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Multiple myeloma

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Abstract
Multiple myeloma is a plasma cell cancer which is for some extend characterized by presence of monoclonal gammopathy in individuals with (MM) as it may also increase in light chain amyloidosis and macroglobulinemia. However, the aetiology of (MM) still not fully understood, recent research has found that MM may be caused by several factor such as; tumour transformation due to series of genetic changes in the cells and it is obvious that changes in microenvironment of bone marrow facilitate tumour growth. Clinically the symptoms of MM vary and depend on the organ involved, in many patients' unexplained back pain or bone pain is the initial clinical presentation. Bones of ribs, pelvis, skull and long bones are observed with multiple lytic lesions in most of patients. The occurrence of clinical symptoms and lesions may predisposed by a variety of factors such as; age, sex, ethnicity, inheritance factors. Although individuals with rheumatoid arthritis or individuals with body mass index higher than 30 kg are at high risk of susceptibility to MM, no obvious risk factor might be determined in most patients.

Keywords: Multiple myeloma, MGUS, M protein, Immunoglobulin (IG)

Introduction
Multiple myeloma is a cancer produced by malignant plasma cells. Basically, normal plasma cells, that are an important part of immune system, are found in the bone marrow. Infection and other disorders that happen during individual's life can be protected by several types of cells that combine together to fight against infections and directed by immune system. The main cell types of immune system are (Lymphocytes), which can be found in different areas of body such as: lymph node, bone marrow and blood stream. Physiologically, lymphocytes can be divided into two major types of cells: T cells and B cells. During infection, B cells become mature and change to plasma cells that make antibodies and help body to protect against infection through attacking and killing infectious agents. In abnormal circumstances plasma cells become cancerous by uncontrolled growth of the cells and they might produce tumour known as (plasmacytoma). In general, these tumours are developed in bone but in rare cases might be found in other tissues. If there is only a single plasma cell tumour, it is called an isolated (or solitary) plasmacytoma, but when there is more than one plasma cell tumour, it is called (multiple myeloma). Over growth of plasma cells in bone marrow in patients with multiple myeloma result in crowd out normal blood forming cells leading to shortage of blood counts. This shortage causes several serious problems depending on the type of cells which were decreased such as: anaemia as a result of abnormality in quantity and quality of RBC, thrombocytopenia in case of shortage of platelet and leukopenia due to low number of WBC. Monoclonal gammopathy (having many copies of same antibody) is a characteristic feature of myeloma cells, but it is not highly specific to multiple myeloma because it can be increased in other diseases such as: light chain amyloidosis and macroglobulinemia. Although, some people have monoclonal gammopathy but it might not be lead to significant problem which is present in patients with multiple myeloma. This situation is called monoclonal gammopathy of undetermined significance (MGUS). Some people with MGUS go on to develop multiple myeloma or other diseases (Anderson, 2005) [3].

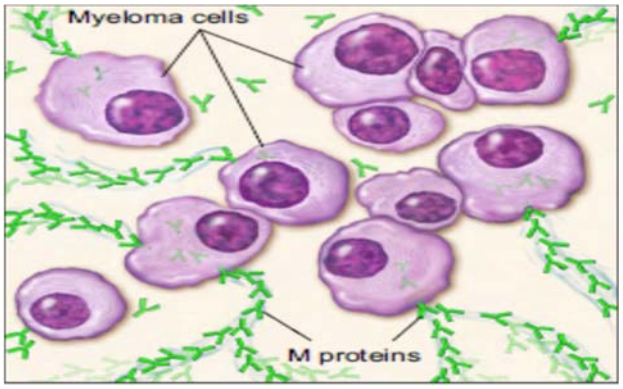

Fig 1: abnormal plasma cells (Myeloma cells) making M proteins. Retrieved form (National cancer institute, 2004) [27]

