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Novel Prognostic Modalities in Multiple Myeloma

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1. Introduction

The therapy for multiple myeloma has made major strides over the last 15 years, by and large due to the advances in molecular biology and the focus on patient-oriented translational investigations. Although the survival outcomes have improved significantly, clinical features such as older age, renal insufficiency at diagnosis, primary plasma cell leukemia and extra-medullary disease remain major therapeutic challenge. The explosion of data from all the clinical, genomic and proteomic investigations has also made it difficult to assimilate all the information and translate it effectively for clinical practice. Although multiple myeloma is still considered by most though leaders as an incurable but treatable disease, the development of novel diagnostic and therapeutic modalities are bringing optimism of potential curability dream of being curable. Over the last decade, new biologic markers and novel imaging modalities have been explored in the context of clinical trials. The present chapter will attempt to summarize these data and propose how to incorporate this knowledge in current clinical practice.

2. Laboratory & pathology tools

2.1. Durie-Salmon staging and the international staging system

The Durie-Salmon Staging (DSS) system [1] was developed as a prognostic model almost four decades ago when the standard of care for myeloma was oral melphalan and prednisone. Over the years, DSS has stood the test of time as a reasonable assessor of disease burden even in the era of novel agents. The major drawback of the DSS was that it does not account for the biologic variability of disease even in patients with comparable disease burden. The Interna-

tional Staging System (ISS) [2] was developed to include some biologic information by incorporating serum albumin as a markers of disease burden and host risk, whereas serum beta-2 microglobulin (β 2M) levels was included as marker of biologic behavior. Both DSS and ISS stratify patients in to stages I, II and III. Although ISS was tested and validated on patient data-set from the pre-novel drug era, ISS III disease remains a major challenge even in intensive treatment approaches such the Arkansas Total Therapy program (See Figures 1A-C).

Incorporating cytogenetic data in prognostication

Like most cancers, multiple myeloma has both inter-patient and intra-patient heterogeneity. The last 15 years have seen major progress in both the understanding of MM disease biology and development of biologically relevant MM therapies. Even with such advances, there are several prominent biologic factors that play a major role in overall prognosis. MM patients can be categorized into genomically defined low risk or high risk depending upon underlying molecular cytogenetic abnormalities identified using either fluorescent in situ hybridization (FISH) and gene expression profiling (GEP). In transplant eligible patients, presence of any cytogenetic abnormality portends poorer PFS and OS as observed in the two Total Therapy 3 trials [3], [4] by the Arkansas Myeloma group (Figure 2 A, unpublished data), whereas there were no difference in cumulative incidence of achieved a partial or complete response (Figure 2 B, unpublished data). The poor prognostic cytogenetic abnormalities include translocation (4; 14), translocation (14; 16), translocation (6; 14), translocation (14; 20), hyperdiploidy, amplification of chromosome 1q21 and deletion 17p, and their presence is associated with shorter overall survival and duration of response to therapy.

Translocation (4; 14) can be found in roughly 10-15% of newly diagnosed MM patients and results in an overexpression of fibroblast growth factor receptor 3 (FGFR3) that in turn drives cellular proliferation and survival. Although it can be argued that bortezomib can now overcome the adverse prognosis associated with translocation (4; 14), it remains a poor prognostic markers in geographic areas where either socioeconomics or medical economics dictate initial choice of therapy for newly diagnosed MM [5]. Translocations (14;16) and (14;20) [6], [7] occur in less than 5% of newly diagnosed MM cases and lead to overexpression of MAF and MAF-B proto-oncogenes, respectively. Deletion 17p results in deletion of the tumor suppressor gene p53 and occurs in ~10% new MM cases [8]. It has been reported that bortezomib may overcome adverse prognosis associated with deletion 17p [9], but it appears that this benefit only happens in “low-risk” MM patients as defined by the Arkansas 70-gene expression profiling risk model [10]. Lastly, amplification of chromosome 1q21 has not only been associated with MGUS to MM progression [11] but also with poor prognosis in MM regardless of therapeutic era [12]. Amongst the many genes over-expressed by 1q21 amplification, are the proteasome genes which appear to portend poor durability of response and may be partly responsible for resistance to bortezomib [12]. In an effort to incorporate biologic information in upfront staging, there have several attempts to combine cytogenetic data with ISS in prognostic models. Neben et al [13] demonstrated that newly diagnosed MM patients with high burden of disease (ISS stages II/III) when presenting with either t (4; 14) or del17p have overall shorter PFS and OS (Figure 2 C).

