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Review

Moving Toward Continuous Therapy in Multiple Myeloma

Francesca Bonello, Giusy Cetani, Luca Bertamini, Francesca Gay, Alessandra Larocca*

Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy

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ABSTRACT

The introduction of novel agents, characterized by favorable toxicity profiles and higher manageability compared to conventional drugs employed in the past, has considerably changed the treatment paradigm for multiple myeloma. Continuous therapy currently represents the standard approach for myeloma patients both at diagnosis and at relapse. In younger patients, long-term maintenance after autologous transplantation significantly improved progression-free survival and overall survival compared to observation. Also in transplant-ineligible patients, continuous treatment with combinations of newer agents and maintenance treatment following a more intense induction phase proved to be superior as compared to fixed-duration therapy. Maintenance and continuous therapy at diagnosis have shown to deepen responses and suppress minimal residual disease. At relapse, continuous therapy allowed better disease control over time. This review covers the main evidence supporting the use of continuous therapy in multiple myeloma as well as the open issues, such as the optimal agents to be used and the optimal candidates for receiving them.

1. INTRODUCTION

Multiple myeloma (MM) accounts for approximately 13% of hematological malignancies, having an incidence of 6.9:100000 people/year, with 32,110 new cases estimated in 2019 [1]. Although treatment options broadly expanded in the last decades, with a significant improvement in overall survival (OS), patients still experience relapses after first-line therapy [2].

Traditionally, conventional therapies were administered for a fixed duration of time/cycles due to low manageability and tolerability. [3–6].

With the introduction of novel agents, continuous therapy has emerged as an effective approach, both in the upfront treatment and at relapse.

Continuous therapy includes two different strategies according to patient characteristics and treatment plan. The first, defined as "maintenance," consists of long-term administration of a reduced-intensity regimen with one or more drugs after induction and consolidation therapy, in patients either responsive or non-progressing. Maintenance therapy plays an important role in transplant-eligible (TE) patients during first-line treatment [7], since its goal is to prolong response and survival. Indeed, in these patients, the main objective of first-line therapy is to deepen treatment response as much as possible, leading to minimal residual disease (MRD) negativity. Maintenance therapy can be a valid strategy to sustain MRD negativity achieved after autologous stem-cell transplantation (ASCT) and, in some cases, to enable MRD negativity in patients remaining MRD positive after induction/consolidation.

In transplant-ineligible (TNE) patients, continuous therapy usually consists of a prolonged administration of the same treatment regimen until disease progression or intolerance. In these patients, the choice of therapy is tailored according to patients' frailty status, in order to preserve quality of life [8]. Maintenance treatment has also been evaluated in this patient setting, proving to be effective in terms of progression free-survival (PFS) and good tolerability. Following the results of the ALCYONE trial and the approval of daratumumab combined with the triplet bortezomib-melphalan-prednisone (VMP), maintenance treatment for TNE patients is thus entering the standard clinical practice. At relapse, obtaining MRD negativity is more difficult due to the progressive selection of resistant clones. In this setting, continuous treatment has traditionally aimed at disease control over time, with a favorable toxicity profile, and this remains true for heavily pretreated patients. In early relapses, however, the administration of newer combination regimens with novel agents—including the second-generation proteasome inhibitor (PI) carfilzomib or the anti-CD38 monoclonal antibody (mAb) daratumumab—allowed the achievement of deep responses, with complete response (CR) rates ranging from 20% to 43% [9–14]. Remarkably, with daratumumab-based combinations, the MRD-negative status was achieved in 12–26% of relapsed patients [11–14].

The optimal drug or combination as maintenance therapy should be convenient, with a good safety profile, thus determining optimal compliance and tolerability. Several trials have evaluated maintenance, showing the benefit of long-term novel agent-based

* *Corresponding author. Email:* alelarocca@hotmail.com
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treatment in both TE patients, and elderly TNE patients. Nevertheless, direct comparisons of drugs or regimens as maintenance are lacking.

In this review we analyze the efficacy and safety data of continuous therapy with novel agents, both in newly diagnosed (ND) and relapsed MM patients, and we address the major open controversies related to this therapeutic approach.

2. CONTINUOUS THERAPY FOR NEWLY DIAGNOSED MYELOMA PATIENTS

The main trials with continuous therapy in newly diagnosed multiple myeloma (NDMM) patients are summarized in Table 1. The main ongoing trials with continuous therapy are summarized in Table 3.

2.1. Continuous Therapy Following ASCT

2.1.1. Immunomodulatory Drugs

Due to their oral administration, immunomodulatory drugs (IMiDs) have always been considered the optimal candidates for maintenance after high-dose therapy and ASCT.

In the IFM-9902 trial, thalidomide maintenance was compared to observation in 597 NDMM patients undergoing ASCT. Thalidomide was given daily at 400 mg with dose reductions according to patient's tolerance. A significant advantage in terms of event-free survival (EFS; 3-year rate: 52% vs 37%, $p = 0.002$) and OS (4-year rate: 87% vs 75%, $p = 0.04$) was observed in the maintenance arm compared to the control group. However, patients receiving thalidomide experienced high rates of toxicity, particularly peripheral neuropathy (68%), asthenia (34%) and constipation (20%), which led to maintenance discontinuation in more than one third of patients [15].

In the MRC IX trial, 820 NDMM patients received age- and performance status-tailored induction treatment, and then were randomized to maintenance with thalidomide (50 mg daily) versus no maintenance. The maintenance arm showed a better PFS compared to the control arm (median PFS: 23 vs 15 months, $p < 0.001$), while no advantage was seen in terms of OS (OS was inferior compared to the control arm in the case of adverse cytogenetics). Moreover, thalidomide was scarcely tolerated, with a median duration of maintenance of 7 months and a discontinuation rate of 52%. The main limiting toxicity was peripheral neuropathy (27% of patients) [16].

Table 1 | Main clinical trials exploring continuous therapy in newly diagnosed myeloma patients.

