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1. Title of Protocol: Maintenance Therapy with Lenalidomide, Dexamethasone and Clarithromycin (Biaxin) Following Autologous/Syngeneic Transplant for Multiple Myeloma.

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2. Introduction and Background

Single agent high dose melphalan combined with autologous stem cell rescue is well established as the standard of care for treating chemoresponsive and chemorefractory Multiple Myeloma. But, relapse continues to remain a major problem after a standard autologous transplant. Moreau et al. (1) compared in a prospective and randomized trial the two most widely used autologous transplant conditioning regiments at that time for treatment of Multiple Myeloma. A total of 282 evaluable newly diagnosed chemotherapy- responsive patients under the age of 65 years old were randomized. 142 patients received melphalan 200mg/m^2 alone. The rest were treated with melphalan 140 mg/m^2, cytoxan and total body radiation (TBI). The median duration of EFS was similar 21 vs. 20.5 months respectively, p=.6. The 45-months survival though was superior for melphalan alone therapy, 65.8% vs. 45.5% (p=. 05). Vesole et al. (2) reported on the SWOG experience in treating patients with chemorefractory Multiple Myeloma using high-dose melphalan followed by autologous stem cell transplantation. Patients up to the age of 70 years were enrolled if they were refractory to VAD or other alkylating agents. All patients were given cytoxan and GM-GSF for collection of peripheral blood stem cells. Upon recovery from autologous transplant, patients were treated with maintenance interferon alfa-2b until disease progression. Of 66 assessable patients, 56 patients went to transplant. The overall response rate to melphalan of transplanted patients was 35% CR, 20% VGPR, and 39% PR. There were 4 deaths (7.1%) from regiment-related transplant toxicity. Overall, the median survival was 19 months based on intent to treat. Three-year actuarial PFS and S was 25% and 31%, respectively. Recently tandem autologous transplants are being offered to treat patients with Multiple Myeloma. But, even tandem autologous transplants result in high relapse rates. Attal et al (3) showed at 4 years the EFS rate was still only 20%. Overall, Cavo et al (4) have shown that tandem autologous transplants prolong the EFS rate by 12 months (p=. 001) and time to progression by 17 months (p=. 0001).

Thus, strategies to prevent relapse after stem cell transplant with novel treatment strategies are needed.

The treatment of Multiple Myeloma over the last couple of years is moving to an appreciation of the interaction of the Multiple Myeloma tumor cells and the microenvironment for tumor cell growth and survival as well as the development of resistance to therapy. Agents to be examined in combined therapy approach include immunodulatory drugs such as Lenalidomide. Lenalidomide's activity includes cytokine inhibition, especially TNF alpha and IL1b, anti-angiogenesis activity through inhibition of bFGF, VEGF and TNF alpha induced endothelial migration, modulation of cell surface adhesion molecules that inhibits Multiple Myeloma cells from binding to stromal bone marrow cells, immune modulator effects including effect on gamma interferon and IL2 and IL12 production, induction of Th1 T cell responses and NK and ADCC activity and finally direct tumor effects inducing apoptosis (Celgene, investigator's brochure). Clinical trials in Multiple Myeloma, including phase I, II and III, have established in a non-transplant setting a daily dose of 25 mg of Lenalidomide as the maximum tolerated dose (MTD) (5-7). Myelosuppression and thrombocytopenia were the DLT. No significant somnolence or constipation occurred. Lower incidence of significant peripheral neuropathy was seen with Lenalidomide than with Thalidomide (Celgene, investigator's brochure, 5-7). There

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was also a lower incidence of DVT and other clot issues reported with Lenalidomide than reported with Thalidomide. The frequency of thrombotic events in the phase II studies have been reported at 12% with Lenalidomide and Dexamethasone. In the first randomized double blind study of Lenalidomide and Dexamethasone vs. Dexamethasone, the median time to progression (TTP) was 37.1 weeks compared to 19.9 weeks with Dexamethasone alone, p<. 0001. In the second study, the median TTP was not reached on the Lenalidomide /Dexamethasone arm vs. 20 weeks with Dexamethasone arm alone, p<0001.

Lenalidomide has to date rarely been studied after autologous transplantation. At U Arkansas, Lenalidomide was given for relapsed disease after transplant (8). Myelosuppression was the dose-limiting toxicity. Because of dose reduction for myelosuppression, a dose of 25 mg of Lenalidomide po daily days 1-21 repeated every 28 days was proposed for future studies. Time to maximum blood levels was 2.8-6.1 hours after taking dose of Lenalidomide. A randomized trial of maintenance therapy with Lenalidomide after autologous transplant to treat Multiple Myeloma is currently ongoing through ECOG.

Clarithromycin is a macrolide antibiotic that has immunomodulatory and anti-inflammatory properties. Clarithromycin suppresses the synthesis of IL1 alpha, IL 1 beta, TNF alpha, IL6, IL5 and IL8. It can also inhibit in vitro tumor induced angiogenesis (9-12). Morris et al (13) studied the effect of Clarithromycin itself as treatment of Multiple Myeloma. Taste perversion, nausea and diarrhea were the most common side effects. Modest increases in liver functions occurred in three patients treated with Biaxin 500 mg po bid. One patient did have a 47% decrease in their M spike and 6 patients had stable disease. By itself, Clarithromycin though is probably not very effective but it appears to amplify the response of IMDs such as thalidomide as shown by Coleman et al (14). Clarithromycin has an additive effect when combined with immunomodulatory molecules and steroids by increasing the area under the curve of selected corticosteroids.