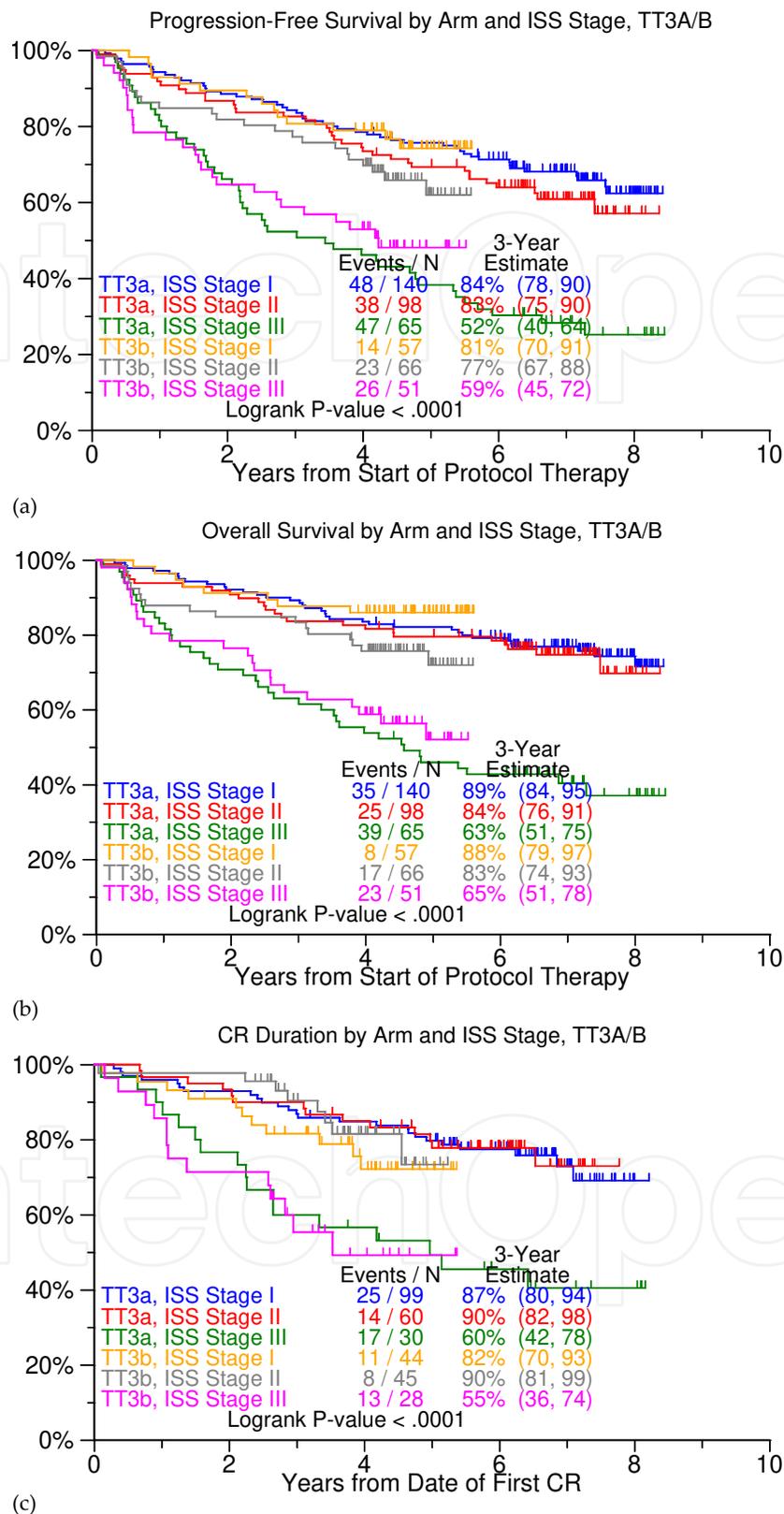


Figure 1. Impact of ISS Stage in Total Therapy 3 trials on progression free survival (a), overall survival (b), and complete response (CR) duration (c).

