MULTIPLE MYELOMA AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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Submitted for the degree of Master of Medicine (in the specialty of Internal Medicine) to the University of the Witwatersrand

ETHICS COMMITTEE APPROVAL

This work was approved by the Human Research Ethics Committee (Medical), University of the Witwatersrand (Clearance Certificate M110502). Please see the appendix to the research document for a copy of the certificate.

DECLARATION

I declare that this thesis is my own unaided work. It is being submitted for the degree of Master of Medicine (in the speciality of Internal Medicine) to the University of the Witwatersrand. This work has not been submitted previously at this or any other University.

I am aware that plagiarism is a serious offense, tantamount to fraud. I have not passed off another author or entity's work, ideas or words as my own; I have not misrepresented my findings as novel or original if there is an existing source; and I have referenced my work appropriately. Please see the appendix to the research document for a copy of the certificate.

Signed_____

18 October 2016

DEDICATION

To my wife, daughter and son

ABSTRACT

Background and aims

Worldwide, multiple myeloma accounts for 0.8% of all cancers diagnosed, with a variable incidence (Alexander, 2007). In South Africa, in 2009, amongst haematological malignancies, multiple myeloma was the fourth most common in males and the third most common in females (Cancer in South Africa, 2009 National Cancer Registry). Yet, there is a paucity of data regarding multiple myeloma in South Africa with few descriptive studies and case reports (Blattner, et al., 1979; du Preez and Branca, 1991; Patel, 2000; Feller, et al., 2009; Webb, et al., 2013).

South Africa has a very high prevalence of human immunodeficiency virus (HIV) infection. In 2010, it was estimated that 5.24 million people in South Africa were HIV-seropositive, with a prevalence rate in the population of 10.5% (Statistics South Africa, 2010). Studies have shown that in HIV-seropositive patients, multiple myeloma occurs at an increased rate, at a younger age and with atypical features e.g. extramedullary plasmacytomas in unusual sites (Cheung, et al., 2005; Grulich, et al., 2007). However, in South Africa, no association between HIV infection and multiple myeloma has been shown (Sitas, et al., 2000; Stein, et al., 2008).

This study describes the demographic, clinical, laboratory and radiological findings of patients presenting with multiple myeloma at a large tertiary hospital in South Africa. In addition it describes the therapy, response to therapy, and survival of these patients. Furthermore, it also describes and compares multiple myeloma in HIV-seropositive and HIV-seronegative patients.

Patients and methods

This retrospective analysis included patients diagnosed with multiple myeloma from 1 January 1998 – 31 December 2010 (13 years). With respect to outcomes the study was concluded on 31 December 2011. Data was processed in Microsoft Excel 2010. Demographic, clinical, laboratory and radiological findings at presentation were documented. Therapy and responses to therapy were noted. Outcomes for the different first-line treatments were contrasted: ANOVA analysis was used to compare progression free survival and Kaplan-Meier survival curves were used to compare overall survival. HIV-seropositive patients were compared with HIV-seronegative patients at presentation: The Welch corrected unpaired t-test was used for continuous data and the Fisher exact test was used for categorical data. Kaplan-Meier survival curves with Chi^2 analysis compared overall survival between HIV-seropositive and HIV-seronegative patients.

Results

A total of 289 patients were included in this study, with 145 males and 144 females (male:female ratio 1:1). The median age at presentation was 58.0 years (range 26 – 86 years) and the peak frequency was in the 50 – 59 year age group i.e. the 6th decade (36.2%). The most frequent clinical features were bone pain (87.4%), constitutional symptoms (77.1%) and symptomatic anaemia (68.9%). Laboratory findings showed anaemia in 91.6% (median haemoglobin 8.8 g/dL), hypercalcaemia >2.75 mmol/L in 35.1% and creatinine >177 µmol/L in 32.0%. The IgG isotype was in seen in 55.0%, the IgA isotype in 19.0%, light chain disease was present in 19.0%, non-secretory multiple

myeloma in 2.4% and the subtype was not characterized in 4.5%. No cases of IgM, IgD or IgE multiple myeloma were recorded. Plasma cell leukaemia was noted in 2.8%. Monoclonal protein was detected in the serum in 93.1% (median 36.7 g/L) and in the urine in 87.6% (median 0.36 g/L). Immuneparesis was common and occurred in 87.9%. The median plasmacytosis in the bone marrow (corrected to assess only adequate smears) was 34.0%. Skeletal survey by radiograph showed lytic lesions in 79.2%, vertebral compression fractures in 43.1%, pathological fractures of the long bones in 14.2% and other fractures (e.g. pathological fractures of the pelvic bones) in 8.6%. The majority of patients presented with stage III disease (75.4%; using the Durie-Salmon criteria and 57%; using the International Staging System). Median overall survival for the 289 patients was 15.9 months. A high proportion of patients died within 3 months of presentation (47.3%) and significantly, 41.9% of patients were lost to follow-up.

With respect to first-line therapy progression free survival was significantly longer (p = <0.0001) for high dose chemotherapy followed by autologous stem cell transplant prior to any relapse (early ASCT) versus melphalan-prednisone (MP), as well as for early ASCT versus cyclophosphamide-vincristine-doxorubicin-high-dose dexamethasone (CVAD) alone. Kaplan-Meier survival curves showed a significant difference between the different first-line therapy groups (p = <0.0044), and the best survival curve was seen in the early ASCT group.

At presentation 6.2% were HIV-seropositive, with a median CD4 count of 313 cells/mm^3 and a median viral load of 19304 copies/mL. Significant findings in HIV-seropositive patients were a younger mean age (i.e. 44.7 years), a greater frequency of clinically evident plasmacytoma and a lesser frequency of immuneparesis. There was

no difference in the Kaplan-Meier survival curves of HIV-seropositive and HIV-seronegative patients (Chi^2 test of the curves p = 0.9073).

Conclusions

The peak frequency of patients diagnosed with multiple myeloma was in the 50 – 59 year age group (36.2%) and the number of males to females was nearly equivalent. The majority of patients presented with an advanced stage of disease (Salmon-Durie stage III or International Staging System stage III) and many died within 3 months of initial presentation. Recipients of early ASCT had a significantly better progression free survival and overall survival as compared to other first-line therapies. HIV-seropositive patients with multiple myeloma presented at a younger age with a higher rate of plasmacytoma and a lower frequency of immuneparesis. There was no difference in overall survival in HIV-seropositive versus HIV-seronegative patients. To the best of our knowledge, this is the largest descriptive study of multiple myeloma in sub-Saharan Africa. Moreover, this is also the largest descriptive study of patients in sub-Saharan Africa who were HIV-seropositive at the time of presenting with multiple myeloma.

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AL-amyloidosis	Light chain amyloidosis
ARV	Antiretroviral
ASCT	Autologous stem cell transplant
BMSC	Bone marrow stromal cells
CHBAH	Chris Hani Baragwanath Academic Hospital
CR	Complete response
CRP	C-reactive protein
CT	Computed tomography
CVAD	Cyclophosphamide-vincristine-doxorubicin-high-dose dexamethasone
ESR	Erythrocyte sedimentation rate
FISH	Fluorescent in-situ hybridization
HIV	Human immunodeficiency virus
IL	Interleukin
IMWG	International myeloma working group
MD	Melphalan-dexamethasone
MGUS	Monoclonal gammopathy of undetermined significance
MP	Melphalan-prednisone
M-Protein	Monoclonal protein
MRI	Magnetic resonance imaging
NCI	National Cancer Institute

OPG   Osteoprotegerin

PFS   Progression free survival

RANK   Receptor activator of NF-κB

RANKL   Rank ligand

VAD   Vincristine, doxorubicin, high-dose dexamethasone

VGPR   Very good partial response

CHAPTER 1: INTRODUCTION

Multiple myeloma is a haematological malignancy characterized by proliferation of monoclonal plasma cells in the bone marrow. These malignant plasma cells produce monoclonal immunoglobulin i.e. monoclonal protein (M-protein). Light and heavy chain M-protein can be detected in the blood and/or urine (Alexander, et al., 2007). In 3% of patients no M-protein is detected i.e. non-secretory multiple myeloma (The International Myeloma Working Group [IMWG], 2003).

Multiple myeloma is a plasma cell dyscrasia. Close attention is required to distinguish symptomatic multiple myeloma from monoclonal gammopathy of undetermined significance (MGUS), smouldering multiple myeloma, solitary plasmacytoma and other plasma cell disorders. The distinction between these entities is important as the management approach varies. This is perhaps best demonstrated in the management of MGUS where periodic monitoring rather than specific therapy remains the standard of care (van de Donck, et al., 2014).

1.1 DESCRIPTIVE EPIDEMIOLOGY

1.1.1 International demographics of multiple myeloma

Of all cancers diagnosed worldwide, multiple myeloma accounts for 0.8% and the incidence is variable. In the United States of America the age adjusted incidence rate is greater in males (7.1 per 100 000 person years) than in females (4.5 per 100 000 person years). Also, the age adjusted incidence rate is higher in people of African descent (11.1 per 100 000 person years) than in Caucasians (5.3 per 100 000 person years) (Alexander, et al., 2007).

1.1.2 South African demographics of multiple myeloma

In 2009, in South Africa, of new cancer cases diagnosed histologically, multiple myeloma accounted for 0.56% in males and 0.52% in females. The age standardized incidence rate was 0.88 per 100 000 person years in males and 0.71 per 100 000 person years in females. Ethnic variability is evident (see table 1.1). In 2009, amongst haematological malignancies, multiple myeloma was the fourth most common in males (after non-Hodgkin lymphoma, leukaemia and Hodgkin lymphoma) and the third most common in females (after non-Hodgkin lymphoma and leukaemia) (Cancer in South Africa, 2009 National Cancer Registry).

Table 1.1 Incidence of multiple myeloma in various ethnicities in South Africa in 2009

(Cancer in South Africa, 2009 National Cancer Registry)

Ethnic group	Percentage of all new cancers diagnosed histologically		Age standardized incidence rate per 100 000 person years	
	Male	Female	Male	Female
African	0.85	0.59	0.72	0.59
White	0.35	0.28	1.31	0.74
Indian/Asian	0.42	0.11	0.47	0.16
Coloured (mixed race)	0.46	1.03	0.93	1.76

1.2 PATHOPHYSIOLOGY

1.2.1 Cytogenetic changes and oncogenic processes

Recently there have been considerable advances in our understanding of how multiple myeloma develops. A model of multi-step progression with primary and secondary oncogenic processes is hypothesized (Bergsagel and Chesi, 2013). In nearly all cases the development of MGUS precedes the development of multiple myeloma. MGUS arises from an enhanced response to antigenic stimulation. Abnormally expressed Toll-like receptors and/or overexpressed interleukin (IL)-6 receptors induce a proliferative stimulus. This abnormal antigenic response in concert with primary cytogenetic transformation may lead to the development of multiple myeloma (Rajkumar, 2009). Primary oncogenic processes can be divided into two subtypes based on the nature of the chromosomal aberration. The first is hyperdiploid multiple myeloma with trisomy of one of chromosomes 3, 5, 7, 11, 15, 19 or 21. The second is non-hyperdiploid multiple myeloma with a variety of translocations all involving the immunoglobulin heavy chain locus on chromosome 14q32. Subsequent dysregulation of the cyclin D gene is considered a common denominator in disease development. Secondary oncogenic processes then hasten progress to symptomatic multiple myeloma. These secondary processes may include loss of chromosome 13, deletion of chromosome 17p, gain of chromosome 1q and loss of chromosome 1p, rearrangements of MYC, and activating mutations involving NF-κB, RAS, or BRAF (Rajkumar, 2009; Bergsagel and Chesi, 2013).

1.2.2 Pathogenesis of bone disease

The hallmark of multiple myeloma is the development of focal osteolytic lesions found in more than 80% of patients at diagnosis (Sanderson and Epstein, 2009). This occurs because bone-resorbing osteoclast activity is unrestrained and bone-forming osteoblast activity is suppressed.

The osteoclast arises from a haematopoietic monocyte precursor which expresses receptor activator of NF-κB (RANK) on its surface. RANK ligand (RANKL) binds with its kindred receptor RANK to promote osteoclast differentiation. Osteoclastogenesis is inhibited by soluble osteoprotegerin (OPG) which acts as a decoy receptor and binds to RANKL (Sanderson and Epstein, 2009). The osteoblast originates from a pool of mesenchymal stem cells in the bone marrow. Osteoblast differentiation is mediated by two important families of growth factors, namely the wnt proteins and the bone morphogenetic proteins. Several downstream stimulatory or inhibitory transcription factors also exert an important influence on osteoblast differentiation (Fakhry, et al., 2013).

Central to the pathogenesis of multiple myeloma is the ability of myeloma cells to bind to and cross talk with bone marrow stromal cells (BMSC). This process activates many pathways and elucidates many factors which confer a survival advantage to the myeloma cells (Munshi, et al., 2008). The interactions between myeloma cells and the BMSC lead to activation of osteoclastogenesis and inhibition of osteoblastogenesis. Multiple mechanisms are involved.   Firstly, osteoclast activity is promoted. Both

myeloma cells and BMSC in the microenvironment adjacent to the tumour cells elaborate a wide array of osteoclast-activating factors. Important osteoclast-activating factors include (but are not limited to) RANKL, inflammatory protein-1 alpha, IL-3 and stroma-derived factor-1 (Yaccoby, 2010). Many other osteoclast-activating factors have been described (Silvestris, et al., 2009). Secondly, it has been shown that myeloma cells may acquire the ability to directly resorb bone (Silvestris, et al., 2009). Thirdly, myeloma cells inhibit osteoblastogenesis by secreting inhibitors of wnt signaling. Two such inhibitors are dickkopf-1 and frizzled related protein-2 (Sanderson and Epstein, 2009); but more have been described (Yaccoby, 2010). Fourthly, the antagonistic effect of OPG on osteoclastogenesis is abrogated. In normal bone, as osteoblasts mature, production of RANKL decreases and production of OPG increases. In multiple myeloma, normal maturation of osteoblasts does not occur and thus the ratio of RANKL to OPG remains high (Yaccoby, 2010). Furthermore, the heparan sulfate proteoglycan syndecan-1 present on myeloma cell surfaces binds OPG (Sanderson and Epstein, 2009).

1.2.3 Risk factors

Many studies have sought to identify specific risk factors in the development of multiple myeloma. Accepted risk factors include increasing age, male gender, genetics, (ethnicity and family history) and MGUS. Possible risk factors include obesity, nutritional influences (low fish consumption and low green vegetable consumption) and some viral infections (herpes simplex virus and human immunodeficiency virus [HIV]) (Alexander, et al., 2007).

The agricultural environment is also a possible risk factor. In a large South African series a statistically significant increased risk was noted for farm work (odds ratio = 3.683; p = 0.00005) or time spent on a farm (odds ratio = 2.363; p = 0.0009) (Patel, 2000). However, the data regarding agricultural exposure is variable, ranging from studies showing no association to others showing a strong association (Alexander, et al. 2007). Moreover, a specific cause within the agricultural environment is yet to be identified.

1.3 PRESENTATION AND MANIFESTATIONS OF MULTIPLE MYELOMA

1.3.1 Bone disease

Other than the classic focal osteolytic lesion, there is also concomitant reduction in systemic bone mass resulting in osteopaenia and osteoporosis. Other important manifestations of myeloma bone disease are bone pain (the most common symptom), vertebral compression fractures, pathological fractures of the long bones and plasmacytoma of bone. Compression fracture and plasmacytoma may result in spinal cord compression (Patel, 2013).

1.3.2 Haematological manifestations

Anaemia is common in multiple myeloma and is found in more than 66% of patients at diagnosis (IMWG, 2003). There are many causes of anaemia in multiple myeloma. These include bone marrow infiltration, chronic renal disease, anaemia of inflammation (also known as anaemia of chronic disease); low erythropoietin levels (independent of renal failure) and shortened survival of red blood cell precursors (VanderWall, et al., 2013). Iatrogenic causes such as blood loss e.g. from non-steroidal anti-inflammatory drugs, and myelosuppression from chemotherapy and radiotherapy must also be considered (Patel, 2013).

Bleeding is a presenting feature in multiple myeloma. Reasons include thrombocytopaenia due to marrow infiltration by plasma cells, qualitative dysfunction from M-protein coating platelets, M-protein interfering with fibrin monomer

polymerization, autoantibodies directed against specific clotting factors and uraemia (Eby, 2009). Bleeding may also result from mechanisms related to light chain amyloidosis (AL-amyloidosis) e.g. liver disease, acquired factor deficiency or infiltration of the vessel wall (Seldin and Skinner, 2008). Furthermore, as indicated below, hyperviscosity is associated with bleeding (Park, et al., 2005). Iatrogenic factors e.g. procedures and toxicity from chemotherapy or radiotherapy must also be remembered (Eby, 2009).

Leucopaenia from marrow replacement or secondary to chemotherapy or radiotherapy may contribute to an increased risk of infection (Patel, 2013).

