How I treat multiple myeloma in younger patients

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Introduction
Therapy for multiple myeloma (MM) has advanced with gratifying speed over the past 5 to 7 years and, with this progress, a degree of uncertainty has arisen about optimal approaches to therapy, particularly in the newly diagnosed patient. Indeed, using modern therapeutic strategies, living with MM for a decade or longer has now become a reality for a significant proportion of patients. Nevertheless, in many instances, randomized trial data which provides definitive evidence based guidance on how best to achieve this goal is lacking. This “How I Treat” article therefore seeks to offer practical guidance in a rapidly changing landscape and outlines our current belief about the goals of therapy and our personal approach to treating the younger myeloma patient.

Our approach to treatment in younger “transplant eligible” patients today is to use combination induction therapies which offer a high percentage likelihood of rapid and deep response. Although still controversial, we thus concur with the belief, that maximizing initial response will for the majority of patients, translate into better long-term disease control and survival. Treatment should therefore, in our opinion, use all available drugs of known effectiveness during initial therapy with careful attention to management of toxicities in a manner which ensures planned delivery of the intended therapeutics. Put differently, we do not favor therapy rationing (saving drugs for later).

Although early clinical trial data are supportive of our opinion confirmatory clinical trials using the best novel agents are not yet available. Ongoing randomized trials comparing lenalidomide / dexamethasone or bortezomib / dexamethasone versus bortezomib, lenalidomide and dexamethasone in combination are ongoing and will directly address the value of combination therapies versus therapeutic rationing. Until such trial results become available, our recommendations to utilize combination
therapies outside of clinical trials represent interpretation of available trial data, some unpublished, and our own clinical experience.

In patients with co-morbidities who are ineligible for, or unwilling to, pursue multi-drug combination therapies and/or high dose therapy, a reasonable alternate goal of treatment is to seek the best continuous disease control with less emphasis on depth of response and more emphasis on obtaining adequate symptom relief while maintaining quality of life. In this situation therapy rationing or layering (adding new drugs in patients not responding to initial therapy) may be more logical. We further believe that treatment should be individualized both in respect to prognostic risk profile and adapted to meet the competing demands of co-morbidities and age.

Although the reality of today’s global economic climate dictates that a balance between benefit and costs will be required, we present here therapeutic strategies independent of pharmacoeconomic considerations, as the latter are often country-specific, variable and likely to change as clinical trial data matures. Finally, given the continuous and rapid advances being obtained through active collaboration between academia, industry, foundations and government agencies it is strongly recommended that eligible patients be offered participation in clinical trials whenever feasible. Indeed, today in many countries where newer therapies are not yet approved this may provide the only means of access to state of the art regimens described below.

When To Treat?
Although the activity of novel agents has advanced to the point that early interventions are now being explored in clinical trials for smoldering myeloma, there is still no
evidence that early treatment will improve survival in asymptomatic and biochemically stable patients. A critical point is that up to 25% of smoldering myeloma patients will not require active treatment for 10 to 15 years, although the majority will in fact progress during that time. The clinician should therefore avoid treating asymptomatic and biochemically stable patients with active therapy, allowing current drug development efforts to mature to their maximal efficacy at a time when systemic treatment does become a necessity. Indeed, some data suggest that early intervention may only serve to identify those patients at early risk for progression, or worse, theoretically to select out more aggressive genetic subclones of myeloma.

Once diagnosed however, we emphasize that smoldering myeloma patients require frequent monitoring to allow treatment to begin before end organ damage is evident, with the use of certain supportive therapies, such as bisphosphonates for osteopenia justified in selected patients.

**What investigations should be performed at diagnosis?**

The tests that guide a decision to start and define treatment paths are those that contribute to an unequivocal diagnosis of symptomatic MM and can afford important prognostic information. The essential tests diagnostic of myeloma are well established. We recommend that in addition to the classical CRAB measurements of calcium, renal function, haemoglobin level, and skeletal survey, the β2-microglobulin, albumin and lactate dehydrogenase (LDH) should be measured, as these latter tests impart prognostic significance. Investigations for the monoclonal protein (M) require both serum and urine (24 hour) samples and today could include the serum free light chain (sFLC) assay, which has become mandatory in non-secretory or oligosecretory MM and is often the first marker of response and progression. SFLC is also of value in solitary
plasmacytoma, amyloidosis and in initial evaluation of MGUS to predict risk of progression to symptomatic MM\textsuperscript{16}.

