Study Design and Clinical Trial Project

Randomized incomplete factorial phase 2 study of low-dose dexamethasone in combination with both or with one of carfilzomib and pomalidomide for relapsed and refractory multiple myeloma

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Introduction

Multiple myeloma (MM) is a malignant plasma cell disorder with potential secondary organ effects including renal, bone, and bone marrow effects as well as neurologic and immune dysfunction. Diagnostic evaluation of MM includes laboratory and radiologic studies along with bone marrow biopsy to confirm diagnosis. Unfortunately, virtually all patients with MM eventually relapse, which is characterized by increasingly shorter periods of remission following each salvage therapy [1]. Related researches have found that the status of MM patients who have received noval agents, including bortezomib (BORT) and lenalidomide (LEN) were also unfavorable [2], which suggests that new treatments for MM patients, especially for RRMM patients, are highly needed.

Pomalidomide (POM) is a distinct immunomodulatory drug with potent antimyeloma activity, and POM plus dexamethasone (DEX) has synergistic antiproliferative effects in LEN-resistant myeloma cells [3]. POM has shown efficacy in RRMM patients who had received multiple prior therapies, either when given alone or with low-dose dexamethasone (DEX) [4]. Carfilzomib (CFZ), a selective and irreversible proteasome inhibitor, was approved in the United States for RRMM patients who had progressed after at least 2 treatments, including lenalidomide and bortezomib. Evidence has shown that CFZ does have significant improvement in overall reaction ratio of RRMM patients with MTD 20/27 mg/m^2 based on previous phase 1 study [5]. Dexamethasone (DEX) is a corticosteroid that prevents the release of substances in the body that cause inflammation. It has been widely used to treat many conditions. It would be useful to release adverse effect of RRMM related treatment. Besides, researches have found that the combination of DEX would yield better treatment effect [7].

Here, we are trying to perform a multicenter, randomized, double-blind incomplete factorial phase 2 trial to compare the efficacy of combination treatment and monotherapies. And the safety will also be evaluated. Previous researches have demonstrated the efficacy of CFZ with LoDEX monotherapy. Given the knowledge that the phase 1 study of has established the maximum tolerated dose of POM (4 mg/day on days 1-21 of a 28-day cycle) [6], our hypothesis is that CFZ and POM with LoDEX combination therapy would be superior to the CFZ with LoDEX monotherapy and the POM with LoDEX monotherapy.

Methods

Patients enrollments

Our patients will be collected from 10 hospitals and medical centers in the United States within 1 year. Eligible patients should be older than 18 who have RRMM and measurable M-paraprotein levels in serum or urine. All patients should have received at least 2 prior antimyeloma therapies, including 2 cycles of LEN and 2 cycles of BORT, given separately or in combination. Patients need to have relapsed after having achieved at least stable disease (SD) for 1 cycle of treatment to 1 prior regimen, as well as having disease progression during or within 60 days (measured from the end of the last cycle) of completing treatment with the last regimen used prior to study entry (and thus have relapsed and refractory disease).

Exclusion criteria are absolute neutrophil counts <1000/mL; platelet counts <75000/mL or <30 000/mL for patients in whom <50% or >=50% of bone marrow nucleated cells are plasma cells, respectively; serum creatinine >=3.0 mg/dL; serum liver transaminase levels > 3.0 X the upper limit of normal; or serum bilirubin >2.0 mg/dL [7]. Additional exclusion criteria includes pregnancy, psychiatric conditions, and/or known drug interaction with Pomalidomide, Carfilzomib and/or Dexamethasone.

Disease progression was defined as any of the following: appearance of new soft-tissue plasmacytomas or increase in size of existing plasmacytoma(s); new lytic bone lesions or an increase in the size of the existing bone lesions; or the development of hypercalcemia (serum calcium >11.5 mg/dL) [7].

All patients would give their written informed consent before entering the study, and would be confirmed by IRB in Washington University.

Treatment assignments

We apply two-cycle treatments, and each cycle will last for 28 days:

- *Pomalidomide*: oral administration 4 mg/day on days 1 to 21 of each 28-day cycle.
- *Carfilzomib*: intravenous infusion over 2 to 10 minutes at a dose of 20 mg/m2 on days 1, 2, 8, 9, 15, and 16 of the 28 days of cycle 1, and at a dose of 27 mg/m2 on the same schedule in cycle 2 and subsequent cycles.
- *Low-dose Dexamethasone*: 40 mg oral on days 1, 8, 15, and 22 of 28-day cycles.

Besides, all patients will receive aspirin (81-100 mg/day) unless contraindicated. If aspirin was contraindicated, patients will receive another form of antithrombotic therapy according to local hospital guidelines or physician preference. All treatment administrations would be facilitated and recorded by trained nurses in each center/hospital.