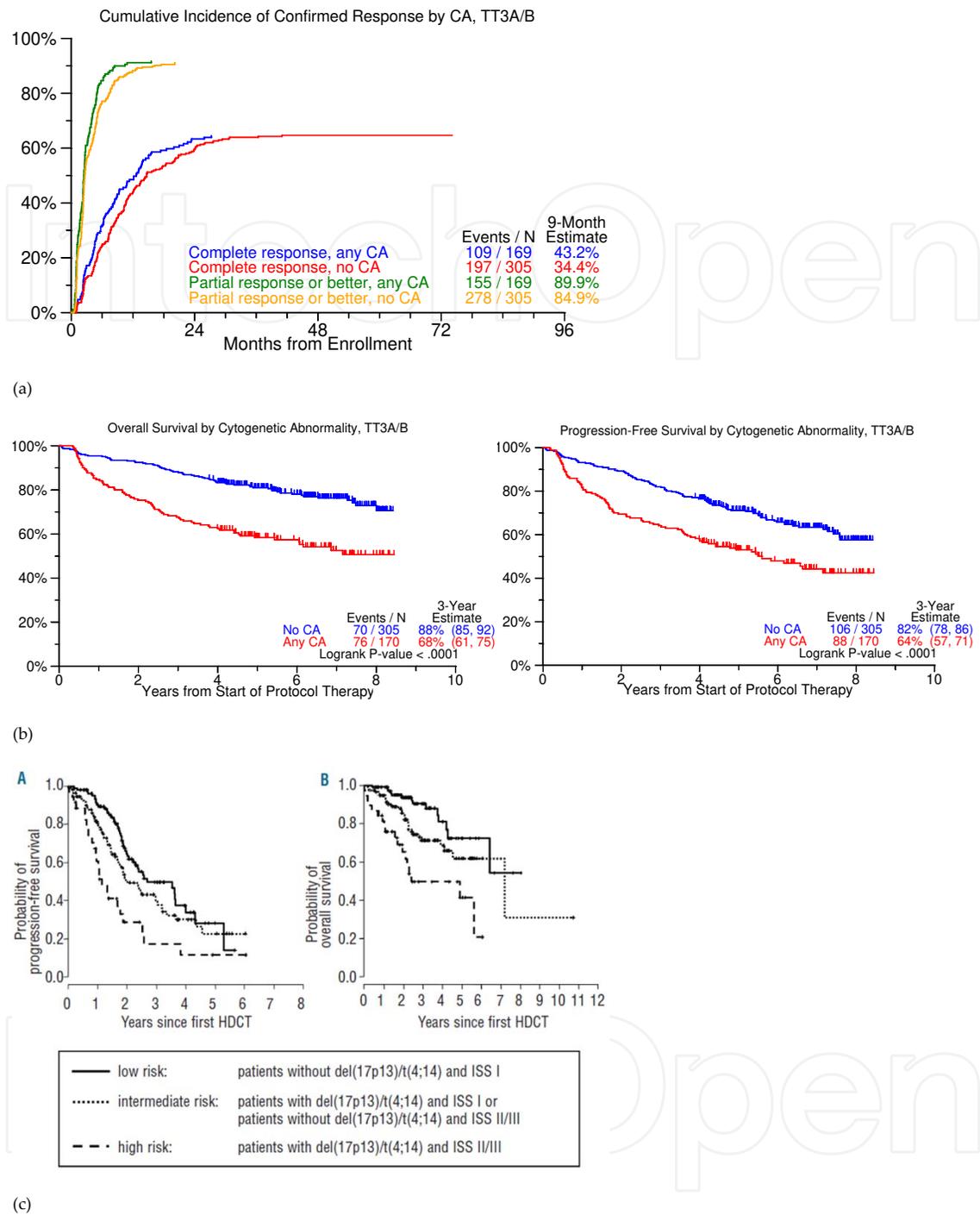


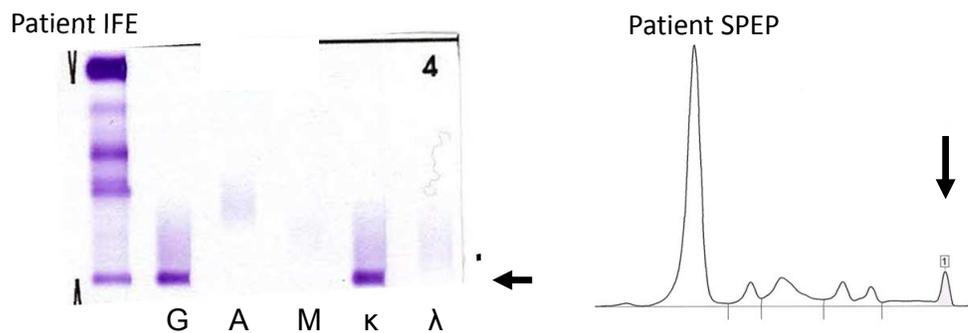
Figure 2. Impact of cytogenetic abnormalities to achieving response (a), overall and progression free survival (b). Combined ISS staging and cytogenetic risk stratification in newly diagnosed MM (c).