Sufficient (usually at least 5ccs) of BM should be obtained not only for morphology, but also for fluorescent in situ hybridization (FISH) analysis of key genetic events (this latter technique must be performed either in purified plasma cells or in combination with immuno-fluorescent detection of light chain restricted plasma cells (cIg-FISH) for t(4;14), t(14;16) and deletion of 17p, as these abnormalities identify high risk disease\textsuperscript{17}. Metaphase cytogenetics should also be garnered when possible (the use of standard metaphase cytogenetics is often of low yield, but when positive for hypodiploidy, deletion of chromosome 13 or complex karyotype (with the exception of hyperdiploidy), imparts a particularly poor prognosis\textsuperscript{18}. Suggested genetic testing of patients is highlighted in table one. Finally, although the conventional skeletal survey remains the standard method for evaluation of bone lesions, magnetic resonance imaging (MRI) is more sensitive and is recommended to exclude spinal cord compression, soft tissue mass in a localized painful area or for assessing BM involvement in patients with solitary plasmacytoma and smouldering myeloma\textsuperscript{19}. The role of PET-CT is less well defined in MM, but can be useful for detecting extra-medullary disease, unsuspected bone lesions and evaluating patients with plasmacytoma as well as non or oligo-secretory MM\textsuperscript{20-22}. We have in our early experience found PET-CT to be of significant interest in many patients, providing re assurance when negative in smouldering disease and often revealing a previously unappreciated extent of disease in higher risk patients (figure one).

**Durable complete response is a desirable endpoint**
There is a growing body of evidence showing an association between depth of response to therapy and improved long-term outcomes, including progressive-free survival (PFS) and overall survival (OS), in MM patients\textsuperscript{3,5,8,23-27}. Using conventional chemotherapy it has been shown that there is a correlation between response before and after transplantation and that the quality of response after transplantation has a marked impact on outcome\textsuperscript{8,27}. Importantly however, studies suggest that if a patient achieves a complete response (CR), this must be durable and that the duration of CR rather than obtaining CR \textit{per se} is the best predictor of OS\textsuperscript{28}. Furthermore, although obtaining a durable CR is of apparent statistical value for the majority of MM patients, there are some subgroups (usually identifiable only after initial therapy has been completed) in which the value of initially obtaining a CR in predicting long term outcome is more questionable. These subgroups include the high genetic risk group of rapid responding but early relapsing patients, those more indolent myelomas which revert to an “MGUS like” profile after therapy and those myeloma patients (increasingly uncommon) with stable non-progressive disease after induction therapy. At present our ability to accurately predict who these individuals are \textit{a priori} before treatment is initiated is limited. Pragmatically, then one must still start with maximal response, including a high expectancy of CR, as a goal.

Trial data and our recommendations below use current definitions of CR but an important caveat for consideration is that these definitions are sub-optimal since a CR is currently based on the rather insensitive criteria of the disappearance of the M-protein by immunofixation, the presence of $<5\%$ plasma cells (PC) in the bone marrow (BM) with complete disappearance of any extra-osseous plasmacytoma\textsuperscript{29}. Even with the incorporation of new criteria such as the absence of clonal PC by
immunohistochemistry to define stringent complete remission (sCR), experience teaches that these tests may still have low relative sensitivity. In order to further improve the assessment of treatment efficacy, more sensitive tools are likely to be required going forward and will be explored in clinical trials both at the BM level (such as multiparametric flow cytometry)$^{26}$ and outside of the BM (e.g. imaging techniques such as MRI or PET-CT)$^{30}$. In addition, when assessing CR, MRI defined lesions may take as many as 18 to 24 months to normalize.