Adverse effects

The most common adverse reactions include fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and fever. The most common serious adverse events were pneumonia, acute renal failure, fever, and congestive heart failure [5-7]. And the severity would be evaluated by Doctors using current evaluated criteria (CTCAE v4.0, appendix I).

Randomizations

Since we are going to recruit patients from different places, a center-stratified randomization will be used to assign participants to different treatment groups. Here we assure that for each center there exists a separate randomization list generated according to block-permuted randomization.

Endpoints

Our endpoints include:

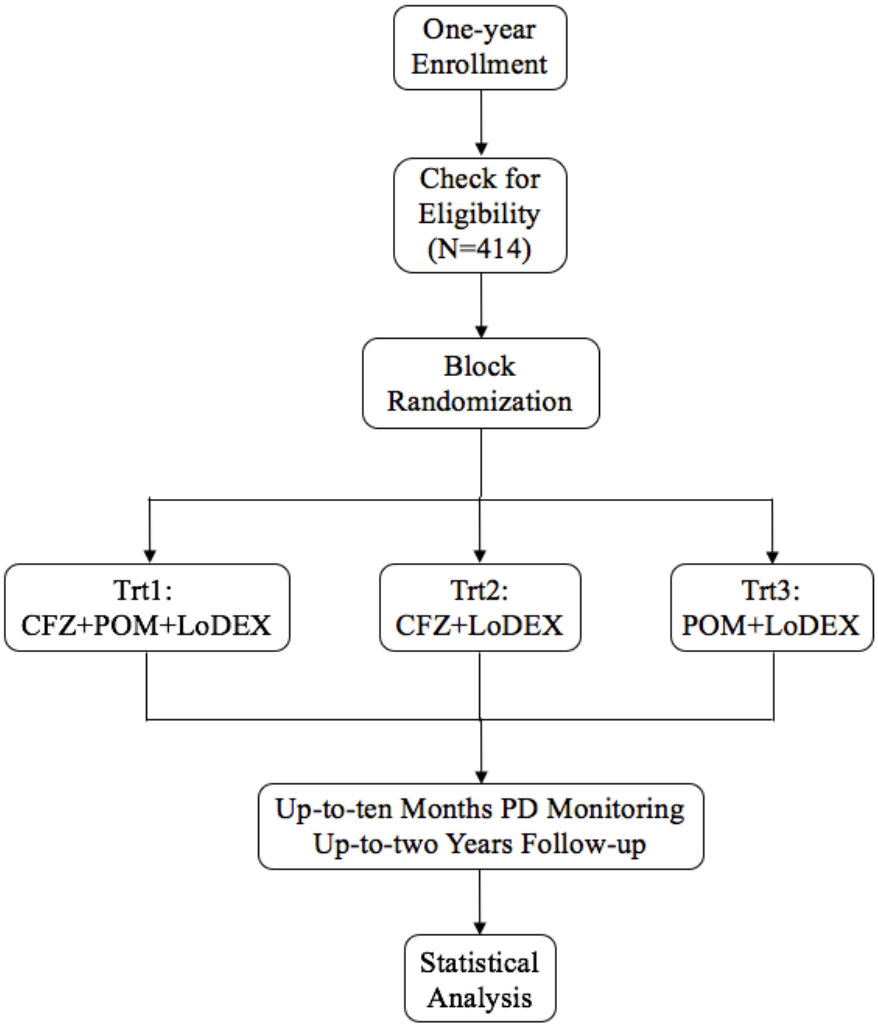
- *Primary endpoint*: progression-free survival (PFS), defined as the time from randomization to the first documentation of disease progression or death from any cause. We will follow patients up to 10 months, since previous studies show that the survival curve will be almost horizontal after 10 months.
- *Second endpoint*: objective response rate (ORR) defined as partial response or better (PRB), which will be collected once a month during the treatment, and duration of response for patients who achieved PRB, overall survival (OS) which will be collected once a months while following patients for 2 years, and safety.

Data collection

Domestic information will be recorded through electronic case report form (CRF, appendix II) designed by physicians with statisticians. Adverse events would be recorded and immediately reported to PIs, and would be analyzed at the end. Severe adverse events (SAE, recorded by Adverse Event CRF, appendix III) would be recorded and reported to FDA or IRB within 24 hours, followed with full documentation within 15 days using the current expedited reporting system in Washington University. Patients would receive monthly routine blood examination that are reviewed by doctors to determine the status of disease. Those data would be recorded in pre-designed data colloction form (Appendix V).

Study Design

The following figure illustrate the main steps in carrying out the research:



All eligible patients would be randomly assigned to 3 equal size treatment groups using block randomization, followed by pre-design treatment for RRMM and monthly examination of status indicators. Patients with disease progression during treatment would still be analyzed for PFS, ORR and OS. Those who finished the treatment will be followed for up to ten months regarding the disease progression status, and additional 1 year for overall survival.

