Evolving paradigms in the treatment of relapsed/refractory multiple myeloma: increased options and increased complexity

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The use of modern therapies such as thalidomide, bortezomib and lenalidomide coupled with upfront high-dose therapy and autologous stem cell transplant (ASCT) has resulted in improved survival in patients with newly diagnosed multiple myeloma (MM). However, patients with relapsed/refractory multiple myeloma (RRMM) often have poorer clinical outcomes and might benefit from novel therapeutic strategies. Emerging therapies, such as deacetylase inhibitors, monoclonal antibodies and new proteasome inhibitors, appear promising and may change the therapeutic landscape in RRMM. A limited number of studies has shown a benefit with salvage ASCT in patients with RRMM, although there remains ongoing debate about its timing and effectiveness. Improvement in transplant outcomes has re-initiated a debate on the timing and possible role for salvage ASCT and allogeic stem cell transplant in RRMM. As the treatment options for management of patients with RRMM become increasingly complex, physicians must consider both disease- and patient-related factors in choosing the appropriate therapeutic approach, with the goal of improving efficacy while minimizing toxicity.

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INTRODUCTION

Multiple myeloma (MM) is a clonal B-cell disorder of terminally differentiated plasma cells that accounts for $\approx 10\%$ of hematologic malignancies. It is the second most common hematologic malignancy in the United States, with an overall incidence rate of 4.4 cases per 100,000 population/year. MM remains largely incurable, thus therapy is initiated when patients are symptomatic with the ultimate goal of improving patients' long-term outcomes. Over the past 10–15 years, the introduction of modern therapies, such as immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs), has led to significant improvements in overall survival (OS). Five-year survival rates have improved, from 34.8% (1998–2001) to 44.6% (2006–2009), in both transplant-eligible and transplant-ineligible patients, primarily due to treatment advancements in newly diagnosed MM (NDMM).

Patients with relapsed and refractory multiple myeloma (RRMM) present a therapeutic challenge. This heterogeneous group of patients has been defined by the International Myeloma Workshop Consensus Panel as having either primary refractory, refractory, relapsed, both relapsed and refractory, or double refractory MM (Table 1). In contrast to NDMM, RRMM responds poorly to IMiDs and PIs. Kumar et al. showed a median survival of only 1.5 years in patients with relapsed MM, and their clinical course was typified by decreasing response duration with increasing number of salvage regimens. Patients with double-refractory MM, who are refractory to both IMiDs and PIs, have an even poorer prognosis, with a median OS and progression-free survival (PFS) of 9 and 5 months, respectively.

Current treatment strategies are based on both patient- and disease-related factors, including pre-existing toxicities, comorbidities, prior response, aggressiveness of relapse and cytogenetics. This review provides an overview of the challenges in the care of patients with RRMM, current treatment options, possible role of hematopoietic stem cell transplant (HSCT), emerging therapies and a proposed strategy for the treatment of patients with RRMM.

THE CHALLENGE IN RRMM—INHERENT DRUG RESISTANCE AND CLONAL EVOLUTION

The genomic complexity and clonal evolution of MM over the course of treatment are thought to contribute to drug resistance and relapse (Figure 1). These occur through either the re-emergence of the dominant clone, linearly acquired mutations within the dominant clone or evolution of a prediagnostic clone with newly acquired mutations. Recent advances in genome sequencing have provided evidence of both clonal heterogeneity and shifting clonal dominance over time. Clonal heterogeneity may explain decreased duration of response (DOR) and would warrant sequential therapy with alternate agents. In contrast, patients with a long DOR to their last therapy may have developed a clonal re-emergence and might be responsive to a previous therapy.

RISK STRATIFICATION IN RRMM

The Mayo Stratification for Myeloma and Risk-Adapted Therapy (mSMART) recommendations provide a road map for risk assessment in NDMM and RRMM. These recommendations suggest that prior cytogenetic abnormalities, as determined by fluorescence in situ hybridization or gene expression profiling, play an important role in risk stratification. Time to relapse should also be considered in determination of risk. Patients who relapse after 24 months of primary therapy are considered standard risk
standards for RRMM include (1) salvage chemotherapy, should be considered for salvage therapy. Current treatment protein concentration with or without associated symptoms. Patients with RRMM and rapidly increasing monoclonal (M) CURRENT TREATMENT OPTIONS FOR RRMM result of phenotypic diversity and clonal heterogeneity in RRMM. not speci agents are incorporated into their therapy. Of note, mSMART does relapse after o

Figure 1. Hypothetical example of clonal evolution and hetero-
geneity in patients with multiple myeloma (MM) over the disease course. MM is characterized by clonal heterogeneity. As the disease progresses and patients receive various therapies, different clones may emerge and become dominant, thus contributing to treatment resistance typical of patients with relapsed/refractory MM. (a) The clonal distribution at diagnosis, prior to treatment with lenalidomide plus dexamethasone. (b) An emergence of clone 2 at relapse, prior to re-treatment with lenalidomide plus dexamethasone. (c) Emergence of a lenalidomide-resistant clone 3. BMSC = bone marrow stromal cells.

and are usually re-treated with the primary regimen. Patients who relapse after <12 months are classified as high risk, and new agents are incorporated into their therapy. Of note, mSMART does not specifically address the treatment challenges that develop as a result of phenotypic diversity and clonal heterogeneity in RRMM.

