8

The Contribution of Prognostic Factors to the Better Management of Multiple Myeloma Patients

Marie-Christine Kyrtsonis, Dimitrios Maltezas,
Efstathios Koulieris, Katerina Bitsani, Ilias Pessach,
Anna Efthymiou, Vassiliki Bartzis,
Tatiana Tzenou and Panayiotis Panayiotidis
Hematology Section – First Department of Propedeutic Internal Medicine
Athens Medical School
Greece

1. Introduction

Multiple myeloma (MM) is an heterogeneous plasma cell disorder of unknown etiology, with a wide range of clinical manifestations and a highly variable disease course. Survival varies from a few months to more than ten years. The disease is characterized by bone marrow (BM) infiltration by malignant plasma cells usually secreting a serum or urine monoclonal immunoglobulin (Ig) component. Progress has been made in the understanding of its pathogenesis including knowledge of BM microenvironment and of cellular and genetic factors implicated in disease mechanisms that are not uniform in all patients, thus partly explaining disease variability. Furthermore, based on these, new very performing biology-based treatment modalities have been developed and are either already available for patients or under evaluation.

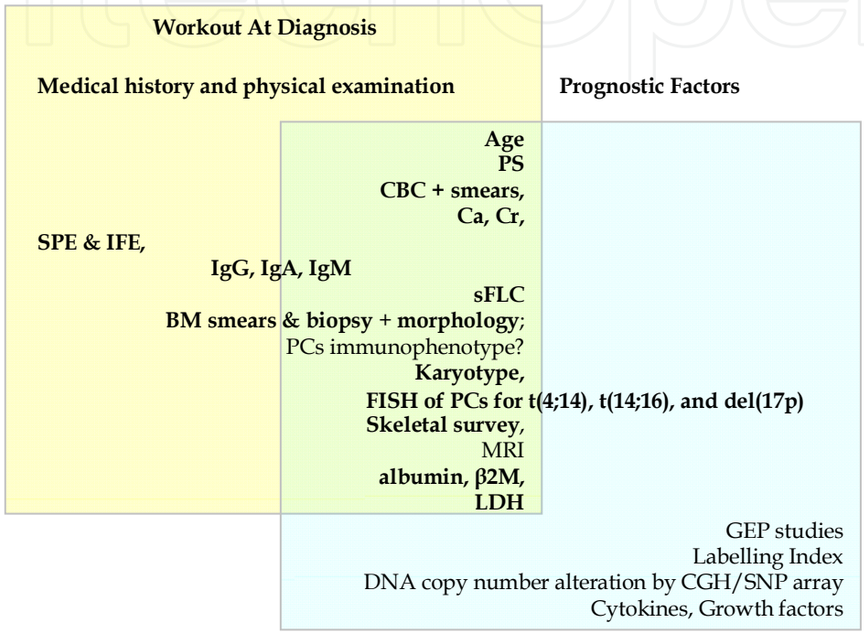
Prognostic factors (PFs) are needed to predict disease behavior and chemosensitivity to a given regimen in order to schedule the most efficient therapeutic approach. They are useful both at diagnosis and during disease course, because ongoing biologic transformations are taking place, related to further disease manifestations after response or resistance to treatment.

Existing PFs can be divided into those expressing host characteristics, reflecting tumor load and associated with malignant plasma cell or BM microenvironment peculiarities.

In the present context, existing knowledge regarding PFs and risk stratification-systems in MM, as well as their contribution in clinical practice, will be summarised. The need for re-evaluation of some established concepts or guidelines as a consequence of the recent therapeutic advances, will be discussed. Focus will be made on symptomatic MM only, because this is the field where PFs and risk-stratification systems can contribute the most to a better disease management.

2. Prognostic factors evaluated before treatment

Routine clinical and laboratory data assessed upon initial evaluation of newly diagnosed symptomatic MM patients include an important number of prognostic factors (Figure 1). Their ability to predict disease outcome has usually been established by retrospective clinical observations. Other important markers of disease behavior emerged more recently and resulted from a better knowledge of disease biology and from advances in laboratory technology. Because of the clinical importance of the information they provide, their evaluation became strongly recommended (Dimopoulos et al, 2011; Munshi et al, 2011).



PS: performance status, CBC: complete blood count, Ca: calcium, Cr: creatinine, Ig: immunoglobulin, PC: plasma cell, β2M: beta2-microglobulin, LDH: lactate dehydrogenase, sFLC: serum free light chain, MRI: magnetic resonance imaging, PET: positron emission tomography. FISH: fluorescence in situ hybridization, GEP: gene expression profiling, SNP: single nucleotide polymorphism

Fig. 1. Recommended Workout And Prognostic Factors for MM Patients at Diagnosis.

2.1 Prognostic factors expressing host characteristics

2.1.1 Age

The median age at the time of disease diagnosis is approximately 70 years and about 37% of patients are younger than 65 years (Durie et al, 2004; Durie et al, 2006). In several studies, younger age was associated with longer survival, both after conventional therapy and high-dose treatment (Kyle R, 1995; Ludwig et al, 2008; Lenhoff et al, 2006). Indeed age is closely related to performance status and the presence of co-morbidities and consequently affects treatment choice. Elderly patients are weaker and present frequently other chronic diseases such as diabetes mellitus, increased blood pressure or cardiac diseases, thus eventually compromising the administration of simple drugs like corticosteroids that are an indispensable component of MM chemotherapy. They also develop more frequently than younger ones, post-therapy cytopenias and are more prone to infections.

2.1.2 Performance status

Performance status (PS), assessed by the Eastern Cooperative Oncology Group (ECOG) or Karnofsky scale, has a considerable impact on patients' outcome (Rajkumar & Buady, 2007). It was shown in a large unselected observational study that the adverse effect of PS on outcome was greater than any other single prognostic variable (Kyle et al, 2003). In addition, patients with a bad PS are not eligible for high dose treatment with autologous stem cell transplantation, independently of age.

2.2 Prognostic factors derived from initial laboratory tests

As already mentioned, during initial MM patients' workout, routine haematology, biochemistry, immunology, histopathology, nuclear medicine and radiology tests are undertaken, both for diagnostic and prognostic purposes. Many of them are included in the Durie–Salmon staging system (Durie & Salmon, 1975) that has been for 30 years the standard risk-stratification model for MM patients and is still in use. It is a disease specific staging system that combines haemoglobin, calcium, paraprotein concentration and skeletal status by x-rays to separate MM patients into 3 distinct prognostic groups, further subdivided according to creatinine value. In addition, "disease mass" corresponding to each stage, was evaluated with complex mathematic calculations, thus suggesting that the aforementioned factors reflect to some extend tumour load, while renal status and extend of BM infiltration at aspiration's site, do not. The major limitations of the Durie-Salmon staging were that evaluation of bone disease by x-rays is observer-dependent and that paraprotein quantification in light chain MM was evaluated by the amount of 24 hours proteinuria.

2.2.1 Complete Blood Count (CBC)

With regard to CBC assessed at diagnosis, anaemia is the most common finding. It confers an adverse prognosis without being an independent factor; it may reflect in part tumor burden although anaemia is mostly due to cytokines' inhibitory activity and to impaired erythropoietin secretion or function. The other blood counts are usually normal. However, all kind of cytopenias (anemia, thrombocytopenia, neutropenia, lymphocytopenia), when observed, present a significant correlation with early death (Augustson et al, 2005). Thrombocytopenia in particular (Cavo et al, 1989) is a rare but powerful independent PF.

2.2.2 Serum creatinine

Renal impairment, due to excessive free light chain (FLC) secretion in urine, is associated with an adverse prognosis (Kyle et al, 2003; Drayson et al, 2005). Until 2001 FLC secretion was estimated by the amount of protein in the urine collected during 24 hours. During the past decade, a new assay was developed which allows precise quantification of serum free light chains (Bradwell, 2001). This method was shown useful for both diagnostic and prognostic purposes (see below in the current chapter).

About 20% of patients have increased serum creatinine at the time of diagnosis, while 10% present acute renal failure and need haemodialysis. Their long term prognosis depends on renal recovery (Wirk et al, 2011), meaning that the correlation between increased creatinine and early death is mostly due to short term complications. Thus, the survival of patients with recovered kidney function is equivalent to those without renal failure.

2.2.3 Serum albumin

Serum albumin, produced in the liver, regulates blood volume by maintaining blood compartment's osmotic pressure and carries several molecules. The first reports of albumin being an important prognostic factor in MM patients came in the late 80s. (Simonsson et al, 1988; Blade et al, 1989). These results were further validated later on (Kyle et al, 2003), leading to the incorporation of albumin into two staging systems, the SWOG (Jacobson et al, 2003) and the currently widely used ISS (Greipp et al, 2005).

2.2.4 Serum calcium

Hypercalcemia is the most common metabolic disorder in MM patients. The main cause is bone destruction, which is induced by mediator proteins (RANKL, MIP-1a, DKK-1 and proinflammatory cytokines) produced by plasmacytes and stromal cells. Elevated serum calcium levels have a toxic effect on the kidneys, enhancing the damage caused by paraprotein. Inappropriate parathyroid hormone-like secretion may also contribute to increased calcium levels.

The importance of elevated serum calcium as an adverse prognostic factor was recognized early and was incorporated into the Durie-Salmon staging system. In addition, calcium levels were shown to constitute an independent predictor of life quality (Wisløff et al., 2007).

2.2.5 Imaging for the evaluation of bone disease

X-rays of the spine, skull, chest, pelvis, humeri, and femora remain the standard to identify MM related bone lesions. Magnetic resonance imaging (MRI) is recommended to evaluate symptoms in patients with normal x-rays results and in all patients with findings suggesting the presence of solitary bone plasmacytoma. In Durie – Salmon staging, the presence of spontaneous fractures (bone scale 3) leads by itself to stage III disease, independently of any other factor. Accordingly, in a series of 158 consecutive MM patients from our department, those (24%) presenting spontaneous fractures at diagnosis had a worse outcome than the others (Figure 2), with a median disease specific survival of 38 versus 90 months (p=0.012).

On the contrary, a recent study on the impact of bone lesions as evaluated by conventional radiography compared survival of patients with bone scale 0 and 1 (no lesions and diffuse osteoporosis) to the others, and failed to prove any difference (Li et al, 2010).

Indeed, the evaluation of Durie-Salmon bone scale 0, 1 and 2 is much more subjective and depends on x-rays quality than scale 3 which involves the presence of fractures. In addition plain radiographs are relatively insensitive and can only demonstrate lytic bone disease when 30% or more of trabecular bone has been lost (Snapper I, 1971; Lecouvet et al, 1999). For all these reasons, Durie proposed in 2006, the incorporation into the system he had developed in the 70s, of MRI and positron emission tomography (PET) scan findings for the precise evaluation of lytic and other bone lesions (Durie BGM, 2006). The new staging was named Durie-Salmon Plus but was not widely adopted.

MRI showed utility as a prognostic factor (Moulopoulos et al, 2005). The Hellenic MM working group evaluated 142 symptomatic MM patients with MRI. Focal marrow lesions were identified in 50% of patients, diffuse marrow replacement in 28%, a variegated pattern in 14%, and normal pattern in 8% of patients. Patients with diffuse pattern had a median

survival of 24 months, while it was longer than 50 months for the remaining patterns. It was shown in addition that patients with more than 7 focal lesions detected by MRI, had a worse outcome, while in contrast, the number of lesions on plain radiography did not contribute to prognosis (Walker et al, 2007).

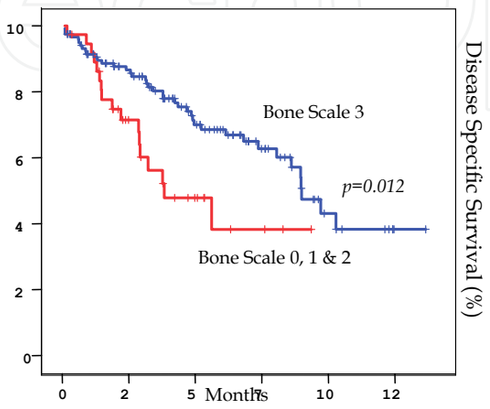


Fig. 2. Survival According to the Presence or Absence of Spontaneous Fractures.