Trial	Number of Patients	Trial Design	Median PFS (Months)	Median OS (Months)
Transplant-eligible patients				
IFM-9902 [15]	597	Thalidomide vs observation after ASCT	3y EFS 52% vs 37% ($p < 0.002$)	3y OS 93% vs 87% ($p = 0.04$)
MRC IX [16]	820	Thalidomide vs observation after ASCT/chemotherapy	23 vs 15 ($p < 0.001$)	NR ($p = 0.4$)
ALLG MM6 [17]	269	Thalidomide-prednisone vs prednisone after ASCT	3y PFS 42% vs 23% ($p < 0.001$)	3y OS 86% vs 75% ($p = 0.004$)
IFM 2005-02 [20]	614	Lenalidomide vs placebo after ASCT	41 vs 23 ($p < 0.001$)	4y OS 73% vs 75% ($p = 0.70$)
RV-MM-PI-209 [21]	273	Lenalidomide vs observation after ASCT or high-dose chemotherapy	41.9 vs 21.6 ($p < 0.001$)	3y OS 88.0% vs. 79.2%; ($p = 0.14$)
CALGB 100104 [22]	460	Lenalidomide vs placebo after ASCT	46 vs 27 ($p < 0.001$)	3y OS 88% vs 80% ($p = 0.03$)
Myeloma XI [24]	2568	Lenalidomide vs observation after ASCT	57 vs 30 ($p < 0.001$)	3y OS 87.5% vs 80.2% ($p = 0.01$)
HOVON 65 [26,27].	827	Borterzomib vs thalidomide after ASCT	35 vs 28 ($p = 0.002$)	91 vs 82 ($p = 0.04$)
GEM05MENOS65 [28]	390	Bortezomib-thalidomide vs thalidomide vs interferon	51 vs 40 vs 33 ($p = 0.003$)	5y OS 78% vs 72% vs 70% ($p = 0.3$)
TOURMALINE-MM3 [33]	656	Ixazomib vs placebo after ASCT	26.5 vs 21.3 ($p = 0.002$)	Immature data
Transplant-ineligible patients				
GISMM2001-A [37,38]	255	Thalidomide vs observation after induction	21.8 vs 14.5 ($p = 0.004$)	45 vs 47.6 ($p = 0.79$)
MM-015 [41,42]	307	Lenalidomide vs observation after induction	31 vs 13 ($p < 0.001$)	3y OS 70% vs 62% (p NS)
Myeloma XI [24]	1852	Lenalidomide vs observation after induction	26 vs 11 ($p < 0.001$)	3y OS 66.8% vs 69.8% ($p = 0.88$)
FIRST [43,44]	1623	Rd vs Rd18 vs MPT	26 vs 21 vs 22 ($p < 0.001$)	59 vs 62 (p NS) 59 vs 49 ($p = 0.02$)
GIMEMA-MM-03-05 [47,48]	511	VMPT-VT vs VMP	35 vs 25 ($p < 0.001$)	5y OS 61% vs 51% ($p = 0.001$)
ALCYONE [56]	706	Dara-VMP vs VMP	NR vs 18 ($p < 0.001$)	Immature data
MAIA [57]	737	Dara-Rd vs Rd	NR vs 31.9 ($p < 0.001$)	Immature data

Abbreviations: PFS, progression-free survival; EFS, event-free survival; OS, overall survival; ASCT, autologous stem-cell transplantation; NR, not reached; R, lenalidomide; d, dexamethasone; V, bortezomib; M, melphalan; P, prednisone;; T, thalidomide; NS, not significant; Dara, daratumumab; Rd 18, Rd 18 cycles; y, years.

In the ALLG MM6 trial, patients were randomized to maintenance with thalidomide plus prednisone versus prednisone alone after ASCT [17]. Increased PFS (3-year PFS: 42% vs 23%, hazard ratio (HR) 0.5, p < 0.001) and OS (3-year OS: 86% vs 75%, HR 0.41, $p = 0.004$) were observed with thalidomide-prednisone.

A meta-analysis of five studies exploring thalidomide maintenance confirmed the advantage in terms of PFS [16]. However, data on OS remain controversial. Thalidomide is not approved as maintenance after ASCT. It could be an option for patients with standard-risk cytogenetics, since it was demonstrated to improve PFS as compared to observation in clinical trials. On the other hand, data on its use in patients with high-risk cytogenetics suggested that it could impair the PFS-2 (PFS calculated from time of relapse also called PFS-2) and OS by selecting resistant clones. A consensus paper by the International Myeloma Working Group (IMWG) discouraged its use in this subset of patients [18]. Moreover, its toxicity profile, especially in terms of peripheral neuropathy, limits its use in the long term. Despite a longer duration of disease control, a worse quality of life was reported in patients receiving thalidomide maintenance versus observation [19].

Lenalidomide is a second-generation IMiD, with a more favorable toxicity profile than thalidomide. Maintenance with lenalidomide after ASCT has been evaluated in large clinical trials. In the French study by Attal and colleagues, PFS was significantly higher in the maintenance arm compared to placebo (median PFS: 41 vs 23 months, HR 0.50, $p < 0.001$), even if the OS was similar in the two groups (3-year OS: 80% vs 84%, p 0.29). Main grade 3–4 adverse events (AEs) related to lenalidomide were hematologic (58% vs 23%, $p < 0.001$), and discontinuation rates due to toxicity were 27% in the lenalidomide versus 15% in the placebo group [20]. In the Italian trial, 273 patients were randomized to lenalidomide maintenance versus observation, after induction followed by ASCT or consolidation with melphalan-prednisone-lenalidomide (MPR). Patients receiving lenalidomide maintenance showed a significant advantage in terms of PFS (median PFS: 41.9 vs 21.6 months, HR 0.44, $p < 0.001$) with no advantage in terms of OS. However, they experienced a higher rate of toxicity, particularly neutropenia (23% vs 0) and rash (4% vs 0), although, only 5% of patients discontinued lenalidomide due to AEs [21]. McCarthy and colleagues proved that maintenance with lenalidomide has a significant advantage, both in terms of time to progression (TTP: 46 vs 27 months, HR 0.48, $p < 0.001$) and OS (3-year probability: 88% vs 80%, HR 0.62, $p = 0.03$) compared to placebo [22].

