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HOW BEST TO USE NEW THERAPIES IN MULTIPLE MYELOMA

David Dingli, MD, PhD and **S. Vincent Rajkumar, MD**
Division of Hematology, Department of Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905

Abstract

Advances in the molecular understanding of myeloma have led to the development of novel agents such as immunomodulatory drugs (IMiDs) and proteasome inhibitors (bortezomib). When used alone, these agents have significant activity against myeloma and responses increase significantly when they are combined with additional agents including glucocorticosteroids and chemotherapeutic agents such as alkylators. There is a drive to use these novel agents in patients with newly diagnosed myeloma, where they lead to impressive response rates with increasing duration of responses. In addition, novel agents are now the mainstays of therapy for relapsed disease. In the following paper, we summarize the key observations from recent completed and ongoing studies that determined the effect of these novel therapies both in the setting of newly diagnosed myeloma and for relapsed disease. We also discuss our approach to the use of these agents in specific myeloma settings.

Keywords

Immunomodulatory agents (IMiDs); Proteasome inhibitors; thalidomide; lenalidomide; bortezomib

A. INTRODUCTION

The last decade has seen a renaissance in our understanding of multiple myeloma (MM) biology, knowledge that has been translated into clinically meaningful improvements in survival.[1] The revolution in genomics has shown that tumors are very diverse [2] and myeloma is no exception. Patients with multiple myeloma are a heterogeneous group, with different cytogenetic abnormalities, disease kinetics, response to therapy and prognosis.[3,4] Recent discoveries on the fundamental molecular mechanisms behind MM cell growth and survival [5] have led to the introduction of novel classes of pharmacologic agents such as the immunomodulatory drugs (IMiDs) [6,7] and proteasome inhibitors (bortezomib).[8] Although these drugs have significant activity against MM when used alone, their activity is increased further when combined with other active agents since they may have complementary mechanisms of action and theoretically reduce the risk of the emergence of resistant clones. However, these novel agents can have significant toxicity. Now that we approach an era of

Correspondence: Professor S. Vincent Rajkumar, MD, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA, Phone: 507 266 2040, Fax: 507 266 4972, rajkumar.vincent@mayo.edu.
Contact details: David Dingli, dingli.david@mayo.edu, Phone: 507 284 3417, Fax: 507 266 4972

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personalized medicine, a one-sized fits all approach to therapy is increasingly outmoded for this disease and patients should be ideally treated by a risk adapted approach conforming to the maxim of optimizing the therapeutic index by balancing efficacy with potential side effects.[9,10] These new agents provide a broader spectrum of compounds that can control but, as yet not cure myeloma and they have to be integrated into the management plan for each unique patient with this disease. We still believe that despite the availability of such an expanded therapeutic armamentarium, when faced with a new diagnosis of MM, the physician has to address early on whether the patient is a potential candidate for autologous hematopoietic stem cell transplantation (ASCT), since this therapeutic modality can improve survival [11,12] and provide patients with considerable times without the need of continuous therapy.[13] If ASCT is a possible option, the patient must be treated with agents that do not compromise hematopoietic stem/progenitor cell collection. It also seems reasonable that after a few cycles of induction therapy, progenitor cells are collected early to minimize their exposure to potentially harmful agents or to therapies that can interfere with their collection and subsequent function. [14,15]

This review is focused on the current data and approach to therapy with approved novel agents. The discussion of other non-approved, and promising new agents is beyond the scope of this review, but is covered in detail elsewhere.[16]

A. PROGNOSIS AT DIAGNOSIS – MYELOMA RISK STRATIFICATION

Performance status, stage, and response to therapy are key factors that affect prognosis. Although at least a partial response to therapy (defined as a 50% or greater reduction in tumor burden) is traditionally considered as evidence of successful treatment, in relapsed refractory myeloma even a minor response (a 25-50% reduction in tumor burden) is often indicative of treatment benefit and cannot be discounted. In addition to these factors, a myeloma risk-stratification that affects choice of therapy based on cytogenetic and proliferative characteristics of the clone is of considerable importance. Similar to essentially every other tumor, multiple myeloma is a heterogenous disease, and it emerges due to the serial accumulation of a number (and variety) of mutations. The presence of recurrent cytogenetic abnormalities and gene expression profiling studies (GEP) has enabled the development of a molecular classification of myeloma.[17-21] These abnormalities have biological and clinical meaning since they are associated with distinct clinical behaviors, response to therapy and prognosis. As a result, the diagnostic evaluation of MM cannot be complete without concomitant bone marrow metaphase cytogenetic studies, interphase fluorescent in situ hybridization (FISH) for known recurrent translocations, [9,10,22] and an assessment of the proliferative fraction of tumor cells either by flow cytometry [23] or with the plasma cell labeling index (PCLI).[9,10,24] Many studies now provide incontrovertible evidence that kinetically active myeloma (PCLI >3%) or the presence of specific cytogenetic abnormalities such del13q, t(4;14), t(14;16), 17p-, hypodiploidy or a complex karyotype are associated with high risk disease.[17,25] In contrast, other cytogenetic abnormalities, especially hyperdiploid myeloma and t(11;14) and a low PCLI imply a good prognosis and can be considered ‘standard risk disease’. These risk factors are being reexamined in the context of novel agent therapy, but the risk stratification is still useful since those classified as “high-risk” are in particular candidates for early incorporation of bortezomib, and for routine maintenance therapy. As an aside, we would like to point out that multiple myeloma does not recognize age and the distribution of cytogenetic abnormalities and their prognostic implications do not depend on age at diagnosis.[26] Patients with standard risk disease benefit from autologous peripheral blood stem cell transplantation (PBSCT), while patients with high risk disease do not acquire a long term benefit.[27,28] Although high risk patients respond to high dose therapy and ASCT and may even achieve a complete response (CR), the duration of such a response is usually in the region of a few months.[28] We believe that these patients (about 25% of all newly diagnosed MM) are

best enrolled in clinical trials testing combinations of novel agents with chemotherapy, although progenitor cells should be collected after significant tumor cytoreduction.