2.2. Serum light chain and heavy chain assays

The measurement of biological markers for multiple myeloma serum and urine specimen has proven to be invaluable in detection and monitoring of disease progression. In fact, the

observation of association of multiple myeloma with the presence of Bence Jones proteins in the urine 150 years ago consisting of immunoglobulin free light chains represents one of the first widely utilized tumor marker assays. Since that time a great deal of effort has gone into the development of new markers for multiple myeloma, as well as more efficient use of existing markers. These include nephelometric determination of serum free light chains (FLC) and more recently intact Ig subsets; IgG κ , IgG λ , IgA κ and IgA λ (heavy/light chain immunoassays or HLC). Both of these markers have exhibited apparent value as diagnostic and prognostic indicators.

As our understanding of the utility of these markers deepens, we achieve better understanding in how to most effectively use these markers in combination with other methods for monoclonal protein detection (See Figure 3). Current international guidelines for identifying monoclonal gammopathies (MG) include serum protein electrophoresis (SPEP), immunofixation electrophoresis (IFE) and serum free light chain (FLC) immunoassays with derived kappa/lambda (κ/λ) ratios [14], [15]. As a first step, Immunofixation (IFE) is typically the assay utilized to identify the clonal isotype and is also generally utilized to provide a qualitative assessment of monoclonal (MC) Igs and light chain proteins, although alternate algorithms have been evaluated [16].



Test	Patient	Reference Interval
Original Clone by IFE	IgG κ	None
SPEP M-protein determination	3.0 g/L	Negative
Total IgG	4.82 g/L	7.14 - 13.94 g/L
HLC IgG κ	4.39 g/L	4.03-9.78 g/L
HLC IgG λ	0.47g/L	1.97-5.71 g/L
HLCr (IgG κ /IgG λ ratio)	9.36	0.98-2.75
FLC κ	2.57 mg/dL	0.33-1.94 mg/dL
FLC λ	0.33 mg/dL	0.57-2.63 mg/dL
FLCr (κ/λ ratio)	7.79	0.26-1.65

Figure 3. Combining serum protein electrophoresis, immunofixation, the free light chain assay and heavy chain assay to profile a patient with newly diagnosed MM.

Free light chain assays

Although monoclonal serum free light chains (FLC) can be quantified by SPEP in some cases, the use of sFLC nephelometric or turbidimetric immunoassay has become standard practice for measuring free kappa (κ) and free lambda (λ) light chains in monoclonal gammopathies and other patient specimens [17]- [19]. These assays measure free light chains and do not react to light chains bound to heavy chain [20]. In addition to high sensitivity and specificity, advantages of the use of serum FLC nephelometric assays involves the use of numerical κ/λ ratios as a clinically sensitive marker of monoclonal FLC production as it also includes suppression of the non-tumor FLC in its calculation [21].

In the decade since introduction of the free light chain serum assay a great deal has been elucidated regarding the clinical value of these assays. The value of serum free light chains in the detection and screening for disease has been well established, culminating in the inclusion of the free light chain measurements into the International Myeloma working group guidelines. The vast majority of multiple myeloma symptomatic patients (95%) exhibit abnormal free light chain ratios [22]. The use of a combination of serum IFE and sFLC chain is proposed to be sufficient to screen/detect disease in new multiple myeloma patients. Furthermore, in contrast to M-spike, the κ/λ ratio (FLCr) has been reported to be a superior prognostic marker for active multiple myeloma, smoldering multiple myeloma and MGUS [24]- [26].

Heavy light chain assays

The observed utility of sFLC κ/λ ratios has prompted interest in the analysis of intact $Ig'\kappa$, $Ig'\lambda$ and $Ig'\kappa/Ig'\lambda$ ratios, which has been made possible with the recent availability of HLC or Hevylite™ immunoassays which have been recently made available from the Binding Site [27], [28]. These assays utilize epitopes which span specific intact heavy and light chain pairings. Thus they can be used to quantitatively measure concentrations of specific antibody species such as $IgG\kappa$, $IgG\lambda$, $IgA\kappa$ and $IgA\lambda$. It should be noted that the Hevylite assay is not specific to a monoclonal protein but the presence of monoclonal protein is often indicated by an abnormal HLC kappa/lambda ratio. Although the clinical utility of these Heavy Light Chain measurements are still being explored, there is indication that HLC $Ig'\kappa/Ig'\lambda$ ratios may have diagnostic value for multiple myeloma and may also have utility in the monitoring of disease state [27]- [29]. Following identification by IFE, monoclonal immunoglobulins are typically quantified by serum protein electrophoresis (SPEP) and total immunoglobulin determinations, although the results of these assays do not always agree [30]. The clinical utility of the HLC assay could be particularly beneficial when measurements of monoclonal immunoglobulins may be adversely affected as a result of procedural challenges associated with electrophoresis and biological variances typically observed in myeloma patients. Finally, recent reports have also suggested that measurement of the HLC ratios and suppression of concentrations of non-clonal HLC proteins of the same class are of prognostic significance in monoclonal gammopathies of undetermined significance (MGUS) [31] and MM [32]. Further work continues to elucidate the degree and clinical prognostic role of HLC measurements.