**Choice of initial drug therapy**

Although success and long term remission has been achieved in many transplant eligible patients using limited treatment regimens such as thalidomide/dexamethasone$^{31}$, bortezomib/dexamethasone$^{32,33}$ and lenalidomide/dexamethasone$^{34}$, complete and very good partial response (VGPR) rates can be substantially increased by combining these various drugs in triplets or even using four drugs together (see below). Preliminary results from ongoing Phase III randomized trials show improved initial response rates and increased frequency of CR after induction therapy in patients randomized to bortezomib and dexamethasone versus VAD chemotherapy, and in patients randomized to bortezomib, thalidomide and dexamethasone versus thalidomide and dexamethasone alone. These initial higher quality responses translate into a higher frequency of CR after transplant and at least in preliminary reports improved PFS. Since, durable CR and PFS appear to be valuable surrogates for long term outcome (as referenced above) and an important platform for potential operational cure, we therefore favour multiple drug, combination, therapies be applied in younger patients able to tolerate toxicities and pursue high dose therapy approaches.
The earliest reports of triplet therapies came from the combination of bortezomib, thalidomide and dexamethasone (VTD)\textsuperscript{35} and the encouraging results have now been replicated using, lenalidomide, bortezomib, and dexamethasone (RVD)\textsuperscript{36}, liposomal doxorubicin, bortezomib, and dexamethasone (DVD)\textsuperscript{37} and cyclophosphamide, bortezomib and dexamethasone (CVD)\textsuperscript{38} as examples. Response rates to these regimens are highlighted in figure 2. A note of caution is that many of these studies are based on relatively small numbers of patients at single, or limited numbers, of centres but cumulatively the message is consistent with frequent, rapid and deep responses seen. While each of these regimens has shown high activity it seems likely that combining all active drug classes will ultimately prove of most value, thus current clinical trials exploring four drug combinations (CVRD\textsuperscript{39}, VRDD, CVDD) are underway, although the impact of toxicity is a key consideration.

While final randomized trial data are still awaited using these regimens, the success of PAD\textsuperscript{40}, VTD\textsuperscript{6}, of melphalan, prednisone and bortezomib in elderly patients\textsuperscript{7} and the promising results of Total Therapy 3 (TT3)\textsuperscript{4}, using all active agents early in treatment, bode well and we believe are likely to be reproduced using the three or four drug cocktails described above. The TT3\textsuperscript{4} programme based on VDT-PACE induction has in particular shown impressive results with 4-year event free survival (EFS) of 78\% and sustained complete response (CR) at 4 years in 87\% of patients initially achieving a CR. Nevertheless, use of conventional chemotherapy drugs including etoposide and cis-platinum as part of an induction platform does not seem to have produced a significant response or survival advantage based on recent Phase 3 trial data\textsuperscript{41} and we believe that the benefits of a second transplant may only be evident in a subset of patients (see below). Thus while final reports from trials are still pending we do not currently use
etoposide and cis-platinum and routine tandem transplant in our own practices preferring a more individualized approach based on genetic risk balanced with patient tolerance of therapy and initial response to induction as described below.

Although response rates are clearly improved with new drug cocktails, proving a consequent overall survival (OS) advantage is likely to be difficult and impractical given the large numbers of patients and the long duration of follow up required\textsuperscript{42}. Clinical studies with OS as an endpoint are further complicated by the availability and constantly changing nature of effective salvage therapies. Thus, using response rates, depth of response achieved and progression free survival as surrogates the three drug cocktails are currently the modality of choice in our practices, even outside of clinical trials with RVD, CVD or VTD, being the most commonly employed (in many countries similar regimens are available only in a clinical trial setting and thus early referral to a specialized centre able to deliver novel drugs in combination may be desirable). Care must be taken to carefully manage the supportive care elements that go with such regimens to minimize side-effects and ensure durable benefit. Finally, there is clearly no future role for the continued use of VAD based regimens or single agent dexamethasone, and arguably even thalidomide and dexamethasone which in our opinion are suboptimal therapies as emphasized in recent trials\textsuperscript{6,31,32,37}. Refractory or progressive disease is now uncommon when using multi drug combinations with overall response rates (>PR) exceed 90% in almost all recent studies. However when presented with a truly refractory patient timely referral for high dose melphalan should be considered, as this group of patients seems to benefit from this approach.
An area of uncertainty is the dose of corticosteroids to use in induction. While responses are faster and deeper with more dose intense steroid use, OS does not seem improved by earlier introduction of high dose dexamethasone and such an approach may be inferior as it has a significantly higher risk of toxicity\(^4\). Thus, we suggest using higher doses of dexamethasone only in patients in whom a rapid response is needed. We therefore recommend higher dose dexamethasone (such as 40mg days 1-4, 9-12 and 17-20) in those with life threatening hypercalcemia, spinal cord compression, incipient renal failure or extensive pain, but lower weekly dosing should be pursued in patients who do not require very rapid tumor reduction, and particularly those in whom multi drug cocktails are being employed, which allows a “steroid-sparing” approach to be utilized.

