
Risk Stratification in Newly Diagnosed Transplant-Eligible Multiple Myeloma

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2.1 Introduction

Complex interplay between biology, chromosomal abnormalities, gene expression profiles (GEP), and staging affects prognostication of multiple myeloma (MM). With novel therapies being developed, it is increasingly important to risk stratify the affected population by using available prognostic markers. Risk stratification is not unique to MM. Like other hematologic malignancies, the ability to predict outcome based on risk group is important when counseling the patient regarding the therapeutic outcomes and risk/benefit of treatment. The risk classification schema for MM has evolved over the years in parallel with changing treatment landscape and diagnostic approaches. Most of the risk factors are derived from data on patients treated in the era before novel agents. The traditional prognostic markers continue to be relevant and in the modern era these are used to investigate how novel agents can influence the patient's risk. The International Myeloma Working Group (IMWG) panel provided its updated recommendations for risk stratification in 2014 [1]. According to IMWG, the high-risk patients are distinguished as having a median overall survival (OS) of 2 years or less despite best therapies and low-risk patients as those who could potentially survive more than 10 years with treatment. Autologous stem cell transplant (ASCT) continues to hold its place for all eligible patients in an era when patients have multiple regimen options for induction, consolidation, and maintenance therapy. Integrating novel prognostic factors and updating risk classification schema within the context of emerging therapeutic paradigms is an area of flux. With increasing treatment choices and improved outcomes, risk

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stratification assumes more importance as fine-tuned therapeutic plans can be developed for different risk groups.

2.2 Why Is Risk Stratification Important?

Risk classification is frequently used by physicians for counseling their patients regarding life expectancy, disease control, health-related quality of life, and treatment complications while weighing the cost and benefit of different therapeutic options. Unlike acute leukemia and Hodgkin lymphoma, MM has little randomized data on benefit of altering treatment for high-risk group or for de-escalating treatment for the low-risk group. Nonetheless, risk grouping provides a useful framework for rational selection taking into consideration the cost of drugs, toxicities, and efficacies. For high-risk disease, physicians and patients may be more inclined to use potent treatments with potentially greater toxicity and expense, whereas for low-risk disease, less toxic and more affordable regimens may be preferred even with a slight compromise in efficacy. These practices may vary according to the divergent viewpoint of cure (choosing a more aggressive approach) vs. control (choosing a less aggressive approach with focus on quality of life). Within the realm of clinical trials, risk stratification is used to define a class of patients to be included or excluded from studies that are designed for a specific risk group. Importantly, risk grouping creates a common nomenclature to allow patients, physicians, institutions, government agencies, and cooperative groups to present and/or compare outcome data in a uniform manner.

2.3 What Markers Determine the Risk?

Several markers reflecting biology, stage, disease burden, host characteristics, and response to therapy have been identified (Table 2.1) that predict outcome in MM. Most of these biomarkers are prognostic, which means they provide information about the outcome at the time of diagnosis or at various times during the recurrent disease, independent of therapy. In contrast, we have few predictive markers, which can provide information on the likelihood of response to a given therapeutic modality. For example, cereblon expression may predict resistance to immunomodulatory drug (IMiD) but by itself is not a prognostic factor [2]. Importantly, prognostic factors define the effects on the patient outcome and are useful in risk stratification, whereas predictive factors define the effect of treatment on the tumor.

Studies conducted in the 1960s and early 1970s identified a number of clinical and laboratory parameters that were proposed for staging myeloma burden [3, 4]. In 1975, Durie/Salmon (DS) myeloma staging system came to light. This system reflects disease burden based on the level and type of monoclonal protein, hemoglobin, calcium, and number of bone lesions [5]. Patients in each of the three stages are defined lower risk vs. higher risk based on creatinine level (substage A: serum creatinine <2 mg/dL; substage B: serum creatinine ≥ 2 mg/day). In the 1980s, serum

Table 2.1 Determinants of risk

Myeloma cell burden	Patient characteristics	Disease biology	Response to treatment
DS staging system	Age	LDH >300 IU/L	CR
ISS	Performance status, frailty	Plasma cell labeling ≥ 1%	Immunophenotypic CR
	Organ function	Conventional cytogenetics	Molecular CR
MRI (≥7 lesions, diffuse bone marrow involvement) FDG-PET (≥3 lesions, SUV >4.2, presence of extramedullary disease)	Comorbidity burden index	Interphase FISH <ul style="list-style-type: none">– CD138 selection– Immunofluorescence of cytoplasmic Ig FISH	PET/MRI CR or resolution of lesions
Extramedullary disease	Geriatric assessment score	Gene expression profiling	
Plasma cell leukemia	Psychosocial profile		

DS Durie-Salmon, *ISS* International Staging System, *MRI* magnetic resonance imaging, *FDG-PET* fluorodeoxyglucose-positron emission tomography, *SUV* standardized uptake value, *LDH* lactate dehydrogenase, *FISH* fluorescence in situ hybridization, *Ig* immunoglobulin, *CR* complete response

β2-microglobulin became known as a reliable predictor of survival duration [6, 7]. In mid-1980s prognostic relevance of conventional cytogenetics by metaphase G-banding was described [8]. Subsequently, chromosomal abnormalities identified by interphase fluorescent in situ hybridization (FISH) were adapted as the key elements for defining risk categories [9]. The three-tier risk stratification system that we commonly use to classify newly diagnosed MM into standard, intermediate, and high risk of relapse is primarily based on the chromosomal abnormalities. Standard-risk disease is characterized by the absence of del(17p), t(4;14)(p16;q32), t(14;16)(q32;q23), or 1q21 amplification (1q21+) and is associated with a median OS of 50.5 months [10]. In contrast, high-risk disease is characterized by the presence of at least one of the previously mentioned abnormalities and is associated with a median OS of 24.5 months ($P < 0.001$) [10]. Patients harboring chromosomal aberrations, such as del(13), t(11;14), t(6;14), or hyperdiploidy in the absence of other high-risk defining features, generally have standard or intermediate-risk disease (Table 2.2).

