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Current approaches to the initial treatment of symptomatic multiple myeloma

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SUMMARY

The treatment of newly diagnosed multiple myeloma has dramatically changed since the emergence of proteasome inhibitors and immunomodulatory drugs. Front-line combination regimens incorporating novel drugs such as thalidomide, bortezomib and lenalidomide, have significantly improved response rates and are the standard of care for induction regimens. Although the timing and role of autologous stem cell transplant are now being questioned, it remains an important part of the treatment paradigm in eligible patients. In addition, the concept of extended sequential therapy has recently emerged, including consolidation and/or maintenance in both the post-transplant setting and in nontransplant candidates. In this article we focus on management strategies in newly diagnosed multiple myeloma, including choice of induction regimens in transplant-eligible and -ineligible patients, as well as the role of autologous stem cell transplant, consolidation therapy and maintenance therapy.

General approach to initial therapy

Currently, only patients with symptomatic myeloma require treatment, with symptoms being defined by the presence of at least one of the following: bony disease, hypercalcemia, renal dysfunction or anemia, which can be attributed to the plasma cell disorder [1]. Those with asymptomatic or smoldering myeloma should be monitored closely without therapy [2], or treated in a clinical trial. When treatment is indicated, the decision about the choice of induction therapy is largely based on transplant eligibility. Patients who are below the age of 65 years and without significant comorbidities are considered transplant eligible, with some centers not setting an upper age limit. There is no established standard induction regimen for transplant-eligible and nontransplant candidates, although melphalan-based regimens are avoided in transplant-eligible patients [3]. While bortezomib and/or immunomodulatory drug-containing regimens are now established as superior to traditional regimens, the specific choice generally depends on the presence of adverse cytogenetics, age, renal dysfunction and other comorbidities, as well as physician preference.

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Heterogeneity of disease, risk classification & risk-adapted therapy

Multiple myeloma is a largely heterogeneous disease often classified into prognostic subtypes by its genetic and molecular aberrations. Cytogenetic abnormalities including monosomies, such as chromosome 13 deletion by standard cytogenetics, and/or t(4;14), t(14;16), 1q21 and del17p have been associated with poor prognosis and shorter survival, whereas those with trisomies and t(11;14) tend to have better outcomes [4,5]. Gene-expression profiling identified subsets of disease associated with recurrent patterns of pathway dysregulations [6] and created gene-expression profiling-based prognostic subgroups [7–9]. More recently, additional complexity was added by the recognition that not only the heterogeneity between subjects, but also within subjects may impact on the course of the disease and response to specific therapies [10].

While this heterogeneity is uniformly recognized, how to treat the different prognostic subgroups is not well established. Several risk-adaptive approaches have proposed treating patients with poor-risk disease more aggressively [11–13], with Mayo Stratification for Myeloma and Risk-Adapted Therapy (mSMART) being the most frequently used algorithm in the USA [11]. While these approaches are appealing, they have not been prospectively validated. Furthermore, there are reports that patients with standard-risk disease may also benefit from aggressive treatment [14]. Since there is currently no established standard for treatment based on prognostic subgroups, it might be prudent to apply caution when deciding on initial therapy and discussing with the patient the pros and cons and rationale of treatment choices, including current risk-adaptive strategies.

Prognostic relevance of initial response

Since the overall survival (OS) in patients with multiple myeloma is often late to emerge (thus, early estimates tend to lack statistical significance) and reflects cumulative disease reduction by initial treatment, as well as multiples lines of rescue, progression-free survival (PFS) has been accepted as a more reasonable end point in randomized trials [15]. However, there is vast evidence to support that achievement of complete response (CR) rate at some point of initial therapy is associated with significantly higher event-free survival (EFS), PFS and OS [16,17] and that the depth of response should be a major end point of initial therapy. This association has been demonstrated for both pretransplant [18,19] and post-transplant [20] response rates. In addition, not only the attainment of CR, but also its durability, is predictive of outcome, as demonstrated by the TT2 trial, where patients who maintained CR for 3 years or longer had significantly higher survival compared with those who relapsed within 3 years [21]. Furthermore, the difference between CR and nCR translated into longer EFS and OS [22]. With the incorporation of stringent complete response (sCR) into response criteria and the emergence of new techniques for detection of minimal residual disease (MRD) [23,24], the relevance of sCR and MRD may prove to be of even more prognostic value [24,25].

