STOP-CA

Statistical Analysis Plan (SAP)

Date: 6/7/2022

Amendments to original SAP (8/18/2016): None

Randomization process

Within the Dana Farber/Harvard Cancer Center, randomized comparative studies are conducted in a manner such that for a blinded randomization, the individual assigning study treatment is not a member of the study team but from the office for the Office of Data Quality (ODQ). Central randomization is performed according to an algorithm provided by the statistician. This was in a permuted blocks algorithm, with block size of 4. Randomized treatment assignment was delivered to research pharmacy at the site in an unblinded fashion, and pharmacy dispense blinded study drug. ODQ has extensive experience working with both local and distant research pharmacies on blinded randomized placebo-controlled studies, and the system is already in place.

Primary End-Point

Our primary endpoint will be the proportion of patients in each group that have a decrease of 10% or more in LVEF to <55% from baseline to 12 months after initiation of anthracyclines.

Assumptions for Sample Size Calculation: We anticipated that 20% of the patients in the placebo group will reach the primary end-point. This assumption is based on significant prior literature; specifically, Limat *et al.* performed a prospective study where they enrolled patients similar to those proposed in this study (lymphoma receiving anthracycline-based chemotherapy) and performed a baseline measurement of LVEF and a measurement at 1 year. Their primary end-point was a more stringent cut-off than recommended by guidelines or being used in this study, a decrease of >15% in LVEF. They found that 20% of their population had a reduction of >15% in LVEF. Using CMR, two studies have tested the percentage of patients with a significant reduction in LVEF after anthracyclines. In a prospective observational study, Drafts and colleagues found that 26% of patients decreased their LVEF to <50% and in a prospective randomized study, Bosch and colleagues found that up to 33% of patients decreased their echocardiographically-derived LVEF to <55%. In the single small, randomized study which also used 40 mg of atorvastatin with 20 subjects in each arm, there was no decrease in LVEF after anthracyclines among patients on statins.

Our base case assumptions are as follows: 20% of the placebo group and 5% of the statin treatment group will meet the primary endpoint and we will be able to enroll 300 patients meeting all inclusion and exclusion criteria. From these, we anticipate a drop-out rate of approximately 10% due to a one-year mortality of ≈5-6% and atorvastatin related side-effects

in 4-5% of patients. The remaining 270 patients will provide us with a > 90% power to detect a 15% difference in the proportions of those achieving the primary end-point at a two-sided significance level of 0.05. Moreover, we will have a 70% power if the difference in the percentage reaching the primary end-point between groups falls as low as 10%.

Analysis Plan: The study is designed as a prospective double-blind randomized study. All statistical analyses will be performed based on intent-to-treat and repeat imaging will be performed at 1 year in all patients. In particular, we will include subjects who could not complete the study protocol due to statin toxicity and patients who started anthracyclines but did not complete the entire scheduled protocol. Chi-square analysis will be used to determine whether statins decrease the primary end-point.

Secondary End-Points Aim 1:

Aim 1a. We will test whether cardiac risks factors (blood pressure, age, sex, glucose or cholesterol levels, prior history of cardiac disease, LVEF at baseline) or cancer specific risk factors (anthracycline dose, radiotherapy) are predictive of the effect of statins on LVEF.

***Analysis Plan*:** In patients treated with statins, we will use a logistic regression model to evaluate whether cardiac risks factors or cancer specific risk factors are predictive of the effect of statins on LVEF. Patients on statins and eligible for statins will be excluded. Therefore, cholesterol levels will be relatively homogenous, and we will not pre-stratify our cohort based on cholesterol. Radiotherapy is not routinely used in the cohort and is used in <5% of cases, there we will also not pre-stratify based on the use of radiotherapy. However, we will use cholesterol values (as a continuous variable) and the use of radiotherapy (as a binary variable) to perform a post-hoc analysis. Additionally, all patients are intended to have the same dose of anthracyclines and dose adjustments are made during therapy in response primarily to toxicities. Therefore, we will additionally test the interaction between the dose of anthracyclines and the effect of statins as a post-hoc analysis.

Aim 1b. We will test whether statins reduce cardiac events. The study is not powered to test the effect of atorvastatin on clinical events.

Adjudication plan: The occurrence of clinical adverse cardiac events will be adjudicated based on consensus opinion of a clinical adjudication committee containing three board-certified cardiologists blinded to experimental group (Drs. Francis, Scherrer-Crosbie and Neilan).

Analysis Plan: All statistical analyses will be performed based on intent-to-treat. Fisher exact tests will be used to determine whether statins decrease the combined end-point of death or heart failure.

Aim 1c. We will test whether statins are safe.

Analysis Plan: Chi-square will be used to test for differences between the two treatment groups for categorical secondary endpoints.

REFERENCES

1. Limat S, Demesmay K, Voillat L, Bernard Y, Deconinck E, Brion A, Sabbah A, Woronoff-Lemsi MC, Cahn JY. Early cardiotoxicity of the chop regimen in aggressive non-hodgkin's lymphoma. Ann Oncol. 2003;14:277-281
2. Drafts BC, Twomley KM, D'Agostino R, Jr., Lawrence J, Avis N, Ellis LR, Thohan V, Jordan J, Melin SA, Torti FM, Little WC, Hamilton CA, Hundley WG. Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. JACC Cardiovasc Imaging. 2013;6:877-885
3. Bosch X, Rovira M, Sitges M, Domenech A, Ortiz-Perez JT, de Caralt TM, Morales-Ruiz M, Perea RJ, Monzo M, Esteve J. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: The overcome trial (prevention of left ventricular dysfunction with enalapril and carvedilol in patients submitted to intensive chemotherapy for the treatment of malignant hemopathies). J Am Coll Cardiol. 2013;61:2355-2362