MULTIPLE MYELOMA THERAPY: PAST, PRESENT, AND FUTURE

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This is to acknowledge that Dr. Anderson has disclosed a financial interest or other relationships with commercial concerns related directly or indirectly to this program. Dr. Anderson will be discussing "off-label" uses in his presentation.

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Interests:
Multiple Myeloma
Waldenstrom's Macroglobulinemia
Amyloidosis
Cancer Immunotherapy
Cancer Vaccines
Cancer testis antigens as targets for T cell therapy of myeloma
Bone Marrow (Stem Cell) Transplantation

Purpose and Overview:
The goal of this discussion is to review the diagnosis and management of multiple myeloma with an emphasis on novel therapies and stem cell transplantation

Objectives:
The educational objectives of this discussion are to:
1). Define symptomatic multiple myeloma and distinguish it from other disorders in the plasma cell disorder spectrum in order to be able to distinguish which patients need therapy.
2). Discuss prognostic features in myeloma that indicate worse prognosis and require more aggressive therapy based on risk stratification.
3). Review the treatment of myeloma from the historical therapies to present day therapies and also therapies in the pipeline that are in late stage clinical trials which may be practice changing.

INTRODUCTION

Multiple Myeloma is a clonal plasma cell malignancy that accounts for > 10% of all hematologic malignancies and 1-2% of all malignancies. It is the second most common hematologic malignancy (after only Non-Hodgkin's Lymphoma). Multiple myeloma is slightly more common in men than in women and is twice as common in African-Americans compared to Caucasians.[1] Approximately 20,000 patients are diagnosed each year in the US, and the frequency is constantly increasing due to aging of the general population.[2] The median age of patients at the time of diagnosis is about 65 years.[3] At present only about 35% of myeloma patients are under age 65 and 37% are older than age 75.[4]

Bone disease (lytic bone lesions and osteopenia leading to high risk of fractures) is the main cause of morbidity and can be detected on routine skeletal radiographs, magnetic resonance imaging (MRI), or fluorodeoxyglucose positron emission tomography/computed tomographic scans (PET-CT) scans. Extramedullary lesions can also occur. Other major clinical manifestations include hypercalcemia, renal failure, anemia, and an increased risk of infections. Together these symptoms make up the acronym CRAB (Calcium elevation, Renal dysfunction, Anemia, and Bone lesions) which is used as a basis for determining if a patient has symptomatic myeloma requiring treatment or not.

Over the past decade exciting progress has been made in the therapy of multiple myeloma with the development of regimens that incorporate the proteasome inhibitor bortezomib[5-8] and lenalidomide.[9,10] Advances in clinical practice have evolved from a deeper understanding of the biology of myeloma cells and their interaction with the bone marrow microenvironment where they reside.[11,12] Most importantly, patients with multiple myeloma who are diagnosed today live longer, with a median survival in excess of 5 years (some estimate median up to 8-10 years), which is significantly longer than those who were diagnosed before the availability of stem cell transplant, bortezomib, and immunomodulatory agents in the current era.[13] However, despite these advances, nearly all patients will ultimately relapse. Therefore, substantial therapeutic challenges remain and additional therapies and combinations are needed. In this discussion I will briefly describe the current practice of myeloma management and also discuss promising new therapies that may change the practice in the coming years.

Differentiating Symptomatic Myeloma from MGUS, Smoldering Myeloma, and other Plasma Cell Disorders

Monoclonal gammopathy of undetermined significance (MGUS):

MGUS can either be a benign of pre-malignant condition that precedes development of myeloma or other plasma cell malignancies and is present in over 3% of the population above age 50. It is characterized by having a monoclonal protein spike (M-spike) on serum electrophoresis, but by definition the spike has to be <3 g/dL, and on bone marrow biopsy there cannot be more than 10% plasma cells. There also must not be any end organ dysfunction from the monoclonal protein. Only approximately 1% per year of MGUS patients will go on to develop a symptomatic malignancy such as

myeloma. After >20 years of follow-up approximately 75% of patients will remain progression-free and will not need treatment, so it is essential that these patients simply be watched carefully with periodic observation and that they not be subjected to treatment that may cause undue side effects.[14]

Risk features that increase the odds of progression from MGUS to symptomatic myeloma include a non-IgG M-spike, an M-spike that is >1.5 g/dL, or abnormal serum free light chains.[15] The survival of low risk patients may be similar to the general population whereas those with 2 or 3 risk features should be observed more closely, at least yearly.

Smoldering Myeloma:

Smoldering Myeloma is characterized by having a monoclonal protein spike (M-spike) > 3g/dL and/or clonal bone marrow plasma cells ≥10%. Either of these criteria can make the diagnosis of myeloma but this subgroup of myeloma patients are characterized by having absence of end organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder. In patients with an IgM M-spike they can also have either IgM MGUS or Smoldering Waldenstrom's Macroglobulinemia as long as they do not have anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the lymphoproliferative disorder.