In 2005, the International Staging System (ISS) was devised and quickly superseded the DS system. ISS is based on two simple inexpensive routine laboratory tests that reflect not just the tumor burden and renal function (β2-microglobulin) but also biologic impact of host-tumor interaction (albumin) [11]. The median OS of ISS stage III patients (serum β2-microglobulin >5.5 mg/mL) was reported as 29 months compared with patients classified as stage I myeloma (serum albumin

Table 2.2 Risk classification based on FISH and conventional cytogenetics

Category	Genes/ chromosomes	Frequency (%)	Risk	Comments
Hyperdiploidy	Usually trisomies involving odd-numbered chromosomes except for chromosome 1, 13, and 21	42	Standard	Hyperdiploidy is an initiating pathogenetic event
Monosomy 13 or del(13q), in the absence of other high-risk abnormalities		15 (metaphase karyotype) 50 (FISH)	Standard	The historically negative impact has been related to overlap with t(4;14) and/or del17p
Ig H translocated		40		
t(11;14) (q13; q32)	<i>CCND1</i> (cyclin D1)	15–20	Standard or intermediate	
t(4;14) (p16; q32)	<i>FGFR-3</i> and <i>MMSET</i>	12–15	High	
t(14;16) (q32; q23)	<i>C-MAF</i>	3	High	
t(14;20) (q32; q11)	<i>MAFB</i>	1	High	
t(6;14) (p21; q32) and other	<i>CCND3</i> (cyclin D3)	<5	Standard	
Combined hyperdiploidy + high-risk cytogenetics		15	Undetermined	It is unclear if the favorable prognostic impact of hyperdiploidy is lost in such cases
Isolated Monosomy 14, lack both IgH translocations and trisomies	Few cases may represent 14q32 translocations involving unknown partner chromosomes	4.5	Undetermined	
Other cytogenetic abnormalities in absence of IgH translocations or trisomy or monosomy 14		5.5	Undetermined	
Normal		3	Standard	

Table 2.2 (continued)

Category	Genes/ chromosomes	Frequency (%)	Risk	Comments
1p deletions	<i>CDKN2C, FAF1, FAM46C</i>	11–30	High	Deletion of 1p32.3 and 1p12 has been associated with impaired OS in myeloma patients receiving ASCT
Gain 1 q21	<i>CKS1B, PMSD4</i>	40	High	Patients with ≥ 3 copies of 1q have a worse treatment outcome The data is conflicting about 1q21+. Some reports have shown 1q21+ to be an independent prognostic factor [61], whereas others have not [63]. Although its role as a poor prognostic factor is controversial, the lack of 1q21+ is useful in identifying patients with standard prognosis [64]
Del 17p	The molecular target of del(17p) may be <i>TP53</i>	7	High	These patients present with more aggressive disease, extramedullary disease, and central nervous system involvement At present, it is not clear what minimum percentage of cells carrying del(17p) is required to confer adverse prognosis. Minimal percentages of 20% and 60% have been recommended

≥ 3.5 mg/mL, serum $\beta 2$ -microglobulin < 3.5 mg/mL), who had a median OS of 62 months. The strength of the ISS is that it is a robust staging system that has been validated and is applicable across geographical areas. It maintains prognostic efficacy in a variety of clinical situations, namely, older (> 65 years) vs. younger patients and treatment with conventional vs. ASCT. The main drawback, however, is that the FISH/cytogenetic features were not included in the derivation of ISS.

In addition to markers used in DS and ISS staging system, high serum lactate dehydrogenase (LDH), an indicator of rapid tumor turnover, is another marker of inferior outcome. It has consistently been associated with short OS in studies conducted before and in the era of novel agents [12, 13]. Within each ISS group, the presence of high LDH is associated with a worse median OS.

GEP signature is also an important tool that provides supplementary information regarding prognosis. The first comprehensive GEP signature of newly diagnosed MM patients was published by the Arkansas group in 2002 [14]. Thereafter, numerous GEP signatures have been identified in the context of retrospective and prospective analyses for both newly diagnosed and relapsed patient populations. Examples include UAMS 70-gene signature [15], EMC 92-gene signature [16], 17-gene signature by UAMS [15], 15-gene signature in the IFM trials [17], and a 6-gene signature in the MRC Myeloma IX trial [18]. GEP signatures are particularly effective in identifying high-risk group comprising 15% of new cases of MM with very poor outcomes. The technology of GEP is robust with good interlaboratory agreement. Unfortunately, widespread adoption of GEP in the clinics has been hindered by concern over variation between published signatures, difficulty in physician interpretation, and the challenge of obtaining sufficient genetic material from limited patient specimens. The IMWG conducted a study to unify the GEP signatures using prognostic modeling and found that the combination of prognostic signatures is generally better than single signature [19]. In this study, the simple average of EMC 92 and HZDC2 indices performed the best across datasets that comprised newly diagnosed and relapsed patients treated with novel agents and ASCT. Beyond lower-resolution genetic analyses like cytogenetics and FISH, clonal and subclonal heterogeneity in MM has been comprehensively characterized by genome-based diagnostic approaches including whole exome sequencing and whole genome sequencing (WGS). Other newer approaches to predict survival include analysis of microRNAs, custom capture mutation analysis, and evaluation of methylation and splicing patterns.

