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Chapter

Prognostic and Predictive Factors in Newly Diagnosed Multiple Myeloma Patients with Early Mortality with Prediction Matrix and Three and Five-Year Overall Survival

Howard R. Terebelo and Leo Reap

Abstract

Survival rates for newly diagnosed multiple myeloma have increased to a remarkable 8–12 years. Novel agents, autologous stem cell transplantation, monoclonal antibodies, improvements in supportive care and attention to minimal residual disease negative all have aided this remarkable journey. With these treatments we are identifying tools to achieve complete remissions. Prognostic factors have an important role in selecting proper patient approaches for trial designs. Prognostic and predictive clinical biomarkers have shaped staging and treatment selections for newly diagnosed multiple myeloma. Here we review the Early Mortality Prediction Matrix to identify those at risk of an early death (<6 months) incorporating both disease biology with patient fitness. We also review current standards of care for multiple myeloma and provide a three and five-year overall survival prediction matrix. We review benefits for MRD negativity and Next-Gen Sequencing. These tools will help clinicians improve upon reducing early mortality in newly diagnosed multiple myeloma patients and provide further framework for improving survival by assessing clinical, biologic and individual multiple myeloma patients.

Keywords: newly diagnosed multiple myeloma, prediction matrix, prognostic factors, prediction factors, progression-free survival, early mortality, novel agents, next-gen sequencing, overall survival

1. Introduction-early mortality

The current era of advances in multiple myeloma (MM) identifies a subset of newly diagnosed multiple myeloma (NDMM) patients with early mortality (EM) within the first 6 months of diagnosis [1–6].

Prognostic and predictive risk factors have been identified by the International Myeloma Working Group (IMWG) based upon the LDH, international staging system (ISS), Stage III disease and adverse cytogenetics [7]. Limitations of this study include patients limited to autologous stem cell transplantation (SCT)

which included only 40% of all patients. Prediction matrix models based upon those created for cardiovascular disease and rheumatoid arthritis [8, 9] which can calculate the risk of specific outcomes such as mortality allowing the differential weighting of risk factors. We can identify patients at risk with NDMM for EM to provide insight in applying different treatment approaches. Prediction tools have been applied in other hematologic malignancies to predict EM. In AML, prediction factors have improved treatment paradigms [10]. In diffuse large B-cell lymphoma, cell of origin and molecular markers along with PET scans have provided earlier treatment interventions to improve outcomes [11, 12].

Real World patients often differ from those enrolled in clinical trials. These patients tend to be older and less fit, have more co-morbidities and less often SCT candidates [13]. An observational patient registry allows broad patient characteristics and treatment outcomes while assessing NDMM patient characteristics, biology, co-morbidities and treatments for progression-free survival (PFS) and overall survival (OS) [13–16].

2. Early mortality in the Connect MM Registry

The Connect MM Registry reported on more than 3000 NDMM to identify and characterize EM. The first cohort included the first 1500 patients. Data was collected from an unselected patient population from routine clinical practices (81% community and 18% academic). Here a prognostic tool to assess the risk of EM based upon weighting of risk factors in elderly, SCT and non-SCT eligible patients was created to construct an Early Mortality Prediction Matrix (EMPM). See **Figure 1.**

For the 102 NDMM patients with EM, 39.2% (2.7% of total enrolled) were due to MM progression and 32.9% were related to non-causes. Common causes of death included heart failure, pneumonia, infections, and renal failure. The other