Serum viscosity is determined by the quantity and type of M-protein. It is further increased by rouleaux formation of red blood cells (Eby, 2009). Normal serum viscosity is 1.8 times that of water. At a level of 5 to 6 times that of water, symptoms of hyperviscosity may develop, with a triad of bleeding, visual disturbance and diverse neurologic manifestations (Park, et al., 2005).

1.3.3 Renal disease

Patients may present with acute kidney injury, chronic kidney disease, proteinuria and a proximal tubulopathy (Stompór, et al., 2012). The underlying pathological processes include myeloma cast nephropathy, direct tubular toxicity from light chains, indirect toxicity from lysosomal enzymes, AL-amyloidosis, monoclonal immunoglobulin deposition disease, cryoglobulinaemic glomerulonephritis and proliferative

glomerulonephritis (Korbet and Schwartz, 2006; Munshi et al., 2008). Furthermore hypercalcaemia, hyperviscosity and hyperuricaemia can cause renal dysfunction (Patel, 2013).

Light chains are normally filtered by the kidneys, reabsorbed and catabolized. In multiple myeloma the excessive light chains may precipitate in the tubules and cause mechanical obstruction. Thus cast nephropathy may develop. Additionally tubule damage results directly from light chain toxic effects as well as indirectly from lysosomal release induced by the light chains (Munshi, et al., 2008). Reversible precipitants are often present. It is therefore important to address dehydration, infections (especially urinary tract infections) and hypercalcaemia. Potentially nephrotoxic drugs e.g. nonsteroidal anti-inflammatories, aminoglycosides, contrast medium or bisphosphonates need to be carefully considered (Korbet and Schwartz, 2006).

Amyloid fibrils are derived from circulating light chains or light chain fragments. Deposition of these fibrils is initially in the mesangium of the glomeruli with later deposits extending into the subendothelium. These amyloid fibrils infiltrate and disrupt the integrity of the basal lamina. Thus, proteinuria (frequently in the nephrotic range) is the most common renal manifestation in AL-amyloidosis (Korbet and Schwartz, 2006).

Monoclonal immunoglobulin deposition disease develops when monoclonal light chains and/or heavy chains are deposited in the basement membranes of the glomeruli, tubules and blood vessels (Lin, et al., 2001). Initially it resembles minimal change

disease. Glomerulopathic light chains freely pass through the glomeruli and accumulate subendothelially in the glomerular basement membrane. This causes submicroscopic damage and albuminuria ensues. Subsequently mesangial cell proliferation develops and the picture is of a proliferative glomerulonephritis. Finally, nodular sclerosis of the glomeruli develops (Stompór, et al., 2012).

1.3.4 Hypercalcaemia

Several mechanisms contribute towards hypercalcaemia. Relative to osteoblast activity, osteoclast activity due to the production of osteoclast-activating factors is excessive, and favours bone resorption and calcium release (Munshi, et al, 2008). Tumour cells can secrete parathyroid hormone-related peptide which simulates the actions of parathyroid hormone (Kitazawa, et al., 2002). Finally, pseudohypercalcaemia is rare, but requires consideration. In this entity, ionized calcium levels are normal but total calcium is reported as high due to calcium binding to the abnormal immunoglobulin (Schwab, et al., 1995).

1.3.5 Infections

There are several reasons for an increased susceptibility to infections in multiple myeloma. These include defects in immune function (such as immuneparesis), associated end organ dysfunction e.g. renal failure, consequences of treatment e.g. mucositis and age-associated problems such as a decline in physiologic reserve and frailty (Nucci and Anaissie, 2009).

With respect to the immune system the primary problem is defective humoral immune function and reduced production of polyclonal immunoglobulin (Kalambokis, et al., 2009). This polyclonal hypogammaglobulinaemia, a reflection of B cell dysfunction, is associated with infection with encapsulated bacteria (Nucci and Anaissie, 2009). Other problems in the immune system which contribute to the increased risk of infection include quantitative and qualitative abnormalities of T cells and T cell subsets, natural killer cell dysfunction, abnormalities of dendritic cell function, neutrophil dysfunction aberrant cytokine production (Dasanu, 2012) and defective opsonisation (Kalambokis, et al., 2009). Infections may also occur in association with neutropaenia, induced by therapy.

1.3.6 Neurological manifestations

Multiple myeloma frequently involves both the central and peripheral nervous system. Dispenzieri and Kyle (2005) have summarized the neurological manifestations. Delirium may reflect metabolic derangements e.g. uraemia or hypercalcaemia. Peripheral neuropathy may result from AL-amyloidosis infiltration or it may be autoimmune or cytokine-related. Plasmacytoma may cause direct compression of adjacent structures e.g. spinal cord, base of skull, facial structures. Vertebral fractures may also result in spinal cord compression, whilst long bone fractures may cause peripheral nerve palsies.

1.3.7 Amyloidosis

Amyloidosis is a heterogeneous group of illnesses characterized by the interstitial deposition of insoluble amyloid protein fibrils in various organs and tissues. Any organ,

except the central nervous system may be affected in AL-amyloidosis; with the kidneys being most frequently involved. The diagnosis of AL-amyloidosis requires biopsy. Affinity for Congo red dye with a unique green birefringence of Congo red–stained material under polarized light is pathognomonic of amyloid fibrils (Seldin and Skinner, 2008). In AL-amyloidosis immunohistochemistry confirms the light chain nature of the precursor protein (Korbet and Schwartz, 2006).

1.3.8 Staging

In 1975 the Durie-Salmon system was introduced (Durie and Salmon, 1975) (see table 1.2). This system correlates tumour cell mass with clinical and laboratory findings that are of prognostic importance in multiple myeloma. These factors are the M-protein level in serum and urine, the haemoglobin level, the serum calcium level, the serum creatinine level and the severity of bone lesions.

Subsequently, serum β_2 microglobulin was determined to be the most powerful pretreatment prognostic factor in patients with multiple myeloma (Durie, et al., 1990). Thus, in 2005, the International Staging System was introduced utilizing serum β_2 microglobulin and serum albumin as parameters (Greipp, et al., 2005) (see table 1.3). This system uses objective data, does not rely on observer interpretation to determine the severity of bone disease and is easier to calculate (Hari, et al., 2009).

A criticism of both the Durie-Salmon system and the International Staging System is that both do not assist with therapeutic choices. Cytogenetic markers provide both

prognostic information and assist with treatment decisions. Based on cytogenetic findings a current approach is to classify patients as high risk, intermediate risk and standard risk disease and to then manage according to the risk stratification (Rajkumar, 2014).

Table 1.2 Durie-Salmon staging system

Stage 1: All of 1-5	
1. Haemoglobin:	>10 g/dL
2. Serum calcium:	Normal
3. Skeletal survey:	Normal or solitary plasmacytoma
4. Serum M-protein:	IgG <50 g/L; IgA <30 g/L
5. Urine M-protein:	<4 g/24hrs
Stage II: Neither stage I nor stage III	
Stage III: One or more of 1-5	
1. Haemoglobin:	<8.5 g/dL
2. Serum calcium:	>3 mmol/L
3. Skeletal survey:	3 or more lytic bone lesions or major fracture
4. Serum M-protein:	IgG >70 g/L; IgA >50 g/L
5. Urine M-protein:	>12 g/24hrs
Subclassification: A or B	
A. Serum Creatinine:	<177 µmol/L
B. Serum Creatinine:	>177 µmol/L
Final Durie-Salmon stage:	IA or IB or IIA or IIB or IIIA or IIIB

Table 1.3 <u>International Staging System</u>

Stage I: Both criteria to be fulfilled	
Serum β2-microglobulin:	<3.5 mg/L
Albumin:	≥35 g/L
Stage II: Neither stage I nor stage III	
Stage III	
Serum β2-microglobulin:	≥5.5 mg/L
Final International staging system:	Stage I or stage II or stage III

1.4 MANAGEMENT, TREATMENT AND SURVIVAL

1.4.1 Historical perspective in relation to therapy

In the 1960's melphalan was the first effective chemotherapeutic agent used in the treatment of multiple myeloma (Alexanian, et al., 1968). In the 1980's and 1990's high-dose chemotherapy with autologous stem cell transplant (ASCT) became the standard of care (Attal, et al., 1996; Lenhoff, et al., 2000). The last two decades have seen the introduction of novel agents targeting the bone marrow microenvironment i.e. immunomodulatory drugs and proteasome inhibitors (Munshi, 2008). Immunomodulatory agents include thalidomide, lenalidomide and more recently, pomalidomide. The proteasome inhibitors include bortezomib, carfilzomib and iaxazomib (Rajkumar, 2014; Ramasamy and Lonial, 2015). These novel agents have greatly improved response rates, depth of response and progression-free survival (Moreau, et al., 2015). Looking towards the future, promising new therapies are emerging (discussed later).

1.4.2 Survival

Prior to the introduction of alkylating agents e.g. melphalan, the overall survival of multiple myeloma was <1 year. Subsequently overall survival has been steadily increasing. At the Mayo clinic, median survival for those diagnosed in the period 1971 - 1996 was 29.9 months (Kyle and Rajkumar, 2009). A recent meta-analysis of 153 multiple myeloma trials published from 1970 – 2011 reported a median overall survival of 39.1 months (Félix, et al., 2013). With the addition of ASCT, a 12-month improvement

in overall survival has been demonstrated (Gertz and Dingli, 2014). And now, in the current era of novel agents, overall survival continues to increase. This has been demonstrated at the Mayo clinic where a median overall survival of 44.8 months has been reported for patients diagnosed after 1996 (Kyle and Rajkumar, 2009).

1.4.3 Management options

Management of multiple myeloma is complex and needs to be individualized. Factors such as adverse prognostic parameters, age, performance status, comorbidities, local resources, budget constraints, and personal preferences need to be considered (Patel, 2013).

In patients newly diagnosed with multiple myeloma it is necessary to identify those who are eligible for ASCT and those who are not. In general ASCT is considered in those who are willing to undergo the procedure, are <65 - 70 years of age, have no significant comorbidities and do not have a poor performance status (Moreau, et al., 2015).

1.4.4 Patients eligible for autologous stem cell transplant

Despite the significant improvements in response obtained by the novel agents, the addition of ASCT remains the standard of care in patients newly diagnosed with multiple myeloma (Gertz and Dingli, 2014; Ramasamy and Lonial, 2015).

In order to reduce tumour cell mass, induction chemotherapy is administered prior to the mobilization of stem cells. For many years the combination of vincristine, doxorubicin

and high-dose dexamethasone (VAD) had been used for this purpose (Rajkumar, 2009). Some institutions add cyclophosphamide as a fourth drug (CVAD).   Of these agents, dexamethasone is considered the most efficacious and is sometimes administered alone (Morgan and Davies, 2005). There are some limitations when using VAD and CVAD. Firstly, vincristine may cause peripheral neuropathy. This may hinder the future use of thalidomide and bortezomib as these two agents are also neurotoxic. Secondly, intravenous administration over 4 days is required, with associated complications. Thirdly, VAD and CVAD have shown inferior responses as compared to novel agents that have been introduced recently (Rajkumar, 2009; Moreau et al., 2015).

In settings where there are few resource constraints numerous induction regimens are available. These include, but are not limited to, thalidomide-dexamethasone (in countries where lenalidomide is not available), lenalidomide-low dose dexamethasone, bortezomib-thalidomide-dexamethasone, bortezomib-lenalidomide-dexamethasone and bortezomib-cyclophosphamide-dexamethasone (Rajkumar, 2014). In the current era, ideally induction therapy should be a triple regimen consisting of a proteasome inhibitor, an immunomodulatory drug and a corticosteroid (Ramasamy and Lonial, 2015).

The usual practice is for patients to receive 2 – 4 cycles of induction therapy after which stem cell harvest is done. Patients then either undergo ASCT as an early consolidation intervention, or induction therapy is continued and ASCT is deferred until relapse (Rajkumar, 2014).

Maintenance treatment has been considered as a mechanism to control the proliferation of residual malignant cells following high-dose chemotherapy and ASCT. Thalidomide after high-dose chemotherapy improves the response rate, event-free survival and overall survival (Attal, et al., 2006). Lenalidomide after ASCT improves progression-free and event-free survival but not overall survival (Attal, et al., 2012). These results have prompted a developing trend to administer maintenance therapy after ASCT. Either an immunomodulatory agent (thalidomide or lenalidomide) or a proteasome inhibitor (bortezomib) is acceptable (Gertz and Dingli, 2014).

1.4.5 Patients not eligible for autologous stem cell transplant

In patients not eligible for ASCT the aim is to administer therapy until disease plateau is reached (Kyle and Rajkumar, 2004). Disease plateau is characterized by a lack of overt clinical symptoms and stable M-protein levels (Morgan and Davies, 2005). Melphalan-prednisone (MP) or melphalan-dexamethasone (MD) has been the standard for several decades and remains a useful regimen. However, MP plus thalidomide is superior to MP (Palumbo, et al., 2006). Similarly, MP plus bortezomib has a better overall survival as compared to MP (Rajkumar, 2014). Thus, the addition of novel agents is preferable to the standard MP (Patel, 2013). Current options for patients newly diagnosed with multiple myeloma but not eligible for ASCT include, but are not limited to, MP, MP plus thalidomide, lenalidomide-low dose dexamethasone, MP plus bortezomib and dexamethasone plus bortezomib (Rajkumar, 2014).

1.4.6 Disease relapse

Almost all patients relapse and strategies to manage disease relapse vary. Consideration should be given to utilizing the very same armamentarium of modalities that are useful as first-line therapy. There are some useful principles in treating disease relapse. Firstly, if relapse occurs >6 months after stopping treatment then the very same regimen used upfront can be recycled. Secondly, treatment of relapsed disease is often extended until further relapse or drug toxicity occurs. Thirdly, an indolent relapse is often adequately treated with MP or other single agents e.g. thalidomide. Fourthly, as mentioned, ASCT can be deferred and utilized successfully as salvage therapy (generally at first relapse) (Rajkumar, 2009, 2014).

1.4.7 Emerging therapies

Several new therapies are presently being investigated. Ramasamy and Lonial (2015) give a good overview of these advances, summarized below. With respect to proteasome inhibitors, ixazomib, with greater biological activity than botezomib, is in phase 3 development; with promising initial results. Oprozomib, a derivative of carfilzomib, is being examined in phase 1 and phase 2 trials. Histone deacetylase inhibitors induce apoptosis and inhibit cell growth. Two histone deacetylase inhibitors, namely vorinostat and panobinostat, are being evaluated in patients with relapsed and refractory multiple myeloma. New monoclonal antibodies are being developed. Elotuzumab, a humanized monoclonal antibody, mediates antibody-dependent cell-mediated cytotoxicity by targeting the cell surface glycoprotein CS1 in myeloma cells. Daratumumab, also a humanized monoclonal antibody, targets CD38-expressing

plasma cells and promotes antibody-dependent cellular phagocytosis, complement-dependent cytotoxicity and apoptosis. Cellular-based therapies such as dendritic cell vaccines, chimeric antigen receptor-based technology and natural killer-based cellular infusions are also under investigation.

1.4.8 Radiation therapy

Radiation therapy in used in the management of multiple myeloma to treat plasmacytoma, spinal cord compression, large painful lytic lesions, impending fractures and post-fracture pain (Talamo, et al., 2015).

1.4.9 Surgical intervention

Involvement of a surgeon is often required, particularly in obtaining a tissue specimen to assist with diagnosis and in the management of skeletal related events. Frequently performed procedures include incision or excision biopsy, open reduction and internal fixation for pathological fractures and decompression laminectomy for spinal cord compression (Patel, 2013).

1.5 CONTEXT TO THE CURRENT STUDY

1.5.1 Multiple myeloma in sub-Saharan Africa

Multiple myeloma in sub-Saharan Africa has not been well described. Gopal and colleagues (2012) highlight the tremendous challenges involved in the diagnosis and management of haematologic malignancies in this region. For example, in 2006, data covering only 11% of Africa was reported to cancer registries. Likewise, only 3 countries forward statistics to the World Health Organization mortality registry. Similarly resources are scarce. In 2008, 9.9% of cancer deaths were as a result of non-Hodgkin lymphoma, Hodgkin lymphoma, leukaemia and multiple myeloma. Yet, haematopoeietic stem cell transplant is available at only 6 institutions in South Africa. Furthermore, 21 sub-Saharan countries have no radiotherapy units (Gopal, et al., 2012).

A limited number of studies on multiple myeloma have been completed in sub-Saharan Africa. Some case series from Nigeria in west Africa have been published. Madu, et al., (2014) reported on 32 cases from 2002 – 2012; Omoti and Omuemu (2007) reported on 30 cases from 1993 – 2003; and Salawu and Durosinmi (2005) reported on 27 patients from 1986 – 2001. In east Africa Mukiibi and Kyobe (1988) described multiple myeloma in Kenya; whilst Shamebo and Tekle-Haimanot (1992) reported on 22 cases from 1983 – 1990 in Ethiopia. In southern Africa Mukiibi and Mkwananzi (1987) looked at multiple myeloma in Zimbabwe. In South Africa Blattner, et al., (1979) described multiple myeloma in a series from 1973 – 1975. Patel (2000), reported on 170 patients from

1992 – 1997. There are also case reports from South Africa (du Preez and Branca, 1991; Webb, et al., 2013).