**How much treatment prior to Stem Cell Transplantation**

For the patient eligible for transplant, our practice is usually to proceed to autologous stem cell collection and transplant after 4-6 cycles of induction therapy. However, since our stated goal of therapy is to maximize the depth and duration of remission, induction therapy can be continued in some patients for as long as the patient is responding and tolerating therapy. We view the optimal contribution of high dose melphalan and stem cell transplant to be as a consolidation of remission after obtaining the best possible response to front line treatment.

One controversial area is what to do if the patient has already achieved a CR prior to transplant. In this decision the role of continued chemotherapy treatment versus proceeding to transplant is less clear and an area of active research. For now, and until clinical trials prove otherwise, we generally prefer to proceed to transplant in most patients even if conventional CR is achieved by induction therapy, but the option to
defer can be discussed with the patient. This reflects our belief that current measures of CR are insufficiently sensitive and residual disease is in many, if not all, patients present but below the level of detection. If the patient is still not in a CR or near CR post transplant, additional consolidation/maintenance therapy, including, but not restricted to a second autologous transplant can, and should, be considered (see below).

The Role of Transplant

Autologous stem cell transplant (ASCT) has been shown in randomized trials to be of value to patients in helping achieve or consolidating CR and is thus employed in the majority of our patients eligible and willing to proceed to transplant. New trials will address whether or not transplant remains useful in the era of novel drugs, but until proven otherwise we believe it is likely to still be of value in achieving a higher frequency and depth of CR in more patients and thus contributing to prolonged survival. Upper age limits vary widely from centre to centre and country to country but in general the overall health of the patient rather than a specific chronologic age is probably most relevant. Earlier studies demonstrated an advantage to a second or tandem transplant only in patients who do not obtain at least a VGPR after the first procedure. However, since CR rates are now achieved over 50-70 percent of the time with effective induction therapies combined with single ASCT, and since responses may be further enhanced by post transplant consolidation / maintenance therapies, we less frequently find need to perform a second (or tandem transplant) early in the disease course. The choice for maintenance therapies which can be employed after transplant will be discussed below.
The timing of ASCT is also an area of active research. Patients are usually more fit for intensive therapy early in the course of the disease but older studies using conventional chemotherapy inductions demonstrated that a delayed ASCT had no adverse impact on OS and is feasible as part of salvage therapy in first relapse\textsuperscript{50,51}. Randomized trials to better define populations served by this approach are planned and a delayed transplant may be considered in some patients doing well on induction drugs, obtaining an excellent response and who are not inclined to pursue the social and quality of life disruptions entailed by high dose melphalan based therapy.

Allogeneic transplant should only rarely be performed outside of clinical trials, as the risk of morbidity and early mortality of even non-myeloablative transplants is considerable and thus not acceptable for most patients in the current era of longer survival\textsuperscript{51-53}. In very young patients, particularly those who experience early relapse or with very high risk features at diagnosis, this therapeutic strategy may however offer some hope of long term disease control and can be considered. Suffice to say that the number of patients undergoing allogeneic transplant at our centers remains low and it is not often performed outside of the clinical trial setting.