2.3 Prognostic factors related to tumor burden and growth fraction

2.3.1 Beta-2-Microglobulin (β_2M)

Beta2-Microglobulin (β_2-M) is a subunit of the MHC class I molecule, associated with the outer membrane of almost all nucleated cells. High serum β_2-M levels are detected in patients with renal impairment, lymphoid malignancies and autoimmune disorders. In MM, β_2-M emerged as a predictor of survival in the late 1970s (Cassuto et al, 1978; Norfolk et al, 1979). Its role in the initial staging and subsequent monitoring of monoclonal plasma cell disorders was studied (Garewal et al, 1984). However, it was not found helpful for monitoring MM disease course, since there are patients that relapse without a previous raise in β_2-M levels, while others show increases without any evidence of disease progression (Cuzick et al, 1990). Several stratification systems of β_2-M in combination with other disease parameters were afterwards proposed (Bataille et al, 1992). In 2005 the International Staging System (ISS) (Greip et al, 2005), based on clinical and laboratory data gathered on 11171 MM patients showed that the combination of β_2-M and albumin separated very efficiently prognostic subgroups. Median overall survival was 62, 44, and 29 months, for patients with ISS stages 1, 2, and 3 respectively. That system was simple and potent and replaced the Durie–Salmon staging system. ISS has important pitfalls; it is not disease specific and cannot separate the small subgroup of patients with a very limited survival, who will benefit from a different therapeutic approach (Rajkumar & Buadi, 2007). Attempts were therefore made to improve ISS prognostication by adding other variables (Table 1), namely LDH (Terpos et al, 2010), serum free light chain ratio (Kyrtsonis et al, 2007b; Snozek et al, 2008) or cytogenetic abnormalities (Avet-Loiseau et al, 2009; Neben et al, 2010).

Study	Model	Results			
Terpos et al, 2010	LDH ≥ or <300 U/L within ISS groups	ISS 1: 27,7%	High LDH 7%	Median OS (months)	22
			Normal LDH 93%		76
		ISS 2: 38%	High LDH 10%		11
			Normal LDH 90%		40
		ISS 3: 34,3%	High LDH 12%		17
			Normal LDH 88%		27
Neben et al, 2010	Low risk: ISS 1 and absence of t(4;14) or del17p13 High Risk: ISS 2/3 and t(4;14) or del17p13 Int risk: All others	Low: 42%	5 years OS (%)		72
		Intermediate: 44%			62
		High: 14%			41
Snozek et al, 2008	Presence of 0,1,2,3 of sFLC abnormal, β_2M≥ 3,5 g/dl, albumin 3,5<g/dl	0 factors: 12,6%	5 years OS (%)		41,5
		1 factor: 29,9%			32
		2 factors: 34,5%			24.5
		3 factors: 23,5%			13.4
Kyrtsonis et al, 2007	Low risk: sFLCR <median and ISS <3 Int risk: Either sFLCR> median or ISS=3 High risk: sFLCR> median and ISS=3	Low: 29%	5 years OS (%)		90
		Intermediate: 46%			56
		High: 24%			24

ISS: International Staging System, OS = overall survival, sFLCR = serum free light chain ratio,β_2 M: B2-microglobulin.

Table 1. Risk-Stratification Models Attempting ISS Prognostication Improvement

2.3.2 Lactate Dehydrogenase (LDH)

Since the late 70s, the relationship between hematological malignancies and elevated LDH has been intensively studied (Talageri et al, 1977). In aggressive lymphoma patients, increased LDH was found linked to high tumor burden and turnover (Vezzoni MA et al, 1983). Later on several investigators reported its prognostic value in MM patients (Simonsson et al, 1987; Barlogie et al, 1989), it was however not incorporated in any widely used staging system, although its ability to identify patients with an especially adverse outcome was shown (Dimopoulos et al, 1991; Kyrtsonis et al, 2007b).

2.3.3 Plasma cell proliferation

Increased plasma cell proliferating potential determined by either labeling index, Ki-67 immunostaining or flow cytometry predicts shorter survival.

Plasma cell labeling index (PCLI) detects the percentage of cells in S-phase, by assessing bromodeoxyuridine uptake (Greipp et al, 1993). High PCLI was associated with both poor overall survival and progression-free survival (Boccadoro et al, 1989).

Ki-67, a nuclear protein expressed in proliferating cells and absent from resting cells, constitutes an excellent marker of the neoplastic growth fraction. Increased Ki-67 immunostaining on BM trephine biopsy specimens was found associated with shorter survival, hypodiploidy and identified an adverse prognostic group within ISS stage 1 patients (Gastinne et al, 2010).

Plasma cell proliferation can also be evaluated by flow cytometry using fluorescent dye which stains nucleic acids to detect the proportion of cells that actively double their DNA (Trendle et al, 1999). Actively proliferating cells' immunophenotype was characterized and is $CD45^{bright}CD11a^{pos}$ (Robillard et al, 2005).

2.4 Prognostic factors reflecting cell and microenvironment characteristics

In this part, prognostic factors related to plasma cell appearance, secretion, expression, genetic lesions and interaction with the BM microenvironment will be presented.

2.4.1 Plasma cell morphology

In older studies, special attention was given to PCs morphology on BM smears (Fritz et al, 1984). The presence of 2% or more plasmablasts in the plasma-cell population, was associated with a shorter survival (Greipp et al, 1998; Rajkumar et al, 1999). Plasmablasts were characterized as follows: fine reticular chromatin pattern in the nucleus; large nucleus less-abundant cytoplasm (Figure 3). In addition plasmablastic morphology was associated with increased presence of cytogenetic abnormalities.

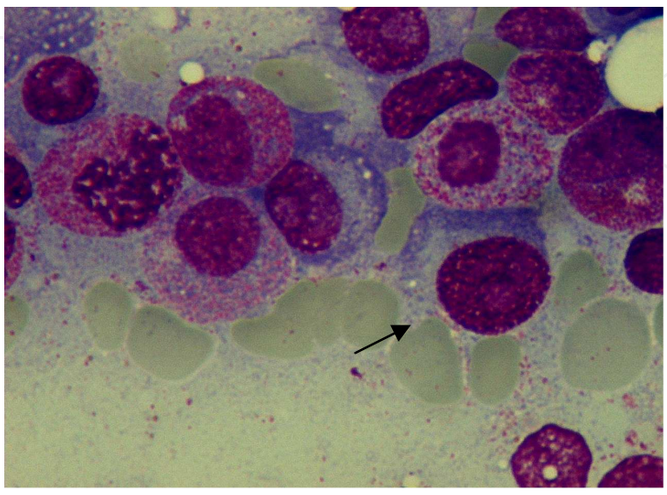


Fig. 3. Presence of Plasma Cells With Plasmablastic Morphology on BM Smears

2.4.2 Immunoglobulin heavy and light chain secretion

The hallmark of MM is the secretion of monoclonal Ig by BM infiltrating PCs. Paraprotein can be detected by serum protein electrophoresis (SPEP) and immunofixation (IFE) and quantified nephelometrically or by SPEP densitometry. About 20% of patients secrete light chains only (LCO) that can be assessed by serum/urine IFE and precisely quantified by the serum free-light-chain (FLC) assay. Although serum monoclonal Ig quantification was one of Durie and Salmon staging system's risk factors and was included in older prognostic algorithms (Bettini R, 1983), it was shown that MM aggressiveness or tumor load is not necessarily related to the amount of serum Ig heavy chain and subsequent stratification models did not retain it as a risk parameter (Kyrtsonis et al, 2009). However, paraprotein type was shown to influence survival; IgG patients enjoy the longest one, followed by IgA while LCO patients have the shortest (Drayson et al, 2006)

With regard to the amount of Ig light chains secreted by malignant plasma cells, they were traditionally grossly evaluated by 24h proteinuria. In 2001, a new assay was introduced which allows precise quantification of serum free light chains (Bradwell et al, 2001; Bradwell et al, 2003). This highly sensitive method offered significant improvement in identifying and monitoring patients with oligo–secretory and LCO disease. In the next years, serum free light chain ratio (sFLCR) was shown a powerful and independent prognostic factor in newly diagnosed MM patients (Kyrtsonis et al, 2007; Snozek et al, 2008). Furthermore, the addition of sFLCR to factors of disease activity (LDH, β2M, genetic abnormalities) provided powerful prognostic models (Kyrtsonis et al, 2007b; Kumar et al, 2010).

Immunoassays using antibodies that target junctional epitopes between the heavy and light chains of each Ig molecule were recently manufactured for the analysis of Ig heavy chain/light chain (HLC) pairs (Hevylite™). These assays allow the precise quantification of the absolute value of the monoclonal IgGκ, IgGλ, IgAκ and IgAλ separately and of their deriving ratios (Keren 2009; Bradwell 2010). Preliminary results suggest that HLC and their ratios are prognostic with regard to time to treatment (Avet-Loiseau et al, 2009b) and overall survival (Koulieris et al, 2010; Ludwig et al, 2010).

2.4.3 Plasma cell genetic abnormalities

Chromosomal abnormalities may be evaluated by conventional karyotype, fluorescence in situ hybridization (FISH), comparative genomic hybridization, or by single nucleotide polymorphism (SNP). Classical cytogenetic analysis is rarely successful because of the low plasma cell proliferation rate; however, any chromosomal abnormality that is detected on standard cytogenetic analysis is associated with a worse outcome. Monosomy or partial deletion of chromosome 13 (del13q14) is a recurrent chromosomal aberration of adverse prognosis, observed in approximatively 50% of patients with abnormal karyotypes. The frequency of the aforementioned finding is much higher when evaluated by FISH that is more sensitive and significantly increases the proportion of patients with chromosomal aberrations. However, It seems that the adverse prognostic effect of 13q deletions, as detected by FISH, is related to other associated abnormalities, such as t(4;14) translocation and partial deletion on chromosome 17p and that patients who have only a chromosome 13 deletion have the same prognosis as those who do not have this abnormality (Avet-Loiseau et al, 2007; Kyrtsonis et al, 2010b). Specific translocations in the Ig heavy chain

region that are detected by FISH, such as t(4;14), deletion 17p13, and chromosome 1 abnormalities, are associated with a poor prognosis and high risk, while standard-risk disease is defined by the presence of hyperdiploidy or t(11;14) (Fonseca et al, 2009; Avet-Loiseau, 2010b). The reported adverse impact of other rarer translocations such as t(14;16) is still under investigation due to the absence of large testing series. Prognostic information provided by GEP and SNP studies recognizes abnormalities throughout the whole genome, but they require plasma cell purification and highly specified centers; they are not routinely available for clinical prognostic evaluation.

2.4.4 plasma cell immunophenotype

Multiparameter flow cytometry (MFC) immunophenotyping can recognize normal plasma cell (N-PC) from malignant ones (MPC) according to cell surface markers (CD19, CD38, CD45, CD56). It was shown that symptomatic MM patients who have more than 5% N-PC/MPC at diagnosis present unique clinical, biological, and cytogenetic signature characterized by higher haemoglobin levels, less extended BM PC infiltration, lower paraprotein levels, and absence of high-risk cytogenetic abnormalities[t(4;14), t(14;16), del17p] (Paiva et al, 2009).

The presence or absence of combined specific cell surface markers predicts outcome. Thus, positive staining for CD19 and CD28, as well as absence of CD117 detected on clonal PC were associated with significantly shorter survival (Bahlis et al, 2007; Paiva et al, 2011).

Ploidy status evaluation, determination of the percentage of S-phase PC and stringent complete remission (sCR) categorization (Durie et al, 2006) are additional prognostic tools provided by MFC immunophenotype.

2.4.5 Prognostic factors derived from plasma cells and microenvironment cells interactions

The contribution of the medullary milieu to MM pathogenesis, was extensively studied during the past 30 years (Mitsiadis et al, 2006). Numerous cytokines and growth factors that sustain myeloma cell survival and proliferation are secreted upon plasma cells' adhesion to stromal cells. The serum concentrations of some of these, namely soluble interleukin-6 receptor (Pulki et al, 2006; Kyrtsonis et al, 2006) and soluble syndecan-1 (Seidel et al 2001, Kyrtsonis et al, 2004), are strongly prognostic for adverse survival.

The formation of new vessels and interactions between plasma cells and osteoclasts (OCs) are other important microenvironment processes accompanied by the secretion of cytokines and soluble factors that may also constitute prognostic factors. Bone marrow neo-vascularization is required to support neoplastic cells' metabolic requirements. The microvessel density correlates with disease stage and prognosis (Vacca et al, 1994; Kumar et al, 2004). Evolution from monoclonal gammopathy of unknown significance to MM, has been found associated with loss of marrow angiogenesis inhibitory activity (Kumar et al, 2004b). Myeloma and stromal cells produce angiogenic growth factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) that may account, in part, for the increased microvessel density observed in the BM. Both factors are specific endothelial cell mitogens and their serum levels were found in correlation with

disease activity markers in MM patients (Sezer et al, 2001). VEGF also induces proliferation and triggers migration of MM cells by increasing vascular permeability (Podar et al, 2001). In addition, hepatocyte growth factor (HGF) stimulates epithelial cells' growth, further induces blood vessel formation and promotes osteoclasts formation and activation; high serum HGF levels predicted poor response to therapy and survival (Di Raimondo et al, 2000). The process of angiogenesis in MM is not yet fully elucidated; it is thought that imbalance of angiogenic regulators including angiopoietins along with other known and unknown factors are additionally involved. Increased serum Angiopoietin-2 or low Angiopoietin-1/Angiopoietin-2 ratio were recently found correlated with markers of disease activity and overall survival (Joshi et al, 2011; Terpos et al, 2011). Moreover, inhibition of neovascularization offers promising therapeutical implications and such mechanisms account in part for the improved anti-myeloma activity of new drugs.