1.5.2 Human immunodeficiency virus and multiple myeloma

Multiple myeloma is not considered an acquired immunodeficiency syndrome defining malignancy. Nevertheless, in a large meta-analysis, in those infected with HIV, multiple myeloma occurred at an increased rate with a standardised incidence ratio of 2.71 (Grulich, et al., 2007). Furthermore, in HIV-seropositive patients, multiple myeloma presents at a younger age and may be associated with atypical features e.g. extramedullary plasmacytomas in unusual sites (Cheung, et al., 2005).

Sub-Saharan Africa has the highest regional prevalence of HIV infection. Worldwide 34 million people are infected, with 68% of those affected living in sub-Saharan Africa (Gopal, et al., 2012). In South Africa, in 2010, it was estimated that 5.24 million people were HIV-seropositive with a prevalence rate in the population of 10.5% (Statistics South Africa, 2010). Despite this high prevalence of HIV infection both Sitas, et al., (2000) and Stein, et al., (2008) failed to show an association between HIV infection and multiple myeloma in South Africa. Similarly, in a report on HIV-related cancers in Zimbabwe from 1990 - 1995, the incidence of multiple myeloma does not appear to have increased significantly (Chokunonga, et al., 1999).

1.5.3 Study aims

The aims of the study were:

1. To describe the demographic, clinical, laboratory and radiological findings of patients presenting with multiple myeloma at a large tertiary hospital in Gauteng, South Africa.

2. To describe the therapy, response to therapy, prognosis and survival of these patients.

3. To describe multiple myeloma in HIV-seropositive patients and to compare these findings with HIV-seronegative patients.

CHAPTER 2: PATIENTS AND METHODS

2.1 PATIENTS

This study was a single center retrospective analysis conducted in the Division of Clinical Haematology, Department of Internal Medicine, at Chris Hani Baragwanath Academic Hospital (CHBAH), which is located in Soweto, Johannesburg, South Africa. The hospital is a public sector institution affiliated to the University of the Witwatersrand. Using the register kept by the division, 351 consecutive patients were identified where a diagnosis of multiple myeloma had been initially documented during the period 1 January 1998 – 31 December 2010. Documents relating to these patients were retrieved from the archives at the Division of Clinical Haematology, the hospital archives, the National Health Laboratory Service computer records and, where relevant and logistically possible, the archives at institutions from whence patients had been referred.

2.1.1 Exclusion criteria

Patients were excluded if their files could not be located, if the information contained in their files was insufficient to prove multiple myeloma, or if the final diagnosis was a plasma cell dyscrasia other than multiple myeloma (see table 2.1). During the period when this research was conducted the Division of Clinical Haematology relocated to new premises and several files were lost.

Table 2.1 <u>Patients excluded</u>

Reason for exclusion	Number
Files not found	<u>38</u>
Insufficient evidence to prove multiple myeloma	<u>6</u>
o Provisional diagnosis made elsewhere with inadequate documentation upon transfer to Chris Hani Baragwanath Academic Hospital	3
o Insufficient evidence to prove multiple myeloma	2
o Patient refused diagnostic investigations	1
Plasma cell dyscrasia other than multiple myeloma	<u>18</u>
o Monoclonal gammopathy of uncertain significance	4
o Solitary plasmacytoma	14
Total exclusions	<u>62</u>

2.1.2 Inclusion Criteria

Patients with a diagnosis of multiple myeloma were included. The current (2014) diagnostic criteria stipulate that for a diagnosis of multiple myeloma to be made, bone marrow findings need to demonstrate ≥10% clonal plasma cells (Rajkumar, 2016) (see table 2.2) However, repeat sampling of the bone marrow may be required as involvement may be focal rather than diffuse (Kyle and Rajkumar, 2009). At our institution bone marrow aspirate and trephine biopsy is performed by a range of doctors, ranging from interns to consultant haematologists. Thus, the quality of the specimen is variable. Furthermore, repeat sampling is not always done. Therefore, in this study, criteria as adopted by the IMWG (2003) were used (see table 2.3). These criteria stipulate no minimum bone marrow plasmacytosis and only require proof of clonality. The National Cancer Institute (NCI) criteria allows for a diagnosis of multiple myeloma

to be made in the absence of a histological specimen. Thus, if the IMWG criteria (2003) were not met, NCI criteria were utilized (Committee of Chronic Leukemia-Myeloma Task Force, 1973) (see table 2.4). Finally, an expert in the field of multiple myeloma (a senior clinical haematologist) was consulted if neither IMWG criteria (2003) nor NCI criteria (1973) were fulfilled, but the diagnosis of multiple myeloma remained the most likely on the basis of strong supporting evidence.

Table 2.2 International Myeloma Working Group criteria (2014)

Both criteria must be met
1. Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma

2. Any one or more of the following myeloma defining events
 	
o Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically
 	
  ▪ Bone lesions: One or more osteolytic lesions on skeletal radiography, computed tomography, or positron emission tomography-computed tomography
 	
  ▪ Anemia: Haemoglobin value of >2 g/dL below the lower limit of normal, or a hemoglobin value <10 g/dL
 	
  ▪ Renal insufficiency: Creatinine clearance <40 mL/minute or serum creatinine >177 µmol/L
 	
  ▪ Hypercalcemia: Serum calcium >0.25 mmol/L higher than the upper limit of normal or >2.75 mmol/L
 	
o Clonal bone marrow plasma cell percentage ≥60%
 	
o Involved: Uninvolved serum free light chain ratio ≥100 (involved free light chain level must be ≥100 mg/L)
 	
o >1 focal lesions on magnetic resonance imaging studies (at least 5 mm in size)

Table 2.3 <u>International Myeloma Working Group criteria (2003)</u>

All three criteria must be met
1. Clonal bone marrow plasma cells or plasmacytoma
2. Monoclonal protein in serum and/or urine (except in true non-secretory multiple myeloma)
3. Related organ or tissue impairment   Bone disease: Lytic lesions or severe osteopaenia/osteoporosis or compression fractures or other pathologic fractures   Anaemia: Normochromic, normocytic with haemoglobin >2 g/dL below the lower limit of normal or haemoglobin <10 g/dL   Renal insufficiency: Creatinine >177 μmol/L   Hypercalcaemia: Serum calcium >0.25 mmol/L above the upper limit of normal or >2.75 mmol/L   Other: Symptomatic hyperviscosity   Amyloidosis   Recurrent bacterial infections (>2 episodes in 12 months)

Table 2.4 <u>National Cancer Institute criteria (1973)</u>

Major criteria
(1) Plasmacytoma on tissue biopsy
(2) Bone marrow plasma cells >30%
(3) Monoclonal peak in serum IgG >35 g/L or IgA >20 g/L; urine light chain >1 g/24 hours
Minor criteria
a. Bone marrow plasma cells 10 – 30%
b. Monoclonal peak less than the level defined above
c. Lytic bone lesions
d. Normal IgM <0.5 g/L, IgA <1g/L, IgG <6g/L
Diagnosis: A minimum of 2 major criteria, or 1 major criterion plus 1 minor criterion, or 3 minor criteria that include a and b   Thus: o   I + b or c or d   o   II + b or c or d   o   III + a or c or d   o   a + b + c or a + b + d

The IMWG criteria (2003) were fulfilled by 274 patients. A further 9 patients fulfilled NCI criteria (1973). And, after expert opinion from a senior clinical haematologist, an additional 6 patients with strong supporting evidence were included (see table 2.5).

It was deemed important that cases worthy of inclusion were not excluded on technical grounds. The following example highlights the reason for including 6 patients on the basis of expert opinion. One patient identified in the archives had a biopsy-proven plasmacytoma, a suboptimal specimen submitted for bone marrow aspirate and

trephine biopsy, a baseline M-protein component that was not traceable in the records, no serum free light chain assessment (this test had not yet been introduced at the laboratory) and no evidence of related end organ damage. Consequently, neither the IMWG criteria (2003) nor the NCI criteria (1973) were fulfilled. However, the patient had a magnetic resonance imaging pathognomonic for multiple myeloma and was therefore included in the series. It is worth noting that inclusion of this patient is consistent with the latest iteration of diagnostic criteria as delineated by the IMWG (2014). However, these criteria were introduced when the present study was already far advanced.

Table 2.5 Patients included

Patients included	Number
Inclusion by IMWG criteria for symptomatic multiple myeloma	274
o Secretory multiple myeloma	267
o Non-secretory multiple myeloma	7
IMWG criteria not fulfilled but inclusion by NCI criteria	9
o Bone marrow findings not documented	6
o Technically inadequate specimens submitted to laboratory	3
IMWG criteria and NCI criteria not fulfilled but multiple myeloma most likely diagnosis (expert opinion with strong supporting evidence)	6
Total included	289

IMWG = International Myeloma Working Group; NCI = National Cancer Institute

2.2 METHODS

All descriptive data was processed in Microsoft Excel 2010.

2.2.1 Presentation and manifestations of multiple myeloma

For patients admitted to the wards presentation was defined as the first day of the admission at which the diagnosis of multiple myeloma was confirmed. For outpatients presentation was defined as the day on which the patient first attended the haematology clinic. Demographic, clinical, laboratory and radiological findings at presentation were documented. Data at presentation prior to the initiation of any supportive therapies (e.g. fluid replenishment, transfusion with blood products, haemodialysis etc.) or specific therapies (e.g. chemotherapy) was recorded. Patients were staged according to the Durie-Salmon staging system (see table 1.2) and the International Staging System (see table 1.3).

2.2.2 Therapy, therapeutic responses and survival

The study was concluded as of 31 December 2011. Patients were classified as alive, dead or lost to follow-up. A patient was considered lost to follow-up if in the preceding 12 months there was no record of an admission or a visit to the haematology clinic. Overall survival was described using the Kaplan-Meier survival curve.

Therapies administered during the course of disease were described. First-line therapy was the regimen administered after diagnosis. Therapy for disease relapse was the

regimen administered after first relapse and for any further relapses. If a patient received a modality more than once (i.e. the regimen was recycled) then only the outcome of the first exposure was documented. Maintenance therapy was not considered.

With respect to the therapies utilized:

1. Melphalan-prednisone (MP) and melphalan-dexamethasone (MD): These two similar regimens were grouped together and designated as MP.

2. Cyclophosphamide (C), vincristine (V), doxorubicin (A) and dexamethasone (D): The standard regimen utilized was CVAD. Occasionally, because of concerns regarding toxicity in an individual patient, an agent was omitted from the CVAD regimen. Thus, during first-line therapy 2 patients received VAD, 4 patients received CAD and 1 patient received CD. During therapy for disease relapse 1 patient received VAD. Patients who received VAD, CAD and CD were included in the larger group of patients who received CVAD.

3. Autologous stem cell transplant (ASCT): CHBAH is an institution where ASCT is performed. Early ASCT was a transplant performed after first-line therapy had been administered and prior to relapse. Late ASCT was a transplant performed at first relapse, or at any other subsequent relapse.

4. Thalidomide: This agent was used in a small group of patients with disease relapse, or generally as part of a clinical trial. In the last 5 years many more patients have been treated with thalidomide, but these patients are not included in the current review.

Criteria specifying therapeutic responses in multiple myeloma have been published (Durie, et al., 2006). These criteria required adaptation for this present study for the following reasons. Firstly, serum free light chains were not measured in patients until 2009. Secondly, bone marrow sampling was not routinely done at the end of a cycle of therapy. Thirdly, the urine M-protein was tested for by means of spot samples and not 24 hour collections.

Depth of response was described by complete response (CR) and very good partial response (VGPR).

CR was defined as:

(1) Negative immunofixation on the serum and urine and

(2) Disappearance of soft tissue plasmacytomas

VGPR was defined as:

(1) A detectable M-protein on serum and urine immunofixation but not on electrophoresis or

(2) ≥90% reduction in serum M-protein plus urine M-protein <100 mg/L

Disease progression was defined as:

(1) An increase in serum M-protein by 25% from the lowest response value with an absolute increase ≥5 g/L and/or

(2) An increase in spot urine M-protein by 25% from the lowest response value with absolute increase ≥200 mg/L and/or

(3) The development of new bone lesions or plasmacytoma

Progression free survival (PFS) was defined as the duration from the start of treatment to disease progression or death (regardless of cause of death), whichever came first.

PFS is the recommended method to report findings and is considered a proxy for overall survival duration (Durie, et al., 2006). Moreover, CR is considered a surrogate marker for PFS (Gertz and Dingli, 2014). Thus PFS and CR were the parameters of focus in this study.

Outcomes for the different first-line treatments were contrasted. ANOVA analysis was used to compare PFS, whilst Kaplan-Meier survival curves compared overall survival. It was not possible to compare the depth of response. This was because too few patients achieved CR or VGPR, and too few patients underwent ASCT.

It was also not possible to directly compare outcomes for regimens used in treating disease relapse. Reasons for this are discussed in the next chapter.

2.2.3 Human immunodeficiency virus-seropositive patients

Demographic, clinical, laboratory and radiological findings in HIV-seropositive patients at presentation were compared with HIV-seronegative patients. For continuous data, the

Welch corrected unpaired t-test was used. For categorical data, the Fisher exact test was used. Kaplan-Meier survival curves with Chi^2 analysis compared overall survival in the two groups.

CHAPTER 3: RESULTS

3.1 DEMOGRAPHIC FINDINGS

A total of 289 patients were included in this study. They were seen during the period 1 January 1998 to 31 December 2010 (13 years). There were 145 males and 144 females, with a male to female ratio of 1:1. Age was not documented for 2 patients. The median age at presentation was 58.0 years (range 26 – 86 years). The median age of the males was 56.5 years and the median age of the females was 59.0 years. The peak frequency was in the 50 – 59 year age group i.e. the 6th decade (36.2%), followed by the 60 – 69 year age group i.e. the 7th decade (28.6%) (see figure 3.1).
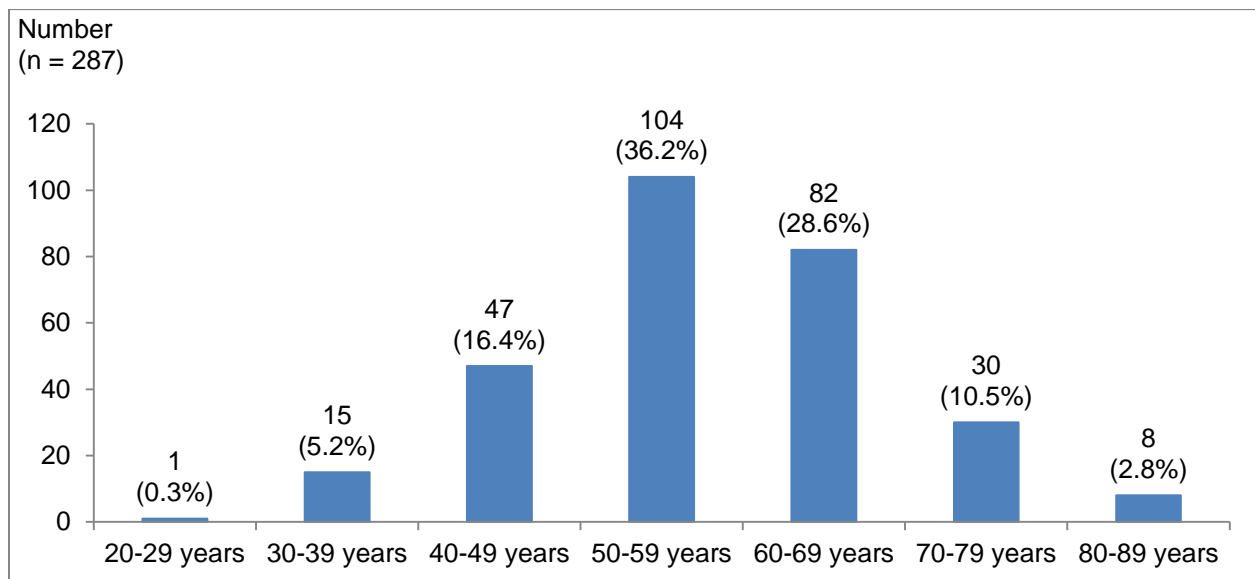
Figure 3.1 <u>Age by decade at presentation</u>

With respect to race 272/289 patients (94.1%) were African, 7/289 patients (2.4%) were White, 6/289 patients (2.1%) were Indian/Asian and 4/289 patients (1.4%) were Coloured (mixed race).