A

	ECOG ≥ 2			ECOG ≥ 2			ECOG < 2			ECOG < 2	
Mobility: No problem in walking about	12%	8%	PC > 150	7%	4%	ISS I, II	3%	2%	Creat ≤ 2	2%	1%
	18%	11%		10%	6%		5%	3%	Creat > 2	3%	2%
	20%	13%		12%	7%	ISS III	6%	4%	Creat ≤ 2	3%	2%
	29%	19%		17%	11%		10%	6%	Creat > 2	5%	3%
	24%	16%	PC ≤ 150	14%	9%	ISS I, II	8%	5%	Creat ≤ 2	4%	2%
	34%	23%		21%	13%		12%	7%	Creat > 2	6%	4%
	37%	26%		23%	15%	ISS III	13%	8%	Creat ≤ 2	7%	4%
	48%	36%		32%	22%		19%	12%	Creat > 2	11%	7%
	Hypertension = Yes			Hypertension = No			Hypertension = Yes			Hypertension = No	
Mobility: some problem in walking about	25%	16%	PC > 150	15%	9%	ISS I, II	8%	5%	Creat ≤ 2	4%	3%
	35%	24%		21%	14%		12%	7%	Creat > 2	7%	4%
	38%	27%		24%	16%	ISS III	14%	9%	Creat ≤ 2	8%	5%
	50%	37%		34%	23%		20%	13%	Creat > 2	11%	7%
	43%	31%	PC ≤ 150	28%	19%	ISS I, II	16%	10%	Creat ≤ 2	9%	6%
	55%	42%		38%	27%		24%	16%	Creat > 2	14%	9%
	59%	46%		42%	30%	ISS III	27%	18%	Creat ≤ 2	16%	10%
	69%	57%		54%	40%		37%	26%	Creat > 2	23%	15%
	Age > 75	Age ≤ 75		Age > 75	Age ≤ 75		Age > 75	Age ≤ 75		Age > 75	Age ≤ 75
Mobility: confined to bed	45%	32%	PC > 150	29%	19%	ISS I, II	17%	11%	Creat ≤ 2	10%	6%
	56%	43%		40%	28%		25%	16%	Creat > 2	14%	9%
	60%	47%		43%	31%	ISS III	28%	18%	Creat ≤ 2	16%	10%
	71%	58%		55%	42%		38%	27%	Creat > 2	24%	16%
	65%	52%	PC ≤ 150	49%	36%	ISS I, II	32%	22%	Creat ≤ 2	20%	12%
	75%	63%		60%	47%		43%	31%	Creat > 2	28%	19%
	77%	67%		64%	51%	ISS III	47%	34%	Creat ≤ 2	31%	21%
	85%	76%		74%	62%		59%	45%	Creat > 2	42%	30%

Figure 1.
A color-coded guide for the clinician identifies which patient (in red) who are at highest risk for EM within six months of diagnosis compared to green and yellow patients who are lowest risk.

28.4% died of other causes or unknown. For those patients surviving more than six months causes of deaths were due to MM (58%) with 5% due to non-myeloma causes. The patients with EM received less triplet therapy (30% vs. 44.7%) and more radiation (24.5% vs. 15.3%) compared with longer surviving patients. EM patients were sicker and less likely to receive triplet therapy.

3. Conclusions

Prior to the era of novel agents, the incidence of EM in NDMM was 10–14% [1, 5, 17, 18]. Novel agents, supportive care, and SCT have improved PFS and OS. The promise of CAR-T therapy, monoclonal antibodies and unique agent BCMA directed against tumor necrosis super family member 17 suggest ongoing improvement for NDMM patients. Key management issues and controversies in EM patients in NDMM patients were passionately presented by Gonsalves [19]. Here the authors defined EM occurring in phase III trials and outlined key management issue strategies for NDMM to mitigate EM and summarizing those patients most at risk. The EMPM here describes parameters to identify NDMM patients at risk for EM, pitfalls in treatment and opportunities to formally address EM in clinical trials.

The prognosis of NDMM patients depends upon staging, patient features, disease biology and treatment outcomes [3]. Risk stratification utilizes the Revised-International Staging System (R-ISS) as devised by the IMWG. The R-ISS is applicable for long-term prognosis but cannot identify those at risk for EM with NDMM [20]. Issues with the R-ISS include a point-based system which is disease specific factors which cannot assess the relative individual of each factor and does not account for patient-specific risk factors. The frailty score, as in the R-ISS, is a point-based system that combines age, functional status and co-morbiditites to predict long-term survival and treatment feasibility in elderly patients with NDMM [20]. Combining the frailty score with the R-ISS stage improves the prognostic value for each score to predict long-term survival. However, neither score alone or when combined has been used to predict NDMM patients at highest risk for EM.

Prognostic studies provide clinicians with a better understanding of the relationship in NDMM patients between the aggressiveness of disease and survival. There are significant gaps in our understanding the optimum ways to risk-stratify NDMM patients when incorporating patient and disease-specific risk factors along with combining the relative contributions of individual risk factors. Existing point-based systems make it difficult to accurately predict outcomes in patients who have a combination of standard and high-risk characteristics [20–23]. Additionally, point-based models are primarily based upon data from interventional clinical trials that may not be representative of Real World NDMM patient populations. The EMPM model here allows differential weighting of the impact of the individual patients and disease-specific risk-factors [24–29].