Osteolyses in MM is caused by OCs proliferating in bony areas adjacent to myeloma cells. This promiscuity favours both cell types to secrete soluble factors sustaining one each other's activity. The main stimulator of OC formation is a member of the TNF family, namely the receptor activator of NF-kappaB ligand (RANKL). RANKL binds to the RANK receptor, on osteoclast progenitors, inducing OC differentiation and maturation while on the contrary, osteoprotegerin (OPG), a natural decoy receptor, blocks RANKL/RANK ligation. In addition, OCs are further regulated by other factors, including TNF, IL-1, IL-6, MIP-1a, while at the same time osteoblast inactivation is induced by IL-3, IL-7 and DKK1. RANKL/OPG ratio, MIP-1a, and DKK1 serum levels were all found of prognostic significance (Terpos et al, 2003a & b; Gavriatopoulou et al, 2009).

3. Prognostic factors of response to treatment

Treatment options for patients with MM at diagnosis and in relapse have dramatically increased. High dose treatment (HDT) with autologous stem cell transplantation (ASCT), thalidomide, lenalidomide, and bortezomib, introduced in the past 2 decades, resulted in improved outcomes and duration of response (Kumar et al, 2008; Lonial S, 2010). In addition, the depth of response seen with these modalities was never observed before, opening horizons for eventual cure. The aforementioned treatments are able to overcome the impact of well-known adverse prognostic factors and risk-stratification models, rendering the establishment of newer, more appropriate ones, mandatory.

3.1 Quality of response and response duration

Achieving complete response (CR) is an important goal based on the general principle that focuses in reaching the lowest tumor burden possible, in an intend to cure. In numerous studies, it was shown that the "quality" of response positively influenced both event free survival (EFS) and overall survival (OS). As "qualitative" responses, very good partial responses (VGPR), near complete responses (nCR) and CR (Blade et al, 1998), were included.

In an attempt to better define deeper CR, stringent CR was introduced as a new category in the recent "uniform international response criteria", concerning patients that, in addition to the previous criteria for CR (Blade et al, 1998), also presented normalization of free light chain ratio (FLCR) and absence of clonal cells as determined either by bone marrow immunfluoresence or immunohistochemistry (Durie et al, 2006). However the

importance of FLCR in this context remains controversial. An important limitation of the definition is that "abnormal" FLCR has not been well defined. FLCR assesses both eventual increase of involved FLC (iFLC) and suppression of the polyclonal one of the same class (pFLC); in addition normal values for kappa and lambda FLCs are not exactly the same. Setting the appropriate normal range for FLCR in general or cutoff for the "high FLCR" group has been proven a challenging task. The mostly widely accepted reference range for FLCR is 0.26-1.65. In our experience, the use of "high" and "low" FLCR with different cutoff values for kappa and lambda patients was more appropriate; we therefore used the median value of each group separately as cut – off (Kyrtsonis et al, 2007; Kyrtsonis et al 2008). Indeed, the median value changes from a patients' series to another. An international consensus agreement defining appropriate normal values is urgently needed. We also believe that the choice of a "high" and "low" cutoff will resolve to some extend, the problem of the so called "discordant" presence of abnormal FLCR with normal IFE (de Larrea CF et al, 2009; Singal et al, 2009), given that absence of minimal residual disease (MRD) does not necessarily mean absence of polyclonal Ig depression involving pFLC and resulting in an abnormal FLCR when using the proposed "lower than 0.26 or higher than 1.65" range, while it would have been "low" FLCR if our system was used. Eventually because of this limitation, although it has been four years since the introduction of the sCR entity, the impact of its achievement has not been yet evaluated in large clinical trials.

Multiparameter flow cytometry (MFC) and polymerase chain reaction (PCR) are very sensitive methods for MRD evaluation (Liu H et al, 2008; Paiva et al, 2011; Corradini et al, 2003; Martínez-Sanchez et al, 2008). A recent study showed that achievement of immunophenotypic response leads to better response duration and OS than CR and sCR. The inclusion of these methods for response evaluation was thus proposed. They are however less widely available.

3.2 Prognostic factors for high dose treatment and autologous transplant

With conventional treatment CR did not exceed 5% while few patients were primary resistant, the median overall survival (OS) being 3 years. The addition of HDT with autologous bone marrow or stem cell rescue increased the CR rate up to 30-40% (Attal et al, 1992; Lenhoff et al, 2000; Barlogie et al, 2004) and median OS to 4-5 years. However, although HDT with ASCT may overcome the adverse prognosis of a significant number of classical adverse PFs, unsatisfactory response duration was observed after high dose treatment and bone marrow transplantation or stem cell rescue in patients with partial or complete deletions of chromosome 13 by conventional cytogenetics (Tricot et al, 1995), t(4;14)(p16;q32), t(14;16)(q32;q23) and 17p13 deletions (Gertz et al, 2005; Avet-Loiseau, 2007), deletions and gains of chromosome 1p21 (Chang et al, 2005) or its associated gene *CKS1B* amplification (Chang et al, 2006). However, a recent retrospective study showed that only HDT with ASCT overcome the adverse prognosis conferred by high FLCR, while the same was not true for novel agents (Maltezas et al, 2011).

An interesting observation was that, symptomatic MM patients with more than 5% normal BM PCs displayed a greater response rate to HDT/ASCT; The CR rate was 64% versus 33% in the rest with significantly longer progression free and overall survival rates (Paiva et al, 2010).

3.3 Prognostic factors for new agents

Over the last years, new therapeutic agents, such as thalidomide, lenalidomide and bortezomib have become approved and available for the treatment of MM (Engelhardt et al, 2006; Pangalis et al, 2006). When they are given alone or in combination with corticosteroids or other agents, they produce high response rates including a considerable percentage of complete remissions (CR) or near CR (nCR). The latter is probably due to their capacity to overcome some markers of adverse prognosis (Table 2).

Marker	ASCT	New Agent			Comments
		Thalidomide	Lenalidomide	Bortezomib	
Age	S	S	O	O	
PS	Ineligible	S	S	S	
LC MM	O	O	O	O	
↓ Hb	O	S	O	O	
↑ Cr	O	S	O	O	
↑ Ca	U	S	O	O	
↑ LDH	S	S	S	S	
FLC/FLCR	O	S	S	S	
sIL-6R	U	U	U	U	
s-syndecan-1	U	U	U	U	
VEGF	U	S	U	U	
HGF	U	S	U	U	
PCLI	S	S	S	U	
Hypodiploidy	U	U	S	U	
Del13q/Δ13[c]	S	S	S	O	
t(4;14)	S	S	S	O	
del 17p13	S	S	S	O	Conflicting data for bortezomib
1p21 lesions	S	S	S	O	
CKS1B amp	S	U	U	O	

S: sustained, O: overcome, U: unknown, [c]: By conventional cytogenetics,

Table 2. Ability of Novel Agents To Overcome Some Markers Of Adverse Prognosis.

3.3.1 Thalidomide

The introduction of thalidomide in MM therapeutics was revolutionary because it constituted the first treatment able to act both on myeloma and microenvironmental cells. Its mechanism of action includes direct inhibition of malignant plasmacytes via immunomodulation of T-cells and enhancement of NK-cells (Davies et al, 2009). It also affects BM stromal cells, creating a hostile microenvironment (Mitsiades et al, 2002). The last is mediated through reduction of expression of angiogenic factors (IL-6, TNF-a, bFGF, VEGF) via gene downregulation in BM endothelial cells (Vacca et al, 2005).

The first important study on thalidomide as a single agent (Singal et al, 1999), showed a response rate of 32% in relapsed-refractory MM patients. Subsequently other investigators confirmed thalidomide efficacy as a single agent or in combination with dexamethasone, chemotherapy or other new agents (Rajkumar et al, 2000; Juliusson et al, 2000; Blade et al, 2001). However, thalidomide does not seem able to overcome established adverse prognostic factors such as advanced stage, age ≥ 65 years, abnormal karyotype, increased LDH and β2M, del q13/Δ13, hypodiploidy, t(4;14), t(14;16), 17p13 deletions, chromosome 1 abnormalities, nor that of increased VEGF and HGF levels (Mileshkin et al, 2007); however it was shown able to reverse the poor prognosis associated with cyclin-D1 negativity and fibroblast growth factor-3 positivity (Kelly et al, 2009). The adverse impact of PCLI was not overcome by Thalidomide (Kapoor et al, 2009).

3.3.2 Lenalidomide

Lenalidomide is an immunomodulatory drug. In combination with dexamethasone it constitutes an effective treatment option for most patients with relapse/refractory MM. In myeloma cells, lenalidomide inhibits cell growth, promotes apoptosis and blocks their adhesion to stromal cells in the BM milieu (Richardson et al, 2002). In stromal cells, lenalidomide reduces the expression of angiogenic factors and several additional factors that support plasma cell growth (Dredge et al, 2002). In addition, lenalidomide stimulates T cells and natural killer cells (Marriot et al, 2002).It may be beneficial regardless of patient age, disease stage and renal function, although the starting dose of lenalidomide should be adjusted for renal impairment and cytopenias (Dimopoulos et al, 2011). It was relatively recently (early 2008) approved in Europe for the treatment of relapse/refractory patients and there are at present only few studies on its effectiveness in the presence of cytogenetic findings conferring adverse prognosis. A study on 100 newly diagnosed patients that received front-line lenalidomide/dexamethasone showed that patients with high risk MM defined by the presence of hypodiploidy, del(13q) by metaphase cytogenetics, del(17p), t(4;14), or t(14;16) and high plasma cell labeling index, had a shorter progression-free survival compared to standard-risk patients (Kapoor et al, 2009). In addition it was shown unable to overcome the adverse prognosis of chromosome 1 abnormalities (Chang et al, 2010).

3.3.3 Bortezomib

Bortezomib (Velcade®) is a reversible inhibitor of the chymotryptic component of the 26S proteasome. Thus, by inhibiting the proteasome, it inactivates key proteins implicated in cell growth and function such as nuclear factor kappa B (NF-κB), leading to the inhibition of cytokines and growth factors, immunoreceptors, adhesion molecules, transcription factors and to the induction of apoptosis. In addition, angiogenesis is downregulated through inhibition of VEGF and IL-6, which are produced by vascular endothelial cells. In addition, normalization of the angiopoietin-1/angiopoietin-2 ratio was shown a surrogate marker of response to bortezomib in relapsed/refractory MM patients (Anargyrou et al, 2008). Furthermore, indirect anti-tumor effects resulting from gene silencing of RANKL have been reported. The drug has an osteoblast activating effect by reducing serum dickkopf-1, resulting in an increase of bone-type alkaline phosphatase (Terpos et al, 2006).

In Europe, it has been licensed only for the treatment of relapsed/refractory MM patients or those with previously untreated MM, who are not eligible for high-dose chemotherapy with ASCT, in combination with melphalan and prednisone, while in the US there are no restrictions.

It was shown able to overcome the adverse effect of deleterious genetic aberrations (13q deletions, t(4;14), amplification *CKS1B* (Chang et al, 2007; Jannagath, 2007; Sagaster, 2007). Drug effectiveness in patients with del(17p) is controversial (Avet-Loiseau et al, 2010b); patients may respond but rapidly relapse. Some subanalyses and prospective studies suggest that up-front bortezomib-based treatment followed by HDT/ASCT and reinductions with bortezomib-lenalidomide-dexamethasone combinations may benefit high-risk patients with t(4;14) or del(17p). Nevertheless a subset of patients will still present early death (Avet-Loiseau, 2010).

4. Prognostic factors related to specific disease manifestations

The prediction of particularly morbid MM manifestations in order to avoid them, if possible, would have been of special interest. Unfortunately, although there are a number of markers that reflect specific manifestations, almost none predict their acute onset. For example, bone disease is more extended when increased concentrations of cytokines and soluble factors involved in bone metabolism are observed, but this is not enough to predict spontaneous fractures. In the same way, patients with polyclonal hypogammaglobulinaemia are more prone to infections but the presence of depressed polyclonal antibodies is not a strong enough predictor of infection in order to administer antibiotics. The most "predictable" disease manifestation is renal failure and evidences of genetic predisposition for peripheral neuropathy are emerging (Corthals et al, 2011).

