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Novel Induction Regimens in Multiple Myeloma

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Abstract Multiple myeloma is the second most common hematologic malignancy and predominantly affects the elderly. The introduction of novel agents such as thalidomide, lenalidomide, and bortezomib has improved progression-free survival, overall survival, and quality of life in myeloma patients. Next generation agents such as carfilzomib hold further promise for increased depth and length of remission. Autologous stem cell transplant remains a useful tool in the treatment of multiple myeloma, but not all patients are eligible for this procedure. As therapy becomes more effective, determination of the right therapy in the right patient becomes paramount. The focus of this review is a critical analysis of combinations of the novel agents in the treatment of newly diagnosed multiple myeloma in both transplant eligible and ineligible patients.

Keywords Multiple myeloma · Transplant eligible · Transplant ineligible · Induction · Novel agents

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Introduction

Multiple myeloma (MM) accounts for 1 % of neoplastic diseases and 13 % of hematologic cancers [1]. It is a plasma cell neoplasm characterized by skeletal destruction, renal failure, and hypercalcemia [2]. The annual age-adjusted incidence in the USA is approximately 4–5 per 100,000, and each year, over 20,000 new cases are diagnosed in the USA. The incidence in African Americans is two to three times more than Caucasians, and the median age at diagnosis is 69 years old. In the past decade, the introduction of proteasome inhibitors and novel immunotherapies has revolutionized the treatment of multiple myeloma and improved overall survival [3]. However, MM remains an incurable disease in the vast majority of patients with median survival of 4 to 6 years.

The goal of treatment in MM is to control the disease, thereby ameliorating or eliminating symptoms, and to improve survival. High-dose chemotherapy, induction therapy, followed by single or double autologous hematopoietic stem cell transplantation (ASCT) has been standard frontline therapy for fitter patients with MM [4, 5]. In elderly or frail patients, ASCT is considered to be too toxic to undergo and primary induction therapy is typically continued until progression or intolerability.

Before there was access to the novel agents thalidomide, lenalidomide, and bortezomib, conventional chemotherapy (CC) options, such as melphalan + prednisone (MP) or vincristine-adriamycin-dexamethasone (VAD), produced relatively weak and short remissions [2]. Most patients with MM were treated either with MP or VAD, with the goal of partial response or disease stabilization. Few patients achieved complete remission (CR); expected overall survival (OS) was on the order of 30 months, and a small percentage of patients achieved durable complete remissions [6]. Furthermore, CC could not be continued for extended periods due to cumulative

chemotherapy toxicity and risk of stem cell damage promoting leukemogenesis [7].

The novel agents, in contrast to CC, are usually well tolerated, even for extended duration of therapy. They have also shown a high rate of deeper remission, especially in combination with alkylating chemotherapy or with each other, and responses often improve with increasing length of treatment [3, 8–15, 16•].

The approach to induction chemotherapy in patients with newly diagnosed MM is often separated by transplant eligibility. We explore novel induction regimens in both transplant eligible and ineligible candidates below.

Induction Regimens in Transplant-Eligible Patients

Thalidomide was first of the novel agents to be used following a single center study which showed a 32 % response rate as monotherapy in relapsed and refractory MM [17]. Following this seminal trial, thalidomide was further developed as the first of the immunomodulatory drug (IMiD) class of novel agents. The exact mechanism of action of the IMiDs is still not known; however, as a class, they have been shown to act as anti-inflammatory agents by decreasing production of pro-inflammatory cytokines (such as TNF-alpha and IFN-gamma), increasing anti-inflammatory cytokine production such as IL-10, stimulating T cell activation, and inhibiting angiogenesis [18]. The binding target of the IMiDs was recently found to be cereblon (CRBN), which was shown to be essential for its teratogenicity [19]. The absolute levels of CRBN and loss of CRBN expression have been correlated with response to IMiDs in patients with MM as well [20, 21]. The first test of thalidomide vs CC in a large setting was a double-blinded, placebo-controlled study which compared 470 newly diagnosed transplant-eligible MM patients randomized to receive thalidomide and dexamethasone vs dexamethasone alone. The combination of thalidomide + dexamethasone demonstrated higher overall response rate (ORR) at 63 vs 46 % and time to progression (median, 22.6 vs 6.5 months) [22]. There were more serious toxicities associated with thalidomide use however, most notably a increased rate of deep venous thrombosis (17 vs 3 %) and peripheral neuropathy (7 vs 4 %). Thalidomide was explored specifically as induction therapy for ASCT and was found to improve response rate during the pre-ASCT period (at least very good partial response 19 vs 14 %) and post-ASCT (60 vs 30.5 %) as compared to CC [23, 24]. There was no OS difference found between the groups however.