The number of patients presenting per year is represented in figure 3.2. Over the duration of the study there was a general upward trend in the patient numbers per year.
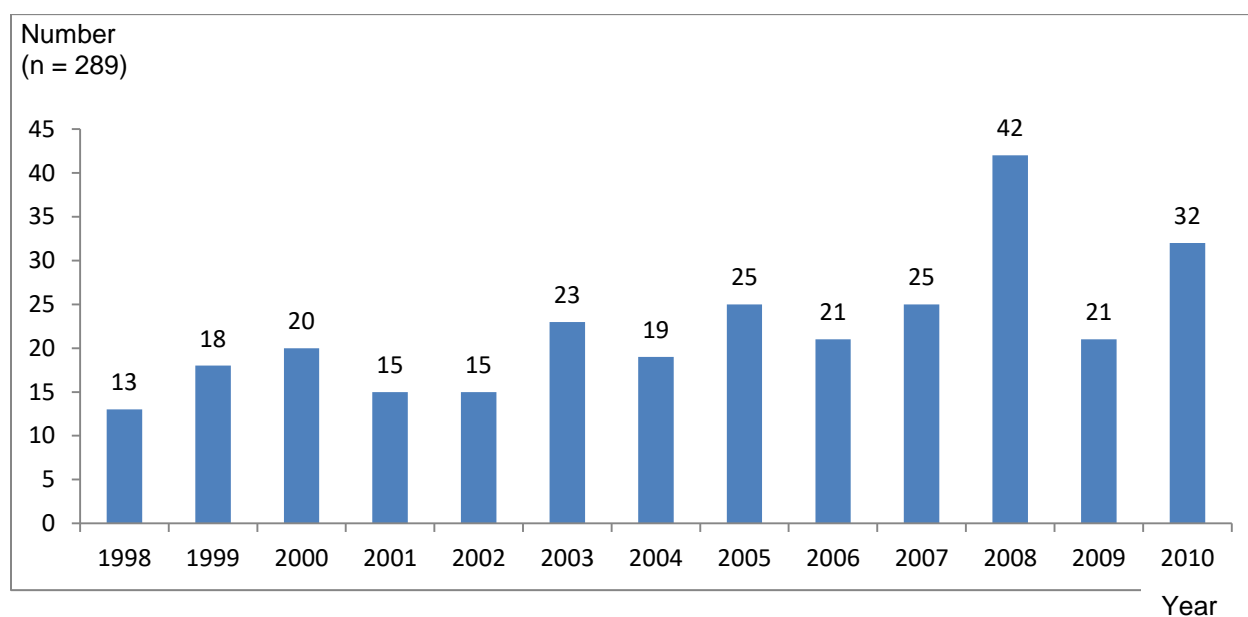
Figure 3.2 Number of patients diagnosed per year of study

Many patients resided far away. In 46/185 patients (24.9%) the address given by the patient was >50 km away from CHBAH.

3.2 CLINICAL FINDINGS

Common clinical features at presentation are shown in table 3.1 and depicted in Figure 3.3. Bone pain (87.4%), constitutional symptoms (77.1%) and symptomatic anaemia (68.9%) were the 3 most frequent presenting features.

Table 3.1 Common clinical features at presentation

Symptom or sign present	Number (n)	Percentage
Bone pain	242 (277)	87.4
Vertebral compression	105 (272)	38.6
Pathological fractures	47 (269)	17.5
Symptoms of anaemia	188 (273)	68.9
Bleeding	43 (271)	15.9
Hyperviscosity	59 (273)	21.6
Renal failure	63 (269)	23.4
Hypercalcaemia	51 (269)	19
Infection	72 (271)	26.6
Paraparesis	67 (271)	24.7
Radiculopathy or peripheral neuropathy	32 (269)	11.9
Clinically apparent plasmacytoma	49 (269)	18.2
Constitutional symptoms	209 (271)	77.1
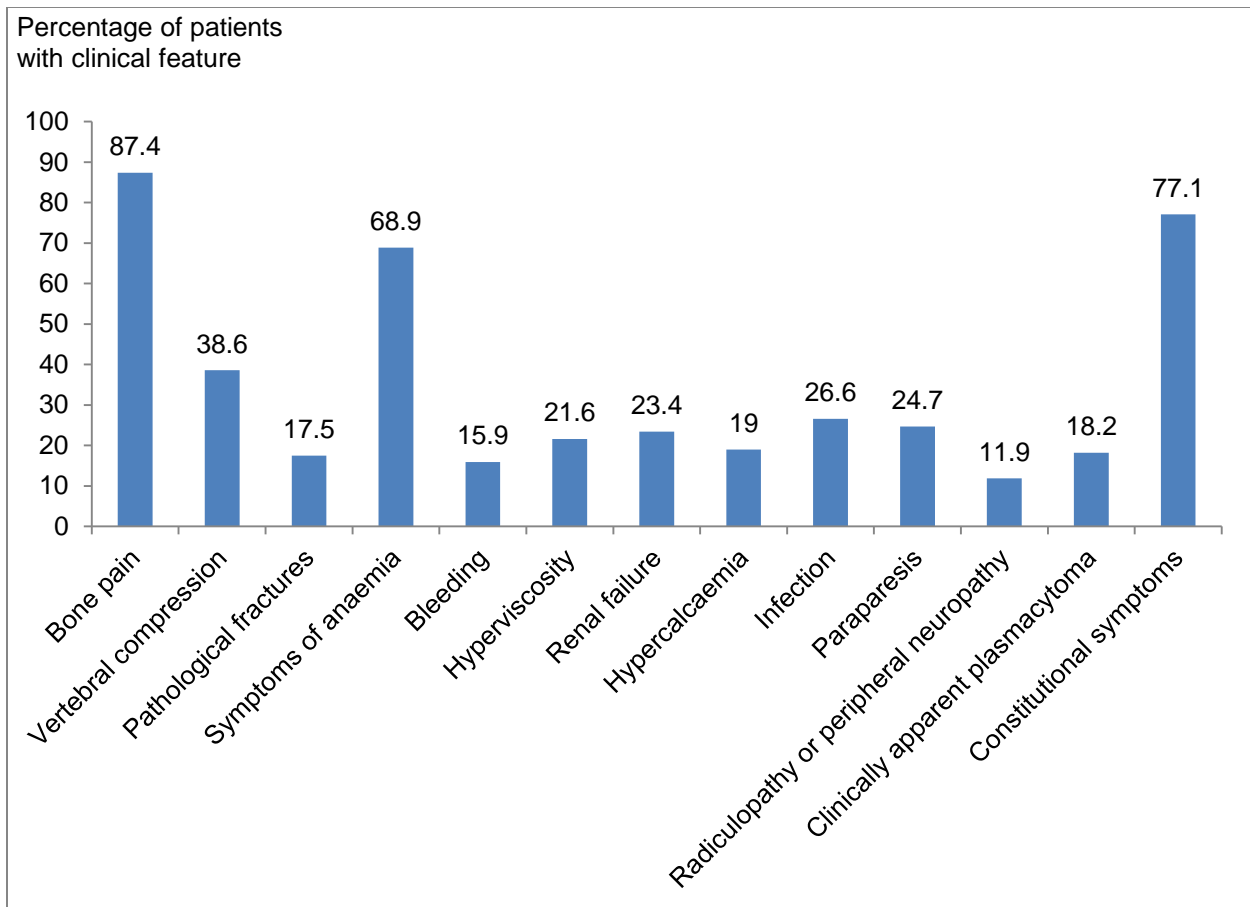
Figure 3.3 <u>Common clinical features at presentation</u>

3.3 LABORATORY FINDINGS

3.3.1 Haematological findings

Relevant haematological findings at presentation are documented in table 3.2. The median haemoglobin (Hb) was 8.8 g/dL. Anaemia, defined as Hb <13 g/dL for males and <12 g/dL for females, was more common in males (95.2%) than in females (87.9%). In total, anaemia was seen in 262/286 patients (91.6%). Severe anaemia (World Health Organization grade 3) (Hb <8 g/dL) was present 103/286 patients (36.0%). Less males (49/145 patients; 33.8%) than females (54/141 patients; 38.3%) had severe anaemia. Leucopaenia (20/285 patients; 7%) and thrombocytopaenia (27/285 patients; 9.5%) were not common findings. Similarly, leukocytosis (32/285 patients; 11.2%) and thrombocytosis (15/285 patients 5.3%) were seldom noted. Neutropaenia was also an infrequent occurrence (5/186 patients; 2.7%). The erythrocyte sedimentation rate (ESR) was greater than 100 mm/hour in 101/182 patients (55.5%). Rouleaux formation was present in 191/252 patients (75.8%).

Table 3.2 <u>Relevant haematological findings at presentation</u>

Laboratory parameter	Number (n)	Percentage	Median	Range
Haemoglobin (g/dL)			8.8	2.8 – 15.6
Total anaemic	262 (286)	91.6		
Males <13 g/dL	138 (145)	95.2		
Females <12 g/dL	124 (141)	87.9		
Severe anaemia (<8 g/dL)	103 (286)	36.0		
Males <8.0 g/dL	49 (145)	33.8		
Females <8.0 g/dL	54 (141)	38.3		
White cell count (x 10^9/L)			6.5	2.7 – 45.9
<4 x 10^9/L	20 (285)	7		
>11 x 10^9/L	32 (285)	11.2		
Platelet count (x 10^9/L)			243	25 – 592
<100 x 10^9/L	27 (285)	9.5		
>400 x 10^9/L	15 (285)	5.3		
Neutrophil count (x 10^9/L)			3.55	1.24 – 19.28
<1.5 x 10^9/L	5 (186)	2.7		
Erythrocyte sedimentation rate (ESR) (mm/hour)			117*	0 – 163*
<20 mm/hour	12 (182)	6.6		
>100 mm/hour	101 (182)	55.5		
Rouleaux formation	191 (252)	75.8		

* In 11 patients the ESR was more than the measurable limit of 120 mm/hour: These data were recorded as 120 mm/hour. In 17 patients the ESR was more than the measurable limit of 150 mm/hour. These data were recorded as 150 mm/hour.

3.3.2 Biochemical findings

Selected biochemical findings at presentation are shown in table 3.3. Urea >8 mmol/L was present in 124/284 patients (43.7%). Creatinine >177 µmol/L was found in 91/284 patients (32.0%). Hypercalcaemia was seen in 136/282 patients (51.8%). Corrected calcium >2.75 mmol/L was noted in 99/282 patients (35.1%). A significant elevation in alkaline phosphatase >200 IU/L was only present in 16/266 patients (6%). Uric acid was >0.45 mmol/L in 129/239 patients (54.0%). Lactate dehydrogenase >450 IU/L was found in 85/219 patients (38.8%). Total protein was >85 g/L in 191/286 patients (66.8%). The median total protein was 99.0 g/L, the median albumin was 31.0 g/L and the median globulin was 66.0 g/L. β2-microglobulin was <3.5 mg/L in 59/241 patients (24.5%) and was >5.5 mg/L in 138/241 patients (57.3%). The C-reactive protein (CRP) was <10mg/L in 76/199 patients (38.2%) and the median CRP was 15.7 mg/L.

Table 3.3 Relevant biochemical findings at presentation

Laboratory parameter	Number (n)	Percentage	Median	Range
Urea (mmol/L)			7.35	1.9 – 75.7
>8 mmol/L	124 (284)	43.7		
Creatinine (μmol/L)			115	31 – 2920
>177 μmol/L	91 (284)	32.0		
Corrected calcium (mmol/L)			2.54	2.03 – 5.08
>2.56 mmol/L	136 (282)	51.8		
>2.75 mmol/L	99 (282)	35.1		
Alkaline phosphatase (IU/L)			89.5	5 – 451
>150 IU/L	39 (266)	14.7		
>200 IU/L	16 (266)	6.0		
Uric acid (mmol/L)			0.47	0.06 – 1.03
>0.45 mmol/L	129 (239)	54.0		
Lactate dehydrogenase (IU/L)			399	44 – 1761
>450 IU/L	85 (219)	38.8		
Total protein (g/L)			99.0[†]	43 – 167[†]
>85 g/L	191 (286)	66.8		
>100 g/L	136 (286)	47.6		
Albumin (g/L)			31.0	13 – 50
<35 g/L	184 (287)	64.1		
<30 g/L	120 (287)	41.8		
Globulin (g/L)			66.0[#]	15 – 145[#]
>30 g/L	246 (285)	86.3		

Laboratory parameter	Number (n)	Percentage	Median	Range
β2-microglobulin (mg/L)			6.5	1.1 – 97
<3.5 mg/L	59 (241)	24.5		
>5.5 mg/L	138 (241)	57.3		
C-reactive protein (mg/L) (CRP)			15.7[‡‡]	1 – 522[‡‡]
<10 mg/L	76 (199)	38.2		

[†]In 39 patients the total protein was more than the measurable limit of 120 g/L: These data were recorded as 120 g/L.

[♯]Globulin is calculated as the difference between total protein and albumin. In 39 patients the albumin level was known but the total protein was more than the measurable limit of 120 g/L. In these data the total protein was recorded as 120 g/L and the globulin level was calculated.

[♯♯] In 13 patients the CRP was less than the measurable limit of 1mg/L: These data were recorded as 1mg/L. In 4 patients the CRP was less than the measurable limit of 3 mg/L: These data were recorded as 3mg/L.

3.3.3 Monoclonal protein characteristics

M-protein characteristics at presentation are given in table 3.4. IgG was the most common isotype occurring in 159/289 patients (55.0%). IgA isotype was found in 55/289 (19.0%). No cases of IgM, IgD or IgE multiple myeloma were recorded. Light chain disease was present in 55/289 patients (19.0%). Non-secretory multiple myeloma was seen in 7/289 patients (2.4%). The subtype was not characterized in 13/289 patients (4.5%). M-protein was detected in the serum in 268/288 patients (93.1%) and the median serum M-protein was 36.7 g/L. M-protein was found in the urine in 220/251 patients (87.6%) and the median urine M-protein was 0.36 g/L. Kappa M-protein was detected in 116/182 patients (63.7%) and lambda M-protein was noted 66/182 patients (36.3%). Immuneparesis was common and occurred in 239/272 patients (87.9%).

3.3.4 Plasma cell leukaemia

Multiple myeloma with peripheral blood involvement of $>2 \times 10^9$/L plasma cells (plasma cell leukaemia) was seen in 8/289 patients (2.8%).

Table 3.4 <u>Monoclonal protein characteristics at presentation</u>

Laboratory parameter	Number (n)	Percentage	Median	Range
Multiple myeloma subtype				
IgG isotype	159 (289)	55.0		
IgA isotype	55 (289)	19.0		
IgM isotype	0 (289)	0		
IgD isotype	0 (289)	0		
IgE isotype	0 (289)	0		
Light chain disease	55 (289)	19.0		
Non-secretory	7 (289)	2.4		
Not characterized (unknown)	13 (289)	4.5		
Serum M-protein (g/L)			36.7^{Δ}	$0 - 105.6^{\Delta}$
Serum M-protein detected	268 (288)	93.1		
Urine M-protein (g/L)			0.36	0 – 32.14
Urine M-protein detected	220 (251)	87.6		
Kappa light chains	116 (182)	63.7		
Lambda light chains	66 (182)	36.3		
Immuneparesis	239 (272)	87.9		

$^{\Delta}$ In 1 patient the paraprotein level was more than the measurable limit of 100 g/L: This data was recorded

as 100 g/L.

3.4 BONE MARROW FINDINGS

3.4.1 Plasma cells

The bone marrow plasmacytosis at diagnosis is provided in table 3.5. The median plasmacytosis was 25%. In 62/249 patients (24.9%) the plasmacytosis was <10%. In 101/249 patients (40.6%) the plasmacytosis was >30%. If bone marrow findings are corrected to assess only adequate quality smears (157 patients) then the median plasmacytosis increased to 34.0% and plasmacytosis of <10% decreased to 16/157 patients (10.2%). However, plasmacytosis >30% showed a similar percentage (64/157 patients; 40.8%).

Table 3.5 Bone marrow plasma cells at diagnosis

Bone marrow plasma cells	Number (n)	Percentage	Median	Range
Bone marrow plasma cells (%)			25.0	0 – 95
<10%	62 (249)	24.9		
>30%	101 (249)	40.6		
Bone marrow plasma cells (%) (Corrected for suboptimal smears)			34.0	0 – 95
<10%	16 (157)	10.2		
>30%	64 (157)	40.8		

3.4.2 Cytogenetic findings

Karyotype analysis and fluorescent in-situ hybridization (FISH) were the 2 modalities utilized to look for cytogenetic abnormalities. Findings are given in table 3.6.

Karyotype analysis was pursued in 108 patients. In 26/108 patients it was not possible to obtain metaphases and in a further 3/108 patients technical problems e.g. laboratory accidents precluded karyotype analysis from being done. Thus, karyotype analysis was successfully performed in 79 patients. In 17/79 patients (21.5%) an abnormal karyotype was found. Hyperdiploidy of one of chromosomes 3, 5, 7, 9, 11, 15, 19 or 21 was noted in 8/17 patients (47.1%). Unspecified hyperdiploidy was found in 4/17 patients (23.5%). A t(11;14) translocation was documented in 1/17 patients (5.9%). Other abnormalities included unspecified aneuploidy, addition or loss of material on a chromosomal arm and marker chromosomes.