4.1 Renal failure

Rapidly increasing sFLCs, observed while monitoring patients, predict imminent renal failure. Approximately 40% of MM patients have renal impairment at clinical presentation and 5-10% will require haemodialysis because of acute renal failure from cast nephropathy. Since the pre-renal load of sFLCs is the direct cause of renal damage, it is logical to monitor for rising concentrations on a regular basis, so that acute renal failure during disease relapse can be avoided by early treatment initiation (Hutchison et al, 2007).

5. Conclusion

In current clinical practice, MM patients' workout at diagnosis, automatically include prognostic factors such as CBC, creatinine, albumin, β_2M, LDH, 24 hours proteinuria, SPE, IFE and quantitative Ig and FLC measurements (with FLCR calculation), bone survey, bone marrow aspiration and biopsy with conventional karyotype. Information provided allows staging as well as additional prognostication based on LDH and FLC/FLCR values, thus helping treatment choices. However, if the decision to make is between thalidomide- and Bortezomib- containing regimens, FISH studies, eventually revealing high risk translocations, are useful. Therefore, they should also be routinely performed. Indeed, other more sensitive and patients' specific prognostic information can possibly be provided by

GEP and SNP studies but, for the time being these highly specified techniques concern research and are not available for clinical purposes.

After treatment, best response depth estimation is important. The introduction of stringent CR improves response evaluation but a more rigorous definition is needed and results of large clinical trials on the impact of sCR achievement are awaited. Possible additional information provided by multiparameter flow cytometry should be explored, if available. The question raised at that time is weather some kind of maintenance would make remission last longer.

During follow-up of MM patients in remission and plateau phase, FLC monitoring allows prevention of renal damage and early recognition of relapse.

At the time of relapse, PFs are once again needed to predict outcome; practically, the same that were determined at diagnosis, should be tested.

In conclusion, prognostic factors and systems have evolved during the past years. They allow a better disease management and contribute to the improvement observed with regard to survival. Unfortunately, there is still a proportion of patients with suboptimal outcomes and disease remains incurable at present.

6. Acknowledgment

We warmly thank Irini Rissakis for technical support.

7. References

Anargyrou, K., Terpos, E., Vassilakopoulos, T.P., Pouli, A., Sachanas, S., Tzenou, T., Masouridis, S., Christoulas, D., Angelopoulou, MK., Dimitriadou, E.M., Kalpadakis, C., Tsionos, K., Panayiotidis, P., Dimopoulos, M.A., Pangalis, G.A. & Kyrtsonis, M-C. (2008). Normalization of the serum angiopoietin-1 to angiopoietin-2 ratio reflects response in refractory/resistant multiple myeloma patients treated with bortezomib. Haematologica, Vol. 93, No.3, (Mars 2008), pp. 451-454, Print ISSN: 0390-6078 Online ISSN: 1592-8721.

Attal, M., Huguet, F., Schlaifer, D., Payen, C., Laroche, M., Fournie, B., Mazieres, B., Pris, J., & Laurent, G. (1992). Intensive combined therapy for previously untreated aggressive myeloma. *Blood*, Vol.79, No.5, (March 1992), pp. 1130-6, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Augustson, B.M., Begum, G., Dunn, J.A., Barth, N., Davies, F., Morgan, G., Behrens, J., Smith, A., Child, J.A., & Drayson, M.T. (2005). Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United kingdom Medical Research Council trials between 1980 and 2002--Medical Research Council Adult Leukaemia Working Party. *J Clin Oncol*, Vol.23, No.36, (December 2005), pp. 9219-26, Print ISSN: 0732-183X Online ISSN: 1527-7755

Avet-Loiseau, H., Attal, M., Moreau, P., Charbonnel, C., Garban, F., Hulin, C., Leyvraz, S., Michalle, M., Yakoub-Agha, I., Garderet, L., Marit, G., Michaux, L., Voillat, L., Renaud, M., Grosbois, B., Guillerm, G., Benboubker, L., Monconduit, M., Thieblemont, C., Casassus, P., Caillot, D., Stoppa, A.M., Sotto, J.J., Wetterwald, M.,

Dumontet, C., Fuzibet, J.G., Azais, I., Dorvaux, V., Zandecki, M., Bataille, R., Minvielle, S., Harousseau, J.L., Facon, T., & Mathiot, C. (2007). Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myelome. *Blood*, Vol.109, No.8, (April 2007), pp. 3489-95, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Avet-Loiseau, H., Durie, B., Haessler, J., Crowley, J., Hoering, A., Barlogie, B., Shaughnessy, J.D. Jr., Sezer, O., Shustik, C., Hajek, R., Goldschmidt, H., Sonneveld, P., Moreau, P., Attal, M., Palumbo, A., Boccadoro, M., Lee, J.H., Westin, J., Turesson, I., San Miguel, J.F., Blade, J., Lahuerta, J.J., Pavlovsky, S., Fantl, D.B., Rajkumar, S.V., & Fonseca, R. (2009). Impact of FISH and Cytogenetics On Overall and Event Free Survival in Myeloma: An IMWG Analysis of 9,897 Patients. *Blood (ASH Annual Meeting Abstracts)*, Vol.114, No.22, (November 2009), abstr 743, ISSN: 0006-4971 Online ISSN: 1528-0020

Avet-Loiseau, H., Harousseau, J.L., Moreau, P., Mathiot, C., Facon, T., Attal, M., Bradwell, A. & Harding, S. (2009). Heavy/Light Chain Specific Immunoglobulin Ratios at Presentation Are Prognostic for Progression Free Survival in the IFM 2005-01 Myeloma Trial. *Blood (ASH Annual Meeting Abstracts)*, Vol 114, 1818, (November 2009), ISSN: 0006-4971 Online ISSN: 1528-0020

Avet-Loiseau, H. (2010). Ultra High-Risk Myeloma. In: *Hematology 2010,* Gewirtz A, Mikhael J, Schwartz B, &Crowther M, pp. 489-93, American Society of Hematology , Print ISSN: 1520-4391 Online ISSN 1520-4383, Washington

Avet-Loiseau H, Leleu X, Roussel M, Moreau P, Guerin-Charbonnel C, Caillot D, Marit G, Benboubker L, Voillat L, Mathiot C, Kolb B, Macro M, Campion L, Wetterwald M, Stoppa AM, Hulin C, Facon T, Attal M, Minvielle S, Harousseau JL. (2010). Bortezomib plus dexamethasone induction improves outcome of patients with t(4;14) myeloma but not outcome of patients with del(17p). *J Clin Oncol.* Vol.28, No. 30, (October 2010), pp. 4630-4, Print ISSN: 0732-183X Online ISSN: 1527-7755

Bahlis, N.J., King, A.M., Kolonias, D., Carlson, L.M., Liu, H.Y., Hussein, M.A., Terebelo, H.R., Byrne, G.E.Jr., Levine, B.L., Boise, L.H., & Lee, K.P. (2007). CD28-mediated regulation of multiple myeloma cell proliferation and survival. *Blood*, Vol.109, No.11, (June 2007), pp. 5002–10, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Barlogie, B., Smallwood, L., Smith, T., & Alexanian, R. (1989). High serum levels of lactic dehydrogenase identify a high-grade lymphoma-like myeloma. *Ann Intern Med*, Vol.110, No.7, (April 1989), pp. 521-5, Print ISSN: 0003-4819 Online ISSN: 1539-3704

Barlogie, B., Shaughnessy, J., Tricot, G., Jacobson, J., Zangari, M., Anaissie, E., Walker, R., & Crowley, J. (2004) Treatment of multiple myeloma. *Blood*, Vol.103, No.1, (January 2004), pp. 20-32, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Bataille, R., Boccadoro, M., Klein, B., Durie, B., & Pileri, A. (1992). C-reactive protein and beta-2 microglobulin produce a simple and powerful myeloma staging system. *Blood*, Vol.80, No.3, (August 1992), pp. 733–737, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Bettini, R., Steidl, L., Rapazzini, P., & Giardina, G. (1983) Prognostic value of the staging system proposed by Merlini, Waldenström and Jayakar for multiple myeloma. *Acta Haematol,* Vol.70, No.6, pp. 379-85, Print ISSN: 0001-5792 Online ISSN: 1421-9662

Bladé, J., Rozman, C., Cervantes, F., Reverter, J.C., & Montserrat, E. (1989). A new prognostic system for multiple myeloma based on easily available parameters. *Br J Haematol*, Vol.72, No.4, (August 1989), pp. 507-11, Print ISSN: 0007-1048 Online ISSN: 1365-2141

Blade, J., Samson, D., Reece, D., Apperley, J., Björkstrand, B., Gahrton, G., Gertz, M., Giralt, S., Jagannath, S., & Vesole, D. (1998). Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and hemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *Br J Haematol*, Vol.102, No.5, (September 1998), pp. 1115–23, Print ISSN: 0007-1048 Online ISSN: 1365-2141

Blade, J., Esteve, J., Rosiño,l L., Perales, M., Montoto, S., Tuset, M., & Montserrat, E. Thalidomide in refractory and relapsing multiple myeloma. *Semin Oncol*, Vol.28, No.6, (December 2001), pp. 588-92, Print ISSN: 0093-7754

Boccadoro, M., Marmont, F., Tribalto, M., Fossati, M.G., Redoglia, V., Battaglio, S., Massaia, M., Gallamini, A., Comotti, B., Barbui, T., Campobasso, N., Dammacco, F., Cantonetti, M., Petrucci, M.T., Mandelli, F., Resegotti, L., & Pileriet, A. (1989). Early responder myeloma: kinetic studies identify a patient subgroup characterized by very poor prognosis. *J Clin Oncol*, Vol.7, No.1, (January 1989), pp. 119–25, , Print ISSN: 0732-183X Online ISSN: 1527-7755

Bradwell, A.R., Carr-Smith, H.D., Mead, G.P., Tang, L.X., Showell, P.J., Drayson, M.T., & Drew, R. (2001) Highly sensitive, automated immunoassay for immunoglobulin free light chains in serum and urine. *Clin Chem*, Vol 47, No 4, (April 2001), pp 673-680, Print ISSN: 0009-9147 Online ISSN: 1530-8561

Bradwell, A.R.,Carr-Smith H.D., Mead, G.P., Harvey, T.C., & Drayson, M.T. (2003). Serum test for assessment of patients with Bence Jones myeloma. *The Lancet*, Vol.361, No.9356, (February 2003), pp. 489-91, Print ISSN: 0140-6736 Online ISSN: 1474-547X

Bradwell AR. (2010). *Serum Free Light Chain Analysis (Plus Hevylite)* (6th edition) The Binding Site Ltd, Birmingham, UK

Cassuto, J.P., Krebs, B.P., Viot, G., Dujardin, P., & Masseyeff, R. (1978). Beta 2microglobulin, a tumor marker of lymphoproliferative disorders. *The Lancet*, Vol.312, No.8096, (October 1978), pp. 950, Print ISSN: 0140-6736 Online ISSN: 1474-547X

Cavo, M., Galieni, P., Zuffa, E., Baccarani, M., Gobbi, M., & Tura, S. (1989). Prognostic variables and clinical staging in multiple myeloma. *Blood*, Vol.74, No.5, (October 1989), pp. 1774-1780, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Chang, H., Trieu, Y., Qi. X., Xu, W., Stewart, K.A., & Reece, D. (2007). Bortezomib therapy response is independent of cytogenetic abnormalities in relapsed/refractory multiple myeloma. *Leuk Res*, Vol.31, No.6, (June 2007), pp. 779-82, Print ISSN: 0145-2126 Online ISSN: 1873-5835

Chang, H., Qi, X., Trieu, Y., Xu, W., Reader, J.C., Ning, Y., & Reece, D. (2006) Multiple myeloma patients with CKS1B gene amplification have a shorter progression-free survival post-autologous stem cell transplantation. *Br J Haematol*, Vol.135, No.4, (November 2006), pp. 486-91, Print ISSN: 0007-1048 Online ISSN: 1365-2141

Chang, H., Qi, X., Jiang, A., Xu, W., Young, T., & Reece, D. (2010). 1p21 deletions are strongly associated with 1q21 gains and are an independent adverse prognostic

factor for the outcome of high-dose chemotherapy in patients with multiple myeloma. *Bone Marrow Transplant*, Vol 45, No 1, (January 2010), pp 117-21, Print ISSN: 0268-3369 Online ISSN: 1476-5365

Chang, H., Jiang A., Qi, C., Trieu, Y., Chen, C., & Reece, D. (2010). Impact of genomic aberrations including chromosome 1 abnormalities on the outcome of patients with relapsed or refractory multiple myeloma treated with lenalidomide and dexamethasone. *Leuk Lymphoma,* Vol.51, No.11, (November 2010), 2084-9, Print ISSN: 1042-8194 Online ISSN: 1029-2403.