Lenalidomide is a derivative of thalidomide with a stronger influence on proinflammatory cytokine production and T and NK cell activation [25]. Lenalidomide in combination with dexamethasone produced impressive RR in first-line therapy in MM, with an ORR of 91 % and a CR rate of 6 % [8]. Lenalidomide + dexamethasone has also been shown to improve post-ASCT outcomes when compared to induction with thalidomide + dexamethasone [26]. Overall response rate to lenalidomide + dexamethasone was 80.3 vs 61.2 % for thalidomide + dexamethasone, and the use of lenalidomide + dexamethasone provided a 9-month increase in progression-free survival (PFS) as compared to thalidomide + dexamethasone (26.7 vs 17.1 months). Survival was also improved on lenalidomide + dexamethasone vs thalidomide/dexamethasone (median OS not reached vs 57.2 months, respectively). In addition to a higher response rate, lenalidomide was also more tolerable than thalidomide with less peripheral neuropathy resulting in longer treatment duration without increased toxicity.

Bortezomib is a slowly reversible inhibitor of the 26S subunit of the proteasome which works to increase the pool of ubiquinated proteins, leading to decreased protein clearance which can alter several critical cellular pathways, including NFkB activation [27]. Bortezomib + dexamethasone was shown in a single arm study to be a highly active regimen for upfront treatment of transplant-eligible patients with MM, with an overall response rate of 66 % and a CR rate of 21 % [28]. The most frequent adverse reactions to bortezomib include peripheral neuropathy and reactivation of herpes zoster infection. When combined with alkylating agents or with lenalidomide, bortezomib combination therapy is highly active, leading to overall response rates of approximately 90 % and CR rates of 40 %, providing an excellent platform for induction therapy prior to consolidation with transplant. For example, the HOVON-65 trial was a randomized phase 3 study that compared induction with VAD vs bortezomib + adriamycin + dexamethasone (PAD) [10]. Patients randomized to the VAD arm received thalidomide 50 mg daily maintenance post-ASCT while the PAD arm received bortezomib biweekly maintenance. Maintenance therapy was continued for up to 2 years post-ASCT. PAD compared favorably to VAD induction prior to ASCT, with superior CR rates pre-ASCT (31 vs 15 %) and post-ASCT (49 vs 34 %). After extended follow-up of 41 months, the PAD group was found to have a superior overall survival, with a 25 % decreased risk of death as compared to the VAD arm. Similar excellent results are seen in the combination of bortezomib and lenalidomide. A clinical phase I/II study of 66 patients receiving lenalidomide + bortezomib + dexamethasone (VRD) before transplantation estimated 18-month progression-free and overall survival for the combination treatment with/without transplantation at 75 and 97 %, respectively, with median follow-up of 21 months [12].

As shown above, three-drug combinations for induction have, for the most part, shown to be superior in overall response and PFS compared with two-drug inductions. In addition of PAD and VRD regimens, cyclophosphamide has been combined with bortezomib and dexamethasone (CyBorD)

with similarly active results. In one phase 2 study, CyBorD was shown to have an overall response rate of 88 % and a CR rate of 39 %. Another three-drug combination of clarithromycin, lenalidomide, and dexamethasone (BiRD) has been shown in a phase 2 study to have a comparable ORR of 90 %, with 39 % CR [15]. A retrospective analysis comparing continuous BiRD vs BiRD followed by ASCT at maximum response showed that PFS and OS were identical [29]. A case matched study which compared 72 patients at New York Presbyterian Hospital-Cornell Medical Center to patients at Mayo Clinic showed that BiRD vs lenalidomide + dexamethasone had better depth of response (CR 45 vs 14 %) and PFS (48.3 vs 27.5 months) with a trend toward longer overall survival (3-year OS 89.7 vs 73.0 %, *P* 0.170).