2.3. Flow cytometry

The diagnosis of multiple myeloma and determining the response to therapy has traditionally been done by morphological evaluation of the bone marrow for neoplastic plasma cells, and protein studies including serum protein electrophoresis, and immunofixation. Flow cytometry (FCM) for plasma cell enumeration in the bone marrow or peripheral blood has not been popular, in part due to the lower yield of plasma cells by FCM [33], [34]. With advent of multi-color flow cytometers, FCM is now recognized as a fast, cheap and sensitive tool to get multiparametric information on the plasma cells in MM. FCM has a distinct advantage over morphological, immunohistochemical, or even molecular tests in distinguishing normal from neoplastic plasma cells when the plasma cell numbers are very low. The availability of standardized consensus guidelines from the European Myeloma Network [33] regarding methodology, antibody panels and combinations, and absolute numbers required for assessment to obtain reliable results for small numbers of neoplastic plasma cells by FCM has improved confidence in using FCM as a diagnostic and prognostic tool in MM.

The main prognostic uses of multiparametric flow cytometry (MFC) in MM include antigenic profile of malignant plasma cells and detection of minimal residual disease detection. Several antigens are differentially expressed on normal and neoplastic plasma cells. These include CD38, CD138, CD45, CD56, CD19, CD117, CD20, CD27, CD28, CD33, CD39, CD40, CD44, CD81, Cyclin C1, and CD34 [34]- [37]. The expression of these antigens is on a continuum; therefore no single antigen can distinguish a normal from neoplastic PC. Results from several large consensus studies have shown that a minimum panel of CD19 and CD56 in addition to the basic CD38, CD138, and CD45 can discriminate neoplastic PC in more than 90% of the instances, and the discriminatory power increases to more than 95% on addition of CD117, CD20, CD28, and CD27 to the panel [35], [36]. In addition to enumeration of neoplastic plasma cells in the bone marrow, several studies have demonstrated the prognostic value of the residual normal plasma cell population in the bone marrow [37] demonstrated that in nearly 80% of patients with MGUS, >5% plasma cells out of the total bone marrow plasma cells are normal (benign, reactive), as opposed to <15% of patients with MM who may have >5% normal plasma cells; a distinction of MGUS from smoldering myeloma can thus be made by assessing the proportion of residual normal PC. The authors further demonstrated that patients with MGUS and SMM with a marked predominance of aberrant plasma cells/ total bone marrow plasma cells (> or = 95%) at diagnosis had a significantly higher risk of progression to symptomatic MM, and in multivariate analysis the percentage of aberrant plasma cells to total bone marrow plasma cells was the most important independent variable together with DNA aneuploidy for progression free survival in both MGUS and SMM [37]. Furthermore, MM patients with >5% normal plasma cells constitute a biologically distinct group with low tumor burden and a better response to HDT/autologous HSCT [38].

Prognostic value of individual antigens

The prognostic significance of individual antigens expressed by the neoplastic plasma cells is less clear. A correlation of CD20 expression with cyclin D1 positivity and presence of t(11;14) and a better outcome has been reported; not all CD20 expressing myelomas express cyclin D1 or t(11;14), and vice versa [39]. The importance of CD20 expression lies in the potential for use

of Rituxumab in these patients. Neural adhesion molecule or CD56 is an aberrant marker expressed in 75% of MM cases. Loss of CD56 is described in plasma cell leukemia and myeloma cells in extramedullary locations [40]; a correlation of CD56 negativity with plasma cell leukemia or circulating myeloma cells and decreased osteolysis is reported [41], but no definite association with aggressive disease is established [42]. Syndecan-1 (CD138), a molecule belonging to the heparin sulphate family, is a universal marker for normal and neoplastic plasma cells [43]. CD138 mediates myeloma cell adhesion, and interaction with the extracellular matrix. CD138 may be shed from the cell surface. Soluble CD138 is a marker of plasma cell apoptosis and some studies have shown soluble CD138 level is a powerful independent prognostic factor both at diagnosis and at plateau phase [44], [45]. Shed CD138 accumulates in the fibrotic stroma; its presence on intravascular and intrasinusoidal plasma cells indicates that its loss is not associated with extramedullary disease [46]. CD45 expression is observed in plasma cells with higher proliferative index and as such may be associated with high-grade myeloma. Recent studies have shown that CD19, CD28, and CD117 provide clinically significant prognostic information; positivity for CD19 and CD28 and lack of expression of CD117 correlate with shorter overall and progression-free survival [46]. Many of these immunophenotypic-clinical outcome associations may be due to the associated genetic abnormalities and not the antigen expression per se—CD28+/CD117- myelomas are often non-hyperdiploid and associated with a higher frequency of t(4;14); CD28 positivity also with 17(p) deletion, and CD20 expression with t(11;14). These –immunophenotypic and genetic correlations need further investigation for validation [46].