Corradini, P., Cavo, M., Lokhorst, H., Martinelli, G., Terragna, C., Majolino, I., Valagussa, P., Boccadoro, M., Samson, D., Bacigalupo, A., Russell, N., Montefusco, V., Voena, C., & Gahrton, G.; Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). (2003). Molecular remission after myeloablative allogeneic stem cell transplantation predicts a better relapse-free survival in patients with multiple myeloma. *Blood*, Vol.102, No.5, (September 2003), pp. 1927-9, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Corthals, S.L., Kuiper, R., Johnson, D.C., Sonneveld, P., Hajek, R., van der Holt, B., Magrangeas, F., Goldschmidt, H., Morgan, G.J., & Avet-Loiseau H. (2011). Genetic factors underlying the risk of bortezomib induced peripheral neuropathy in multiple myeloma patients. *Haematologica*, (Epub ahead of print, July 2011), Print ISSN: 0390-6078 Online ISSN: 1592-8721

Cuzick, J., De Stavola, B.L., Cooper, E.H., Chapman, C., & MacLennan, I.C. (1990). Long-term prognostic value of serum beta 2 microglobulin in myelomatosis. *Br J Haematol*, Vol.75, No.4, (August 1990), pp. 506–510, Print ISSN: 0007-1048 Online ISSN: 1365-2141

de Larrea, C.F., Cibeira, M.T., Elena, M., Arostegui, .JI., Rosiñol, L., Rovira, M., Filella, X., Yagüe, J., & Bladé, J. (2009). Abnormal serum free light chain ratio in patients with multiple myeloma in complete remission has strong association with the presence of oligoclonal bands: Implications for stringent complete remission definition. *Blood*, Vol.114, No.24, (December 2009), pp. 4954-6, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Davies, F.E., Raje, N., Hideshima, T., Lentzsch, S., Young, G., Tai, Y.T., Lin, B., Poda, K., Gupta, D., Chauhan, D., Treon, S.P., Richardson, P.G., Schlossman, R.L., Morgan, G.J., Muller, G.W., Stirling, D.I., Anderson, K.C. (2001). Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. *Blood*, Vol.98, No.1, (July 2001), pp. 210-6, Print ISSN 0006-4971 Online ISSN 1528-0020

Dimopoulos, M.A., Barlogie, B., Smith T.L., & Alexanian, R. (1991). High serum lactate dehydrogenase level as a marker for drug resistance and short survival in multiple myeloma. *Ann Intern Med*, Vol.115, No.12, (December 1991), pp. 931-5 Print ISSN: 0003-4819 Online ISSN: 1539-3704

Dimopoulos, M., Kyle, R., Fermand, J.P., Rajkumar, SV., San Miguel, J., Chanan-Khan, A., Ludwig, H., Joshua, D., Mehta, J., Gertz, M., Avet-Loiseau, H., Beksaç, M., Anderson, K.C., Moreau, P., Singhal, S., Goldschmidt, H., Boccadoro, M., Kumar, S., Giralt, S., Munshi, N.C., & Jagannath, S. (2011). Consensus recommendations for

standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3. *Blood*, Vol.117, No.18, (May 2011), pp. 4701-5, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Dimopoulos, M.A., Palumbo, A., Attal, M., Beksaç, M., Davies, F.E., Delforge, M., Einsele, H., Hajek, R., Harousseau, J.L., da Costa, F.L., Ludwig, H., Mellqvist, U.H., Morgan, G.J., San-Miguel, J.F., Zweegman, S., & Sonneveld, P.; European Myeloma Network. (2011). optimizing the use of lenalidomide in relapsed or refractory multiple myeloma: consensus statement. *Leukemia*, Vol.25, No.5, (May 2011), pp. 749-60, Print ISSN: 0887-6924, Online ISSN: 1476-5551

Di Raimondo, F., Azzaro, M.P., Palumbo, G., Bagnato, S., Giustolisi, G., Floridia, P., Sortino, G. & Giustolisi, R. (2000). Angiogenic factors in multiple myeloma: high levels in bone marrow than in peripheral blood. *Haematologica*, Vol.85, No.8, (August 2000), pp. 800–805,Print ISSN: 0390-6078 Online ISSN: 1592-8721

Drayson, M., Begum, G., Basu, S., Makkuni, S., Dunn, J., Barth, N., & Child, J.A. (2006). Effects of paraprotein heavy and light chain types and free light chain load on survival in myeloma: an analysis of patients receiving conventional-dose chemotherapy in Medical Research Council UK multiple myeloma trials. *Blood*, Vol.108, No.6, (September 2006), pp. 2013-19, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Dredge, K., Marriott, J.B., Macdonald, C.D., Man, H.W., Chen, R., Muller, G.W., Stirling, D., & Dalgleish, A.G. (2002). Novel thalidomide analogues display anti-angiogenic activity independently of immunomodulatory effects. *Br J Cancer*, Vol.87, No.4, (November 2002), pp. 1166–72, Print ISSN: 0007-0920 Online ISSN: 1532-1827

Durie, B.G., & Salmon, S.E. (1975). A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer*, Vol.36, No.3, (May 1975), pp. 842–54, Online ISSN: 1097-0142

Durie, B.G., Kyle, R.A., Belch, A., Bensinger, W., Blade, J., Boccadoro, M., Child, J.A., Comenzo, R., Djulbegovic, B., Fantl, D., Gahrton, G., Harousseau, J-L., Hungria, V., Joshua, D., Ludwig, H., Mehta, J., Morales, A.R., Morgan, G., Nouel, A., Oken, M., Powles, R., Roodman, D., San Miguel, J., Shimizu, K., Singhal, S., Sirohi, B., Sonneveld, P., Tricot, G., & Van Ness, B. Myeloma management guidelines: a consensus report from the Scientific Advisors of the International Myeloma Foundation. (2003). *Hematol J*, Vol.4 No.6, pp. 379-98 [Erratum in: *Hematol J* 2004;5:285], Print ISSN: 1466-4860

Durie, B.G. M. (2006). The role of anatomic and functional staging in myeloma: Description of Durie/Salmon plus staging system. *Eur J Cancer*, Vol.42, No.11, (July 2006), pp. 1539-43, Print ISSN:0959-8049 Online 1879-0852

Durie, B.G., Harousseau, J-L., Miguel, J.S., Bladé, J., Barlogie, B., Anderson, K., Gertz, M., Dimopoulos, M., Westin, J., Sonneveld, P., Ludwig, H., Gahrton, G., Beksac, M., Crowley, J., Belch, A., Boccadaro, M., Cavo, M., Turesson, I., Joshua, D., Vesole, D., Kyle, R., Alexanian, R., Tricot, G., Atta,l M., Merlini, G., Powles, R., Richardson, P., Shimizu, K., Tosi, P., Morgan, G., & Rajkumar, S.V. (2006). International uniform response criteria for multiple myeloma. *Leukemia*, Vol.20, No.9, (September 2006)

pp. 1467-73, [Errata, Leukemia 2006; 20:2220, 2007;21:1134], Print ISSN: 0887-6924 Online ISSN: 1476-5551

Drayson, M., Begum, G., Basu, S., Makkuni, S., Dunn, J., Barth, N., & Child, J.A. (2006). Effects of paraprotein heavy and light chain type and free light chain load on survival in myeloma: An analysis of patients receiving conventional dose chemotherapy in Medical Research Council UK Multiple Myeloma trials. *Blood*, Vol.108, No.6, (September 2006), pp. 2013-9, Print ISSN: 0006-4971, Online ISSN: 1528-0020

Engelhardt, M., & Mertelsmann R. (2006). 160 years of multiple myeloma Progress and challenges. *Eur J Cancer*, Vol.42, No.42, (July 2006), pp. 1507-9, Print ISSN: 0959-8049

Fonseca, R., Bergsagel, P.L., Drach, J., Shaughnessy, J., Gutierrez, N., Stewart, A.K., Morgan, G., Van Ness, B., Chesi, M., Minvielle, S., Neri, A., Barlogie, B., Kuehl, W.M., Liebisch, P., Davies, F., Chen-Kiang, S., Durie, B.G., Carrasco, R., Sezer, O., Reiman, T., Pilarski, L., & Avet-Loiseau, H.; International Myeloma Working Group. (2009). International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. Leukemia, Vol.23, No.12, (December 2009), pp 2210-21, Print ISSN: 0887-6924 Online ISSN: 1476-5551

Garewal, H., Durie, B.G., Kyle, R.A., Finley, P., Bower, B., & Serokman, R. (1984). Serum beta 2-microglobulin in the initial staging and subsequent monitoring of monoclonal plasma cell disorders. *J Clin Oncol*, Vol.2, No.1, (January 1984), pp. 51-7, Print ISSN: 0732-183X Online ISSN: 1527-7755

Gastinne, T., Leleu, X., Duhamel, A., Moreau, A.S., Frank, G., Andrieux, J., Lai, J.L., Coiteux V., Yakoub-Agha, I., Bauters, F., Harousseau, J.L., Zandecki, M., & Facon, T., On behalf of the Intergroupe Francophone du Myelome (IFM).[1]On behalf of the Intergroupe Francophone du Myelome. (2010). Plasma cell growth fraction using Ki-67 antigen expression identifies a subgroup of Multiple Myeloma patients displaying short survival within the ISS stage I. *Eur J Haematol*., (August 5 2010), (Epub ahead of print doi: 10.1111/j.1600-0609.2007.0915), Print ISSN: 0902-4441 Online ISSN: 1600-0609

Gertz, M.A., Lacy, M.Q., Dispenzieri, A., Greipp, P.R., Litzow, M.R., Henderson, K.J., Van Wier, S.A., Ahmann, G.J., & Fonseca, R. (2005). Clinical implications of t(11;14)(q13;q32), t(4;14)(p16.3;q32), and -17p13 in myeloma patients treated with high-dose therapy. *Blood*, Vol.106, No.8, (October 2005), pp. 2837-40, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Greipp, P.R., Lus, J.A., O'Fallon, W.M. Katzmann, J.A., Witzig, T.E., & Kyle, R.A. (1993). Plasma cell labeling index and beta 2-microglobulin predict survival independent of thymidine kinase and C-reactive protein in multiple myeloma. *Blood*, Vol.81, No.12, (June 1993), pp. 3382–7, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Greipp, P.R., Leong, T., Bennett, J.M., Gaillard, J.P., Klein, B., Stewart, J.A., Oken, M.M., Kay, N.E., Van Ness, B., & Kyle, R.A. (1998). Plasmablastic Morphology—An Independent Prognostic Factor With Clinical and Laboratory Correlates: Eastern Cooperative Oncology Group (ECOG) Myeloma Trial E9486 Report by the ECOG

Myeloma Laboratory Group. *Blood*, Vol.91, No.7 (April 1998), pp. 2501-7, Print ISSN: 0006-4971, Online ISSN: 1528-0020

Greipp, P.R., San Miguel, J., Durie, B.G., Crowley, J.J., Barlogie, B., Bladé, J., Boccadoro, M., Child, J.A., Avet-Loiseau, H., Kyle, R.A., Lahuerta, J.J., Ludwig, H., Morgan, G., Powles, R., Shimizu, K., Shustik, C., Sonneveld, P., Tosi, P., Turesson, I., & Westin, J. (2005). International Staging System for Multiple Myeloma. *J Clin Oncol*, Vol.23, No.15, (May 2005), pp. 3412-20, Print ISSN: 0732-183X Online ISSN: 1527-7755

Fritz, E., Ludwig, H., & Kundi, M. (1984). Prognostic Relevance of Cellular Morphology in Multiple Myeloma. B*lood,* Vol.63, No.5, (May 1984), pp. 1072-9, Print ISSN: 0006-4971, Online ISSN: 1528-0020

Gavriatopoulou, M., Dimopoulos, M.A., Christoulas, D., Migkou, M., Iakovaki, M., Gkotzamanidou, & M., Terpos, E. (2009). Dickkopf-1: a suitable target for the management of myeloma bone disease. Expert Opin Ther Targets, Vol.13, No.7, (July 2009), pp. 839-48, Print ISSN: 1472-8222 Online ISSN : 1744-7631

Hutchison, C.A., Cockwell, P., Reid, S., Chandler, K., Mead, G.P., Harrison, J., Hattersley, J., Evans, N.D., Chappell, M.J., Cook, M., Goehl, H., Storr, M., & Bradwell, A.R. (2007). Efficient removal of immunoglobulin free light chains by hemodialysis for multiple myeloma: in vitro and in vivo studies. *J Am Soc Nephrol*, Vol.18, No.3, (March 2007), pp. 886-95, Print ISSN: 1046-6673 Online ISSN: 1533-3450