A. DEPTH OF RESPONSE AND OUTCOME

For many tumors, eradication of a higher fraction of tumor cells is associated with an improvement in survival. Thus, achieving the lowest level of minimal residual disease can be an important goal of therapy, especially if the tumor is curable. In such a scenario, reaching a state with a very small tumor burden is a necessary step in the path to cure. Following this line of reasoning, there has been considerable discussion about the importance depth of response in myeloma. The accepted definitions of response in myeloma were recently updated.[29] It is often the case that achieving a complete response (CR) [30] or very good partial response (VGPR) [31] in myeloma is associated with an improved outcome. As a result, it has been argued that achieving higher CR rates is an important end point of therapy – perhaps even a benchmark by which regimens are compared.[30,32,33] Recently, multiparameter flow cytometry has been used to assess the depth of response and the presence of minimal residual disease in myeloma. This analysis showed that patients with a deeper response have superior survival.[34,35] However, this does should not be interpreted that CR should be achieved at all costs. Cure requires that the patient maintains a CR and here lies the problem since many patients with high risk disease achieve CR only to relapse rapidly.[28] Moreover, there can be disparities between the depth of response achieved based on the various techniques used to refine such an endpoint.[36] There are many patients with MM who have stable disease for a long time without therapy even if they achieve less than a CR or VGPR with the best available therapy. Therefore, while a response is essential for an improvement in survival and quality of life, it is not universally accepted that the depth of response by itself is a good guide to improved survival.[37-39]

A. INDUCTION THERAPY FOR TRANSPLANT ELIGIBLE PATIENTS

With the introduction of novel agents, the best induction in transplant eligible patients is not resolved. Superiority is often determined by the response rate, and if the depth of response prior to ASCT is indeed important [35], then for otherwise healthy patients, a regimen that leads to a high frequency of deep responses may be justified. However, the morbidity and mortality associated with pre-transplant induction is also an important factor to consider.

B. Thalidomide-based induction

For many years, the combination of vincristine, doxorubicin and dexamethasone (VAD) had been the most popular induction regimen but in head to head comparisons with thalidomide and dexamethasone (TD), the latter was superior. Although this was a retrospective analysis, the patients were well matched: TD was associated with superior responses (partial response, PR or better 76% versus 52%, $p < 0.001$).[40] As expected, the incidence of venous thromboembolism was higher in the thalidomide treated group. TD had no impact on progenitor cell collection. The HOVON and GMMG-HD3 groups have randomized patients with newly diagnosed myeloma to induction therapy with 3 cycles of VAD or TAD (with thalidomide replacing vincristine).[41] Each arm had 201 patients and both groups were well balanced for the standard risk factors. The patients treated with TAD had a higher overall response rate before transplantation (≥VGPR 33% versus 15%, $p<0.001$). Post transplantation, responses improved to 49% and 32% ($p<0.001$).[41] The impact of these improved response rates on the time to progression and overall survival are still not reported.

Rajkumar et al conducted a large, randomized international Phase 3 trial that compared TD with dexamethasone and placebo.[42] This study observed an improvement both in overall response rates (63% versus 43%, $p<0.001$) as well as a longer time to progression (22.6 versus

6.5 months, p<0.001) for patients randomized to the TD arm. While comparing between studies can be difficult, it appears that dexamethasone alone is equivalent to VAD in achieving initial tumor control [40,43], with the added benefits of lower toxicity and oral administration. This further suggests that doxorubicin also has little to add when combined with dexamethasone although this may change with new combinations of therapy. However, TD is clearly superior to dexamethasone alone and probably patients should not be treated with this single agent.[43] Another advantage of TD is that it is an oral regimen with minimal myelosuppression although it is associated with its own toxicity including a significant risk of deep venous thrombosis (DVT), peripheral neuropathy constipation and somnolence. The risk of thromboembolic events can be reduced if current guidelines for the prevention of IMiD induced DVT are followed.[44]

B. Lenalidomide-based induction

The adverse risk profile of thalidomide prompted the development of derivatives, with Lenalidomide (Len) being the first to enter the market. The combination of dexamethasone with Len (Len-Dex, dexamethasone 40mg days 1 – 4, 9 to 12 and 17 to 20) is safe and associated with high activity in newly diagnosed MM. In a Phase II study of Len-Dex, VGPR or better responses were observed in 56% of patients, with an overall response rate of 91%.[45] In this cohort, 91% of the patients were alive at 2 years from diagnosis, with an event free survival of 74%. Importantly, patients who remained on maintenance therapy with Led-Dex had an overall survival similar to those who had consolidation therapy with ASCT.[46] More recently, in an open label, randomized controlled trial, standard dose Len-Dex was compared with Len-dex (oral dexamethasone at 40mg on days 1, 8, 15 and 22 per 4 week cycle). After 4 cycles of therapy, patients could continue on therapy or proceed to ASCT if they were eligible. Not unexpectedly, the response rate was superior with the higher dose of dexamethasone (PR or better 79% versus 68%, p=0.008). However, the superior response rates of high dose dexamethasone did not lead to longer progression free survival (19.1 months versus 25.3 months, p=0.026).[47] Surprisingly, the overall survival at 2 years was 87% for patients on Len-dex compared to 75% with Len-Dex (p=0.006). Patients who did not proceed to transplantation had an overall survival at 2 years of 91% compared to 80%, while the median progression free survival was 22 months compared to 19.3 months.[47] These short-term results compare favorably with much more intensive regimens that include tandem transplantation.[48] However, long-term follow-up of these patients is necessary to fully assess the benefits of this gentler approach to myeloma control. If these responses persist, this is a clear example of less being actually more since a significant reduction in total dexamethasone dosing from 480mg to 160 mg per cycle, reduced the expected toxicity and early mortality without compromising efficacy.[49] Although thalidomide does not appear to compromise progenitor cell collection[50,51], there have been some concerns that lenalidomide interferes with progenitor cell mobilization.[52-54] Fortunately, recent studies suggest that a few cycles of Len-dex have no adverse effect on progenitor cells procurement for ASCT.[52] The impact of Len-dex on progenitor cell collection is essentially eliminated when patients are mobilized with a combination of cyclophosphamide and growth factor rather than growth factor alone.[55] Moreover, with the availability of the CXCR4 inhibitor plerixafor, progenitor cell collection is not a problem.[14,15] Recent guidelines suggest that patients on Len-dex should have progenitor cells collected not later than after 4 cycles of therapy.[14]