Dexamethasone is used to treat Multiple Myeloma because it inhibits survival signals, inhibits TNF alpha, BCL2 and IL6 and also induces growth arrest of Multiple Myeloma cells.

Recently, the combination of Clarithromycin with Lenalidomide and Dexamethasone has been studied as front-line therapy to treat Multiple Myeloma. Niesvizky reported the results of the preliminary study at ASH 2005 (15). When used as front-line therapy, the combination regimen had a high CR/near CR rate of 36%. Overall, total CR and PR rate was 86%. In general responses were seen within 1-2 months after starting therapy. The therapy was given in 28 days cycles with Lenalidomide 25 mg po daily for 21 days, Dexamethasone 40 mg po weekly and Clarithromycin 500 mg po bid. Patients also received low dose aspirin once daily, prophylactic Bactrim and a proton pump inhibitor. More than half of the patients had advanced Myeloma with 40% having poor prognostic features by cytogenetics. By FISH analysis, del 13q14 was seen in 33%, and t4, 14 in 4%. One percent of the patients had documented thrombosis/emboli events. Fourteen percent of patients required blood transfusion. Other grade 3 or higher toxicities reported included anemia, neutropenia, and thrombocytopenia, increase liver enzymes, anxiety, insomnia, tremors, hyperglycemia, syncope and colon perforation.

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A number of different regimens are being currently studied as maintenance therapy after autologous transplant to try to prolong the time to disease relapse or progression and to try to increase the DFS and survival rates. To date, most of the regimens have contained Thalidomide. Attal M et al (16) updated at ASH 2005 the outcome of using Thalidomide/Aredia vs. Aredia vs. observation after autologous transplant. The group that received both Thalidomide and Aredia had a longer time to relapse (a year EFS rate was 50, 35 and 37%, respectively (p=.003)), and had a survival advantage. Brinker et al (17) showed that patients who received Thalidomide as maintenance therapy after autologous transplant compared to those who received it as salvage therapy after autologous transplant had better survival at 65 months vs. 54 months, respectively, p=.05. At FHCRC, we have experience in treating Multiple Myeloma patients with Thalidomide, Clarithromycin and Dexamethasone (BLT-D) as maintenance therapy after autologous transplant (submitted abstract ASH, 2006). In 23 patients treated (stage II, n=6, stage III, n=17) 26% had poor prognostic cytogenetics, 61% had elevated beta 2 microglobulin at diagnosis and 30% still had elevated beta 2 microglobulin at transplant. Forty-eight percent had previously received Thalidomide before transplant. All were conditioned with melphalan 200 mg/m^2 for transplant. Patients were treated with Thalidomide beginning at 50 mg po daily for 14 days, and then increased to daily doses of 100 mg po. Biaxin was given at a dose of 250 mg po bid and Dexamethasone 20 mg po weekly. After one year, Biaxin and Dexamethasone were stopped and patients continued on Thalidomide as long at tolerated and/or until disease progression was documented. The median time to start the maintenance therapy after recovery from acute toxicity of autologous transplant was 102 days (range 40-120 days). Four patients stopped Thalidomide because of peripheral neuropathy and four had dose reduction of thalidomide because of peripheral neuropathy. Eight patients also had dose reduction of Dexamethasone because of toxicity. One patient stopped Biaxin because of a skin rash. In patients who still had detectable Multiple Myeloma after autologous transplant before starting maintenance therapy, 46% were shown to go into complete remission. Seventy-eight percent of the patients remain alive without disease progression, with a median follow-up 20.5 months (range 6-25). One of the issues long-term is the peripheral neuropathy seen with Thalidomide that requires dose reduction or stopping therapy completely. Since Lenalidomide is now FDA approved and appears to have less peripheral neuropathy toxicity, it seems reasonable to study it as maintenance therapy after transplant.

We are proposing this study of Lenalidomide, Clarithromycin and Dexamethasone as maintenance therapy after autologous transplant for Multiple Myeloma as it may be better tolerated than BLT-D. Since autologous transplant patients have lower tumor burden after transplant but may be less able to tolerate maximum doses of Lenalidomide, Clarithromycin and Dexamethasone, especially because of issues of myelosuppression, we are proposing the following treatment schedule. Lenalidomide will begin at 25 mg po daily for 14 days, one week off for every 21 days cycle. If necessary Lenalidomide dosing can be decreased down to 20mg, 15 mg then 10 mg po daily for toxicity. Clarithromycin will be given at 250 mg po bid. Dexamethasone will be given 20 mg po weekly. If platelet counts are >50,000 cells/mm^3, aspirin 325 mg po daily will be added for DVT prophylaxis. If patients can not take aspirin, therapeutic anti-coagulation with warfarin or low molecular weight heparin will be given. Patients will also continue on monthly IV Bisphosphonates therapy.