2.4 What Is the Value of Combined Prognostic Models?

Because individual prognostic factors do not capture the full heterogeneity in outcome, several studies have used models combining ISS with FISH cytogenetics and other prognostic features (Table 2.3). These combined models more accurately segregate patients into risk groups that better predict outcome for transplanted MM patients. Integrated prognostic models have shown to outperform prediction based on conventional clinical and cytogenetic factors alone.

Table 2.3 Staging systems and risk classification systems for newly diagnosed multiple myeloma

Classification	Stage	Frequency (%)	OS
DS [5] (substage A: serum creatinine <2 mg/dL; and substage B: serum creatinine ≥2 mg/day)	I All the following: Hb > 10 g/dL Ca ≤ 12 mg/dL Normal or solitary plasmacytoma on skeletal survey Serum M protein <50 g/L for IgG; <3 g/dL for IgA; Bence Jones protein <4 g/24 h	7.5 (IA) 0.5 (IB)	50% at 62 months 50% at 22 months
	II Neither stage I nor stage III	22 (IIA) 4 (IIB)	50% at 58 months 50% at 34 months
	III One of the following: Hb < 8.5 g/dL Ca > 12 mg/dL Advanced lytic bone lesions (scale 3) Serum M protein >7 g/dL for IgG; >5 g/dL for IgA; Bence Jones protein >12 g/24 h	49 (IIIA) 17 (IIIB)	50% at 45 months 50% at 24 months
ISS [11]	I Serum β2-microglobulin <3.5 mg/L, serum albumin ≥3.5 g/dL	30	50% at 62 months
	II Not fitting to stage I or II	37.5	50% at 44 months
	III Serum β2-microglobulin ≥5.5 mg/L	34	50% at 29 months
mSMART (http://www.msma.org)	Standard All other cytogenetics including trisomies (hyperdiploidy), t(11;14), t(6;14)	NA	NA
	Intermediate t(4;14) 1q gain High PC-S phase	NA	NA
	High del (17p13) t(14;16) t(14;20) LDH ≥2 times institutional upper limit of normal Features of primary plasma cell leukemia High-risk gene expression profiling signature	NA	NA

(continued)

Table 2.3 (continued)

Classification	Stage	Frequency (%)	OS
ISS + Cytogenetic abnormalities in ASCT-eligible [60]	Favorable ISS stage I and not (4;14) or del(17p13)	42	72% at 60 months
	Intermediate Neither favorable nor poor	44	62% at 60 months
	Poor ISS stage II/III and t(4;14) or del(17p13)	14	41% at 60 months
ISS + Cytogenetic abnormalities in ASCT eligible and ineligible patients with NDMM [61]	Favorable ISS stage I/II and no t(4;14), t(14;16), +1q21, del(13), del(17) or ISS stage I with 1 CA	38	50% at 68 months
	Intermediate ISS stage I and >1 CA, or ISS stage II/III and 1 CA, or ISS III and no CA	48	50% at 41 months
	Ultra-high ISS II/III with >1 CA	14	50% at 19 months
ISS + CA in ASCT eligible and ineligible patients with NDMM [62]	Favorable ISS I/II and no t(4;14) or del(17p13)	51	77% at 48 months
	Intermediate ISS III and no t(4;14) or del(17p13) or ISS I and t(4;14) or del(17p13)	29	45% at 48 months
	Poor ISS II/II and t(4;14) or del(17p13)	20	33% at 48 months
ISS + CA + LDH in ASCT-eligible patients with NDMM [21]	Score 0 No adverse factors of the other categories	47–63	93% at 24 months
	Score 1 Only one adverse factor of categories 2 and 3	28–34	85% at 24 months
	Score 2 High LDH, ISS III, no t(4;14) or del(17p13)	2–5	67% at 24 months
	Score 3 t(4;14) and/or del(17p13), and ISS III, and/or high LDH	5–13	55% at 24 months

Table 2.3 (continued)

Classification	Stage	Frequency (%)	OS
Revised ISS in ASCT-eligible and ASCT-ineligible with NDMM [20]	Stage I <ul style="list-style-type: none"> Serum albumin ≥ 3.5 gm/dL Serum beta-2-microglobulin < 3.5 mg/L No high-risk cytogenetics Normal serum LDH 	28	82% at 46 months
	Stage II	62	62% at 46 months
	Not fitting stage I or III		
GEP signatures	Stage III <ul style="list-style-type: none"> Serum beta-2-microglobulin > 5.5 mg/L High-risk cytogenetics [t(4;14), t(14;16), or del(17p)] or elevated serum LDH 	10	40% at 46 months
	UAMS 70-gene [15]		
	High risk	13	28% at 60 months
	Low risk		78% at 60 months
	IFM 15-gene [17]		
	High risk	25	47% at 36 months
	Low risk		90% at 36 months
	EMC 92-gene [16]		
	High risk (validation set of MRC IX- transplant eligible)	20	50% at 40 months
	Low risk		50% at 62 months