Patient co-morbidities have been associated with higher mortality in various clinical trials of patients with MM [4, 30–37]. For some NDMM patients, co-morbiditites are both a direct cause of death and places patients at risk for early disease-related mortality by limiting their ability to tolerate therapy [4, 31, 33, 34]. Though the decline the EM to 6.8% reflects the benefit of novel agents and supportive care there are other considerations here. NDMM patients with EM tend to be older and poorer in health with higher rates of co-morbidities (especially diabetes), greater burden of disease, and high-risk features cytogenetics and Stage III disease. The EMPM demonstrates that a lower mobility score, age > 75, history of hypertension, thrombocytopenia, higher ECOG performance status, high ISS disease stage and renal insufficiency were associated with a higher likelihood of EM. Multivariate

analysis did not independently find anemia, del(17q) mutation, low self-care score from EQ-SD, hypercalcemia, diabetes and R-ISS score, beta-2 microglobulin and albumin did not predict EM. NDMM patients with EM received more radiation therapy which delayed the initiation of therapy and limited their ability to receive triplet therapy. The EMPM has been validated by bootstrapping for internal cross-validation [38–40]. A high degree of concordance was observed when applying the model using data from patients form the Phase 3 MM-015 trial and the phase 3 FIRST trial despite more rigorous eligibility criteria [41].

This matrix has the potential to be a clinically useful tool for NDMM patients who are at risk for EM and for analyses of specific patient populations, selection of therapy, identification of new targets for treatment and standardized comparisons between trials.

High-quality systematic research to identify patients at risk for EM have not been studied prospectively. The EMPM is the first weight-based model that accounts for both patient and disease-specific risk factors. This model can facilitate early recognition for NDMM patients at high risk for EM to assist physician selection of personalized treatments, avoidance of nephrotoxic agents, monitoring of steroid dosing in diabetic patients, prompt initiation of doublet or triplet therapy and limiting radiation fields when applicable and the use of prophylactic antibiotics. The EMPM can be applied in routine clinical practice and considered in a risk-adaptive approach. Clinical trials of reducing EM patients in NDMM can be designed for new areas of research.

4. Three and five-year overall survival in NDMM

Over the past 60 years, dramatic changes have been made in the treatment of multiple myeloma. These advances have radically altered the disease landscape and prognosis for newly diagnosed patients, turning a previously untreatable illness toward one of a chronic disease [42]. Here we discuss a brief history of treatments and prognostic features in NDMM, the development of novel treatment regimens, and the use of a prediction matrix in 3-year, and 5-year overall survival (OS).

4.1 Historical background of prognostic features

In 1850, Dr. Henry Bence Jones described the first case of myeloma. His patient presented with fatigue, arthralgias, and polyuria. His urine was found to precipitate an unusual protein upon healing, now known as Bence Jones protein. In 1873, Rustizky was found to have multiple osseous masses in a similar patient, giving rise to the name multiple myeloma. In 1889, Kahler presented a large review of the disease, leading it to be called Kahler disease. Over the subsequent several decades, advances in x-ray imaging, microscopy, and electrophoresis allowed for further characterization of the disease. In 1953, immunoelectrophoresis identified excess monoclonal heavy and/or light chains as characteristic for the disease process seen in multiple myeloma [43].

Untreated, NDMM has a median overall survival of two years. In 1958, Blokhin introduced chemotherapy in MM with a mixture of racemic phenylalanine and nitrogen mustards like sacrosine. In 1962, Bergsagel pioneered the use of melphalan and glucocorticoids, creating the combination of melphalan with prednisone (MP), still in use today. However, complete remissions (CR) were rare. In 1983, McElwain and Powles introduced the use of high-dose therapy with melphalan, with CR achieved in a proportion of patients [44]. Those who achieved CR with MP had a median survival of eight years.

Despite the initial advances, the median OS remained at about three years. Remarkably, the current median OS now ranges from 8 to 12 years [45]. However, individual outcomes are varied, with 20% of patients surviving less than 2 years and 40% surviving more than 10 years after diagnosis [46]. Considerable advances in understanding of the pathobiology of multiple myeloma over this time have greatly aided in the ability to select prognostic factors in NDMM. Advances in treatment that have been contributed greatly to survival are reviewed below.