In summary, autologous transplants can cause remissions in Multiple Myeloma patients. But, relapse after autologous transplant remains a major problem. Post transplant maintenance therapy may be able to change the outcome of these transplant patients. The combination of Lenalidomide, Clarithromycin and Dexamethasone in a small non-transplant pilot study has shown significant disease responses. It is reasonable to attempt to add this combination therapy as maintenance treatment for Myeloma patients post autologous transplant and to evaluate whether it is well tolerated and will improve their outcome.

3. Objectives

1. Evaluate the toxicity of the use of Lenalidomide/Biaxin/Dexamethasone as maintenance therapy after autologous/syngeneic transplant
2. Evaluate the median time to disease progression
3. Evaluate survival

4. Patient Selection

A. **Inclusions**

1. Any autologous or syngeneic patient who underwent high dose melphalan (≥140 mg/m^2) therapy/PBSC or BM rescue for any stage of multiple myeloma and did not participate in another clinical transplant trial which is also evaluating long – term disease free survival or survival.
2. Platelet count (transfusion independent) > 50,000 cells/mm^3 and absolute granulocyte count > 1500 cells/mm^3 for 5 calendar days after recovery from high dose therapy.
3. Patients should be between 30 days to 120 days after transplant.
4. Willingness and ability to comply with FDA-mandated REV ASSIST Program, Celgene System for Lenalidomide Education and Prescribing Safety.
5. Signing a written informed consent form.

B. **Exclusions**

1. Karnofsky score less than 70.
2. A left ventricular ejection fraction less than 45% immediately pre transplant. Patients with congestive heart disease with transplant, history of MI, or history of coronary artery disease.
3. Total bilirubin greater than 2 mg/ml (unless history of Gilbert's disease), SGOT or SGPT > 2.5 x upper limit of normal.
4. Calculated by Cockeroft-Gault formula or measured serum creatinine clearance < 25 ml/minute
5. Pregnant and/or lactating females.
6. Patients who cannot give informed consent.
7. Patients with untreated systemic infection.

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8. Patients with history prior to transplant of treatment with combination therapy Lenalidomide/Biaxin and Steroid without response.
9. Patients allergic to Lenalidomide, Biaxin or Dexamethasone.
10. Referring physician not registered with REV ASSIST program or unwilling to oversee the care of the patients on study and comply with the FDA-mandated REV ASSIST Program.
11. Patients unwilling to practice adequate forms of contraception if clinically indicated until 30 days after stopping therapy. Male patients on study need to be consulted to use latex condoms (even if they have had a vasectomy) every time they have sex with a woman who is able to have children while they are being treated and for 30 days after stopping drugs. (see section 9.*iv*)
12. Patients with ≥ grade 3 peripheral neuropathy.
13. Prior history of uncontrollable side effects to Dexamethasone therapy.
14. A prior history of HIV positivity with pre-transplant evaluation.

5. Evaluation and Counseling of Patient

The patient will be completely evaluated. The protocol will be discussed thoroughly with the patient and family and the attending physicians will describe all known risks to the patient. Alternative forms of therapy will be presented as objectively as possible and the risks and hazards of the procedure explained to the patient. Consent will be obtained using forms approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center. A summary of the conference will be dictated for the medical record.

6. Protocol Registration

Patients will be assigned to the protocol by the attending physician and registered through the Registration Office (206-667-4728), Monday through Friday, 8 am to 4 pm. Registration will be through the final clinical coordinator sheet. After hours, the Registration Office can be reached by paging (206) 995-7437.

7. Plan of Treatment

- Clarithromycin 250 mg po bid.
- Dexamethasone 20 mg po q week.
- Starting dose of Lenalidomide will be 25 mg po daily on days 1-14, one week off, every 21 days. Lenalidomide should be taken 4 hours or more after last daily dose of Clarithromycin.

Therapy will start when patients have recovered from acute toxicity. Platelet count should be ≥ 50,000 cells/mm^3 and ANC ≥ 1500 cells/mm^3 for at least five consecutive days before starting therapy.

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All therapy will continue for one-year duration. Biaxin will then be stopped and Dexamethasone will then be tapered off per schedule: Dexamethasone 10 mg po weekly for two weeks, then Dexamethasone 4 mg po weekly for two weeks then stop. Lenalidomide will continue as long as tolerated and/or until disease progression.

A. Dose modifications during first year of Lenalidomide, Clarithromycin and Dexamethasone

i. Dose Reduction Levels of Lenalidomide

Dose level 1: 10 mg po daily on days 1-14, one week off, every 21 days

Dose level 2: 15 mg po daily on days 1-14, one week off, every 21 days

Dose level 3 20 mg po daily on days 1-14, one week off, every 21 days

Dose level 4: Starting dose 25 mg po daily on days 1-14, one week off, every 21 days

ii. Dose modifications recommendations

Toxicity will be graded per CTCAE, NIH/NCI, Version 3, except for blood/bone marrow.

For grade ≥ 3 peripheral neuropathy, hold Lenalidomide and resume at next lower dose reduction level when recovered to grade <2.

For grade 3 nausea, vomiting or diarrhea, stop Clarithromycin totally.

For grade 3 SGOT, SGPT, stop both Clarithromycin and Lenalidomide. DO not resume Clarithromycin. Hold Lenalidomide and resume at next lower dose reduction level when recovered to grade <2.