Only approximately 10% per year of Smoldering Myeloma patients will go on to develop symptomatic myeloma requiring treatment during the first 5 years, 3% per year during the next 5 years, and 1.5% per year thereafter. After >20 years of follow-up approximately 25% of patients will remain progression-free, so it is essential that these

patients simply be watched carefully with close observation and no treatment to avoid undue side effects.[15]

Patients with Smoldering Myeloma can be stratified into risk categories based on presence or absence of abnormal serum free light chain levels and whether or not they have an M-spike >3 g/dL or marrow plasmacytosis >10%. Previous studies did not show any benefit of treating these patients before development of symptoms. However, there is recent data suggesting that intervention with therapy such as the novel agent lenalidomide may improve survival, and randomized studies are currently underway in the US to help confirm this.[16] These patients should be observed closely outside of a clinical trial, every 3-6 months depending on their risk features and stability of their M-spike.

Symptomatic Multiple Myeloma:

Symptomatic Myeloma is characterized by having either >3 g/dL M-spike or >10% bone marrow plasma cells and also evidence of end organ damage, which could be any of the following CRAB symptoms: hypercalcemia with calcium >11.5, renal insufficiency with creatinine >2 or creatinine clearance <40 ml/min, anemia with hemoglobin <10 g/dL or >2 g/dL below normal range, or bone lesions (either lytic lesions on skeletal survey, severe osteopenia, or pathologic fractures). These symptoms warrant treatment and the urgency of treatment depends on the severity and acuteness of the symptoms.

When multiple myeloma is suspected clinically, patients should be tested for the presence of a monoclonal protein using a combination of tests that should include a serum protein electrophoresis, serum immunofixation, and the serum free light chain

(FLC) assay. With these sensitive tests at least 98% of myeloma patients will have a detectable monoclonal protein, but up to 2% of patients with myeloma have true non-secretory disease with no evidence of an M protein on any of the above studies yet have bone lesions or other features of the disease requiring therapy.

History of Multiple Myeloma Therapy

The first case report of a patient with myeloma was described in 1844. The classic proteinuria was first described by Dr. Henry Bence Jones in 1847, and the disease itself was named in 1873. However, the cardinal features of the diagnosis of myeloma were not well described until the 1940's, and there was no effective treatment until the late 1950's with the use of melphalan.[17] Later came the use of high dose melphalan with autologous stem cell rescue/transplant in the late 1980's, which further improved survival, and in the past decade novel agents have been introduced which have even further improved survival. A timeline of advances in myeloma diagnosis and therapy is shown in Figure 1.[18]

Early Therapies for Myeloma (Alkylators and Corticosteroids)

A paper in 1947 by Nils Alwall of the University of Lund in Sweden advocated the use of urethane for treatment of myeloma.[17] One of his patients had a marked decrease in globulin, a decrease in plasma cells in the bone marrow, and an increase in hemoglobin after urethane treatment. For the next 20 years, urethane was the treatment of choice for multiple myeloma based on the response of one patient. Finally in 1966, the Eastern Solid Tumor Group reported a prospective study of patients with multiple myeloma who were randomized to urethane vs placebo. No difference in survival was

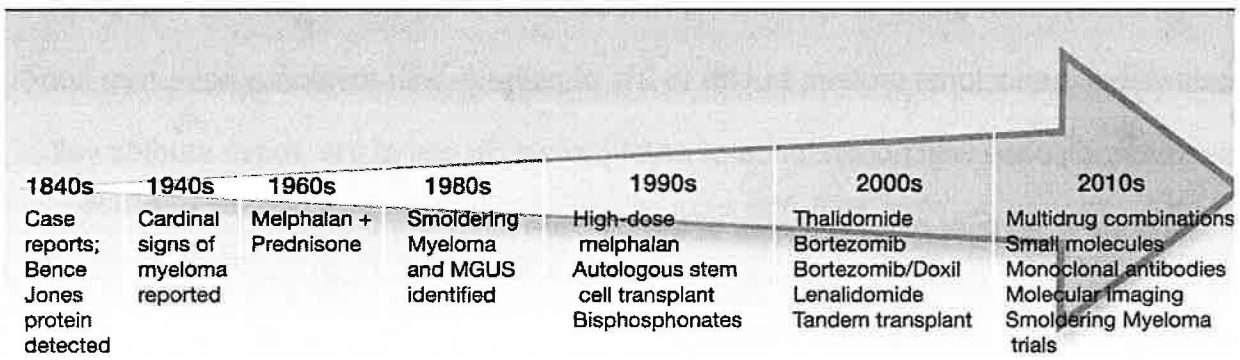

Figure 1: Milestones in Myeloma diagnosis and therapy. From reference (18)