CURRENT TREATMENT OPTIONS FOR RRMM

Patients with RRMM and rapidly increasing monoclonal (M) protein concentration with or without associated symptoms should be considered for salvage therapy. Current treatment standards for RRMM include (1) salvage chemotherapy, (2) salvage autologous stem cell transplant (ASCT), (3) allogeneic HSCT and (4) post-transplant consolidation/maintenance therapy. Given the concern for acquired drug resistance and clonal evolution of disease, upfront clinical trials incorporating emerging therapies, with/or without addition of stem cell transplant, are being increasingly employed.

SALVAGE CHEMOTHERAPY OPTIONS IN RRMM

Monotherapy and combination therapies

IMiDs. IMiDs, including thalidomide, pomalidomide and lenalidomide, possess anti-myeloma effects via binding to cereblon, a critical component of the E3 ubiquitin ligase complex. This results in enhanced ubiquitination and degradation of Aiolos (IKZF3) and Ikaros (IKZF1), which are important for myeloma cell survival (Figure 2a).24 Thalidomide was the first IMiD evaluated in patients with RRMM. A systematic review of phase II studies demonstrated the single-agent efficacy of thalidomide in RRMM, with an overall response rate (ORR; defined as partial response (PR) or better) of 30% and a median OS of 14 months.25 PFS and 3-year survival probabilities were significantly improved when patients with RRMM were treated with thalidomide/dexamethasone compared with conventional chemotherapy (PFS, 17 vs 11 months (P = 0.02); 3-year survival probability, 60% vs 26% (P = 0.002)).26 Thalidomide-associated peripheral neuropathy (PN) and venous thromboembolism are the main side effects seen with prolonged use. Lenalidomide is a more potent thalidomide derivative. Phase I and II trials demonstrated single-agent efficacy of lenalidomide in patients with RRMM, with PR rates of 24–29%.27 MM-009/MM-010 phase III trials demonstrated superior PFS and OS in patients with RRMM receiving lenalidomide/dexamethasone compared with placebo/dexamethasone (Table 2).28,29

Pomalidomide is another potent derivative of thalidomide. A phase I study of single-agent pomalidomide in patients with RRMM was efficacious (ORR, 21%; PFS, 4.6 months; OS, 18.3 months).30 The phase II MM-002 study demonstrated an improvement in PFS with pomalidomide/low-dose dexamethasone compared with pomalidomide alone in patients with double-refractory MM (Table 2).31 The pivotal phase III MM-003 trial demonstrated a significantly longer PFS and OS with pomalidomide/low-dose dexamethasone compared with high-dose dexamethasone (Table 2).32 An ongoing phase III trial (OPTIMISMM, MM-007) is evaluating the safety and efficacy of pomalidomide in combination with bortezomib and dexamethasone (Table 3).33

PIs. PIs (i.e., bortezomib and carfilzomib) alter the ability of the proteasome to degrade intracellular proteins that have been targeted for destruction, leading to altered protein homeostasis and plasma cell apoptosis (Figure 2a).34–36 Bortezomib was the first PI developed for the treatment of MM. Two phase III trials have demonstrated the efficacy of bortezomib in patients with RRMM (Table 2).37,38 In the APEX trial, patients treated with i.v.
Figure 2. MOA of agents approved or under development for MM. Agents approved or under development for MM target key biological pathways that drive MM cell proliferation and survival. (a) Approved agents include proteasome inhibitors (proteasome inhibitors target the proteasome, which plays a role in the normal degradation and clearance of intracellular misfolded and unfolded proteins. This inhibition leads to protein accumulation and eventual apoptosis), IMiDs (the CRBN E3 ubiquitin ligase complex marks protein with ubiquitin for degradation. The binding of an IMiD to this complex leads to the degradation of two key proteins, Aiolos (IKZF3) and Ikaros (IKZF1), ultimately killing MM cells) and DAC inhibitors (DAC inhibitors target proteins in the nucleus and cytoplasm. HDACs deacetylate target nuclear proteins implicated in gene regulation, including histones and tumor suppressor genes. DACs, which target cytoplasmic proteins, namely HDAC6, play a role in protein metabolism through the formation of aggresomes that transport proteins to be degraded by lysosomes. DAC inhibitors target HDAC6, blocking aggresome formation and subsequent protein degradation, thus leading to protein accumulation and apoptosis). (b) Agents under development: CAR-T cells (CAR-T cells are engineered to recognize target tumor cells and induce cell death), mAbs (mAbs utilize antibody-dependent cellular toxicity (targeting of cell surface proteins such as CS1 and CD38) to induce apoptosis; antibody drug conjugates (e.g., indatuximab ravtansine) target cells expressing the recognized receptor, leading to receptor internalization and release of cytotoxic chemotherapy and cell death), oncolytic virotherapy (viruses stimulate MM apoptosis through many complex mechanisms, including direct virus-mediated cytotoxicity and indirect enhancement of immune responses) and KSP inhibitors (KSPs facilitate early mitosis by separating microtubules. KSP inhibitors block this process, thereby serving as antimitotic agents in rapidly dividing MM cells). Adapted with permission from Novartis Pharmaceuticals Corporation. A = antigen; ADCC = antibody-dependent cell-mediated cytotoxicity; CAR = chimeric antigen receptor; CRBN = cereblon; HDAC = histone deacetylase; HSP90 = heat-shock protein 90; i = inhibitor; IMiD = immunomodulatory drug; KSP = kinesin spindle protein; mAb = monoclonal antibody; MM = multiple myeloma; MOA = mechanism of action; NK = natural killer; TCR = T-cell receptor.
bortezomib had significantly higher rates of ORR, PFS and 1-year survival compared with high-dose dexamethasone. However, there was a significantly higher rate of PN with bortezomib (all grades: 36% vs 9%; \( P < 0.01 \)). The MMY-3021 trial demonstrated that s.c. bortezomib was comparable in efficacy to i.v. bortezomib and resulted in significantly reduced PN (38% vs 53%; \( P = 0.04 \)).