Statistical analysis

Sample size calculation

Our sample size calculation is based on the primary endpoint. To show that the combination therapy has longer remission time than any monotherapies, we only need to perform a two-sample power analysis between the combination therapy group and one of monotherapy groups, which has the smaller difference of median survival compared with the combination therapy group. For example, if CFZ+LoDEX has the smaller difference of median survival compared with CFZ+POM+LoDEX, and the power analysis shows that 100 patients are enough to detect the difference, 100 patients will also be enough to detect the difference between POM+LoDEX and CFZ+POM+LoDEX.

Based on previous studies, we know that 14% patients have disease progression beyond 10 months under CFZ with LoDEX monotherapy [5], 21% patients have disease progression beyond 10 months under POM with LoDEX monotherapy [7], and we expect the combination therapy to increase survival beyond 10 months to 35%. Therefore, we will use a two-sided log-rank test to calculate the sample size, and the result will be adjusted to account for right censoring. Moreover, necessary tests for proportional hazards assumption will be performed. Within each group, to have 80% power at a significance level of 0.05, we need 138 patients to detect an increase in survival at 10 months from lower to 0.35. Hence, in total we need 414 patients, and we will enroll these eligible patients within 1 year.

In United States, the number of new cases of myeloma was 6.6 per 100,000 men and women per year, and the number of deaths was 3.3 per 100,000 men and women per year, reported by NIH [8]. These rates are age-adjusted and based on 2010-2014 cases and deaths. In 2017, it is estimated that there will be 30,280 new cases of myeloma and an estimated 12,590 people will die of this disease. Among the target patients, we expect 60% of them would be eligible for our criterior, and 20% of them would be willing to participate. Therefore, it is feasible for us to recruit 414 patients from 10 hospitals and medical centers in the United States within 1 year.

Efficacy

PFS. We will use survival analysis to analyze our time-to-event data. The Kaplan-Meier estimator will be used to estimate PFS at the specific time points, and we will obtain a plot of product-limit survival function versus survival time based on exponential distributed assumption. Furthermore, a multivariate Cox regression model will be used to to test the hypothesis of the superiority of the combination therapy to any monotherapies, after adjusting for interested covariates. HRs and 95% CIs will be provided as well.

OS and ORR. For overall survival, we will use the same strategies like overall PFS. For objective response rate, we will introduce a binary variable to indicate whether cancer shrinks or disappears after the treatment. Under the assumption of binary distribution, we will construct a logistic regression model to test whether there is any difference of ORRs between the combination therapy and the monotherapies after adjusting for covariates. The corresponding ORs, 95% CIs and p-values will be provided.

Safety

The safety of treatments will be assessed by adverse events in both individual level, such as analysis of relationship to treatment, and aggregate level, such as the percentage of each adverse event with the corresponding grade within each therapy group. We will engage the statistical adverse events reporting system in our study, which collects the most up-to-date source of information regarding serious outcome such as mortality and provides valuable

information for interim monitoring of safety by an IRB or DSMB. Our CRF of AE will be given in the appendix. Comparasion among three groups will be conducted.

Limitations

The major problem of the study design is that some of patients will have disease progression during treatment periods, and will also be included in our models. It is difficult to determine whether treatments have effects or not, because the efficacy of any treatment can only be assessed when a treatment has finished. Unfortunately, however, the proportion can be up to 50% [7]. But it's also improper to exclude them from the analysis, due to the potential selection bias it may cause. Therefore, these cases will definitely influence our results.

References

[1] Kumar SK, Therneau TM, Gertz MA, et al. Clinical course of patients with relapsed multiple myeloma. Mayo Clin Proc. 2004;79(7):867-874.

[2] Kumar SK, Lee JH, Lahuerta JJ, et al. International Myeloma Working Group. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. Leukemia. 2012;26(1):149-157.

[3] Rychack E, Mendy D, Miller K, et al. Overcoming resistance; the use of pomalidomide (POM) and dexamethasone (DEX) in re-sensitizing lenalidomide (LEN)-resistant multiple myeloma (MM) cells. Haematologica. 2011;96(Suppl 1): S126. Abstract P-328.

[4] Lacy MQ, Hayman SR, Gertz MA, et al. Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma. J Clin Oncol. 2009;27(30):5008-5014.

[5] Herndon TM, Deisseroth A, Kaminskas E, et al. U.S. Food and Drug Administration approval: carfilzomib for the treatment of multiple myeloma. Clin Cancer Res. 2013;19(17):4559-4563.

[6] Richardson PG, Siegel D, Baz R, et al. Phase 1 study of pomalidomide MTD, safety, and efficacy in patients with refractory multiple myeloma who have received lenalidomide and bortezomib. Blood. 2013;121(11):1961-1967.

[7] Richardson P G, Siegel D S, Vij R, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study[J]. Blood. 2014;123(12): 1826-1832.

[8] Surveillance, Epidemiology, and End Results Program. N.p., n.d. Web. 11 Jan 2015.