DS Durie and Salmon, *ISS* International Staging System, *NDMM* Newly diagnosed multiple myeloma, *CA* cytogenetic abnormality, *LDH* lactate dehydrogenase, *GEP* gene expression profiling, *ASCT* autologous stem cell transplant, *mSMART* Mayo Stratification of Myeloma and Risk-Adapted Therapy, *Hb* hemoglobin, *Ca* calcium, *UAMS* University of Arkansas for Medical Sciences, *IFM* Intergruppe Francophone du Myélome, *NA* not available, *OS* overall survival

IMWG published revised ISS (R-ISS) in 2015 that incorporates the original ISS, cytogenetic abnormalities, and serum LDH [20]. R-ISS provides a comprehensive and practical risk stratification of newly diagnosed MM, including both young and elderly patients, that allows a clear identification of three stages with different survival durations. R-ISS stage I includes ISS stage I, no high-risk cytogenetic abnormalities, and normal LDH; R-ISS stage III includes ISS stage III with high-risk cytogenetic abnormalities and/or high LDH levels; and R-ISS stage II includes all the remaining. High-risk cytogenetic abnormalities included del(17p), t(4;14), and/or t(4;16), whereas all other cytogenetic/FISH markers were considered standard risk. Patients with R-ISS stage I, II, and III had 5-year OS rates of 82%, 62%, and 40%, respectively. Another study that combined ISS, cytogenetic abnormalities, and LDH defined four risk categories: in the very low-risk category, the 2-year OS was 93%. In contrast, the 2-year OS was 55% in the very high-risk category [21]. ISS has also been combined with GEP classifiers. By combining the EMC 92-gene classifier with ISS, patients were effectively stratified into four risk groups, including a

distinctive low-risk group of 38% and a high-risk group of 17% [19]. In summary, combined risk models including ISS and genetic risk stratification robustly characterize those patients who have a high risk of early death from progression within the first 2 years of MM diagnosis.

2.5 Does Depth of Treatment Response Affect Risk Stratification?

Although pretreatment disease characteristics remain the hallmark of prognostication, posttreatment parameters such as minimal residual disease (MRD) assessment and degree of response to therapy possess the ability to further refine the prognosis. Not only does response to treatment provide a synopsis of therapeutic resistance, it also helps determine the impact of dosage, compliance, and other unknown biology factors influencing the effectiveness of treatment. The proportion of patients achieving CR has increased through the introduction of novel agents and use of ASCT, necessitating more stringent definitions for assessing the exact magnitude of response in MM. The IMWG revised the reporting criteria, adding immunophenotypic CR and molecular CR categories [22]. Thus, more sensitive approaches like multiparameter flow cytometry (MFC) and molecular techniques like allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and NGS are being adapted for response and MRD assessment. More than a decade ago, Rawstron et al. first identified MRD as an independent predictor of relapse in patients undergoing ASCT [23]. Based on the MRD, they divided the homogeneous group of patients in conventional CR into two new groups: one with a high level of MRD and an associated high probability of relapse and a second with low or undetectable MRD and excellent prognosis. This data has been further corroborated in two pivotal studies by the Spanish and UK groups in the context of large multicenter clinical trials. In an analysis of 295 newly diagnosed patients, the Spanish group demonstrated that patients who became MRD negative by MFC at day 100 post-ASCT had a significantly favorable outcome ($P = 0.002$) with progression-free survival (PFS) of 71 months and OS not reached [24]. In contrast, patients who continued to show detectable MRD had a PFS of 37 months and OS of 89 months. Patients with both persistent MRD and high-risk disease had the worst outcome (3-year time to progression: 0% and 3-year OS 32%) [25]. In a very similar analysis evaluating 397 patients from the UK Myeloma IX study with MFC, the MRD was associated with a significantly inferior PFS (15.5 vs. 28.6 months, $P < 0.001$) and OS (59 vs. 80.6 months, $P = 0.018$) [26]. In the intensive pathway, the patient cohorts with different prognoses and was stratified based on combined MRD status and cytogenetic risk group. Median PFS for favorable cytogenetics was 44.2 and 33.7 months for MRD negative and MRD positive, respectively, whereas median PFS for adverse cytogenetics was 15.7 and 8.7 months for MRD negative and MRD positive, respectively [26]. More recently, these observations were reproduced using ASO-PCR [27] and NGS [28], which again corroborated the prognostic value of MRD assessment in transplant-eligible MM patients.

It can be concluded that MRD positivity usually portends adverse prognosis. However, patients achieving MRD negativity also eventually relapse, and at this point we still do not know if we should alter our management for patients per MRD status. Global efforts are underway to standardize and harmonize criteria of automated MRD testing in MM to ensure uniform assessment of response and clinical prognostication. MRD-driven prospective clinical trials (incorporating MRD negativity as primary endpoint) are ongoing to compare and evaluate the efficacy of different treatment strategies, particularly in the consolidation and maintenance settings, and to adapt/modify treatment according to the MRD status. These trials will hopefully provide the rationale for the use of MRD assessment in the future risk stratification schema.