FISH analysis was attempted in 90 patients. In 3 patients a suboptimal specimen precluded analysis. Thus, in 87 patients FISH was successful. The same probes were not routinely applied to all 87 specimens. With respect to primary genetic anomalies the most frequently performed test was for t(4;14) translocation, with 4/58 patients (6.9%) testing positive. Very few patients were tested for the other primary translocations associated with multiple myeloma. As far as secondary genetic abnormalities are concerned, deletion 13 was demonstrated in 26/80 patients (32.5%) and 1/80 patients (1.25%) had hyperploidy of chromosome 13. Deletion 17p was present in 4/59 patients (6.8%) and hyperploidy of chromosome 17 was seen in 3/59 patients (5.1%).

Table 3.6 <u>Cytogenetic findings at diagnosis</u>

Karyotype findings	Number (n)	Percentage
Hyperdiploidy (of one of chromosomes 3, 5, 7, 9, 11, 15, 19 or 21)	8 (17)	47.1
Unspecified hyperdiploidy	4 (17)	23.5
Unspecified aneuploidy	3 (17)	17.6
Translocation t(11;14)	1 (17)	5.9
Other translocations	2 (17)	11.8
Other abnormalities	10 (17)	58.8
Fluorescent in-situ hybridization findings	**Number (n)**	**Percentage**
Translocation t(4;14)	4 (58)	6.9
Translocation t(11;14)	1 (7)	14.3
Translocation t(6;14)	0 (3)	0
Translocation t(14;16)	0 (3)	0
Translocation t(14;20)	0 (3)	0
Unspecified chromosome 14q32 rearrangement	1 (58)	1.7
Deletion 13	26 (80)	32.5
Hyperploidy of chromosome 13	1 (80)	1.25
Deletion 17p	4 (59)	6.8
Hyperploidy of chromosome 17	3 (59)	5.1

3.5 RADIOLOGICAL FINDINGS

3.5.1 Radiograph findings

The radiograph findings at presentation are presented in table 3.7. Lytic lesions were documented in 194/245 patients (79.2%). Vertebral compression fractures were common in 91/211 patients (43.1%). Pathological fractures of the long bones occurred less frequently in 30/211 patients (14.2%). Other fractures (e.g. pathological fractures of the pelvic bones) were only seen in 17/211 patients (8.6%). The radiograph showed soft tissue lesions suspicious for plasmacytoma in 37/213 patients (17.4%).

Table 3.7 Radiograph findings at presentation

Radiograph finding	Number (n)	Percentage
Lytic lesions	194 (245)	79.2
Vertebral compression fractures	91 (211)	43.1
Long bone fractures	30 (211)	14.2
Other fractures	17 (211)	8.6
Suspicious for plasmacytoma	37 (213)	17.4

3.5.2 Computed tomography findings

Computed tomography (CT) scans were done in 55 patients (see table 3.8). Three patients had more than one anatomical region surveyed; thus 58 imaging studies were done. Most frequent scans were of the spine (25 studies) and the head and neck (24 studies). Other anatomical regions e.g. thorax, abdomen or limbs were seldom scanned (9 studies). Lytic lesions were seen in 39/55 patients (70.9%). In addition to being detected on dedicated spinal views compression fractures were also noted on some patients who had a thoracic CT or abdominal CT study done. Thus, vertebral compression fractures were seen in 18/29 patients (62.1%). Soft tissue lesions suspicious for plasmacytoma were reported in 36/55 patients (65.5%).

Table 3.8 Computed tomography scans at presentation

Computed tomography study	Number (n)	Percentage
Site of study		
Cervical, thoracic and lumbar spine	25 (58)	43.1
Head and neck	24 (58)	41.4
Other	9 (58)	15.5
Findings		
Lytic lesions	39 (55)	70.9
Vertebral compression fractures	18 (29)	62.1
Suspicious for plasmacytoma	36 (55)	65.5

3.5.3 Magnetic resonance image findings

Magnetic resonance imaging (MRI) was done in 83 patients (see table 3.9). Most MRI scans were of the spine (81/83 patients; 97.6%). Only 2/83 patients had another anatomical region scanned by MRI. Bone marrow infiltration was noted in 58/81 patients (71.6%). Vertebral compression fractures were seen in 66/80 patients (82.5%). Soft tissue lesions suspicious for plasmacytoma were reported in 54/83 patients (65.1%).

Table 3.9 <u>Magnetic resonance image studies at presentation</u>

Magnetic resonance image study	Number (n)	Percentage
Site of study		
Cervical, thoracic and lumbar spine study	81 (83)	97.6
Other study	2 (83)	2.4
Findings		
Bone marrow infiltration	58 (81)	71.6
Vertebral compression fractures	66 (80)	82.5
Suspicious for plasmacytoma	54 (83)	65.1

3.5.4 Imaging trends

Figures 3.4 and 3.5 depict the increase in the number of scans ordered during the study period. Both the absolute number of scans as well as the number of scans done per patients per year increased.
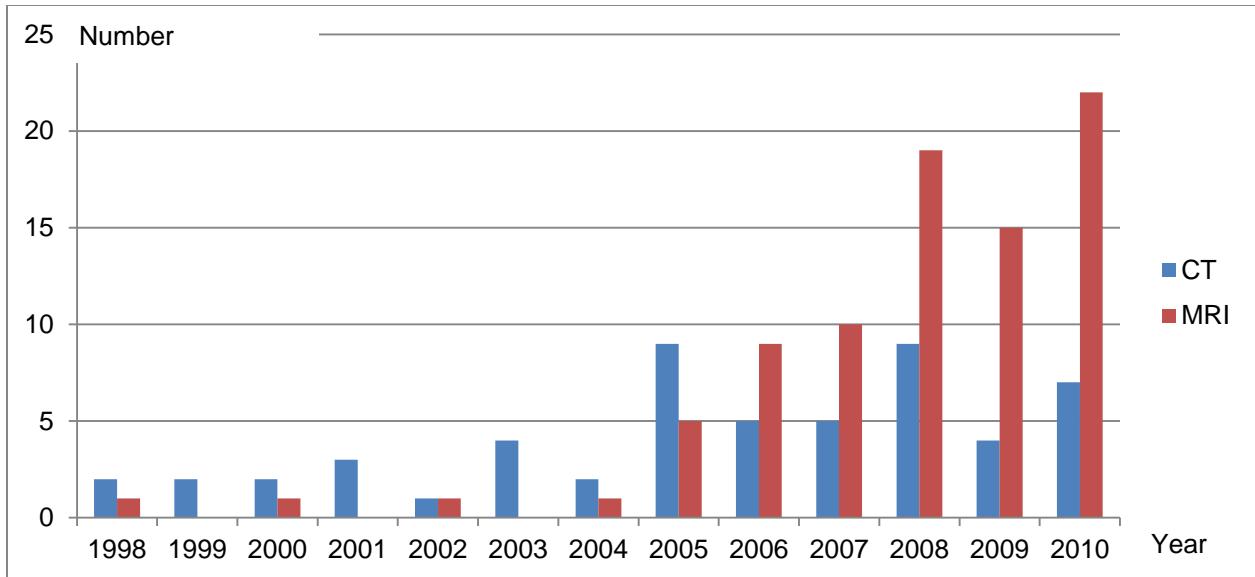
Figure 3.4 <u>Absolute number of scans per year</u>

CT = Computed tomography; MRI = Magnetic resonance imaging
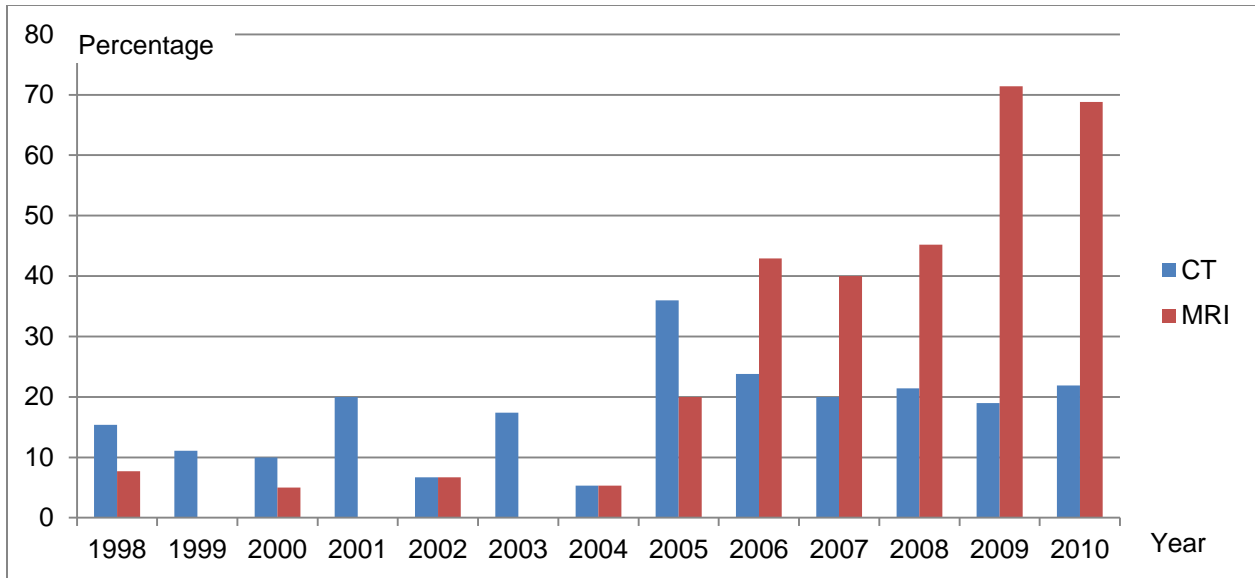
Figure 3.5 Number of scans as a percentage of patients presenting per year

CT = Computed tomography; MRI = Magnetic resonance imaging

3.6 STAGING

3.6.1 Durie-Salmon staging

The Durie-Salmon stage was determined in 276 patients (see figure 3.6). Very few patients presented with stage I disease (23/276 patients; 8.3%). The majority (208/276 patients; 75.4%) presented with stage III disease.
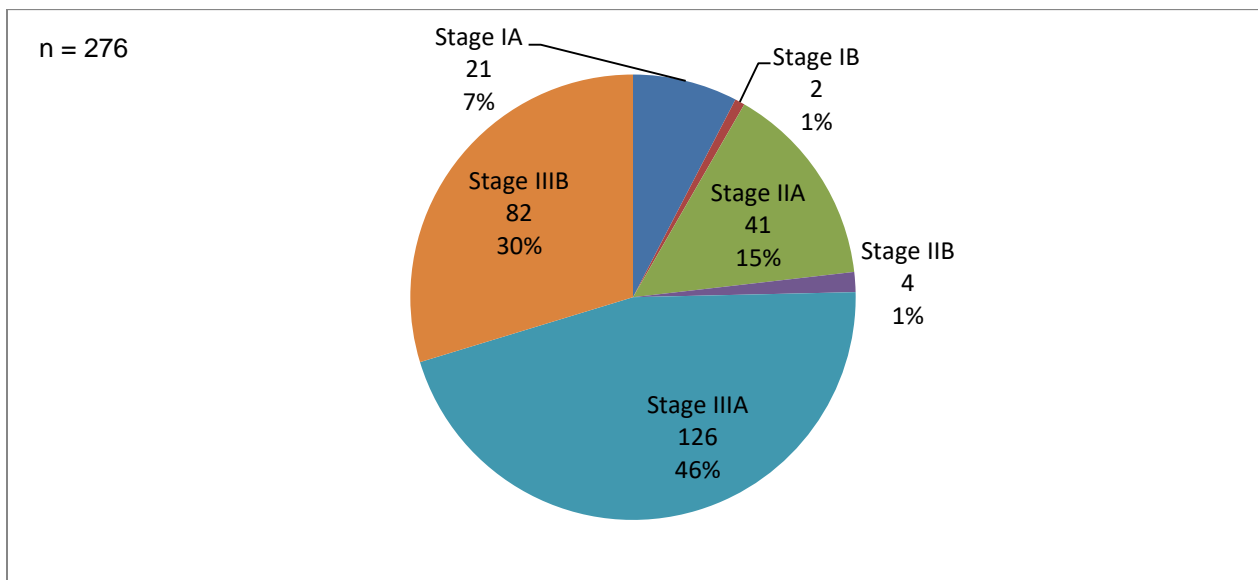
Figure 3.6 Durie-Salmon stage at presentation

3.6.2 International Staging System

The International Staging System was calculated in 241 patients (see figure 3.7). Once again very few patients presented with stage I disease (31/241 patients; 13%) and most (137/241 patients; 57%) presented with stage III disease.

n = 241

Stage I
31
13%

Stage II
73
30%

Stage III
137
57%
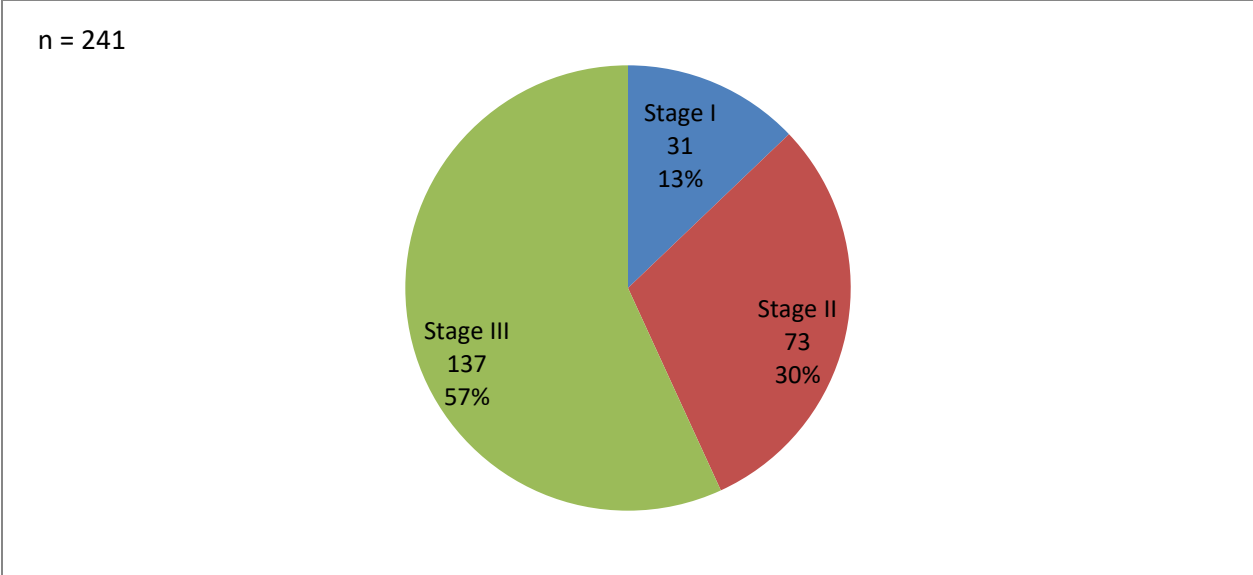
Figure 3.7 International Staging System at presentation

3.7 SURVIVAL AND OUTCOMES

Patient outcomes are shown in table 3.10. A significant number (121/289 patients; 41.9%) were lost to follow-up. There were 165 patients who were either alive or dead. Of these patients not lost to follow-up a high proportion (78/165 patients; 47.3%) did not survive more than 3 months.

Table 3.10 Patient outcomes

Outcome	Number (n)	Percentage
Alive	27 (289)	9.3
Dead	141 (289)	48.8
Lost to follow-up	121 (289)	41.9
Survival ≤3 months	78 (165)	47.3
Survival >12 months	58 (165)	35.2

A Kaplan-Meier survival curve describes overall survival for all patients in the study (see figure 3.8). Median overall survival was 15.9 months for the 289 patients assessed.
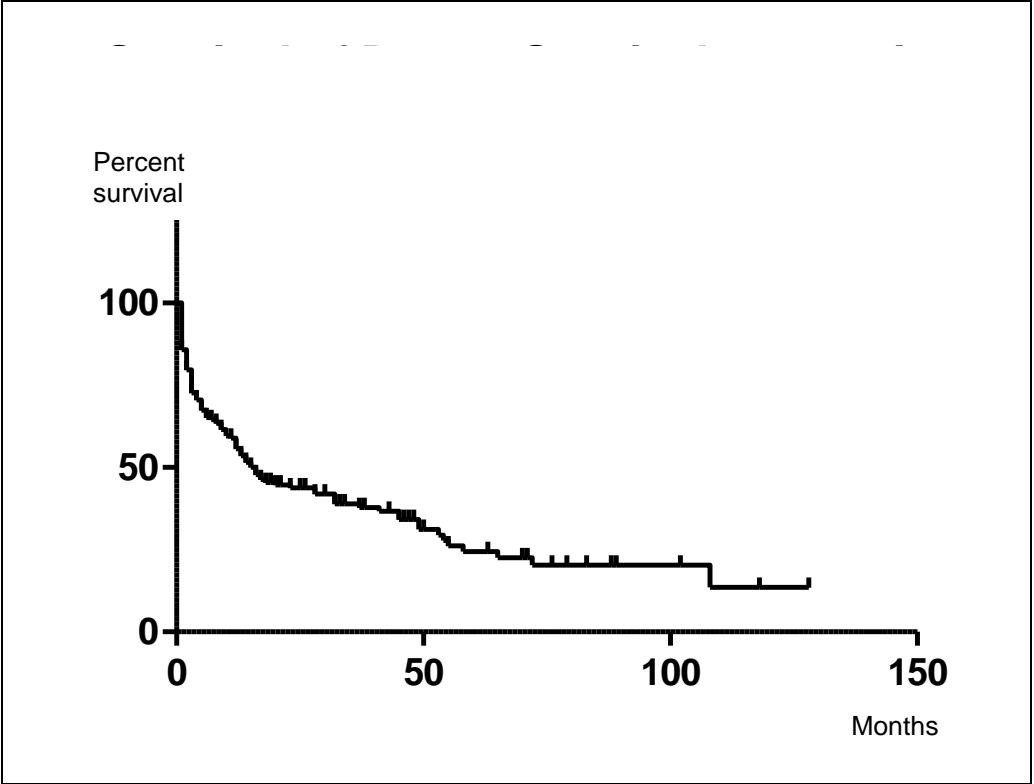
Figure 3.8 <u>Kaplan-Meier survival curve: Overall survival for 289 patients</u>

3.8 FIRST-LINE THERAPY

3.8.1 First-line therapeutic modalities

In 16/289 patients (5.5%) no records regarding first-line chemotherapy were found. Thus 273 patients had records forthcoming. First-line chemotherapy was withheld in 32/273 patients (11.7%) as they were too ill to receive cytotoxic agents. Specific first-line therapy was administered in 241/273 patients (88.3%) (see table 3.11). Until the end of 2002 MP was the only treatment offered. In total MP was given as first-line therapy to 159/241 patients (66.0%). From 2003 CVAD was also utilized as first-line therapy. This was the regimen administered in 73/241 patients (30.3%). Within this first-line CVAD group early ASCT was done in 9/241 patients (3.7%) whilst 6/73 patients (8.2%) had ASCT deferred until first relapse. The first patient to undergo ASCT in 2003 received MP as induction therapy. All other patients undergoing an early ASCT received CVAD for induction.