A meta-analysis of the three trials with updated follow-up (median 80 months) showed a median PFS of 53 months for patients receiving lenalidomide maintenance versus 24 months in the observation/placebo groups (HR 0.48, $p = 0.001$) with a consistent benefit also in OS (NR vs 86 months, HR 0.75, $p = 0.001$) [23].

In the Myeloma XI study, TE patients received maintenance with lenalidomide versus observation after ASCT. After a median follow-up of 31 months, the median PFS was 57 months with lenalidomide and 30 months with observation (HR 0.48, $p < 0.0001$) and the 3-year OS was 87.5% and 80.2%, respectively (HR 0.69, $p = 0.01$) [24].

An Italian study observed that adding steroids to lenalidomide main tenance did not improve efficacy. Furthermore, long-term steroids administration was not well tolerated, with more than a third of patients requiring prednisone dose reductions during the study [25].

Lenalidomide maintenance at the dose of 10 mg daily until disease progression has been approved by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), since it demonstrated a significant PFS and OS advantage compared to observation/placebo and a favorable toxicity profile. The benefit of lenalidomide maintenance in high-risk patients is still debated.

2.1.2. Proteasome Inhibitors

The HOVON-65/GMMG-HD4 study evaluated the use of bortezomib as maintenance. NDMM patients underwent maintenance with thalidomide (50 mg/day) versus bortezomib (1.3 mg/m^2 every 15 days) after ASCT for up to 2 years. Bortezomib maintenance showed better PFS (35 vs 28 months, HR 0.75, $p = 0.002$) and OS (91 vs 82 months, HR 0.77, $p = 0.049$) compared to thalidomide [26,27]. This benefit was particularly relevant for patients with myeloma-related renal impairment and unfavorable cytogenetics (del17), whereas there was only a trend for improved OS in patients with t(4;14) and 1q gain. Rates of maintenance discontinuation due to AEs were lower in the bortezomib group (11% vs 30%, $p < 0.001$).

A Spanish study evaluated maintenance with bortezomib plus thalidomide (VT) compared to thalidomide alone or interferon after ASCT. The VT arm obtained a better median PFS (51 vs 40 vs 33 months respectively, $p = 0.003$) but was burdened by a higher rate of peripheral neuropathy (49 vs 34% in the thalidomide arm) [28]. Bortezomib is not approved as maintenance treatment after ASCT. According to the above results, it represents an interesting option, especially for high-risk patients. Remarkably, bortezomib has never been evaluated as continuous treatment until disease progression, due to concerns about its long-term tolerability (maximum duration of bortezomib maintenance was 2 years).

The second-generation PI carfilzomib is currently under evaluation in the frontline setting, and its role in maintenance is being assessed [29].

In the FORTE trial, patients are randomized to receive carfilzomib-lenalidomide-dexamethasone (KRd) induction and consolidation with and without ASCT, or carfilzomib-cyclophosphamide-dexamethasone (KCd) induction and consolidation including ASCT, followed by maintenance with carfilzomib plus lenalidomide *versus* lenalidomide alone. The trial is ongoing, and preliminary data showed impressive response rates, which were higher in the groups receiving KRd with and without ASCT compared to KCd [30]. Of note, a phase I/II trial is currently investigating MRD status as a guide for frontline KRd treatment duration [31]. Carfilzomib maintenance is under evaluation also in combination with mAbs such as isatuximab in the ongoing GMMG-CONCEPT trial [32]. Results from these trials will shed light on the role of carfilzomib and its use as maintenance approach.

Ixazomib is an orally available third-generation PI. In the phase III, randomized TOURMALINE-MM3 study, NDMM patients received maintenance with ixazomib or placebo following ASCT for up to two years. After a median follow-up of 31 months, median PFS was 26.5 months in the ixazomib arm *versus* 21.3 months in the placebo arm (HR 0.72, $p = 0.0023$) [33]. The Spanish group is evaluating maintenance with lenalidomide-dexamethasone (Rd) with or without ixazomib after ASCT (NCT02406144). Maintenance duration will be MRD driven, with MRD-negative patients at 2 years

stopping maintenance and MRD-positive patients continuing Rd for up to 5 years.

A phase I/II study by the US team evaluated ixazomib-lenalidomide-dexamethasone (IRd) followed by single-agent ixazomib maintenance in patients with NDMM, and showed a median PFS of 35.4 months. During maintenance, an improvement in the CR rate was observed (from 28% to 44%), thus prolonging long-term outcomes. Ixazomib was well tolerated, with few AEs and no patient discontinuing maintenance due to toxicity [34]. As in the TOURMALINE-MM3, no second primary malignancies (SPM) were noted with single-agent ixazomib maintenance.

Ixazomib represents a promising candidate for maintenance treatment due to its oral administration and favorable results from clinical trials; consequently, it could enter the market in the near future.

2.1.3. Monoclonal Antibodies

The rising interest in the use of mAbs as maintenance strategy prompted the development of several ongoing clinical trials. The CASSIOPEIA trial evaluates the addition of the anti-CD38 mAb daratumumab to standard bortezomib-thalidomide-dexamethasone (VTd) as induction regimen followed by ASCT and, subsequently, maintenance treatment with daratumumab versus observation [35]. The MRD-negativity rate was significantly higher in the daratumumab-VTd arm versus VTd arm (64% vs 44%, $p < 0.00001$). Data on PFS are not mature yet, although a significant reduced risk of progression was observed in patients in the daratumumab group (HR 0.47, $p < 0.0001$). Data on maintenance are not yet available. With the present follow-up, adding daratumumab to VTd does not seem to increase overall toxicity.

The ongoing phase II GRIFFIN trial is comparing induction with daratumumab in combination with bortezomib-lenalidomide-dexamethasone (VRd) versus VRd. After ASCT, patients in the daratumumab-VRd arm will receive daratumumab and lenalidomide maintenance, while in the control arm patients will receive lenalidomide alone (NCT02874742).

