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Review Article

How do we Consider Multiple Myeloma. One Institute, 20 Years of Experience

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Abstract

Multiple myeloma, a malignant proliferation of plasma cells, is still incurable. This disease, 1% of all human malignancies, is responsible for almost 2 % of the whole cancer related mortality. In this review the authors summarize their 20 years experience in the field of myeloma research aiming to find factors predisposing to myeloma and looking for prognostic markers. In the last two years (2012 and 2013) this team diagnosed and treated 259 myeloma patients: 119 in 2012 and 140 in 2013.

FINDING GENETIC/ ENVIRONMENTAL PREDISPOSITIONS

Familial multiple myeloma

Our study group demonstrated on the example of two families in which siblings developed multiple myeloma (MM), that inherited similarities in the metabolizing enzyme genes *GSM1,GST1, GSTP1* or in HLA markers and the same early life carcinogenic exposure might lead to the development of myeloma in siblings [1].

High tumour risk in the family

In a cohort of 125 myeloma patients, 39 had family members with different type of tumors and 28 myeloma patients had coexistent or secondary malignancies. This data demonstrated a 40 fold increase in tumor incidence in contrast to the general population [2].

HAEMOCHROMATOSIS GENE STATUS

When the authors compared MM and myelodysplasia (MDS) – two chronic hematological malignancies of the elderly – looking for differences in their iron parameters and *HFE* gene status, they found that in the MDS group approximately 50% of the patients had mutated *HFE* gene while MM patients showed a mutation frequency below the general population, which difference manifested in their iron parameters as well. The conclusion was that *HFE* gene related iron overload caused oxidative stress probably does not play significant role in myeloma [3].

IL6 / IL6R GENETIC POLYMORPHISM

IL-6 serum levels are elevated in MM, this is why it is often called myeloma cytokine. Its level reflects tumor mass and high levels herald poor prognosis. This was why we conducted a study of the Asp358Ala SNP of the *IL6-R* and -174 G>C- SNP of the *IL6* promoter gene in MM. One hundred myeloma patient's polymorphism results were compared with healthy controls', but we found no difference [4].

This study however gave rise to a speculation on the signal transduction process when myeloma and myelodysplasia had been compared on the basis of *HFE* gene status. As we demonstrated earlier *HFE* gene mutation frequency is low in MM and high in MDS but *IL-6* level is high in both conditions [3-5].

It is therefore plausible to say that the development of MM or MDS, would rely simple on the HFE gene status - as IL6 probable influences hepcidin synthesis partly through HFE downstream signal route in the liver. Hepcidin level is high in myeloma and low in MDS and probable the lowest in MDS patients with *HFE* genetic mutation [6].

TUMOR NECROSIS FACTOR ALPHA (TNF-ALPHA) GENETIC POLYMORPHISM

TNF-alpha is an important survival factor for MM that drives MM cells in the cell cycle and promotes long term growth of these malignant cells. On the one hand it acts in a synergistic manner with IL-6, but also may use pathways independent of IL-6 having a growth-promoting effect at least equal to that of IL-6. TNF-alpha and lymphotoxin-alpha (LT-alpha or LTA) are both cytokines of the tumor necrosis factor family with similar biological activities. Polymorphisms of cytokine genes may affect their expression levels. Allelic distribution of–308 G>A (*TNF* 1/2) polymorphism of the *TNF-alpha*, and the +252 A>G promoter polymorphism of the *LT-alpha* gene, were tested in 94 MM cases and 141 controls.

Significantly less MM patients carried the *TNF2* allele ($p = 0.018$) and the *TNF2-LTA 252G* haplotype ($p = 0.025$) compared to the control group. The difference was, however, restricted to females, and the relatively younger (<69 years) subjects. These findings – in agreement with those of other groups – indicate that carriers of the TNF2 allele or those of the TNF2-LTA 252G haplotype have a decreased risk for multiple myeloma. Since both rare alleles can be considered as high producer which is associated with a more pronounced ability to mount TNF-alpha or LTA for different stimuli, it seems that high production of these cytokines in patients as compared to controls have a protective effect instead of facilitating the development of MM. It is possible that interactions of the TNF-alpha and LTA with the TNF-receptor-associated factors (an important constituent of the noncanonical NF-kB pathway) may be responsible for the observed protective effect [7].