Detection of minimal residual disease and prognosis

According to the IMWG response criteria [25], [47], complete remission (CR) in MM requires absence of demonstrable monoclonal protein by serum electrophoresis or immunofixation, disappearance of soft tissue plasmacyomas, and <5% bone marrow plasma cells. Since morphological evaluation of the bone marrow has limited sensitivity, the IMWG proposed additional criteria including absence of clonal plasma cells based on immunohistochemical staining of bone marrow sections, and a normalized free light chain ratio to further define stringent CR. We (unpublished observation) and others [48] have observed that oligoclonal plasma cell proliferations are common after auto HSCT and may disturb the free light chain ratios and limit interpretation of plasma cell clonality by immunohistochemical or in-situ hybridization studies on the bone marrow biopsies. Figure 4 show an example of MFC performed in on a 6-color instrument. Simultaneous analysis of multiple discriminatory antigens allows separation of a small proportion of aberrant plasma cells within a background of reactive plasma cells. The predictive prognostic role of MRD by MFC of plasma cells has been demonstrated both in the pre- and post transplant setting. Dingli et al [49] demonstrated that detection of circulating myeloma cells in the peripheral blood by FCM prior to auto-HSCT is an independent prognostic factor for overall survival and time to disease progression in multivariate analysis. In a prospective study of MRD assessment by MFC of plasma cells in 295 newly diagnosed MM patients uniformly treated in the GEM2000 protocol, both the progression-free survival ($p < 1.001$) and overall survival ($p = 0.002$) were longer in patients who

were MRD negative by MFC of plasma cells on day 100 following auto-HSCT [50]. The predictive value of MFC persists even in patients who are negative for MM by immunofixation.

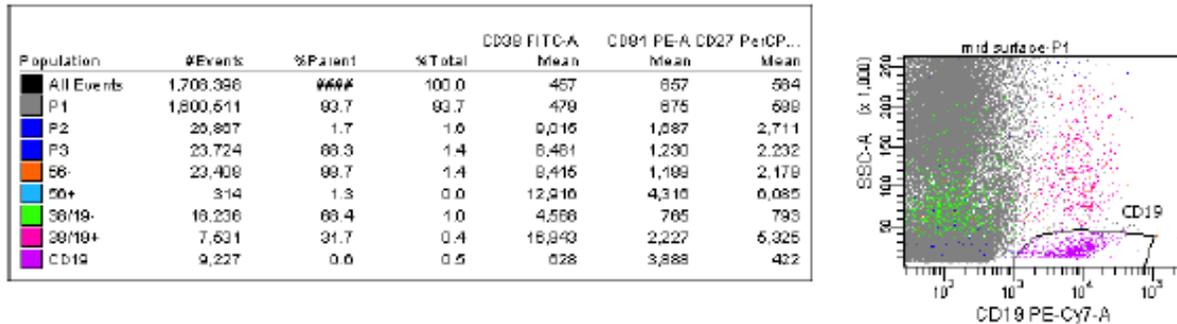


Figure 4. Dot plots showing cell gating strategies to evaluate minimal residual disease in Note that the selected cells in green are CD45-, CD38 (low), CD27-, CD19-, CD81(weak to negative), and CD56- in contrast to the normal residual plasma cells (red) that are CD45+, CD38(bright), CD27+, CD19+, CD81+, and CD56-, and normal B- cells (purple) that are CD45+, CD19+, and CD81+, but negative for CD38, and CD27. Total 1.7 million events are analyzed. The abnormal/normal plasma cell ratio can be calculated from the numbers in the table (2.38%).