Mark et al have performed a Phase II trial evaluating the efficacy of clarithromycin (**Bi**axin), lenalidomide (**R**evlimid) and dexamethasone (BiRD) in 72 patients with newly diagnosed myeloma. Patients received clarithromycin 500mg twice a day starting on day 2 of the first cycle, lenalidomide at 25mg from day 1 to 21 and dexamethasone 40mg on days 1-3, 8, 15 and 22 of cycle 1 and weekly in subsequent cycles with treatment repeated every 28 days. A PR or better response was seen in 90% of the patients, including a stringent CR (sCR) in 38.9%

and VGPR or better in another 34.7% of patients.[55] Although patients experienced a response soon after starting therapy, the depth of response improved with time: the average time to achieve a VGPR was 5 months while the average time to reach sCR was almost 9 months. For patients who elected to continue on BiRD instead of consolidation with ASCT, the event free survival was 75% at 2 years.[55] BiRD therapy did not compromise progenitor cell collection or ASCT even though the average time from initiation of therapy to progenitor cell collection was 353 days.

B. Bortezomib-dexamethasone induction

Bortezomib, is the first of a kind, reversible inhibitor of the 26S proteasome. Its introduction as a therapeutic agent for myeloma was a milestone and provided new hope for patients especially those with high risk disease. The NF-κB pathway is critical for myeloma cell growth and survival. The activity of NF-κB is blocked by the Inhibitor of KappaB (IκB) which is normally degraded in the proteasome. By blocking IκB degradation, bortezomib indirectly inhibits NF-κB and negates an important growth signal for myeloma cells.[56,57] Since the proteasome is also indirectly responsible for regulation of the cell cycle, bortezomib also interferes with this fundamental cell process by modulating the degradation of p21, p27 and other proteins that are critical for checkpoint control. As a consequence, there is activation of p53 and caspases that result in cellular apoptosis.

Jagannath et al, initially enrolled 32 previously untreated patients with myeloma to either bortezomib alone or the addition of dexamethasone in the absence of at least a partial response after 2 cycles and less than a CR after 4 cycles.[58] Subsequently, additional patients were enrolled and extended follow-up of these patients has been reported recently.[59] The majority of patients required the addition of dexamethasone and 27 of the 49 (55%) patients subsequently proceeded to ASCT. The overall response rate was 90%, including a VGPR or better in 42% of patients. After a median follow-up of 49 months, the median survival has not been reached but estimated to be 67% at 4 years.[59] Although this study was not randomized and is probably underpowered due to its size, there was no difference in outcome between patients who elected to undergo ASCT consolidation compared to those who did not receive ASCT.

Harousseau et al also studied the activity of bortezomib in newly diagnosed multiple myeloma. They enrolled 50 transplant eligible patients to therapy with intravenous bortezomib 1.3 mg/m^2 on days 1, 4, 8 and 11 and dexamethasone 40mg on days 1-4 and 9-12 for cycles 1 and 2 and days 1-4 only for cycles 3 and 4. After 4 cycles of therapy, the PR rate was 66% including 21% CR and another 10% VGPR. The patients subsequently underwent ASCT when the response rates improved further: 33% achieved CR and 21% reached VGPR. The main side effect in this study was peripheral neuropathy that was Grade 2 or 3 in 14%.[60] The Spanish PETHEMA group evaluated a regimen where 40 transplant eligible patients alternate between bortezomib and dexamethasone.[61] The response rates were again high: the PR rate after 4 cycles of therapy was 65%. One of the interesting aspects of this study was the ability to determine the depth of response to bortezomib versus dexamethasone in the same patient. Perhaps surprisingly, the largest reductions in tumor burden (as measured by the monoclonal protein) were observed after cycles with dexamethasone therapy and not after bortezomib.[61] In both of these studies, therapy with bortezomib did not compromise progenitor cell mobilization.

Given the encouraging results with bortezomib in the upfront setting, the IFM opened a large randomized 4 arm trial (IFM 2005/01) in patients with newly diagnosed myeloma. Patients were randomized to induction therapy with 4 cycles of VAD or 4 cycles of bortezomib and dexamethasone (Vel/D). In each arm, patients were further randomized for consolidation therapy with or without two additional cycles of dexamethasone, cyclophosphamide, etoposide

and platinum (DCEP) before proceeding to ASCT.[62] Hematopoietic progenitor cells were collected between cycles 3 and 4 of induction therapy. As expected, neurologic symptoms were significantly more common in the Vel/D arm (36% versus 11%). Although more patients on Vel/D achieved CR and nCR before ASCT, there was no statistically significant difference in CR and nCR (28 vs 38%, p=0.127) *after* transplant. However VGPR or better responses were superior with Vel/D (66 vs 50%, p=0.021). The two additional cycles of consolidation with DCEP did not improve the CR rates.[62] The duration of response in these patients has not been reported as yet and results of long term follow up of this trial are awaited.