Two phase III trials with daratumumab are ongoing and recruiting patients. The EMN18 study has been designed to compare daratumumab plus bortezomib-cyclophosphamide-dexamethasone (VCd) with standard VTd induction followed by ASCT and maintenance with ixazomib with or without daratumumab. The Perseus trial will compare daratumumab-VRd followed by daratumumab and lenalidomide maintenance to VRd followed by lenalidomide maintenance. Daratumumab discontinuation during maintenance will be MRD-driven.

Anti-SLAMF7 elotuzumab-based maintenance after ASCT is currently under evaluation as well. A phase II study of elotuzumab and lenalidomide as maintenance after ASCT shows that this combination is well tolerated with more than one third of patients improving their response during maintenance [36].

2.2. Continuous Therapy in TNE Patients

2.2.1. Immunomodulatory Agents

Thalidomide was the first IMiD evaluated as continuous therapy in elderly patients. An Italian study compared induction with melphalan-prednisone-thalidomide (MPT; six cycles) followed by thalidomide maintenance versus standard melphalan-prednisone (MP; six cycles) without maintenance. A significant PFS advantage was observed in patients receiving thalidomide maintenance versus control group (21.8 vs 14.5 months, $p = 0.004$) without benefit in terms of OS (45 vs 47.6 months, $p = 0.79$). Moreover, median survival from progression was shorter in the MPT-T arm (11.5 vs 24.3 months, $p = 0.01$), suggesting that relapses after thalidomide-containing regimen could be more chemo-resistant [37]. In the thalidomide arm a higher rate of grade ≥3 AEs was reported (48% vs 25%, $p < 0.001$), particularly in terms of venous thromboembolism (12% vs 2%, $p = 0.001$), infections (10% vs 2%, $p = 0.01$) and peripheral neuropathy (8% vs 0%, $p = 0.001$) [38]. In the Myeloma IX trial, thalidomide maintenance for TNE patients was compared to observation following induction with dose-reduced cyclophosphamide-thalidomide-dexamethasone (CTd) or MP. Median PFS was 11 versus 9 months (HR 1.35, $p = 0.014$) and median OS 38 versus 39 months (HR 1, $p = 0.99$). The median duration of maintenance was short (6 months), mainly because of treatment-related AEs [16].

Lenalidomide represents a better candidate for continuous therapy due to its more favorable toxicity profile, especially in terms of neurological toxicity, as demonstrated in two randomized trials comparing MPT followed by thalidomide maintenance with MPR followed by lenalidomide maintenance [39,40].

In the MM-015 trial, induction with MPR followed by lenalidomide maintenance was compared to MPR and to MP without maintenance. The median PFS was 31 months in the MPR-R arm versus 13 months for MPR (0.49, $p < 0.001$) and 14 months for MP (HR 0, 40, $p < 0.001$). Lenalidomide maintenance was associated to a consistent PFS advantage compared with placebo (26 vs 7 months, $p < 0.001$) and was well tolerated. However, the 3-year OS probability was not significantly different between the three arms (70% with MPR-R, 62% with MPR, and 66% with MP) [41,42].

The more recent phase III Myeloma XI trial investigated the role of lenalidomide maintenance versus observation in TNE patients after induction with CRD or CTD. The median PFS was 26 months with lenalidomide and 11 months with observation (HR 0.44, $p < 0.0001$), but no significant difference in OS was seen (3-year OS: 66.8% vs 69.8%, HR 1.02, $p = 0.88$) [24]. In TNE patients, maintenance with IMiDs is not approved. Evidence from clinical trials suggested that maintenance with lenalidomide could be beneficial in terms of PFS and that this drug is better tolerated than thalidomide. Just as with TE patients, concerns emerged about the prolonged upfront thalidomide use in high-risk patients, due to the possibility of selecting resistant clones. To date, the available data on OS did not show a clear benefit of maintenance treatment with either thalidomide or lenalidomide.

Apart from being adopted as maintenance strategy after induction without ASCT, lenalidomide was also evaluated as continuous frontline treatment. In the phase III FIRST trial, lenalidomide-dexamethasone (Rd) treatment until disease progression or intolerance was compared to Rd administered for 18 cycles and to standard MPT for 12 cycles. In the Rd arms, lenalidomide was administered at 25 mg daily on days 1–21 of 28-day cycles. Continuous Rd proved to be more effective than Rd18 and MPT in terms of PFS (median PFS: 26 vs 21 vs 22 months respectively, HR for continuous Rd vs MPT 0.69, $p < 0.001$; and HR for continuous Rd vs Rd 18 0.70, $p < 0.001$) [43]. The time to next treatment (TTNT) was

approximately 10 months longer with continuous Rd (36.7 months) compared to Rd18 (28.5 months) [44]. The median OS was significantly longer in the continuous Rd group versus MPT group (59 vs 49.1 months, HR 0.78, $p = 0.02$). However, no significant differences were reported in terms of OS between continuous Rd and Rd18 (59 vs 62 months, HR 1.01, 95% confidence interval [CI] 0.86–1.20). Patients treated with Rd experienced a lower rate of grade ≥3 AEs compared to MPT, particularly in terms of neutropenia (28% vs 45%) and neuropathy (1% vs 9%), whereas infections were more frequent (29% vs 17%). Grade 3–4 infections were more frequent with continuous Rd than Rd18. Following the results of the FIRST trial, Rd as continuous therapy became one of the standards of care for the upfront treatment of TNE patients. Moreover, Rd represents the backbone for the triplets under evaluation in major phase III trials with novel agents such as mAbs (daratumumab) and PIs (ixazomib).

Part of long-term AEs associated to continuous Rd treatment are likely driven by glucocorticoids. Indeed, steroids are not easily tolerated in the long term, especially in elderly patients. Preliminary results of the phase III RV-MM-PI-0752 trial showed that discontinuing dexamethasone after the first cycles of Rd did not impair treatment efficacy (PFS: 18.3 months with Rd-R vs 15.5 months with Rd, HR 0.93, p = ns), but resulted in less treatment-related AEs and less dose reductions and discontinuations [45]. The doublet Rd administered until disease progression has been approved by both FDA and EMA and represents one of the standards of care for TNE patients.