**Consolidation and Maintenance therapy after transplant**

Three separate Phase 3 studies found thalidomide maintenance to improve overall survival (table 2)\textsuperscript{3,48,49}. Despite these findings thalidomide is not being routinely used for maintenance in many centers, presumably reflecting concerns about cumulative toxicity. Lenalidomide may offer the same advantages with less toxicity and large randomized trials are now addressing its role in the post transplant setting. It has become our practice to use maintenance routinely when patients have not achieved a CR
after stem cell transplant or when genetic risk markers suggest a very high risk of early relapse\(^9\). In our opinion either thalidomide or lenalidomide is likely to prove suitable. There is insufficient data on bortezomib maintenance on which to form an opinion. It is not known how long maintenance should be continued but we generally use indefinitely and taper dosing for tolerance. Anti-coagulation does not seem to be a requirement in the maintenance setting.

**Prognosis and Genetics**

As noted above, extremes of genetic subtypes of MM require special attention. Genetically high risk patients, defined by the presence by FISH of t(4;14) with an associated high beta-2-microglobulin, a t(14;16), a deletion of p53 on chromosome 17, by the presence of deletion of chromosome 13 or hypodiploidy by conventional cytogenetics are one such class (Table 3)\(^9\). In such patients, bortezomib-based treatments appear (based on preliminary evidence) to be of some value in ameliorating genetic risk\(^4,7,54\) although long term follow-up is still required before a firm conclusion can be drawn on this topic. The value added by high dose melphalan and transplant is much less certain in these patients, as event free survivals in high genetic risk patients were very short after transplant in the era before novel drugs became available\(^55,56\). Indeed very high risk patients continue to do poorly compared to those with low risk genetics even with tandem transplant procedures\(^2\). Of some encouragement, a significant improvement in survival for high risk patients has been seen when novel drugs such as thalidomide or bortezomib are added e.g. to tandem transplant as in the total therapy 2 successor total therapy 3. Despite this high risk patients remain substantially challenging and longer term induction therapy to maximal response followed by indefinite maintenance could be employed as an alternative to early
transplant. In contrast patients with hyperdiploid myeloma and absence of other poor prognosis factors such as elevated LDH or β-2 microglobulin appear to have a generally good prognosis and seem to do well on relatively simple regimens such as lenalidomide and dexamethasone and this approach may be suitable for those low risk patients who do not wish more aggressive therapy.

Patients not wishing or not suitable for high dose melphalan and transplant

In the patient who does not wish transplant through choice, then induction therapy as above e.g. VTD, VRD or CVD can be prolonged to maximal response as an alternative to transplant with maintenance considered in those not achieving CR or at high risk for early relapse. Alternative regimens in younger patients who do not plan to receive a transplant could employ alkylating agents in combinations such as melphalan, prednisone and bortezomib (MPV) or cyclophosphamide, thalidomide and dexamethasone (CTD); either of which could also be considered based on availability of drugs. Less aggressive treatment, with for example, lenalidomide and low dose dexamethasone, may be appropriate for patients not requiring a very rapid response to initial therapy and who are at reduced risk of early relapse based on low risk clinical features (e.g. low β-2 microgloblin, low LDH, absence of high risk genetic features).

In patients with significant co-morbidities precluding transplant, combination therapies may be challenging to administer and in such patients we more often opt for an initially less toxic and invasive approach to treatment with lenalidomide and low dose dexamethasone being one suitable regimen. In these cases the goal would be to obtain the best possible response while managing toxicities. The optimal longevity of therapy
under these conditions is not known so generally we treat until intolerance of therapy for any reason or progression.

**Issues around mobilization of stem cells**

Following current induction therapies, stem cells can be collected in numbers adequate to perform up to two autologous stem cell transplants. Nevertheless, in patients who have received prior melphalan\(^{59}\) or prolonged treatment with lenalidomide\(^{60,61}\), failure to collect has emerged as a concern and in such patients alternative collection strategies can be considered. We therefore avoid melphalan and usually limit the number of prior cycles with lenalidomide-based therapy (usually four cycles) before collection and employ mobilization regimens in those patients who have received more than four cycles which incorporate cyclophosphamide\(^{62}\) or plerixafor\(^{63}\). With such measures, the success of collection is higher and almost all patients receiving prior lenalidomide can collect sufficient cells in support of at least one single intensification with ASCT using high dose melphalan\(^{39}\).