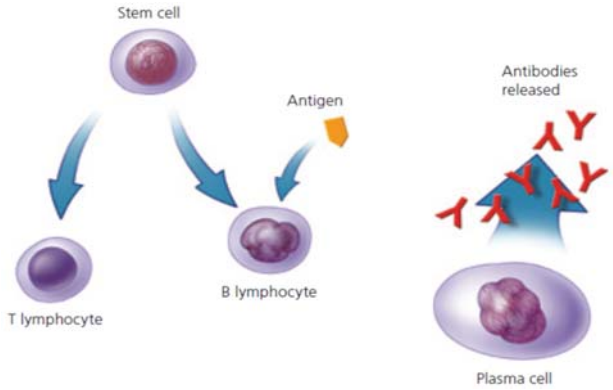

Fig 2: Origins of plasma cells that develop from stem cells in the bone marrow like other types of blood cells. Physiologically, Stem cells can develop into B cells (B lymphocytes) and move to the lymph nodes, then mature, and then travel throughout the body. During infection, when foreign substances (antigens) enter the body, B cells develop into plasma cells that produce immunoglobulin (antibodies) to help fight infection and disease. Retrieved from Nau and Lewis, 2008 [28]

Epidemiology

In multiple myeloma (MM) monoclonal proteins are formed by proliferated malignant plasma cells which can results in renal dysfunction, bone lesions, hypercalcemia and limitation of body defence mechanism to fight against infection. MM is a Worldwide distributed type of cancer, approximately ranges 0.8% of all cancer diagnosis, which is about 102,000 recent cases and each year approximately 72,000 patients with MM will die which is equal to 1.0% number of death caused by all types of cancer (*Ferlay et al. 2010*) [11]. Geographically, the incidence of MM is highest in industrialized countries such as; North America, Australia and Europe. Although, causes is not fully understood, the susceptibility of people to MM in these countries tends to be increasing, while comparing to those countries the incidence of MM remain stable in Asian countries (*Parkin et al. 2011*). The incidence in African American nations among other nations have the highest level which is about twice to number of infected people of other ethnicity (*Howlader, 2011*) [14]. Similar patterns of incidence and mortality to their place of origin have been detected in Arab Americans when they travel to the metropolitan Detroit area and Asians that migrated to California suggesting that, environmental factors may play less of a role in the Aetiology of MM (*Schwartz et al. 2004 and Clarke et al. 2011*) [9, 40].

Although individuals with rheumatoid arthritis or individuals with body mass index higher than 30 kg are at high risk of susceptibility to MM, no obvious risk factor might be determined in most patients with this disease (*Sirohi, 2006*) [39]. The incidence of MM is high in people older than 50 as MGUS is present in 2% in these people which the rate of development to MM may be 1% annually (*Kyle et al. 2002*) [20]. In addition, many familial aggregations have seen with autosomal dominant pattern, rising by 2-4 folds (*Altieri et al., 2006*) [1]. There are variations in incidence of MGUS according to differences in ethnicity, which in African American and men in Ghana have a highest rate (*Landgren et al., 2006*) [22]. Depending on a study that examined same age groups of people, the incidence of MGUS is 5.8% among Ghanian people, 3.2% in American Caucasian, 2.4% in Japan and 1.7% among French people (*Iwanaga et al. 2007*) [15].

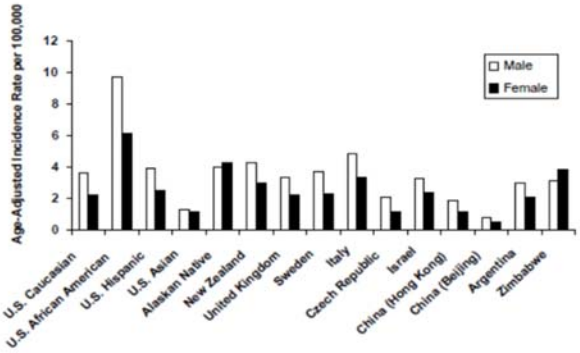

Fig 3: incidence rate of multiple myeloma per 100,000 people men and women. Retrieved form (Alexander *et al*., 2007) [2].