B. Bortezomib-containing combination regimens

Extensive *in vitro* studies suggest that bortezomib can be combined with other anti-myeloma agents with a synergic effect. Indeed, bortezomib can sensitize myeloma cells to drugs that alone have rather limited activity against this disease.[63] As a result, several groups are evaluating the impact of combination therapies that include bortezomib. The combination of **B**ortezomib, **T**halidomide and **D**examethasone (**BTD**) is being studied by various groups. [64, 65] In one study, Wang et al treated 38 patients with newly diagnosed myeloma using the BTD regimen. Patients were initially started on thalidomide at 100mg every evening and if tolerated, this was increased to 200mg after one week. In addition, they received dexamethasone 20 mg/m^2 daily on days 1-4, 9-12 and 17-20 with bortezomib (1.3 mg/m^2) on days 1, 4, 8 and 11. Therapy was repeated every 4 weeks for a maximum of 3 cycles. Although the number of patients enrolled was small, some of the results were remarkable since 11 patients could proceed to ASCT after only one cycle of therapy because the regimen leads to rapid and significant tumor cytoreduction. An objective response was observed in 87% of patients. Another benefit of such a short duration of therapy is the potential to reduce the incidence of adverse effects since some of them are common to more than one agent used (e.g. neuropathy). This regimen may also be an attractive strategy in situations such as acute renal failure due to myeloma kidney when a rapid reduction in monoclonal protein production is important to salvage renal function.

The combination of bortezomib (**V**elcade), **T**halidomide and **D**examethasone (**VTD**) is being compared to TD prior to ASCT in a Phase III trial by the GIMEMA group. In this study, patients randomized to the VTD arm receive standard dose bortezomib with dexamethasone 40mg on days 1, 2, 4, 5, 8, 9, 11 and 12 as well as thalidomide 200mg daily for 63 days. Patients randomized to TD received thalidomide 200mg daily and dexamethasone 40mg on days 1-4 and 9-12 of each 21 day cycle. The study is still ongoing and only interim results have been reported. The combination of VTD leads to CR or nCR in 38% of patients compared to 7% in the TD arm ($p<0.001$). At least 60% of patients in the VTD arm achieved a VGPR or better response compared to 25% with TD ($p<0.001$). In those patients who proceeded to ASCT, the CR and nCR rate increased to 57% with VTD compared to 28% with TD while the respective VGPR rates were 77% and 54%). VTD was associated with a higher incidence of skin rash and neuropathy.[65] Long term follow-up of these patients is also awaited to determine the impact of these impressive responses on the time to progression as well as survival.

Given the single agent activity of bortezomib, lenalidomide and dexamethasone (**VRD**) against myeloma, it was natural to test the three drug combination in patients with newly diagnosed myeloma. Richardson et al have evaluated VRD in a Phase I/II trial in patients with new onset myeloma. The patients received lenalidomide 15 to 25mg for 14 days, bortezomib 1.0 – 1.3 mg/m^2 on days 1, 4, 8 and 11 and dexamethasone 40mg on days 1, 2, 4, 5, 8, 9, 11 and 12 for cycles 1 – 4 and 20mg on the same days for cycles 5 -8 with cycles repeated every 21 days. During the course of the trial, the dexamethasone dose was reduced to 20 mg due to toxicity. Therapy was well tolerated and the incidence of both thrombosis and neuropathy being low. All patients responded to therapy with 74% achieving a VGPR or better response and CR and

nCR rate of 44%.[66] As a result, **VRd** (with lower dose of dexamethasone compared with VRD) is now being tested in many phase III trials in the US and Europe. In addition, in the EVOLUTION trial, patients with a new diagnosis of myeloma are being randomized to one of three therapeutic arms that combine novel agents with alkylators and dexamethasone: (i) Bortezomib, dexamethasone and lenalidomide (VDR); (ii) bortezomib, dexamethasone, cyclophosphamide and lenalidomide (VDCR); and (iii) bortezomib, dexamethasone and cyclophosphamide (VDC). The results from this trial are eagerly awaited.

Reeder et al have evaluated the safety and efficacy of a combination with cyclophosphamide, bortezomib and dexamethasone (**CyBorD**) in previously untreated myeloma.[67] In this trial, patients received standard dose bortezomib and dexamethasone 40mg on days 1-4, 9 – 12 and 17-20 together with oral cyclophosphamide 300 mg/m^2 on days 1, 8, 15 and 22 of a 28 day cycle. The patients experienced rapid responses with an 80% reduction in the M-protein within 2 cycles. Moreover, 71% of patients reached a VGPR or better response if they completed 4 cycles of therapy, and 88% of patients had at least a partial response. For patients who proceeded to ASCT, the CR/nCR rate was 70%. The durability of these impressive responses require further follow-up.

The efficacy of bortezomib (**P**S-341) combined with doxorubicin (**A**driamycin) and **D**examethasone (**PAD**) was evaluated in 21 patients with newly diagnosed MM.[68] Patients enrolled in this study received standard dose bortezomib with oral dexamethasone 40mg on days 1-4, 8-11 and 15-18 of cycle 1 and on days 1-4 of cycles 2-4. With respect to the anthracycline, the patients were divided into 3 groups who received 0, 4.5 or 9mg/m^2 of doxorubicin on days 1-4 with a total of 14 patients receiving the highest dose level. The overall response rate was 95% including 62% who achieved a VGPR or better. Painful peripheral neuropathy was reported in almost half of the patients and with most of this occurring after the second cycle of therapy.[68] In a subsequent analysis, the same group reported extended follow-up of 2 cohorts of patients treated with this regimen. The first cohort was treated as discussed already (PAD1) while a second cohort (PAD2) received bortezomib at 1.0mg/m^2 on days 1, 4, 8 and 11 with doxorubicin at 9mg/m^2 and the same schedule for dexamethasone. With PAD2, a VGPR or better response was observed in 42% of the patients. After ASCT, the respective response rates were 81% VGPR or better for PAD1 and 53% for PAD2. However, these differences were not statistically significant. Moreover, there was no difference in progression free survival or time to retreatment.[69]