**Supportive care**

Although easy to overlook during a busy clinic, modern MM therapy requires expert attention to supportive care. This involves careful patient education about the likely side effects of each drug and the drug combinations being used, and the supportive care adjustments required. Supportive care can be categorized into those measures required for all patients and those that address only specific drugs.

For every patient, an emphasis on adequate hydration, low impact exercise, avoidance of nephrotoxic drugs, pain control and chemotherapy education should be accompanied
by use of a bisphosphonate and other measures appropriate for prevention and treatment of osteoporosis or osteolytic disease, when present. Consideration of the long term consequences of bisphosphonate use should be made, with appropriate and frequent dental evaluation and care recommended. Hematopoietic growth factors can, and should, be used in anemic or neutropenic patients. Attention, regarding infection and infection prophylaxis is critical. The routine use of a quinolone or other prophylactic antibiotic during the first few months of therapy seems to be important in patients receiving higher doses of corticosteroids. Pneumococcal and influenza vaccination is appropriate, even if unlikely to provide complete humoral immunity. Herpes zoster prophylaxis with acyclovir should be used in all patients receiving a proteasome inhibitor and in the post-ASCT setting. Anti-fungal prophylaxis can be used in more intensive approaches and especially with steroids and with high dose dexamethasone, prophylaxis against Pneumocystis carinii (PCP) is prudent.

Other specific measures include the risks and management of neuropathy, low blood counts and diarrhea common to the proteasome inhibitors and long term lenalidomide use. The cornerstone of managing neuropathy associated with bortezomib is dose-reduction and schedule change, as severe neuropathy is potentially avoidable and most neuropathies partially reversible with careful attention to dose, schedule and therapy change where required. Recent evidence suggests that once weekly dosing may be helpful in this regard, although efficacy may be compromised.

Neuropathy and constipation with thalidomide or low blood counts with lenalidomide are well recognized and can again be managed by dose adjustment and growth factor support. Thrombosis is relatively common when an IMiD is employed with steroids,
and is particularly frequent when treating newly diagnosed patients and when using these drugs in concert with an anthracycline or alkylator. Thromboprophylaxis with immunomodulatory agents is therefore mandatory when used in combination therapy during induction. For patients at low risk of thrombosis receiving lenalidomide or thalidomide with daily aspirin (325 or 81mg), DVT rates are low, but still around 5-10%. For patients at higher DVT risk due to other factors such as prior history, immobility, use of anthracyclines, and smoking, then therapeutic anti-coagulation utilizing either low molecular weight heparin or coumadin is recommended. Patients on thalidomide or lenalidomide should also be monitored for hypothyroidism. Weight gain, insomnia, hyperglycemia, gastric irritation and anxiety may all need to be countered in patients receiving steroids. In addition to the comments above, some recently emerging literature suggests that avoidance of certain natural herbal supplements (e.g. green tea in bortezomib-treated patients) is prudent, as there may be antagonism.

It is worth remembering that amyloidosis is a potential complication in all myeloma patients and should be remembered as a possible contributing factor in patients presenting with hypotension, nephrotic range proteinuria, persistent diarrhoea, neuropathy, heart failure and fatigue.

**Practical Considerations**

In the United States, lenalidomide is not yet FDA approved in newly diagnosed patients, and its use is therefore “off label” but readily accessible. In many other countries access to lenalidomide and indeed bortezomib is more restricted. Under such circumstances the choice of initial therapy will be dictated by the realities of availability. For that reason
clinical trials may currently offer the best option for many patients and thus referral to a center with access to novel agents through trials is highly recommended. Outside of a trial setting cyclophosphamide, anthracyclines and steroids in younger patients are good choices for therapy to which we would encourage the addition of thalidomide, bortezomib or lenalidomide as available.

In countries in which novel agents have not yet been approved for up-front treatment, we recommend the use of the best available conventional induction regimens (e.g. VAD or VBMCP/VBAD or CTD, for 4-6 cycles) followed by ASCT; nevertheless if after the first initial 3-4 cycles the patient has achieved <PR the use of a salvage therapy based on novel agents (i.e. VD, RD, VTD or VRD) may be available before the transplant and is recommended.

