Developments in the Field of Myeloma in the Last Decade

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Abstract The plasma cell disorders constitute a heterogeneous group of diseases. Accumulation of knowledge in the field has helped us to understand these diseases better, stage them more precisely, prognosticate more accurately and manage them more effectively. The paradigm shift in the management of multiple myeloma over the last one-and-a-half decades shows no signs of slackening. In addition to novel therapies, better supportive care and high-dose melphalan with autologous hematopoietic stem cells have contributed to this positive outcome. This review summarizes the developments in this sphere in the recent past.

Keywords Multiple myeloma · Biology · Novel drugs · Autologous transplants

A lot has happened and a lot continues to happen regarding our understanding of the plasma cell disorders and their management [1–3]. The field is so vast and dynamic that one can only enumerate the knowledge and refer readers to original articles for details. It is clear that the plasma cell dyscrasias, the commonest one being myeloma, are a group of heterogeneous diseases; all myelomas are not born equal and all myelomas do not grow equally. Accumulation of wealth of knowledge in the field has helped us to understand the disease better, stage better, prognosticate better and manage better. There has been a paradigm shift in the management of multiple myeloma in last one-and-a-half decades and this progress shows no signs of slackening [4].

In addition to novel therapies, better supportive care and high-dose melphalan with autologous hematopoietic stem cells have contributed to this positive outcome.

New IMWG definition of active myeloma [5] is:

- Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
 - Hypercalcemia: serum calcium >0.25 mmol/l (>1 mg/dl) higher than the upper limit of normal or >2.75 mmol/l (>11 mg/dl)
 - Renal insufficiency: creatinine clearance <40 ml/min or serum creatinine >177 μ mol/l (>2 mg/dl)
 - Anemia: hemoglobin value of >20 g/l below the lowest limit of normal, or a hemoglobin value <100 g/l
 - Bone lesions: one or more osteolytic lesion(s) on skeletal radiography, CT, or PET/CT. If the bone marrow has $<10\%$ plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.
- Any one or more of the following biomarkers of malignancy (MDEs, or myeloma defining events)
 - 60% or greater clonal plasma cells on bone marrow examination
 - Serum involved/uninvolved free light chain ration of 100 or greater, provided the absolute level of the involved light chain is at least 100 mg/l. (a patient's light chain—either kappa or lambda—is the one that is above the normal reference range; the “uninvolved” free light chain is the one that is typically in, or below, the normal range)
 - More than one focal lesion on MRI that is at least 5 mm or greater in size.

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IMWG molecular classification: testing recommendations

- At a minimum, baseline genetic information should be obtained in all myeloma cases
- Testing must be done with either cytoplasmic immunoglobulin-enhanced FISH or FISH carried out on the nuclei from purified plasma cells
- Minimum FISH panel should include t(4; 14)(p16; q32), t(14; 16)(q32;q23), and 17p13 deletions
- More comprehensive panel should include testing for t(11; 14)(q13; q32), chromosome 13 deletion, ploidy category, and chromosome 1 abnormalities
- At a minimum, all clinical trials should consider incorporation of GEP (gene-expression profiling).

Interpretation of genetic results:

Hyperdiploid karyotype: a more indolent form and usually tends to carry favourable outcome.

t(11; 14)(q13; q32): occurs in about 15% with a heterogeneous prognosis.

t(4; 14)(p16; q32): short remission even after high-dose therapy. Presents more frequently with smoldering multiple myeloma (SMM).

t(14; 16)(q32; q23): occurs in 5–7%; associated with higher frequency of chromosome 13 deletions. More aggressive in nature.

Chromosome 13 deletion: detected in 50%; 85% are monosomy; and 15% interstitial. Closely associated with other high risk features like t(4; 14)(p16; q32), hence a poor prognosis abnormality.

Deletion 17p13: a most important poor prognostic abnormality. Uncommon in MGUS and common in primary/secondary plasma cell leukemia.

Chromosome 1: may occur either in short or long arm. A GEP signature for high-risk disease.

Prognostic Features: Revised IMWG Criteria [6] (Table 1)

With the availability of information from cytogenetic abnormalities and the surrogate marker, serum LDH level, it has become useful to include these parameters for more accurate assessment of long term survival. This can now be routinely applied in practice.