Although three-drug regimens have proven to be effective, likely more so than two-drug regimens in transplant-eligible patients, there is evidence that four-drug regimens may represent overtreatment and could be inferior to three-drug regimens due to increased toxicity. In the EVOLUTION study, a randomized phase 2 trial, bortezomib, cyclophoshamide, lenalidomide, and dexamethasone (VDCR) was compared to three-drug regimens of VRD, CyBorD, and a modified VDC which had an increased dosing schedule of cyclophosphamide than CyBorD [30••]. The study showed that VDCR had a similar response rate in terms of 1-year progression-free survival but was associated with more hematological toxicities in comparison to VDC and VDR. Of note, the modified VDC regimen achieved the best overall response, with almost half of the patients achieving complete remission but also had the smallest treatment arm, thereby necessitating additional studies to explore its superiority.

The latest three-drug regimen to be explored involves the use of Carfilzomib (carfilzomib), an epoxyketone-based and irreversible inhibitor of the 26S subunit of the proteasome [31]. In a phase 1/2 study of the combination of carfilzomib + lenalidomide + dexamethasone (CRD) in upfront treatment of transplant-eligible MM, ORR was impressive at 100 % in patients treated with at least 4 cycles of therapy [32•]. Stringent complete response (SCR) rate was 61 % in those patients completing 8 cycles of therapy. Also striking is that a significant proportion (90 %) of patients achieving CR had immunophenotypic remission (flow cytometry negative status for residual MM). Although still in evolution, the evidence is building that achievement of a minimal residual disease negative state in MM is a highly favorable prognostic outcome and will likely become the benchmark for further evaluation of treatment regimens [33••].

When discussing induction regimens for transplant-eligible multiple myeloma, one needs to take into account the potential impact of the drug combination on the ability to harvest stem cells [34]. Notably, it has been found that extended lenalidomide use (greater than 6 months) can significantly inhibit stem cell harvest after mobilization with the standard regimen of single agent filgastrim [35, 36]. Given this data, it is often suggested that hematopoietic stem cell harvest occur no later than after 4 cycles of a lenalidomide-based induction regimen [34]. Later studies have shown that either adding cyclophosphamide or plerixafor to filgastrim can abrogate the lenalidomide effect, regardless of the length of prior lenalidomide exposure and lead to adequate harvests to support two stem cell transplants [37, 38]. Given the data above, the length of induction therapy with lenalidomide is no longer a barrier to stem cell collection. There have been no data thus far showing that thalidomide, bortezomib, or carfilzomib have negative influence on the ability to collect stem cells.

Transplant Ineligible

Although many transplant centers have an age cutoff for transplant eligibility, it is well established that chronological age alone is not reliable in estimating life expectancy, functional reserve, or the risk of complications from cancer chemotherapy [39•]. Performance status does not necessarily correlate with age and is the most important determinant of transplant tolerability and potential for morbidity [40]. Co-existing medical issues, such as diabetes, cardiovascular disease, and limited mobility, can complicate the delivery of and reduce tolerability to chemotherapy [41]. In those patients who are deemed transplant-ineligible, MP was considered standard therapy since the 1960s and remained so for three decades [42]. The typical CR rate was <4 %, and median OS was only 29 to 36 months [43]. Still, a meta-analysis by the Myeloma Trialists' Collaborative Group, which analyzed data from large trials of various conventional chemotherapy regimens, found that no combination showed any survival advantage over MP [44]. More recently, a large randomized trial by the Intergroupe Francophone du Myélome (IFM) found no difference in OS between MP and dexamethasone-containing conventional chemotherapy regimens, and the morbidity associated with the dexamethasone-based regimens was significantly higher than that with MP [45]. Melphalan/prednisone and other conventional chemotherapy regimens are still considered acceptable initial treatment for patients who do not expect to undergo ASCT, but they generally should be reserved for a small number of patients with serious comorbidity and/or poor performance status [46]. Fortunately, novel agents have been successfully incorporated into modern treatment regimens for elderly patients with encouraging results.