2.2.2. Proteasome Inhibitors

The triplet VMP, administered as fixed-duration therapy for 9 cycles, represents one of the standards of care for TNE MM patients [46]. Bortezomib maintenance after a bortezomib-based induction has been evaluated in clinical trials.

The GIMEMA study compared standard induction with VMP plus thalidomide (VMPT) followed by maintenance with bortezomib and thalidomide (VT) versus VMP alone. The median PFS was 35.3 versus 24.8 months (HR 0.58, $p < 0.001$), and the 5-year OS was 61% versus 51% (HR 0.70, $p = 0.01$). In the updated analysis, VMP-VT treated patients also reported a benefit in terms of OS. Remarkably, the difference between median PFS and TTNT was approximately 1 year in the VMPT-VT group and 3 months in the VMP group. Toxicity rates were higher in the VMP-VT group, especially in terms of neutropenia and peripheral neuropathy, with higher treatment discontinuation rates (28% vs 16%, $p = 0.001$). However, less than 5% of patients experienced new or worsened toxicity during maintenance [47,48].

Bortezomib maintenance was evaluated in combination with thalidomide (VT) versus prednisone (VP) after induction with VMP or VTd in the GEM05MAS65 trial. No significant differences in terms of PFS (39 vs 31 months, $p = 0.1$) and OS (5-year OS: 69% vs 50%, $p = 0.1$) were seen between the two maintenance strategies. Overall, patients improving their response during maintenance had a significantly longer PFS compared to patients without response upgrade (47 vs 32 months, HR 0.56, $p = 0.02$), as well as a prolonged OS (5-year OS: 81% vs 54%, HR 0.4, $p = 0.02$) [49].

The second-generation PI carfilzomib is currently approved in the relapsed/refractory (RR) setting. Two phase I/II trials explored the efficacy and safety of the combination KCd followed by carfilzomib maintenance in NDMM TNE patients [50,51]. One trial used the once-weekly schedule of carfilzomib, whereas the other used the twice-weekly schedule. Both trials demonstrated a high efficacy profile (median PFS: 35.7 and 35.5 months respectively; 3-year OS: 72% and 75%) with acceptable toxicity. The two schedules were compared in a recently published meta-analysis, showing no significant differences in the once- versus twice-weekly schedule [52]. The efficacy was also maintained in patients with high-risk cytogenetics.

In a recent phase I/II trial, the addition of carfilzomib to MP (KMP) followed by carfilzomib maintenance demonstrated high efficacy and a favorable safety profile [53]. These results prompt the evaluation of carfilzomib-based continuous therapy in the first-line setting in larger randomized phase III trials.

The third-generation PI ixazomib represents a promising target for continuous therapy in the elderly setting, due to its convenient oral administration. The triplet ixazomib-lenalidomide-dexamethasone followed by ixazomib maintenance was evaluated in 65 patients at diagnosis. Among elderly TNE patients, the median PFS was 21.4 months, and 37.5 months for those able to receive maintenance. Remarkably, tolerability in the elderly patients was similar to that in the overall population, and AEs were mainly limited to the induction phase [34]. A phase III trial of ixazomib-Rd versus placebo-Rd in NDMM TNE patients (NCT01850524) is ongoing. Ixazomib was also evaluated in combination with cyclophosphamide and dexamethasone followed by ixazomib maintenance and in combination with melphalan and prednisone plus ixazomib maintenance in two phase I/II trials. The median PFS was 23.5 and 22.1 months respectively [54,55]. To date, no PI has been approved as upfront continuous therapy for TNE MM patients. However, encouraging results obtained with carfilzomib and ixazomib may change the treatment landscape in the near future.

2.2.3. Monoclonal Antibodies

The mAb daratumumab was recently evaluated in combination with the two current standards of care for TNE patients in two large randomized studies.

The phase III ALCYONE trial compared the combination of daratumumab plus VMP versus VMP alone in elderly patients at diagnosis. Patients received 9 cycles of standard VMP in both arms, whereas daratumumab was continued until disease progression or intolerance in the experimental arm. The median PFS was not reached in the daratumumab-VMP arm versus 18.1 months in the VMP arm (HR 0.50, $p < 0.001$), while the median OS was not reached in both groups. Remarkably, the MRD negativity rate in the daratumumab-VMP arm was much higher (22% vs 6%, $p < 0.001$). The addition of daratumumab did not increase toxicity rates except for infections (grade ≥3, 23% vs 15%) [56]. Daratumumab-VMP has been approved by both the FDA and EMA as upfront treatment for TNE patients.

The phase III MAIA study investigated upfront treatment with the triplet daratumumab-Rd versus Rd alone. The median PFS was not reached in the daratumumab group and was 31.9 months in the control group (HR 0.56, $p < 0.001$). MRD-negative patients were 24.2% versus 7.3% respectively ($p < 0.001$). The OS data are not

yet mature to draw definite conclusions. Grade 3–4 neutropenia (50% vs 35%) and infections (32% vs 23%) were more frequent with the triplet daratumumab-Rd [57]. However, a longer follow-up is needed in order to evaluate the benefit of continuous treatment with daratumumab.

The anti-SLAM7 mAb elotuzumab is currently being tested in combination with Rd in a phase III trial (NCT01335399) and results are awaited in the near future.

3. CONTINUOUS THERAPY IN RELAPSED/REFRACTORY MYELOMA PATIENTS

The main trials with continuous therapy for relapsed/refractory multiple myeloma (RRMM) patients are summarized in Table 2.

3.1. Immunomodulatory Agents

Continuous therapy with Rd at relapse proved to be effective in phase III trials. A pooled analysis of the MM-009 and MM-010 trials including 704 RRMM patients receiving either Rd or placebo-dexamethasone until disease progression or intolerance confirmed a survival advantage. After a median follow-up of 48 months, the median PFS was 11.1 versus 4.6 in the Rd group versus the placebo-dexamethasone group ($p < 0.001$) and the median OS was 38 versus 31.6 months, respectively ($p = 0.45$) [58].