Carfilzomib is a second-generation PI that has proven efficacy in RRMM. In the phase II study PX-171-003-A0, carfilzomib achieved an ORR of 16.7%, with a median DOR of 7.2 months. The phase II study PX-171-004 was designed to assess the effects of carfilzomib in bortezomib-naive patients who had received only 1–3 prior lines of therapy. One cohort was treated with 20 mg/m² per cycle, while a second cohort was treated with 20 mg/m² in cycle 1.
followed by 27 mg/m² in subsequent cycles. The ORR was 42.4 and 52.2% in cohorts 1 and 2, respectively. The median DOR was 13.1 months in cohort 1 and was not reached in cohort 2.⁴⁰ In the phase II study PX-171-003-A1, patients who received a median of 5 cycles of BTZ/dexamethasone in patients with RRMM (Table 2).⁴⁹,⁵⁰ PANORAMA 1 was the first phase III clinical trial in a decade to demonstrate a significant and clinically relevant efficacy for an agent with a novel mechanism of action in RRMM.³⁴,⁴⁷ It has been hypothesized that dual targeting of the proteasome and aggrevome pathways through PIIs and DACi may be effective in patients with RRMM.³⁴ Furthermore, DACi have been shown to increase expression of epigenetically silenced tumor suppressor genes in vitro.⁴⁴ Panobinostat, a potent pan-DACi, demonstrated synergetic activity when combined with bortezomib or lenalidomide in preclinical studies.⁵⁷,⁵⁸ Key phase II (PANORAMA 2) and 3 (PANORAMA 1) clinical trials evaluated panobinostat/bortezomib or lenalidomide in patients with RRMM (Table 2).⁴⁹,⁵⁰ PANORAMA 2 showed that the addition of panobinostat to dexamethasome or bortezomib elicited responses in patients who were previously refractory to bortezomib.⁵⁹ In PANORAMA 1, there was a significant improvement in PFS with panobinostat/bortezomib/dexamethasone compared with placebo/bortezomib/dexamethasone (Table 2).⁵⁰ PANORAMA 1 was the first phase III trial in a decade to demonstrate a significant and clinically relevant efficacy for an agent with a novel mechanism of action in RRMM. Panobinostat was recently approved by the US Food and Drug Administration for the treatment of relapsed MM patients who had received ≥ 2 prior regimens, including bortezomib and an IMiD.

**Table 2.** Selected published clinical trials for the treatment of relapsed/refractory multiple myeloma

| Study phase, N | Treatment | ORR (≥ PR), % | PFS, months | OS, months | Safety, percentage of grade ≥ 3 AE |
|---------------|-----------|---------------|-------------|------------|----------------------------------|
| APEX³⁸ Phase III, N = 669 | BTZ vs D | 38 vs 18 (P < 0.001) | 6.2 vs 3.5 (P < 0.001) | 80% vs 66% (P = 0.003) | Thrombocytopenia (30 vs 6), neutropenia (14 vs 1), anemia (10 vs 11) |
| MM-009³⁹ Phase III, N = 353 | Len/D vs Pbo/D | 60.2 vs 24.0 (P = 0.001) | 11.3 vs 4.7 (P < 0.001) | Neutropenia (41 vs 5), thrombocytopenia (15 vs 7), VTE (15 vs 4) |
| MM-010³⁸ Phase III, N = 351 | Len/D vs Pbo/D | 60.2 vs 24.0 (P < 0.001) | 11.3 vs 4.7 (P < 0.001) | Neutropenia (30 vs 2), thrombocytopenia (11 vs 6), VTE (11 vs 5) |
| MMY-3021³⁷ Subcutaneous BTZ vs placebo | 42 vs for both | 10.4 vs 9.4 | 72.6% vs 76.7% (P = 0.50) | Thrombocytopenia (13 vs 19), neutropenia (18 vs 18), anemia (12 vs 8) |
| Phase III, N = 222 | Intravenous BTZ | (4 cycles) | (P = 0.39) | 1-year survival rate | Thrombocytopenia (29), anemia (24), lymphopenia (20) |
| PX-171-003-A1¹¹ | Carfilzomib | 23.7 | 3.7 | 11.6 | 1.5 |
| Phase II, N = 266 | Pom/D vs Pom | 33 vs 18 | 4.2 vs 2.7 | 16.5 vs 13.6 | Neutropenia (41 vs 48), anemia (22 vs 24), thrombocytopenia (19 vs 22) |
| MM-002³⁸ Phase II, N = 221 | Pom/D vs Pom | 31 vs 10 | 4.0 vs 1.9 | 12.7 vs 8.1 (P = 0.03) | Neutropenia (48 vs 16), anemia (33 vs 37), thrombocytopenia (22 vs 26) |
| MM-003³⁸ Phase III, N = 302 | Pom/Low D vs High D | 61 vs 55 (P < 0.0001) | 12.0 vs 8.1 (P < 0.0001) | 33.6 vs 30.4 (P = 0.26) | Lymphopenia (53 vs 40), diarrhea (26 vs 8) |
| PANORAMA 1³⁵ | Panobinostat/BTZ/D | (P = 0.09) | (P < 0.0001) | (P = 0.02) | (P = 0.001) |
| Phase III, N = 768 | Pom/Low D vs Pbo/BTZ/D | 61 vs 55 | 12.0 vs 8.1 | 33.6 vs 30.4 (P = 0.26) | Lymphopenia (53 vs 40), diarrhea (26 vs 8) |
| ASPIRE³⁴ Phase III, N = 792 | Carfilzomib/Len/Low D vs Pbo/Len/D | 87.1 vs 66.1 | 26.3 vs 17.6 | NR | Diarrhea (4 vs 4), fatigue (8 vs 6) |

