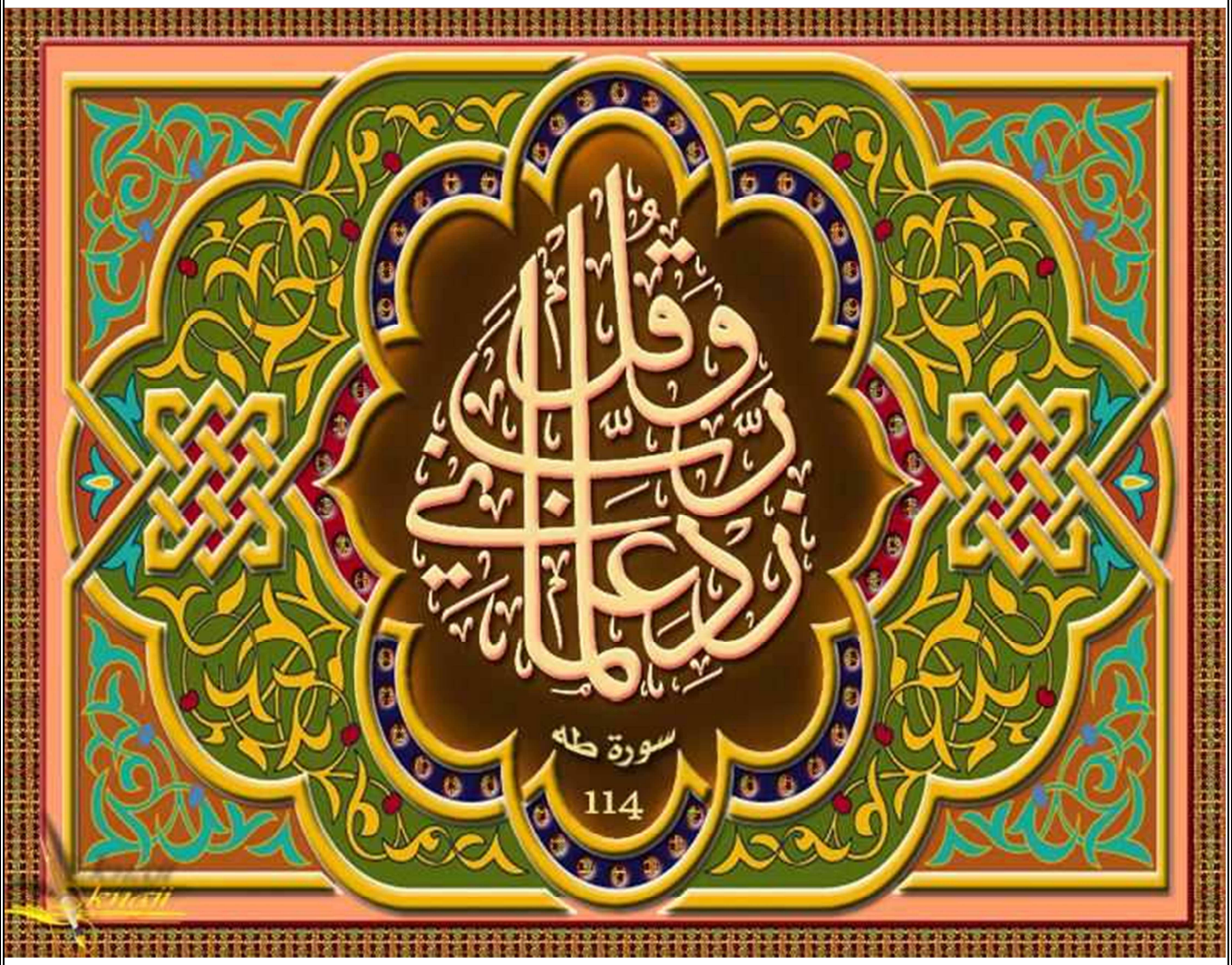
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Essay

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دراسة الجديد في تشخيص و علاج أورام نخاع العظام (الميولوما المتعددة)

مقال

توطئة للحصول على درجة الماجستير فى علاج الأورام بالاشعاع والطب النووى

مقدمة من

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ABBREVIATIONS

A: adriamycin

BAP: bone alkaline phosphatase

BM: bone marrow

BMSCs: bone marrow stromal cells

C: cyclophosphamide

CDRs: complementarity determining regions

CR: complete response

CRAB: Calcium (elevated), Renal failure, Anemia, Bone lesions

DVT: deep venous thrombosis

FISH: fluorescence in situ hybridization

FLC: free light chain

HDT: high dose therapy

HGF: hepatocyte growth factor

HLA: human leukocyte antigen

HSP: heat shock proteins

Ig: immunoglobulin

IMF: International Myeloma Foundation

ISS: International Staging System

M: melphalan

MGUS: monoclonal gammopathy of undetermined significance

MM: Multiple Myeloma

MMSET: multiple myeloma SET domain

P: prednisone

PCL: Plasma cell leukemia

PCLI: plasma cell labeling index

PCR: Polymerase chain reaction

PR: partial response

SC: stromal cells

sCR: stringent complete response

SD: stable disease

SHM: somatic hypermutation

SMM: smoldering multiple myeloma

SWOG: Southwest Oncology Group

TC classification: Translocation and cyclin D expression classification

TNF-α: tumor necrosis factor-α

V: vincristine

VGPR: very good partial response

VLA: very late antigen

Introduction

Multiple myeloma is a plasma cell dyscrasia characterized by a clonal proliferation of lymphoid B cells and infiltration of the BM by plasma cells **(Rajkumar, 2005).** It is the second most common hematologic malignancy, and is responsible for at least 2% of cancer-related deaths **(Raje and Longo, 2008).**