4.2 Prognosis in NDMM

For many years, the factors contributing to the highly variable prognosis in myeloma were unclear. Early on, immunoglobulin isotype was shown to play a role in prognosis, with monoclonal 1gA production (21%) associated with a worse prognosis [47]. The degree of plasma cell burden is only an issue in plasma cell leukemia [48, 49].

In 1975, the Durie-Salmon staging system was adopted, stratifying individuals by relative plasma cell burden (anemia), hypercalcemia, number of lytic lesions visible on x-ray, and serum urine M-protein levels [50]. However, the number of lytic lesions on x-ray is observer-dependent and created challenges with respect to enrollment and reproducibility between trials.

Thirty years later in 2005, Griepp and colleagues established the international staging system (ISS), utilizing the beta-2 microglobulin level and albumin level to appropriately risk-stratify patients. The ISS can predict EFS and OS regardless of age, geographic region, study site, standard-dose vs. high-dose therapy (HDT), or the use of novel agents [51].

Discovery of specific cytogenetic abnormalities correlates with prognosis in multiple myeloma and overall survival. Plasma cells typically have a low-proliferative index, and so cytogenetic abnormalities are detected in a small number of patients. Interphase FISH was found to be useful in identifying specific cytogenetic aberrations [52].

4.3 1gH rearrangements

As the heavy chain of the immunoglobulin molecule is constitutively activated on the 14th chromosome within plasma cells, translocations involving the immunoglobulin heavy chain haven been shown to play a strong role in myeloma pathogenesis and occur in up to half of NDMM patients. Among these 1gH translocations, five appear to be recurrent: t(4;14) and t(11;14), t(4;16) and t(14;20) [53]. The translocations t(4;14) and t(11;14) are not the most common abnormalities involving the 1gVH gene in myeloma, each seen in approximately 15% of patients. These translocations lead to overexpression of FGRF3 and BCL2, respectively. T(4;14) is regarded as high-risk abnormality with inferior median OS. t(11;14) and hyperdiploidy have been reported in some studies to predict a more favorable outcome. T(11;14) is observed in 16–24% of MM patients and has specifically gained interest with the use of the novel agent venetoclax, a BCL2 inhibitor. Currently, the use of venetoclax was stopped due to an early signal for increased death in early clinical trials due to a higher rate of infections [54]. A large, US, multicenter prospective observational cohort study did not demonstrate any impact of t(11;14) on PFS, or OS [55]. Further clinical trials investigating its use in myeloma are currently pending. T(14;16) and T(14;20) are relatively rare, seen in approximately 1.5–3% of patients and lead deregulation of the oncogenes c-MAF and MAFAB, respectively. Though a pivotal trial from the Mayo Clinic was suggestive of poor prognostic correlation with the presence of t(14;16), larger series are uncertain [53].

4.4 del (13)

Though commonly seen in association with other cytogenetic abnormalities in NDMM, del(13) alone does not predict poor outcomes. When occurring in MGUS and SMM it does not influence progression to myeloma. The finding has called into question the use of del(13) in NDMM prognostication [56]. However in the presence of concomitant t(4;14) or del17p, poor prognosis is suggested

del(17p).

The loss of the short term arm of chromosome 17, or del(17p), leads to loss of TP53 and appropriate DNA repair. 17p deletions occur in 8–10% of NDMM patients and has remained a poor risk feature not over by current use of novel therapies. Without adequate DNA repair function, the rate of clonal mutagenesis and subsequent treatment resistance rises more rapidly. Del(17p) is acquired at a median of 35.6 months after the time of diagnosis, with a median PFS of 5.4 months after acquisition. Consequently, as compared to non-del(17p) patients, median OS is significantly worse [57, 58].

4.5 Hyperdiploidy and other cytogenetic abnormalities

In recent years, high-throughput genomic studies using SNP or CGH arrays have accelerated our understanding of genetic changes within NDMM. Hyperdiploidy generally confers a more favorable prognosis in NDMM. The presence of certain trisomies, such as trisomy 3 and trisomy 5, may partially abrogate the negative prognostic features of other cytogenetic abnormalities. In contrast, the presence of trisomy 21 may potentiate the effects of negative prognostic features. Recently identified chromosomal abnormalities, such as gain of 1q and loss of 1q have also been shown to predict for poorer outcomes. One univariate analysis identified poorer prognosis with deletions of 1p, 2p, 14q, 16q, and 22q. Conversely, amplifications of chromosome 5, 11, 15 and 19 were associated with improved outcomes [56]. Chromosome 1q gain has become the most important chromosomal gain abnormality. In a recent update, high risk cytogenetics are presently considered to be del(17p), a p53 mutation, t(4;14), t(14;16),or gain 1q [59]. Similar to lymphoma, the presence of any two or three risk factors is considered 'double-hit' or 'triple-hit' myeloma, respectively.