**Table 3.** Selected ongoing clinical trials in the treatment of relapsed/refractory multiple myeloma

| Study | Treatment | Primary end point | Estimated study completion date |
|-------|-----------|-------------------|--------------------------------|
| NCT01985126¹³² | Daratumumab | ORR | October 2016 |
| OPTIMISM/MM-007 (NCT01734928)³³ | Pom/BTZ/D vs Pbo/BTZ/D | PFS | January 2017 |
| Phase III, N = 782 | Daratumumab/BTZ/D vs Pbo/BTZ/D | PFS | March 2017 |
| NCT02136134¹⁴⁴ | ELOQUENT-2¹¹⁵ | Elotuzumab/Len/D vs Pbo/Len/D | PFS | March 2018 |
| Phase III, N = 480 | Carfilzomib/D vs BTZ/D | PFS | March 2019 |
| NCT01566537¹⁰⁰ | Ixazomib/Len/D vs Pbo/Len/D | PFS | May 2019 |
| Phase III, N = 703 | Daratumumab/Len/D vs Pbo/Len/D | PFS | September 2020 |
| NCT02076009¹⁰⁸ | Carfilzomib/Len/Low D vs Pbo/Len/D | PFS | September 2020 |

**Abbreviations:** AE = adverse event; BTZ = bortezomib; D = dexamethasone; High = high-dose; Len = lenalidomide; Low = low dose; NR = not reached; ORR = overall response rate; OS = overall survival; Pbo = placebo; PFS = progression-free survival; Pom = pomalidomide; PR = partial response; VTE = venous thromboembolism.
Combination therapies in RRMM. A number of clinical trials have been designed to test the combinatorial effects of novel agents. In a phase II trial, patients with relapsed MM or RRMM were treated with lenalidomide, bortezomib and dexamethasone (VRd); 6% of the patients had received prior lenalidomide. The ORR was 64%, with a median PFS of 9.5 months and OS of 30 months. Common toxicities were sensory neuropathy, fatigue and neutropenia.51 Another phase II trial compared cyclophosphamide, pomalidomide and dexamethasone (CyPomD) with pomalidomide and dexamethasone in patients with lenalidomide-refractory RRMM. At a median follow-up of 15 months, the ORR was superior in the CyPomD group (65% vs 39%; \( P = 0.04 \)).52 A multicenter phase I/II trial of carfilzomib, pomalidomide and dexamethasone (CarPomD) was conducted in patients who had received a median of 6 prior lines of therapy. The ORR was 70%, and the median duration of survival and PFS were 17.7 months and 9.7 months, respectively.53 In the phase III trial ASPIRE, patients with relapsed MM were randomized to carfilzomib, lenalidomide and dexamethasone versus lenalidomide and dexamethasone. PFS (26.3 vs 17.6 months; \( P < 0.001 \)) and 24-month OS rates (73.3% vs 65%); \( P = 0.04 \)) were significantly improved with carfilzomib.54 Other combination therapies that include pegylated liposomal doxorubicin, bendamustine and melphalan with dexamethasone, IMiDs and Pts are listed in Table 4. Collectively, these studies suggest that combination therapies with novel agents may improve the disease course in RRMM.

**Table 4.** Selected combination chemotherapy trials for the treatment of relapsed/refractory multiple myeloma

| Study phase, N | Treatment | ORR (\( \geq PR \)), % | PFS, months | OS | Safety (all grades), % |
|---------------|-----------|------------------------|-------------|----|------------------------|
| **Pegylated liposomal doxorubicin** | | | | | |
| Orlowski et al.17 | PLD/BTZ vs BTZ | 44 vs 41 | 9.3 vs 6.5 (\( P < 0.001 \)) | At 15 months: 76% vs 65\% (\( P = 0.03 \)) | Nausea (46 vs 37), diarrhea (43 vs 34), neutropenia (35 vs 20) |
| Berenson et al.18 | PLD/BTZ/Len/Dex | 49 | 9 | NR | Fatigue (40), thrombocytopenia (35), neutropenia (35) |
| **Bendamustine** | | | | | |
| Lau et al.19 | Ben/Thal/Dex | 46 | 19 | 7.2 months | Anemia (78), neutropenia (83), thrombocytopenia (65), pain (40), infection (48), neuropathy (35) |
| Lentzscht et al.20 | Ben/Len/Dex | 76 | 6.1 | NR | Thrombocytopenia (83), neutropenia (79), anemia (59), leukopenia (59), fatigue (45), diarrhea (35), hypocalcemia (31), hypoglycemia (31), nausea (28) |
| Ludwig H et al.21 | Ben/BTZ/Dex | 61 | 9.7 | 25.6 months | Infection (66), thrombocytopenia (38), anemia (18) |
| Melphalan | Palumbo A, et al.22 | Mel/Thal/Pre | 42 | 9 | 14 months | Anemia (100), thrombocytopenia (100), neutropenia (100), neuropathic pain (48), infection (21) |
| N = 24 | | | | | |

