UPDATES IN THE PATHOGENESIS AND MANAGEMENT OF MULTIPLE MYELOMA

ESSAY

Submitted For Partial Fulfillment Of
Master Degree In
Internal Medicine

BY

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2009

Acknowledgement

Thanks ***to "Allah"*** from start to end, that this work has been completed.

I am greatly indebted to ***Prof. Dr. Hanan Hamed Abd Elhamid,*** Professor of internal medicine and haematology, faculty of medicine, Ain shams university, for her kind supervision, sincere guidane and valuble suggestions. Her encouragement and support were the driving force behind the accomplishment of this work.

My deep respect and thank goes to ***Prof. Dr. Maris Soliman Ayoub,*** Assistant Professor of internal medicine and haematology, faculty of Medicine, Ain shams university, for her great help and valuable advice.

It is a great pleasure to express my thanks to ***Dr. Ghada Metwally Elgohary*** lecturer of internal medicine and haematologyy, faculty of medicine, Ain shams university, who gave me her great support, great knowledge and experience.

Mohamed Nasr Gad Mohamed

List of abbreviations

B2M	Beta2 microglobuline.
BMSCs	bone marrow stromal cells..
BMSCs	Bone marrow stromal cells
CAM-DR	Cell adhesion mediated drug resistance.
CASPases	Cytosolic aspartate–specific proteases
CDK	cyclin-dependent kinase
CDR	complementarity determining regions.
CT	Computed Tomography.
ERK	extracellular signal-related kinase
FDG-	Fluorodeoxy glucose.
FGFR3	Fibroblast growth factor receptor3.
HDT	high dose therapy.
HMCLs	human myeloma cell lines.
HSP	Heat shock proteins
IGF-1	insulin-like growth factor 1
IgH	Immunoglobulin heavy chain
IL-6	interleukin-6..
JAK	Janus kinase
MAPK	mitogen-activated protein kinase.
MGUS	monoclonal gammopathy of undetermined significance.
MRI	Magnetic Resonance Image
OAFs	Osteoclastactivating factors.
PCL	plasma cell leukemia.
PET	Positron emission tomography.
PI3-K	Phosphatidyl inositol-3 kinase

POEMS	Polyneuropathy,Organomegally,endocrinopathy,monoclonal gammopathy,skin changes
RANKL	receptor activator of NF-KB.
STAT	Signal transducer and activator of transcription..
VAD	Vincristine,adriamycine,dexamethazone
VCAM	vascular cellular adhesion molecule.
VEGF	Vascular Endothelial Growth Factor.
RAG	Recombinase-Activating Genes
FISH	fluorescence in situ hybridization
PCs	Plasma cells
GSK	glycogen synthase kinase
TNF	Tumor necrosis factor
NF-κB	nuclear factor kappa B
LFA1	leukocyte function-associated antigen1
VCAM	vascular cellular adhesion molecule
SCID	severe combined immunodeficient
PI3-K	phosphatidylinositol-3 kinase
FKHR	forkhead transcription factor
PTHrP	parathyroid hormone-related protein
IAPs	inhibitors of apoptosis
DAP	The Death-Associated Protein
TRAIL	TNF-Related Apoptosis Inducing Ligand

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Introduction

Plasma cell disorders (plasma cell dyscrasias) are uncommon. They begin when a single group (clone) of plasma cells multiplies excessively and produces a large quantity of a single type of antibody (immunoglobulin). Plasma cells develop from B lymphocytes, a type of white blood cell that normally produces antibodies, which help the body fight infection. Plasma cells are present mainly in bone marrow and lymph nodes. Every plasma cell divides repeatedly to form a clone, composed of many identical cells. The cells of a clone produce only one specific type of antibody. Because thousands of different clones exist, the body can produce a vast number of different antibodies to fight the frequent exposure to infectious microorganisms**(Rajkumar et al .,2006).**