ANC≤1000 cells/mm^3 or platelets less than 30,000 cells/mm^3, hold Lenalidomide to ANC≥ 1500 cells/mm^3 and/or platelets greater than 30,000 cells/mm^3, then resume at next lower dose reduction.

Any patient with purpuric, vascular, exfoliative or bullous rash, which is suspicious for Steven- Johnson's syndrome or toxic epidermal necrolysis, must stop all therapy immediately and patient should not resume therapy. For any other macular/papular skin rash, discontinue Lenalidomide and Clarithromycin and see if the skin rash resolves. Continue Dexamethasone therapy. Restart Lenalidomide alone at next lower

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dose reduction level following appropriate clinical evaluation and after skin rash has resolved. Do not restart Clarithromycin.

For all other grade 3 non-hematological toxicity deemed related to Lenalidomide, hold drug until < grade 2, then resume at next lower dose reduction level.

If patients are off of Lenalidomide for > 30 days, discontinue all therapy. If patients are not able to tolerate because of toxicity, dose reduction level 1 of Lenalidomide then discontinue all therapy on the study.

All patients who develop a DVT or pulmonary emboli will have Lenalidomide therapy held until they are therapeutically anti-coagulated and then can resume at next dose reduction level of Lenalidomide if medically appropriate.

All patients who develop any non-hematological grade 4 toxicity except DVT or pulmonary emboli will have all therapy stopped and therapy will not be reinitiated after resolution of toxicity.

Dexamethasone can be decreased to 10 mg po weekly and then if needed changed to prednisone 50 mg po every other day according to treating physicians discretion for toxicity second to steroids. If patient can not tolerate either of the altered steroid schedules, steroid therapy should be stopped completely. Once steroid therapy is dose reduced or stopped, it cannot be restarted or steroid dose increased.

B. Dose Modifications of Lenalidomide after Completion of 1st Year of Lenalidomide, Clarithromycin (Biaxin) and Dexamethasone

i. Dose Reduction Levels of Lenalidomide

Dose level 1: 10 mg po daily on days 1-14, one week off, every 21 days

Dose level 2: 15 mg po daily on days 1-14, one week off, every 21 days

Dose level 3: 20 mg po daily on days 1-14, one week off, every 21 days

Dose level 4: Starting dose 25 mg po daily on days 1-14, one week off, every 21 days

For grade ≥ 3 peripheral neuropathy, hold Lenalidomide and resume at next lower dose reduction level when recovered to grade <2.

For grade 3 SGOT, SGPT, hold Lenalidomide and resume at next lower dose reduction level when recovered to grade <2.

ANC≤1000 cells/mm^3 or platelets less than 30,000 cells/mm^3, hold Lenalidomide to ANC≥ 1500 and/or platelets greater than 30,000 cells/mm^3, then resume at next lower dose reduction.

Any patient with purpuric, vascular, exfoliative or bullous rash, which is suspicious for Steven- Johnson's syndrome or toxic epidermal necrolysis, must stop all therapy immediately and patient should not resume therapy.

For all other grade 3 non-hematological toxicity deemed related to Lenalidomide. Hold drug until < grade 2, then resume at next lower dose reduction level.

If patients are off of Lenalidomide for > 30 days, discontinue all therapy. If patients are not able to tolerate because of toxicity, dose reduction level 1 of Lenalidomide then discontinue all therapy on the study.

All patients who develop a DVT or pulmonary emboli will have Lenalidomide therapy held until they are therapeutically anti-coagulated and then can resume at next dose reduction level of Lenalidomide

All patients who develop any non-hematological grade 4 toxicity except DVT or pulmonary emboli will have all therapy stopped and therapy will not be reinitiated after resolution of toxicity.

8. Evaluation

A. Pre treatment evaluation

1. Complete history and physical exam including Karnofsky performance status.
2. CXR (PA and Lateral).
3. CBC with differential and platelets.
4. Serum chemistry: creatinine, glucose, total protein, blood urea nitrogen (BUN), total carbon dioxide (CO_2), albumin, total bilirubin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), LDH, calcium, chloride, potassium, sodium, phosphorous and magnesium.
5. Quantitative immunoglobulins.
6. SPEP with immunofixation. Serum free light assay only if light chain or non-secretory disease.
7. 24 hour urine collection for UPEP with immunofixation, total protein, Bence Jones quantification and creatinine clearance (if abnormal pre-transplant).
8. Bilateral bone marrow biopsies and aspirates.
9. EKG (12 lead).
10. PT/PTT/INR.
11. Urine for microanalysis and macroanalysis.
12. Pregnancy test of childbearing women.

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13. Thyroid studies: TSH, T3, T4.

B. During therapy the following tests are recommended:

1. CBC with differential and platelets after starting therapy every two weeks for first three months, then monthly.
2. Monthly Serum chemistry: creatinine, glucose, total protein, blood urea nitrogen (BUN), total carbon dioxide (CO_2), albumin, total bilirubin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), LDH, calcium, chloride, potassium, sodium, phosphorous and magnesium.
3. Monthly physical examination.
4. SPEP with immunofixation every three months. Serum free light assay only if light chain or non-secretory disease.
5. 24 hour urine collection for UPEP with immunofixation, total protein and Bence Jones quantification every three months, if abnormal pre-transplant.
6. Thyroid function tests: TSH, T4, T3 every three months
7. Yearly bilateral bone marrow aspirates and biopsies and skeletal survey.
8. Pregnancy testing of childbearing women as outlined in section 9 iv.

