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Retrospective study on pomalidomide-PACE as a salvage regimen in aggressive relapsed and refractory multiple myeloma

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Abstract

Objectives: Despite major advances in treatment options for multiple myeloma (MM), patients refractory to the main drug classes and those with aggressive, especially extramedullary disease, still face a dismal outcome. For these patients, effective therapeutic options are urgently warranted.

Methods: In this retrospective study, we report on the safety and efficacy of the intensive combination regimen of pomalidomide plus cisplatin, doxorubicin, cyclophosphamide, and etoposide (Pom-PACE) in patients with relapsed refractory MM (RRMM) or plasma cell leukemia (PCL). A study population of 20 consecutive patients treated with Pom-PACE at two academic centers was included for analysis. All patients had to have a confirmed relapse according to International Myeloma Working Group criteria and adequate organ function prior to the start of therapy. Data were collected by reviewing medical charts. Exploratory analyses were performed with regard to efficacy and safety.

Results: Patients were heavily pretreated with a median number of four prior therapies (range: 1–10). All patients were exposed to immunomodulators, proteasome inhibitors, and alkylating agents, 80% were double-class refractory, 40% were triple-class refractory. Extramedullary MM or PCL were present in 15 patients (75%). Overall response rate (ORR) was 68%, with 31% achieving at least a very good partial response. Responses were achieved rapidly with an ORR of 64% after one cycle. Median progression-free survival was 8.9 months (0.92–not reached [NR]) and median overall survival was 11.8 months (3–40.6). Pom-PACE was associated with

significant toxicity. All evaluable patients experienced Grade 4 hematological toxicity. However, no treatment related mortality was observed.

Conclusion: Pomalidomide-PACE was able to induce rapid responses in heavily pretreated, aggressive RRMM with a manageable toxicity profile and therefore offers an effective salvage regimen and a potential bridging strategy to further treatment options such as chimeric antigen receptor T-cell therapy.

KEYWORDS
multiple myeloma, pomalidomide, salvage regimen

Novelty Statement

What is the new aspect of your work?
Pomalidomide plus cisplatin, doxorubicin, cyclophosphamide, and etoposide (Pom-PACE) has not been published as an effective salvage regimen in RRMM.

What is the central finding of your work?
Pom-PACE is effective in aggressive and extramedullary relapses of multiple myeloma patients.

What is the specific clinical relevance of your work?
Pom-PACE is an effective salvage regimen for aggressive extramedullary, relapsed, and refractory multiple myeloma and a useful bridging strategy before chimeric antigen receptor T-cell therapy.

1 | INTRODUCTION

Prognosis of multiple myeloma (MM) patients has been significantly improved over the past decade due to the advent of novel agents, in particular immunomodulatory drugs (Imids), proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies (CD38AB), and the widespread implementation of high-dose melphalan with autologous transplantation (ASCT).[1] However, MM is still a largely incurable disease, and patients eventually relapse.[2,3] Patients with relapsed refractory MM (RRMM) after treatment with the three major drug classes (so-called triple-exposed) or even refractory to these drugs (triple-refractory) still face an inferior outcome[4–8] despite the very promising developments in the field of chimeric antigen receptor t-cells (CAR-Ts) and bispecific monoclonal antibodies.[9–15] Furthermore, treatment with CAR-T cells or bispecifics is very resource-intensive and is currently not widely available to all patients in every healthcare setting. CAR-T cells in particular still harbor the additional challenge of significant manufacturing time, making it difficult to apply to patients with very aggressive relapse.[10]

Among RRMM, patients with extramedullary disease (EMD) or those with secondary plasma cell leukemia (PCL) have been recognized as a particularly difficult-to-treat population with very inferior survival.[5,7,16] EMD is associated with an increased rate of cytogenetic high-risk features such as deletion 17p as well as adverse gene expression profiling-70 scores.[17] These patients often present with a very aggressive relapse, requiring successful remission-inducing therapy within days.