In plasma cell disorders, one clone of plasma cells multiplies uncontrollably. As a result, this clone produces vast amounts of a single antibody (monoclonal antibody) known as the M protein. In some cases (such as with monoclonal gammopathies), the antibody produced is incomplete, consisting of only light chains or heavy chains (functional antibodies normally consist of two pairs of two different chains called a light chain and heavy chain). These abnormal plasma cells and the antibodies they produce are limited to one type, and levels of other types of antibodies that help fight infections fall. Thus, people with plasma cell disorders are often at higher risk of infections**(Rajkumar et al .,2006).**The ever-increasing number of abnormal plasma cells also invades and damages various tissues and organs, and the antibody produced by the clone of plasma cells can sometimes damage vital organs, especially the kidneys and bones Plasma cell disorders

include gammopathies of undetermined significance, multiple myeloma, macroglobulinemia, and heavy chain diseases. These disorders are more common among older people**(Rajkumar et al .,2006).**

Multiple **myeloma** is a B-cell malignancy with terminally differentiated plasma cell phenotype. The characteristic findings in MM are lytic bone disease, renal insufficiency, anemia, hypercalcemia, and immunodeficiency. The most common presenting symptoms are fatigue, bone pain, and recurrent infections(**Kyle et al.,2003**).

The introduction of melphalan and prednisone for the treatment of multiple myeloma was followed by only minor advances in the management of the disease for almost 20 years**(Kyle and Rajkumar.,2006).**

The failure of other agents, alone or in combination, to extend survival beyond three years prompted a new treatment strategy in the early 1980s: myeloablative doses of melphalan supported by an infusion of autologous hematopoietic stem cells was introduced, After this approach was found to be superior to conventional chemotherapy for the initial treatment of myeloma, the efficacy of two sequential courses of high-dose therapy, each supported by an infusion of autologous stem cells (Tandem transplantation), was tested. As compared with a single infusion of stem cells, two infusions significantly prolonged both overall and event-free survival, particularly among patients who did not enter remission after receiving the first transplant**(Cavo et al.,2004).** The benefit of melphalan-based tandem transplantations was greatest in patients whose myeloma cells had a normal karyotype: these patients had an estimated probability of remaining in remission at 10 years of nearly 20 percent, suggesting that long-term control and even cure myeloma are possible with tandem transplantation**(Barlogie et al.,2004).**

More recent advances in the management of myeloma include the identification of new ways to overcome drug resistance**(Kyle and Rajkumar.,2006) .**Also important is recognition of the pivotal role of the bone marrow microenvironment in promoting the growth, survival, and resistance of myeloma cells to conventional chemotherapy. As a result of this work, new classes of agents for the treatment of myeloma have been introduced. These include thalidomide; lenalidomide; a potent analogue of thalidomide; and the proteasome inhibitor bortezomib. Meanwhile, the concept of targeting the bone marrow microenvironment (the "soil") in a way that interferes with the growth of the myeloma "seed" emerged as the rationale for trials of new agents in combination with established therapies in an attempt to enhance cytotoxicity, reverse drug resistance, and increase the probability of curing myeloma**(Richardson et al.,2005).**

Although response to therapy traditionally has not been a good predictor of long-term outcome, most recent studies suggest that response is an adequate surrogate indicator of improvement in survival. For instance, a recent phase 3 study by the Intergoupe Francophone du Myelome (IFM) showed clear improvements in response and survival with the addition of thalidomide to a melphalan regimen compared with both standard melphalan and prednisone and high-dose therapy with stem cell transplantation**(Facon et al.,2006).** Also the use of lenalidomide in combination with dexamethasone was proved to have significant clinical activity as first line therapy for multiple myeloma(**Donna et al.,2007).**

With increased understanding of the interactions between the malignant plasma cell and the bone marrow environment, cell receptor interactions, and intracellular signaling pathways, the number of potential therapeutic targets and novel treatments has grown. Below are examples of selective agents that

target either the **myeloma** cell, the bone marrow microenvironment, and/or cell surface receptors **(Richardson et al.,2006).**

Targeting myeloma cell

Akt Inhibition and Recruitment of Death Receptors

Perifosine (octadecyl-[1,1-dimethyl-piperidinio-4-yl]-phosphate) is a synthetic novel alkylphospholipid. This is a member of a novel class of antitumor agents that interact with the cell membrane and modulate intracellular growth signal transduction pathways. **(Richardson et al.,2006).**

Heat Shock Protein Inhibitors: Geldanamycin and Tanespimycin The heat shock proteins (HSP) are part of a ubiquitous chaperone complex that facilitates the proper folding, prevents misfolding or aggregation, and preserves the 3-dimensional conformation of a number of intracellular proteins.(Siegel et al.,2006).