2.4. Gene expression profiling

GEP was first used to study MM by De Vos and colleagues in 2001 [51]. In these early experiments, human myeloma cell lines and plasma cell leukemia patient samples were analyzed on small-scale, filter-based complementary DNA arrays to identify genes involved in intercellular signalling. Subsequently, Stewart et al used a combination of high-throughput DNA sequencing and microarrays using DNA samples from several cases of plasma cell leukemia to establish a comprehensive list of genes that are expressed in MM [52]. GEP analyses in MM have evolved tremendously over the last decade and helped with getting a global biologic understanding of the disease.

GEP also helps identify different signatures that confer an adverse outcome as shown by the University of Arkansas for Medical Sciences (UAMS) 70-gene signature (GEP-70) as proof of concept that identifies 13-20% “high risk” newly diagnosed patients with short progression free and overall survival even when with the Total Therapy approach[3],[4], [53]. The GEP-70 model has 30% of the informative genes mapped to chromosome 1 and poor prognosis is associated with 1q21 amplified genes. A UAMS 17-gene signature has also been reported, primarily using the 1q21 amplified genes, which could predict outcome as well as the 70-gene signature [54] but has not replaced the GEP-70. The UAMS GEP-80 gene signature [12] was discovered when comparing pre- and post-bortezomib GEP studies in newly diagnosed MM treated on the Total Therapy 3 trials[3],[4]. This signature was used to identify patients who may be resistant to bortezomib therapy and it showed both higher PSMD4 expression levels and higher 1q21 copy numbers affecting clinical outcome adversely. The UAMS GEP-80 high risk signature provides additive and complimentary information to the UAMS GEP-70 signature.

The prognostic validity of the GEP-70 high risk signature has been confirmed in several independent patient cohorts (IFM 99 trial [55], ECOG E4A03 trial [55], HOVON-65 trial [57]). The Intergroupe Francophone du Myélome (IFM) have developed a 15-gene model [55], which described a set of genes that control proliferation and chromosomal instability. This model was able to identify high risk group in UAMS population but with less statistical significance. It was also interesting to note that IFM-15 and UAMS GEP-70 gene models do not share any common genes, which likely reflects the redundancy in the genes and pathways with prognostic significance in MM. Recently, the EMC-92 gene model has been reported on the HOVON65 clinical trial patients, with no overlapping genes compared with UAMS 70-gene signature and it identifies an additional 3-4% high risk MM patients to the existing GEP signatures [57].

Patients with low risk disease usually survive on a median about 6-7 years or longer when compared to those with high risk disease, who survive on a median ~ 3 years. On the other hand those with intermediate risk have been shown to have comparable survival to low risk patients in studies where there was early use of bortezomib plus ASCT [58]. The disease subset with GEP70 high risk signature, translocation (14; 16), translocation (14; 20), and deletion 17p remains a challenge. Clinical trials addressing this difficult group of newly diagnosed patients are now being conducted, such as the SWOG-1211(NCT01668719) study [59], to establish guiding posts for future trials.

3. Emerging role of magnetic resonance imaging & 18-Flouro-Deoxy-Glucose (FDG) positron emission tomography

Imaging techniques are also considered as important prognostic tools. The metastatic bone survey (MBS), a whole body x-ray, has been used as a standard for evaluating bone disease (osteolytic lesions or osteopenia). Unfortunately, the MBS does not detect bone destruction until more than 70% of the bone has decalcified [60]. The DSS¹ has associated poor prognosis to patients with > 2 MBS osteolytic lesions, a feature seen in 33% of newly diagnosed MM patients [61]. It also appears that the MBS related poor prognosis still holds true in the era of novel agents [62], [63].

Magnetic resonance imaging (MRI) and more recently, positron emission tomography integrated with computed tomography (PET/CT) using radionuclide¹⁸F labeled with fluoro-deoxyglucose (18F-FDG) have demonstrated effective detection of bone lesions, marrow involvement and in the case of the latter; demonstrating active or inactive disease and their use can provide vital prognostic information (See Figure 5). Studies utilizing the PET/CT and MRI by the Arkansas group [61]- [63] and the Italian group [64] have looked at the prognostic implications of the number of focal lesions (FL), the uptake of FDG expressed as standardized uptake value (SUV), presence of extramedullary disease (EMD), at baseline and after treatment in previously untreated myeloma patients. The results from these studies showed that FL number adversely affected over survival (OS) and event free survival (EFS) independently, as

did presence of EMD and failure of FDG suppression. Higher SUV of the most active FL (SUV^{\max}) on PET/CT is also associated with poor outcomes ($SUV^{\max} > 3.9$ [62] or $SUV^{\max} > 4.2$ [64]).