Barlogie et al also incorporated bortezomib in their multiagent program for myeloma therapy.[48] The new protocol is Total Therapy 3 where patients are induced with 2 cycles of VTD-PACE (bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide and etoposide), followed by tandem ASCT and subsequent consolidation with 2 cycles of VDT-PACE. The patients are then treated with VTD for one year and then for an additional 2 years with dexamethasone and thalidomide.[48] The CR rates have improved and the response durations have increased compared to TT2 with or without thalidomide, implying that the addition of bortezomib is improving outcomes.[70]

B. Choice of induction in standard-risk patients

It is clear that the novel agents alone or in combination have unprecedented activity against myeloma with rapid and deep reductions in tumor burden. The question then is which regimen is optimal for a patient with standard risk myeloma? Unfortunately, there is as yet no simple answer to this question, since the results from large, randomized studies are still awaited. Although rapid and deep responses may be important, the duration of the response, toxicity (tolerability) as well as cost of therapy, have to be taken into consideration. Given the nature of our referral practice, if patients do not wish to enroll in a clinical trial, we offer Len-dex, since the regimen is convenient, well tolerated, safe, and provides high response rates,

including VGPR or better in over 40% of patients. For patients with high-risk patients or in patients where a very rapid reduction in tumor burden is required (e.g. renal failure), we offer enrollment in a trial with a bortezomib-based regimen or treat with a combination such as CyBorD or VDT (see below).

A. INDUCTION THERAPY FOR HIGH RISK MYELOMA

Approximately 15 to 25% of patients with a new diagnosis of myeloma have high risk disease (defined in Table 1). Although the data here is more limited, it appears that these patients benefit the most from bortezomib containing regimens since this agent neutralizes the adverse prognostic impact of cytogenetic abnormalities such as del13 or t(4;14).[26,60,61,71,72] Several studies have now shown (although in subgroup analysis) that patients with these abnormalities not only respond to therapy but can have prolongation of their time to progression (unlike therapy with other agents). For example, Harousseau et al found an objective response rate of 67% in patients with del13 and a PR or better in all patients with t(4;14) or isolated del(17p).[60] No difference in response rates were observed in patients with and without IgH translocations including t(4;14) and t(14;16) in the PETHEMA study.[61] The response rate to CyBorD in high-risk myeloma is in the range of 75 – 94%.[67] Similarly, the combination of bortezomib, dexamethasone and thalidomide (VDT) essentially eliminates the adverse prognostic impact of del13 and t(4;14).[65] The only common agent in these diverse regimens is bortezomib, which has earned its place as the drug of choice for high risk disease.

A bortezomib containing regimen is the treatment of choice for patients with high-risk multiple myeloma and in situations where a rapid reduction in tumor burden is required.

A. BORTEZOMIB AND CONDITIONING FOR ASCT

Since the combination of bortezomib and melphalan may be synergistic, the IFM is conducting a multicenter, Phase II study where patients are conditioned with both bortezomib and high-dose melphalan for ASCT. In addition to melphalan 200mg/m^2 on day −2, the patients received bortezomib 1.0mg/m^2 on days −6, −3, +1 and +4. The primary endpoint of the study was the rate of VGPR or better responses at 3 months after ASCT. The regimen was not associated with a worse toxicity or longer duration of cytopenias. The VGPR or better response with such a conditioning regimen was about 67 - 72%.[73] However, the long term impact on either overall survival or time to progression has not been reported.

A. NOVEL AGENTS AND MAINTENANCE THERAPY AFTER ASCT

Before the era of novel agents, recognition that melphalan dose escalation could improve responses opened the path to high-dose therapy and ASCT which translated into an improved survival for patients with this disease.[12,74,75] Some patients can have very prolonged responses after ASCT even in the absence of additional therapy. However this is the exception and not the rule and most patients will relapse and require further therapy. This raises the question of whether maintenance therapy after ASCT can prolong the response duration and have an impact on survival. This important question is being addressed by various groups.

B. Thalidomide maintenance

Barlogie et al, designed Total Therapy 2 (TT2) that randomized patients to a complex induction regimen using combination chemotherapy and novel agents followed by planned tandem ASCT.[76] Half of the patients were randomized to receive thalidomide continuously from the time of enrollment (induction) until either disease progression or the patients experienced defined adverse drug reactions. The cohort of patients enrolled on the thalidomide arm had a significantly higher CR rate compared to the controls (62% versus 43%, $p<0.001$) that was

translated into a higher event free survival (EFS) at 5 years (56% versus 44%, p=0.01). However, thalidomide maintenance had no impact on overall survival (65% at 5 years)[76], because patients who relapsed on thalidomide had a median survival of 1.1 years while patients who relapsed without maintenance therapy survived a median of 2.7 years (p=0.001). These results suggest that while thalidomide maintenance can suppress the malignant clone for a longer time interval, it selects for cells that tend to be resistant to therapy, negating any long term impact on survival. Moreover, patients who relapse off thalidomide, presumably have a higher chance of a response to further therapy at that time. This study did show that patients with high risk myeloma, as defined by cytogenetic abnormalities, benefit from maintenance therapy with thalidomide after ASCT. In this subgroup of patients, thalidomide improved the 5 year overall survival from 51% to 70% (p=0.01).[77] These differential effects of thalidomide, reported by the Arkansas group were also observed in the MRC Myeloma IX study.[78] Maintenance with thalidomide after ASCT improved PFS, especially in patients who achieved less than a VGPR after ASCT. However, survival after relapse in these patients was quite poor. Patients with the 17p- fared particularly poorly with thalidomide therapy during induction and maintenance. The biological mechanisms behind these observations are not clear.[78]

Two studies published to date have shown an improvement in survival with thalidomide maintenance alone after ASCT.[79,80] Attal et al, randomized 597 patients to no maintenance (arm A), pamidronate (arm B) and thalidomide with pamidronate (arm C), starting two months after tandem transplantation (IFM 99 02).[79] The CR rate was 55, 57 and 67% for arms A, B and C respectively (p=0.03) while the 3 year EFS was 36, 37 and 52% for the same arms (p<0.009). At 4 years from diagnosis, OS was 77, 74 and 87% (p<0.04) for each respective arm. However, the investigators now indicate that the OS differences are no longer significant with longer-follow up. More recently Abdelkefi et al reported their experience with 195 patients with myeloma initially treated with TD followed by randomization to either tandem ASCT or a single ASCT followed by maintenance thalidomide (100mg daily) starting 90 days after transplant and continued for 6 months.[80] The two arms had similar CR/VGPR rates (40 and 41%) after the first transplant and these increased to 54% and 68% at 6 months after the second transplant or 6 months of thalidomide therapy (p=0.04). The patients on the thalidomide arm had a higher 3 year PFS (85% versus 57%, p=0.02) and overall survival (85% versus 65%, p=0.04). Thalidomide was of benefit for patients with less than an optimal response (i.e. less than VGPR).