In 2015, with the advent of cytogenetic profiles, a revised version of the ISS (R-ISS) was adopted, incorporating LDH and high-risk cytogenetics of t(4;14), t(14;16), and del(17p) into the scoring system [60, 61]. These objective systems have allowed for more reproducible results and the ability to more accurately compare patients within clinical trials [61].

However, establishment of baseline disease characteristics are critical for long term prognosis [62]. These newer staging systems do not account for several features that have been shown to correlate to long-term outcomes in myeloma, such as the use of novel myeloma therapies, triplet therapy, autologous stem cell transplant, patient performance status, renal function, a history of diabetes, or MRD status.

Novel agents in multiple myeloma have allowed for significant progress in the treatment of newly diagnosed patients, with more than doubling of the average survival with less toxicity [47].

a. Alkylating agents

In the early 1960's melphalan and cyclophosphamide were the first alkylating agents introduced in the treatment of NDMM demonstrated equivalent activity. In 1972, Harley evaluated other alkylating agents in NDMM, with the use

of melphalan, carmustine, and cyclophosphamide, melphalan and prednisone. (MP) was established as the gold standard for treatment, paving the way to several decades of comparison against other combinations of agents, including cyclophosphamide, carmustine, vincristine, and adriamycin. Ultimately, combination therapies improved the response rate in NDMM but did not improve OS compared to MP. MP has a response rate of 50–60%, median PFS of 18 months, and an OS of 30–60 months [63]. To date, melphalan and cyclophosphamide remain effective treatment options and are commonly used in autologous stem-cell transplant conditioning. Combination alkylating agent regimens (such as VD-PACE or VDT-PACE) remain typically reserved for more aggressive disease, as in plasma cell leukemia or refractory MM.

b. Glucocorticoids

Glucocorticoids directly induce apoptosis of plasma cells. This is believed to occur via induction of IkB production that negatively regulates NFkB, resulting in downregulation of IL-6 and other pro-inflammatory cytokines, which facilitates apoptosis of the myeloma clones. In the late 1960's prednisone was added to melphalan, but adoption was slowed due to concerns over the known osteoporosis effect of chronic steroid therapy [44]. Since then, glucocorticoids (particularly dexamethasone) have remained a backbone of therapy. Single-agent dexamethasone is no longer advocated in the treatment of NDMM.

c. IMiDs

An international, randomized phase III trial demonstrated that thalidomide with dexamethasone was superior to dexamethasone alone, with an ORR or 63% vs. 46% and a PFS of 14.9 months vs. 6.5 months [59]. FDA approval in the USA in 1998 of Thalidomide was cautiously accepted due to historical concerns regarding the drug-associated phocomelia was displayed in infants 30 years earlier as antiemetic therapy in pregnancy. Thalidomide is used throughout Europe to date in the treatment of myeloma. Lenalidomide was FDA approved in 2005 based upon rate and lower toxicity profile on a retrospective single-institution case–control study of lenalidomide-dexamethasone vs. thalidomide dexamethasone demonstrated lenalidomide was better tolerated, had a higher ORR of 80% vs. 61%, higher VGPR rate 34 vs. 12%, and improved PFS of 27 months vs. 17 months, establishing lenalidomide with dexamethasone as an appropriate induction option [64]. In 2013, pomalidomide, a second-generation IMiD, was developed for use in relapsed/refractory disease. Though shown to have clear activity in NDMM via several immunomodulation pathways, the precise mechanism of action of these agents remain elusive. Irreversible peripheral neuropathy and increased thrombotic risk remain primary side effects of these agents. Prophylaxis with low-dose aspirin daily is adequate prevention.

d. Proteasome inhibitors

The primary function of plasma cells is to produce immunoglobulin, which occurs on a constitutive basis and requires assembly within 26 s proteasome. Excess accrual of protein within the cell creates proteotoxic stress, leading to cell apoptosis and death. As a result, proteasome inhibitors have been shown to have potent efficacy within the treatment of myeloma. Bortezomib, a boron-containing dipeptide, was the first proteasome inhibitor to be introduced for

the treatment of multiple-myeloma. Monotherapy bortezomib FDA approval in 2003 demonstrated an ORR of 27% and a 10% CR rate. In combination with dexamethasone, ORR improved to 88% and CR + VGPR rate of 19%, with a 1-year OS of 87% [65]. Other proteasome inhibitors, including carfilzomib and ixazomib, have been developed and are FDA approved in the relapsed-refractory setting.