Aetiology

The aetiology of multiple myeloma is still not fully understood. This depends partly on the low frequency of the disease which makes its identification difficult; and partly depends on the fact that the risk factors which play an important role in malignant diseases in general, such as tobacco consumption and diet have not been found obviously involved in multiple myeloma aetiology. However, major attempt are currently started to unravel the aetiology of haematological malignancies in general and of multiple myeloma in particular (*Boffetta et al. 2007*) [8], the cause of MM is still poorly understood, but recent research has found that MM may be caused by several factor such as; tumour transformation due to series of genetic changes in the cells and it is obvious that changes in microenvironment of bone marrow facilitate tumour growth *(Raja, 2010*) [35]. In rare cases, MM may result from developing MGUS after months or even years which is regarded as a precancerous, in most patient with MM, translocation of immunoglobulin gene (Ig) are present which approximately 70% of them have translocation of heavy chain and 20% of them have translocation of light chain. Moreover, abnormalities in chromosome can results in MM particularly in chromosome number 13 that some parts are missing and leading to aggressiveness and resistance of myeloma cells against therapy. About 50% of all people with myeloma have abnormality in location of chromosomes in their myeloma cells, when part of one chromosome has switched with part of another chromosome (translocated). *(Palumbo, 2011*) [32].

Pathophysiology

Physiologically, immunoglobulin composed of two chains, one heavy and one light chain that attached to each other. Immunoglobulin, which acts to fight against infection are produced by plasma cells and has several types (IgG, IgM, IgD, IgE, and IgA). In cancerous plasma cells M protein which refers to abnormal immunoglobulin are overproduced. Abnormal light chain proteins (κ or λ), cytokines are produced by myeloma cells which stimulates osteoclast (function to break down old bones) and supress the activity of osteoblast (function to re build of new bones), this result in highly susceptibility of patients with MM to bone disorders particularly bone fracture. Due to over production of M protein which causes hyperviscosity of light chain protein that results in organ damage like in kidney and invasive bone lesions and causes bone disorders and hypercalcemia due to excessive bone dissolving by osteoclasts. In addition to bone marrow invasion which causes anaemia and immunological disorders that contribute in recurrent infections. Most recent MM cases are thought to happen "de novo", however more than 1 in 5 individuals with MGUS have a chance to get MM, it is not fully understood how MGUS progress into MM (*Kyle, 2003*) [44]. An increased level of M protein to (1.5 g/dL or greater), non-IgG MGUS, and ratio of abnormal free light chain increase the risk of multiple myeloma to 58% over 20 years, if all these risk factors are present (*Kyle, 2002*) [20]. Patients with MGUS should be monitored with laboratory tests 1-2 times per year (*Smith, 2005).*

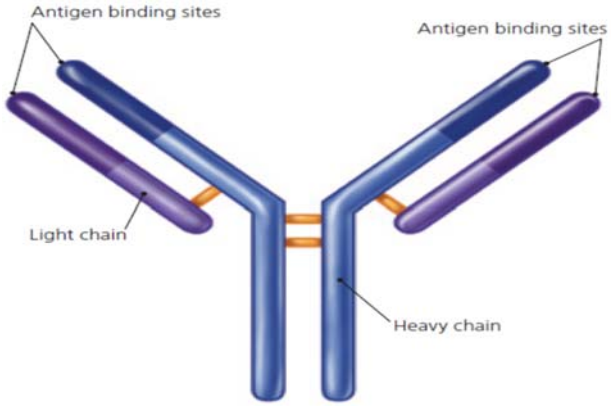

Fig 4: immunoglobulin molecule containing two heavy chains with one smaller light chain attached to each. Retrieved from Nau and Lewis, 2008 [28].

Clinical and laboratory finding

Clinical finding of MM

Clinical signs of MM vary and depend on the organ involved, which in many patients' unexplained back pain or bone pain is the initial clinical presentation. Bones of ribs, pelvis, skull and long bones are observed with multiple lytic lesions in most of patients. Because of bone dissolving feature by osteoclasts in vertebral region, lower extremities are weak and paraesthesia's can be observed in some patients. In case of bone weakness in spine region, spinal nerves pressed and collapsed, which is result in sudden pain, numbness and muscle weakness. (*Kyle et al. 2003* [44] *and Reccardi et at. 1991*) [38]. Sometimes proteins that produced by Myeloma cells may be toxic and cause nerve damage and numbness. Occasionally, due to high blood viscosity by large amount of proteins produced by myeloma cells, blood flow to brain impaired, signs of dizzy, confusion and stroke like symptoms are observed. Hypercalcemia that results from bone dissolving by osteoclasts leads to anorexia, nausea, and polydipsia. Recurrent infection is common in patients with MM especially pneumonia, when the patient get infection, the body defence mechanism is an able to fight against it and it will last for a long time because of impaired antibody and decreases the amount of WBC. In 25% of patients, weight loss are observed and fever is a rare symptom at presentation. It is important to note that one in three patients with MM is asymptomatic at presentation with incidental abnormalities in creatinine, calcium and HB panels. Kidney damages by myeloma protein are another symptom that observes in rare case at early of the disease but it might be detected with blood test. When kidneys impairment starts, they fail to excrete excess salt, fluid and waste product, which can results in weakness and swelling of legs (*Rajkumar, 2008*) [37].