**Summary**

In summary, we recommend that in patients with newly diagnosed MM active treatment should be reserved until symptoms and/or end organ dysfunction are present or imminent. When treatment begins, the goal is a rapid and high quality response with post induction consolidation and maintenance to sustain a durable CR being optimal. In pursuit of this goal, 3 drug triplets (VTD, RVD, CVD) are examples of highly active new combinations which can be employed, with high response rates and frequent CR. We believe that this approach will translate into longer survival and will be validated as clinical trials mature. For the majority of younger patients, consolidation with high dose melphalan and ASCT after 4-6 cycles of induction therapy is recommended. For patients failing to achieve CR after transplant or with high risk genetic features, routine maintenance therapy with thalidomide or lenalidomide should be considered.
prognostic risk profile of a patient should be determined, using both clinical and genetic features of the MM. As high risk patient may gain only modest benefit from ASCT alone a consolidation/maintenance strategy e.g. thalidomide or lenalidomide post induction therapy could be employed as an alternative. For patients who do not wish to pursue high dose therapy with low genetic risk and particularly patients who are unfit to pursue ASCT a durable response may be achieved using less toxic treatment approaches such as low dose dexamethasone with lenalidomide or bortezomib. In all patients careful attention to supportive care is critical to avoid early complications which compromise subsequent therapeutic outcome. Therapy must be individualized with geography, out of pocket cost, drug availability, social considerations (such as caregivers at home), co-morbidities and patient preference all being considered, as all may influence treatment choice. Fortunately today such choice exists with many potent regimens available. Many large phase 3 trials are underway in MM patients and should be strongly considered for all patients.
All authors were fully involved in writing this manuscript

Disclosures:
Paul Richardson: Advisory board and speakers bureau for Millenium and Celgene.
A. Keith Stewart: Consultant for Millenium, Proteolix; research support from Millenium; advisory board for Celgene, Genzyme; honoraria from Ortho Biotech.
Jesus San-Miguel: Advisory board for Millennium, Celgene, Janssen-Cilag.
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Table 1

Genetic tests to be performed in myeloma patients at diagnosis:

<table>
<thead>
<tr>
<th>Essential Tests for All Patients</th>
<th>Desirable Tests</th>
<th>Investigational Tests for Trials</th>
</tr>
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<tbody>
<tr>
<td>• Plasma cell specific FISH analysis</td>
<td>• Cytogenetics</td>
<td>• Gene expression profiling</td>
</tr>
<tr>
<td>o t(4;14) (p16;q32)</td>
<td>• Plasma Cell Specific FISH analysis</td>
<td>• aCGH/SNP arrays</td>
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<td>o t(14;16) (q32;q23)</td>
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### Table 2

**PHASE III TRIALS OF THALIDOMIDE CONTAINING MAINTENANCE AFTER ASCT**

<table>
<thead>
<tr>
<th>Study</th>
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<tr>
<td>BARLOGIE</td>
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<td>44</td>
<td>At 8 years</td>
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<tr>
<td>ATTAL</td>
<td>CONTROL</td>
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<td>At 3 years post randomization for EFS,</td>
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<td></td>
<td>4 years after diagnosis for OS</td>
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<tr>
<td></td>
<td>THALIDOMIDE</td>
<td>52</td>
<td>87</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1

Myeloma deposits are identified by PET-CT in a relapsing patient in the left femur, ribs, thoracic and lumbar spine, left iliac crest and a previously unsuspected extramedullary lesion is identified behind the left orbit.
Figure 2

The overall, >VGPR and nCR/CR rates for a selection of Phase II and Phase III trials incorporating novel agents is shown. A continuous improvement in response is seen with the combination of newer agents. A cautionary note is that many of these are small single center experiences and evidence that early responses translate into longer term survival is not yet available. References for these trials are as follows VAD\textsuperscript{71}, TD\textsuperscript{31}, RD\textsuperscript{43}, PAD\textsuperscript{37}, VTD\textsuperscript{6}, CVD\textsuperscript{38}, RVD\textsuperscript{36}, CVRD\textsuperscript{39}. 

![Graph showing response rates for different induction regimens]
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