Currently, Rd represents the backbone of the most effective three-drug regimens approved in the relapsed setting, usually combined with a third novel agent, such as new-generation PIs or mAbs.

The third-generation IMiD pomalidomide showed to be able to overcome the resistance to other IMiDs in heavily pretreated patients. This is particularly important considering the extensive use of lenalidomide in first-line treatments. In the MM-03 trial, pomalidomide-dexamethasone (Pd) showed an advantage in terms of PFS (4 vs 1.9 months, HR 0.48, $p < 0.0001$) and OS (12.7 vs 8.1 months, HR 0.74, $p = 0.285$) compared with high-dose dexamethasone alone, and the benefit was also maintained in lenalidomide- and bortezomib-refractory patients [59].

In the phase IIIb STRATUS trial assessing the efficacy of continuous Pd in RRMM patients, the median PFS was 4.6 months and the median OS was 11.9 months [60]. Remarkably, most patients (80.2%) were double refractory. The randomized OPTIMISMM trial evaluated second-line therapy with pomalidomide-bortezomib-dexamethasone (Poma-Vd) in lenalidomide-refractory patients compared to Vd [61]. The triplet showed significant improvement in PFS (median 11.2 vs 7.1 months, HR 0.61, $p < 0.001$) despite a higher incidence of hematological toxicity and infections.

3.2. Proteasome Inhibitors

Carfilzomib showed significant efficacy with an acceptable safety profile in combination with IMiDs in RRMM patients. The ASPIRE trial compared the triplet KRd versus standard Rd, until progression or intolerance. The KRd arm showed an improved median PFS (26.1 vs 16.6 months, HR 0.66, $p < 0.001$), as well as an advantage in terms of OS (48.3 vs 40 months, HR 0.79, $p = 0.0045$) [10]. The toxicity profile was similar in both arms, with the exception of a higher incidence of cardiovascular AEs (hypertension 14% vs 7%), diarrhea (42% vs 34%) and fever (29% vs 21%) in the KRd group [9]. Although treatment with KRd is allowed until disease progression, carfilzomib can be discontinued after 18 cycles, since safety and tolerability data after 18 cycles are still insufficient. Rd can be continued according to patient tolerance, becoming a sort of maintenance after a reinduction. Encouraging data emerged also from phase I/II studies exploring efficacy and safety of the carfilzomib-pomalidomide-dexamethasone combination in lenalidomide-refractory RRMM patients [62].

Carfilzomib at higher doses in combination with dexamethasone (Kd) proved to be superior to standard Vd in heavily pretreated patients. The median PFS was 18.7 months versus 9.4 months (HR 0.53, $p < 0.0001$) respectively [63]. An interim analysis detected an OS benefit with Kd (47.6 vs 40 months, HR 0.79, $p = 0.1$). Patients treated with bortezomib experienced a higher rate of peripheral neuropathy (32% vs 6%), whereas cardiovascular events were higher in the carfilzomib arm (hypertension 25% vs 9%). Discontinuation rates were similar in the two study groups [63].

Table 2 | Main clinical trials exploring continuous therapy in relapsed/refractory myeloma patients.

Trial	Number of Patients	Trial Design	Median PFS (Months)	Median OS (Months)
MM-009 + MM-010 pooled analysis [58]	704	Rd vs placebo-dex	11 vs 4.6 ($p < 0.001$)	38 vs 31.6 ($p = 0.045$)
MM-03 [59]	322	Poma-dex vs high-dose dex	4 vs 1.9 ($p < 0.0001$)	13.1 vs 8.1 ($p = 0.009$)
ASPIRE [10]	792	KRd vs Rd	26 vs 16.6 ($p < 0.001$)	48 vs 40 ($p = 0.0045$)
ENDEAVOR [63]	929	Kd vs d	18.7 vs 9.4 ($p < 0.001$)	47.6 vs 40 ($p = 0.1$)
TOURMALINE-MM1 [64]	722	Ixa-Rd vs Rd	20.6 vs. 14.7 ($p = 0.01$)	Immature data
POLLUX [11,12]	569	Dara-Rd vs Rd	NR vs 17.5 ($p < 0.0001$)	1-year OS 92.1% vs 86.8%
ELOQUENT-2 [67,68]	646	Elo-Rd vs Rd	19.4 vs 14.9 ($p < 0.0001$)	48 vs 40
CASTOR [14]	498	Dara-Vd vs Vd	NR vs 7.2 ($p < 0.0001$)	Immature data

Abbreviations: PFS, progression-free survival; OS, overall survival; R, lenalidomide; dex, d, dexamethasone; Poma, pomalidomide; V, bortezomib; K, carfilzomib; Ixa, ixazomib; Elo, elotuzumab; Dara, daratumumab; NR, not reached.

Table 3 | Main ongoing clinical trials with continuous therapy.

Trial	Patient Population	Regimen	Status
NCT02203643	NDMM, TE	KCD-ASCT vs KRD12 vs KRD-ASCT followed by maintenance with KR vs R	Active, enrollment completed
NCT02874742	NDMM, TE	Dara-VRD-ASCT followed by Dara-R maintenance vs VRD-ASCT followed by R maintenance	Active, enrollment completed
NCT03896737	NDMM, TE	Dara-VCD-ASCT vs VTD-ASCT followed by maintenance with Ixa-Dara vs Ixa	Active, recruiting
NCT03710603	NDMM, TE	Dara-VRD-ASCT vs VRD-ASCT followed by maintenance with Dara-R vs R	Active, recruiting
NCT03829371	NDMM, TNE	Rd vs VMP	Active, recruiting
NCT01850524	NDMM, TNE	Ixa-Rd vs Rd	Active, enrollment completed
NCT01335399	NDMM, TNE	Elo-Rd vs Rd	Active, enrollment completed
NCT03180736	RRMM	Dara-Pd vs Pd	Active, enrollment completed
NCT03275285	RRMM	Isa-Kd vs Kd	Active, enrollment completed

Abbreviations: NDMM, newly diagnosed multiple myeloma; TE, transplant eligible; TNE, transplant ineligible; RRMM, relapsed/refractory multiple myeloma; ASCT, autologous stem-cell transplantation; K, carfilzomib; Cy, cyclophosphamide; D,d, dexamethasone; R, lenalidomide; KRd 12, KRd 12 cycles; V, bortezomib; T, thalidomide; Ixa, ixazomib; M, melphalan; P, prednisone; Elo, elotuzumab; Isa, isatuximab.