Jacobson, J.L., Hussein, M.A., Barlogie, B., Durie, B.G., & Crowley, J.J. (2003). Southwest Oncology Group: A new staging system for multiple myeloma patients based on the Southwest Oncology Group (SWOG) experience. *Br J Haematol*, Vol.122, No.3, (August 2003), pp. 441-50, Print ISSN: 0007-1048 Online ISSN: 1365-2141

Jagannath, S., Richardson, P.G., Sonneveld, P., Schuster, M.W., Irwin, D., Stadtmauer, E.A., Facon, T., Harousseau, J.L., Cowan, J.M., & Anderson, K.C. (2007). Bortezomib appears to overcome the poor prognosis conferred by chromosome 13 deletion in phase 2 and 3 trials. *Leukemia*, Vol.21, No.1, (January 2007), pp. 151-7, Print ISSN: 0887-6924 Online ISSN: 1476-5551

Joshi, S., Khan, R., Sharma, M., Kumar, L., & Sharma, A. (2011). Angiopoietin-2: a potential novel diagnostic marker in multiple myeloma. *Clin Biochem*, Vol.44, No.8-9, (June 2011), pp. 590-5, Print ISSN: 0009-9120

Juliusson, G., Celsing, F., Turesson, I., Lenhoff, S., Adriansson, M.;, & Malm, C. (2000). Frequent good partial remissions from thalidomide including best response ever in patients with advanced refractory and relapsed myeloma. *British Journal of Haematology*, Vol.109, No.1, (April 2000), pp. 89-96, Print ISSN: 0007-1048 Online ISSN: 1365-2141

Kapoor, P., Kumar, S., Fonseca, R., Lacy, M.Q., Witzig, T.E., Hayman, S.R., Dispenzieri, A., Buadi, F., Bergsagel, P.L., Gertz, M.A., Dalton, R.J., Mikhael, J.R., Dingli, D., Reeder, C.B., Lust, J.A., Russell, S.J., Roy, V., Zeldenrust, S.R., Stewart, A.K., Kyle, R.A., Greipp, P.R., & Rajkumar, S.V.(2009). Impact of risk stratification on outcome among patients with multiple myeloma receiving initial therapy with lenalidomide and dexamethasone. *Blood*, Vol.114, No.3, (July 2009), pp. 518-21, Print ISSN: 0006-4971, Online ISSN: 1528-0020

Kelley, T.W., Baz, R., Hussein, M., Karafa, M., & Cook, J.R. (2009). Clinical significance of cyclin D1, fibroblast growth factor receptor-3 and p53 immunohistochemistry in plasma cell myeloma treated with a thalidomide-based regimen. *Human Pathology* , Vol.40, No.3, (May 2009), pp. 405-12, Print ISSN: 0046-8177 Online ISSN: 1532-8392

Keren D.F.(2009). Heavy/Light-Chain analysis of monoclonal gammopathies. *Clin Chem*, Vol.55, No.9, (September 2009), pp. 1606-8, Print ISSN: 0009-9147 Online ISSN: 1530-8561

Koulieris, E., Kyrtsonis, M.C., Kafassi, N., Maltezas D., Bartzis., Tzenou, T., Dimou, M., Georgiou, G., Mirbahai, L., Panayiotidimm P., Bradwell, A., & Harding, S. (2010). Heavy Chain Ratio (HLCR) IgG{kappa}/IgG{lambda} or IgA{kappa}/IgA{lambda}: Experience and Clinical Implications In Multiple Myeloma at Diagnosis and During Disease Course. *Blood (ASH Annual Meeting Abstracts)*, Vol.116, No.21, (November 2010), abstr 5019, ISSN: 0006-4971 Online ISSN: 1528-0020

Kumar, S., Gertz, M.A., Dispenzieri, A.,Lacy, M,Q., Wellik, L.A., Fonseca, R., Lust, J.A., Witzig, T.E., Kyle, R.A., Greipp, P.R. & Rajkumar, S.V. (2004). Prognostic value of bone marrow angiogenesis in patients with multiple myeloma undergoing high-dose therapy. *Bone Marrow Transplant*, Vol.34, No.3, (August 2004), pp. 235–239, Print ISSN: 0268-3369 Online ISSN: 1476-5365

Kumar, S., Witzig, T., Timm, M., Haug, J., Wellik, L., Kimlinger, T., Greipp, P., & Rajkumar, V. (2004). Bone marrow angiogenic ability and expression of angiogenic cytokines in myeloma: evidence favoring loss of marrow angiogenesis inhibitory activity with disease progression. *Blood,* Vol.104, No.4, (August 2004), pp. 1159-65, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Kumar, S.K., Rajkumar, S.V., Dispenzieri. A., Lacy, M.Q., Hayman, S.R., Buadi, F.K., Zeldenrust, S.R., Dingli, D., Russell, S.J., Lust, J.A., Greipp, P.R., Kyle, R.A., & Gertz, M.A. (2008). Improved survival in multiple myeloma and the impact of novel therapies. *Blood,* Vol.111, No.5, (Mar 2008), pp. 2516–20, Print ISSN: 0006-4971, Online ISSN: 1528-0020

Kumar, S., Dispenzieri, A., van Wier, S., Katzmann, J.A., Snyder, M., Blood, E., DeGoey, R., Henderson, K., Kyle, R.A., Bradwell, A.R., Greipp, P.R., Rajkumar, S.V.,& Fonseca, R. (2010). Relationship between elevated immunoglobulin free light chain and the presence of IgH translocations in multiple myeloma. *Leukemia*, Vol.24, No.8, (August 2010), pp. 1498-1505, Print ISSN: 0887-6924 Online ISSN: 1476-5551

Kyle, R.A. (1995). Prognostic factors in multiple myeloma. *Stem Cells*, Suppl 2, (August 1995), pp. 56-63, Print ISSN: 1066-5099 Online ISSN: 1549-4918

Kyle, R.A., Gertz, M.A., Witzig, T.E., Lust, J.A., Lacy, M.Q., Dispenzieri, A., Fonseca, R., Rajkumar, S.V., Offord, J.R., Larson, D.R., Plevak, M.E., Therneau, T.M., & Greipp, P.R. (2003). Review of 1,027 patients with newly diagnosed multiple myeloma. *Mayo Clinic Proceedings*, Vol.78, No.1, (January 2003), pp. 21–33, Print ISSN: 0025-6196

Kyrtsonis, M.C., Dedoussis, G., Baxevanis, C., Stamatelou, M., & Maniatis, A. (1996). Serum interleukin-6 (IL-6) and interleukin-4 (IL-4) in patients with multiple myeloma (MM). *Br J Haematol*, Vol.92, No.2, (February 1996), pp. 420-22, Print ISSN: 0007-1048 Online ISSN: 1365-2141

Kyrtsonis, M.C., Dedoussis, G., Zervas, C., Perifanis, V., Baxevanis, C., Stamatelou, M., & Maniatis A.M-C. (1996). Soluble interleukin-6 receptor (sIL-6R), a new prognostic factor in multiple myeloma. *Br J Haematol*, Vol.93, No.2, (May 1996), pp. 398-400, Print ISSN: 0007-1048 Online ISSN: 1365-2141

Kyrtsonis, M.C.,Vassilakopoulos, T.P., Siakantaris, M.P., Kokoris, S.I., Gribabis, D.A., Dimopoulou, M.N., Angelopoulou, M.K., & Pangalis G.A. (2004). Serum syndecan-1, basic fibroblast growth factor and osteoprotegerin in myeloma patients at diagnosis and during the course of the disease. *Eur J Haematol*, Vol.72, No.4, (April 2004), pp. 252-8, Print ISSN: 0902-4441 Online ISSN: 1600-0609

Kyrtsonis, M-C., Vassilakopoulos, T.P., Kafasi, N., Sachanas, S., Tzenou, T., Papadogiannis, A., Galanis, Z., Kalpadakis, C., Dimou, M., Kyriakou, E., Angelopoulou, M.K., Dimopoulou, M.N., Siakantaris, M.P., Dimitriadou, E.M., Kokoris, S.I., Panayiotidis, P., & Pangalis, G.A. (2007). Prognostic value of serum free light chain ratio at diagnosis in multiple myeloma. *Br J of Haematol*, Vol.137, No.3, (May 2007), pp 240-3, Print ISSN: 0007-1048 Online ISSN: 1365-2141

Kyrtsonis, M.C., Vassilakopoulos, T.P., Kafasi, N., Maltezas, D., Anagnostopoulos, A., Terpos, E., Elefterakis-Papaiakovou, E., Pouli, A., Repousis, P., Delimpasi, S., Anargyrou, A., Stefanoudaki, C., Michalis, E., Sachanas, S., Tzenou, T., Masouridis, S., Dimou, M., Angelopoulou, M.K., Dimopoulou, M.N., Siakantaris, M., MD1,Dimitriadou, E., Kokoris, S.I., Kalpadakis, C., Panayiotidis, P., Dimopoulos, M.A., & Pangalis, G.A. (2007). The addition of sFLCR improves ISS prognostication in multiple myeloma. *Blood (ASH Annual Meeting Abstracts)*, Vol.110, Abstr 1490, Print ISSN 0006-4971 online ISSN 1528-0020

Kyrtsonis M.C., Vassilakopoulos T.P., Maltezas, D., Kafasi, N., Terpos, E., Eleftherakis-Papaiakovou, E., Repousis, P., Pouli, A., Delimpasi, S., Anargyrou, K., Stefanoudaki, A., Michalis, E., Sachanas, S., Tzenou, T., Dimou, M., Gavrieletopoulou, M., Panayiotidis, P., Dimopoulos, M.A., & Pangalis G.A. Hellenic Myeloma, Study Group. (2008). Suggested risk-stratification models including serum free light chain ratio for improved prognistication in multiple myeloma. *Hematology Meeting Reports* , Vol.2, No.2, (September 2008), pp. 32, ISSN 1970-7339

Kyrtsonis, M.C., Maltezas, D., Tzenou, T., Koulieris, E., & Bradwell, A.R. (2009). Staging Systems and Prognostic factors as a Guide to Therapeutic Decisions in Multiple Myeloma. *Semin Hematol* Vol.46, No.2, (April 2009), pp. 110–7, Print ISSN: 0037-1963 On line ISSN: 1532-8686

Kyrtsonis, M-C., Maltezas, D., Koulieris, E., Zaroulis, C., Tzenou, T., Sachanas, S., Bartzis, V., Georgiou, G., Dimou, M., Siakavellas, S., Vassilakopoulos, T.P., Angelopoulou, M.K., Koutra, E., Mouzaki, A., Pangalis, G.A., & Panayiotidis, P. (2010) Response to Bortezomib in Refractory/Relapsed Multiple Myeloma Patients: A Single Center Experience with Discussion on Specific Issues. *The Asia-Pacific Journal of Oncology & Hematology*, Vol.2, No.1, (February 2010), pp. 1-11, Print ISSN 1759-6637

Kyrtsonis, M-C., Bartzis, V., Papanikolaou, X., Koulieris, E., Georgiou, G., Dimou, M., Tzenou, T., & Panayiotidis, P. (2010) Genetic and Molecular Advances in Multiple

Myeloma: A Route to Better Understand Disease Heterogeneity. *The Application Of Clinical Genetics*, Vol.3, (July 2010), pp. 41-51, ISSN: 1178-704X

Lecouvet, F.E., Malghem, J., Michaux, L., Maldague, B., Ferrant, A., Michaux, J.L., & Vande Berg, B.C. (1999). Skeletal survey in advanced multiple myeloma: radiographic versus MR imaging survey. *Br J Haematol*, Vol.106, No.1, (July 1999), pp. 35–9, Print ISSN: 0007-1048 Online ISSN: 1365-2141

Lenhoff, S., Hjorth, M., Holmberg, E., Turesson, I., Westin, J., Nielsen, J.L., Wislöff, F., Brinch, L., Carlson, K., Carlsson, M., Dahl, I.M., Gimsing, P., Hippe, E., Johnsen, H.E., Lamvik, J., Löfvenberg, E., Nesthus, I., & Rödjer, S. (2000). Impact on survival of high-dose therapy with autologous stem cell support in patients younger than 60 years with newly diagnosed multiple myeloma: a population-based study. Nordic Myeloma Study Group. *Blood*, Vol 95, No 1, (January 2000), pp7-11 {Erratum in: *Blood*, Vol.116, No.13, (September 30, 2010), pp. 2402. Johnsen, H [corrected to Johnsen, H E]}, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Lenhoff, S., Hjorth, M., Westin, J., Brinch, L., Bäckström, B., Carlson, K., Christiansen, I., Dahl, I.M., Gimsing, P., Hammerström, J., Johnsen, H.E., Juliusson, G., Linder, O., Mellqvist, U.H., Nesthus, I., Nielsen, J.L., Tangen, J.M., & Turesson, I. (2006). Impact of age on survival after intensive therapy for multiple myeloma: a population-based study by the Nordic Myeloma Study Group. *Br J Haematol*, Vol.133, No.4, (May 2006), pp. 389-96, Print ISSN: 0007-1048 Online ISSN: 1365-2141