Abbreviations: Ben = bendamustine; BTZ = bortezomib; Dex = dexamethasone; Len = lenalidomide; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PLD = pegylated liposomal doxorubicin; Pom = pomalidomide; Mel = melphalan; Thal = thalidomide; Pre = prednisone. *Thrombocytopenia and anemia are grade \( \geq 3 \).

**SALVAGE ASCT IN RRMM**

Initial studies revealed that ASCT following high-dose therapy resulted in prolonged control of disease and improved OS.55,56 However, additional studies are needed to determine the optimal timing of salvage ASCT in RRMM.57 Several retrospective, registry-based or single-center experiences of salvage ASCT after a previous ASCT suggest a benefit with this approach, with an approximate ORRs of 65% and PFS and OS approaching 12 and 32 months, respectively (Table 5).58-66 A phase II study evaluating the efficacy of salvage ASCT compared with conventional chemotherapy demonstrated improvement in PFS, but not OS. Patients with an adverse cytogenetic risk profile had poorer outcomes, suggesting that ASCT may not be beneficial in this subset of patients.56 Michaelis et al. showed that 187 patients who underwent a second ASCT for disease relapse/progression, from 1995 to 2008 had a 1-year non-relapse mortality rate of 2%, a complete response (CR) rate of 25% and a PR rate of 43%, while the risk of relapse or progression was 51, 82 and 91% at 1, 3 and 5 years, respectively. Multivariate analysis showed that a longer interval (\( \geq 36 \) months) from the first ASCT to relapse or progression predicted decreased risk of relapse or progression following the second transplant (relative risk, 0.63).61 Overall, the use of salvage ASCT in patients with RRMM appears to improve PFS compared with conventional chemotherapy alone. Patients with more aggressive disease, and those with a prolonged response to the first ASCT, appear to benefit the most. Most of the initial studies published using salvage ASCT are limited by being mainly retrospective, having inherent biases in patient selection, and the use of non-modern induction therapies. Future prospective studies are necessary to assess the true impact of salvage ASCT in the context of current, more effective therapies.

**ALLOGENEIC STEM CELL TRANSPLANT (ALLO-SCT) IN RRMM**

Allo-SCT is potentially curative in patients with MM; however, its role and timing are still subject to debate.68-70 Following allografting, the immune reaction of donor T cells against myeloma-specific antigens has resulted in the achievement of complete remissions and progression, with complete remission rates up to 73%.71 A complete molecular remission rate up to 50% has been reported following allo-SCT in MM.72,73 Allo-SCT with myeloablative conditioning has been reported to result in long-term PFS, with a plateau in survival curves suggesting possible curative benefit in some patients.75,76 However, transplant-related mortality is an important challenge to this approach.75,77,78 A retrospective case-matched analysis by the European Group for Blood and Marrow Transplantation compared 189 myeloma patients treated with allo-SCT with an equal number of patients who received ASCT. Results showed inferior median survival with allo-SCT compared with ASCT, with a median survival of 18 and 34 months, respectively (\( P = 0.001 \).)
mainly attributed to increased transplant-related mortality in allo-SCT (41 vs 13% for ASCT, \( P = 0.0001 \)), not compensated for by a lower rate of relapse and progression (Table 5). Transplant-related mortality may be decreased in patients who receive a reduced-intensity or nonmyeloablative conditioning, allo-SCT following an initial ASCT. \(^{79,80}\) In this tandem approach, cyto reduction is achieved with ASCT, and allo-SCT generates a graft-versus-myeloma effect that may be curative. However, results from published studies using this approach appear conflicting in patients with NDMM. \(^{81-83}\) Associated with patient heterogeneity, different conditioning regimens and graft-versus-host disease (GVHD) prophylaxis used. Importantly, benefits from an allo-SCT may only become apparent after a long-term follow-up, which most of the published studies lack. However, it remains to be determined whether allo-SCT should be offered as part of the initial therapy in patients with high-risk disease like RRMM or only as a salvage therapy.