The ALLG have evaluated the impact of alternate day prednisolone (AP) versus thalidomide and AP starting 6 weeks after high dose therapy and a single ASCT.[81] Patients enrolled in the thalidomide arm were to remain on the drug for up to a year while AP was continued until progression. Almost 60% of the patients remained on the thalidomide for the intended duration of therapy. The PFS at 3 years was 42% versus 23% in favor of thalidomide (p<0.001) with overall survival being 86% versus 75% (p<0.004) respectively. The improvement in response duration and survival was not restricted to patients who achieved a suboptimal response (i.e. less than a VGPR) to ASCT. In contrast to the TT2 and MRC trials, survival from the time of relapse was the same for patients treated with and without thalidomide.[82]

B. Bortezomib maintenance

Studies on the impact of bortezomib maintenance after transplant are ongoing [83] while the impact of maintenance therapy with lenalidomide is being evaluated in a study being conducted by the Cancer and Leukemia Group B.

B. Approach to maintenance

Based on the above studies, we generally suggest that patients with high-risk disease may benefit from routine maintenance after transplantation. Although studies have employed

thalidomide as maintenance, either lenalidomide or weekly bortezomib may be alternatives. Patients with standard-risk disease who achieve less than an optimal response to transplant may also benefit from "maintenance therapy" administered for a short-period of time ("consolidation" rather than true maintenance). The role of lenalidomide is being addressed by at least two large randomized studies (IFM and CALGB).

Other patients (those without high-risk disease and standard-risk patients achieving VGPR or better with ASCT) should be observed without any form of consolidation or maintenance until further studies are completed. Immunomodulatory drugs and bortezomib can effectively salvage patients with standard risk disease when they relapse after transplantation. However, routine use of these agents after transplant increases the risk of resistance – hence the shorter survival of patients in the thalidomide arm after relapse/progression. Moreover, maintenance therapy is associated with a risk of toxicity and cost considerations also have to be taken into account.

A. INITIAL THERAPY IN NON-TRANSPLANT ELIGIBLE PATIENTS WITH STANDARD RISK DISEASE

Age by itself should not a contraindication for ASCT.[84] While in many countries patients above the age of 65 years are generally excluded from ASCT, in the United States, patients up to 75 years of age who are otherwise in good health (i.e. no significant cardiac, pulmonary, hepatic and renal disease), can undergo ASCT safely.[85]

B. Thalidomide-dexamethasone

Rajkumar et al have compared thalidomide and dexamethasone (TD) with dexamethasone (D) alone in a double blind, placebo controlled trial.[42] Patients enrolled in the TD arm received thalidomide started at 50mg that was escalated to 200mg by the start of cycle 2 and standard dose dexamethasone at 40mg on days 1-4, 9-12 and 17-20 for the first 4 cycles and subsequently on days 1-4 only. Patients enrolled in the other arm, received a placebo and dexamethasone as in the TD arm. The overall response rate was 63% versus 46% ($p<0.001$) in favor of the TD arm while the time to progression was 22.6 versus 6.5 months respectively ($p<0.001$). Ludwig *et al* have compared standard melphalan and prednisone (MP) with **TD** (thalidomide 200mg daily with dexamethasone 40mg on days 1 – 4 and 15-18 on even cycles and 1-4 on odd cycles).[86] Patients enrolled in the TD arm had a higher response rate and deeper responses (VGPR or better 26% versus 13%, p=0.0066, PR 68% versus 50%, p=0.0023). However the TTP was similar in both arms (16.7 versus 20.7 months, p=0.2), while OS was inferior in the TD group (41.5 versus 49.4 months, p=0.024). Moreover, TD was associated with significantly more toxicity (grade 2 – 3 neuropathy 25 versus 8%). Consequently, we do not recomment TD as initial therapy in non-transplant candidates.

B. Melphalan, prednisone, thalidomide (MPT)

Palumbo *et al* have randomized elderly patients to either MP or MP with thalidomide (**MPT**). MP was given every 4 weeks for a total of 6 cycles while thalidomide (100mg daily) was maintained until relapse or progression.[87] Patients in the MPT arm had higher response rates (PR or better 76% versus 47.6%; CR+nCR 27.9% versus 7.2% respectively). These higher response rates translated in longer TTP (21.8 versus 14.5 months, p=0.004) but OS was not different: 45 months for MPT and 47.6 for MP (p=0.79).[88] As expected, toxicity (thromboembolism, neuropathy and infection) was significantly higher in the MPT arm.[87]