Table 3.11 First-line therapeutic modalities

First-line regimen	Number (n)	Percentage
MP	159 (241)	66.0
CVAD	73 (241)	30.3
Early ASCT	9 (241)	3.7

3.8.2 First-line therapy: Depth of response

With respect to first-line therapy, in patients receiving MP, CR was achieved in 3/72 patients (4.2%) whilst VGPR was attained in 4/72 patients (5.6%) (see table 3.12). Administration of CVAD resulted in CR in 7/55 patients (12.7%) and VGPR in 2/55 patients (3.6%). Early ASCT lead to CR in 5/9 patients (55.6%) and VGPR in 1/9 patients (11.1%).

Table 3.12 Depth of response to first-line therapy

Regimen	CR (n)	Percentage	VGPR (n)	Percentage
MP	3 (72)	4.2	4 (72)	5.6
CVAD	7 (55)	12.7	2 (55)	3.6
Early ASCT	5 (9)	55.6	1 (9)	11.1

CR = complete response; VGPR = very good partial response

3.8.3 First-line therapy: Progression-free survival

Progression-free survival (PFS) after first-line therapy was determined in 141 patients (see table 3.13). Overall median PFS was 6 months and ranged from 0 – 87 months. Only 30/141 patients (21.3%) had PFS >12 months. When early deaths were excluded, i.e. deaths occurring ≤3 months after commencing therapy, overall median PFS rose to 10.5 months. In patients who received MP median PFS was 4 months, and when early deaths were excluded then median PFS rose to 9 months. In those administered CVAD median PFS was 8 months, and when early deaths were excluded PFS rose to 9 months. Early ASCT had a median PFS of 45 months, with no early deaths. On ANOVA

analysis PFS was significantly longer (p = <0.0001) for early ASCT versus MP as well as for early ASCT versus CVAD.

Table 3.13 First-line treatment: Progression-free survival in months

Progression free survival (PFS)	Number (n)	Percentage	Median (Mean)	Range
PFS: All first-line treatment			6	0 – 87
≤3 months	53 (141)	37.6		
>12 months	30 (141)	21.3		
PFS: Corrected for early deaths			10.5	
PFS: MP			4 (8.08)	0 – 78
≤3 months	42 (86)	48.8		
>12 months	17 (86)	19.8		
PFS: Corrected for early deaths			9	
PFS: CVAD			8 (8.3)	0 – 24
≤3 months	11 (48)	22.9		
>12 months	7 (48)	14.6		
PFS: Corrected for early deaths			9	
PFS: Early ASCT			45 (41.7)	0 – 87
≤3 months	0 (7)	0		
>12 months	7 (7)	100		

3.8.4 First-line therapy: Comparison of overall survival

Kaplan-Meier survival curves compared overall survival between patients receiving different first-line therapy (see figure 3.9). There was significant difference between the groups (p = <0.0044). The best survival curve was seen in the early ASCT group. Patients treated with CVAD had a better survival curve than those treated with MP.
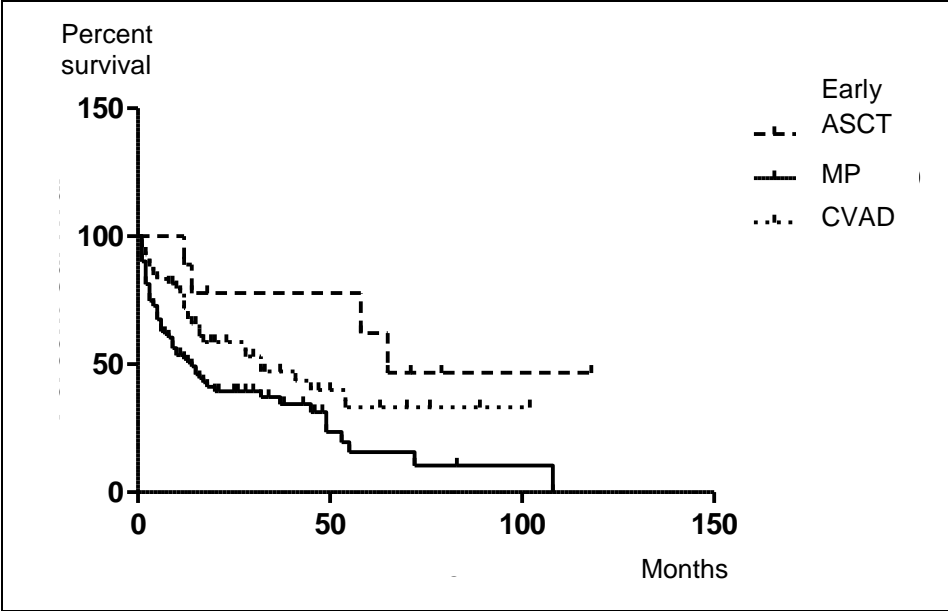
Figure 3.9 Kaplan-Meier survival curves: Comparison of overall survival between

patients treated with different first-line therapy

3.9 THERAPY FOR DISEASE RELAPSE

3.9.1 Therapeutic modalities for disease relapse

Whilst receiving first-line treatment, or having completed first-line treatment, 90 patients died and 95 patients were lost to follow-up. Therefore, after conclusion of first-line therapy, 56 patients were tracked and 47 patients relapsed and were treated (see table 3.14). Of these 47 patients, 8 were given a third line of therapy and 1 of these patients received a fourth line of therapy.

Table 3.14 Therapeutic modalities utilized for disease relapse

Therapies for disease relapse	Utilized as:		
	Second-line	Third-line	Fourth-line
MP	20	4	0
CVAD	12	0	0
Thalidomide	5	2	0
Late ASCT	6	2	1
Other chemotherapy	4	0	0
Total	47	8	1

3.9.2 Therapy for disease relapse: Depth of response

With respect to the MP regimen CR was achieved in 1/24 patients (1.9%) and VGPR in 1/24 patients (1.9%) (see table 3.15). In those receiving CVAD 1/12 patients (8.3%) attained CR. Late ASCT resulted in CR in 2/9 patients (22.2%).

Table 3.15 Disease relapse: Depth of response for therapeutic modalities utilized

Regimen	Complete response (n)	Percentage	Very good partial response (n)	Percentage
MP	1 (24)	4.2	1 (24)	4.2
CVAD	1 (12)	8.3	0 (12)	0
Thalidomide	0 (7)	0	0 (7)	0
Late ASCT	2 (9)	22.2	0 (9)	0

3.9.3 Therapy for disease relapse: Progression-free survival

Progression-free survival (PFS) for therapy for disease relapse was determined in 30 patients (see table 3.16). Overall median PFS was 11 months and ranged from 0 – 33 months. PFS >12 months occurred in 9/30 patients (36.7%). When early deaths were excluded overall median PFS rose to 12 months. In patients who received MP median PFS was 10 months and there were no early deaths. In those given CVAD median PFS was 9 months, and this median did not change when corrected for early deaths. The median PFS for late ASCT for disease relapse was 20 months and this median increased to 21 months when corrected for early deaths. Only seven patients received thalidomide. Data for four patients treated with thalidomide showed median PFS of 13 months with no early deaths.

Table 3.16 Therapy for disease relapse: Progression-free survival in months

Progression free survival (PFS)	Number (n)	Percentage	Median	Range
PFS: All subsequent treatment			11	0 – 33
≤3 months	4 (30)	10		
>12 months	9 (30)	36.7		
PFS: Corrected for early deaths			12	
PFS: MP			10	4 – 27
≤3 months	0 (11)	0		
>12 months	4 (11)	36.4		
PFS: CVAD			9	0 – 33
≤3 months	2 (9)	22.2		
>12 months	1 (9)	11.1		
PFS: Corrected for early deaths			9	
PFS: Late ASCT			20	3 – 24
≤3 months	1 (6)	15.4		
>12 months	4 (6)	30.8		
PFS: Corrected for early deaths			21	
PFS: Thalidomide			13	12 – 25
≤3 months	0 (4)	0		
>12 months	2 (4)	50		

It was not possible to compare outcomes between the different regimens used to treat disease relapse. Firstly, the number of patients in each treatment group was small. Secondly, therapies were often recycled making comparisons difficult. For example, during the course of disease 1 patient received the following therapies: 1st MP; 2nd CVAD; 3rd MP; 4th thalidomide; 5th CVAD; 6th late ASCT; 7th MP; 8th CVAD; 9th MP. In this patient late ASCT was the fourth different type of therapy given to the patient, but chronologically the sixth line of therapy administered, as MP and CVAD were recycled. It is problematic to compare the outcome of this late ASCT with a late ASCT that was done at first relapse. Thirdly, too few patients achieved CR or VGPR, preventing assessment of depth of response.

3.10 EXTERNAL BEAM IRRADIATION AND SURGICAL PROCEDURES

3.10.1 External beam irradiation

Throughout the course of disease 90/274 patients (32.8%) received external beam irradiation to 148 sites (see table 3.17). The most common site irradiated was the spine.

Table 3.17 External beam irradiation throughout the course of disease

External beam irradiation site	Number (n)	Percentage
Skull and facial bones	20 (148)	13.5
Spine (cervical, thoracic and lumbar spine)	69 (148)	46.6
Thorax (ribs, sternum, clavicle, scapula)	17 (148)	11.5
Pelvis and sacrum	17 (148)	11.5
Upper limb (humerus and radius)	11 (148)	7.4
Lower limb (femur and tibia)	14 (148)	9.5

3.10.2 Surgical procedures

In 70/274 patients (25.5%) involvement from a surgeon was required (see table 3.18). The most frequent procedure was surgical biopsy to obtain a tissue specimen (35/70 patients; 50%). Another common intervention was open reduction and internal fixation for a pathological fracture (27/70 patients; 38.6%). Surgical spinal decompression was performed in 9/70 patients (12.9%). Other, less common procedures, included debridement of septic wounds, insertion of drains and even evisceration of an eye in one patient.

Table 3.18 <u>Surgical procedures throughout the course of disease</u>

Surgical procedure	Number (n)	Percentage
Biopsy	35 (70)	50
Open reduction and internal fixation	27 (70)	38.6
Spinal decompression	9 (70)	12.9
Debridement of septic wound	3 (70)	4.3
Drain insertion	2 (70)	2.9
Other surgical procedures	4 (70)	5.7

3.11 HUMAN IMMUNODEFICIENCY VIRUS-SEROPOSITIVE PATIENTS

In this study 18/289 (6.2%) were HIV-seropositive at presentation with multiple myeloma. There were more HIV-seropositive patients during the latter years of the study period (see figure 3.10).
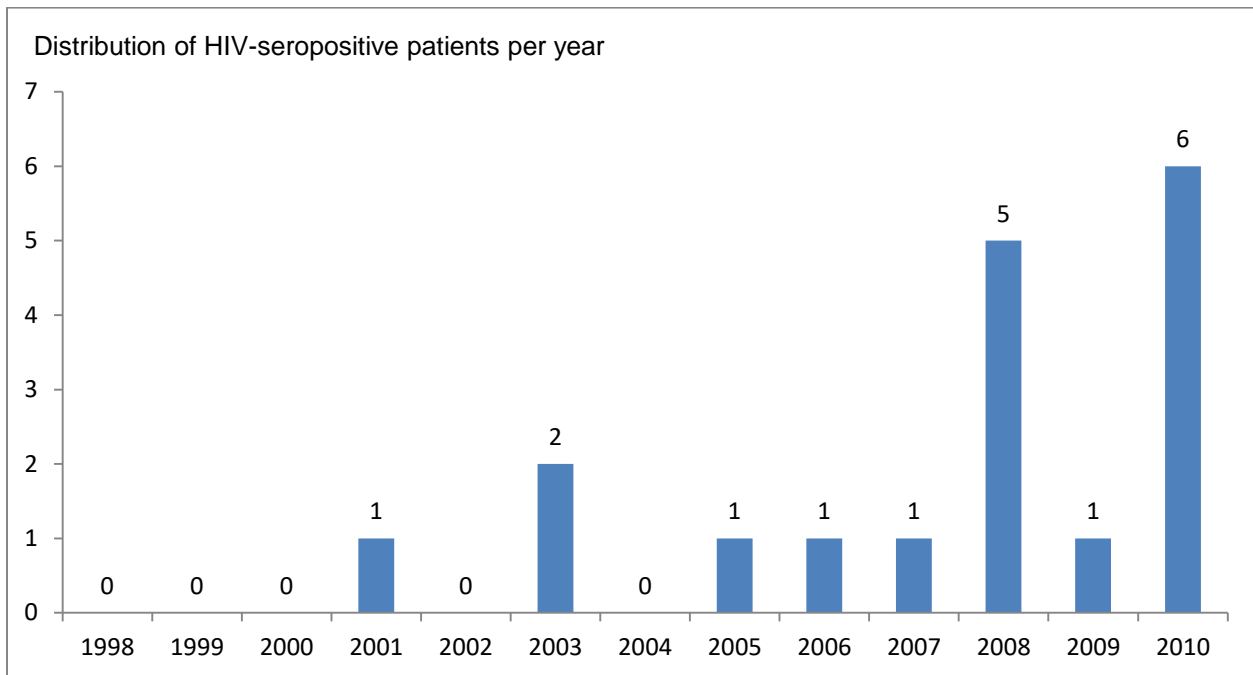
Figure 3.10 Distribution of HIV-seropositive patients per year

At presentation only 3 patients were on antiretroviral (ARV) therapy. The median CD4 count was 313 cells/mm^3 and the median viral load was 19304 copies/mL (see table 3.19).

Table 3.19 CD4 count and viral load of HIV-seropositive patients at presentation

Laboratory parameter	Number (n)	Percentage	Median	Range
CD4 count (cells/mm^3)			313	8 – 1228
CD4 count ≤ 50 cells/mm^3	2 (17)	11.8		
CD4 count 51 – 200 cells/mm^3	2 (17)	11.8		
CD4 count 201 – 350 cells/mm^3	5 (17)	29.4		
CD4 count 351 – 500 cells/mm^3	2 (17)	11.8		
CD4 count 501 – 1000 cells/mm^3	5 (17)	29.4		
CD4 count 1001 – 1500 cells/mm^3	1 (17)	5.9		
Viral load (copies/mL)			19304	28 – 620 000
Viral load <40 copies/mL	1 (12)			

Pertinent demographic, clinical, laboratory and radiological findings in HIV-seropositive patients at presentation were compared with HIV-seronegative patients (see table 3.20). Significant findings in HIV-seropositive patients were a younger mean age (i.e. 44.7 years), a greater frequency of clinically evident plasmacytoma and a lesser frequency of immuneparesis. There were no other significant differences.

