STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official Title

The Effect of B Cell Maturation Antigen (BCMA) Polymorphisms on Treatment Response and Survival in Patients With Multiple Myeloma

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Sponsor: Başakşehir Çam and Sakura City Hospital

Collaborator: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Principal Investigator: İstemi Serin, MD

1. Objective

The aim of this study is to investigate the effect of B cell maturation antigen (BCMA) polymorphisms on treatment response and survival in patients with multiple myeloma.

2. Background

B cell maturation antigen (BCMA), also called tumor necrosis factor receptor superfamily member 17 (TNFRSF17), is a type III transmembrane protein that lacks a signal peptide and contains cysteine-rich extracellular domains. Together with two other members of the tumor necrosis factor receptor (TNFR) superfamily, the B cell activating factor receptor (BAFF-R) and the transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), BCMA regulates B cell proliferation and survival, as well as maturation and differentiation into plasma cells. These three functionally related receptors bind the cognate ligands B cell activating factor (BAFF) and/or a proliferation-inducing ligand (APRIL), ensuring the long-term survival of B cells at different developmental stages. Specifically, BCMA is induced only in late memory B cells committed to plasma cell differentiation and is present on all plasma cells. During plasma cell differentiation from B cells, BCMA expression is induced, whereas BAFF-R expression decreases.

In this study, we aim to examine BCMA polymorphisms and their association with treatment response and survival in patients with multiple myeloma.

3. Study Design

This is a single-center, retrospective, observational case-control study. Stored genomic DNA samples and clinical data of 320 patients with multiple myeloma and 100 healthy controls will be analyzed.

4. Methods

Polymorphisms in the BCMA (TNFRSF17) gene will be analyzed by next-generation sequencing (NGS). A total of 320 patients with multiple myeloma and 100 healthy controls, whose DNA samples have already been isolated and for whom treatment and survival data are available, will be included in the study.

In addition to demographic data such as age and sex, Durie-Salmon stage, International Staging System (ISS) stage, Eastern Cooperative Oncology Group (ECOG) performance status, laboratory data at diagnosis, first-line treatment, progression-free survival (PFS), overall survival (OS), mortality, and follow-up duration will be recorded.

At the initial evaluation, all patients were considered eligible for autologous stem cell transplantation (ASCT) and received four cycles of induction therapy with VCD (bortezomib, cyclophosphamide, and dexamethasone). Patients achieving at least partial response proceeded to ASCT, followed by maintenance therapy with LD (lenalidomide and dexamethasone). Treatment response will be assessed according to the International Myeloma Working Group (IMWG) 2016 response criteria.

5. Outcome Measures

Primary outcome: Percentage of patients achieving partial response or better after four cycles of first-line induction therapy, compared across BCMA genotypes.

Secondary outcomes: Progression-free survival and overall survival according to BCMA genotype; frequency of BCMA genotypes in patients with multiple myeloma and healthy controls.

6. DNA Isolation

Leukocytes were isolated from peripheral blood samples collected in 2-mL EDTA tubes from patients and control individuals, and genomic DNA was extracted from the leukocytes using the Quick-DNA Miniprep Plus Kit (Zymo Research) according to the manufacturer's instructions. DNA samples have been stored at -20°C.

7. Statistical Analysis

All data will be analyzed using SPSS version 21. Differences in genotype frequencies between the patient and control groups will be compared using the chi-square test, and Fisher's exact test will be used when necessary. Odds ratios (ORs) with 95% confidence intervals will be calculated using a logistic regression model adjusted for sex and age. Observed genotype frequencies will be compared with those expected under Hardy-Weinberg equilibrium. The association of genotypes with treatment response will be evaluated using the chi-square test or Fisher's exact test. Survival probabilities will be estimated using the Kaplan-Meier method, and differences between groups will be compared using the log-rank test. Stepwise Cox regression analysis will be used to confirm the significance of risk factors; variables with $p < 0.10$ in univariate analysis will be included in the multivariate model. A p value < 0.05 will be considered statistically significant.

8. Study Coordinators and Location

The study is carried out in collaboration with the Laboratory of Medical Genetics of Istanbul University. Associate Professor İstemi Serin, Dr. Tahir Alper Çınlı, Prof. Dr. Sacide Pehlivan and team members are responsible for the study. Laboratory analyses are carried out at the Medical Biology and Genetics Laboratories of Istanbul University, Istanbul Faculty of Medicine, without any charge or financial concern.

9. Sponsor and Support

The name of the supporting company will be included in both the financial support and acknowledgment sections of any publication arising from the study. A working budget of approximately 20,000 € is required for the planned study. No other financial support is required.