Laboratory finding of MM

In some patient the symptoms suggest that a person might have multiple myeloma, the following lab tests on blood and/or urine, x-rays of the bones, and a bone marrow biopsy are usually performed.

Complete blood count

Complete blood count used to measure the rate of red cells, white cells, and platelets in the blood. Levels of blood cells will be low if myeloma cells occupy large space of the bone marrow.

Quantitative immunoglobulins

In this test different types of antibodies in blood (IgA, IgD, IgE, IgG, and IgM.) are measured to detect any abnormally high or low if present. In patient with MM, the level of one type may be higher than others.

Electrophoresis

Serum protein electrophoresis (SPEP) is a test used to measure the total amount of Immunoglobulin in the blood and detect abnormality in immunoglobulin. In MM abnormal immunoglobulin can be detected because they are monoclonal, But detection of exact type of abnormal antibody like (IgG or other type) require further test such as immunofixation or immunoelectrophoresis. This abnormal protein is recognized by other different names, including monoclonal immunoglobulin, M protein, M spike, and paraprotein.

Free light chains

The amount of light chain in this test is detected and it is useful in rare case when M-protein is not detected by SPEP, because SPEP measures immunoglobulin in total it cannot quantify the amount of light chains.

Immunohistochemistry

In this test, biopsy sample treated with an artificial antibody to find myeloma cells by attaching this antibody to specific molecule on the cell surface of the biopsy and cause color change that can be seen by using microscope.

Cytogenetic

Cells are looked at under a microscope to observe the chromosomal translocations that can happen in some cases of

MM. By this test myeloma cells divide according to quantity and quality of chromosomes which helps in expecting out comes. This test is time effective as it takes 14-21 days for lymphoma cells to grow before they become ready to be watched by microscope.

Fluorescent in situ hybridization

FISH is similar to cytogenetic testing. It uses special stain which only attaches a particular part of chromosome of blood or bone marrow samples. FISH might able to find more chromosomal changes (such as translocations) that can be seen under a microscope in standard cytogenetic tests, as well as some changes too small to be seen with usual cytogenetic testing. FISH is commonly used in several medical centres because of its accuracy in providing results in a couple of days (*Anderson, 2005*) [3].

Classification of multiple myeloma according to stages

Staging is a process of finding out the rate of progressing of cancer and it has an important role in treatment by choosing the drug of choice and has importance in finding out the prognosis of the patients with MM. Durie-Salmon system (DSS) is one of the method used for staging of MM. DSS is based on four criteria in staging of MM:

1. Amount of monoclonal immunoglobulin, which large amount it may suggest large number of plasma cells are present and they produce abnormal protein.
2. Calcium amount in blood, as calcium is a major component of bone and when bone dissolving by osteoclast in MM, amount of calcium abnormally increased in blood.
3. Severity of bone damage, multi area of bone damage that can detect by X-ray indicates advance stage of MM
4. The amount of HB: low HB level indicates that bone marrow is occupied by plasma cells and less amount of RBC is produced by bone marrow.
5. Based on these factors this system divide MM into 3 stages depending on the size of tumour present.

Stage I: in this stage the number of myeloma cells are low and characterised by, slightly low level of HB which is just below normal range, on X-ray examination non area of bone damage or one area of bone damage can be detected, blood calcium level is normal and monoclonal immunoglobulin content in blood and urine is normal.

Stage II: in this stage a moderate number of abnormal plasma cells are found.

Stage III: In this stage large number of myeloma cells are found and characterised by presence of significantly low level of HB (below 8.5 g/dl), high amount of calcium in blood (more than 12 mg/dl), more than 3 area of damage on bone may be detected on X-ray examination and presence of large amount of monoclonal immunoglobulin in blood or urine (Durie, 1975) [10].