Targeting Myeloma Cells and the Bone Marrow Microenvironment ProteasomeInhibitors:NPI-0052

NPI-0052 is a novel proteasome inhibitor NPI-0052 triggers apoptosis in MM cells, but is distinct from bortezomib in its chemical structure**,(Bethesda,2007).** A recent preclinical study demonstrated that orally administered NPI-0052 is cytotoxic to MM cells, with reduced toxicity against normal cells compared with bortezomib. It is currently being evaluated in a Phase I trial. Ultimately, these 2 proteosome inhibitors may be combined since they have different kinetics and cellular responses. **(Chauhan et al.,2006).**

Monoclonal Antibodies

A number of monoclonal antibodies (Mabs) are in clinical trials that

target the **myeloma** cell directly and/or the bone marrow microenvironment. These include Mabs to IGF receptor, IL-6, CD56, CD40, CD138, anti-CS1, CD70, and CD74.

Anti-IL-6;Tocilizumab

IL-6 is involved in multiple pathways in **myeloma**; secretion occurs from the malignant plasma cell, as well as from the microenvironment, resulting in autocrine and paracrine stimulation. This results in **myeloma** cell proliferation. Tocilizumab, a humanized anti-IL-6 receptor Mab that specifically blocks cell-to-cell signaling, is currently being studied in MM. **(Yoshio-Hoshino et al.,2007) .**

Aim of the essay

The aim of the essay is to review the recent up dates in the pathogenesis and management of multiple myeloma.

Epidemiology

According to the most recent data from the Surveillance, Epidemiology, and End Results (SEER) program, multiple myeloma is a relatively uncommon malignancy in the United States, representing 1% of all malignancies in whites and 2% in African Americans. Among hematologic malignancies, it constitutes 10% of the tumors and ranks as the second most frequently occurring hematologic cancer in the United States after non-Hodgkin's lymphoma. At any one time, the prevalence of myeloma is over 53,000, and estimated new cases in 2007 were approximately 19,900; 10,790 patients died from myeloma in 2002. The disease is more common in men and has average annual age-adjusted (1970 U.S. standard) incidence rates per 100,000 among whites of 6.6 in men and 4.1 in women, whereas for African Americans the incidence is 14.0 in men and 9.5 in women**(Devita et al .,2008)**.The increased incidence in African Americans is not explained by factors such as social or economic condition, household size, or family income. The incidence data for other ethnic groups including native Hawaiians, female Hispanics, Native American from New Mexico, and Alaskan natives also show higher myeloma rates relative to U.S. whites in the same geographic group; however, the Chinese and Japanese populations have a lower incidence than whites. The incidence of multiple myeloma has slowly increased in the U.S. white population since 1970; however, the incidence among African Americans has increased more prominently during the 1970s and 1980s and is still increasing in the 1990s,The incidence rise with age,better diagnostic techniques and higher average age of general population may in part explain the rising incidence over the last several decades.Atrend toward more frequent myeloma in patients under age of 55 year implies important environmental causative factors **(Devita et al .,2008).**

Aetiology

The cause of MM is largely unknown.Some possible aetiologic factors include:

1- genetic predisposition

The genetic susceptibility is probably related to the way individuals deal with environmental toxins and antigen exposure. Indeed, a large individual variation in activity along xenobiotic metabolic pathways has been implicated in the susceptibility to childhood acute lymphoblastic leukemia (ALL)**(Sinnett et al .,2003).** Several of these participating enzymes metabolize environmental carcinogens. Multiple variants in genes coding for detoxification and DNA repair enzymes have been described**(Meyer andZanger .,1997).**

Although more than 99% of human DNA sequences are the same for all individuals, variations in DNA sequence in the remaining less than 1% can have a major impact on how humans respond to environmental insults. Single nucleotide polymorphisms (SNPs) are the most frequent forms of DNA variation and disease-causing gene mutations**(Meyer andZanger .,1997).**

2- Environmental and occupational factors

Environmental and occupational exposures have been implicated in the etiology of myeloma. Exposure to ionizing radiation is the most convincing risk factor for MM. MM occurred after a long, latent period in atomic bomb survivors exposed to high dose radiation**(Shimizu et al .,1990).** Studies performed on radiologists also suggest a link with long-term exposure to