2.6 What About Imaging-Based Response for Risk Stratification?

Sensitive imaging during and after treatment has the potential to improve the definition of MRD and risk stratification by providing information on patchy bone marrow disease and extramedullary sites, complementing MRD assessment in bone marrow sample obtained from single site. MRD-negative patients, who continue to be immunofixation positive or negative, may still have focal lesions or extramedullary sites of active disease. In this respect, lesions that are equivocally positive on MRI or fluorodeoxyglucose-positron emission tomography (FDG-PET) can be subjected to sampling. The application of FDG-PET as a monitoring tool showed that persistence of FDG activity after induction or ASCT was associated with poor PFS and OS. Importantly, 23% of patients who achieved CR but were still positive on PET-CT had significantly shorter 4-year estimate of PFS in comparison with that of PET-negative patients (30% vs. 61%; $P = 0.02$) [29]. In the total therapy (TT) 3 trial for newly diagnosed MM, the presence of more than three FDG-avid focal lesions in the GEP-defined low-risk group served as an independent predictor associated with inferior OS and EFS. The entire high-risk group fared poorly [30]. In addition, this trial showed that a decrease in FDG SUV (max) before ASCT conferred a survival benefit, reflecting the importance of complete suppression of tumor metabolism in MM. Persistence of greater than three focal lesions at day 7 after the start of induction therapy, irrespective of GEP-defined risk, was associated with high risk of relapse or death in TT3A and TT3B clinical trials [31]. Walker and colleagues [32] reported the results of a prospective evaluation of MRI before and after treatment with TT2 trial. They showed that seven or more lesions on MRI in the presence of CA were associated with 5-year OS of 37% as opposed to 76% OS in the absence of both features. Furthermore, resolution of lesions, determined by MRI after therapy predicted for superior OS. Similarly, the Heidelberg group showed that the number of focal lesions on whole body MRI after ASCT is associated with both PFS and OS [33]. Altogether, this indicates that persistence of PET and MRI lesions identifies a group of patients with an inferior response to therapy and that residual focal lesions after treatment may represent the source of relapse. However, it is

important to emphasize that focal lesions may show altered signals for several months after therapy, in both responding and nonresponding patients because of treatment-induced necrosis and/or inflammation. Standardization of response definitions by sensitive imaging tools and comparison with bone marrow-based MRD methods, including targeted biopsies, is needed before additional refinements in response criteria based on imaging can be made.

2.7 Do Novel Therapeutics Ameliorate Adverse Impact of High-Risk Cytogenetics?

Over the past 20 years, treatment options for MM have expanded multifold, and the therapies available to patients are more effective. Specifically, IMiDs and proteasome inhibitors (PIs) have contributed to improved PFS and OS and are now considered integral part of treatment before and after ASCT for newly diagnosed patients. Risk stratification has been reviewed in the context of emerging novel therapeutics, distinguishing between therapies that only *improve* the outcomes of high-risk patients when compared with previous therapies vs. those that *overcome* high-risk status, thereby reclassifying these patients as standard risk.

2.7.1 Impact of Proteasome Inhibitors

Most evidence of modifying adverse impact of high-risk cytogenetics in newly diagnosed transplant-eligible patients is available with bortezomib. The data using other approved PIs, i.e., carfilzomib and ixazomib, is not yet mature in frontline setting. Patients with deletion 13 by conventional cytogenetics once considered having high-risk disease, now with the use of bortezomib-based therapies, have an outcome approaching that of intermediate- or standard-risk MM. In a matched-pair analyses of two large phase 2 and 3 trials in relapsed and refractory setting, SUMMIT (Study of Uncontrolled Myeloma Managed With Proteasome Inhibition Therapy) [34] and APEX (Assessment of Proteasome Inhibition for Extending Remissions) [35], Jagannath and colleagues showed that the response and survival were comparable in bortezomib-treated patients with or without del(13) by cytogenetics as an independent prognostic factor [36]. In addition, studies show that historically poor prognostic value associated with del(13/13q) actually stems from its surrogate association with other high-risk features, especially t(4;14) and del(17p) that are concomitantly present in up to 80% of patients harboring del(13/13q) [37].

Whether the novel drugs modify prognostic impact of t(4;14) and del(17p) is still a matter of debate. Chromosomal aberrations t(4;14) and del(17p) have been associated with worse PFS and OS in multivariable analyses independent of ISS stage, even in those undergoing ASCT. These two cytogenetic abnormalities are categorized as high risk based on R-ISS staging. Some, but not all, studies have shown that the negative prognostic implications of t(4;14) and del(17p) can be at least improved (but not overcome) with bortezomib in newly diagnosed transplant-eligible patients.

Notably, this evidence comes from post hoc subgroup analyses of trials that were not specifically targeted or powered for high-risk cytogenetics group.

In HOVON-65/ GMMG-HD4 trial of ASCT, bortezomib as a part of induction and maintenance was compared with VAD (vincristine, doxorubicin, and dexamethasone) induction and thalidomide maintenance [38, 39]. Overall, patients with t(4;14) showed a significantly worse median PFS (21.7 vs. 35.7 months; $P = 0.0002$) and 3-year OS (55% vs. 82%; $P = 0.0003$) compared with patients lacking this aberration. Although the bortezomib arm achieved better results in patients with t(4;14), this did not reach statistical significance. In the same trial, a subgroup analysis of 37 patients with del(17p) demonstrated significantly longer median PFS (26.2 vs. 12.0 months; $P = 0.024$) and improved 3-year OS (69% vs. 17%; $p = 0.028$) in the bortezomib arm than those assigned to VAD. Nonetheless, the 3-year OS of 85% in patients without del(17p) indicates that bortezomib does not completely overcome the adverse prognosis of this abnormality. The IFM group studied the outcome of 507 patients treated with bortezomib and dexamethasone induction before ASCT compared with a cohort of 512 patients treated with VAD [40]. Bortezomib improved both EFS and OS for patients with t(4;14) but not for those with del(17p) when compared with patients treated with VAD induction within the same period.