### POST-TRANSPLANT CONSOLIDATION/MAINTENANCE THERAPY IN RRMM

Modern therapies with comparatively fewer side effects may be employed as consolidation/maintenance therapy after an autologous and/or allo-SCT. Offidani et al.\(^ {84}\) showed in a phase II study

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**Table 5.** Selected studies using salvage ASCT or Allo-SCT in the treatment of relapsed/refractory multiple myeloma

| Clinical study | N | Efficacy post-ASCT2 | Post-ASCT2 TRM incidence |
|----------------|---|---------------------|-------------------------|
| **ASCT**       |    |                     |                         |
| Cook G et al.\(^ {59}\) | 106 case-matched pairs\(^ {4b,c}\) (ASCT2 vs conventional chemotherapy) | ORR: 64% | Within 100 days: 7% |
| Gonsalves WI et al.\(^ {60}\) | 98\(^ {a,b}\) (ASCT2 after ASCT1 performed between 1994 and 2009) | ORR: 86% | 1 year: 7% |
| Jimenez-Zepeda et al.\(^ {61}\) | 81\(^ {a,b}\) (ASCT2 performed between 1992 and 2009) | Median PFS: 10.3 months | 5 years: 12% |
| Lemieux E et al.\(^ {62}\) | 81\(^ {b,d}\) (HDT + ASCT2 performed between 1995 and 2009 after front-line or tandem ASCT) | ORR, day 100: 97% | 4% |
| Michaelis LC et al.\(^ {63}\) | 187\(^ {a,b,c}\) (ASCT2 performed between 1995 and 2008) | Median PFS: 16.4 months | Within 100 days: 2.6% |
| Morris C et al.\(^ {64}\) | 745\(^ {a,b,c,e}\) (ASCT2 after ASCT1 performed between 1993 and 2002) | Median PFS: 18 months | 3 years: 2% |
| Sellner L et al.\(^ {66}\) | 200\(^ {a,b,e}\) (ASCT2 after ASCT1 and HDT + melphalan induction therapy between 1995 and 2010) | ORR, day 100: 80% | No ASCT2 before relapse/TRM: 1.00 |
| **Allo-SCT**    |    |                     |                         |
| Bensinger W et al.\(^ {75}\) | 80\(^ {d}\) (allo-SCT after HDT± modified TBI) | ORR: 59% | Within 100 days: 44% |
| Bjorkstrand BB et al.\(^ {76}\) | 189 case-matched pairs (allo-SCT vs ASCT) | 4.5-year PFS probability: 20% | 3 years: 41% vs 13% |
| Qazilbash MH et al.\(^ {79}\) | 40\(^ {f}\) (Allo-SCT vs ASCT2 between 1992 and 2004) | ORR: 86% vs 72% | (allo-SCT vs ASCT; \( P = 0.001 \)) |
| Mehta J et al.\(^ {78}\) | 42 case-matched pairs (allo-SCT between 1992 and 2006 vs ASCT2) | ORR: 69% vs 64% | Within 100 days: 11% vs 7% |
| Efebera Y et al.\(^ {80}\) | 51\(^ {f}\) (allo-SCT between 1996 and 2006) | Median PFS: 7.3 vs 6.8 months | Overall: 27% vs 14% |
| Coman T et al.\(^ {86}\) | 52\(^ {b,d}\) (Len after allo-SCT between 2006 and 2009) | Median PFS: 13 vs 29.5 months | 1-year probability: 43 ± 8 vs 10 ± 5% |

Abbreviations: Allo-SCT = allogeneic stem cell transplant; ASCT1 = initial autologous SCT; ASCT2 = second autologous SCT; HDT = high-dose chemotherapy; HR = hazard ratio; Len = lenalidomide; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TBI = total body irradiation; TRM = transplant-related mortality. \(^ {a}\)Excluded patients participating in a tandem ASCT program. \(^ {b}\)Retrospective study. \(^ {c}\)Registry-based study. \(^ {d}\)Multicenter study. \(^ {e}\)Included patients participating in a tandem ASCT program. \(^ {f}\)Less-intensity myeloablative conditioning was performed prior to allo-SCT.
evaluating the effectiveness of bortezomib-based induction therapy, followed by consolidation/maintenance therapy in patients with RRMM, 37% CR, 34.5% very good PR (VGPR) and 4.5% PR with ORR 76%. Maintenance lenalidomide after induction therapy with liposomal doxorubicin, vincristine, dexamethasone and lenalidomide led to an ORR of 53%, a median PFS of 10.5 months and a median OS of 19 months.85 In addition, these modern therapies modulate T-cell responses, and play a pivotal role in graft-versus-myeloma effects. Following relapse after allo-SCT, use of lenalidomide with or without dexamethasone has shown efficacy, partially through an immunomodulatory GVHD effect to enhance intrinsic anti-MM activity.86 Following reduced-intensity or nonmyeloablative conditioning allo-grafting, a cohort of patients with progressive disease treated with lenalidomide developed a flare of GVHD, with improved outcomes.87,88 Preclinical studies also have highlighted the immunomodulatory role of bortezomib on GVHD following an allo-SCT.89,90 Bortezomib induced selective depletion of alloreactive T lymphocytes, decreased the production of Th1 cytokines and allowed the emergence of a suppressor T-cell subset.91,92 Bortezomib in combination with lenalidomide developed a promising role of bortezomib on GVHD following an allo-SCT.89,90 Bortezomib induced selective depletion of alloreactive T lymphocytes and novel agents resulted in increased CR (>50%) in patients with only PR after allo-SCT.97 Treatment of relapsing patients with modern therapies following allo-SCT may enhance the graft-versus-myeloma effect while directly inhibiting tumor growth.98 Future studies are necessary to determine the efficacy and safety of these strategies in RRMM.

**EMERGING THERAPIES IN RRMM**

Novel therapies that target different mechanisms of action, including immunotherapy with monoclonal antibodies, are promising, and will expand our therapeutic armamentarium in the fight against MM. Their favorable safety profiles as mono-therapy in patients with RRMM will enable combinatorial use with ASCT/allo-SCT to further improve long-term disease control.