Although, DSS still used by some doctors, its value becomes limited because, another method for staging MM has recently been developed which is international staging system (ISS). This system depends on levels of albumin and beta-2 microglobulin in blood in addition to platelet count, kidney function and age of the patient. This system divides myeloma into 3 stages:

Stage I: Serum beta-2 microglobulin is less than 3.5 (mg/L) and the albumin level is above 3.5 (g/L)

Stage II: serum beta-2 microglobulin level is between 3.5 and 5.5 mg/L (with any albumin level), or the albumin is below 3.5 g/L, while the beta-2 microglobulin is less than 3.5mg/L.

Stage III: Serum beta-2 microglobulin is more than 5.5 mg/L (*Greipp et al. 2005*) [12].

Risk factors

MM like other diseases can be predisposed by a variety of factors such as; age, sex, ethnicity, inheritance factors. It has been observed that people with MGUS are highly susceptible to MM with additional predispose factors including; body weight, low fish and green vegetable consumption and pathological condition such as in people with AIDS (*Alexander et al. 2007*) [2]. Approximately 99% of new MM cases are in people with ages more than 40 years and the incidence has been increased reaching to peak level in people with age between 80-84 as shown by the SEER database (*Kyle et al. 2004*) [21]. According to ethnicity, higher rates of MM have consistently observed in American Africans. Several studies have shown that patients with MGUS are at high risk of MM. In the Mayo Clinic study, a cohort of 1,384 patients diagnosed with MGUS were followed prospectively from1960 to 1994. The total risk of developing to MM was 1% per year. (*Kyle et al. 2004*) [21]. Stratification model for risk of progression was developed using data from the Mayo Clinic cohort, however there are no confirmed features that determine which patients with MGUS will progress to MM. Elevating M-protein levels are associated with higher risks of progressing to MM, with the degree of risk depending on the percentage of M-protein, like: 14% for < 0.5mg/dL, 16% for 1.0mg/dL, 25% for 1.5mg/dL, 41% for 2.0mg/dL, 49% for 2.5mg/dL, and 64% for 3.0mg/dL. Furthermore, patients with abnormal serum free light chains have higher risks of MM comparing to patients with normal ratio ($p<0.001$). Inheritance is another risk factor as proved by several studies people who have a family history of MM especially those with HLA alleles are in higher risk of MM particularly first degree relatives (*pottern et al. 1992*) [33].

Diagnosis

MM can be differentiated form MGUS and smoldering MM by end organ damage appearance. Bone disorders such as compression fractures and/or dissolving bone lesion are regarded as an important marker in diagnosis of MM which can be detected by ordinary radiograph, magnetic resonance imaging (MRI) or computed tomographic scan (CT) scan. Blood count disorders present in 2/3 patients which is mainly include depletion the number of RBC due to abnormal plasma cell occupation of bone marrow, renal failure present in 50% of patients and hypercalcemia are regarded as other key points in diagnosis of MM. serum protein electrophoresis (SPEP) in 93% of patients and serum immunofixation (IFE) in 82% are used to detect M-protein in patients with MM (*Kyle et al. 2003*) [44]. In patient with MM there is lack of heavy chain expression in the M-protein and they are considered to have light chain myeloma. By urine protein electrophoresis (UPEP) and urine IFE the sensitivity of detecting of monoclonal protein with MM will rise to 97%. The remaining patients who are negatively diagnosed by serum or protein electrophoresis, clonal paraprotein of their serum free light-chain can be detected by using Immunofixation techniques. Individuals with marrow plasmacytosis, monoclonal plasma cell disorders are

distinguished form polyclonal reactive plasmacytosis which present in autoimmune diseases, metastatic carcinoma, chronic liver disease, acquired immunodeficiency syndrome (AIDS), or chronic infection based on κ/λ staining. Bone lesions in a patient with MGUS due to an unrelated metastatic carcinoma may be mistaken for MM If there is any doubt, a biopsy of one of the lytic lesions is necessary. Blood of anaemic patient with Multiple myeloma is typically normochromic and normocytic, however, macrocytosis with vitamin B12 deficiency has been detected (*Baz, 2004*) [7] approximately 10-15% of patients have thrombocytopenia, and even fewer have leucocytosis—both conditions reflect severe plasma cell infiltration of the bone marrow. Full blood count showing circulating plasma cells are uncommon, unless the disease is progressed. Erythrocyte sedimentation rates are typically more than 50 mm per hour; however patients with Bence Jones myeloma often have values of less than 20 mm per hour (*San, 2006*) [45].