GLUTHATIONE S-TRANSFERASE METABOLIC ENZYME POLYMORPHISM

Gluthatione S-transferases (*GSTs*) are a large family of drug-metabolizing enzymes that participate primarily in the detoxification of genotoxic agents. The genes encoding GSTM1, GSTT1 and GSTP1 enzymes are polymorphic in humans. The null genotypes of *GSTM1* and *GSTT1* with gene deletion do not express the enzyme, and in case of the *GSTP1* variants the result is altered enzyme function. It was therefore hypothesized that genetic polymorphism of *GSTM1*, *GSTT1* and *GSTP1* may influence the risk of the development of MM. In a study the authors found *GSTM1* genotype frequencies similar among 100 cases and 100 controls. There were 47.5 % homozygous or heterozygous carrier of the gene, and 52.5 % null genotypes (homozygous gene deletion) in the group of MM patients, and 51.5 % positive and 48% null genotypes among controls, respectively. There was no statistically significant difference between cases and controls for the *GSTT1* polymorphism either, as there were 73.3 % positive and 26.7 % null genotypes among cases, whereas 74.7 % positive and 25.3% null among controls. Also there was no significant difference in the genotype frequency of *GSTP1* or combined *GST*- genotypes in cases and controls with the only exception that in patients with *GSTT1* deletion (null genotype) there was no homozygous *GSTP1 Val/Val* genotype present. The literature is controversial on this topic, however the authors suggest that *GSTM1, GSTT1* and *GSTP1* genetic polymorphisms does not influence the risk for MM significantly in the Hungarian population [8].

EXTRAMEDULLARY / INVASIVE MYELOMA

Unusual presentations of a disease can often shed light on aspects of the pathomechanism that cannot be clarified otherwise. Little is known about the basic processes that allow malignant plasma cells (PC) to grow outside the bone marrow environment.

Myeloma with skin propagation and soft tissue penetration

There is evidence that histamine may be involved in tumor growth. Histidine decarboxylase (HDC) is a key enzyme of histamine synthesis.

A 70 year-old female patient with MM (IgG lambda, stage IA) developed purple coloured papular skin infiltrates involving both legs and was refractory to melphalan-prednisolon-thalidomide (MPT) therapy. She also had expansive bone lesions, fibro-nodular lung manifestations besides the skin lesions. Finally heart and renal amyloidosis developed leading to the patient's death.

The skin infiltrating cells were HDC negative PCs in contrast to the bone marrow PCs which were HDC positive. This loss of HDC during skin invasion could be an acquired characteristic similar to the upregulation of adhesion molecules like CD44 which renders MM cells able to disseminate. This highlights that changes may occur not only on cell surface level involving adhesion and angiogenesis, but also in the metabolism of such conservative molecules as HDC. The better understanding of histamine metabolism might lead to the development of new therapeutic targets that can affect tumor propagation [9].

Myeloma with pleural invasion

Pleural fluid can be seen approximately in 6% of multiple myeloma patients. In contrast pleural fluid caused by PC infiltration is only 1%. Other causes can be amyloidosis, heart failure, nephrosis, low serum albumin level and coexistent systemic mastocytosis [10].

We report here the case of a 68 yrs old female patient who presented with both pleural and pericardial fluid with high LDH concentration (2387 U/l), a total protein concentration of 41 g/l. Flow cytometry analysis of the fluid showed PCs with high CD38 and CD56 expression characteristic for MM cells.

The bone marrow showed 20% PCs with FISH aberrations t (14;16) and 1q21 amplification. The diagnosis was MM (IgG kappa, ISS II) without kidney failure or bone lesions.

Despite two courses of bortezomib-thalidomid-dexamethason (VTD) chemotherapy the disease progressed with increasing pleural fluid. She had pleurodesis and further treatment with 2 cycles MPT. Despite all these measures the patient died in renal insufficiency, cardio-pulmonary insufficiency and hypercalcaemia 5 monts after the diagnosis. The autopsy revealed plasma cell infiltrates in the pleura, pericardium, heart and lung parenchyma.

FINDING PROGNOSTIC FACTORS

It's a typical experience of those dealing with myeloma patients for over 10-20 years that there are a small proportion of patients with good response regardless of what chemotherapy protocol used. These patients often maintain their remission over 10 years even in the era before the new agents (bortezomibe, thalidomide and lenalidomide) in contrast to the majority of patients who relapsed and died much earlier.