9. Drugs - Toxicities and Complications

All non-hematological toxicities will be graded by the NCI common toxicity criteria. Hematological toxicity will be graded according to the BMT study section.

Pregnant women are excluded from the trial and all men and women of childbearing potential will be required to practice adequate forms of contraception. Women of childbearing potential will be required to have a pregnancy test within 24 hours of starting Lenalidomide.

A. Lenalidomide

i. Chemistry:
Lenalidomide, 3(-4-amino-1-oxo 1,3-dihydro-2H-isoindol-2-yl) piperdine -2,6-dione; REVLIMID). Lenalidomide is an immunomodulatory drug. The empirical formula for Lenalidomide is $C_{13}H_{13}N_3O_3$ and the gram molecular weight is 259.25. Lenalidomide is off-white to pale yellow in color. It is provided as 5-10-15-and 25-mg capsules for oral administration. Inactive ingredients in the capsules also include anhydrous lactose, microcrystalline cellulose, croscarmellose sodium and magnesium state. Lenalidomide should be stored at room temperature (15-30°C and protected from moisture. It is stable for at least 24 months when packaged in push-through blister foils or HDPE bottles.

ii. Pharmacology and pharmacokinetics:
Clinical pharmacokinetics studies have shown that Lenalidomide when administered as a single 200-mg dose has a half-life of elimination that ranged from 3.2 hours to 8.7 hours. Initially, there is a rapid decrease in plasma levels, then there is a less

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rapid decline. Peak plasma levels occur between 0.6-1.5 hours post dose being given. Co-administration with food delays absorption but does not alter the extent of absorption. With multiple doses, steady state plasma concentrations were obtained within four days. Sixty-eight percent of the orally administered Lenalidomide is excreted by the kidneys. No pharmacokinetic or pharmocodynamic interactions between Lenalidomide and warfarin have been observed. The interaction with digoxin if any is small and digoxin levels should thus be followed based on clinical judgment in patients receiving both digoxin and Lenalidomide.

iii. Toxicity profile:
Below are listed the side effects which occurred in patients treated with Lenalidomide in other clinical trials.

Frequent (chance of 10-50% that this will happen) side effects include: fatigue, nausea, rash, diarrhea, constipation, vomiting, pyrexia, cough, insomnia, pruritis, peripheral edema, dyspnea, back pain, anorexia, abdominal pain and dizziness, headache.

In addition, the following severe adverse events have been reported in patients treated with Lenalidomide in previous research studies.

Occasional (chance of 1-10% that this will happen) side effects include: thrombosis or pulmonary emboli, leucopenia, thrombocytopenia, neutropenia, dyspnea, pneumonia, anemia, dehydration, vomiting, asthenia, increased pain and kidney failure.

Rare (chance of less than 1% that this will happen) side effects include: pancytopenia, hyperuricemia, sinusitis, fatigue, arthritis, diffuse gastritis, diverticulitis, abnormal liver function test, blood transfusion reaction, thyroid disorders, myositis, myocarditis with congestive heart failure, respiratory failure, pulmonary edema, pulmonary hypertension, interstitial lung disease, ischemic colitis, hepatitis, arrhythmia, increased pressure in the eye, retinal hemorrhage, fainting, condition characterized by weight loss and malnutrition, encephalopathy, development of new cancer and anaphylaxis.

Recent data suggests that Multiple Myeloma patients receiving the combination of Lenalidomide and Dexamethasone are at an increased risk for developing deep vein thrombosis. Patients will be instructed to take aspirin to reduce that risk. If patient is unable to take aspirin, warfarin or low molecular weight heparin will be used.

There has been an increased frequency of secondary malignancies (including AML/MDS) in multiple myeloma patients being treated with melphalan, prednisone and lemalidomide post-autologous transplant.

Lenalidomide is in a class of drugs that have been shown to be associated with birth defects.

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iv. Special toxicity considerations:

a. Women
Women of childbearing potential must confirm to the best of their knowledge that they intend not to become pregnant during the study. Women of childbearing potential will have a pregnancy test obtained within 24 hours prior to the starting of Lenalidomide. They must also use preferentially two effective contraception methods (see below) during their participation in the study. Barrier methods alone, (i.e., condoms) are not sufficient. Preference is to use at least one highly effective method and one additional effective method at the same time.

Highly Effective Methods	Additional Effective Methods
Intrauterine device (IUD)	Latex condom
Hormonal (birth control pills, injections, implants)	Diaphragm
Tubal ligation	Cervical Cap
Partner's vasectomy	

In women of childbearing potential, highly effective birth control methods must be used throughout and for at least 30 days after stopping Lenalidomide therapy.

If a patient of childbearing potential has sex without birth control, or if for any reason thinks she may be pregnant, Lenalidomide must be IMMEDIATELY stopped.

In all women of child bearing potential, pregnancy tests will be done before and during treatment. Pregnancy tests are to be done every week during the first 4 weeks of treatment. Thereafter, a pregnancy test will be done every 4 weeks if menstrual cycles are regular or every 2 weeks if cycles are irregular. Pregnancy testing will be done if menstrual period is unexpectedly missed or unusual menstrual bleeding occurs. A pregnancy test will be done 30 days after a woman of child bearing potential stops taking Lenalidomide.