Geriatric Assessment in Myeloma

Myeloma is a disease of older people—the median age being 65 years or more in developed world and a decade younger in the emerging world. As we get older, various illnesses, especially non-communicable diseases (NCDs) set in. This increases the risk of treatment-related morbidity in this age group. It is very important to define the risk in a given patient—the IMWG has recommended the following criteria for older myeloma patients [7] (Table 2).

Response to Treatment

As myeloma still remains an incurable disease and the current focus is on achieving a best possible deep response, various definitions of depth of response have been developed [8]. The IMWG criteria have been accepted widely for clinical practice and trials. A best possible molecular response appears to maintain a prolonged relapse free survival. Patients achieving a less than partial response to initial therapy have a poor prognosis [9].

Current Status of Management of Myeloma

There is clear evidence that in last two decades progression-free and overall survival for people diagnosed with myeloma have improved significantly [1–4, 10]. The reasons include improved supportive care, high-dose chemotherapy with autologous blood stem cell transplantation and the advent of novel drugs. The benefit is more pronounced in younger patients than in older ones. In elderly myeloma, the biology of the disease may not be more aggressive, but advanced age, compromised performance status and multiple comorbidities do not allow

Table 1 Revised IMWG criteria for prognosis

Prognostic factors	Criteria
ISS stage	
I	Serum beta2M < 3.5 mg/l, serum albumin $\geq$ 3.5 g/dl
II	Not stage I or III
III	Serum beta2M $\geq$ 5.5 mg/l
CA by interphase FISH	
High risk	Presence of del(17) and or translocation t(4; 14) and/or t(14; 16)
Standard risk	No high risk CA
LDH	
Normal	Serum LDH < upper limit of normal
High	Serum LDH > upper limit of normal
R-ISS	
I	IISS stage I and standard risk CA by iFISH and normal LDH
II	Not R-ISS stage I or II
III	ISS stage III and either high risk CA by iFISH or high LDH

Table 2 Geriatric assessment of multiple myeloma

Additive total score	Patient status	No. of patients (%)	% (95% CI)		Cumulative incidence at 12 months (%)	
			OS	PFS	Treatment discontinuation	Gr 3–5 hematologic AEs
0	Fit	340 (39)	84 (78–89)	48 (41–56)	16	22
1	Intermediate-fitness	269 (31)	76 (67–82)	41 (32–49)	21	26
≥2	Frail	260 (30)	57 (45–68)	33 (25–41)	31	34

delivery of effective drugs in full doses. This is an unmet need as myeloma is a disorder of older people.

Supportive care includes use of bisphosphonates for bone disease, prevention of deep vein thrombosis, adequate hydration and dialysis for renal impairment, prevention and treatment of various infections, effective management of hypercalcemia, and blood component transfusions. Prolonged bisphosphonate therapy contributes to improvement in overall survival.

As high-dose chemotherapy, melphalan cannot be used for everyone, with elderly and people with significant comorbidities and/or poor performance at a high risk of significant morbidity and mortality. Myeloma patients are categorised into, (1) Transplant-eligible and, (2) Transplant-ineligible ones. The arbitrary cut-off in most countries is 65 years, but biological age is more important than chronological age.

Currently, the treatment phases are—(1) initial or induction therapy, which includes ASCT in eligible cases, (2) consolidation therapy in selected cases after ASCT and maintenance therapy. For transplant-ineligible patients, physicians usually continue maintenance with single or a doublet after a first few months of initial therapy that may have been a doublet or triplet. Patients presenting with evidence of renal involvement (detected in ~20%) need to be investigated in greater detail and managed carefully.

Transplant-Ineligible Myeloma Patients

While age is a relatively less important factor, we need to keep in mind that as age advances, our ability to withstand stronger therapy diminishes [7]. Hence, in this heterogeneous group of population other factors to be assessed carefully are co-morbidities like performance status, co-morbidities of the respiratory system and the heart, and finally, personal apprehensions of potentially toxic therapy. IMWG has developed a geriatric assessment tool that predicts the risks of serious morbidity and mortality of proposed treatment (Table 2). While managing elderly myeloma patients, these factors must be assessed prior to institution of anti-myeloma drugs [11]. The patients and the families must be explained every aspect and allow them to decide when more than one option is available.