Induction regimens in transplant candidates

The goal of induction in transplant-eligible patients is to reduce the initial disease burden in order to achieve a durable response post-transplant, as well as to reverse organ damage and improve symptoms. Induction therapy is administered for 2–4 months prior to transplant, although the optimal duration of treatment is not well established. Two-drug novel combinations, including thalidomide plus dexamethasone (TD) and bortezomib plus dexamethasone (VD) [26,27], as well as three-drug novel regimens, including thalidomide plus adriamycin plus dexamethasone (TAD) and bortezomib plus adriamycin plus dexamethasone (PAD) [28,29], have shown good tolerability and superior response rates compared with previously used vincristine plus adriamycin plus dexamethasone (VAD).

Lenalidomide plus low-dose weekly dexamethasone (Rd) is also commonly used owing to its consistent efficacy, convenience and favorable toxicity profile [30,31], although none of the ongoing randomized studies with Rd versus other two- or three-drug regimens have been reported to date. VD may be favored to Rd in patients with renal insufficiency [32] or in those with unfavorable cytogenetics [14,33].

Two Phase III studies have demonstrated superiority of a three-drug induction regimen with bortezomib plus thalidomide plus dexamethasone (VTD) over TD [34,35], with pretransplant CR rates of 35 versus 14%, respectively, reported in one study [35]. Furthermore, the same three-drug combination using attenuated doses of bortezomib plus thalidomide (vtD) resulted in higher response rates compared with VD alone [36]. These pretransplant differences in response rates were carried over to the post-transplant period with CRs and/or very good partial response (VGPR) rates statistically higher in the three-drug arms, compared with two-drug induction arms. However, the impact of induction on time to events is less clear. Although both VTD versus TD trials demonstrated superior PFS in the VTD arms, in one of the trials [34], patients on the VTD arm received post-transplant VTD consolidation, whereas those on the TD arm received TD consolidation. However, the second trial suggests that PFS may be longer with VTD regardless of what maintenance therapy was used [35]. There was no difference in OS between both arms in both trials, although longer follow-up is required. Finally, a recent meta-analysis suggests that the addition of bortezomib to induction regimens in transplant-eligible patients improves response rates, PFS and OS [37].

Whether the addition of a fourth drug to a three-drug regimen will further improve treatment outcomes is not clear. The EVOLUTION Phase II randomized study compared two three-drug regimens, bortezomib plus cyclophosphamide plus dexamethasone (VCD or CyborD) and bortezomib plus lenalidomide plus dexamethasone (VRD), with a four-drug combination of bortezomib plus lenalidomide plus cyclophosphamide plus dexamethasone (VDCR). Overall, response rates were comparable between arms, with CR rates after four cycles of 22, 24 and 25%, respectively, with a trend to a superior CR rate of 47% in the modified VCD arm [38]. In another, single-arm Phase I/II trial, pegylated liposomal doxorubicin was added to lenalidomide plus bortezomib plus dexamethasone (RVD) in front-line treatment of myeloma, combining two active regimens: bortezomib plus pegylated liposomal doxorubicin plus dexamethasone (VDD) [18] and lenalidomide plus bortezomib plus dexamethasone [39] into RVDD [40]. After four cycles of treatment with this combination, response rates appeared better than historical response rates to RVD with a trend to superior PFS [40]. The overall activity and tolerability of RVD (or VRD) has been commonly recognized based on single arm Phase I/II trial and this regimen is among the most commonly used front-line treatments for newly diagnosed multiple myeloma with peripheral neuropathy as its most limiting toxicity. CyborD, or its variant VCD [38], has similar efficacy in single-arm Phase II studies and is almost as commonly used as RVD in clinical practice.

More recently, carfilzomib, a new generation proteasome inhibitor was approved for relapsed and refractory myeloma, and its combinations have emerged as another potential choice of initial therapy prior to transplant. Early results from single-arm Phase I/II clinical trials with carfilzomib plus cyclophosphamide plus thalidomide plus dexamethasone (CYCLONE), and carfilzomib plus thalidomide plus dexamethasone (CARTHADEX) [41], appear to place these regimens among the most active regimens prior to transplant.