Patients can not breast-feed a baby while being treated with Lenalidomide.

Patients can NEVER donate blood or eggs from the ovaries while being treated with and for 30 days after stopping Lenalidomide.

If a patient has a positive pregnancy test while taking Lenalidomide or within a 30 day time-frame after discontinuing treatment, she will be monitored through the term of the pregnancy and continue to be monitored for 30 days after delivery (premature, aborted fetus, full term pregnancy) or until considered to be no longer pregnant.

b. Men
Men must agree to use a latex condom every time they have sex with a woman while taking Lenalidomide and for 30 days after stopping the drug, even if they have had a successful vasectomy. Male patient must be instructed to tell the doctor if he has sex

with a woman without using a latex condom, or if he thinks for any reason that his partner may be pregnant.

Male patient can NOT be a sperm or blood donor while being treated with and for 30 days after stopping Lenalidomide.

v. Administration:
Oral Route
Starting dose of Lenalidomide will be 25 mg po daily on days 1-14, one week off, every 21 days. Lenalidomide will be combined with Clarithromycin (Biaxin) and Dexamethasone. Lenalidomide should be taken 4 hours or more after last daily dose of Clarithromycin (Biaxin). After one year of therapy with Clarithromycin (Biaxin) and Dexamethasone, Clarithromycin (Biaxin) will be stopped. Dexamethasone will then be tapered off. Patient will remain on Lenalidomide at same dose when stopped Biaxin and Dexamethasone as long as tolerating and/or to disease progression.

vii. How Supplied:
Lenalidomide is commercially available. Patients, prescribers and dispensing pharmacies must be registered in the FDA-mandated REV ASSIST program.

B. Biaxin (Clarithromycin)
Biaxin is a semi-synthetic macrolide antibiotic. Chemically, it is 6-0-Methylerythromycin. Clarithromycin (Biaxin) is rapidly absorbed from the gastrointestinal tract after oral administration.

Dose for Clarithromycin (Biaxin) is 250 mg po bid for one year, then stop. Clarithromycin is commercially available.

NOTE: Biaxin, as standard therapy, is dose reduced for renal insufficiency. If the creatinine clearance is less than or equal to 30 ml/minute the dose of Biaxin should be decreased by 50%, which is 250 mg by mouth each day.

Side effects:
Diarrhea, nausea, abnormal taste, dyspepsia, abdominal pain or discomfort, headache and rare serum liver abnormalities.

C. Dexamethasone
Dexamethasone is a synthetic adrenocortical steroid. Designated chemically as 9-fluoro-11β, 17, 21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione. It causes varied metabolic effects. It modifies the body's immune responses and expresses potent anti-inflammatory effects. Dexamethasone is rapidly absorbed from the gastrointestinal tract after oral administration.

Dose for Dexamethasone is 20 mg po every week for one year. Dexamethasone will be tapered off after one year. Dexamethasone will be tapered off per following schedule:

Dexamethasone 10 mg po weekly for two weeks, then Dexamethasone 4 mg po weekly for two weeks then stop. Dexamethasone is commercially available.

The primary provider can reduce the dose of Dexamethasone for toxicity. Dexamethasone dose may be reduced to 10 mg orally once a week. If after the Dexamethasone dose has been reduced to 10 mg orally once a week, the patient is still unable to tolerate the side effects, the patient can be treated instead with prednisone 50 mg orally every other day. If patient can not tolerate either of later steroid schedules, the steroid therapy will be discontinued.

The MOST COMMON side effects (seen in more than 30% of patients) are: increase in appetite, impaired or delayed wound healing, increased risk of infection, peripheral edema, weight gain, weakness of muscles, increased blood glucose, insomnia, heartburn, irritability and nausea.

Less common (occur in 10% to 29% of patients) side effects of treatment with dexamethasone include: mood swings, dizziness and headache.

In addition, cataracts, reduction in bone density and low levels of hormones released by the adrenal glands have been reported following long-term use.

More serious, but RARE (seen in less than 10% of patients) side effects of treatment with dexamethasone include: anaphylaxis, angioedema, bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, hypertension, pulmonary edema, syncope, tachycardia, blood clots, convulsions, depression, exophthalmos and glaucoma.

10. Monitoring and Dose Modifications

For dose modifications, please see section 7 Plan of Treatment.

Patients will be withdrawn from the treatment for the following reasons:

1. They desire to withdraw from study for any reason.
2. The treatment appears detrimental in the judgment of primary physician.
3. They develop progression of disease defined in section 15.
4. They develop non-hematological grade IV toxicity, except DVT and pulmonary emboli.
5. They are unable to resume Lenalidomide therapy more than 30 days after initial stopping of Lenalidomide therapy for toxicity or can not tolerate dose reduction level one of Lenalidomide.
6. Repeated noncompliance to protocol in view of principal investigator.
7. They develop significant skin rash suspicious for Stevens - Johnson syndrome or Toxic epidermal necrolysis.