Management of common medical emergencies in myeloma patients

Hyperviscosity

Hyperviscosity is a syndrome that may develop in patients when the level of paraprotein in serum is high, predominantly those of IgA and IgG3 type. Hyperviscosity may results in blurred vision, headaches, mucosal bleeding and difficulty in breathing due to heart failure. All patients with high protein levels should have ophthalmoscopy to determine retinal vein distension, haemorrhages and papilloedema. In general, symptoms of hyperviscosity appear when the level of paraprotien is rise 4-5 mPa, which is equal to IgM level of at least 30 g/l, IgA level of 40 g/l and IgG level of 60 g/l *(Mehta and Singhal, 2003)* [24]. When the symptoms of hyperviscosity occurred in patients, plasma exchange must be performed urgently, but when plasma exchange facilities are not available isovolaemic venesection may be useful. Over the next few days further exchange requirements should be monitored by symptoms and requirement for blood transfusion. Immediate reduction of protein levels is obligatory and anti-myeloma treatment should be used promptly.

Hypercalcaemia

During acute phase of MM, more than 30% of myeloma patients may have hypercalcaemia with symptoms of central nervous system dysfunction (confusion, coma), muscle weakness, pancreatitis, constipation, thirst, polyuria, shortening of the Q-T interval on ECG and acute renal insufficiency. Patients with hypercalcaemia must be treated immediately along with active treatment of hypercalcaemia (hydration and intravenous bisphosphonates) to minimise long term renal damage. Patients with mild form of hypercalcaemia (2.6-2.9 mmol/l) can be treated with oral and/or intravenous rehydration. While moderate to severe hypercalcaemia (≥ 2.9mmol/l) needs intravenous rehydration with normal saline. Sufficient urine output must be monitored by intravenous loop diuretics such as furosemide to avoid volume overload and heart failure and stimulates excretion of calcium via urination. Bisphosphonate should be given to all patients with moderate to severe hypercalcaemia. In patients with hypercalcaemia malignancy randomised controlled trial has shown that zoledronic acid is superior to pamidronate *(Major et al. 2001)* [23]. If the calcium level remains high after 3 days a further dose of zoledronic acid might be given. In patients with renal impairment a modification of dose is necessary by reducing pamidronate dose to (30mg), in addition to the use of (corticosteroids and calcitonin) in Patients with refractory hypercalcaemia.

Cord compression

Spinal cord compression from extra medullary foci of disease is another complication in individuals with MM. It occurs in 5% of patients and it requires immediate screening and management *(Kyle et al. 2003)* [44]. Clinical manifestation of spinal cord compression depends on the tissue involvement (bone or soft tissue disease), level of spinal nerves and rate of development of cord compression but commonly include sensory loss, paraesthesia, limb weakness, walking difficulty and sphincter disturbances. Dexamethasone 40 mg daily for 4 days should be started and MRI or CT scan should be performed as soon as possible depending on the situation of the patients. For soft tissue disease local radiotherapy is the treatment of choice and should be commenced urgently, preferably within 24 hours of the diagnosis of cord compression. Surgery is usually accepted for emergency decompression in the setting of structural compression and/or to stabilize the spine and is usually consolidated by post-operative radiotherapy. *(Rades et al. 2006)* [34].

Early infection

Early infection is one of the incidences that is associated with MM due to deficits in both humeral and cellular immunity, reduced mobility and performance status which are all related to the disease and its treatment. Study Auguston et al in 2005 has reported that more than 10% of patients die of infective causes within 60 days of diagnosis *(Augustson et al. 2005)* [5]. Study has reported that high dose of steroid in elderly or in poor performance patients may be detrimental with increased toxicity and higher mortality rate in the short-term and consideration should be given to the use of lower doses in this group *(Morgan et al. 2009 and Rajkumar et al. 2009)* [25].