The IFM have compared MP with **MPT** or reduced-intensity autologous transplant (melphalan 100 mg/m^2) in patients older than 65 years with newly diagnosed myeloma (IFM 99-06).[89] Again MPT was associated with higher response rates compared to MP (VGPR or better 47%

versus 7%, p<0.0001). Interestingly, the response rates with MPT were similar to MEL100 with ASCT and clearly superior to MP but transplantation did not give a superior EFS or OS compared to MPT (OS 38.3 and 51.6 months respectively). These results clearly contrast with those of Palumbo *et al* and it seems that in the IFM trial, the MP arm had a significantly inferior overall survival compared to the Italian study (33.2 versus 47.6 months) despite a higher proportion of elderly patients (>70 years) in the latter.[88,89] In another study by the IFM (IFM 01/01), patients older than 75 years of age were randomized to MP with placebo or MPT every 6 weeks for a total of 12 cycles.[90] A partial response was achieved in 62% of patients on MPT versus 31% with MP and VGPR or better responses were observed in 21% and 7% respectively, (p<0.001). Patients in the MPT arm had a median OS of 44 months compared to 29.1 months for the MP and placebo arm (p=0.028). Despite higher toxicity, the median duration of thalidomide therapy was more than 1 year. Many patients in the MP arm received thalidomide after relapse: however, survival from the time of progression was the same in both groups (9.8 versus 9.3 months). Therefore in this study, thalidomide did not prolong survival after relapse or progression. [90]

The HOVON 49 study is evaluating the impact of MP versus MPT in elderly patients with a new diagnosis of myeloma.[91] Thalidomide is given at 200mg daily with melphalan at 0.25mg/kg and prednisone 1mg/kg, both for 5 days for a maximum of 8 cycles. Patients who achieve a good response on thalidomide are maintained on the drug at 50mg daily until progression. MPT was associated with a higher overall response (66% versus 47%, p<0.001) and the event free survival was 13 months versus 9 months in favor of thalidomide addition (p<0.001). However, patients on the MPT arm experienced higher neurotoxicity.[91] In another randomized study of MP versus MPT, the Nordic myeloma group did not find any significant difference in progression or overall survival (29 versus 33 months) between patients treated with either regimen. Moreover, there was a tendency for higher early mortality for patients treated with MPT. [92] A meta-analysis of all the trials comparing MP with MPT conducted so far, does however suggest that the addition of thalidomide to MP improves not only response rates but also prgression free and overall survival. [93] This analysis will be reported at ASH in 2009.

B. Melphalan, prednisone, lenalidomide (MPR)

Given that lenalidomide can be better tolerated and safer than thalidomide, Palumbo *et al* conducted a phase I/II study of MP with lenalidomide (**MPR**) in 54 patients with newly diagnosed myeloma.[94] The median age was 71 years and the maximum tolerated dose of lenalidomide was 10mg (days 1 – 21) with 0.18mg/kg of melphalan (days 1 – 4) and prednisone 2mg/kg (days 1 – 4). Therapy was repeated every 28 days and aspirin alone was used for thromboprophylaxis. The Patients tolerated this combination well with the main toxicity being hematologic (neutropenia and thrombocytopenia). A VGPR or better response was seen in 47.6% of patients, including CR in 24.8%. Survival at one year was 100% and EFS was 92%. Although the number of patients was small, MPR seemed to have similar impact on EFS in patients with del13 and t(4;14).[94] Based on this data, an international study comparing MP with MPR has been initiated while ECOG is conducting a study comparing MPT with MPR.

B. Bortezomib-based therapy

In the VISTA trial, 682 patients were randomized to 9 cycles of therapy with MP or MP plus bortezomib (**MPV**) (1.3mg/m^2 on days 1, 4, 8, 11, 22, 25, 29 and 32 of cycles 1 – 4 and days 1, 8, 22 and 29 of cycles 5 – 9).[95] Compared to MP, 71% of patients treated with MPV had a partial response compared to 35% in the control arm. CR rates were also higher (30% and 4%) respectively. The response duration in patients who achieved CR with MPV was about 24 months. The median TTP was 24 months with MPV compared to 16.6 months with MP (p<0.001). After a median follow up 16.3 months, 13% of patients on MPV and 22% of patients on MP have died (p=0.008). Grade 2 or worse neuropathy was reported in almost 30% of the

patients on MPV, although the severity of this problem reportedly decreased with time. Therefore, MPV gives superior results compared to MP, although this is associated with higher toxicity and frequent visits, especially for the first 4 cycles. In a subsequent analysis, the VISTA investigators showed that even in the non-transplant setting, achieving a CR was associated with a superior TTP in patients on MPV and this impact was regardless of the time to achieve CR. In other words, patients who achieved CR after the first 4 cycles had a similar benefit to patients who achieved CR within the first 4 cycles of therapy. Therefore this study implies that patients should continue with therapy until a maximum or best response is achieved as long as they can tolerate therapy.[96]

The GIMEMA group has conducted a trial where patients were treated with 4 cycles of **PAD** followed by progenitor cell mobilization using cyclophosphamide 3g/m^2 and G-CSF. Subsequently, the patients received melphalan 100mg/ m^2 with ASCT support.[97] The response rates were impressive with a PR of 97.1% including a VGPR or better of 61.8%. Following ASCT, the VGPR or better response increased to 80% including 30% CR. As expected the main toxicities were hematologic with grade 3 - 4 thrombocytopenia and neutropenia in13.5% and 8.1% of patients respectively, and symptomatic neuropathy in 21.6%. The long term impact of this approach on duration of response and survival is at present unknown, but it appears that this rather intensive therapy can be tolerated by a select group of elderly patients.

Mateos et al are studying the effect of VMP versus VTP in patients older than 65 years with newly diagnosed myeloma.[98] Patients received bortezomib at 1.3mg/m^2 on days 1, 4, 8, 11, 22, 25, 29 and 32 of cycle 1 and then weekly (days 1, 8, 15 and 22) for five more cycles. The patients also received prednisone at 60mg/m^2 on days 1 – 4 and either oral melphalan at 9mg/ m^2 on days 1 – 4 or thalidomide at 100mg daily for a total of 6 cycles (31 weeks). In an interim analysis, the overall response rates were similar (80% versus 87% for VMP and VTP respectively). The CR rates were 18% versus 23% in favor of VTP without any difference in the time to achieve CR. Patients treated with VMP had higher hematologic toxicity (grade 4 neutropenia or thrombocytopenia) while non-hematologic toxicity was higher with VTP, suggesting that thalidomide may not be the best agent to combine with bortezomib.[98]