A bortezomib and dexamethasone-based regimen is preferred in these patients due to its favourable pharmacological profile. A weekly subcutaneous route is being increasingly used as it could reduce the risk of debilitating neuropathy by 50%. A third drug like thalidomide, cyclophosphamide or doxorubicin could be added to obtain a deeper response. IMWG recommends use of lenalidomide too. However, creatinine clearance should be monitored and dose adjusted.

The principle is to stabilise the disease to a plateau phase with improvement and maintenance of a reasonable quality of life (QoL) [12]. Current recommendations are, lenalidomide-dexamethasone for patients with adequate renal functions, non-aggressive disease, presence of peripheral neuropathy due to any cause, and away from well-equipped medical facilities as initial therapy till the achievement of a best response or plateau phase. This is followed by low-dose lenalidomide maintenance for a limited period of 18–24 months or until the disease progresses [13]. In others with renal impairment, aggressive disease, extramedullary disease and close to a medical facility should receive bortezomib based regimens like, doublet of bortezomib + dexamethasone or triplets like VMP of bortezomib, oral melphalan and prednisolone as initial therapy till a best response (usually achieved after 4–8 cycles) followed by bortezomib-based regimen.

Transplant Eligible Patients

In patients eligible to receive high-dose chemotherapy, most commonly melphalan 200 mg/m² BSA, followed by autologous blood stem cell transplantation (ASCT) is used. Older patients also could be candidates if one is in good biological health. Peripheral blood (PBSC) has completely replaced bone marrow as the source of stem cells [14]. It is safe with a mortality risk of 0–1% at most centers. More often than not, the procedure is done within the first few months of initial therapy, although late transplants can also be done safely. A randomised clinical trial is on to find if both procedures offer equal benefit or otherwise.

The standard initial therapy now is any three-drug combination comprised of one novel drug (bortezomib,

lenalidomide or thalidomide), a chemotherapeutic agent like cyclophosphamide and dexamethasone—CyBorD. Another three drug combination is comprised of two novel agents (bortezomib, thalidomide or lenalidomide) with dexamethasone—VTD, VRD, etc. [14, 15]. Both approaches produce excellent responses; however, a recent trial showed that VRD producing the best response. While offering combination therapy, existing co-morbidities should be evaluated optimally.

Consolidation therapy in 2–4 cycles following ASCT is being increasingly used. It may help in achieving a deeper response which in turn translates into longer PFS and OS.

Maintenance therapy—currently almost every patient with myeloma is encouraged to receive prolonged therapy with one of the novel agents (lenalidomide, thalidomide or bortezomib) at a lower and tolerated dose; some prefer to add a corticosteroid [15].

Management of Relapsed Myeloma [16]

Being a heterogeneous group of diseases and depending on the aggressiveness of first-line therapy, the timing of relapse and refractoriness is decided. However, as an incurable disease almost all, barring a small number will experience relapse. At relapse, a full evaluation needs to be done. Often, a relapsed myeloma might be more difficult to manage effectively. If a late relapse occurs, agents used earlier would be effective. Currently, a three-drug combination of bortezomib, lenalidomide and dexamethasone appear to produce a best response. Newer myeloma drugs in combination with older drugs, especially lenalidomide, have shown better responses. In the treatment algorithm, a second autologous transplant should be discussed. IMWG has recommended a guideline to treat these cases [17].

Recently Approved Agents

As many as six new agents (four in 2015) with different mechanisms of action, have been approved by FDA in recent years. A few of these will become a component of first-line therapies in coming years. Experts opine that carfilzomib (a proteasome inhibitor) and daratumumab, a monoclonal anti-CD38 antibody, have the greatest potential. The approved agents are,

- Proteasome inhibitors: carfilzomib [18, 19] and ixazomib [20]
- IMiDs: pomalidomide [19]
- Monoclonal antibodies: daratumumab [21, 22] elotuzumab [23]
- HDAC inhibitors: panobinostat [24]

Conclusion and the Future

There has been remarkable improvement in our ability to manage multiple myeloma. Standard-risk patients live beyond five years of disease progression and overall survival is improving too, a reflection of the highly effective newer molecules. Younger patients should be counselled for autologous transplantation and a longer maintenance therapy. Older patients need very careful evaluation before offering a safe and effective treatment approach. The challenge will be to incorporate very effective newer drugs into currently used initial treatment and maintenance therapies.

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