Two randomized clinical trials evaluated the induction regimen of bortezomib, thalidomide, and dexamethasone (VTD) against thalidomide and dexamethasone (TD) within the context of ASCT and maintenance therapy in newly diagnosed MM. In the trial by Cavo and colleagues, incorporation of VTD before and after double ASCT allowed the adverse effects of t(4;14) to be overcome with improvement in 3-year PFS to 69%. This was analogous to the 3-year PFS of 74% for patients without t(4;14) ($p = 0.66$) [41]. In contrast, patients in the TD arm retained the adverse impact of t(4;14) and experienced comparatively poor 3-year PFS than those without (37% vs. 63%; $p = 0.013$). Benefit was also observed in patients with del(17p13) treated with VTD compared to TD. The median PFS was 12 months in the TD group vs. 22 months in the VTD group ($P = 0.01$). The median OS was 24 months in the TD group vs. not reached at 54 months in the VTD group ($P = 0.003$). In the second trial (Spanish PETHEMA GEM05) where patients received a single course of ASCT and were randomized to thalidomide or interferon alfa-2b or VT maintenance, the cytogenetically defined high-risk group patients including t(4;14) and del(17p13) had a significantly shorter PFS than those with standard risk, irrespective of the treatment [42]. Although high-risk patients had improved median PFS with VTD compared to patients treated with TD (23.5 months vs. 8.9 months, $P = 0.04$), the VTD regimen was not able to overcome the poor prognostic impact of high-risk cytogenetics. This result was in contrast with the Italian study mentioned above. The University of Arkansas TT2 regimen did not include bortezomib and patients with t(4;14) and del(17p) had significantly shorter EFS and OS compared to those without the translocation [43]. This difference disappeared in the bortezomib-containing TT3 regimen, in which bortezomib was added to the induction, consolidation, and maintenance phases of multidrug treatments [44].

In conclusion, it seems that although bortezomib-based regimens improve, to some extent, the PFS and OS in patients with high-risk cytogenetics, this

improvement is quite modest and not sufficient to fully overcome the prognosis. A comparison of studies showing favorable results with studies showing less favorable results suggests that the prolonged treatment including bortezomib-based induction therapy before tandem ASCT and bortezomib maintenance may overcome the risk of t(4;14) [45]. Therefore, randomized, prospective clinical trials are needed to resolve whether prolonged bortezomib treatment can truly improve and/or overcome the high-risk impact of del(17p) and t(4;14).

2.7.2 Impact of immunomodulatory agents

Thalidomide does not abrogate the adverse effect of t(4;14), t(14;16), t(14;20), and del(17) or del(17p) and gain(1q) in transplant-eligible patients [46]. The benefit of lenalidomide in patients with high-risk cytogenetics undergoing ASCT is less clear. Two recent phase III randomized studies comparing ASCT with standard chemotherapy deserve mention [47, 48]. Newly diagnosed patients aged 65 years or younger in each of these studies were treated with four cycles of Rd induction and subsequent autologous stem cell collection using cyclophosphamide and granulocyte colony-stimulating factor (G-CSF) mobilization. Consolidation and maintenance were different in the two studies. Palumbo and colleagues [47] randomized patients to receive consolidation with six cycles of melphalan, prednisone, and lenalidomide (MPR) or two courses of ASCT and maintenance with lenalidomide or no maintenance. Gay and colleagues [48] randomized patients to receive consolidation with six cycles of chemotherapy (cyclophosphamide and Rd) or two courses of ASCT and maintenance with lenalidomide or lenalidomide and prednisone. Both studies showed significantly shorter PFS and OS for the chemotherapy arm compared with the ASCT arm. In a post hoc analysis of patients assigned to chemotherapy, those with high-risk cytogenetic abnormalities had worse PFS (15.7 months vs. 47.1 months) and OS (52% vs. 87%) than did those with standard-risk cytogenetic abnormalities [48]. High-risk was defined by the presence of del(17p), t(4;14), or t(14;16). The difference in PFS between high-risk and standard-risk patients (33.4 months vs. 46.8 months) was less evident with ASCT. In RV-MM-209 trial, patients had insignificant improvement in PFS favoring ASCT for high-risk (HR 0.3, 95% CI 0.37–1.42, $P = 0.40$) and standard-risk group (HR 0.49, 95% CI 0.24–0.62) [47]. Unfortunately, the low number of patients in each subgroup combined with the number of patients not evaluable for cytogenetic risk limited the value of these analyses.

In a study of newly diagnosed MM patients treated with Rd induction, the high-risk group, defined by the presence of hypodiploidy, del(13q), del(17p), t(4;14), t(14;16), or plasma-cell labeling index of 3% or greater, had a shorter PFS (18.5 months vs. 36.5 months $P < 0.001$) and less durable responses compared with standard-risk group. Although the 3-year OS of 77% for high-risk group of patients was not statistically different from OS of 86% for standard risk, $P = 0.4$ [49]. In contrast, in the phase 3 E4A03 study comparing lenalidomide with either high or

low-dose dexamethasone in patients with newly diagnosed MM, the 2-year OS in patients with high-risk cytogenetic abnormalities was significantly shorter compared with standard risk (76% vs. 91%, respectively, ($P = 0.004$)) [50]. In both these studies it is not clear how many patients went on to receive ASCT. In the maintenance setting, the Intergroupe Francophone du Myélome (IFM) found that lenalidomide maintenance was associated with an improvement in PFS from 24 to 42 months ($P < 0.0001$). In patients with del(17p), lenalidomide maintenance was associated with an improvement in PFS from 14 to 29 months ($P < 0.02$), but it did not overcome this risk. In patients with t(4;14), the improvement in PFS was from 24 to 28 months ($P < 0.04$) [51].