Palumbo et al are conducting a randomized trial comparing VMP with VMPT.[99] For the VMP arm, patients received bortezomib at 1.3mg/m^2 on days 1, 8, 15 and 22 with oral prednisone at 60mg/m^2 on days 1 – 4 and melphalan at 9mg/m^2 on days 1 – 4. Patients enrolled in the VMPT received the same treatment with the addition of thalidomide at 50mg daily. In both arms, patients could receive up to 9 cycles of therapy. The VMPT arm was associated with a higher response rate (VGPR 59% versus 37%, p=0.003) although to date there is no difference in overall survival between the two groups (89.5% versus 88.7% at 3 years). However, for patients who achieved CR (28% versus 10%, in favor of VMPT), the 2 year PFS was 100% for VMPT and 79% for VMP (p=0.02). Thus, while VMPT can give higher response rates, it may be too early to evaluate the long term impact of this regimen on response duration or overall survival.

B. Lenalidomide-low dose dexamethasone

As discussed earlier under induction therapy for patients who are candidates for SCT, lenalidomide plus low-dose dexamethasone is a well tolerated and effective regimen in elderly patients, and represents an oral, non-alkylator based option Choice of therapy

Based on these results, we conclude that the time proven combination of MP is no longer the standard of care for patients who are not considered eligible for ASCT. The addition of thalidomide or bortezomib with MP is a better option for elderly patients with newly diagnosed myeloma. We generally prefer MPT in standard-risk patients, and reserve VMP for patients with high-risk disease. Perhaps, whether MP is combined with thalidomide, lenalidomide or

bortezomib depends more on convenience, expense, and comorbidities. In addition, to MP+ regimens, we have increasingly used Len/dex as a less toxic alternative that is well tolerated by patients.[47] ECOG is currently conducting a trial comparing MPT with MPR and the results of this trial are awaited. As the data from ongoing trials that compare the various combinations of novel agents and chemotherapy matures, the optimal choice of initial therapy in elderly patients will become increasingly defined.

A. BRIEF COMMENT ON APPROACH TO THERAPY OF RELAPSED DISEASE

At no other time in the history of multiple myeloma did patients and physicians have such an armamentarium of agents to use for relapsed disease. Nowadays, it would be unusual for patients to relapse and not be treated with these agents. Thalidomide, lenalidomide and bortezomib alone or in combination with dexamethasone all have significant activity in the relapsed setting [6,69,71,100,101] and the choice of agent to be used will depend on prior therapy, whether the patient relapsed on or off therapy and comorbidities. In the pivotal APEX trial, the proteasome inhibitor bortezomib was compared with dexamethasone in patients who had received 1 to 3 prior regimens. Bortezomib was associated with higher response rates and an improved 1 year OS (80% versus 66%, p=0.003). The superiority of bortezomib remained even after significant cross-over from the dexamethasone to the bortezomib arm (29.8 versus 23.7 months, p=0.027).[102]

The efficacy of lenalidomide and dexamethasone in setting of relapsed multiple myeloma has been confirmed in two, essentially identical phase III randomized, double blind trials (MM-009 and MM-010).[103,104] Compared to dexamethasone and placebo, Len-Dex led to higher overall response rates (60% versus ~20%, p<0.001), that translated into a longer response duration (TTP of 11.2 versus 4.7 months). Moreover, OS has not been reached in the MM-010 trial and 29.6 months for Len-Dex compared to ~20.4 months for the control arm. Although the efficacy of lenalidomide was best if the drug was used initially after relapse, responses were seen regardless of whether the patients had prior ASCT or not. Moreover, lenalidomide was also effective in patients with prior exposure to thalidomide. [105]Combinations of lenalidomide and dexamethasone with liposomal doxorubicin, cyclophosphamide, vincristine or bortezomib are being tested. [106,107] Ideally, patients with relapsed disease should be encouraged to enroll in clinical trials evaluating the impact of combination therapy or the use of novel agents.

In addition to the established novel agents, a new proteasome inhibitor carfilzomib, and a new immunomodulatory agent, pomalidomide [108] are very promising. Both drugs are entering regulatory trials. Although numerous other agents have shown preclinical activity and are being tested in clinical trials, the ones that appear to warrant further study are histone deacetylase inhibitors, heat shock protein inhibitors, insulin-like growth factor receptor inhibitors, and interleukin 6 inhibitors.

A. SUMMARY

We conclude that novel agents are not only increasing responses in patients with myeloma but also improving survival and quality of life. The novel agents have non-overlapping toxicities and appear to act synergistically is various combinations. The long term impact of three or four drug combinations including novel agents together with standard chemotherapy and glucocorticosteroids is not yet clear. Hopefully, the impressive response rates being reported are durable and will translate into meaningful and long term improvement in survival if not yet cure.

PRACTICE POINTS

- Risk stratification of multiple myeloma at diagnosis is essential for proper therapy of patients
- Patients that are potentially eligible for stem cell transplantation should not receive alkylator based therapy at induction
- In patients with standard risk disease, a gentle approach is reasonable
- Bortezomib based regimens are optimal if rapid tumor cytoreduction is necessary and in the presence of renal insufficiency
- Patients with high risk myeloma should be treated with a bortezomib based regimen
- Aiming for a complete response is important in patients with high risk disease
- Patients with a less than optimal response to ASCT may benefit from maintenance therapy with thalidomide
- Transplant ineligible patients should be treated with MPT or VMP depending on the biological characteristics of their disease
- Appropriate thromboprophylaxis is important for patients on IMiD therapy
- Enrollment in clinical trials is greatly encouraged

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Table 1

Risk stratification of newly diagnosed multiple myeloma

Standard Risk	High Risk
Hyperdiploid clone	Hypodiploidy
t(11;14)	del13 (by cytogenetics)
t(6;14)	t(4;14)
	t(14;16)
	t(14;20)
	17p13-
PCLI < 3%	PCLI >3%