Table 1. Major milestones in therapeutic options for myeloma. From reference (13)

	Milestone	Notes
1962	Melphalan-prednisone (MP)	Introduction of melphalan in the 1960s associated with improved survival. More intense chemotherapy regimens increased response rates, but no improvement in survival compared to MP
1996	Autologous SCT	Several randomized trials demonstrated a survival advantage for ASCT compared to conventional chemotherapy (CCT).
1999	Thalidomide (Thalomid)	Improved response rates and PFS compared to dexamethasone alone. When added to MP, it improves survival compared to MP alone.
2003	Bortezomib (Velcade)	Bortezomib improves survival compared to high-dose dexamethasone in patients with relapsed myeloma.
2003	Tandem autologous SCT	Tandem SCT has improved survival compared with single transplantation, but only in those failing to achieve a very good partial response to first transplantation.
2005	Lenalidomide (Revlimid)	Lenalidomide and dexamethasone have improved survival compared with dexamethasone in relapsed myeloma in phase III trials.

demonstrated.[19] This demonstrates that all must be looked at in a prospective, randomized manner in order to decide whether the new treatment is better than the old.

A timeline of major therapeutic advances in multiple myeloma is outlined in Table 1. The first important advance in myeloma therapy was made in 1958 by Blokhin et al from Russia and 4 years later by Bergsagel et al from MD Anderson Cancer Center, demonstrating the benefit of melphalan (sarcolysin, L-phenylalanine mustard) in the treatment of multiple myeloma with an objective response in about 50-60% of patients.[17] It was next noted that steroids such as prednisone also had single agent activity in myeloma. The classic regimen of melphalan plus prednisone (MP) was established in a randomized trial of 183 myeloma patients led by Alexanian et al, in which survival was 6 months longer with MP compared with melphalan alone.[20] The median survival of patients with myeloma was less than a year before introduction of alkylating agents such as melphalan in the 1960s, which resulted in improved survival to a median of around 3 years. MP therefore became the standard of care for myeloma treatment for the next 3 decades.

During that time many investigators also developed a wide variety of chemotherapy combinations agents such as VAD (vincristine, adriamycin, dexamethasone) and combinations of alkylating agents such as carmustine, cyclophosphamide, melphalan, vincristine, and prednisone (the M-2 protocol), all of which were at one time touted as being better than MP. A meta-analysis by the Oxford Myeloma Trialists summarizes 35 years of clinical investigation in the treatment of multiple myeloma, including 27 trials and 6633 patients. The response rate of the

various combinations of chemotherapy was superior to melphalan and prednisone, but there was no difference in response duration or overall survival.[21] Furthermore, It was previously claimed that patients with unfavorable prognostic features did better with a combination of alkylating agents, but that could not be confirmed in this study since there was no subset of myeloma patients who responded better with a combination than with single agents. Therefore MP remained a standard therapy for decades.

High dose Chemotherapy with Augologous Stem Cell Transplant/Rescue

High dose chemotherapy and autologous stem cell transplantation (ASCT) was introduced in the 1980's, and multiple randomized trials in the 1990's and 2000's using ASCT with high dose melphalan and peripheral blood stem cell rescue demonstrated a 12 month survival advantage for this modality compared with conventional chemotherapy, generally from 42 months with chemotherapy to 54 months with ASCT, leading to the use of ASCT as a standard of care since the 1990's.[22,23] Even today autologous stem cell transplantation should be considered if a patient is less than 76 years of age and without significant comorbidities since no other therapy has yet proven superior to high dose chemotherapy and ASCT. Therefore patients who may be candidates for stem cell transplant (either directly after induction therapy or for relapse) should not receive alkylator induction therapy before stem cell collection, because it is known to be stem cell toxic and decreases stem cell yields.

Studies have also been performed to determine if tandem autologous transplants are more effective than a single transplant. A French group reported that the 7-year event-free and overall survival was superior in patients who received a double

transplant.[24] However, further analysis determined that the main subgroup of patients that benefit from the tandem transplant (done 3-6 months after the first one) are generally those that were not able to achieve deep remission with at least a 90% reduction of their monoclonal protein with the first transplant. Another area of active investigation has been the use of allogeneic stem cell transplantation from HLA matched related or unrelated donors to try to achieve a graft versus myeloma effect, which may cure a small subset of patients. However, results have been mixed and the latest trials to not show a benefit from this approach due to excessive toxicity from graft versus host disease, and there is still a high rate of relapse, so allogeneic transplants for myeloma should currently only be done in the context of a clinical trial.