Treatment

Chemotherapy

Even though treatment is not necessary in some patients with MM such as smoldering (Asymptomatic) MM, oncology referral is suggested in all patients. Treatment must be performed at the time of need because earlier treatment has no effect on death and may increase the hazard of acute leukaemia (*Kyle, 2002 and Hey, 2003*) [20]. Patients with smoldering multiple myeloma must receive close supplement with laboratory examinations every three to four months (*Kyle, 2007 and Smith, 2005*) [18]. In general, autologous stem cell transplantation (ASCT) is regarded as a typical treatment for patients with symptomatic MM whose ages are less than 65 years and for older patients who are physically able to go through the treatment. Studies showed that Patients who get AS CT with high dose induction chemotherapy such as vincristine (Vincasar), doxorubicin (Adriamycin), and dexamethasone or dexamethasone and thalidomide (Thalomid), which help to prevent myelo suppression by affecting stem cell collection, can survive for approximately 68 months (*Sirohi et al. 2005* [41] *and National comprehensive cancer network, 2007*) [26] Although, patients with symptomatic MM are not physically suitable for ASCT using chemotherapy like melphalan (Alkeran) and

prednisolone (Prelone) with or without thalidomide are the best strategy for initial treatment, care should be taken under consideration in using Thalidomide due to its side effects such as neuropathy which is some time irreversible and venous thrombosis (*Rajkumar, 2005*) [3]. Occasionally, myeloma cells might cause bone to be soften, weaken, and even break. Drugs called bisphosphonates are given intravenously such as pamidronate (Aredia®) and zoledronic acid (Zometa®) can help bones stay strong by slowing down this process. Although, bisphosphonates have great importance in preventing further bone dissolving, it has a rare but serious side effects called osteonecrosis of the Jaw (ONJ) and loss of teeth in that area.

Radiotherapy

This type of treatment uses high energy x-ray or particles that enter tissues of body and terminate myeloma cells, particularly in bones that have not respond to chemotherapy and plasmacytomas. In external beam radiation therapy, the radiation is aimed at the cancer from a machine outside the body and is the most common type of radiation therapy most often used to treat multiple myeloma or solitary plasmacytoma. Radiotherapy is like diagnostic therapy with exception to time of exposure in each. The course for treatment is longer and may continue for several weeks.

Biologic therapies

Biologic therapy are proteins that are normally found in blood used to prevent body form infection even cancer. Some white blood cells and bone marrow cells release a hormone like substance known as Interferon that can decrease the growth of myeloma cells when given as a drug. In patients who have been treated with chemotherapy, Interferon given can lead to myeloma remission. Erythropoietin is another biologic therapy given for anaemia correction by reducing the need of blood transfusion in patients who are receiving chemotherapy.

But the FDA advises that in some patients with MM, this drug leads to decreasing the survival rates and cancers re-growing when they use this type of drug.

Surgical treatment for MM

Even though surgery is occasionally used to remove single plasmacytomas, it is hardly used in treating MM. but in emergency situations such as spinal cord compression that cause paralysis, severe muscle weakness, or numbness, surgery may be necessary also in elective surgery to support weakened bones metal rods or plates can be used to prevent fractures (*Barlogie et al. 2004*) [6].

Current research of MM

Studies have been done around the world each year in many medical centres, universities, and other institutions to improve the way of treatment and how to find the cause of MM. Recently; researchers have found that support tissue (stromal cells) is a precursor for interleukin-6 production which is a strong growth factor for MM, and ultimately cause bone dissolving and destruction. Some studies efforts are dedicated on emerging techniques to block the function of IL-6. Moreover, RANKL which is another growth factor has been found that enhance cells responsible for dissolving of bones. Amount of RANKL in bone marrow of people with MM observes to be made larger than normal. Drug named *denosumab* was studied in patients with MM to block RANKL but later on they found that patients treated with *denosumab* are more likely to die than patients used bisphosphonates for treatment. Another improvement in finding suitable treatment is using a form of arsenic or arsenic trioxide for treatment of MM with farnesyl transferase that blocks an important molecule in tumor growth and drugs that block growth of blood vessels has been studied. Improving transplants have been concentrated by researchers as a treatment strategy in individuals with MM. Recent approach is to follow an autologous (self) transplant with an allogeneic one (donor). Currently, outcomes have been mixed, and more studies are required. In the last several years a completely new test called *gene expression profiling* has developed. By this test we can know when the patients with MM will need chemotherapy treatment (Smith, 2005) [18].

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