Li, Si-dan., Wang,Ya-fei., Qi, Jun-yuan., & Qiu, Lu-gui. (2010). Clinical Features of Bone Complications and Prognostic Value of Bone Lesions Detected by X-ray Skeletal Survey in Previously Untreated Patients with Multiple Myeloma. *Indian J Hematol Blood Transfus*, Vol.26, No.3, (July-Sept 2010), pp. 83–88, Print ISSN: 0971-4502 Online ISSN: 0974-0449

Liu, H., Yuan, C., Heinerich, J., Braylan, R., Chang, M., Wingard, J., & Moreb, J. (2008). Flow cytometric minimal residual disease monitoring in patients with multiple myeloma undergoing autologous stem cell transplantation: A retrospective study. *Leuk Lymphoma*, Vol.49, No.2, (February 2008), pp. 306-14, Print ISSN: 1042-8194 Online ISSN: 1029-2403

Lonial, S. (2010). Presentation and risk stratification – improving prognosis for patients with multiple myeloma. *Cancer Treatment Reviews*, Vol.36, Suppl 2, (May 2010), pp. S12–7, ISSN: 0305-7372

Ludwig, H., Nachbaur, D.M., Fritz, E., Krainer, M., & Huber, H. (1991). Interleukin-6 is a prognostic factor in multiple myeloma. *Blood*, Vol .77, No.12, (June 1991), pp. 2794-5, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Ludwig, H., Durie, B.G., Bolejack, V., Turesson, I., Kyle, R.A., Blade, J., Fonseca, R., Dimopoulos, M., Shimizu, K., San Miguel, J., Westin, J., Harousseau, J.L., Beksac, M., Boccadoro, M., Palumbo, A., Barlogie, B., Shustik, C., Cavo, M., Greipp, P.R., Joshua, D., Attal, M., Sonneveld, & P., Crowley, J. (2008). Myeloma in patients younger than age 50 years presents with more favorable features and shows better survival: an analysis of 10 549 patients from the International Myeloma Working Group. *Blood*, Vol.111, No.8, (April 2008), pp. 4039-47, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Ludwig, H., Mirbahai, L., Zojer, N., Bradwell, A., & Harding, S. (2010). The Ratio of Monoclonal to Polyclonal Immunoglobulins Assessed with the Hevylite Test Predicts Prognosis, Is Superior for Monitoring the Course of the Disease and Allows Detection of Monoclonal Immunoglobulin In Patients with Normal or Subnormal Involved Immunoglobulin Isotype. *Blood (ASH Annual Meeting Abstracts)*, Vol 116, No 21, (November 2010), Abstr 4038, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Maltezas, D., Dimopoulos, M.A., Katodritou, I., Repoussis, P., Pouli, A., Terpos, E., Panayoitidis, P., Delimpasi, S., Michalis, E., Anargyrou, K., Gavriatopoulou, M., Stefanoudaki, A., Kafassi, N., Tzenou, T., Koulieris, E., Bartzis, V., Dimou, M., Vassilakopoulos, T.P., Zervas, K., & Kyrtsonis, M.C. Hellenic Myeloma Study Group. (2011). The prognostic impact of sFLCR-ISS is conserved in MM patients treated withnew agents but not in those that underwent ASCT. *Haematologica*, Vol.96, Suppl.1, (May 2011) , Abstr P199, ISSN 0390-6078

Marriott, J.B., Clarke, I.A., Dredge, K., Muller, G., Stirling, D., & Dalgleish, A.G. (2002). Thalidomide and its analogues have distinct and opposing effects on TNF-α and TNFR2 during co-stimulation of both CD4+ and CD8+ T cells. *Clin Exp Immunol* , Vol.130, No.1, (October 2002), pp. 75-84, Print ISSN: 0009-9104 Online ISSN: 1365-2249

Martínez-Sanchez, P., Montejano, L., Sarasquete, M.E., García-Sanz, R., Fernández-Redondo, E., Ayala, R., Montalbán, M.A., Martínez, R., García Laraña, J., Alegre, A., Hernández, B., Lahuerta, J.J., & Martínez-López J. (2008). Evaluation of minimal residual disease in multiple myeloma patients by fluorescent-polymerase chain reaction: The prognostic impact of achieving molecular response. *Br J Haematol*, Vol.142, No.5, (September 2008), pp. 766-74, Print ISSN: 0007-1048 Online ISSN: 1365-2141

Mileshkin, L.,Honemann, D., Gambell, P., Trivett, M., Hayakawa, Y., Smyth, M., Beshay, V., Ritchie, D., Simmons, P., Milner, A.D., Zeldis, J.B., & Prince, H.M. (2007). Patients with multiple myeloma treated with thalidomide: evaluation of clinical parameters, cytokines,angiogenic markers, mast cells and marrow CD57+ cytotoxic T cells as predictors of outcome. *Hematologica,* Vol.92, No.8, (August 2007), pp.1075-82, Print ISSN: 0390-6078 Online ISSN: 1592-8721

Mitsiades, N., Mitsiades, C.S., Poulaki, V., Chauhan, D., Richardson, P.G., Hideshima, T., Munshi, N.C., Treon, S.P., & Anderson, K.C. Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: Therapeutic implications. *Blood*, Vol.99, No.12, (June 2002), pp. 4525-4530, Print ISSN 0006-4971 Online ISSN 1528-0020

Mitsiades, N., Mitsiades, C., Munshi, N., Richardson, P., & Anderson, K. (2006). The role of the bone microenvironment in the pathophysiology and therapeutic management of multiple myeloma: Interplay of growth factors, their receptors and stromal interactions. *Eur. Jour. Cancer*, Vol.42, No.11, (July 2006), pp. 1564-73, Print ISSN: 0959-8049

Moulopoulos, L.A., Gika, D., Anagnostopoulos, A., Delasalle, K., Weber, D., Alexanian, R., & Dimopoulos, M.A. (2005). Prognostic significance of MRI of bone marrow in

previously untreated patients with multiple myeloma. *Ann Oncol*, Vol.16, No.11, (Novenber 2005), pp. 1824-8, Print ISSN 0923-7534 Online ISSN 1569-8041

Munshi, N.C., Anderson, K.C., Bergsagel, P.L., Shaughnessy, J., Palumbo, A., Durie, B., Fonseca, R., Stewart, A.K., Harousseau, J-L., Dimopoulos, M., Jagannath, S., Hajek, R., Sezer, O., Kyle, R., Sonneveld, P., Cavo, M., Rajkumar, S.V., San Miguel, J., Crowley, J. & Avet-Loiseau, H. (2011). Consensus recommendations for risk stratification in multiple myeloma: report of the International Myeloma Workshop Consensus Panel 2. *Blood*, Vol.117, No.18, (May 2011), pp. 4696-4700, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Neben, K., Jauch, A., Bertsch, U., Heiss, C., Hielscher, T., Seckinger, A., Mors, T., Müller, N.Z., Hillengass, J., Raab, M.S., Ho, A.D., Hose, D., & Goldschmidt, H. (2010). Combining information regarding chromosomal aberrations t(4;14) and del(17p13) with the International Staging System classification allows stratification of myeloma patients undergoing autologous stem cell transplantation. *Haematologica*, Vol.95, N. 7, (July 2010), pp. 1150-7, Print ISSN: 0390-6078 Online 1592-8721

Norfolk, D., Child, J.A., Cooper, E.H., Kerruish, S., & Ward, A.M. (1980). Serum beta 2 microglobulin in myelomatosis: Potential value in stratification and monitoring. *Br J Cancer*, Vol.42, No.4, (October 1980), pp. 510-15, Print ISSN 0007-0920 Online 1532-1827

Paiva, B., Vidriales, M.B., Mateo, G., Pérez, J.J., Montalbán, M.A., Sureda, A., Montejano, L., Gutiérrez, N.C., García de Coca, A., de las Heras, N., Mateos, M.V., López-Berges, M.C., García-Boyero, R., Galende, J., Hernández, J., Palomera, L., Carrera, D., Martínez, R., de la Rubia, J., Martín, A., González, Y., Bladé, J., Lahuerta, J.J., Orfao, A., & San-Miguel, J.F.; GEM (Grupo Español de MM)/PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) Cooperative Study Groups.(2009). The persistence of immunophenotypically normal residual bone marrow plasma cells at diagnosis identifies a good prognostic subgroup of symptomatic multiple myeloma patients. *Blood*, Vol.114, No.20, (November 2009), pp. 4369–72, Print ISSN: 0006-4971, Online ISSN: 1528-0020

Paiva, B., Almeida, J., Pérez-Andrés, M., Mateo, G., López, A., Rasillo, A., Vídriales, M.B., López-Berges, M.C., Miguel J.F., & Orfao, A. (2010). Utility of flow cytometry immunophenotyping in multiple myeloma and other clonal plasma cell-related disorders. *Cytometry B Clin Cytom*, Vol.78, Suppl 1, (July 2010), pp. S47-60, Print ISSN: 1552-4949 Online ISSN: 1552-4957

Paiva, B., Martinez-Lopez, J., Vidriales, M.B., Mateos, M.V., Montalban, M.A., Fernandez-Redondo, E., Alonso, L., Oriol, A., Teruel, A.I., de Paz, R., Laraña, J.G., Bengoechea, E., Martin, A., Mediavilla, J.D., Palomera, L., de Arriba, F., Bladé, J., Orfao, A., Lahuerta, J.J., & San Miguel, J.F. (2011). Comparison of Immunofixation, Serum Free Light Chain, and Immunophenotyping for Response Evaluation and Prognostication in Multiple Myeloma. *J Clin Oncol*, Vol.29, No.12, (April 2011), pp. 1627-33, Print ISSN: 0732-183X Online ISSN: 1527-7755

Pangalis, G.A., Kyrtsonis, M.C., Vassilakopoulos, T.P., Dimopoulou, M.N., Siakantaris, M.P., Emmanouilides, C., Doufexis, D., Sahanas, S., Kontopidou, F.N., Kalpadakis, C., Angelopoulou, M.K., Dimitriadou, E.M., Kokoris, S.I., & Panayiotidis, P. (2006).

Immunotherapeutic and immunoregulatory drugs in haematologic malignancies. *Current Topics in Medicinal Chemistry*, Vol.6, No.16, pp. 1657-86, ISSN: 1568-0266

Podar, K., Tai, Y.T., Davies, F.E., Lentzsch, S., Sattler, M., Hideshima, T., Lin, B.K., Gupta, D., Shima, Y., Chauhan, D., Mitsiades, C., Raje, N., Richardson, P., & Anderson, K.C. (2001). Vascular endothelial growth factor triggers signaling cascades mediating multiple myeloma cell growth and migration. *Blood*, Vol.98, No.2, (July 2001), pp. 428-435, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Pulkki, K., Pelliniemi, T.T., Rajamäki, A., Tienhaara, A., Laakso, M., & Lahtinen, R. (1996). Soluble interleukin-6 receptor as a prognostic factor in multiple myeloma. Finnish Leukaemia Group. *Br J Haematol*, Vol.92, No.2, (February 1996), pp. 370-4, Print ISSN: 0007-1048 Online ISSN: 1365-2141

Rajkumar, S.V., Fonseca, R., Lacy, M.Q., Witzig, T.E., Therneau, T.M., Kyle, R.A., Litzow, M.R., Gertz, M.A., & Greipp, PR. (1999). Plasmablastic Morphology Is an Independent Predictor of Poor Survival After Autologous Stem-Cell Transplantation for Multiple Myeloma. *J Clin Oncol*, Vol.17, No.5, (May 1999), pp. 1551-57, Print ISSN: 0732-183X Online ISSN: 1527-7755

Rajkumar, S.V., Fonseca, R., Dispenzieri, A., Lacy, M.Q., Lust, J.A., Witzig, T.E., Kyle, R.A., Gertz, M.A., & Greipp, P.R. (2000). Thalidomide in the treatment of relapsed multiple myeloma. *Mayo Clin Proc*, Vol.75, No.9, (September 2000), pp. 897-901, Print ISSN: 0025-6196 Online ISSN: 1942-5546