Efficacy and feasibility of combining novel agents such as PIs or Imids with conventional chemotherapy were first studied in the TOTAL-THERAPY trials.[18,19] The first regimen published was the combination of thalidomide, cyclophosphamide, etoposide, and dexamethasone[20] later on expanded to include cisplatin and doxorubicin (DT-PACE)[19] and lastly, bortezomib (VDT-PACE).[21] A recent real-world analysis of velcade thalidomide dexamethasone, platine, adriamycin, cyclophosphamid, etoposide in RRMM highlights the continued role PACE-based regimens might play in the era of novel agents, especially as a potential bridging strategy to ASCT of CAR-Ts.[22] While these regimens, especially VDT-PACE, show efficacy in heavily pretreated patients,[23–25] significant side effects remained an issue, especially with regard to peripheral neuropathy (PNP) given the neurotoxic potential of bortezomib, thalidomide, and cisplatin. Furthermore, bortezomib and thalidomide might not be an ideal combination partner also with regard to efficacy, as many patients in this setting are already refractory to these particular agents. To address these issues, combination regimens including second generation Imids or PIs, such as lenalidomide and/or carfilzomib (KRD-PACE or KD-PACE), have been explored recently.[26,27]

Pomalidomide is a second-generation Imid that has shown efficacy in late lines of therapy in RRMM,[28,29] and is less associated with PNP than thalidomide or PIs. Additionally, pomalidomide has been

shown to overcome resistance in RRMM patients when combined with cyclophosphamide[30] and might thus be an ideal combination partner to PACE-based regimens. In this retrospective, multicenter study, we report on safety and efficacy of pomalidomide plus PACE (Pom-PACE) in 20 heavily pretreated RRMM patients.

2 | PATIENTS AND METHODS

In this retrospective study, we analyzed 20 consecutive patients with MM or PCL that were treated with Pom-PACE in the Department of Hematology, Oncology, Hemostaseology and Stem Cell Transplantation at the RWTH University Hospital in Aachen or in the Department of Hematology, Oncology and Rheumatology at the University Hospital in Heidelberg, Germany, between January 2015 and June 2021.

Inclusion criteria to be offered treatment with Pom-PACE were a confirmed relapse of MM according to International Myeloma Working Group (IMWG) criteria that was deemed clinically to be aggressive, either by the presence of EMD, PCL, or early relapse/refractoriness to prior therapy. Furthermore, patients' had to have an Eastern Cooperative Oncology Group performance status of 0–2 and adequate renal and cardiac function as assessed by creatinine clearance and echocardiography prior to the start of therapy. Refractoriness to pomalidomide was an exclusion criterion. Presence of EMD was assessed by computed tomography scans or magnetic resonance imaging prior to the start of therapy.

Treatment consisted of cisplatin 10 mg/m^2, doxorubicin 10 mg/m^2, cyclophosphamide 400 mg/m^2, etoposide 40 mg/m^2, and dexamethasone 40 mg intravenously on Days 1–4. Cisplatin, cyclophosphamide, and etoposide were given continuously over 24 h, doxorubicin and dexamethasone were given as a short infusion or bolus injection. Pomalidomide (4 mg) was given orally every second day on Days 1–21. Given the continuous infusion of cisplatin, cyclophosphamide, and etoposide, patients had to be admitted to the hospital for at least 96 h for each cycle, with the potential prolongation of hospital stay or re-admittance in case of complications. The treatment cycle was repeated on Day 29, if possible, for up to four cycles, depending on the physician's decision as well as the further treatment strategy.