Therefore, from the available evidence, it can be concluded that there is no clear and consistent evidence of an improvement in PFS or OS with lenalidomide-based induction (Rd or CRd without bortezomib) in high-risk newly diagnosed MM patients undergoing ASCT.

2.8 How Do We Prioritize Treatment for Transplant-Eligible Newly Diagnosed MM According to the Risk Category?

As we move into 2016, early ASCT for all eligible patients remains the standard of care irrespective of risk stratification. In the absence of comparative phase III studies, focused on a risk category, it is challenging to make categorical recommendations regarding the risk-aligned management strategies for transplant-eligible newly diagnosed MM. Besides risk stratification, other factors must always be taken into consideration when prognosticating patients for treatment selection, such as host-related factors (age, performance status, organ function, comprehensive geriatric assessment, and comorbidities) and tumor-related factors (plasma cell proliferation rate, extramedullary disease [EMD], and plasma cell leukemia [PCL]).

Two phase III randomized studies (discussed above) using Rd-based regimens show that PFS is better with early ASCT, but the transplant itself does not provide a meaningful benefit in OS [47, 48]. Missing in these studies was the use of a PI, which is believed to be key to improved survival for high-risk patients. Ongoing large collaborative studies (the European Myeloma Network 02 trial and the IFM/Dana–Farber Cancer Institute 2009 trial; ClinicalTrials.gov numbers NCT01208766, NCT01191060, and NCT01208662) are evaluating effective drug combinations that include a PI and an IMiD vs. ASCT, the benefit of early vs. late transplantation, and the effects of varying the duration of maintenance therapy. At the 2015 American Society of Hematology (ASH) meeting in Orlando, the results from the IFM part of the study were presented, showing that the PFS was longer in the arm with three cycles of RVd followed by upfront ASCT, followed by two additional cycles of RVd and 1 year of lenalidomide maintenance [52]. In the upfront ASCT arm, 93% of patients underwent ASCT, and five toxic deaths occurred during mobilization or in the actual transplant phase (1.4%). ASCT was found to improve PFS (HR 1.5, 95% CI 1.2–1.9). The 3-year post-randomization PFS was 61% in the upfront ASCT arm

vs. 48% in the delayed ASCT arm. OS was not statistically different between the two arms. In the absence of data confirming the detrimental effect of delayed ASCT, reserving ASCT for future use at disease progression is another treatment option that must be discussed clearly with the patients. The major deterrent to delayed ASCT is the concern that considerable proportion of patients may not continue to be eligible or fit to receive transplantation at the time of relapse, as shown in a study where only 43% of patients (treated with conventional chemotherapy frontline) could receive ASCT at the time of relapse [48].

In the absence of randomized data comparing efficacy, choosing the best induction regimen among a wide range of combinations can be challenging. Depth of response prior to ASCT appears to correlate with the PFS and OS [53]. Three-drug induction incorporating an IMiD and a PI has shown to generate deeper responses than two-drug regimens such as VD or Rd. [54]. The idea is to accelerate and maintain responses given the high risk of genetic instability and propensity to rapidly progress in the face of suboptimal therapy. In real-life practice RVD and VCD (aka CyBorD) are the commonly used regimens in the USA and VTD in other parts of the world. A phase 2 EVOLUTION study suggests that RVD and VCD yield similar results [55]. In a head-to-head comparison within a phase III randomized trial, the overall response rate was significantly higher in the VTD arm, 92.3% vs. 83.4% in the VCD arm ($p = 0.01$), when used as induction prior to ASCT. Similarly, in a retrospective matched pair analysis of patients randomly assigned to the VTD arm of the GIMEMA-MMY-3006 study and patients who received VCD induction in the EMN-02 showed that VTD increased the CR rate three times more than VCD (19 vs. 6%, $P < 0.001$) [56]. This improvement was retained across high-risk cytogenetics as defined by the presence of $t(4;14)$ and/or $del(17p)$ (23% vs. 8%, $P = 0.03$) and among patients with ISS stage II + III (20% vs. 4%, $P < 0.001$). An IMiD and a PI, in combination with dexamethasone, should be the preferred combination, especially for high-risk patients. Because of stringent requirements, older patients and those with comorbidities have generally been excluded from frontline clinical trials. Therefore, information is lacking about how best to manage patients with hepatic or renal failure, preexisting cardiac or vascular disorders, or gastrointestinal and malabsorption syndromes. VCD has been a reasonably safe option for those with suboptimal renal function, with the option to switch to RVD (for high-risk patients) after renal activity is restored. In patients presenting with PCL or extensive EMD, in whom a fast response is required, or for those with rapid progression to induction, more intensive regimens, such as continuous-infusion cisplatin, doxorubicin, cyclophosphamide, and etoposide (PACE), combined with bortezomib or carfilzomib and dexamethasone are used taking adequate prevention measures for tumor lysis syndrome to avoid the risk of irreversible disease complications [57].

Induction treatment is generally continued up to best optimal response, usually 4–6 cycles, after which all transplant-eligible patients proceed with autologous peripheral blood stem cell (PBSC) collection. Stem cells are collected after GCSF

and plerixafor mobilization for at least one and usually more than one ASCT. Collecting PBSC early during treatment ensures that stem cells are healthy and are less exposed (both in quantity and quality) to potentially mutagenic therapies.