It is always a great challenge to estimate the prognosis upfront and to predict from which treatment the patient would benefit the most. There were various attempts from the Durie and Salmon model to the SWOG's ISS score for this purpose. The ISS is generally considered to be the best of these models and is now widely used, however it has certain limitations (eg. in renal insufficiency when B2MG is elevated) and that this test is not necessarily available in all general hospitals.

The AMWBC and A/M score

In 2008 our group published the AMWBC score based the

initial WBC and the ratio of serum albumin and the M-component level [11]. This separated patients into the following subgroups: those with A/M above or below 1.0 and those with WBC above or below 4.5 x 10^9/l. (POR 2008) Based on this findings we created the AMWBC score (Table 1).

Patients with score 0 had good prognosis, whereas those with score 1 had interim, and those with score 2 had poor prognosis according to this retrospective analysis of more than one hundred cases. When we compared the different scoring systems, it seemed that AMWBC is better than DS and as good as ISS or even expressing more sharply the difference at the critical 2 years survival endpoint (Table 2).

Later, in 2012 we calculated the A/M score in a different group of patients in the era of novel agents and found that is of comparable value [12] (Figure 1).

The other noteworthy conclusion emerged from these studies is that the initially low WBC is not related to either bone marrow infiltration or the presence of antineutrophil antibodies, but suspected to the coexistance of MDS which could substantially affect the prognosis of myeloma. Although it is difficult to prove on morphological basis the presence of MDS in a bone marrow heavily infiltrated by PCs, there are a number of case reports on the coexistence of these two conditions and the effectiveness of the same compound for both conditions would provide an indirect confirmation to this [13]. From the point of therapy those who are involved in this coexistance of these two diseases, might be candidates for BMT.

Table 1: Prognostic Score Index calculation.

Score	0	1
WBC	≥4.5 x10^6/l	< 4.5 x10^6/l
A/M	≥1	< 1

Table 2:

scores / survival in months	AMWBC	DSS	ISS
I	45. 5	43. 3	62
II	38. 7	48.9	44
III	23. 8	28. 4	29

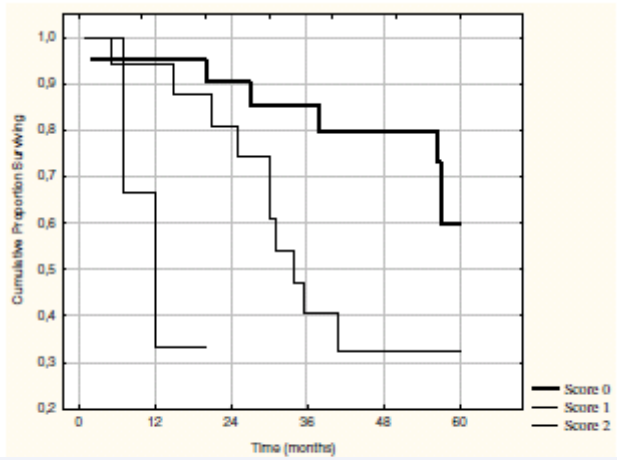

Figure 1 Survival at 5 years endpoint according to the AMWBC score in patients treated with novel agents (n=56).

GENOME WIDE ASSOCIATION STUDY

International Multiple Myeloma Research (IMMEnSE) consortium genotyped single nucleotide polymorphisms (SNPs) rs6746082 (2p23.3), rs4487645 (7p15.3) and rs1052501 (3p22.1) in 1139 MM cases and 1352 controls and provided further evidence for their role as determinants of MM risk. The identification of high risk myeloma settings would contribute to design more targeted therapies [14].

The polymorphisms rs2227667 (*SERPINE1*) was found to be associated with myeloma risk in women in contrast to the list of others had been tested like: rs17501108 (*HGF*), rs3136685 (*CCR7*), rs16944 (*IL1B*), rs12147254 (*TRAF3*), rs1805087 (*MTR*), rs1800629 (*TNF-α*), rs7516435 (*CASP9*), rs1042265 (*BAX*), rs2234922 (*mEH*), and rs1801133 (*MTHFR*). 1498 MM cases and 1934 controls were genotyped in the context of the IMMEnSE consortium, and meta-analyzed our results with previously published ones [15].

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