The combination of thalidomide/dexamethasone has been compared with dexamethasone monotherapy and with MP in the elderly. When compared with dexamethasone alone, thalidomide/dexamethasone resulted in significantly higher response rates (63 vs 46 %) but grade ≥3 adverse events were more common with an 18 % rate of venous thrombotic events in the thalidomide/dexamethasone arm [47]. In the

comparison of thalidomide/dexamethasone with MP, ORR was higher at 68 vs 52 %; however, grade 3/4 toxicity was greater with thalidomide/dexamethasone, and OS was significantly shorter (41.5 vs 49 months) [48]. The combination of MP + thalidomide (MPT) has been tested in five randomized studies in the non-transplant-eligible population. The first of these studies, by the Italian Multiple Myeloma Study Group (GIMEMA), found that adding thalidomide to dexamethasone significantly improved the CR rate and ORR (defined here as ≥partial response) in patients 60 to 85 years of age [49]. However, there was no significant advantage with respect to OS after a median 38 months of follow-up.

In a separate trial, IFM 99–06, MPT significantly extended survival for older patients (65 to 75 years of age) with previously untreated multiple myeloma [50]. The MPT regimen was better than MP in terms of CR (16 vs 4 %) and OS (52 vs 33 months). Median follow-up (51.5 months) was substantially longer than that in the Italian study discussed above, and other differences included patient age (no patient older than 75 years vs 25 % patients with advanced age in the Italian study), number of MP cycles (12 vs 6), thalidomide dose (up to 400 vs 100 mg/day), and use of maintenance thalidomide in the Italian study [49, 50]. At the time of first relapse, about 15 % of patients were unable to receive salvage therapy, and as the IFM investigators note, this strongly suggests that optimum frontline treatment is of major importance in elderly patients with myeloma.

In the more recent IFM 01/01 trial, which was limited to patients ≥75 years of age, MPT as initial therapy again significantly prolonged OS (44 vs 29 months) compared with MP [51]. At the time of relapse, 81 % of patients in the MP group and 53 % of those in the MPT group received thalidomide, bortezomib, and/or lenalidomide, and survival time after progression was similar in the two groups. Again, this finding supports using the most active frontline treatment in elderly patients since effective salvage therapy may not recapture the PFS benefit of starting the most effective regimen at the outset. Given the strong OS benefit seen for MPT, this regimen became standard of care for non-transplant candidates.

Bortezomib has also been combined successfully with MP in non-transplant candidates with a proven survival benefit. In a randomized trial by San Miguel et al., bortezomib, melphalan-prednisone (VMP) was found to be superior to melphalan-prednisone with higher overall response (7 vs 35 %), complete response rates (30 vs 4 %, $P<0.001$), and a nearly 1 year (56.4 vs 43.1 months) improvement in overall survival in previously untreated transplant-ineligible patients [14, 52••].

Results of the combination of carfilzomib-MP have recently been reported in patients over 65 in a phase 1/2 study [53•]. The maximum tolerated dose of carfilzomib in this population was 36 mg/m^2 which is equivalent to the result found in the CRD study reported above in the transplant-eligible population. Dose-limiting toxicities were febrile and hypotensive infusion reactions at a dose of 45 mg/m^2. This combination was highly active, with an overall response rate of 90 %, a PFS of 21 months, and an estimated 3-year survival rate of 80 %. While longer follow-up is needed to accurately determine PFS and OS benefits, these results represent an exciting new option for the elderly.

Lenalidomide has also been combined with MP in this patient population. In the large MM-015 clinical trial, patients ineligible for ASCT were randomized to lenalidomide + MP followed by lenalidomide maintenance until disease progression (MPR-R) vs MPR for 9 months vs MP for 9 months [16•]. Overall response rate was higher for the lenalidomide containing regimens, 77 % MPR-R vs 68 % MPR vs 50 % MP. Importantly, length of treatment correlated tightly with progression-free survival, with the median PFS for MPR-R at 31 vs 14 months for MPR and 13 months for MP. The study was not powered to get information for OS however.