Emerging novel agents and therapies

e. Within the past 5 years, several agents have become available in the treatment of multiple myeloma. Notable agents, Dartumumab, a monoclonal antibody against CD-38, has displayed promising efficacy. Belantamab mafadotin, an antibody-drug conjugate between the B-cell maturation antigen (BCMA) and MMAF (a chemotherapy payload) was recently FDA approved for relapsed/refractory disease. BCMA CAR-T cell therapy also shows promise in the relapsed/refractory setting. Though not yet approved in NDMM, these agents, along with others, show promise in the treatment of newly-diagnosed and relapsed-refractory patients.

In 2005, OS in NDMM was 4.6 years, increasing to 6.1 years by 2010. Over the past decade, the adoption of immunomodulatory agents and proteasome inhibitors in triplet therapy extended median OS to greater than 7 years. These gains were predominantly driven by triplet therapy in the elderly and by reducing early mortality in the disease [53, 66].

4.6 Triplet therapy

For many years, monotherapy or doublet regimens were commonly used in the treatment of NDMM. However, with the progressive development of the previously discussed treatment options over the past decades, numerous clinical trials have investigated their use in combination in two-, three-, and four-drug regimens in an attempt to achieve deeper reductions in clonal disease burden. Generally, three-drug combinations (i.e., VCD, VRD, VTD) have been shown to derive the highest ORR and VGPR compared with two-drug regimens and remain the standard of care for fit patients prior to autologous stem cell transplantation (SCT). A Southwest Oncology Group trial randomized 525 patients to either RVD or RD and maintained on RD until progression, with the three-drug combination displaying a better median PFS of 43 months vs. 30 months and median OS 75 vs. 64 months (HR 0.7, $p = 0.025$). As part of triplet therapy, lenalidomide, bortezomib, and dexamethasone (RVD) currently remain standard of care for induction. Though the addition of a fourth drug has not yet shown clear benefit to date, its use likely marks the future, with daratumumab-containing regimens appearing promising. Recently, the GRIFFIN trial compared daratumumab with RVD vs. RVD in NDMM and demonstrated that D-RVD significantly improved strict CR rates and MRD-negativity in transplant-eligible patients [67].

4.7 Autologous stem cell transplant

In the early 1980's, high dose therapy (HDT) with melphalan followed by autologous stem cell transplant (SCT) was performed by McElwain on a patient with plasma cell leukemia. This demonstrated some benefit, but initial adoption was limited due to toxicity of the transplantation process. In the late 1980's, Barlogie further investigated the use of SCT and developed the framework for

SCT in the 1980's and 1990's as part of the standard of care for eligible patients following induction. This led to several prospective, randomized clinical trials in the 1990's which demonstrated superior ORR, PFS, and OS in individuals up to age 65, whereas others demonstrated no survival advantage. Today, SCT following induction therapy in eligible patients remains standard of care. Steady advances in SCT outcomes have occurred over the past 30 years, with patients treated in 2014 or later having superior OS and reduced excess risk for MM death. Second stem cell transplantation may be considered in those with progression-free survival (PFS) or more than three years. Similarly models have supported the potential for cure, estimated at 6.3% to 31.3% depending on the year of treatment [55]. Whether novel agents will supplant HDT followed by SCT backed by minimal residual disease (MRD) continues to be explored. Consideration of myeloablative regimens beyond high-dose melphalan is another venue to be explored for increasing and deepening the CR and MRD negative status.

