
# The Role of Immunomodulatory Drugs In the Management of Multiple Myeloma

**Thesis**

Submitted for Partial Fulfillment of the MD Degree in
Radiation Oncology and Nuclear Medicine
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# دور الأدوية المعدلة للمناعة في علاج الأورام الميلومية

**رسالة مقدمة من**

**الطبيب/ وليد فؤاد السيد مراد**

توطئة للحصول علي درجة الدكتوراه في
علاج الأورام بالإشعاع والطب النووي

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# I-Introduction

- Multiple Myeloma is part of a spectrum of diseases labeled Plasma Cell Dyscrasia. The incidence of Multiple Myeloma is increasing at an alarming rate in the United States with 13,000-15,000 new cases diagnosed each year. African-American men have the highest incidence rate and Caucasian women the lowest incidence rate.[1]

- Plasma cells are the cells responsible for forming antibodies against bacteria and foreign proteins. For reasons that are unclear, these cells lose their ability to respond to controlling signals from a hierarchy of immune cells. Plasma cells then divide and form abnormal proteins which results in damage to the bone, the bone marrow, and/or other organs of the body. One of the reasons Myeloma has not curable is the ability of the cancer cell to protect itself from chemotherapy by becoming dormant "sleep" (inactive).our research has shown that these cells can be activated in patients without causing any harm. The myeloma cell is controlled by several immune cells and proteins. There is data to suggest that patients have a disrupted immune system and a role for cytokines (proteins controlling the immune system) in maintaining multiple myeloma in an inactive state following

the initial decrease of tumor load by chemotherapy. (2)

- There is no curative therapy available for multiple myeloma. Maintenance with chemotherapy after initial response is not effective in controlling the disease and carries significant risks. The results of different therapeutic modalities for Multiple Myeloma have not changed the course of the disease significantly since the late 1960's. Therefore, the new treatment modalities are a must to control the disease.(3)

- Therapeutic clinical trials at the Cleveland Clinic's Multiple Myeloma Program focus on studying the possible deficits in the immune system as well as the local environment of the tumor. This information is used in developing innovative therapies to repair these defects and correct the abnormalities in the disease micro environment. Cleveland Clinic's Multiple Myeloma Program is currently studying the effect of Immunomodulators (IMiDs) with or without chemotherapy on the activated cells. The IMiDs are a group of unique, orally bioavailable agents that have been refined using the parent IMiD compound, thalidomide, as a structural template.(4)

- IMiDs appear to have a different safety profile from thalidomide. From the published data, they

appear to have manageable side effects in addition to Studies of IMiDs have shown a significant clinical benefit in Multiple Myeloma, along with an improved safety profile and probable improved activity compared with thalidomide. It is anticipated that lenalidomide and other IMiDs will become a significant addition to the therapeutic armamentarium for Multiple Myeloma therapy because of their more potent immunomodulatory properties and their better tolerability. Further studies of these orally bioavailable agents in patients with Multiple Myeloma are warranted not only in combination with other biologics and chemotherapeutic agents but with thalidomide as well.[5]

# II-Aim Of The Work

- The aim of this study is to highlight the new advances in the treatment of Multiple Myeloma.

# III-Review Of Literature

- Physiology: Short resume about Physiology of the plasma cells.
- Pathology: Pathology of multiple myeloma.

- Mechanism of action: mechanism of action of immuno-modulators drugs in treatment of multiple myeloma.

# III- Patients And Methods

- Not less than *40* patients suffering from multiple myeloma (*20* newly diagnosed & *20* relapsed / refractory cases) will be treated at Cleveland Clinic multiple myeloma center by using the new therapeutics named Immunomodulators (IMiDs):

**Revlimid (Lenalidomide)**

- As single agents or in combination to dexamethasome and/or chemotherapeutic agents.
- Pretreatment full clinical, laboratory, biological markers, radiological and hematological evaluation.
- The plan for the treatment will be then discussed according to the evaluative and diagnostic data previously collected from each patient.
- Follow up via pretreatment evaluation tools and biological markers, coagulation parameters, and myeloma paraprotein levels.
- Early studies in newly diagnosed &/or relapsed-refractory multiple myeloma using IMiDs as a single agent and in combination with chemotherapy and/ or dexamethasome.

# Pegy. Doxorubicin (Doxil®), Vincristine, Dexamethasone and Revlimid (DVd-R) A Phase II Study For Newly Diagnosed &/or Relapsed/Refractory Multiple Myeloma (MM)

## A. Study Objectives

### 1. Primary

- To identify the maximum tolerated dose (MTD) of Revimid™ or Revlimid-(R) in combination with Doxil®, vincristine and dexamethasone (DVd) as treatment for subjects with relapsed or refractory multiple myeloma (MM).

### 2. Secondary

- To evaluate the overall safety of Revimid™ or Revlimid when combined with DVd as treatment for subjects with relapsed or refractory MM.
- To evaluate the preliminary efficacy of Revimid™ or Revlimid when combined with DVd
- To evaluate the effect of combination DVd-R on biological markers, coagulation parameters and myeloma paraprotein levels.

# B. Study Design

- This is a study of Revimid™ or Revlimid plus Doxil®, vincristine, and dexamethasone (DVd-R). The study will be a standard dose-escalation study to determine the MTD within the first 35 days of therapy with Revimid™ or Revlimid in combination with fixed doses of Doxil 40® mg / m2 IVPB Day 1, vincristine 2.0 mg IVP Day 1 and dexamethasone 40 mg PO daily days 1 - 4. A maximum enrollment of 40 subjects is anticipated for this study.