11. Supportive Care

Patients will continue PCP and VZV prophylaxis at dosing per Standard Practice Guidelines throughout the first year of therapy. Anti-emetics and blood product support will be according to Standard Practice Guidelines. CMV monitoring will be per Standard Practice Guidelines. Erythropoietin can be used for chronic anemia that is red blood cell transfusion dependent. Prophylaxic antifungal therapy may be considered (i.e. Nystatin or Mycelex) with steroid therapy.

In addition,
1). Coated aspirin 325 mg po daily if platelets > 50,000 cells/mm^3
2). Monthly IV Bisphosphonates per Standard Practice Guidelines.

In patients who can not tolerate aspirin, alternative therapeutic anti-coagulation with Coumadin (INR around 2), or low molecular weight heparin can be used.

Antacids or H2 receptor blockers may be given if clinically indicated with steroid therapy. Note: Protonix may change metabolism of Clarithromycin (Biaxin).

Because of Lenalidomide, male patients on study (even if they have had a vasectomy) need to be consulted to use latex condoms every time they have sex with a woman who is able to have children while they are being treated and for 30 days after stopping Lenalidomide. Women need to practice contraception protection if there is any possibility that they can become pregnant while receiving Lenalidomide and for 30 days after stopping therapy (see section 9).

Patients may not receive additional cancer therapy while participating in the study.

12. Protocol Enrollment and Special Considerations

Projected Target Accrual
ETHNIC AND GENDER DISTRIBUTION CHART

TARGETED/PLANNED ENROLLMENT: Number of Subjects (*must provide actual numbers. I.e. no range*)			
Ethnic Category	*Sex/Gender*		
	Females	Males	Total
Hispanic or Latino	1	1	2
Not Hispanic or Latino	12	18	30
Ethnic Category Total of All Subjects*	13	19	32
Racial Categories			
American Indian/Alaska Native	1	1	2
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	0	1	1
White	11	16	25
Racial Categories: Total of All Subjects *	13	18	32

13. Guidelines for Serious Adverse Event Reporting

A. Adverse Drug Reaction Reporting
Every three months during the first year of maintenance therapy, referring oncologists will be asked to assess the highest grade toxicity reached during the last few months of expected toxicity including: nausea, vomiting, skin rashes, DVT, pulmonary emboli, neutrophil and platelet count, Neuropathy-sensory.

In addition, they will be asked to report within a week of the development of serious adverse events (SAE), all thrombosis/emboli and all other Non-hematological grade IV toxicity that resulted in stopping therapy.

All unexpected and serious adverse events that fulfill a reason for expedited reporting as defined below will be reported to FHCRC Institutional Review Office (IRO) (Fax: 206-667-6831) as soon as possible but within at least 7 calendar days of the PI being aware of the event. The initial report will be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) will be documented on a follow-up. Any suspected fetal exposure to Lenalidomide will be reported immediately to the FHCRC IRB and the FDA via the MedWatch number at 1-800-FDA-1088 and also to Celgene. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Celgene's drug safety department fax number is: 732-271-4115.

The address of Celgene Corporation is:
Celgene
Medical Affairs

7 Powder Horn Drive
Warren, New Jersey 07059
Attn: Drug Safety

All other grade 3 or higher toxicities that are not SAEs will be reported on yearly updates to the FHCRC IRB.

B. Definitions

Adverse Event - Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, medical treatment or procedure and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, medical treatment or procedure whether or not considered related to the medicinal product.

Life-threatening Adverse Event – Any adverse event that places the patient or subject, in view of the investigator, at immediate risk of death from the reaction.

Unexpected Adverse Event – An adverse event, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product.

Serious Adverse Event (SAE) – Any adverse event occurring that results in any of the following outcomes:

- death;
- a life-threatening adverse event (real risk of dying);
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant disability/incapacity;
- a congenital anomaly;
- requires intervention to prevent permanent impairment of damage;
- pregnancy.

To ensure no confusion or misunderstanding exist of the differences between the terms "serious" and "severe," which are not synonymous the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) or a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is* not *the same as "serious," which is based on patient/event* outcome or action *criteria usually associated with events that pose a threat to a

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patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory obligations.

Attribution - The FHCRC designation for the determination of whether an adverse event is related to a medical product, treatment or procedure will be as follows:

- Related – includes adverse events that are definitely, probably, or possibly related to the medical treatment or procedure;
- Not Related – includes adverse events are doubtfully related or clearly not related to the medical treatment or procedure.

If an event which meets the SAE definition occurs following the signature of the consent form but before study day 1 (first time study medication is dispensed) the event is not reportable as an SAE.

The following categories will be used to describe the severity of events that are not listed in the NCI Common Toxicity Scale:

1. Mild: Patient is aware of sign or symptom but is able to tolerate it (little or no interference with usual activity pattern). Does not generally warrant medical intervention.
2. Moderate: Sign or symptom causes enough discomfort to interfere moderately with usual activity pattern). May warrant medical intervention.
3. Severe: Sign or symptom causes considerable discomfort and interferes drastically with usual activity pattern. Generally warrants medical intervention.