The TOURMALINE-MM1 trial compared the triplet ixazomib-Rd versus Rd until progression or intolerance. The median PFS was significantly longer in the ixazomib group (20.6 vs 14.7 months, HR 0.74, $p = 0.01$), whereas, after a median follow-up of 23 months, the median OS was not reached in either arm. Thrombocytopenia, rash and gastrointestinal toxicities (diarrhea, vomiting, constipation) were more frequent in the experimental arm, despite self-reported quality of life being similar in the two groups [64].

3.3. Monoclonal Antibodies

The anti-CD38 antibody daratumumab showed to be active as a single agent in heavily pretreated patients [65]. Outstanding results were seen with continuous therapy with daratumumab in combination with Rd or with Vd in patients who had received at least one previous line of therapy.

In the POLLUX study, continuous therapy with daratumumab-Rd proved to be superior to standard Rd in terms of PFS (not reached vs 17.5 months HR 0.44, $p < 0.0001$), while OS data require longer follow-up. Neutropenia, diarrhea and infections were more frequently observed in the daratumumab arm, with no significant differences in discontinuation rates due to toxicity between the two groups (7% vs 9%) [11,12]. A 3-year follow-up of the study demonstrated a sustained PFS benefit and deeper responses in the daratumumab-Rd arm. A higher rate of sustained MRD-negativity was also shown with continuous daratumumab [13].

The phase III CASTOR trial compared the triplet daratumumab-Vd for 9 cycles followed by daratumumab maintenance to standard Vd for 9 cycles. The daratumumab-Vd arm reached a significant advantage in terms of median PFS (not reached vs 7.2 months, HR 0.39, $p < 0.001$); while OS data are still immature. However, the triplet was associated with a greater number of AEs [14].

The ongoing phase III APOLLO trial is exploring the subcutaneous daratumumab-Pd triplet versus Pd in approximately 300 RRMM patients previously exposed to PIs and lenalidomide (NCT03180736). Pd combined with the other anti-CD38 mAb isatuximab is being investigated in the ongoing phase III ICARIA trial (NCT02990338) on RRMM patients treated with ≥2 previous lines of therapy. Preliminary data showed a substantial benefit in terms of overall response rate (ORR; 60.4% vs 35.3%, $p < 0.001$) and PFS (median PFS, 11.5 vs 6.5, HR 0.59, $p = 0.001$) for the triplet arm. The triplet induced a slightly higher rate of grade 3–4 infections (42.8% vs 30.2%) and neutropenia (84.9% vs 70.1%) [66]. Another phase III ongoing trial is evaluating the combination of isatuximab with Kd in RRMM patients (NCT03275285).

The anti-SLAMF7 mAb elotuzumab showed efficacy in combination with IMiDs. In the ELOQUENT-2 trial, continuous therapy with elotuzumab in combination with Rd proved to be more effective than Rd in terms of PFS (19.4 vs 14.9 months, HR 0.70, $p < 0.001$) [67] and OS (48 vs 40 months) [68]. Of note, the triplet did not increase toxicity rates. The elotuzumab-pomalidomide-dexamethasone triplet was evaluated in the ELOQUENT-3 trial. The median PFS in the elotuzumab-Pd arm was 10.3 months versus 4.7 months in the Pd arm.

4. DISCUSSION

The available data indicate that continuous therapy is an effective and feasible strategy to treat MM patients, both at diagnosis and relapse. Particularly, most randomized trials showed that continuous therapy until disease progression provides better outcome than fixed-duration therapy, especially in the frontline setting. A recent meta-analysis comparing continuous versus fixed-duration therapies in NDMM patients showed a significant advantage in terms of PFS (HR 0.54, $p < 0.001$), PFS-2 (HR 0.61, $p < 0.001$) and OS (HR 0.71, $p = 0.04$) with continuous therapy. This advantage was also maintained in high-risk patients according to the Revised International Staging System (R-ISS), and high-risk patients treated with continuous therapy had a remarkably better PFS than standard risk-patients treated with fixed-duration therapy. In addition, continuous treatment with novel agents led to a discontinuation rate due to AEs of less than 10% [69].

The evolution of continuous therapy as a new treatment paradigm for MM has been made possible with the introduction of novel

agents such as IMiDs and PIs. The idea of controlling the disease with the continuous administration of effective anti-MM agents is not recent. However, in the past, available drugs showing some efficacy such as melphalan and interferon were burdened by high-toxicity profiles that made their long-term administration impossible. Other agents, such as steroids, failed to demonstrate a substantial benefit when administered as maintenance treatment [3–6]. IMiDs revolutionized this concept, entering the market as orally available, better tolerated agents. Nowadays, due to toxic effects and impaired outcome in high-risk patients, prolonged thalidomide administration is being abandoned in favor of lenalidomide, which appears better tolerated both in young and elderly patients. PIs are also emerging as possible candidates for prolonged therapy, and ixazomib could be the next agent to enter the market soon.

In NDMM patients, the main goal of a continuous approach is to deepen the response, achieving MRD negativity, which is associated with prolonged PFS and OS. To date, the most convincing evidence supporting continuous therapy (CT) comes from lenalidomide maintenance post-ASCT and from continuous lenalidomide-based treatment in TNE patients [44,70]. Indeed, a meta-analysis showed that almost one third of patients who were still MRD positive after induction/consolidation became MRD negative during maintenance, thus obtaining a significant prolongation of PFS (HR 0.19, $p < 0.001$) [71]. Results from the Myeloma XI trial showed a better PFS in MRD-negative patients receiving maintenance compared to MRD-negative patients not receiving maintenance, suggesting the benefit of a continuous strategy even in MRD-negative patients [72]. However, the cut-off used for MRD negativity in the study is sub-optimal (10^{-4}) and prospective randomized trials comparing continuous treatment versus discontinuation in MRD-negative patients with a cut-off of 10^{-5} or 10^{-6} are needed.