Table 3.20 Pertinent demographic, clinical, laboratory and radiological findings at

presentation in HIV-seropositive versus HIV-seronegative patients

Parameter	HIV-seropositive	HIV-seronegative	P value
Demographic findings			
Age [Mean (SD)]	44.7 (8.7)	58.5 (10.8)	< 0001
Male gender [Percentage]	53.0	49.8	1.000
Bone marrow findings			
Plasmacytosis [Mean (SD)]	30.3 (25.9)	28.9 (23.6)	0.8490
Clinical manifestations			
Bone pain [Yes│No] (n)[¶]	14│3 (17)	228│32 (260)	0.4593
Compression fractures [Yes│No] (n)	6│10 (16)	99│157 (256)	1.000
Other fractures [Yes│No] (n)	2│13 (15)	45│209 (254)	1.000
Anemia [Yes│No] (n)	12│3 (15)	176│82 (258)	0.4051
Bleeding [Yes│No] (n)	4│11 (15)	39│217 (256)	0.2694
Hyperviscosity [Yes│No] (n)	1│14 (15)	58│200 (258)	0.2043
Infection [Yes│No] (n)	7│9 (16)	65│190 (255)	0.1420
Renal failure [Yes│No] (n)	3│13 (16)	60│193 (253)	0.7702
Hypercalcaemia [Yes│No] (n)	1│15 (16)	50│203 (253)	0.3211
Paraparesis [Yes│No] (n)	4│13 (17)	63│191 (254)	1.000
Peripheral neuropathy [Yes│No] (n)	3│13 (16)	29│224 (253)	0.4169
Clinically evident plasmacytoma [Yes│No] (n)	7│10 (17)	42│210 (252)	0.0197**
Constitutional symptoms [Yes│No] (n)	11│5 (16)	198│57 (255)	0.3746
Laboratory findings (serum)			
Haemoglobin (g/dL) [Mean (SD)]	9.3 (1.5)	8.8 (2.5)	0.2754
White cell count (x 10^9/L) [Mean (SD)]	6.6 (2.25)	7.5 (4.29)	0.3843
Platelet count (x 10^9/L) [Mean (SD)]	237 (103)	240 (100)	0.8905
Neutrophil count (x 10^9/L) [Mean (SD)]	3.96 (1.6)	4.49 (2.9)	0.2879

Parameter	HIV-seropositive	HIV-seronegative	P value
Laboratory findings (serum) (continued)			
ESR (mm/hour) [Mean (SD)]	103 (48)	95 (48)	0.6450
Urea (mmol/L) [Mean (SD)]	8.4 (7.7)	12.4 (12.6)	0.0648
Creatinine (µmol/L) [Mean (SD)]	202 (323)	254 (360)	0.5203
Corrected calcium (mmol/L) [Mean (SD)]	2.77 (0.66)	276 (0.57)	0.9201
Alkaline phosphatase (IU/L) [Mean (SD)]	108 (72.8)	103 (62.4)	0.7813
Uric acid (mmol/L) [Mean (SD)]	0.511 (0.19)	0.505 (0.20)	0.9144
Lactate dehydrogenase (IU/L) [Mean (SD)]	522.3 (249)	481.9 (285)	0.5838
C-reactive protein (mg/L) [Mean (SD)]	50.98 (102)	41.9 (71.9)	0.8009
Protein (g/L) [Mean (SD)]	99.4 (22.0)	97.4 (23.2)	0.7184
Albumin (g/L) [Mean (SD)]	30.5 (7.6)	31.9 (8.3)	0.4719
Globulin (g/L) [Mean (SD)]	68.5 (22.9)	65.3 (27.1)	0.5742
β2-microglobulin (mg/L) [Mean (SD)]	13.7 (18.7)	10.7 (12.8)	0.5899
M-protein (g/L) [Mean (SD)]	30.3 (21.7)	38.5 (28.2)	0.1587
Immuneparesis [Yes│No] (n)	9│7 (16)	230│26 (256)	0.0011**
Laboratory findings (urine)			
M-protein (g/L) [Mean (SD)]	1.1 (2.6)	1.7 (3.3)	0.4504
Radiograph findings			
Lytic lesions [Yes│No] (n)	14│2 (16)	184│45 (229)	0.7437
Vertebral fractures [Yes│No] (n)	3│10 (13)	88│110 (198)	0.1576
Long bone fractures [Yes│No] (n)	1│12 (13)	29│169 (198)	0.6983
Other fractures [Yes│No] (n)	2│11 (13)	15│183 (198)	0.2817
Suspicious for plasmacytoma [Yes│No] (n)	4│10 (14)	33│166 (199)	0.2724

¶ Yes = The number of patients in whom the finding was positive e.g. 14 HIV-seropositive patients had bone pain; No = The number of patients in whom the finding was negative e.g. 3 HIV-seropositive patients had no bone pain; (n) = The total number of patients for whom the finding was documented e.g. 17 HIV-seropositive patients had notes regarding the presence or absence of bone pain

Details of first-line therapy were not available in 2 HIV-seropositive patients. First-line treatment was administered in 13/16 patients (81.3%). MP was given to 4/13 patients (30.8%) and CVAD to 9/13 patients (69.2%). No HIV-seropositive patient underwent either early or late ASCT. Disease relapse was treated in 4/13 patients (30.8%); with MP utilized in 3 of the 4 patients and CVAD in 1 of the 4 patients. Only 1 patient required a third line of therapy, and thalidomide was used in this case.

Kaplan-Meier survival curves (see figure 3.11) compared overall survival between HIV-seropositive and HIV-seronegative patients. Chi^2 test of the curves showed no difference in overall survival between the 2 groups (p = 0.9073).
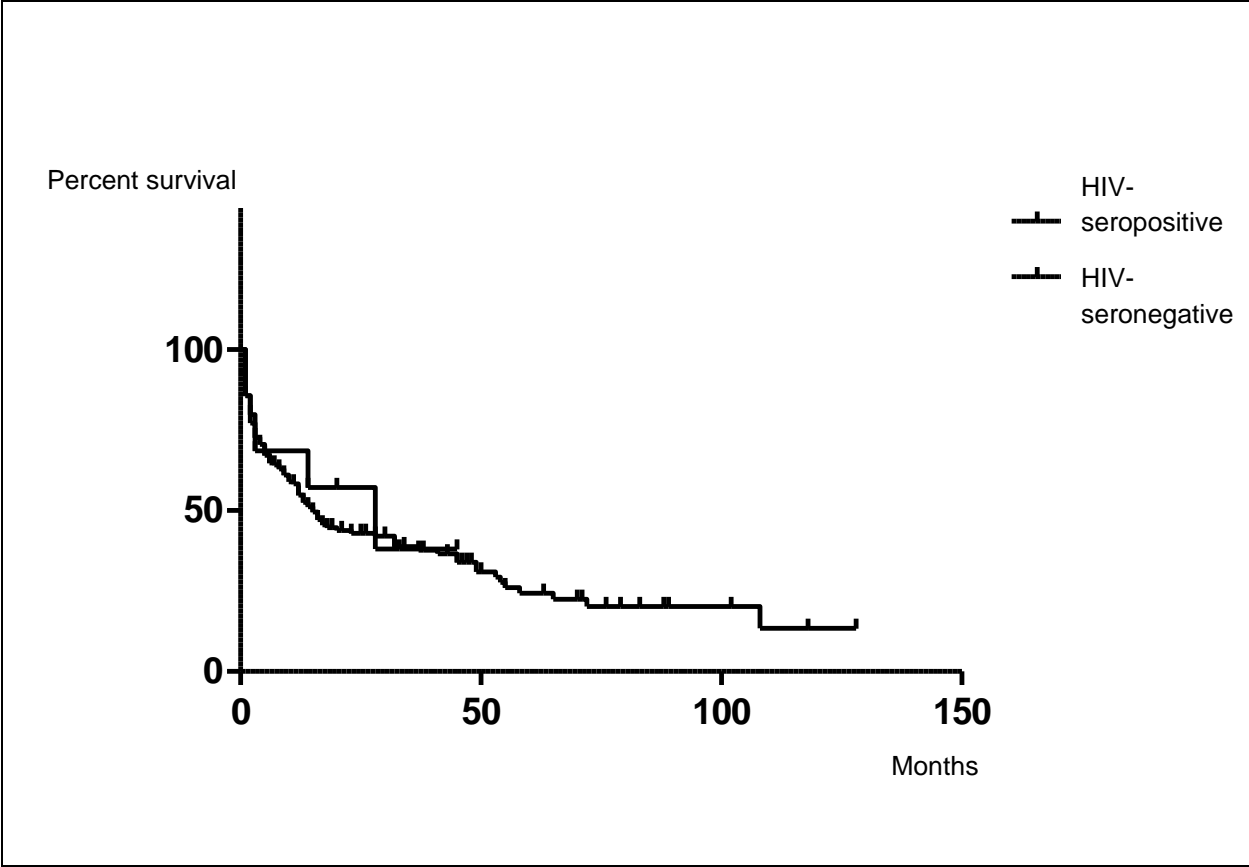
Figure 3.11 Kaplan-Meier survival curve: Overall survival of HIV-seropositive versus HIV-seronegative patients

CHAPTER 4: DISCUSSION

4.1 DEMOGRAPHIC FINDINGS

In this study the number of male and female patients was nearly equal. This is unusual as male gender is a known risk factor for multiple myeloma (Alexander, et al., 2007). Most other multiple myeloma studies show a slight male predominance (Patel, 2000; Phekoo, et al, 2004).

The median age at presentation was 58 years (range, 26 – 86 years) and most patients were aged 50 – 59 years of age. This is younger than patients with multiple myeloma in developed counties. Large studies from the United States of America (Kyle, et al., 2003) and the United Kingdom (Phekoo, et al., 2004) showed a median age at diagnosis of 66 and 73 years respectively. However, patients with multiple myeloma in developing countries, particularly in sub-Saharan Africa tend to present at a younger age. In 3 studies from Nigeria (Salawu and Durosinmi, 2005; Omoti and Omuemu, 2007; Madu, et al., 2014), the median ages at presentation were 60 years, 54 years and 62 years respectively. A study from Ethiopia showed a mean age of 51.5 years at presentation (Shamebo and Tekle-Haimanot, 1992); whilst data from a South African series showed a mean age at presentation of 61 years (Patel, 2000). The younger age at presentation may be a reflection of a younger demographic (age structure of the population). In 2010 (the last year of patient enrolment), in South Africa, estimated life expectancy at birth was 53,3 years for males and 55,2 years for females. Only 7.6% of the national population was 60 years or older (Statistics South Africa, 2010).

The majority of patients (94.1%) were black, African and predominantly indigent. This is a reflection of the surrounding population that CHBAH serves.

There was a general upward trend in the number of patients presenting per year. CHBAH is located in Gauteng province in South Africa. This province has experienced the fastest population growth in the country. In 2004, the mid-point of enrolment into the study, the Gauteng population was 8 847 740 (19% of the national total) (Statistics South Africa, 2004). In 2010, the last year of entry into the study, the total rose to 11 191 700 (22.4% of the national total) (Statistics South Africa, 2010). The increase in patient numbers reflects the burden of a greater population.

4.2 PRESENTATION AND MANIFESTATIONS OF MULTIPLE MYELOMA

4.2.1 Bone disease and radiological findings

Bone pain was found in 87.4% of patients and was the most common symptom. Conventional radiographic assessment by skeletal survey showed lytic bone disease in 79.2%. Vertebral compression fractures confirmed on radiograph, computed tomography or magnetic resonance imaging were present in 38.6%. Pathological fractures, typically of the long bones, were manifest in 17.5%. These findings are in keeping with the usual presentation of multiple myeloma (Kyle and Rajkumar, 2009; Sanderson and Epstein, 2009).

In this series skeletal survey was utilized to screen for bone disease. Plain radiographs of the skull, chest, cervical, thoracic and lumbar spine, pelvis, humeri and femora were obtained. Advantages of skeletal survey by plain radiograph include wide availability, low cost and easy screening of many anatomical regions (Dimopolous, et al., 2011). In contrast, CT and MRI were requested as focused investigations for specific indications. However, CT and magnetic MRI are more sensitive to detect bone disease (Rajkumar, 2009). For a lytic lesion to be detected by plain radiograph 30 – 50% of trabecular bone needs to have been resorbed. Furthermore, plain radiographs are not suited to assess multiple myeloma-associated osteoporosis and visualization of the spine and pelvis is poor. Thus MRI is now the gold-standard (Dimopolous, et al., 2015).

In this review vertebral compression fractures were detected by plain radiographs in 91/211 patients (43.1%), by CT in 18/29 patients (62.1%) and by MRI in 66/80 patients (82.5%). Similarly, soft tissue lesions suspicious for plamacytoma were revealed by plain radiographs in 37/213 patients (17.4%), by CT in 36/55 patients (65.5%) and by MRI in 54/83 patients (65.1%). There are two reasons for the higher yield of CT and MRI. Firstly, as noted, CT and MRI are more sensitive in detecting bone disease and soft tissue lesions. Secondly, as explained, CT and MRI were done for specific indications thus reflecting a selection bias. Lytic lesions were identified by plain radiograph in 198/245 patients (80.8%) and by CT in 39/55 patients (70.9%). However, CT scans were done for specific indications at specific sites, predominantly of the head, neck and spine (49/58 patients; 84.5%). Since CT was not used to survey bones more globally it is possible that lytic lesions at other sites were missed. Similarly, MRI studies were almost exclusively of the spine (81/83 patients; 97.6%) and showed bone marrow infiltration in 58/81 patients (71.6%). Again, it is possible that some patients had normal spinal MRI but focal infiltration at other skeletal sites. However, this is in contrast to recent consensus stating that 90% of focal lesions can be detected on MRI of the spine and pelvis (Dimopolous, et al., 2015).

4.2.2 Haematological findings

Symptomatic anaemia was evident in 68.9% of patients at presentation. When assessed at the laboratory, anaemia was shown in 91.6% (95.2% of males and 87.9% of females). This is higher than is typically reported. However, anaemia will develop in >

95% of patients at some stage during the course of the disease, so this finding is not unexpected. The median haemoglobin value (8.8 g/dL) is in keeping with the presentation of most patients (VanderWall, et al., 2013).

In this study, bleeding was noted in 15.9%. Interestingly, in contrast to findings in this study, more recent reviews have not found bleeding to be a presenting feature in multiple myeloma (Eby, 2009).

Clinical features of hyperviscosity were documented in 21.6%. This is usually not a common presenting feature in multiple myeloma, occurring in 2 – 6% (Eby, 2009). Hyperviscosity may present with a wide array of clinical features, none necessarily specific to the entity. These include mucocutaneous bleeding, blurred vision, loss of sight, strokes, convulsions, delirium, altered level of consciousness, headache, lethargy, dizziness, vertigo, cognitive impairment and heart failure. Fundoscopic changes are possibly more suggestive with sausage-shaped retinal veins, haemorrhages and sometimes papilloedema (Park, et al., 2005; Kwaan, 2013). To determine the true extent of hyperviscosity it would have been necessary to measure serum viscosity and to correlate symptoms with M-protein levels. It is possible that the frequency of features attributable to hyperviscosity has been overestimated.

4.2.3 Renal dysfunction

Patients presented with clinical features attributable to renal disease in 23.4%. Laboratory measurement of creatinine >177 µmol/L was documented in 32%. This is in

keeping with studies from the USA (Kyle, et al., 2003) and Europe (Knudsen, et al., 1994) where renal dysfunction occurred in 25-50% of patients at presentation.

4.2.4 Hypercalcaemia

Clinical findings in keeping with hypercalcaemia were present in 19%. Laboratory determination revealed corrected calcium >2.75 mmol/L in 35.1%.   Typically hypercalcaemia occurs in approximately 15 - 20% of patients at diagnosis (IMWG, 2003; Kyle, et al., 2009).

4.2.5 Infection

Infection is an important manifestation of multiple myeloma but is not well documented as a presenting feature (Munshi, et al., 2008; Kalambokis, et al., 2009). In this study overt infection was found in 26.6%.

4.2.6 Neurological manifestations

Patients presented with paraparesis in 24.7%. No distinction was made whether paraparesis was as a consequence of compression from plasmacytoma, pathological vertebral compression fractures, or from other causes. This is more than a recent study of 442 patients with multiple myeloma treated with radiation therapy (Talamo, et al., 2015) where spinal cord compression was noted in 10%.

4.2.7 Amyloid

AL-amyloidosis can be suspected on the basis of clinical findings. Diagnosis, however, requires tissue biopsy. In this series almost no biopsies were documented and the number of patients presenting with amyloidosis could not be reliably determined.

4.2.8 Disease stage

The clinical utility of the Durie-Salmon staging system and the International Staging System is limited (Rajkumar, 2014). Furthermore, there is poor concordance between the two systems. There are reasons for this poor correlation. Firstly, no variables are shared between the two systems. Secondly, multiple myeloma is a heterogenous disease at cytogenetic level. Thirdly, the Durie-Salmon stage correlates with myeloma cell mass whilst the International Staging System has origins as a statistical model (Hari, et al., 2009).

With respect to Durie-Salmon stage, in this review 23/276 patients (8.3%) presented with stage I disease, 45/276 patients (16.3%) with stage II disease and 208/276 patients (75.4%) with stage III disease. By way of contrast, from a large database (Greipp, et al., 2005) the frequency of patients with Durie-Salmon stages I, II and III was 8%, 26% and 66% respectively. Thus, in this current study, a large percentage of patients had stage III disease.