New PIs

Oral PIs (i.e., ixazomib and oprozomib) are currently in clinical development. These agents show promising activity in NDMM as well as in patients with RRMM and are more easily administered (Table 3). Ixazomib has demonstrated enhanced proteasomal inhibition.99 In a phase II trial evaluating single-agent ixazomib in patients with relapsed MM, the ORR was 34%. Common toxicities included thrombocytopenia, fatigue and nausea, while the incidence of PN was relatively low (18%).99 An ongoing phase III trial is evaluating the efficacy of ixazomib/lenalidomide/dexamethasone compared with placebo/lenalidomide/dexamethasone in RRMM (Table 3).100 Also ixazomib maintenance is being investigated post allo-SCT in high-risk MM (BMT CTN 1302). Oprozomib has also demonstrated antitumor activity in several phase I clinical studies.101,102 Gastrointestinal toxicities were common, and PN was rare.

### Table 6. Emerging therapies

| Name                          | Mechanism of action | Route administered | Trial, phase | Combinations                                      |
|-------------------------------|---------------------|--------------------|-------------|--------------------------------------------------|
| **Proteasome inhibitors**     |                     |                    |             |                                                  |
| Ixazomib                      | Reversible PI       | p.o. or i.v.       | Phase I/II123 NCT01564537, phase III | Lenalidomide, dexamethasone |
| Oprozomib                     | Irreversible PI     | p.o.               | NCT01881789, phase I/II | Lenalidomide, dexamethasone, cyclophosphamide |
| Marizomib                     | Irreversible PI     | i.v.               | NCT02103335, phase I | Pomalidomide, dexamethasone |
| **Monoclonal antibodies**     |                     |                    |             |                                                  |
| Elotuzumab                    | Anti–CS1            | i.v.               | NCT01239797, phase III | Lenalidomide, dexamethasone |
| Daratumumab                   | Anti-CD38           | i.v.               | NCT02076009, phase III | Lenalidomide, dexamethasone |
| SAR650984                     | Anti-CD38           | i.v.               | NCT01749969, phase II | Lenalidomide, dexamethasone |
| Indatuximab ravtansine        | Anti-CD138          | i.v.               | NCT01638936 phase I/IIa | Lenalidomide, dexamethasone |
| Tabalumab                     | Anti-BAFF           | i.v.               | NCT00689507, phase I | Bortezomib |
| Pembrolizumab                 | Anti-PD-1           | i.v.               | NCT02036502, phase I | Lenalidomide, dexamethasone |
| Pidilizumab                   | Anti-PD-1           | i.v.               | NCT02077959, phase I/II | Lenalidomide |
| **Small molecules and signaling pathway inhibitors** | | | | |
| Vemurafenib                   | BRAFV600E           | i.v.               | NCT01524978, phase II | None |
| CPI-0610                      | BET inhibitor       | p.o.               | NCT02157636, phase I | None |
| Ibrutinib                     | Btk inhibitor       | p.o.               | NCT01962792, phase I/IIb | Carfilzomib, dexamethasone |
| Filanesib                     | KSP inhibitor       | i.v.               | NCT02092922, phase II | None |
| **Other novel therapies**     |                     |                    |             |                                                  |
| Edmonston strain of measles   | Oncolytic           | i.v.               | NCT02192775, phase II | None |
| virus                         | virotherapy         |                    |             |                                                  |
| CAR therapy                   | Anti-BCMA           | i.v.               | NCT02215967, phase I | Cyclophosphamide, fludarabine |
|                              | Anti-CD138          | i.v.               | NCT01886976, phase I/II | None |

Abbreviations: BAFF = B-cell activating factor; BCMA = B-cell maturation antigen; Btk = Bruton tyrosine kinase; BET = bromodomain and extraterminal; CAR = chimeric antigen receptor; i.v. = intravenous; KSP = kinesin spindle protein; PD-1 = programmed death 1; PI = proteasome inhibitor; p.o. = per oral.
Monoclonal antibodies

Elotuzumab is a humanized monoclonal antibody specifically targeting CS1, a glycoprotein highly expressed on the surface of MM cells. Binding of elotuzumab leads to recruitment of natural killer cells and tumor cell death via antibody-dependent cellular cytotoxicity (Figure 2b). Elotuzumab has recently been granted breakthrough status based on results from a phase II study evaluating elotuzumab/lenalidomide/dexamethasone in patients with RRMM. This combination therapy achieved an ORR of 84%, including 14% with stringent CR (sCR)/CR and 43% VGPR. Median PFS was 29 months. Common treatment-related adverse events included gastrointestinal symptoms, muscle spasms, fatigue and upper respiratory tract infection. Notably, efficacy was greatest among lenalidomide-naive patients. A phase III trial (ELOQUENT-2) evaluating elotuzumab in patients with RRMM showed an ORR in the elotuzumab group of 79% versus 66% in the control and among lenalidomide-naive patients. A phase III trial (ELOQUENT-2) evaluating elotuzumab treatment in patients with RRMM showed disease progression or death after a 2-year follow-up (Table 3).104