4.8 Solitary plasmacytoma

Solitary plasmacytomas are uncommon and account for only 6% of all plasma cell neoplasms. They are defined as the presence of a single osseous lesion (medullary) or in the soft tissue outside of the bone (extramedullary) without evidence of bone marrow, clonal plasmacytosis, or CRAB criteria. The incidence of solitary plasmacytomas has increased with increased radiographic imaging use over the past thirty years; incidence increased by 10% from 1999 to 2004 as compared to 1992–1998. Patients with less than 10% plasma cells by bone marrow biopsy can be managed with therapies against the solitary lesion alone, typically 40–50 cGy of radiation or surgical excision alone depending on the location. These patients will eventually progress to MM over the subsequent years but have a generally favorable prognosis, with PFS 63% at 10 years. Extramedullary plasmacytoma has an even more favorable prognosis with myeloma-specific death seen in less than one-third of patients. Progression to MM typically occurs within 5 years from initial diagnosis. Features suggestive of high risk for progression include persistent monoclonal protein after treatment of the solitary lesion, detectable clonal plasma cells in the bone marrow, age 40–60 years old, and individuals of African-American descent. Despite the marked difference in long-term prognosis to NDMM, previous staging systems have not accounted for the presence or absence of solitary plasmacytoma at diagnosis [68].

4.9 Performance status

Baseline performance status has long been understood to play a prominent role in prognosis in NDMM, with unfit patients often remaining ineligible for SCT, the use of triplet therapy, and certain novel therapies. Without these therapies, disease control is less common, and outcomes are worsened. Furthermore, clinical trials commonly select for fit patients (typically.

ECOG 0–1), reducing the generalization of data to community setting, where less fit patients are encountered with greater frequency.

4.10 Renal function

Baseline renal function in NDMM patients is an essential part of long-term prognosis. Impaired renal function at baseline limits the usage of novel agents that can be administered, as many are renally cleared. Persistent renal dysfunction limits what therapeutic options are available and thus long-term outcomes

are worse [69]. As cyclophosphamide is hepatically cleared, cyclophosphamide, bortezomib, and dexamethasone remains standard induction regimen in individuals with compromised renal function. Melphalan, which is cleared through spontaneous hydrolysis, is another renal-independent therapeutic option. Previous risk-stratification systems have not addressed this conundrum with renal dysfunction.

4.11 Diabetes

Comorbidities present in NDMM patients play a strong role in what therapies may be available [70]. Diabetes mellitus, owing to concomitant progressive renal dysfunction and peripheral neuropathy, may limit the use or dose of certain novel therapies. Both IMiDs and proteasome inhibitors may worsen peripheral neuropathy, potentially limiting the dose able to be given or as a class altogether depending on the severity of neuropathy. Diabetic nephropathy poses similar limitations.

4.12 Minimal residual disease

In every NDMM patient, there are an average of 3 to 5 clones present. These clones undergo mutations at varying degrees throughout the treatment course, with progression of disease presenting expansion of resistant clones over time. As a result, multiple myeloma is not considered to be a curable disease, and so an evolving treatment aim has been for maximal disease burden reduction [71]. The ability to reduce disease burden beneath the threshold of detection, known as minimal residual disease (MRD), has been shown to be an important prognostic indicator for survival and long-term outcomes. MRD has traditionally been detected by flow cytometry (sensitive to 10^4 cells) and next generation sequencing (NGS) (sensitive 10^6 cells). An evolving consensus is that achieving MRD-negative status at the time of induction therapy should be the goal of therapy. Though not-yet involved in staging systems, MRD-focused treatment assessments are becoming increasingly important with time [72].

4.13 Next-generation sequencing

NGS when it comes to FISH (seq-FISH) has improved sensitivity and similar specifically relative to clinical FISH studies and appears to identify a higher number of high-risk NDMM patients. These studies are currently ongoing to incorporate into routine staging systems [4, 29].

4.14 Predictive models in NDMM

Multiple advances in long-term survival have been made over time, with the potential for cure by some models. Heterogeneity of prognostic factors in multiple myeloma makes accurate prognostication difficult on an individual level. As a result, the use of prediction matrix and prognostic tools have aided our ability to assess overall survival. Furthermore, owing to the selection bias present within clinical trials populations, survival estimates derived from clinical trials limit the applicability to all "Real World" patients. The CONNECT ® registry was created as a prognostic model for OS in an unselected community and academic setting [66]. Prognostic models should take into account myeloma biology, patient comorbidities and include performance status and mobility assessment [73]. Next Gen Sequencing will offer a more comprehensive approach to treatment and the goal of a MRD negative NDMM patient.

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Author details

Howard R. Terebelo[1,2]* and Leo Reap[1,2]

1 Ascension Providence Hospital, Department of Hematology and Oncology, Southfield, Michigan, USA

2 Michigan State University, East Lansing, Michigan, USA

*Address all correspondence to: hiccup@comcast.net

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