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

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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.

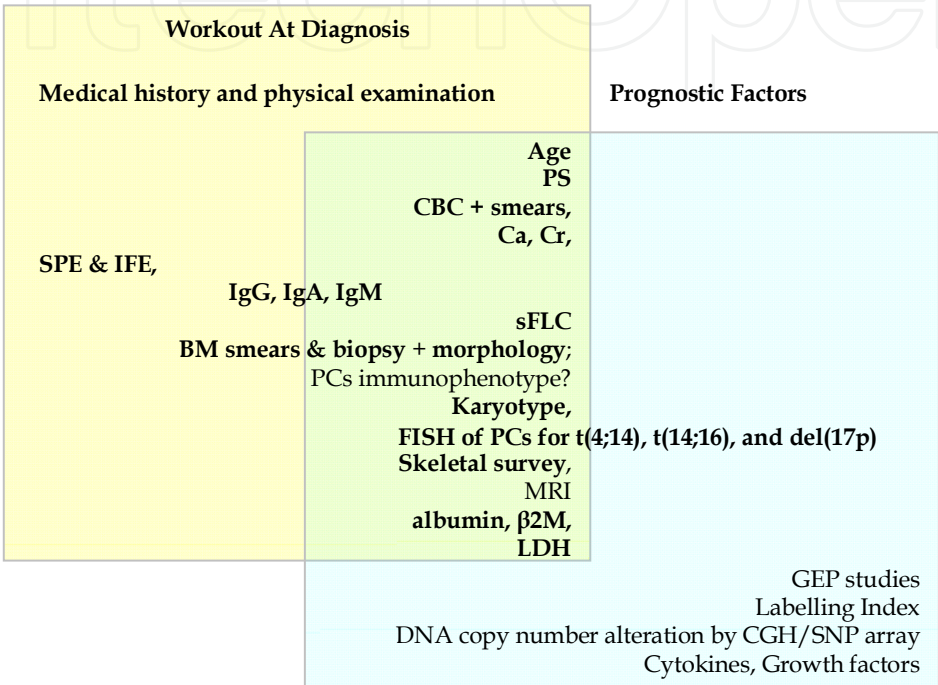
Prognostic factors (PFs) are needed to predict disease behavior and chemosensitivity to a given regimen in order to schedule the most efficient therapeutic approach. They are useful both at diagnosis and during disease course, because ongoing biologic transformations are taking place, related to further 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 extent tumour load, while renal status and extent 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).

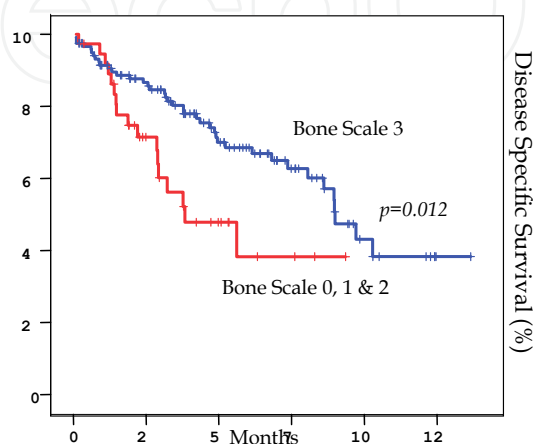


Fig. 2. Survival According to the Presence or Absence of Spontaneous Fractures.

2.3 Prognostic factors related to tumor burden and growth fraction

2.3.1 Beta-2-Microglobulin (β_2 M)

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 (Kyrtsolis 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 ₂ M≥ 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
Kyrtsolis 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,β₂M: 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; Kyrtsolis 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.

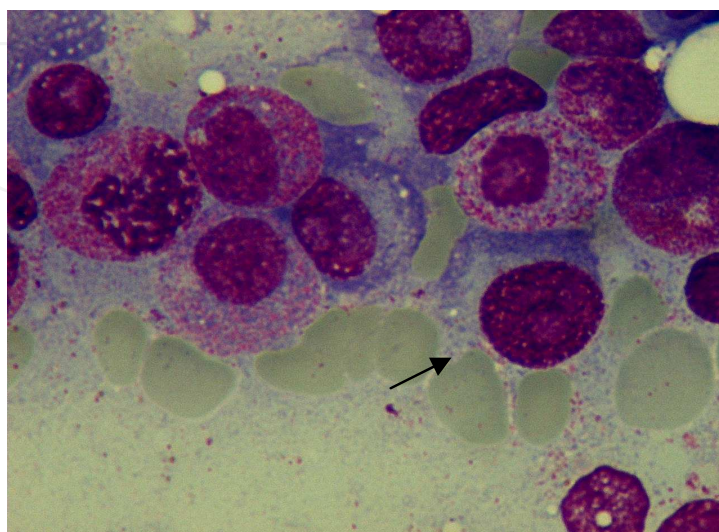


Fig. 3. Presence of Plasma Cells With Plasmablastic Morphology on BM Smears

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 (Kyrtsolis 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 (Kyrtsolis et al, 2007; Snozek et al, 2008). Furthermore, the addition of sFLCR to factors of disease activity (LDH, β 2M, genetic abnormalities) provided powerful prognostic models (Kyrtsolis 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 IgG κ , IgG λ , IgA κ and IgA λ 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 approximately 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; Kyrtsolis 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; Kyrtsolis et al, 2006) and soluble syndecan-1 (Seidel et al 2001, Kyrtsolis 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 (Kyrtsolis et al, 2007; Kyrtsolis 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 extent, 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-Sánchez 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 $\beta 2M$, del q13/ $\Delta 13$, 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- κ B), 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_2 M, 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 whether 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.

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7. References

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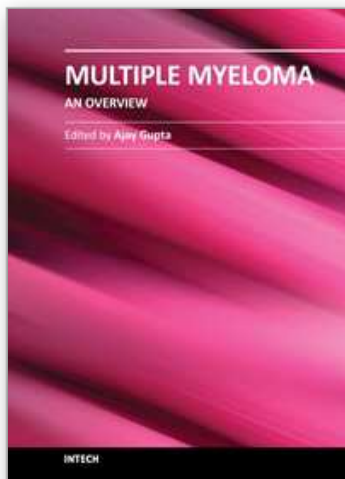
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Multiple Myeloma - An Overview

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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.

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