With respect to the International Staging System, in this cohort 31/241 patients (12.9%) presented with stage I disease, 73/241 patients (30.3%) with stage II disease and

137/241 patients (56.8%) with stage III disease. Greipp, et al., (2005) determined that 28%, 33% and 39% of patients presented with stage I, II and III disease respectively. Thus, again in this present series, a greater percentage had stage III disease as compared to other large databases.

4.2.9 Survival

A high proportion of patients (78/165 patients; 47.3%) died ≤3 months after presentation and diagnosis. This may, firstly, reflect the high proportion of patients presenting with symptomatic, advanced stage disease, with complications of multiple myeloma. Secondly, in a resource constrained environment, access to a high care unit or an intensive care unit is limited. And, thirdly, a high number presented with paraplegia with associated complications (67/271 patients; 24.7%). Figure 3.8, depicting overall survival, is a parabolic-like curve, initially steep with subsequent flattening out, highlighting early attrition. The median overall survival of 15.9 months also draws attention to the high number of early deaths. However, by including patients that died ≤3 months after presentation as well as by including the high number of patients lost to follow-up, it is possible that overall survival has been underestimated.

4.3 CYTOGENETIC AND MONOCLONAL PROTEIN FINDINGS

4.3.1 Cytogenetic findings

Only 129 patients had cytogenetic studies done (some patients had both karyotyping and FISH analysis performed). There are several reasons for this. Firstly, cytogenetic studies are not performed at our hospital laboratory but rather at another institution in Johannesburg. For optimal analysis prompt delivery to the cytogenetics laboratory is required. Unfortunately this does not always happen and specimens degenerate. Secondly, 24.9% of patients lived >50 km away from our hospital. Many of these patients would have likely presented to their regional hospital where the initial workup would have been done including, very often, sampling of the bone marrow. However, these regional hospitals do not stock the specialized laboratory tubes required to transport cytogenetic specimens nor do these hospitals have regular and reliable transport to ferry specimens to the central cytogenetics laboratory. Therefore, cytogenetic studies are not requested by doctors working at these hospitals. Furthermore, repeat bone marrow sampling for the sole purpose of obtaining a cytogenetic specimen are not performed as a matter of routine. Thirdly, there is limited capacity to process cytogenetic samples and consequently a delay in obtaining results. Outstanding laboratory reports are often only collected at visits when the patient returns to the outpatient clinic. In this study many patients were lost to follow-up (41.9%). These patients did not return to the outpatient clinic and so doctors were not prompted to trace outstanding results.

An abnormal karyotype was found in 17/79 (21.5%). The yield of karyotype analysis in multiple myeloma is usually low (≤20%) (Dimopoulos, et al., 2011). Hyperploidy of one of chromosomes 3, 5, 7, 11, 15, 19 or 21 was noted in 47.1%. Hyperdiploidy of these chromosomes is the primary genetic abnormality in approximately 50% of patients (Bergsagel and Chesi, 2013); and the results of this study correspond.

In the other 50% of cases the primary genetic abnormality is a chromosomal translocation involving chromosome 14q32. Important translocations include t(4;14); t(11;14); t(6;14); t(14;16) and t(14;20) (Rajkumar, 2009; Landgren, et al., 2014). In this study 58 patients were analyzed by FISH for the t(4;14) translocation which was present in 4/58 (6.9%). These results are less than the reported frequency of 15% for a t(4;14) translocation (de Mel, et al., 2014). Too few patients had FISH analysis done for the other primary genetic translocations associated with multiple myeloma.

4.3.2 Monoclonal protein findings

M-protein as detected on protein electrophoresis and/or immunofixation was found in the serum in 93.1% and in the urine in 87.6%. An IgG M-protein was seen in 55%, an IgA M-protein was seen in 19%, light chain disease was present in 19% and non-secretory multiple myeloma was observed in 2.4%. These are all in keeping with typical descriptions of multiple myeloma (Patel, 2000; IMWG, 2003; Munshi, et al., 2008).

4.4 MANAGEMENT AND TREATMENT

4.4.1 First-line therapy

The majority of patients received MP as first-line therapy (66%). Until the end of 2002, it was the only therapy offered to all patients. CR was attained in 4.2%. In patients treated with MP, CR is seldom achieved, with reported rates <5% (Rajkumar, 2009). Median PFS for patients treated with MP was 4 months. Also, 48.8% of patients receiving MP died ≤3 months after presentation and diagnosis. When corrected for early deaths, median PFS rose to 9 months.

The high number of early deaths in the MP group may reflect the patient profile of those who received this regimen. Patients treated with MP tended to be older, likely with comorbidities and a poorer performance status. This is especially true for the years after 2002, when CVAD and ASCT became therapeutic options, and MP was utilized in patients not eligible for ASCT. Overall the median age of the patients treated with MP was 62 years (range 26 – 86 years).

From 2003, CVAD was an alternative regimen for selected patients, and was generally given to those where future ASCT (either early or deferred) was a possibility. In total 73/241 patients (30.3%) received CVAD as first-line therapy. Of these patients, 6/73 (8.2%) had an ASCT at first relapse, 25/73 patients (34.2%) received CVAD but did not continue on to ASCT, 23/73 patients (31.5%) died, and 19/73 patients (26.0%) were lost to follow-up. The CVAD regimen resulted in CR in 12.7% of patients, which is more than

that achieved with MP. Median PFS for patients treated with CVAD was 8 months and 22.9% died ≤3 months after presentation and diagnosis. Patients who were given CVAD as first-line therapy had better overall survival as compared to patients treated with MP (see figure 3.9).

These results differ from our understanding that combination chemotherapy e.g. CVAD may have better response rates but no overall survival benefit (Rajkumar, 2009). However, the findings may reflect a selection bias. As noted, patients who received CVAD were considered possible candidates for ASCT and were younger (median age 53 years; range 31 – 67 years), likely with fewer comorbid conditions and better performance status. Moreover, when the CVAD and MP groups were corrected for early deaths, both had median PFS of 9 months.

The first ASCT took place in 2003. The median age of patients receiving early ASCT was 52 years (range 35 – 57 years). In total 9 patients were treated with early ASCT. MP was the induction regimen in the first recipient of ASCT. This is unusual as melphalan is generally avoided as it can hinder adequate stem cell harvest (Rajkumar, 2009). CVAD was the induction regimen in the other 8 patients. In recipients of early ASCT, CR was achieved in 5/9 patients (55.6%) and a median PFS of 45 months was attained. ANOVA analysis showed a significantly longer PFS for early ASCT versus MP and for early ASCT versus CVAD. In addition, overall survival was best for early ASCT (see figure 3.9).

There are limitations interpreting the outcomes achieved with early ASCT. Firstly, the number of patients who underwent early ASCT was small (only 9 patients). Secondly, again, these results may reflect selection bias. But the findings are in keeping with reports that overall survival is improved by 12 months in those who receive ASCT (Rajkumar, 2014).

4.4.2 Therapy for disease relapse

The data regarding PFS for disease relapse appears to contrast with our understanding that the duration of remission decreases with each regimen (Rajkumar, 2014). For example, in patients receiving first-line therapy with MP median PFS was 4 months as compared to 10 months when MP was used for disease relapse. Similarly, first-line therapy with CVAD resulted in median PFS of 8 months versus 9 months when utilized for disease relapse. However, first-line endpoints were skewed by the high number of early deaths in those who received first-line therapy with MP, where an early death rate of 48.8% was noted, or CVAD, where an early death rate of 22.9% was recorded. It is therefore difficult to compare first-line PFS with PFS in disease relapse.

Despite the lack of a direct comparison between the different regimens used for disease relapse it does appear that patients who underwent late ASCT had a more favourable outcome with median PFS of 20 months and 2/9 patients (22.2%) achieving CR.

The data for thalidomide is limited and skewed. During the study period, several patients were enrolled into a thalidomide trial, which utilized a separate database.

Those patients that did well continued on the trial. The data presented in this study therefore only reflects those patients that voluntarily withdrew, or withdrew because of intolerable or severe side-effects, or withdrew because the disease progressed whilst enrolled in the trial. This is supported by the finding that 0/7 patients achieved CR or VGPR, pointing to the fact that those who did well remained on the trial. PFS was determined in only 4/7 patients i.e. too few to meaningfully comment on thalidomide outcomes.

4.4.3 Radiation therapy

In a recent large series of patients with multiple myeloma, 149/442 patients (34%) received radiation therapy to 262 different anatomical sites during the course of their disease. This is an average of 1.8 sites per patient (Talamo, et al., 2015). Similarly, in this study 90/274 patients (32.8%) received radiation therapy to 148 sites over the duration of their illness. This equates to 1.6 sites per patient. Table 4.1 provides details of the different anatomical sites and shows that the frequency of the sites requiring radiation therapy was very similar in the 2 studies.

Table 4.1 <u>Two studies: Comparison of different sites irradiated (by percentage)</u>

Sites irradiated	Talamo study	van der Walt study
Skull and facial bones	10%	13.5%
Spine (cervical, thoracic and lumbar spine)	36%	46.6%
Thorax (ribs, sternum, clavicle, scapula)	14%	11.5%
Pelvis and sacrum	11%	11.5%
Upper limb (humerus and radius)	8%	7.4%
Lower limb (femur and tibia)	16%	9.5%
Soft tissue	5%	Not determined

4.4.4 Surgical procedures

The need for surgical assistance in 25.5% of patients highlights the multi-disciplinary nature of managing multiple myeloma.

4.5 HUMAN IMMUNODEFICIENCY VIRUS-SEROPOSITIVE PATIENTS

Multiple myeloma has been reported to occur at an increased rate in HIV-seropositive patients (Grulich, et al., 2007). However, this association has not been established in South African studies (Sitas, et al., 2000; Stein, et al., 2008). In this study 6.2% of patients were HIV-seropositive. This rate is less than the background seroprevalence of HIV-infection in the total population of South Africa, which in 2001 was 9.4% and in 2010 was 10.5% (Statistics South Africa, 2010).

In this series, 12/18 HIV-seropositive patients (66.7%) presented in the years 2008, 2009 and 2010. Increasing access to ARV therapy does not explain this distribution, as only 3 patients were taking treatment at presentation. Also, an increase in patients being tested for HIV does not explain the trend, as all patients managed by the Division of Clinical Haematology are routinely screened (with patient consent) for the disease. The increase in HIV-seropositive patients may reflect population growth in Gauteng province and may mirror the general increase in the number of patients presenting per year (see figure 3.2) (Statistics South Africa, 2004; Statistics South Africa, 2010).

This study corroborates reports from other studies regarding the presentation of HIV-seropositive patients presenting with multiple myeloma (Cheung, et al., 2005; Feller, et al., 2009; Coker, et al., 2013). Firstly, HIV-seropositive patients tend to be younger. In this study the mean age was 44.7 years, as compared to a mean age of 58.5 years in patients who are HIV-seronegative. This may, in part, reflect the younger demographic

of HIV-seropositive patients. In South Africa, in 2010, in the age group 15 – 49 years, the percentage of HIV-seropositive patients was 17.3%. This was higher than the background seroprevalence of HIV-infection of 10.5% in the total population (Statistics South Africa, 2010). Secondly, plasmacytoma is a more frequent finding in HIV-seropositive patients. In this series 7/17 (41.2%) demonstrated such lesions whereas in HIV-seronegative patients this manifestation was noted in 42/210 (20%).

In HIV-seropositive patients, immuneparesis was noted in 9/16 (56.3%); whereas in HIV-seronegative patients this finding was more frequent in 230/256 (89.8%). This difference was significant. In HIV-seropositive patients polyclonal hypergammaglobulinaemia (a diffuse elevation of proteins in the gamma region on serum protein electrophoresis) is common (Coker, et al., 2013). This may neutralize the effect of the immuneparesis and may account for the variation in the two groups.

At presentation there was no difference in the incidence of overt and opportunistic infections between patients who were HIV-seropositive and patients who were HIV-seronegative.

In HIV-seropositive patients the median CD4 count was 313 cells/mm^3, and the range was very broad from 8 – 1228 cells/mm^3. Irrespective of the CD4 count all HIV-seropositive patients were commenced on ARV therapy. Both groups of patients received similar chemotherapeutic regimens, but no HIV-seropositive patient underwent ASCT. No difference was found in the overall survival of HIV-seropositive versus HIV-

seronegative patients. This is contrary to reports noting that multiple myeloma in HIV-seropositive patients runs a more aggressive course with a reduction in overall survival (Cheung, et al., 2005; Feller, et al., 2009; Coker, et al., 2013). However, the small number of HIV-seropositive patients in this current study is a limitation.

In view of small numbers within the HIV-seropositive group it was not possible to meaningfully assess some findings. Only 5 patients had a CT scan done. A MRI scan was only performed in 6 patients. Cytogenetic studies were conducted on only 6 patients. Outcomes with regard to first-line treatment were determined in only 5 patients.

4.6 CONCLUSION

4.6.1 Strengths

This is, to the best of our knowledge, the largest descriptive study of multiple myeloma in sub-Saharan Africa. It is representative of the community the hospital serves in the most populous province in South Africa, namely Gauteng (Statistics South Africa, 2010). This study adds to the findings from an earlier study of 170 patients from the same hospital (Patel, 2000). Thus, multiple myeloma at our institution has been described in detail over the period 1992 - 2010.

A unique aspect of this study is the analysis of HIV-seropositive patients presenting with multiple myeloma. Descriptions of these patients are limited to small series and case reports, which may favour reporting the rare and unusual. This series, the largest description of such patients in sub-Saharan Africa, validates some of the conclusions reached previously.

There is sparse literature describing multiple myeloma in sub-Saharan Africa and this study of a large cohort contributes to filling this void.

4.6.2 Limitations

This study has several limitations. Firstly, and perhaps most significant, is the retrospective nature of the study, hampered by incomplete and inadequate data in some patients.

Secondly, the study describes findings at a single center in South Africa and the results may not be applicable more broadly. The patients reviewed were predominantly African (94.1%), with the White, Indian/Asian and Coloured population groups compromising 2.4%, 2.1%, and 1.4% respectively. This does not match the ethnic distribution in the total population where 79.4% are classified as African, 9.2% as White, 2.6% as Indian/Asian and 8.8% as Coloured (Statistics South Africa, 2010).

Thirdly, the high number of patients lost to follow-up is a concern. One possible reason is that many patients lived far away from the hospital e.g. 24.9% resided >50km away. These patients relied on the services of their regional hospitals. This includes transport and the initial management of complications that may have arisen during treatment e.g. neutropaenic sepsis. Therefore, some of the patients lost to follow-up may have demised at their regional centers. Another possible reason for the high rate of loss to follow-up is patients choosing to return to their family support structures in their home provinces. For the period 2006 – 2011 it was estimated that net migration into the Gauteng was 364 400, with most coming from the more rural provinces of Limpopo and Eastern Cape (Statistics South Africa, 2010). These provinces are far away from Soweto, limiting opportunity for follow-up.

Fourthly, some of the treatment groups e.g. early ASCT, had very small numbers. In addition, as noted, the better outcomes achieved with some modalities e.g. early ASCT may reflect a selection bias rather than an effect of therapy.

Fifthly, the number of HIV-seropositive patients was small which precluded sub-group analysis. Also, within the HIV-seropositive group, the lack of clear notes regarding ARV therapy and inconsistent serial determinations of CD4 counts and viral load counts barred any analysis of this data.

4.6.3 Conclusions

The following conclusions, detailed below, can be arrived at from this study.

Firstly, patients with multiple myeloma tended to be younger than is typically described, with a peak frequency (36.2%) in the 50 – 59 year age group. Moreover, this study was unusual as the number of males to females was nearly equivalent.

Secondly, the clinical, laboratory and radiological findings at presentation were not different to those documented in other descriptive studies. However, there was a tendency for a greater proportion of patients to present with a more advanced stage of disease.

Thirdly, many patients died shortly after presentation. This high early death rate may be consequent to the trend of presenting at a later stage of disease, with more acute complications of the disease (e.g. infection, renal dysfunction etc.).

Fourthly, recipients of ASCT as an early intervention showed an improved PFS and overall survival. In addition, CVAD alone as a first-line modality showed better overall survival. Whilst therapies for disease relapse were not directly compared, the raw data points to an improved PFS in patients who underwent late ASCT.

Fifthly, HIV-seropositive patients with multiple myeloma presented at a younger age with a higher rate of plasmacytoma. Immuneparesis was also found less frequently in HIV-seropositive patients. Comparing HIV-seropositive with HIV-seronegative patients showed no other differences at presentation, and no difference in overall survival.

4.6.4 Recommendations

To comprehensively describe multiple myeloma in South Africa a collaborative effort between the public and private healthcare sectors as well as between tertiary hospitals in the different provinces is needed. Also, a prospective case-control study is required to properly ascertain differences between HIV-seropositive patients presenting with multiple myeloma and HIV-seronegative patients.

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APPENDIX

This work was approved by the Human Research Ethics Committee (Medical), University of the Witwatersrand (Clearance Certificate M110502). Attached in this appendix is a copy of the clearance certificate.

This research report has been submitted to WriteCheck [http://en.writecheck.com]. This online, subscription-based, plagiarism checker uses the same database as Turnitin [http://turnitin.com]. Attached in this appendix is a copy of the certificate.