patient demographics (age, gender), genetic profiles, disease stage at diagnosis, and previous treatment history. Variables such as response rates and biomarker levels (specifically, M protein levels) will be quantitatively analyzed to assess treatment efficacy and disease progression.

Statistical Analysis Plan:

The study will have the following steps:

Statistical modeling: We will first develop statistical models to describe the M-protein dynamics over time for different treatments. The models considered will include single-phase exponential curves and multi-phase (n-phasic) exponential curves with n-1 turning points. These models are the most plausible to consider because the study aims to investigate the dynamics of treatment responses in multiple myeloma (MM) cells by analyzing M-protein levels, and cell populations typically change at an exponential rate. Additionally, visual inspection of the data will help identify the number of phases that best represent the observed patterns in patients' data. Finally, we will use clinical trial data to fit these models and identify the one that provides the best fit for each patient.

Statistical analysis: we will then employ Kaplan-Meier survival analysis to estimate time-to-event outcomes, and Cox proportional hazards modeling to explore the effects of various treatments on survival. Kaplan-Meier curves of interest may include survival time from the end of the trial until death or the end of follow-up, as well as time from treatment initiation to disease progression. These analyses will be performed for patients categorized by their best-fitting model. This approach will allow us to identify differences in treatment responses between patients with distinct response patterns and investigate the underlying reasons for these differences.

Biology-based mathematical modeling: we will develop biology-based mathematical models to explain the response dynamics under different treatment scenarios. Differential equations will be used to model changes over time in MM cell populations, accounting for key biological processes

such as cell proliferation, death, and differentiation.

Model Validation: We will validate the models by comparing the predicted outcomes with actual clinical data, refining and adjusting model parameters as necessary to improve accuracy. This final analysis will help us identify the most suitable biology-based model, offering a theoretical biology explanation for the observed trial results.

Data required: to answer the reviewer's question, in addition to the M protein level data, it would be helpful to have information on the presence of secondary clones, if available. If immunofixation has been performed, knowing the isotype of the clones would be valuable as well. However, if this data is not available, M protein level data alone will be sufficient.

Software Used:

R

Project Timeline:

Project Start Date: When YODA-datasets are received

Model Development: 2 months

Initial Analysis and Model Refinement: 2 months

Full Analysis and Drafting of Manuscript: 4 months

Submission of Manuscript and Results Reporting to YODA Project: 8 months after the beginning of the project

Dissemination Plan:

The results will be prepared for submission to peer-reviewed journals such as Clinical Cancer Research. We anticipate presenting findings at major conferences such as the AACR annual meeting. The study's results will also be shared with the participating clinical trial groups and through open-access publications to maximize reach and impact within the medical and research community.

This comprehensive approach ensures that your study not only replicates and validates previous research but also explores new dimensions of treatment efficacy and safety, thereby significantly contributing to the field of multiple myeloma treatment research.

Bibliography:

[1] Matsui W, Huff CA, Wang Q, Malehorn MT, Barber J, Tanhehco Y, et al. Characterization of clonogenic multiple myeloma cells. Blood. 2004;103:2332–6.

[2] Sullivan PW, Salmon SE. Kinetics of tumor growth and regression in IgG multiple myeloma. J Clin Invest. 1972;51:1697–708.

[3] Hokanson JA, Brown BW, Thompson JR, Drewinko B, Alexanian R. Tumor growth patterns in multiple myeloma. Cancer. 1977;39:1077–84.