In contrast to the data presented for transplant-eligible patients, two-drug regimens may have equal to greater efficacy compared to three drugs in the elderly and frail. In the MM-020 study, 1623 patients were randomized to either lenalidomide/dexamethasone given until disease progression vs lenalidomide/dexamethasone for 72 weeks (18 cycles) vs MPT for 72 weeks [54••]. Continuous lenalidomide + dexamethasone was associated with higher progression-free survival (25.5 months) vs (20.7 months) in the 18-cycle lenalidomide + dexamethasone group vs 21.2 months in the MPT group. Continuous lenalidomide + dexamethasone was also associated with higher OS, with a hazard ratio of 0.75, and less grade 3 or 4 adverse events when compared to MPT. Thus, length of therapy in the elderly could be just as important as choice of agents used, similar to the findings seen in the MM-015 study discussed above.

The case for longer use, two drugs in the elderly is further supported by the UPFRONT study, which randomized non-transplant candidates to either bortezomib/dexamethasone (VD) vs bortezomib/thalidomide/dexamethasone (VTD) vs VMP for eight 21-day cycles, all followed by single-agent bortezomib maintenance [55•]. Interestingly, although patients on the VTD and VMP arms had deeper responses compared to VD (51 vs 40 vs 37 % VGPR or better response), PFS and OS were equivalent in all the arms: 1-year PFS estimates were 57.4 % (VD), 63.8 % (VTD), and 67.3 % (VMP); 2-year OS estimates were 73.7 % (VD), 73.6 % (VTD), and 77.6 % (VMP). Patients assigned to the VD arm were able to receive a median of 8 cycles of therapy, as compared to 6 for VTD and 7 for VMP which again argues that length of therapy may be just as important for outcomes as choice of therapy in the elderly. Since length of therapy naturally correlates with tolerability, a two-drug choice for the elderly or frail, be it bortezomib/dexamethasone or lenalidomide/dexamethasone given until disease progression, is preferred in most instances,

pending further maturation of the carfilzomib-MP combination data. The CLARION study (Phase 3 Study of Carfilzomib, Melphalan, Prednisone vs Bortezomib, Melphalan, Prednisone in Newly Diagnosed Multiple Myeloma) is a phase 3 multicenter, open-label randomized clinical trial which began in March 2013 evaluating efficacy and toxicity of carfilzomab, melphalan and prednisone (CMP) vs bortezomib, melphalan, and prednisone (VMP) in transplant-ineligible patients with newly diagnosed multiple myeloma. The results of the CLARION study will further examine the safety of CMP in the elderly; however, without a comparison trial, CMP cannot be said to be more efficacious than car-dexamethasone alone in the same population.

A bevy of new agents are on the horizon for the treatment of MM and have already shown promise in trials in relapsed or refractory patients [56]. Such new therapeutics include ixazomib (a boronic acid proteasome inhibitor similar to bortezomib which is available orally), pomalidomide (an IMiD with more powerful immunomodulatory activity than lenalidomide), and oprozomib (an oral epoxyketone proteasome inhibitor, similar to carfilzomib). Of particular interest in the relapsed or refractory population are two new monoclonal antibodies against MM currently being tested in clinical trials. Elotuzumab, an antibody against SLAMF7, and daratumomab, an antibody against CD38, both target malignant plasmacytes with high specificity and may synergize with available agents to enhance overall response. The agents listed above have not been tested in the upfront setting however, and more data is needed before commentary can be made as to their role in the induction.

Conclusion

The introduction of novel therapies for the treatment of multiple myeloma in the last 15 years has drastically improved median survival time and prognosis of patients with MM. In transplant-eligible patients, the three-drug regimens CyBorD, RVD, and BiRD appear to be the most effective with tolerable adverse effect profile and PFS benefit. Carfilzomib in combination with lenalidomide and dexamethasone has been shown to induce deep responses to the point of negative minimal residual disease state on flow cytometry and thus raises the bar for further induction therapy testing.

In transplant-ineligible patients, continuous use of two-drug regimens, bortezomib/dexamethasone or lenalidomide/dexamethasone, have shown superior overall response and progression-free survival with enhanced tolerability compared to three-drug regimens. Until the data for carfilzomib-MP is mature, we would recommend using a two-drug regimen in the frail and elderly patient with MM.

New agents for the treatment of MM are under investigation in the relapsed or refractory disease state. As these agents are approved and move to the upfront setting, we can expect to yet more exciting and promising results for both the transplant eligible and ineligible patient population.

Compliance with Ethics Guidelines

Conflicts of Interest Karie D. Runcie declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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