As myeloma patients present with a variety of symptoms not specific to the disease, the diagnosis of myeloma is quite often delayed. The initial evaluation includes a hemogram, complete skeletal radiographic survey, serum urine protein electrophoresis and immunofixation, in addition to quantitative immunoglobulin levels, urinary protein excretion in 24 hours, as well as bone marrow aspiration and biopsy **(Munshi et al., 2008).**

The outcome for patients with multiple myeloma is highly variable with a range from less than 6 months to greater than 10 years. This variability derives from heterogeneity in both myeloma cell biology and multiple host factors. There was a need for a simple, reliable staging system for multiple myeloma that can be applied internationally for patient classification and stratification. A combination of serum beta-2 microglobulin ($S\beta_2M$) and serum albumin provided the simplest, most powerful and reproducible three-stage classification. This new International Staging System (ISS) consists of the following stages: stage I, $S\beta_2M$ less than 3.5 mg/L plus serum albumin 3.5 g/dL (median survival, 62 months); stage II, neither stage I nor III (median survival, 44 months); and stage III, $S\beta_2M$ 5.5 mg/L (median survival, 29 months). It was concluded that the ISS staging system is broadly useful and that is well provide a sound base for more advanced studies in the future **(Greipp et al., 2005).**

However, the ISS was not powerful enough to recognize the highest-risk patients. The assessment of chromosomal abnormalities, such as t(4;14) or del(17p), has been shown to be useful in refining identifications of these patients **(Avert-loiseau et al., 2007).** Although powerful, genetic abnormalities targeted small subsets of patients and don't account for all the heterogeneity in the clinical outcome. Molecular signatures capturing gene expression data recently emerged as powerful tools to identify patients at high risk of death, as well as to define biologic entities associated with risk groups **(Rosenwald et al., 2002).**

Myeloma cells was found to be from high-risk patients overexpressed genes involved in mitosis and its surveillance, whereas the profile of myeloma cells from very low-risk patients was more heterogeneous and included hyperdiploid MM gene signatures**.** The International Myeloma Working Group plans to develop a second staging system using conventional and FISH cytogenetics, molecular genetics, proteomics, and S-phase analysis for use by reference centers and eventually for all patients with myeloma **(Decuax et al., 2008).**

There have been three distinct phases in development of therapy for multiple myeloma. First in the 1960s, melphalan was confirmed as the first active antimyeloma agent. The combination of melphalan with prednisone (MP) became one of the standards of therapy. Even with more complex chemotherapy regimens, CR was rare and all patients ultimately relapsed. The next improvement in therapy was high-dose chemotherapy supported by autologous stem cell transplant (ASCT) in the 1980s **(Munshi, 2008).**

The third has been our understanding that the bone marrow microenvironment.supports myeloma cell growth, survival, and development of

drug resistance. This has led to a change in the treatment paradigm to target not only the tumor cells but also the bone marrow microenvironment. Four new drugs-thalidomide (T), bortezomib (V), lenalidomide (R), and pegylated-liposbmal doxorubicin—have been approved for myeloma in last five years, completely changing the therapeutic scenario **(Munshi, 2008).**

Aim of the Work

To elucidate the new advances in the pathogenesis and management of multiple myeloma.

1-Epidemiology

Multiple Myeloma (MM) is a malignant clonal B-cell tumor of slowly proliferating plasma cells within the bone marrow. MM accounts for 10% of all hematologic cancers**.** The age-adjusted annual incidence of MM is 4.3 cases per 100,000 white men, 3 cases per 100,000 white women, 9.6 cases per 100,000 black men, and 6.7 cases per 100,000 black women **(Ailawadhi et al., 2012).**

An estimated 19,920 patients (Male 11,190 and female 8,730) were diagnosed as having multiple myeloma in the United States in 2009, and approximately another 10,690 patients will die of this disease a year (Male 5,640 and female 5,050) **(Jemal, 2011).**

Myeloma is rare among people of Asian descent, with an incidence of only 1-2 cases per 100,000 populations. The incidence data for other ethnic groups including Native Hawaiians, Hispanics, American Indians from New Mexico, and Alaskan Natives also show higher myeloma rates relative to U.S. whites in the same geographic area; however, the Chinese and Japanese populations have a lower incidence than whites **(Kyle et al., 2007).**

The median age of patients with MM is 68 years for men and 70 years for women. Only 18% of patients are younger than 50 years, and 3% of patients are younger than 40 years. The disease is more common in men and has average annual age-adjusted incidence rates per 100,000 of 4.7 in men and 3.2 in women among whites, whereas the incidence is 10.2 in men and 6.7 in women among African Americans **(Rajkumar and Kyle, 2007).**