Patients carrying high-risk cytogenetic abnormalities seem to benefit more from a PI-based continuous therapy, and the new consensus by the IMWG suggests the use of these agents in this setting [73]. A double maintenance strategy, based on both IMiDs and PIs, can be more effective and is being explored in ongoing clinical trials such as the FORTE study.

In TNE patients, when tailoring treatment decision according to the patient's frailty, gentler approaches are usually recommended for intermediate-fit and frail patients. In fact, the goal of therapy in intermediate-fit/frail patients can hardly be the achievement of MRD negativity, but rather preserving quality of life. However, results from the ALCYONE trial showed a greater rate of MRD negativity in patients receiving VMP plus daratumumab followed by daratumumab maintenance compared to those receiving fixed-duration VMP, with an acceptable rate of toxicity [56]. Ongoing trials are evaluating maintenance therapy with second-generation PIs alone or plus IMiDs and with mAbs. These drugs and combinations, which could have a potential efficacy in standard- as well as in high-risk disease, could become available in the maintenance setting in the near future.

In RRMM patients, the focus of treatment is to control the disease while preserving a good quality of life. Continuous therapy up to disease progression is a key approach to prolong the time to subsequent relapses. In this regard, combinations with lenalidomide outperformed those with bortezomib, which were given for a fixed duration [74]. Next-generation agents have been developed to limit the emergence of drug-resistant clones, especially in case of adverse cytogenetic features.

Although there is much evidence supporting the use of continuous therapy in MM, some questions are still unanswered. It remains to be defined whether all patients require maintenance therapy or not, or if the choice of the agents should be dictated by disease and patient characteristics and by the optimal duration of maintenance. A possible strategy could be to tailor therapy to the needs of an individual patient in order to avoid over- and undertreatment, particularly in patients with high-risk features and in patients who achieved MRD negativity. Prolonging life expectancy of MM patients implies dealing with possible long-term drug-induced toxicities. In particular, prolonged approaches with newer generations of IMiDs increase the risk of SPM, especially when administered together or after alkylating agents, such as melphalan. A large analysis from the Center for International Blood and Marrow Transplant Research (CIBMTR), with 4,161 MM patients receiving ASCT, identified a risk of SPM of 6.1% at 7 years from transplant [75]. In 2014, a meta-analysis of nine trials including lenalidomide as first-line treatment reported a significantly higher 5-year cumulative incidence of hematologic malignancies in patients treated with lenalidomide-containing regimens (HR 1.55, 95% CI 1.03–2.34). However, the risk of mortality related to SPM is significantly lower than the risk of mortality related to MM. SPM risk should be carefully discussed with patients, outweighing the benefits of therapy versus the potential risk of developing secondary malignancies. The increased long-term administration of carfilzomib prompted the development of evidence-based indications for the management of carfilzomib-related cardiovascular toxicity, which may impact treatment efficacy [76].

In conclusion, it is fundamental for physicians to appropriately consider two aspects before selecting therapy: (i) which patients might benefit more from continuous treatment and (ii) which agent should be used. To do so, patient fitness and disease characteristics such as cytogenetic risk and patient's willingness to undergo long-term treatment should be taken into account. Orally available agents not requiring frequent hospital access, such as IMiDs and ixazomib, or drugs that can be rapidly delivered, such as subcutaneous bortezomib or daratumumab, represent the first choice. Finally, a manageable safety profile is necessary to allow good quality of life and to maximize patient compliance.

5. FUTURE DIRECTIONS

New molecules and drug combinations are under evaluation in clinical trials, and some of them will likely enter the clinical practice in the future. The nuclear export protein inhibitor selinexor has been recently approved by the FDA for heavily pretreated MM patients following the results of the STORM trial. The anti-BCl2 venetoclax is under evaluation as well. These compounds are showing efficacy in relapsed patients and will also be investigated as frontline treatments [77,78].

Concerning already available agents, new routes of drug administration are under evaluation in order to limit hospital access and improve quality of life. Once-weekly administration of carfilzomib proved to be comparable to the approved twice-weekly schedule in terms of efficacy and safety in the A.R.R.O.W. study and in a

recently published meta-analysis on TNE patients [52,79]. Daratumumab is currently approved as intravenous infusion. The use of subcutaneous daratumumab in clinical trials showed similar response rates and toxicity profile as the intravenous administration, with a marked reduction in the duration of administration [80]. Ongoing trials are using the subcutaneous route, which will likely become a standard practice soon.

Duration of maintenance or continuous therapy is still an open issue in the frontline setting. Some retrospective analyses showed that patients continuing maintenance for a longer time (more than 2 years) have a better outcome, as compared to patients stopping maintenance after a shorter time (1 or 2 years) [81,82]. However, prospective comparisons of different maintenance durations have not been conducted yet. With the advent of MRD evaluation, it should be defined whether continuing maintenance in patients with sustained MRD negativity could be beneficial and safe compared to stopping treatment. Several ongoing trials, such as the EMN17, are designed with an MRD-driven approach to maintenance duration and they will help to clarify this issue.

CONFLICT OF INTEREST

FG has received honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Takeda, and served on the advisory boards for Amgen, Bristol-Myers Squibb, Celgene, Janssen, Roche, Takeda, and AbbVie. AL has received honoraria from Amgen, Bristol-Myers Squibb, Celgene and Janssen; has served on the advisory boards for Bristol-Myers Squibb, Celgene, Janssen, and Takeda. The remaining authors declare no competing financial interests.

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AUTHORS' CONTRIBUTIONS

All the authors provided substantial contributions to the conception or design; acquisition, analysis, or interpretation of data. All the authors were involved in the first draft; critical revision for important intellectual content and final approval of the version to be published. Alessandra Larocca and Francesca Gay were involved in supervision. All the authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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