# C. Study Endpoints

## 1. Primary

- Safety (type, frequency, severity, and relationship of adverse events to DVd-R).

## 2. Secondary

- Myeloma paraprotein response.
- Correlation of exploratory biological and coagulation studies with myeloma paraprotein response.

# D. Study Duration

- Study drug treatment continues for a maximum of 6 cycles, until lack of therapeutic effect is documented, or study drug, is discontinued for any reason.

# E. Study Population

## *A. Inclusion Criteria*

- Understand and voluntarily sign an informed consent form.
- Age >18 years at the time of signing the informed consent form.
- Able to adhere to the study visit schedule and other protocol requirements.
- Diagnosed with active multiple myeloma and be considered to have disease progression after at least 2 cycles of anti-myeloma treatment or have relapsed with progressive disease after treatment.
- Measurable myeloma paraprotein levels in serum (≥ 0.5g/dL) or urine (≥ 0.2 g excreted in a 24-hour collection sample).
- ECOG Performance Status of 0-2 (Performance status of 3 and 4 will be allowed if related to bony disease.
- Bilirubin < 2 x upper limits of normal (ULN).
- Liver enzymes (ALT or AST) < 3 x ULN.

- Must have adequate bone marrow function:
    - Absolute neutrophil count > 1,000 cells/mm3 (1.0 x 109/L)
    - Platelets > 100,000 cells/mm3 (100 x 109/L)
    - Hemoglobin > 8 g/dL
- Must have adequate renal function: creatinine < 2.5 mg/dL.
- Must have 2-d echocardiogram indicating LVEF > 50% within 42 days prior to first dose of study drug.
- Women of childbearing potential (WCBP)† must have a negative serum or urine pregnancy test within 7 days of starting study drug. In addition, sexually active WCBP must agree to use adequate contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) while on study drug. WCBP must agree to have pregnancy tests every 4 weeks while on study drug.

## *B. Exclusion Criteria*

- Severe infection requiring intravenous antibiotic treatment.
- Life expectancy of less than 3 months.
- Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in-situ

cervical cancer, or other cancer from which the subject has been disease-free for at least 5 years.

- Solitary bone or solitary extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia.
- Subjects who have received > 500mg/m2 of doxorubicin alone, or Doxil® alone, or doxorubicin plus Doxil®.
- Prior treatment with IMiDs.
- Prior development of > grade 2 allergic reaction/ hypersensitivity while taking thalidomide.
- Prior development of a > grade 3 rash or any desquamation while taking thalidomide.
- History of cardiac disease, with New York Heart Association Class II or greater.
- Uncontrolled medical problems such as diabetes mellitus, coronary artery disease, hypertension, unstable angina, arrhythmias), pulmonary, hepatic and renal diseases unless renal insufficiency is felt to be secondary to multiple myeloma.
- Any investigational agent or systemic anti-myeloma therapy within 28 days of the first dose of treatment.
- Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.
- Pregnant or lactating females.
- Any condition, including the presence of laboratory abnormalities, which places the

subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.

## *C. Allowable Concomitant Therapy*

- Standard radiation therapy to treat extra-skeletal and/or skeletal tumor sites. If radiation is needed during the study period, the investigator must document that there is no sign of progressive disease leading to radiation as a treatment. Comparisons of area to be radiated with baseline bone survey films must be provided to document lack of disease progression.

- Erythropoietin for severe symptomatic anemia.

- GM-CSF is the only growth factor that will be allowed if necessary in the induction phase.

- Aredia or Zomita and Immunoglobulin therapy will be allowed at any stage of the therapy.

# V-Results And Cases

# VI-Discussion

# VII-Summary

# VIII-Conclusion

# IX-References


1- Jemal A, Murray T, Samuels A et al. Cancer statistics, 2005. CA Cancer *J Clin* 2005;22;4-30
2- Fonseca R, et al. Clinical and biologic implications of recurrent genomic aberrations in myeloma. *Blood* 2003;101:4569.
3- Seidl S, Kaufmann H, Drach J. New Insight into the pathophysiology of multiple myeloma. *Lancet Oncol*. 2003;4:557.
4- Weber D, et al. Thalidomide alone or with dexamethasone for previously untreated multiple myeloma *J Clin Oncol 2003;2:2116.*
**5-** Dimopoulos MA, et al. Treatment of plasma cell dyscrasias with thalidomide and its derivatives. *J Clin Oncol* 2005;21:4444.

## العلاج المصاحب المسموح به

- العلاج الإشعاعي في حالة الحاجة إلى الإشعاع خلال فترة الدراسة، ويتعين على المحقق تسجيل عدم وجود مؤشرات لزيادة المرض تؤدي استخدام الإشعاع كعلاج. يجب تقديم مقارنات المنطقة المعالجة بالإشعاع مع صور الخط القاعدي للعظام لتسجيل عدم زيادة المرض.
- لأعراض الأنيميا الحادة: الأرثروبيوتين.
- GM-CSF هي العامل النموي الوحيد الذي سيسمح به في حالة الضرورة خلال المرحلة الاستهلالية.
- العلاج باستخدام: الزوميتا أو أرديا و جلوبيونات مناعية مسموح به في أي مرحلة من مراحل العلاج.

# النتائج والحالات

# المناقشة

# الملخص العربي