A Phase I/II study of the combination of carfilzomib plus lenalidomide plus low-dose dexamethasone (CRd) in initial treatment of both transplant and nontransplant candidates, showed rapid and consistent efficacy, with 67% disease reduction after one cycle and 100%

of patients achieving PR, 88% achieving VGPR and 67% achieving nCR/CR at the completion of four cycles [24]. Per study design, most patients continued CRd treatment with excellent tolerability and improvement of the depth of response with continuation of treatment. After completion of eight or more cycles, 78% of patients reached at least a nCR and 61% sCR, with 92% of evaluated patients having no evidence of MRD by multiparameter flow cytometry. These response rates and early results of time to events are among the best reported to date, including results of treatment with sequential therapy with tandem transplant [24,34]. Importantly, even after up to 24 months of treatment with CRd, there was no emergence of clinically significant peripheral neuropathy. Although still early, the CRd regimen appears to signal a potential for significant improvement of treatment of multiple myeloma beyond existing strategies.

In summary, while there is a trend in clinical practice to use two-drug novel combination regimens for patients with standard-risk disease and three-drug bortezomib-based regimens in high-risk disease, it may be prudent to use a three-drug bortezomib-based combination regimen in all patients, regardless of risk assessment, with RVD or CVD being the most preferred combinations owing to good tolerability and consistently high response rates. While emerging data on carfilzomib for initial therapy are very promising, its role in the front-line setting requires further studies.

Autologous stem cell transplant

High-dose chemotherapy [42,43] with an autologous stem cell rescue is considered the standard of care in younger patients with myeloma and has been shown to not only increase response rates but also to prolong the OS compared with conventional chemotherapy [44,45]. Patients under the age of 65 years are generally considered fit for transplant [44,46–48]. However, many retrospective studies have shown that the decision whether to proceed with autologous stem cell transplant (auto-SCT) may need to be made on an individual basis and the ‘physiologic’ as opposed to the actual age [49–52].

In the era of novel active regimens, the role of transplant has been questioned. Most studies to date support the role of transplant as part of treatment strategy. It is clear that transplant further improves the depth of response, even after the most active front-line regimens, including VTD [53] and RVDD [40,53], providing a rationale for ongoing recommendations, including the current category 1 NCCN guidelines [54]. Recently, a randomized Phase III trial showed superior 18 month PFS but no difference in OS in the transplant arm after initial treatment with Rd compared with Rd followed by extended treatment with melphalan plus prednisone plus lenalidomide (MPR); however, further follow-up is needed [55].

There is also much debate as to whether transplant should be part of the initial therapy or if it can be delayed to the time of relapse. The only randomized trial completed to date to address the question of early versus late auto-SCT did not show a survival difference, although the EFS, average time without treatment and quality of life of patients undergoing an early transplant were superior [56]. A *post-hoc* landmark analysis of a randomized clinical trial of lenalidomide plus Rd or high-dose dexamethasone (RD) [31] showed no difference in survival in transplant versus nontransplant arms, although the authors later reported that 1-, 2- and 3-year survival probability favors early transplant [57]. A landmark analysis of Phase I/II trials of lenalidomide plus bortezomib plus dexamethasone [39] also demonstrated similar 18-month survival rates in patients with and without transplant; however, in both trials the sample sizes are small, follow-up period is relatively short and the results are subject to selection bias due to lack of randomization. In patients over the age of 65 years, oral therapy with melphalan plus prednisone plus thalidomide (MPT) was

superior to auto-SCT with reduced-dose melphalan [58]. In summary, further evidence is required to support delaying transplant to the time of relapse and this question is currently being addressed in an ongoing IFM/DFCI trial, in which transplant candidates receive initial RVD followed by transplant versus extended RVD [ref?].

Single versus tandem auto-SCT

Several studies have also addressed the role of an upfront, tandem transplant with inconsistent results [47,59–61]. A subgroup analysis, although not powered to detect this difference, suggested that a second transplant improves survival in patients who failed to achieve high-quality responses (nCR and VGPR) after the first transplant [59,60]. Although these studies have been criticized for drawing such conclusions, they remain the best available evidence we have to support a tandem transplant in this category of patients.