Introduction of non-chemotherapy myeloma therapeutics with novel mechanisms of action (Novel Agents)

Major changes began in the late 1990s, when thalidomide was found to be active even in refractory disease. The past decade has been marked by the FDA approval of 3 new agents with novel mechanisms of action (thalidomide, bortezomib and lenalidomide) with many more in the pipeline. As a result, treatment paradigms in this disease are frequently changing, as some of the previous treatment strategies have been replaced by newer therapies and combinations. In newly diagnosed myeloma patients younger than 75 years, induction regimens including dexamethasone plus either thalidomide or bortezomib or lenalidomide followed by high dose melphalan and ASCT have significantly increased response rates. In elderly patients, oral melphalan and

prednisone (MP) has been combined with novel agents to significantly improve response rates and survival.[6] The future challenge is to define the optimal sequence and combination of these drugs to significantly impact the natural history of the disease.

Thalidomide

The introduction of thalidomide represented a major milestone in the treatment of myeloma. Shortly after its teratogenic properties were discovered, thalidomide was considered as a possible treatment against cancer due to it's antiangiogeneis properties. The FDA approved thalidomide for the treatment of leprosy in July 1998. In a landmark trial that enrolled 84 relapsed/refractory myeloma patients, Barlogie's group in Arkansas showed that 32% of patients responded to oral thalidomide, making it the first new drug with single-agent activity for myeloma in more than 3 decades.[25] Initial results with thalidomide were confirmed by several other centers, in all phases of the disease. Response rates in relapsed disease are approximately 50% with the combination of thalidomide and dexamethasone, and 65% with a 3-drug combination of thalidomide, steroids, and cyclophosphamide. Several other combination chemotherapy regimens containing thalidomide have since been developed. In the early 2000's the combination of thalidomide/dexamethasone (Thal/Dex) became the most commonly used induction regimen for the treatment of newly diagnosed myeloma in the United States. In an Eastern Cooperative Oncology Group (ECOG) randomized trial of 202 patients, the responses were significantly higher with Thal/Dex compared with dexamethasone alone (63% vs 41%, respectively, $P = .002$).[26] Based on this trial, in May 2006 the FDA granted accelerated approval for Thal/Dex for the treatment of newly diagnosed myeloma.

Another advance in the field has been the combination of MP with novel agents such as thalidomide. MP plus thalidomide (MPT) was compared to MP in randomized trials and found to induce superior progression free and overall survival.[7] Therefore, in the non-transplant eligible patient setting, novel agents added to alkylator chemotherapy have become a standard of care.

Mechanisms and Side Effect Profile of Thalidomide and other Imids

Thalidomide and it's daughters lenanidomide and the investigational analogue pomalidomide are referred to as a class of therapeutics called immunomodulatory agents (Imids). They have several mechanisms of action including antiangiogenesis properties, stimulation of T-cells and natural killer cells, and downregularion of cytokine production. They suppress growth factors such as interleukin-6, tumor necrosis factor-alpha, inhibit myeloma cell adhesion and blood vessel growth cytokines such as vascular endothelial growth factor. The main side effects of Thalidomide include peripheral neuropathy (often irreversible), deep vein thrombosis (requiring full dose anticoagulation for prevention), sedation, and constipation. This is in contrast to the analogue lenalidomide which does not cause neuropathy, causes less risk of DVT (requiring only aspirin prophylaxis), causes less sedation and constipation, but causes marrow suppression and cytopenias with decrease in stem cell yields if given for more than 4 cycles before stem cell collection.

Bortezomib (Velcade)

Bortezomib, a boronic acid dipeptide and a first in class proteasome inhibitor essentially like plugging up a garbage disposal, and the altered protein levels leads to cellular apoptosis, with malignant, transformed, and proliferating cells being more

susceptible.[27] It specifically interferes with the 26S proteasome, which is responsible for degrading proteins that control transcription, the cell-proliferation cycle and metabolism. Intravenous bortezomib demonstrated striking antimyeloma activity in the initial phase 1 study,[28] and in the randomized phase III Assessment of Proteasome inhibition for Extending Remission (APEX) trial, bortezomib therapy improved 1-year overall survival from 66% to 80% compared with dexamethasone alone in relapsed myeloma patients.[29] These results led to the approval of bortezomib by the FDA in May 2003. Bortezomib has also been effectively combined with intravenous liposomal doxorubicin in a trial that demonstrated, for the first time in a randomized manner, the antimyeloma activity of anthracyclines.[30]

In a large phase III trial, the 3 drug combination velcade/melphalan/prednisone (VMP) had a significantly superior response rate compared to MP (71% vs. 35%, $P < 0.001$).[6] Overall survival was also significantly superior with VMP compared to MP, and there was data showing that bortezomib may overcome some high risk cytogenetic features including translocation 4;14.[6] In newly diagnosed myeloma, response rates as high as 90% have been observed by combining bortezomib with thalidomide, and dexamethasone (VTD), but the risk of neuropathy also increases.[31]

The major drawback of traditional bortezomib dosing (days 1, 4, 8, 11) is the risk of peripheral neurotoxicity and the need for intravenous administration. The neuropathy with bortezomib can occur abruptly and can be significantly debilitating in a subset of patients. Recent studies show that reducing the dose of bortezomib or changing to once weekly dosing at least in combination regimens shows similar efficacy with significantly lower risk of neurotoxicity.[32] Furthermore, a recent study also demonstrates that

bortezomib can also be given subcutaneously with significantly less risk of neuropathy yet similar response rates and duration of remission in relapsed myeloma.[33] Unlike lenalidomide, bortezomib does not appear to have any adverse effect on stem-cell mobilization.

Lenalidomide (Revlimid)

An analog of thalidomide known as lenalidomide (trade name Revlimid, formerly CC-5013) has been the latest FDA approved treatment added to the arsenal of myeloma therapies in 2006 and is an immunomodulatory agent that is more potent than thalidomide yet has a more favorable side effect profile. The combination of lenalidomide and dexamethasone was compared with dexamethasone in 2 large randomized trials in the United States and Europe and showed superior survival in relapsed myeloma.[34] More recently it has also been shown to be more effective when given with once weekly dexamethasone compared to high dose pulsed dexamethasone 12 days per month, likely due to better tolerability and less risk of having to stop therapy due to infections, clots, or side effects.[35] Response rates in newly diagnosed myeloma are in the 89-91% range with 56% achieving >90% reduction of their monoclonal protein.

Multi-Agent Combination Induction Therapy

The 3 drug regimens lenanidomide/borzezomib/dex (RVD) and cytoxan/bortezomib/dexamathasone (CyBorD) currently appear to be the most effective therapies available with toxicity profiles similar to what would be expected with the individual drugs.[36,37] Preclinical data indicate synergistic cytotoxicity can occur from combining lenalidomide (which induces caspase-8-mediated apoptosis) with bortezomib

(which induces caspase-9-mediated apoptosis) in models of myeloma. In phase II studies RVD achieved responses in 61% of patients with relapsed, refractory multiple myeloma who were often refractory to each of the three agents alone. In the setting of newly diagnosed disease, RVD produced an overall response rate of 100%, with 74% of patients achieving at least a very good partial response, and 52% of patients showing complete or near-complete responses.[37]

Although results with all these three-drug combinations (VTD, VRD, and CyBorD) show that we can improve response rates and delay progression compared to two-drug combinations (Rev/dex and Vel/Dex), there are no data on whether the early incorporation of the third drug results in prolongation of overall survival, and what detrimental effect adding the third drug has on quality of life, especially given the neurotoxicity associated with bortezomib and thalidomide. Therefore many prefer to save these regimens for patients with high risk disease who are known to have poor outcomes with standard therapy, or for those that do not have a great response after the first 2-3 cycles of standard induction therapy.

Lenalidomide as Maintenance Therapy

Although thalidomide has shown modest improvement in survival benefit as maintenance therapy in two randomized trials, it's neurotoxicity precludes its routine use as maintenance therapy. However, more recently two randomized studies have shown delayed time to progression with lenalidomide as post-ASCT maintenance therapy, and one of them is also showing an improved overall survival.[38,39] One potential problem is that patients in the control arm of these trials lacked uniform access to the active drug (lenalidomide) at relapse, and it is not clear whether the improvements will be

neutralized, because patients in the control arm can always initiate the same therapy at the time of first relapse. One noted risk with prolonged lenalidomide maintenance therapy is also the risk of acquiring a second primary malignancy in about 2.5-3% more patients in the lenalidomide arms compared to the placebo arms.[40]

Risk Stratified Therapy

Since 1975, the Durie-Salmon staging system has been used to stratify patients with multiple myeloma. However, this staging system has limitations, especially in the prediction of patients who will do very poorly, as does the international staging system, and these systems are not useful for guiding therapy decisions. Besides stage, important prognostic factors that stratify patients into high risk and standard risk are deletion 13 or hypodiploidy on conventional karyotyping, deletion 17p, or immunoglobulin heavy chain translocations t(4;14) or t(14;16) on interphase fluorescent in situ hybridization (FISH), or high risk signature on gene expression profiling.[41] The

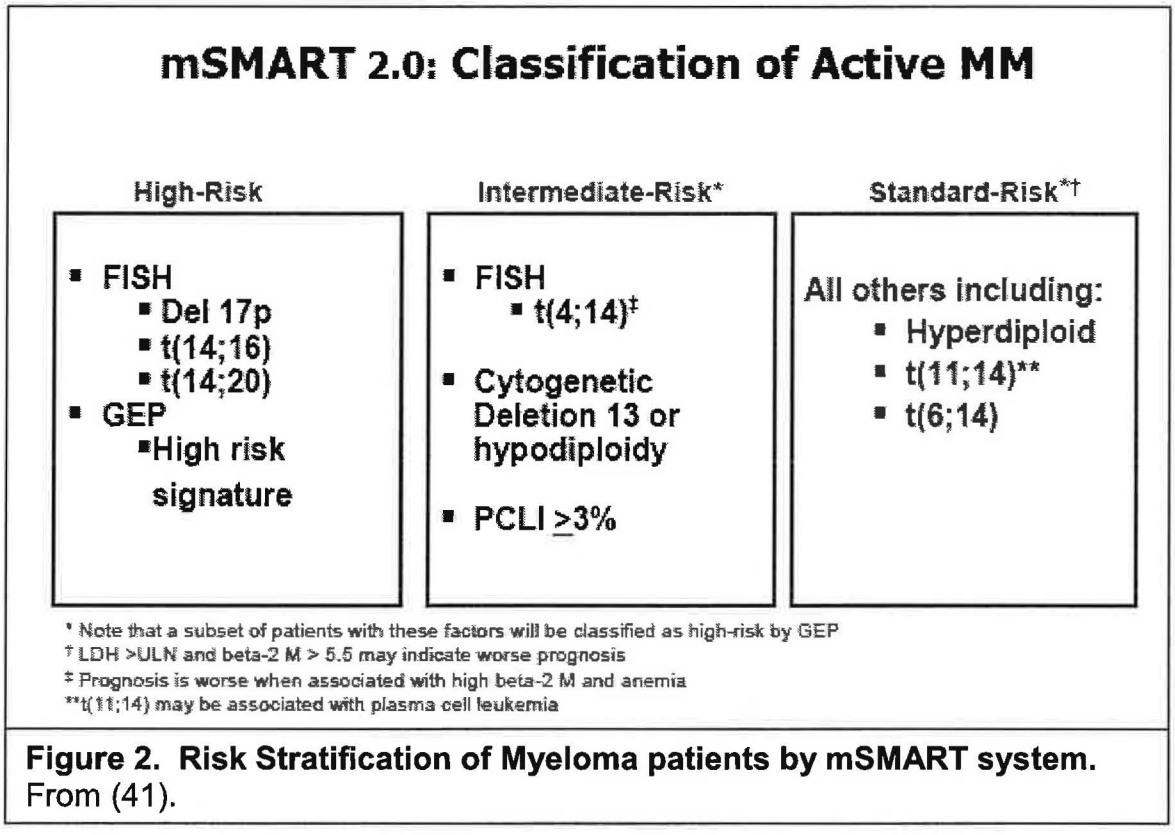

Figure 2. Risk Stratification of Myeloma patients by mSMART system. From (41).

presence of any one or more of these high-risk factors classifies a patient as having high-risk myeloma. Although some of these factors may be overcome by use of the new novel agents, the 17p deletion appears to still cause worse prognosis. At the Mayo Clinic, a system has been devised to stratify newly diagnosed myeloma into standard-risk and high-risk disease using the Mayo stratification for myeloma and risk-adapted therapy classification (mSmart, Table II).[41] Patients with standard risk myeloma have a median survival of 6–7 years while those with high-risk disease have a median survival of less than 2–3 years despite tandem autologous stem-cell transplantation (ASCT). Therefore treatment algorithms have been proposed that incorporate the risk stratification into the treatment decisions and generally recommend 3 drug induction regimens followed by stem cell transplant and then prolonged consolidation or

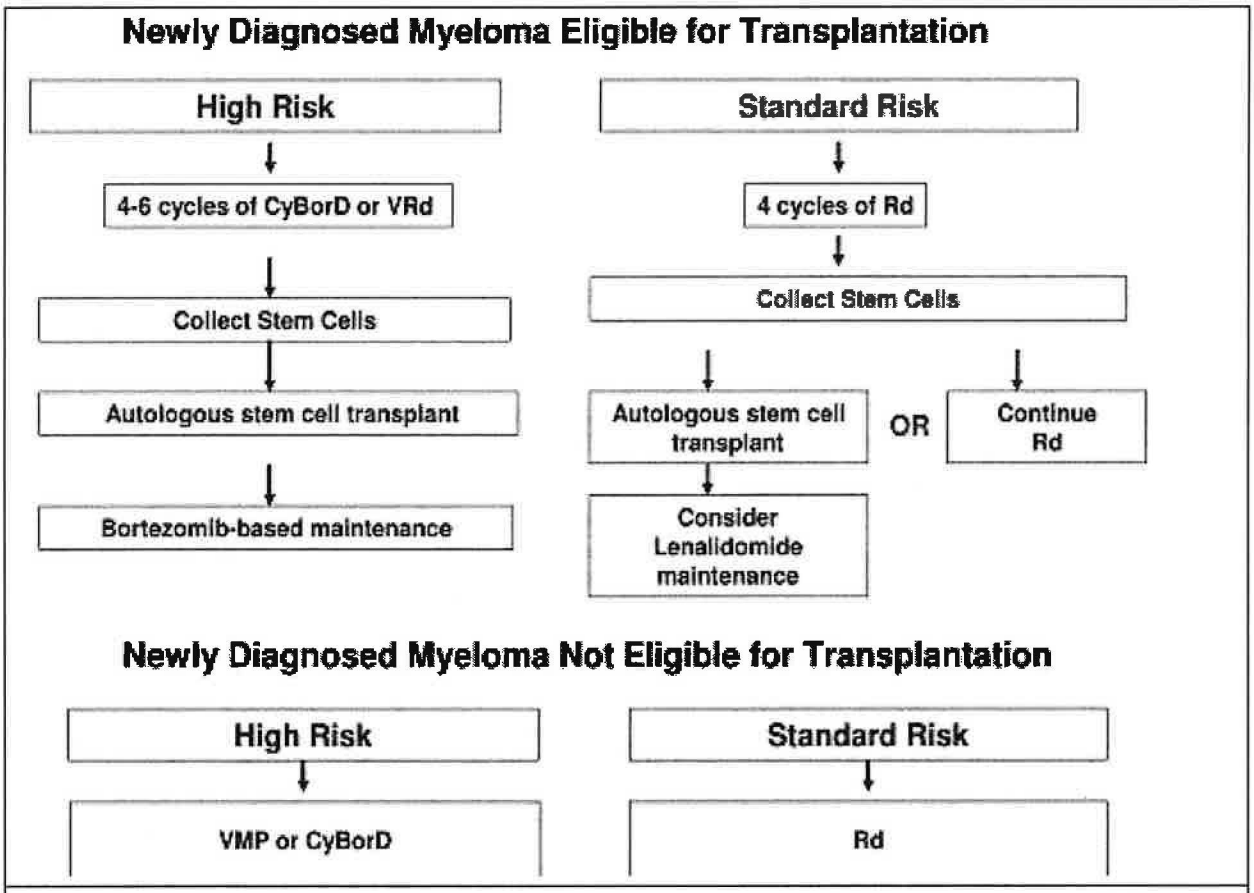

Figure 3. Risk Adapted Therapy Algorithm which has been proposed. From (42).

maintenance therapy for patients with high risk disease, whereas they favor the use of less toxic regimens such as revlimid and weekly dexamethasone for standard risk patients.[42]

Based on recent data, high-risk patients require a CR for long-term survival and hence clearly need an aggressive strategy.[43] On the other hand, standard-risk patients have similar overall survival regardless of whether CR is achieved or not and therefore have the option of pursuing either an aggressive or a gentler sequential approach.

Improved Survival of Myeloma patients in the Past Decade

Thanks to the FDA approval of these novel agents and risk stratified therapies, patients with multiple myeloma who are diagnosed today live longer than those diagnosed before the current era, with a median survival in excess of 5 years, and some estimate a median surivival of up to 8-10 years. In a retrospective study at Mayo Clinic, survival of more recent myeloma patients is now significantly longer when compared to those diagnosed before the availability of stem cell transplant, bortezomib, and immunomodulatory agents in the current era (Figure 4).[13]

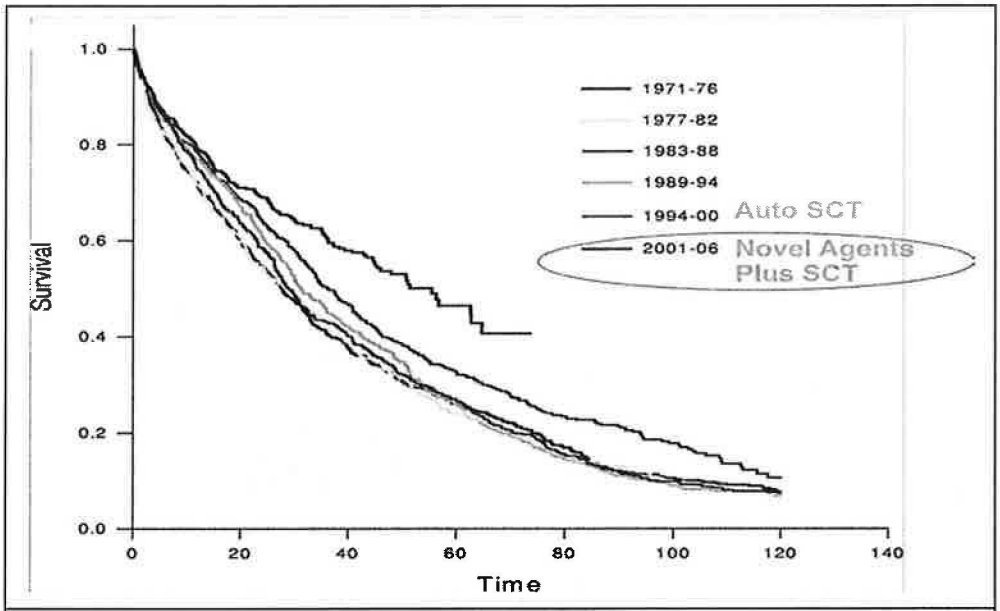

Figure 4. Overall Survival from year of Myeloma diagnosis.
From (13).

Emerging Therapies in Myeloma

Although we now have several effective treatment combinations, all patients eventually become resistant to the approved myeloma therapies, and they are not curative. Therefore new therapies are still needed. This discussion will highlight the exciting preliminary results of some of the most promising new agents in late phase clinical trials. These are also listed in Table II.[44]

Pomalidomide:

Pomalidomide, a new imid analog of thalidomide and lenalidomide appears to have significant activity in relapsed refractory myeloma, even in patients failing lenalidomide and bortezomib.[45] Phase III studies are ongoing.

Carfilzomib:

Another emerging option is carfilzomib, a novel keto-epoxide tetrapeptide proteasome that has shown single agent activity in relapsed refractory multiple

Table 2 | Promising novel agents in clinical trials in multiple myeloma showing excellent activity and favorable toxicity profile in in early trials. From (43).

Drug	Category	Comments
Carfilzomib (IV) MLN 9708 (Oral)	Proteasome inhibitors	Ongoing phase III trial Oral proteasome inhibitors in phase I–II trials
Pomalidomide	Immunomodulatory drugs	Ongoing phase III trial NCT01311687119
Perifosine	Phosphatidylinositol 3-kinase pathway inhibitor	Ongoing phase III trial NCT0100224881
Elotuzumab	Anti-CS-1 antibody	Ongoing phase III trials NCT01239797120 NCT01335399121
Vorinostat Panobinostat	Histone deacetylase inhibitors	Phase III NCT01023308123

myeloma.[46] It can work even in patients are failing bortezomib, and although it is a twice weekly intravenous infusion, it does not appear to cause significant neuropathy. A phase III study comparing Rev/Dex/Carfilzomib with Rev/Dex for relapsed myeloma has just completed accrual.

MLN 9708

This is an oral proteosome inhibitor which when combined with revlimid and dexamethasone in a phase II study (3 oral drugs) has shown 100% response rates without significant neuropathy.[47]

Histone Deacetylase Inhibitors:

Two promising histone deacetylase inhibitors have been combined with bortezomib or lenalidomide in recent trials and results suggest at least additive benefit, though it remains to be determined if the added toxicity from thrombocytopenia and diarrhea is worth the improved disease response.

Elotuzumab:

One other highly promising new agent is the anti-CS-1 antibody, elotuzumab. CS-1 is a cell surface glycoprotein present on plasma cells and a subset of NK cells but otherwise has very limited expression on non-tumor tissues, so this makes it a relatively tumor-specific target. Early studies have shown strong activity when combined with lenalidomide and dexmathasone in heavily treated and refractory patients.[48,49]

Advances in Supportive Care

Numerous improvements in supportive care have greatly improved the outcome of myeloma patients over the past decade. Some of the most important advances are the advent of bisphosphonates to treat hypercalcemia and to prevent bone lesions and fractures, the use of vertebroplasty and kyphoplasty to treat vertebral fractures, and judicious use of prophylactic antibiotics in selected patients. A recent randomized study actually showed not only a decrease in skeletal related events but also an increase in overall survival associated with monthly zoledronic acid therapy.[50]

CONCLUSIONS:

Overall survival in myeloma has improved significantly in the last decade with the emergence of the novel agents thalidomide, bortezomib, and lenalidomide as well as after the advent of autologous stem cell transplantation in the 1990's. These drugs are now being incorporated earlier into myeloma therapy and have changed the treatment paradigm. Recent survival results raise the hope that we are moving closer to making myeloma a chronic disease, if not a curable one.

The approach to treatment of myeloma should be stratified based on prognostic factors indicating expected survival with standard therapies. However, drug resistance and relapse is seen in the almost all myeloma patients, and new therapies are still needed. Many therapies in the pipeline appear to work even in refractory patients and will likely be practice changing. This is a very exciting time in the field of multiple myeloma, and we are going to see many advances in the years ahead.

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