Granulocyte-colonisation stimulation factor (G-CSF) support was not obligatory but was encouraged. All patients received antithrombotic prophylaxis with standard low-molecular weight heparin while hospitalized, which was suspended when platelet counts dropped to <30–50/nL depending on individual risk evaluation. With regard to prophylactic anti-infective strategies, antiviral prophylaxis against herpes simplex and varicella zoster virus with acyclovir as well as prophylaxis against *Pneumocystis jirovecii* pneumonia with trimethoprim/sulfamethoxazole were strongly recommended for all patients. Antifungal, non-pneumocystis prophylaxis, or antibacterial prophylaxis were not routinely administered.

Data collection was performed by reviewing medical charts, including the review pf discharge letters from external medical providers in case of admission to other hospitals due to an adverse event. High-risk cytogenetics were defined as the presence of at least one of the following: deletion 17p, translocations t(4;14) or t(14;16), gain 1q. Response was evaluated according to IMWG criteria, including assessment by imaging techniques in the case of EMD.[31] Overall response

TABLE 1 Patients' characteristics at start of pomalidomide plus cisplatin, doxorubicin, cyclophosphamide, and etoposide.

Patients' characteristics	*n* (%)
Age	
Median (years)	57.6
Range (years)	43.9–60.6
Gender	
Female	10 (50)
Performance status (ECOG)	
0	8 (40)
1	10 (50)
2	2 (10)
Paraprotein subtype	
IgG	12 (60)
IgA	4 (20)
κ or λ light chain	3 (15)
Asecretory	1 (5)
Time from diagnosis	
Median (years)	3.0
Range (years)	0.4–10.4
Number of prior therapies	
Median	4
Range	1–10
Refractory to last therapy	18 (90)
Type of prior therapies	
Autologous stem cell transplantation	19 (95)
Proteasome inhibitor (PI) exposed	
Bortezomib	19 (95)
Carfilzomib	17 (85)
Imunomodulatory drugs (Imid) exposed	
Lenalidomide	20 (100)
Pomalidomide	0 (0)
Anti-CD38 antibody exposed	
Daratumumab/isatuximab	9 (45)
Double-refractory (Imid, PI)	18 (90)
Triple-class refractory	8 (40)
Cytogenetic testing ($n = 16$)	
High risk	11 (55)
Deletion 17p	7 (44)
t(4;14)	2 (13)
t(14;16)	1 (6)
Gain 1q	6 (38)
Plasma cell leukemia	2 (10)
Extramedullary disease	13 (65)

Abbreviation: ECOG, Eastern Cooperative Oncology Group; IgA, immunoglobulin A.

TABLE 2 Response assessment.

	Response after Cycle 1 (response assessment available: $n = 14$)		Best response (response assessment available: $n = 16$)	
	n	%	*n*	%
PD	2	14	2	13
SD	2	14	2	13
MR	1	7	1	6
PR	8	57	6	38
VGPR	1	7	3	19
nCR	0	0	2	13
ORR	9	64	11	68

Note: No response assessment according to IMWG criteria was available in six and four patients after Cycle 1 and at best response, resp., due to either hyposecretory myeloma or missing data point.
Abbreviations: MR, minimal response; nCR, near complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

rate (ORR) was defined as achieving a partial response (PR) or better, and duration of response (DOR) was defined as time from Day 1 of cycle one Pom-PACE to disease progression or death in patients who achieved a PR or better. Clinical benefit rate (CBR) was defined as patients receiving at least a stable disease (SD).

With regard to statistical methods, clinical characteristics were analyzed in a descriptive manner, median and range were given for continuous variables. Time-to-event analyses and associated 95% confidence intervals were estimated with the use of Kaplan–Meier methods. Patients proceeding to allogeneic stem cell transplantation were censored with regard to progression-free survival (PFS) at the time of transplant.[32] All statistical analyses were performed using Graphpad version 5. Safety analysis was performed using CTCAE V.5.0 criteria.

All patients provided written informed consent for retrospective data analysis. This study was approved by the local ethics committees (EK395/21 and S-096/2017).

3 | RESULTS

Median age at start of Pom-PACE was 57.6 years (range 43.9–66.3 years), 50% were male. Median time from diagnosis to Pom-PACE was 3 years (0.4–10.4 years), and median lines of prior therapies was 4 (1–10). Ninety percentages of patients were refractory to their last line of therapy. All patients were exposed to Imid and PI, 90% were double-refractory (Imid and PI), 40% were triple-refractory (Imid, PI, and CD38AB). Ninety-five percentages of patients were exposed to an alkylating agent or had undergone prior ASCT. At start of Pom-PACE, 65% of patients had EMD and 10% had PCL. Three patients had hyposecretory, one patient had asecretory MM, all of them with EMD. In seven patients with available biopsy and assessment of proliferation at start of Pom-PACE, median Ki67 was 60% (range 30%–100%). High-risk cytogenetics was present in 55%. Clinical characteristics of patients are summarized in Table 1 (values are mean).

Patients received a median of 2 cycles of Pom-PACE (range 1–4). Best ORR in IMWG-evaluable patients was 68% (11/16) with PR in six (38%), very good partial response (VGPR) in three (19%), and near complete response (nCR) in two (13%). CBR was 88% (14/16) with an additional three patients achieving a minimal response (two) or SD (one). Two patients were primary refractory (Table 2). Formal response evaluation according to IMWG criteria was not possible in four patients due to a hyposecretory MM or missing data point. Responses were achieved very rapidly, with 9 out of 14 patients with available response assessment after Cycle 1 already reaching a PR or better at that time point, corresponding to an ORR of 64% after one cycle.

At a median follow up of 15 months, median PFS was 8.9 months (0.92–NR) and median overall survival (OS) was 11.8 months (3–40.6) (Figure 1). The median DOR was 15 months in our patient cohort.

With regard to subsequent therapies, Pom-PACE was used as a bridge to transplant in five (25%) patients (two autologous and three allogeneic). Patients that underwent autologous or allogeneic transplantation as consolidation following Pom-PACE had a median OS of 11.1 months; patients without subsequent transplant had a median OS of 11.1 months. In eight (40%) patients with an adequate response and no intention to transplant, treatment was deescalated, mainly to pomalidomide/dexamethasone. In three patients, Pom-PACE had to be discontinued due to significant toxicity and in two patients due to progressive disease. Two patients declined further follow-up.

Pom-PACE was associated with significant toxicity. Hematologic toxicity was pronounced, but manageable. All patients with available data experienced neutropenia common toxicity criteria (CTC) Grade 4 (11/11) and thrombocytopenia CTC Grade 4 (15/15). G-CSF support was given in 72% (13/18), red blood cell transfusions in 94% (15/16), and platelet transfusions in 75% (12/16) of patients with available data.

With regard to non-hematologic toxicity, febrile neutropenia was common and reported in 61% (11/18) of patients with available data. Re-admission to the hospital in-between cycles was required in 50% (9/18) of patients, resulting in 14 additional hospital stays. The main

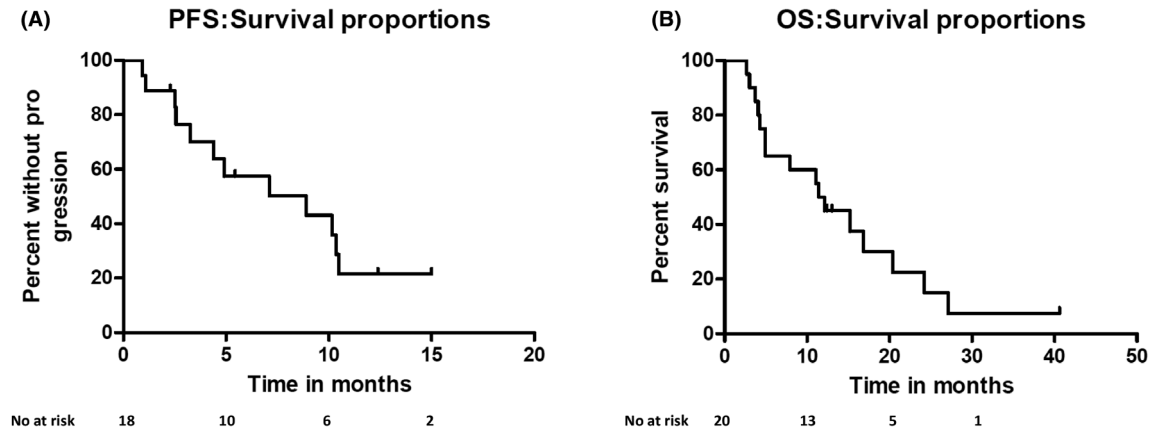

FIGURE 1 Progression-free survival (PFS) (A) and overall survival (OS) (B).

reasons for re-admission were febrile neutropenia or a pre-scheduled re-admission during critical cytopenia. Severe complications occurred in three patients: one case of cerebral toxoplasmosis after the fourth cycle of Pom-PACE, one case of severe skin infection requiring operative debridement and a mesh graft, and one case of perforated sigma diverticulitis requiring a descendostoma. Of note, despite the potential nephrotoxicity and neurotoxicity of cisplatin, only two cases of reduced renal function and no cases of new or worsening PNP were observed.

4 | DISCUSSION

In this retrospective study, we report a high ORR to pomalidomide combined with a backbone of intensive cytotoxic chemotherapy (Pom-PACE) in a cohort of heavily pretreated RRMM, with the majority with aggressive EMD or PCL. Responses were obtained very rapidly. The Pom-PACE regime could be successfully applied as a bridging strategy to transplant or deescalated after response induction to standard pomalidomide/dexamethasone therapy.

While the overall prognosis of patients with MM has significantly improved and the advent of novel T-cell engaging therapies opens up new possibilities, patients with multi-refractory disease, especially those with aggressive extramedullary relapse, remain a challenging patient population.[5–7] These patients often require intensive, rapidly response-inducing therapy to avoid organ failure. In this setting, various combinations of conventional, cytotoxic chemotherapy, in particular the PACE regimen, with novel agents have been assessed.[18–21,23–25]

While cross-trial comparisons are fraught with bias, especially in highly heterogenous RRMM patient populations, the ORR of 68% achieved with Pom-PACE in our cohort is within range of those observed with VDT-PACE or KD-PACE,[23,27] while avoiding some of the drug-specific adverse events associated with the latter regimens.

A VGPR or better was achieved in 31% of our patients. While the sample size is obviously too small to allow for statistical risk factor analysis, it might be of interest to note that patients achieving VGPR or better included those with deletion 17p, EMD, PCL, or triple-class refractory status. One common feature of patients with superior response might be a slightly younger age (median age 51.7 years); however, this remains speculative. Furthermore, it is noteworthy, that patients with a VGPR or better seemed to achieve a similar median PFS (10.1 months), but a much longer OS (20.4 months) compared to the overall patient cohort. This might be indicative of a more chemosensitive disease allowing potentially deriving a more significant benefit from subsequent therapies.

In a small study of RRMM patients treated with VDT-PACE an ORR of 54% was achieved.[23] The median PFS was only about a third of that achieved with Pom-PACE (3.1 vs. 8.9 months). Of note, the patient population in the VDT-PACE study was less refractory (triple-refractory 8% vs. 40%) and had a lower rate of EMD (36% vs. 65%) compared to our patient cohort. Efficacy in the EMD cohort is of special interest as EMD is a negative prognostic factor for PFS in bispecific T-Cell engager and CAR-T cell therapy.

In a retrospective study of RRMM treated with KD-PACE, an ORR of 77% was observed.[27] Again, the proportion of triple-refractory patients was lower (19% vs. 40%) and fewer patients had EMD (8% vs. 65%) compared to our patient cohort. Interestingly, patients induced with KD-PACE that were able to be bridged to ASCT or allogeneic transplantation experienced a significantly superior PFS (8.3 vs. 2.3 months) and OS (16.7 vs. 4.3 months) compared to those without further consolidating therapy. In contrast, only 3/10 patients in our cohort with an OS of 12 months or longer received consolidating transplantation. Out of three patients in our cohort with an OS of 24 months or longer, only one had received a consolidating allogeneic transplant, while two had been deescalated to standard pomalidomide/dexamethasone.

With regard to adverse events, it has to be stated that all PACE-based regimens are associated with significant toxicity and have to be administered to well-selected patients in centers with experience in managing intensive cytotoxic chemotherapy. However, in patients with adequate fitness and organ function, the toxicities associated

with Pom-PACE were manageable, and no fatal complications were observed in our patient cohort. While the most common toxicity was hematotoxicity, the most serious adverse events were infectious complications. Therefore, G-CSF support is recommended and anti-infective prophylaxis strategies should be considered following Pom-PACE. A remaining autograft backup should be used in these cases to reduce long-term cytopenia.

Compared with other PACE-based regimens, it is worth noting that no thromboembolic complications (in contrast to several observed with VDT-PACE) and no cardiac complications (in contrast to those observed with KD-PACE) occurred in our patient cohort treated with Pom-PACE. In addition, we observed no new or worsening PNP in our patients.

With the introduction of T-cell engaging therapies, in particular CAR-T cells or bispecific antibodies, to clinical practice, new and highly potent treatment options have opened up for RRMM patients questioning prior indications for conventional chemotherapy. However, we think that for a select patient population, effective combination therapies of novel agents and cytotoxic chemotherapy, such as the Pom-PACE regimen, might still constitute a useful tool in the anti-myeloma armamentarium. While both b-cell maturation antigen (BCMA) CAR-T cells and anti-BCMA bispecific antibodies are by now approved by food and drug association and European medicines agency, these therapies are still not available to all patients and might only be administered by highly specialized centers. Furthermore, while several efforts are underway to shorten production time, effective bridging strategies are still often necessary, especially in highly aggressive disease. In addition, RRMM with EMD seems to be associated with a shorter PFS[5,7,16] following CAR-T cell therapy and thus remain a difficult-to-treat patient population even in the CAR-T era, requiring specialized care and highly potent therapeutic strategies.

As a retrospective real-world analysis, our study is associated with several limitations. The main point is the heterogeneity of the patient population and the small sample size limiting statistical analyses, as well as carrying the intrinsic risk of a potential selection bias of patients by the treating physicians. Furthermore, not all data points of interest were available for all patients at all time points as data collection was performed based on electronic patient files. Incidence of certain adverse events might therefore be underestimated.

In summary, the combination of pomalidomide with the cytotoxic chemotherapy backbone PACE was shown to induce rapid responses in a large proportion of patients with RRMM, many of whom with EMD. Given the significant toxicity profile, patients should be selected and monitored carefully. In the era of CAR-T cell therapy, it may be applied as an effective bridging or debulking strategy.

AUTHOR CONTRIBUTIONS

DG and NG conceived the idea of the manuscript, collected data, and made the statistical analysis and were responsible for the first draft. All authors were involved in proofreading, revisions, and improvement of the first manuscript. All authors approved the submitted version, and critically revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

Martin Kirschner reports advisory board activity for Böhringer-Ingelheim, Bayer, BMS, Chugai, Roche and honoraria for Novartis, Böhringer Ingelheim. Tim H. Brümmendorf reports consultancy for Pfizer, Novartis, Janssen, Merck, Incyte, Gilead and research funding from Pfizer and Novartis. Deniz Gezer reports advisory board activity for AMGEN, Takeda and Celgene and travel money from AMGEN, Celgene and Bristol-Myers Squibb. Nicola Giesen reports advisory board activity for AstraZeneca, MSD, Pfizer, Sanofi, Takeda and honoraria for Abbvie, AstraZeneca, GSK, Hexal, MSD, Pfizer, Takeda. Hartmut Goldschmidt reports advisory board activity for Adaptive Biotechnology, Amgen, BMS, Janssen, Sanofi; research funding from Amgen, BMS, Celgene, GlycoMimetics Inc., GSK, Heidelberg Pharma, Hoffmann-La Roche, Karyopharm, Janssen, Incyte Corporation, Millenium Pharmaceuticals Inc., Molecular Partners, Merck Sharp and Dohme (MSD), MorphoSys AG, Pfizer, Sanofi, Takeda, Novartis; travel grants from Amgen, BMS, GlaxoSmithKline (GSK), Janssen, Novartis, Sanofi, Pfizer; research grants from Amgen, Array Biopharma/Pfizer, BMS/Celgene, Chugai, Dietmar-Hopp-Foundation, Janssen, Johns Hopkins University, Mundipharma GmbH, Sanofi and honoraria activity for Amgen, BMS, Chugai, GlaxoSmithKline (GSK), Janssen, Novartis, Sanofi, Pfizer. Marc S. Raab reports advisory board activity for BMS, Amgen, GSK, Janssen, Sanofi, Pfizer, AbbVie, Takeda, travel money from BMS, Amgen, Janssen; research funding from BMS, Janssen, Sanofi, Heidelberg Pharma and honoraria activity for BMS, Janssen, AbbVie, Sanofi. Carsten Müller-Tidow reports research funding from Pfizer and Bioline RX.

DATA AVAILABILITY STATEMENT

All relevant data are included in the manuscript and are free to access after potential publication. There is no data to cite in this manuscript.

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REFERENCES

1. Landgren O, Iskander K. Modern multiple myeloma therapy: deep, sustained treatment response and good clinical outcomes. *J Intern Med*. 2017;281(4):365-382.
2. Kumar SK, Dimopoulos MA, Kastritis E, et al. Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study. *Leukemia*. 2017;31(11):2443-2448.
3. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111(5):2516-2520.
4. Suarez-Londono JA, Rohatgi A, Antoine-Pepeljugoski C, Braunstein MJ. Aggressive presentation of plasmablastic myeloma. *BMJ Case Rep*. 2020;13(4):e234436.

5. Chavan SS, He J, Tytarenko R, et al. Bi-allelic inactivation is more prevalent at relapse in multiple myeloma, identifying RB1 as an independent prognostic marker. *Blood Cancer J*. 2017;7(2):e535.
6. Schürch CM, Rasche L, Frauenfeld L, Weinhold N, Fend F. A review on tumor heterogeneity and evolution in multiple myeloma: pathological, radiological, molecular genetics, and clinical integration. *Virchows Arch*. 2020;476(3):337-351.
7. Weinhold N, Ashby C, Rasche L, et al. Clonal selection and double-hit events involving tumor suppressor genes underlie relapse in myeloma. *Blood*. 2016;128(13):1735-1744.
8. Robak P, Drozdz I, Szemraj J, Robak T. Drug resistance in multiple myeloma. *Cancer Treat Rev*. 2018;70:199-208.
9. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *Lancet*. 2021;398(10297):314-324.
10. San-Miguel J, Dhakal B, Yong K, et al. Cilta-cel or standard care in lenalidomide-refractory multiple myeloma. *N Engl J Med*. 2023;389(4):335-347.
11. Delforge M, Otero PR, Shah N, et al. Analysis of patient-reported experiences up to 2 years after receiving idecabtagene vicleucel (ide-cel, bb2121) for relapsed or refractory multiple myeloma: longitudinal findings from the phase 2 KarMMa trial. *Leuk Res*. 2023;129:107074.
12. Munshi NC, Anderson LD, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *N Engl J Med*. 2021;384(8):705-716.
13. Moreau P, Garfall AL, van de Donk NWCJ, et al. Teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med*. 2022;387(6):495-505.
14. Chari A, Minnema MC, Berdeja JG, et al. Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. *N Engl J Med*. 2022;387(24):2232-2244.
15. Lesokhin AM, Tomasson MH, Arnulf B, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. *Nat Med*. 2023;29(9):2259-2267.
16. Deng S, Xu Y, An G, et al. Features of extramedullary disease of multiple myeloma: high frequency of p53 deletion and poor survival: a retrospective single-center study of 834 cases. *Clin Lymphoma Myeloma Leuk*. 2015;15(5):286-291.
17. Bansal R, Rakshit S, Kumar S. Extramedullary disease in multiple myeloma. *Blood Cancer J*. 2021;11(9):161.
18. Dimopoulos MA, Weber D, Kantarjian H, Delasalle KB, Alexanian R. HyperCVAD for VAD-resistant multiple myeloma. *Am J Hematol*. 1996;52(2):77-81.
19. Lee C-K, Barlogie B, Munshi N, et al. DTPACE: an effective, novel combination chemotherapy with thalidomide for previously treated patients with myeloma. *J Clin Oncol*. 2003;21(14):2732-2739.
20. Moehler TM, Neben K, Benner A, et al. Salvage therapy for multiple myeloma with thalidomide and CED chemotherapy. *Blood*. 2001;98(13):3846-3848.
21. Barlogie B, Anaissie E, van Rhee F, et al. Incorporating bortezomib into upfront treatment for multiple myeloma: early results of total therapy 3. *Br J Haematol*. 2007;138(2):176-185.
22. Kikuchi T, Tsukada N, Kunisada K, et al. Real-world clinical outcomes in patients with relapsed and refractory multiple myeloma receiving VTD-PACE treatment in the era of monoclonal antibodies. *Ann Hematol*. 2023;102(12):3489-3497.
23. Lakshman A, Singh PP, Rajkumar SV, et al. Efficacy of VDT PACE-like regimens in treatment of relapsed/refractory multiple myeloma. *Am J Hematol*. 2018;93(2):179-186.
24. Krem MM, Reynolds SB, Hashmi H, et al. The VR-DCEP regimen rescues mobilization failures and controls refractory disease in multiple myeloma. *Bone Marrow Transplant*. 2019;55:1451-1453.
25. Griffin PT, Ho VQ, Fulp W, et al. A comparison of salvage infusional chemotherapy regimens for recurrent/refractory multiple myeloma. *Cancer*. 2015;121(20):3622-3630.
26. Parrondo RD, Roy V, Sher T, Alegria V, Chanan-Khan AA, Ailawadhi S. Use of KRD-PACE as salvage therapy in aggressive, relapsed/bortezomib-refractory extramedullary multiple myeloma: a report of two cases and literature review. *Case Rep Hematol*. 2020;2020:4360926.
27. Alsouqi A, Khan M, Dhakal B, et al. KD-PACE salvage therapy for aggressive relapsed refractory multiple myeloma, plasma cell leukemia and extramedullary myeloma. *Clin Lymphoma Myeloma Leuk*. 2021;21(8):526-535.
28. Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. *Lancet*. 2019;394(10214):2096-2107.
29. Dimopoulos MA, Dytfeld D, Grosicki S, et al. Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. *N Engl J Med*. 2018;379(19):1811-1822.
30. Weisel K, Sonneveld P, Spencer A, et al. A comparison of the efficacy of immunomodulatory-free regimens in relapsed or refractory multiple myeloma: a network meta-analysis. *Leuk Lymphoma*. 2019;60(1):151-162.
31. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International myeloma working group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12):e538-e548.
32. Delgado A, Guddati AK. Clinical endpoints in oncology – a primer. *Am J Cancer Res*. 2021;11(4):1121-1131.

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