Daratumumab and SAR650984, humanized monoclonal antibodies specific for CD38, can target tumor cells for elimination via antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity and phagocytosis. Daratumumab may also initiate CD38-mediated signal transduction, leading to cell death. In preliminary studies, daratumumab has demonstrated promising activity in combination with lenalidomide and dexamethasone.105 Most common adverse events were diarrhea and neutropenia, with no dose-limited toxicities. Median time to response was 4.3 weeks, with 75% PR, 15% CR and 30% VGPR. Daratumumab earned breakthrough designation based on phase I results that demonstrated notable single-agent activity with an acceptable safety profile in heavily pretreated patients.106 On the basis of these data, two phase III studies are further evaluating daratumumab in RRMM (Table 3).107,108 SAR650984 has demonstrated efficacy as a single agent in a phase I study. SAR650984-associated toxicities included fatigue, nausea, pyrexia, cytopenias, cough and gastrointestinal symptoms. The median time to response was 4.6 weeks, with an ORR of 33% in the highest-dose cohort (>10 mg/kg).109 In combination with lenalidomide and dexamethasone, the ORR was 64.5%, with 6% sCR, 26% VGPR and 32% PR; the median PFS was 6.2 months. Of note, over 95% of patients had received prior IMiD therapy. The ORR was 62.5% among patients who relapsed after or were refractory to prior lenalidomide-containing therapy.109,110

Indatuximab rтовансее is a chimeric anti-CD138 monoclonal antibody conjugated to DM4, a maytansinoid cytotoxic agent. After binding to CD138+ myeloma cells, the conjugated antibody is internalized. DM4 is metabolized in the lysosome and released into the cytoplasm, where it inhibits tubulin polymerization, leading to cell death (Figure 2b). Preliminary results from a phase I/IIa trial of indatuximab in combination with lenalidomide and dexamethasone in 30 evaluable patients revealed an ORR of 78%, with 10% sCR/CR and 33% VGPR. The most common adverse events were diarrhea, fatigue, nausea and hypokalemia.111

Tabalumab, an anti-BC-cell activating factor antibody, inhibits interactions between the myeloma cell and its microenvironment that are necessary for survival.112 Programmed death 1-specific antibodies, such as pembrolizumab and pidilizumab, enhance the tumor-specific T-cell response.113 Two clinical trials are currently evaluating the potential for chimeric antigen receptor (CAR) T cells

Figure 3. Proposed treatment guidelines for management of relapsed/refractory multiple myeloma (RRMM). Treatment decisions are guided by previous therapeutic exposure, comorbidities, risk assessment and disease- and/or treatment-related symptoms. The availability of new therapies has increased the complexity of the treatment algorithm for RRMM. BTZ = bortezomib; C = cyclophosphamide; CFZ = carfilzomib; CTD = cyclophosphamide, thalidomide and dexamethasone; D = dexamethasone; GEP = gene expression profiling; Len = lenalidomide; PLD = pegylated liposomal doxorubicin; PAN = panobinostat; POM = pomalidomide; RIC = reduced-intensity or nonmyeloablative conditioning; T = thalidomide; TD = thalidomide and dexamethasone.
that are engineered to target B-cell maturation antigen or CD138. The small-molecule inhibitors vemurafenib, CPI-0610, ibritinib, and flanesib (Table 6) and the potent PI marizomib are also in early stages of development. Oncolytic virotherapy (Figure 2b and Table 6) is also emerging as a promising therapy for RRMM. New therapeutic agents currently under development for RRMM are included in Table 6.

PROPOSED TREATMENT GUIDELINES FOR RRMM

Introduction of modern therapies, new and emerging therapies, and improvements in transplant outcomes have increased treatment options for patients with RRMM. The challenge for the physician is to choose the appropriate therapy or combination of therapies to improve outcome. Here we propose a road-map for treatment of patients with RRMM that takes into consideration disease- and patient-related factors, prior treatment response, and history of toxicity (Figure 3). When available, we highly recommend enrolment of patients in clinical trials designed to answer unresolved issues in the treatment of patients with RRMM.

EXPERT COMMENTARY

Despite substantial progress, myeloma remains an incurable disease plagued by multiple relapses and increasing resistance to therapy. The past decade has been marked by the unraveling of the pathobiological process underlying myeloma pathogenesis, the emergence of new therapies and improvement in transplant technology, which paves the way for improved responses even in patients with double-refractory MM. While randomized trials have shown superiority of modern therapies over older regimens like mephalan-prednisone, very few have shown superiority of one modern therapy over the other in terms of OS and patient-reported quality-of-life. Approach to therapy is often dictated by regional availability of drugs, HSCT technology and varied regulatory frameworks that exist in different parts of the world. Thus, there remains marked heterogeneity in how NDMM or RRMM are treated around the world.

Use of new genomic and molecular prognostic tools throughout the disease course may give better insights into the clonal dynamics of the myeloma cell and pave the way for targeted and personalized therapy approaches. Validation of promising biomarkers will help to stratify patients based on risk and potential therapeutic benefit. With the increased complexity of treatment options for patients with RRMM, physicians must understand the guidelines for administration of new agents in the context of the patient’s therapeutic and disease history. The strategy provided here may help facilitate a clear path through the complex treatment landscape in RRMM.

CONFLICT OF INTEREST

RFC declares no potential conflicts of interest. AAK has received research grants from Novartis Pharmaceuticals and Celgene, whose products are discussed in this article.

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