14. Records

Clinical Statistics maintains a patient database at FHCRC to allow storage and retrieval of patient data collected from a wide variety of sources. The investigator will ensure that data collected conform to all established guidelines for coding, collection, key entry and verification. Each patient is assigned a unique patient number to assure patient confidentiality. Patients will not be referred to by this number, by name, or by any other individual identifier in any publication or external presentation. The licensed medical records department, affiliated with the institution where the patient receives medical care, maintains all original inpatient and outpatient chart documents. Patient research files are kept in a locked room. They are maintained by the FHCRC data collection staff which is supervised by an A.R.T. Access is restricted to personnel authorized by the Division of Clinical Research.

Patients will be followed for treatment-related toxicities and primary referring physicians will be contacted for updates on patient's condition. The maintenance of up-to-date records, including clinical information, will be necessary to follow the study design for years after this particular study is closed.

All institutional NCI, state and federal regulations concerning informed consent and peer judgment will be fulfilled. Written consent will be obtained from all patients entering this study.

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15. Statistical Considerations

Targeted accrual will be 32 patients over 2-3 years. The primary objective of the study is to evaluate the toxicity of this proposed treatment with Clarithromycin (Biaxin), Dexamethasone and Lenalidomide. The first three months of therapy will be used as the time period to evaluate toxicity for stopping rules. Toxicity that meets stopping rules will be determined based on the number of patients that are withdrawn from study for significant toxicity (grade IV non-hematological, except DVT and Pulmonary emboli) and the number of patients who stop therapy for toxicity and are withdrawn from study as they could not recover adequately and resume Lenalidomide therapy by 30 days from the initial stopping of the drug. We shall consider the withdrawal rate to be excessive, and hence the therapy to be too toxic, if the true withdrawal rate from the study exceeds 15% in the first three months.

Since both patients who received only one autologous transplant or two autologous transplants are eligible to participate in this study. We will analyze toxicity of each of these groups individually. The withdrawal rate will be examined after every 5th enrolled patient becomes evaluable in each group. If evidence is sufficiently strong to suggest that the true rate exceeds 15% at any of these points in that group, the study will by terminate for toxicity purposes for treating patients in that group.

Sufficient evidence will be taken to be a lower limit to the corresponding one-sided 80% confidence interval that exceeds 15%. Operationally, any of the following observed rates would lead to conclusion that this regimen is too toxic by these standards: 2/5, 3/10, 4/15, 5/20, 6/25, etc. If the true probability of withdrawal from the study is 5%, the probability of deeming this regimen as too toxic after 30 patients have been treated is approximately .03. On the other hand, if the true probability of withdrawal is .30, then the probability of judging this regimen as too toxic after 30 patients is approximately .94.

With the semi-continuous monitoring of the withdrawal rate, the estimate of this rate, should the study run to completion, will be biased slightly downward. Without consideration of this bias, 30 patients will allow us 80% confidence that the estimated withdrawal rate will be within approximately .094 of the true rate under the assumption that the true rate is 20%.

When patients complete the first year of therapy and are continued on Lenalidomide alone, data will be collected annually regarding toxicity and outcome. But, such toxicities will not count towards the stopping rules. If $\geq$ 50% of patients are able to have completed first year of therapy, then the therapy will be felt appropriate also for future investigation.

FHCRC PDMC per institution guidelines will conduct an annual review.

A second endpoint is time to disease progression. Patients will be followed for initial response to therapy and for progression of disease. Response criteria will be scored accordingly:

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1. Complete response: complete disappearance of all clinically measurable disease, including immunofixation negative on SPEP and UPEP, <5%plasma cells in bone marrow (if done) and stable bone disease (if done).
2. Near complete remission: 100% reduction in serum or urine monoclonal protein but immunofixation positive still, <5%plasma cells in bone marrow (if done) and stable bone disease (if done).
3. Partial response: greater than or equal to 50% reduction in quantifiable serum M spike on SPEP with immunofixation, greater than or equal to 90% decrease in quantifiable 24 hour urine globulin excretion on UPEP with immunofixation (which still exceeds 200mg/24 hr) or no increase in size or number of lytic bone lesions. For non-secreting disease, reduction in plasma cells in BM by > 50% of initial number.
4. Progression of disease: For bone lesions, there needs to be a >25% increase in the sum of all known bone sites. A new lytic bone lesion on osseous survey previously not detected also will be considered as progression of disease. > 25% increase in serum M spike on SPEP (> 5g/L) and/or > 25% increase in urine M spike on UPEP (> 200 mg/24 hours).
   For patients with non-secretory myeloma only, bone marrow plasma cells should increase by > 25% and at least 10% in absolute terms.
5. Stable disease: all other patients not able to be graded as CR, near CR, PR or PD.

Prior to the use of Velcade and biological modifiers like Thalidomide or Lenalidomide, the median time to progression for chemoresponsive disease after autologous transplant with high dose melphalan alone is 21 months. If the median time to disease progression is 23 months or longer for chemoresponsive patients treated on this protocol, the therapy will be felt to be promising. The median time to progression for chemorefractory disease after autologous transplant with high dose melphalan alone is 7 months. If the median time to disease progression is 9 months or longer for chemorefractory patients treated on this protocol, the therapy will be felt to be promising.

If this regimen is deemed to be potentially efficacious and is not regarded as too toxic, a larger phase III study that more carefully evaluates efficacy will be designed. The goal of the subsequent study will be to show that the efficacy rate associated with this regimen is statistically better than no maintenance therapy after an autologous transplant.

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