Allogeneic stem cell transplant

The role of allogeneic stem cell transplant (allo-SCT) in newly diagnosed multiple myeloma has been evaluated with mostly disappointing outcomes [61–65]. Even with the introduction of nonmyeloablative regimens, the risk of mortality and rates of GVHD remain too high compared with its poorly established benefits, in a disease that can now be controlled beyond 6–7 years in most patients [62,66,67]. Although in some trials, patients who received a reduced-intensity allogeneic transplant from a sibling donor following an autologous transplant had lower incidence of disease relapse compared with those who received a tandem autologous transplant, the allogeneic transplant arm had a higher cumulative incidence of nonrelapse mortality [63,68]. Also, while some showed a plateau in survival after an allogeneic transplant [69], others did not confirm this finding [64,65] and, at this time, its application is not recommended outside of clinical trials. A more detailed evaluation of allo-SCT is outside the aim of this article.

In summary, while upfront, single auto-SCT remains the standard of care in younger patients with multiple myeloma and tandem auto-SCT should be reserved for those who do not achieve at least a VGPR after the first transplant, the role of allo-SCT in upfront treatment of multiple myeloma remains investigational.

Treatment of nontransplant candidates

Oral melphalan plus prednisone (MP) [70], which was previously the standard of care in nontransplant candidates, has now been largely replaced by melphalan-based novel combination regimens. MPT was studied in six randomized trials, resulting in significantly higher response rates [58,71–76], and in three of the six trials, improved the OS [58,71,74]. Similar results were demonstrated in a meta-analysis where MPT resulted in a superior PFS and OS [77]. Although this combination was associated with high rates of grade 3 and 4 toxicities, including neutropenia and peripheral neuropathy [58,73], at lower doses of melphalan the treatment was more tolerable [73].

An alternative to MPT is a combination of bortezomib plus melphalan plus prednisone (VMP). In the VISTA trial, VMP was shown to be superior to MP with a 5-year OS of 46 versus 34%, respectively [14,78]. In addition, the survival benefit over MP in the trial was found to be 13.3 months, compared with the 6.6-month benefit with MPT [78]. The most common adverse effect of this regimen was peripheral neuropathy, with grade 3/4 occurring in approximately 13% of patients in the VMP arm, but improved in 79% of patients within 2 months and resolved completely in 60% of patients by 6 months [14,79]. On additional evaluation of this regimen, similar efficacy and lower rates of peripheral neuropathy were demonstrated with weekly bortezomib dosing [80].

There are currently no randomized data comparing VMP to MPT; however, VMP with weekly bortezomib has been compared with bortezomib plus thalidomide plus prednisone (VTP) [80] and bortezomib plus melphalan plus prednisone plus thalidomide (VMPT) [81]. A prospective trial comparing VTP with VMP, both followed by bortezomib-based maintenance, showed similar rates of CR/nCR (35 and 32%, respectively), and similar 3-year OS with a trend towards superior outcome in the VMP arm (65 and 74%, respectively) [80]. When compared with VMP, the four-drug regimen VMPT followed by bortezomib and thalidomide maintenance (the VMP arm did not receive maintenance) resulted in higher response rates and PFS, but no difference was noted for OS at 3 years [81]. Whether the addition of a fourth agent in induction, VT maintenance or both contributed to superior PFS is not clear; however a landmark analysis showed statistical benefit of VT maintenance [82].

Lenalidomide is also an attractive option in this population of patients. A prospective randomized trial of MPR versus MPR followed by lenalidomide maintenance (MPR-R) versus MP showed better response rates in the MPR versus MP arms (33 vs 12% achieved at least a VGPR, respectively) and superior PFS of 31,14 and 13 months in MPR-R, MPR and MP arms, respectively, although the OS was similar in all three arms at 3 years [83]. The role of the lenalidomide maintenance portion of this trial is discussed below.

Non-MP-based regimens such as Rd and RVD (VRD) are increasingly used in nontransplant candidates owing to their high efficacy and favorable side-effect profiles [31,39,84]. More recently, carfilzomib-based combinations including carfilzomib plus melphalan plus prednisone (CMP) [85] and carfilzomib plus cyclophosphamide plus dexamethasone (CCd) [86] have emerged as highly active in nontransplant patients based on early results from single-arm Phase I/II studies, although more data from prospective trials are needed to evaluate the efficacy of nonmelphalan-based regimens in transplant-ineligible patients, including the results of an ongoing MPT versus Rd trial.

In summary, melphalan-based novel regimens such as MPT, VMP and MPR-R, clearly established their superiority over MP. MPT and VMP are used as standard of care in many countries, with no evidence of clear superiority of one regimen over other. A role of VMPT-VT, MPR-R and other regimens including non-MP-based combinations in the front-line setting is emerging but needs further evaluation.