Newer agents including next-generation PI (carfilzomib, ixazomib), IMiD (pomalidomide), or monoclonal antibodies/immunotherapies (elotuzumab, daratumumab, PD-1/PDL-1 inhibitors) seem to be effective for high-risk MM group in small nonrandomized studies; however systematic studies are being conducted in frontline setting (during induction and/or consolidation) for transplant-eligible patients with high-risk or standard-risk MM, and their results will be important for optimizing regimens.

Tandem ASCT has been shown to improve response for patients achieving less than very good partial response (VGPR) after one ASCT, but these studies were conducted before the use of PI and IMiD. Although tandem ASCT combined with bortezomib-based induction and maintenance may improve PFS in patients with t(4;14) and/or del(17p), this strategy is not routinely implemented as the evidence is not corroborated from stratified randomized studies. Randomized studies comparing early vs. delayed transplant (NCT01208662) or single vs. tandem ASCT (NCT01208766) are ongoing to clarify which populations should proceed for early or tandem ASCT and which population should wait for delayed ASCT.

Lenalidomide (single agent) maintenance until progression is recommended for patients who can tolerate it, based on randomized phase III data and subset analyses proving efficacy in improving PFS for standard-risk patients. For high-risk patients with PCL, t(14;16), del 17(p), and 1q+ or GEP70 score, combined PI and IMiD maintenance should be considered because they do not do well with single agent maintenance. In the recent report, VRD maintenance for up to 3 years, followed by single agent lenalidomide maintenance until progression has shown promising results in terms of PFS (median 32 months) and OS (>90% at 3 years) in patients with high-risk cytogenetics [58]. Ongoing studies are examining RVD, carfilzomib-lenalidomide-dexamethasone (KRD), daratumumab, and other new agents in terms of content (single agent vs. combined) and duration (short vs. long) of maintenance therapy.

Allogeneic SCT is not clearly established as a standard treatment approach for most MM patients. In a recent meta-analysis evaluating six trials comparing tandem ASCT vs. ASCT followed by reduced intensity allogeneic SCT, the latter approach was shown to be associated with a higher CR rate and transplant-related mortality without clear benefit in PFS and OS, and the majority of patients relapsed after tandem autologous-allogeneic SCT [59]. For high-risk GEP-70, del(17p), t(4;14), +1q, or plasma cell leukemia, especially with multiple high-risk abnormalities, or in combination with higher stage or high LDH, eligible young patients should be considered for clinical trials examining allogeneic SCT. Novel strategies in the context of allogeneic SCT are being studied that would reduce transplant-related mortality and improve long-term outcomes.

2.9 Summary and Conclusions

Risk stratification at diagnosis is recommended for all patients as it helps with predicting response and in some cases with selecting treatment. Consensus guidelines from the IMWG support a comprehensive cytogenetic and FISH evaluation in all patients with MM at the time of diagnosis and at relapse. FISH panel is used for detection of t(11;14), t(6;14), t(4;14), t(14;16), t(14;20), del(17p13), 1q+, trisomies of odd-numbered chromosomes, and del(1p32). Conventional cytogenetics (karyotyping) is helpful for detection of deletion 13, monosomy 13, or hypodiploidy. Combined models, such as R-ISS, provide improved outcome prognostication and should be routinely adapted in clinic. Risk stratification should continue over time because risk factors can change, thus altering an individual's risk for progression. Studies of GEP are uncovering biological heterogeneity with prognostic significance, and wherever possible GEP data should be collected within or outside of the clinical trials to provide a framework within which newer technologies such as mutational analysis and NGS can be integrated. The use of FDG-PET-CT provides additional predictive information when used at diagnosis and after treatment. There is unequivocal evidence, irrespective of study design, chemotherapy protocol, and MRD measurement method, that MRD is a strong and independent prognostic factor. Future prognostic models in MM are likely to integrate GEP, functional imaging, and MRD within existing risk classification, which would influence the choice of treatment.

Treatment selection based on risk stratification, especially for high-risk patients who constitute about 15–20% of newly diagnosed transplant-eligible population, is an ongoing theme of most clinical trials. Managing high-risk patients continues to be a challenge, and a coordinated effort to put these patients on clinical trials will be required to efficiently determine the optimal therapies. In high-risk MM, highly synergistic combination therapies including next-generation IMiDs and PIs, monoclonal antibodies, and immunotherapy-based approaches are being investigated within the context of induction, consolidation and maintenance regimens, tandem transplantation, second transplantation at the time of relapse, and nonmyeloablative allogeneic stem cell transplantation. Some examples of ongoing studies testing novel strategies in high-risk MM patients include *in vivo* purging with daratumumab after induction (prior to ASCT), activated marrow infiltrating lymphocytes with ASCT followed by lenalidomide and tadalafil, nonmyeloablative allogeneic transplant followed by bortezomib, matched-donor stem cell transplant using Flu-Bu4, allogeneic transplant using bortezomib given together with Flu-Mel conditioning with or without total marrow irradiation, maintenance ixazomib after allogeneic SCT, and vaccine therapy after ASCT.

In conclusion, there have been significant improvements in the outcomes for patients with MM over the past 20 years related to the use of high-dose melphalan and availability of IMiDs and PIs. The outcome is expected to further improve with emerging therapeutics that target the molecular heterogeneity of the disease. Thus, refining molecular classification and risk classification in MM remains an important goal of ongoing research, so that biology-based individualized treatment can be delivered to many MM patients in the future.

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