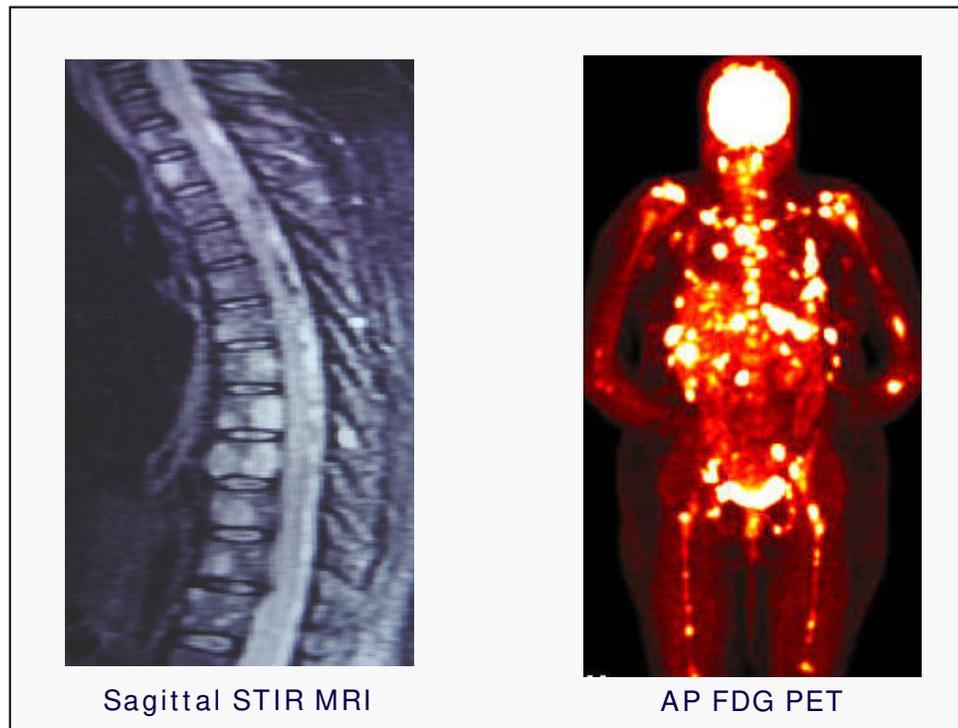


Figure 5. Left panel shows MRI focal lesion on sagittal STIR images; right panel shows AP FDG uptake on PET

Specifically, baseline PET focal lesions > 3 (32% of newly diagnosed MM) and baseline MRI focal lesions > 7 (36% of newly diagnosed MM) were associated with shorter EFS and OS in Total Therapy 3 trials. It was also observed that complete suppression of FDG before the first autologous stem cell transplant (ASCT) conferred a favorable effect on outcome especially seen in the GEP 70 – defined high risk patients [61], [62]. More recently, it has also shown that absence of PET suppression by Day 7 of first induction cycle in MM patients treated on the Total therapy 3 trials have shorter progression free survival (PFS) and OS [65]. These observations have important implications and would need further validation in the era of novel therapy induction regimens. One could potentially identify high risk patients based on imaging response that would require change in therapeutic strategy, similar in fashion to how PET is employed in aggressive lymphomas.

PET/CT and MRI are not yet established as a standard for diagnosis and disease evaluation, as concerns have arisen due to heterogeneity of visual criteria and inconsistency in interpretation of results [66]. In current practice, the PET/CT can be employed in patients presenting with solitary plasmacytomas where the clinical suspicion for systemic disease is high, or when patients are relapsing biochemically but bone marrow biopsy provides ambiguous results. The use of MRI and PET/CT is presently limited to clinical investigations, partly due to the

economic implications of broader usage in clinical practice. These concerns may be alleviated may be in the future with development of more efficient and cost-effective technologies.

4. Conclusion and future directions

Our understanding of MM has grown many folds over the last 2 decades with a better understanding of the genomic heterogeneity associated with this disease. We are just beginning to combine the clinical and biologic prognostic markers in newly diagnosed multiple myeloma patients in efforts to better stratify patients and choosing appropriate therapies. There are multinational efforts, such as the CoMMpass study, aiming to provide for a comprehensive understanding of the disease in the era of novel agents [66]. With the advances in drug development, we are getting closer to developing a risk-adaptive therapeutic strategy for majority of MM patients. There is a robust pipeline of novel targeted agents on the horizon for MM. It appears that there will be enough effective and tolerable therapeutic agents in the oncologist's armamentarium that the treatment strategy will take in to account both the clinical and biologic risk factors for a truly personalized medicine experience. The advances in diagnostic and prognostic tools will also provide impetus for a response-adaptive strategy which will likely be incorporated in the therapeutic matrix as the data emerges over the next decade.

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