Role of consolidation & maintenance

Since the depth of response to treatment correlates with outcomes [87–89], both consolidation and maintenance therapies are now being employed to deepen the initial response and prevent relapse, respectively.

While the role of post-transplant consolidation has not been thoroughly explored, there is evidence that higher levels of CR can be obtained with additional therapy. In a randomized trial, bortezomib administered 3 months post-transplant for a total of six cycles, versus observation, increased CR/nCR rates from 20 to 45% [90]. VTD has also been evaluated in the post-transplant setting and significantly increased CR rates, as well as rates of molecular remission measured by PCR in a single-arm trial [91]. A more recent study by Cavo *et al.* demonstrated superiority of VTD induction followed by post-transplant VTD consolidation compared with TD induction followed by TD consolidation, and showed that VTD consolidation statistically contributed to deepening a response after transplant [34]. Finally, a single-arm study of RVD induction followed by two additional cycles of RVD post-transplant improved sCR/CR rates from 36 to 48% [92].

Maintenance therapy is defined as any treatment after completion of induction, with or without auto-SCT. Thalidomide maintenance has been evaluated in both the post-transplant

[93–97] and nontransplant settings [45,47–49] and although it prolonged PFS, the data for OS were inconsistent. Furthermore, treatment was overall poorly tolerated [93,94] and patients with unfavorable cytogenetics did not appear to benefit from therapy [96,97].

Lenalidomide maintenance post-transplant was studied in two separate Phase III, randomized trials and resulted in improvement in PFS in the lenalidomide group in both [98,99], and a survival benefit at 3 years (88 vs 80%) in one of the trials [99]. In transplant-ineligible patients, MPR-R significantly improved the median PFS compared with the nonmaintenance arms (MPR and MP) [83]. A landmark analysis provided statistical evidence of the significant contribution of lenalidomide maintenance to improved PFS in the MPR-R arm of the study [100]. An important point to note is that all three studies reported a higher risk of secondary malignancies in the lenalidomide arms, with an incidence of approximately 7–8% at 3 years [83,98,99].

The role of bortezomib maintenance was evaluated in a Phase III HOVON-65/GMMG-HD4 trial. Patients enrolled in the PAD induction arm received post-transplant bortezomib maintenance administered every 2 weeks for 2 years. At 2 years, the OS was 49% in the PAD and bortezomib maintenance arm compared with 34% in the VAD induction followed by thalidomide maintenance arm [29]. In the nontransplant setting, VT maintenance improved CR rates [81,101] and in one study contributed to prolonged PFS [101] and possibly OS [102].

In summary, both consolidation and maintenance therapies improve the depth of response after induction. The role of consolidation needs to be further explored in prospective trials before definite recommendations can be made. Lenalidomide maintenance is best supported by Phase III evidence, although the duration of maintenance therapy needs to be clarified. The role of thalidomide in maintenance is diminishing owing to tolerability. Currently, there is a lack of clear, randomized data to support the use of bortezomib in maintenance.

Conclusion & future perspective

Incorporation of immunomodulatory drugs and proteasome inhibitors into the treatment of multiple myeloma, as well as the emergence of sequential therapy including consolidation and maintenance, have significantly improved outcomes in both transplant and nontransplant candidates. Ongoing prospective evaluations are necessary to better define first the preferred initial treatment in both transplant and nontransplant settings, second the role of early versus late auto-SCT and third the role of consolidation, as well as the optimal maintenance and its duration. Finally, recent emergence of a new generation of agents including carfilzomib, ixizomib and elotuzmab will likely further expand the treatment choices for newly diagnosed multiple myeloma and contribute to ongoing improvements in treatment outcomes.

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■ of interest

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Practice Points

- The choice of initial therapy for symptomatic myeloma is still largely guided by eligibility for an autologous stem cell transplant, which remains the standard of care in younger patients with multiple myeloma.
- For all patients who are candidates for autologous stem cell transplant, triplet, bortezomib-based regimens with or without an immunomodulatory drug may be the most optimal.
- In nontransplant candidates, melphalan-based, novel drug combinations remain a reasonable option, although nonmelphalan induction regimens are currently being evaluated in this population.
- Post-transplant consolidation therapy can further improve the depth of response, although its role needs to be further explored in randomized trials.
- Post-transplant lenalidomide maintenance prolongs progression-free survival and overall survival, although its role is less established in nontransplant candidates.