Rajkumar, S.V. & Buadi, F. (2007). Multiple myeloma: New staging systems for diagnosis, prognosis and response evaluation. *Best Practice & Research Clinical Haematology,* Vol. 20, No. 4, (December 2007), pp. 665–80, Print ISSN: 1521-6926

Richardson, P.G., Schlossman, R.L., Weller, E., Hideshima, T., Mitsiades, C., Davies, F., LeBlanc, R., Catley, L.P., Doss, D., Kelly, K., McKenney, M., Mechlowicz, J., Freeman, A., Deocampo, R., Rich, R., Ryoo, J.J., Chauhan, D., Balinski, K., Zeldis, J., & Anderson, K.C. (2002). Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. *Blood,* Vol.100, No.1, (November 2002), pp. 3063–7, Print ISSN 0006-4971 Online ISSN 1528-0020

Robillard, N., Pellat-Deceunynck, C., & Bataille, R. (2005). Phenotypic characterization of the human myeloma cell growth fraction. *Blood*, Vol.105, No.12, (June 2005), pp. 4845-8, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Sagaster, V., Ludwig, H., Kaufmann, H., Odelga, V., Zojer, N., Ackermann, J., Küenburg, E., Wieser, R., Zielinski, C., & Drach, J. (2007). Bortezomib in relapsed multiple myeloma: response rates and duration of response are independent of a chromosome 13q-deletion. *Leukemia*, Vol.21, No.1, (January 2007), pp. 164-68, Print ISSN: 0887-6924 Online ISSN: 1476-5551

Seidel, C., Sundan, A., Hjorth, M., Turesson, I., Dahl, I.M., Abildgaard, N., Waage, A., & Borset, M. (2000). Serum syndecan-1: a new independent prognostic marker in multiple myeloma. *Blood*, Vol.95, No.2, (January 2000), pp. 388-92, Print ISSN: 0006-4971, Online ISSN: 1528-0020

Sezer, O., Jakob, C., Eucker, J., Niemöller, K., Gatz, F., Wernecke, K., & Possinger, K. (2001). Serum levels of the angiogenic cytokines basic fibroblast growth factor (bFGF),

vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) in multiple myeloma. *Eur J Haematol*, Vol.66, No.2, (February 2001), pp. 83-88, Print ISSN: 0902-4441 Online ISSN: 1600-0609

Simonsson, B., Brenning, G., Källander, C., & Ahre, A. (1987) Prognostic value of serum lactic dehydrogenase (S-LDH) in multiple myeloma. *Eur J Clin Invest*, Vol.17, No.4, (August 1987), pp. 336-9, Print ISSN: 0014-2972 Online ISSN: 1365-2362

Simonsson, B., Källander, C.F., Brenning, G., Killander, A., Gronowitz, J.S., & Bergström, R. (1988). Biochemical markers in multiple myeloma: a multivariate analysis. *Br J Haematol*, Vol.69, No.1, (May 1988), pp. 47-53, Print ISSN: 0007-1048 Online ISSN: 1365-2141

Singhal, S., Mehta, J., Desikan, R., Ayers, D., Roberson, P., Eddlemon, P., Munshi, N., Anaissie, E., Wilson, C., Dhodapkar, M., Zeldis, J., & Barlogie, B. (1999). Antitumor activity of thalidomide in refractory multiple myeloma. *The New England Journal of Medicine,* Vol.341, No.21, (November 1999), pp. 1565-71, Print ISSN 0028-4793 Online ISSN 1533-4406

Singhal, S., Vickrey, E., Krishnamurthy, J., Singh, V., Allen, S., & Mehta, J. (2009). The relationship between the serum free light chain assay and serum immunofixation electrophoresis, and the definition of concordant and discordant free light chain ratios. *Blood*, Vol.114, No.1, (July 2009), pp. 38-9, Print ISSN: 0006-4971, Online ISSN: 1528-0020

Snapper, I., & Khan A. (1971). *Myelomatosis: Fundamentals and Clinical Features*, University Park Press, ISBN 0839105886 9780839105886 Baltimore

Snozek, C.L., Katzmann, J.A., Kyle, R.A., Dispenzieri, A., Larson, D.R., Therneau, T.M., Melton, L.J., Kumar, S., Greipp, P.R., Clark, R.J., & Rajkumar, S.V. (2008). Prognostic value of the serum free light chain ratio in newly diagnosed myeloma: proposed incorporation into the international staging system. *Leukemia*, Vol.22, No.10, (October 2008), pp. 1933-37, Print ISSN: 0887-6924 Online ISSN: 1476-5551

Talageri, V.R., Nadkarni, J.S., & Gollerkeri, M.P. (1977). Evaluation of plasma lactate dehydrogenase (LDH) isoenzymes in cancer patients. *Indian J Cancer*, Vol.14, No.1, (March 1977), pp. 42-9, Print ISSN: 0019-509X

Terpos, E., Szydlo, R., Apperley, J.F., Hatjiharissi, E., Politou, M., Meletis, J., Viniou, N., Yatagana,s X., Goldman, J.M., & Rahemtulla, A. (2003). Soluble receptor activator of nuclear factor kappaB ligand-osteoprotegerin ratio predicts survival in multiple myeloma: proposal for a novel prognostic index. *Blood,* Vol. 102, No.3, (August 2003), pp. 1064-9, Print ISSN: 0006-4971 Online ISSN: 1528-0020

Terpos, E., Politou, M., Szydlo, R., Goldman, J.M., Apperley, J.F., & Rahemtulla, A. (2003). Serum levels of macrophage inflammatory protein-1 alpha (MIP-1alpha) correlate with the extent of bone disease and survival in patients with multiple myeloma. Br J Haematol, Vol.123, No.1, (October 2003), pp.106-9, Print ISSN: 0007-1048 Online ISSN: 1365-2141

Terpos, E., Heath, D. J., Rahemtulla, A., Zervas, K., Chantry, A., Anagnostopoulos, A., Pouli, A., Katodritou, E., Verrou, E., Vervessou, E-C., Dimopoulos, M.A. & Croucher, P.I. (2006). Bortezomib reduces serum dickkopf-1 and receptor activator of nuclear factor-κB ligand concentrations and normalises indices of bone remodelling in

patients with relapsed multiple myeloma. *Br J Haematol*, Vol.135, No.5, (December 1996), pp. 688–692, Print ISSN: 0007-1048 Online ISSN: 1365-2141

Terpos, E., Katodritou, E., Roussou, M., Pouli, A., Michalis, E., Delimpasi, S., Parcharidou, A., Kartasis, Z., Zomas, A., Symeonidis, A., Viniou, N.A., Anagnostopoulos, N., Economopoulos, T., Zervas, K., & Dimopoulos, M.A.; Greek Myeloma Study Group, Greece. (2010). High serum lactate dehydrogenase adds prognostic value to the international myeloma staging system even in the era of novel agents. *Eur J Haematol*, Vol.85, No.2, (August 2010), pp. 114-9, Print ISSN: 0902-4441 Online ISSN: 1600-0609

Terpos, E., Anargyrou K., Katodritou E., Kastritis E., Papatheodorou A., Christoulas D., Pouli A., Michalis ., Delimpasi S., Gkotzamanidou M., Nikitas N., Koumoustiotis V., Margaritis D., Tsionos K., Stefanoudaki E., Meletis J., Zervas K., & Dimopoulos, M.A. (2011). Circulating angiopoietin-1 to angiopoietin-2 ratio is an independent prognostic factor for survival in newly diagnosed patients with multiple myeloma who received therapy with novel antimyeloma agents. *Int J Cancer*, (April 2011), (Epub ahead of print), Print ISSN: 0020-7136 Online ISSN: 1097-0215

Trendle, M.C., Leong, T., Kyle, R.A., Katzmann, J.A., Oken, M.M., Kay, N.E., Van Ness, B.G., & Greipp, P.R. (1999). Prognostic Significance of the S-phase Fraction of Light-Chain-Restricted Cytoplasmic Immunoglobulin (cIg) Positive Plasma Cells in Patients with Newly Diagnosed Multiple Myeloma Enrolled on Eastern Cooperative Oncology Group Treatment Trial E9486. *American Journal of Hematology,* Vol.61, No.4, (August 1999), pp. 232–7, Print ISSN: 0361-8609 Online ISSN: 1096-8652.

Tricot, G., Barlogie, B., Jagannath, S., Bracy, D., Mattox, S., Vesole, D.H., Naucke, S., & Sawyer J.R. (1995). Poor prognosis in multiple myeloma is associated only with partial or complete deletions of chromosome 13 or abnormalities involving 11q and not with other karyotype abnormalities. *Blood*, Vol.86, No.11, (December 1995), pp. 4250-56, Print ISSN: 0006-4971, Online ISSN: 1528-0020

Vacca, A., Ribatti, D., Roncali, L., Ranieri, G., Serio, G., Silvestris, F., & Dammacco, F. (1994). Bone marrow angiogenesis and progression in multiple myeloma. *Br J Haematol*, Vol.87, No.3, (July 1994), pp. 503–508, Print ISSN: 0007-1048 Online ISSN: 1365-2141

Vacca, A., Scavelli, C., Montefusco, V., Di Pietro, G., Neri, A., Mattioli, M., Bicciato, S., Nico, B., Ribatti, D., Dammacco, F., Corradini, P. (2005). Thalidomide downregulates angiogenic genes in bone marrow endothelial cells of patients with active multiple myeloma. *J Clin Oncol* , Vol.23, No.23, (August 2005), pp. 5334–46, Print ISSN: 0732-183X Online ISSN: 1527-7755

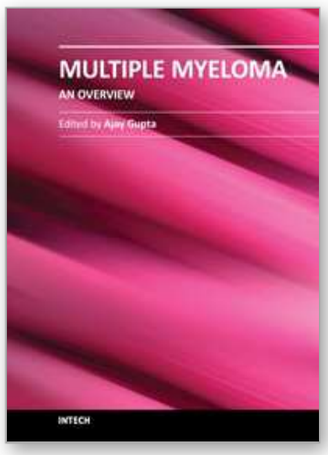
Vezzoni, M.A., Lucchini, R., Giardini, R., Raineri, M., Murone, M., & Vezzoni, P. (1983). Lactate dehydrogenase levels in cellular extracts of human malignant lymphomas. *Tumori*, Vol.69, No.4, (August 1983), pp. 279-82, Print ISSN: 0300-8916

Walker, R., Barlogie, B., Haessler, J., Tricot, G., Anaissie, E., Shaughnessy, J.D. Jr., Epstein, J., van Hemert, R., Erdem, E., Hoering, A., Crowley, J., Ferris, E., Hollmig, K., van Rhee, F., Zangari, M., Pineda-Roman, M., Mohiuddin, A., Yaccoby, S., Sawyer, J., & Angtuaco, E.J. (2007). Magnetic resonance imaging in multiple myeloma: diagnostic

and clinical implications. *J Clin Oncol*, Vol.25, No.9, (March 2007), pp. 1121-28, Print ISSN: 0732-183X Online ISSN: 1527-7755

Wirk, B. (2011). Renal failure in multiple myeloma: a medical emergency. *Bone Marrow Transplant*, Vol.46, No.6, (June 2011), pp. 771-83, Print ISSN: 0268-3369 Online ISSN: 1476-5365

Wisloff, F., Kvam, A.K., Hjorth, M., & Lenhoff, S. (2007). Serum calcium is an independent predictor of quality of life in multiple myeloma. *Eur J Haematol*, Vol.78, No.1, (January 2007), pp. 29-34, Print ISSN: 0902-4441 Online ISSN: 1600-0609.



Multiple Myeloma - An Overview

Edited by Dr. Ajay Gupta

ISBN 978-953-307-768-0
Hard cover, 274 pages
Publisher InTech
Published online 20, January, 2012
Published in print edition January, 2012

Multiple myeloma is a malignant disorder characterized by the proliferation of plasma cells. Much insight has been gained into the molecular pathways that lead to myeloma and indeed much more remains to be done. The understanding of these pathways is closely linked to their therapeutic implications and is stressed upon in the initial chapters. Recently, the introduction of newer agents such as bortezomib, lenalidomide, thalidomide, liposomal doxorubicin, etc. has led to a flurry of trials aimed at testing various combinations in order to improve survival. Higher response rates observed with these agents have led to their integration into induction therapies. The role of various new therapies vis a vis transplantation has also been examined. Recent advances in the management of plasmacytomas , renal dysfunction, dentistry as well as mobilization of stem cells in the context of myeloma have also found exclusive mention. Since brevity is the soul of wit our attempt has been to present before the reader a comprehensive yet brief text on this important subject.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen