Received: 30 August 2021 | Revised: 5 November 2021 | Accepted: 15 November 2021

DOI: 10.1002/hon.2949

WILEY

ORIGINAL ARTICLE

Salvage therapy with "Dara-KDT-P(A)CE" in heavily pretreated, high-risk, proliferative, relapsed/refractory multiple myeloma

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Abstract

The multi-agent therapy "VDT-PACE" represents an established regimen in relapsed/refractory multiple myeloma (RRMM). Here, we report on our experience with a "modified VDT-PACE" incorporating new generation anti-MM agents daratumumab and carfilzomib ("Dara-KDT-P(A)CE"). We retrospectively analyzed 38 patients with RRMM treated with "Dara-KDT-P(A)CE". The median age was 62 (range 45–82) years, and the patients were heavily pretreated with a median of 5 (range 2–12) prior lines of therapy. Twenty-one (55%) patients suffered from penta-refractory MM. High-risk cytogenetics was present in 31 (81%) patients. The patients received a median of 2 (range 1–10) cycles of this therapy, and the overall response rate (ORR) was 70%. Patients with penta-refractory MM and high-risk cytogenetics showed similar ORR of 65% and 79%, respectively. The median progression-free survival (PFS) and overall survival were 4.1 (95% CI 2.7–5.4) and 8.4 (95% CI 6.7–10.0) months, respectively. Patients with lactate dehydrogenase >250 IU/L showed significantly shorter PFS in comparison with others patients ($p = 0.006$). We used this regimen as bridging therapy prior to chimeric antigen receptor T-cell infusion in four patients. In conclusion, "Dara-KDT-P(A)CE" is an effective salvage therapy for patients with heavily pretreated, multi-refractory, high-risk RRMM lacking alternative options.

KEYWORDS
Dara-KDT-P(A)CE, multiple myeloma, refractory, salvage

Klaus Martin Kortüm and Leo Rasche have contributed equally.

1 | INTRODUCTION

The survival outcome of patients with multiple myeloma (MM) has been dramatically improved by the introduction of proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and monoclonal antibodies (mAbs) in the last few decades.[1] Currently, novel immunotherapies, for example, antibody drug conjugates (ADCs), bispecific T-cell engagers (BiTEs), and chimeric antigen receptor modified (CAR) T-cells are bringing new hope to patients with relapsed/refractory (RR) MM.[2–4] In particular, B-cell maturation antigen (BCMA) targeted CAR T-cells have shown impressive efficacy with an overall response rate (ORR) of up to 100% in RRMM patients.[5–8] However, a recent meta-analysis of Roex et al. has demonstrated a median progression-free survival (PFS) of merely 12.2 months in RRMM patients receiving BCMA CAR T-cells,[9] indicating an ongoing need for salvage strategies including treatment of relapse after BCMA-directed therapies. Moreover, the optimal bridging therapy for RRMM patients waiting for a slot of immunotherapy trials or during the CAR T-cell manufacturing process is undefined. Taken together, the management of heavily pretreated, multi-refractory, high-risk RRMM patients despite advancements in the field of novel immunotherapies remains challenging, and effective treatment strategies using already approved agents are highly warranted.

So far, the "VDT-PACE" regimen (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide), which was initially developed by the Arkansas group to overcome cross-resistance in newly diagnosed MM in analogy to the treatment of acute lymphocytic leukemia,[10] is an established salvage therapy for RRMM patients.[11] More recently, carfilzomib-based therapies have been reported to be effective in RRMM.[12,13] Additionally, daratumumab and pomalidomide containing multi-agent therapy "Pom-PAD-Dara" (pomalidomide, bortezomib, doxorubicin, dexamethasone, and daratumumab) has shown promising anti-MM activity.[14] Thus, incorporation of these new-generation anti-MM agents such as carfilzomib, daratumumab, and pomalidomide into "VDT-PACE" might improve the anti-MM activity of this regimen. Here, we report on our single-center experience with the multi-agent salvage therapy "Dara-KDT-P(A)CE" (daratumumab, carfilzomib, dexamethasone, thalidomide, cisplatin, cyclophosphamide, and etoposide). The aim of our current study was to analyze the efficacy and safety profile of this regimen and its modifications in patients with heavily pretreated high-risk RRMM.

2 | METHODS

2.1 | Patients and therapy

This is a retrospective single-center analysis of RRMM patients treated with "Dara-KDT-P(A)CE" and its modifications. All procedures were performed according to the institutional and national ethical standards and the Declaration of Helsinki. Informed consent was obtained from all patients included in this study. We collected and analyzed data of 38 patients who received "Dara-KDT-P(A)CE" from May 2018 to June 2021 at our institution. RRMM was defined according to the International Myeloma Working Group (IMWG) recommendations.[15] Patients harboring at least one of the following alterations were considered as high-risk cytogenetics: t(4; 14), t(14; 16), t(14; 20), gain1q21, and del(17p).[16] We retrieved and evaluated patients' demographic data, subtype of MM, cytogenetics, relapse pattern, laboratory features, prior treatments, response to therapy, adverse events (AEs), and survival outcome.

"Dara-KDT-P(A)CE" is composed of daratumumab 16 mg/kg body weight on days 1, 8 as intravenous (IV) infusion; carfilzomib 20/27 mg/m^2 body surface area (BSA) IV over 30 min on days 1, 2, 8, 9; dexamethasone 40 mg orally on days 1, 2, 8, 9; thalidomide 100 mg orally qd at bedtime on days 1–21; cisplatin 10 mg/m^2 BSA IV over 60 min on days 4–7; doxorubicin 10 mg/m^2 BSA IV over 60 min on days 4–7; cyclophosphamide 400 mg/m^2 BSA IV over 60 min on days 4–7; etoposide 40 mg/m^2 BSA IV over 60 min on days 4–7. In the first patients receiving "Dara-KDT-P(A)CE", we did not administer doxorubicin due to potential severe hematological and/or cardiologic toxicities. Therefore, in this regimen, "A" was written in brackets. The therapy cycle was repeated on day 29. This regimen was modified as per the treating physician's discretion (Table 1). Dexamethasone, paracetamol, famotidine, and clemastine were given as premedication prior to daratumumab. The patients received thrombosis prophylaxis (e.g., enoxaparin 40 mg qd as subcutaneous injection or aspirin 100 mg qd orally), anti-infective prophylaxis for *Pneumocystis jirovecii* (e.g., co-trimoxazole 960 mg qod orally) and herpes virus (e.g., acyclovir 400 mg bid orally). Hematopoietic growth factors and transfusion of erythrocyte or platelet concentrate were administered as per institutional practice and international guidelines.[17]

2.2 | Response, survival outcome, and adverse events

Response evaluation was performed after each cycle according to the current guidelines of IMWG.[18] Overall response rate (ORR) was defined as the proportion of patients who achieved a partial remission (PR) or better. Overall survival (OS) was defined as the time between start of "Dara-KDT-P(A)CE" and death or the last follow-up. PFS was defined as the period from initiation of "Dara-KDT-P(A)CE" to relapse or progression or the last follow-up, if no relapse or progression was observed. AEs during chemotherapy were classified as per the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

2.3 | Statistical analysis

For descriptive statistics, data are given as absolute numbers and percentage, and if not otherwise stated as median and range. Survival outcome was analyzed using Kaplan–Meier method. We used log-rank test to compare the survival outcome between subgroups.

TABLE 1 Dosing and dose modification of the regimen

Agent	Dosing
Daratumumab	16 mg/kg on days 1,8 I.V.
Carfilzomib	27 mg/m^2 on days 1,2,8,9 I.V.
Cisplatin	10 mg/m^2 on days 4–7 I.V.
Doxorubicin	10 mg/m^2 on days 4–7 I.V.
Etoposide	40 mg/m^2 on days 4–7 I.V.
Cyclophosphamide	400 mg/m^2 on days 4–7 I.V.
Dexamethasone	40 mg on days 1,2,8,9 P.O.
Thalidomide	100 mg on days 1–21 P.O.
Dose modifications, *n* (%)	
Daratumumab	
Not administered	10 (26)
16 mg/kg	28 (74)
Carfilzomib	
20 mg/m^2	2 (5)
27 mg/m^2	24 (63)
36 mg/m^2	9 (24)
56 mg/m^2	3 (8)
Thalidomide	
100 mg	28 (73)
Replaced with pomalidomide 2 mg	9 (24)
Replaced with pomalidomide 4 mg	1 (3)
Cisplatin	
Not administered	4 (11)
3.75 mg/m^2	1 (3)
5 mg/m^2	11 (29)
7.5 mg/m^2	7 (18)
10 mg/m^2	15 (39)
Doxorubicin	
Not administered	29 (76)
10 mg/m^2	8 (21)
5 mg/m^2	1 (3)
Cyclophosphamide	
Not administered	1 (3)
150 mg/m^2	1 (3)
200 mg/m^2	11 (29)
300 mg/m^2	8 (21)
400 mg/m^2	17 (44)
Etoposide	
15 mg/m^2	1 (3)
20 mg/m^2	11 (29)
30 mg/m^2	8 (21)
40 mg/m^2	18 (47)

Abbreviations: I.V., intravenous; P.O., per os.

These analyses were performed with GraphPad Prism 5.0 (GraphPad Software Inc.). A *p*-value less than 0.05 was deemed to be statistically significant.

3 | RESULTS

3.1 | Patients' characteristics

We identified 38 RRMM patients who were treated with "Dara-KDT-P(A)CE" and its modifications. More than half of the patients were male (n = 24, 63%), and the median age at start of "Dara-KDT-P(A)CE" was 62 (range 45–82) years. The median time between diagnosis of MM and initiation of "Dara-KDT-P(A)CE" was 50 (range 9–287) months. The majority of the patients had high-risk cytogenetics (n = 31, 81%). Extramedullary disease (EMD) was present in 19 (50%) of the patients, with 4 (12%) patients showing non-secretory EMD progression at treatment start.

The patients were heavily pretreated with a median of 5 (range 2–12) prior lines of therapy. All patients were treated with at least one PI and at least one IMiD, and all except one (n = 37, 97%) patient received daratumumab in the prior lines of therapy. Thirty-four (89%) and 4 (11%) patients underwent autologous (auto) and allogeneic (allo) stem cell transplant (SCT), respectively. BCMA-targeted ADCs, CAR T-cells, and BiTEs were administered in four (11%), two (5%), and one (3%) patients, respectively. The vast majority of our patients (n = 37, 97%) were refractory to the last line of therapy, with 36 (95%), 27 (71%), 30 (79%), 30 (79%), and 37 (97%) patients being refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab, respectively. Twenty-one (55%) patients showed penta-refractory (daratumumab, pomalidomide, lenalidomide, carfilzomib, and bortezomib) MM. Fifteen (39%) patients had elevated lactate dehydrogenase (LDH) levels prior to therapy initiation. We summarized the patients' characteristics in Table 2.

3.2 | Treatment and response to therapy

Overall, the patients received a median of 2 (range 1–10) cycles of "Dara-KDT-P(A)CE"-like therapy, with eight (21%) patients being treated with ≥4 cycles. The main reason for therapy discontinuation was progressive disease (PD) (n = 27, 79%). In respect to carfilzomib dosing, we balanced between efficacy and toxicity, but overall aimed for the highest tolerable dose per patient. In this context, 2 (5%), 24

TABLE 2 Patients' characteristics

Parameter	
Patients, *n*	38
Gender, *n* (%)	
Male	24 (63)
Female	14 (37)
Age at diagnosis of MM, median, years (range)	58 (35–79)
Age at starting Dara-KDT-P(A)CE, median, years (range)	62 (45–82)
Time between diagnosis of MM and start of Dara-KDT-P(A)CE, median, months (range)	50 (9–287)
Subtype, *n* (%)	
IgG	23 (60)
IgA	10 (26)
IgD	1 (3)
LC	4 (11)
ISS stage, *n* (%)	
I	13 (34)
II	12 (32)
III	8 (21)
NA	5 (13)
Cytogenetics, *n* (%)	
High risk[a]	31 (81)
Standard-risk	7 (19)
Prior lines of therapy, *n* (%)	
2–3	11 (29)
4–5	9 (24)
≥6	18 (47)
Response status at start of Dara-KDT-P(A)CE, *n* (%)	
Refractory to the last line of therapy	37 (97)
Progression from remission	1 (3)
Penta-refractory[b]	21 (55)
Relapse pattern, *n* (%)	
Serologic progression	34 (89)
Non-secretory EMD	4 (11)
EMD with secretory activity	15 (39)
Laboratory values prior to Dara-KDT-P(A)CE, median (range)	
LDH, IU/L	223 (116–1339)
GFR, ml/min	74 (44–108)
Hemoglobin, g/dl	9.8 (7.5–15.5)
WBC, $\times 10^3$/μl	4.1 (1.3–10.4)
ANC, $\times 10^3$/μl	2.2 (0.3–7.7)
PLT, $\times 10^3$/μl	124 (32-724)

(Continues)

TABLE 2 (Continued)

Parameter	
Prior treatment, *n* (%)	Exposed/refractory
IMiDs	38 (100)/36 (95)
Lenalidomide	37 (97)/30 (79)
Pomalidomide	31 (82)/30 (79)
PIs	38 (100)/37 (97)
Bortezomib	38 (100)/36 (95)
Carfilzomib	28 (74)/27 (71)
Monoclonal antibodies	
Daratumumab	37 (97)/37 (97)
Elotuzumab	10 (26)/9 (24)
Prior SCT	
Autologous SCT	34 (89)
Allogeneic SCT	4 (11)
Prior BCMA-directed novel immunotherapy	
ADC	4 (11)
CAR-T-cell	2 (5)
BITE	1 (3)
Best response to Dara-KDT-P(A)CE (data evaluable in 34 patients), *n* (%)	
VGPR	10 (29)
PR	14 (41)
MR	8 (24)
PD	2 (6)

Abbreviations: ADC, antibody drug conjugate; ANC, absolute neutrophil count; BCMA, B-cell maturation antigen; BITE, bispecific T-cell engager; CAR-T-cell, chimeric antigen modified T-cell; Dara-KDT-P(A)CE, pomalidomide, bortezomib, doxorubicin, dexamethasone, daratumumab; EMD, extramedullary disease; GFR, glomerular filtration rate; IMiDs, immunomodulatory drugs; ISS, The Multiple Myeloma International Staging System; LC, light chain; LDH, lactate dehydrogenase; MM, multiple myeloma; MR, minor response; NA, not available; PD, progressive disease; PIs, proteasome inhibitors; PLT, platelet count; PR, partial remission; SCT, stem cell transplant; VGPR, very good partial remission; WBC, white blood cell count.

[a]Defined as presence of at least one of the following: del(17p), gain1q21, t(4; 14), t(14; 16), and t(14; 20).

[b]Defined as refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab.

(63%), 9 (24%), and 3 (8%) patients were treated with carfilzomib at doses of 20, 27, 36, and 56 mg/m^2 BSA IV twice weekly, respectively. The majority of our patients ($n = 28$, 73%) received thalidomide 100 mg qd orally, because thalidomide showed less hematotoxicity than other IMiDs such as lenalidomide and/or pomalidomide.[19] We replaced thalidomide with pomalidomide 2 or 4 mg qd orally in 10 (27%) patients with sufficient hematopoiesis that had tolerated thalidomide well in the first cycle. Doxorubicin was not given in the majority of the patients ($n = 29$, 76%), as experience from our institution had demonstrated markedly increased risk of cardiac AEs after concomitant administration of doxorubicin and carfilzomib.[20] Due to renal failure, cyclophosphamide and cisplatin were not administered in one (3%) and four (11%) patients, respectively.[21] Cisplatin, cyclophosphamide, and etoposide were dose reduced in 19 (50%), 20 (53%), and 20 (53%) patients, respectively. Dose modifications were summarized in Table 1. In general, modifications of "Dara-KDT-P(A)CE" were guided by the tolerability of this regimen, especially severe toxicities. We used this regimen as bridging therapy prior to CAR T-cell in four (11%) patients. Five (13%), two (5%), and one (3%) patient received auto-SCT, allo-SCT, and BiTE infusion after "Dara-KDT-P(A)CE", respectively.

Follow-up data on the best response to "Dara-KDT-P(A)CE" were available in 34 (89%) patients, while 4 (11%) patients were lost to follow-up. Focusing on patients with response data, the ORR was 70%, with 10 (29%) and 14 (41%) patients achieving very good partial remission (VGPR) and PR, respectively. No patient could obtain a complete remission (CR). Ten (30%) patients showed no response to "Dara-KDT-P(A)CE". Response data were available in 20 (95%) of the 21 patients with penta-refractory MM and, among these patients, 6 (30%) and 7 (35%) of them achieved VGPR and PR, respectively, yielding an ORR of 65%. In the 31 patients with high-risk cytogenetics, the best response to therapy was evaluable in 29 (94%) of them, and we observed an ORR of 79% including 34% ($n = 10$) VGPR and 45% ($n = 13$) PR in this patient group. We summarized the ORR in different patient subgroups in Figure 1.

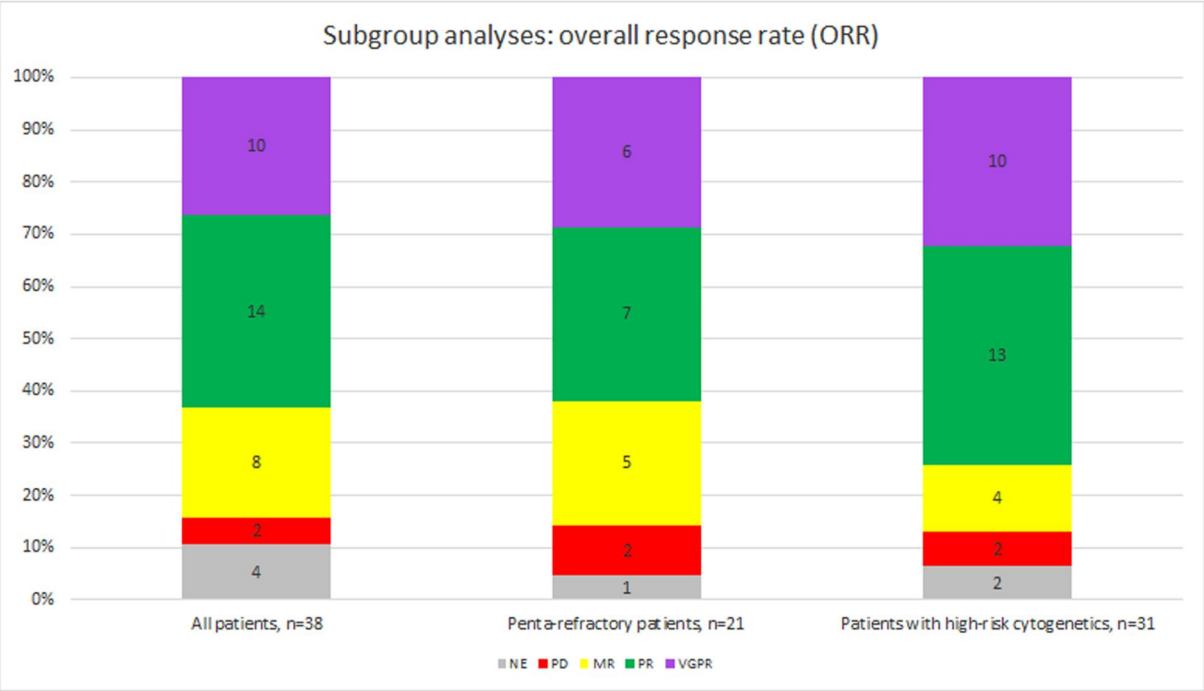

FIGURE 1 The overall response rate (ORR) in the entire group was 70%. Patients with penta-refractory multiple myeloma and high-risk cytogenetics showed similar ORR of 65% and 79%, respectively. MR, minor response; NE, not evaluable; PD, progressive disease; PR, partial remission; VGPR, very good partial remission

3.3 | Survival analyses

In the entire group, the median PFS and OS were 4.1 (95% confidence interval [CI] 2.7–5.4) and 8.4 (95% CI 6.7–10.0) months, respectively (Figure 2). LDH elevation (>250 IU/L) was associated with a significantly shorter PFS (median PFS: 3.1 vs. 6.0 months, $p = 0.006$, Figure 3) and OS (median OS: 6.9 vs. 12.0 months, $p = 0.005$, Figure 3). Patients suffering from EMD showed a trend toward inferior OS compared to those without EMD (median OS: 7.6 months vs. not reached, $p = 0.08$, Figure 4). However, we observed no significant difference in PFS between the both groups ($p = 0.27$, Figure 4). Additionally, patients who received novel immunotherapy within clinical trials (CAR T-cell and BiTE) or consolidation with auto- or allo-SCT after "Dara-KDT-P(A)CE" showed a trend toward superior PFS (median PFS: 3.7 vs. 5.9 months, $p = 0.09$, Figure 5) and a significantly superior OS (median OS: 7.9 months vs. not reached, $p = 0.01$, Figure 5). In terms of survival outcome, we did not see any significant difference in patients with high-risk cytogenetics (PFS: $p = 0.15$, OS: $p = 0.99$) or penta-refractory MM (PFS: $p = 0.16$, OS: $p = 0.84$) (figures not shown).

3.4 | Adverse events

We analyzed the safety data during the treatment. Overall, hematological AEs were the most common AEs, which were documented in all patients in our cohort. Hematological AEs grade ≥3 were shown in 34 (89%) patients. We observed anemia, leukopenia, neutropenia, and thrombocytopenia grade ≥3 in 25 (66%), 31 (82%), 27 (71%), and 29 (76%) patients, respectively (Table 3). Patients with leukopenia and/or neutropenia grade ≥3 were treated with (pegylated) granulocyte colony stimulating factor (G-CSF). Transfusion of erythrocyte and platelet concentrate was given according to the treating physician's discretion. Non-hematological AEs grade ≥3 were documented in 18 (47%) patients. Neutropenic fever ($n = 10$, 26%) was the most common non-hematological AE grade ≥3 in our cohort. Six (16%) patients suffered from pneumonia grade ≥3 after this therapy. Acute heart failure grade ≥3 was documented in four (11%) patients with all four patients presenting pulmonary edema and pleural effusion, and one of them showed hepatic congestion. Among the nine patients who concurrently received carfilzomib and doxorubicin, we did not observe any cardiac AEs. Two (5%) patients died of neutropenic fever during the treatment and, at the time point of death, both patients showed a minor response (MR) of MM.

4 | DISCUSSION

To date, the therapy of late-stage aggressive RRMM remains challenging. Patients with penta-refractory MM, particularly, have very poor outcome.[22,23] In this study, we retrospectively evaluated data of patients with heavily pretreated high-risk RRMM that was treated with "Dara-KDT-P(A)CE" and its modifications.

"Dara-KDT-P(A)CE" represents a multi-agent combination therapy utilizing some of the most recent anti-MM drugs along with conventional chemotherapy. In total, we observed an ORR of 70% in

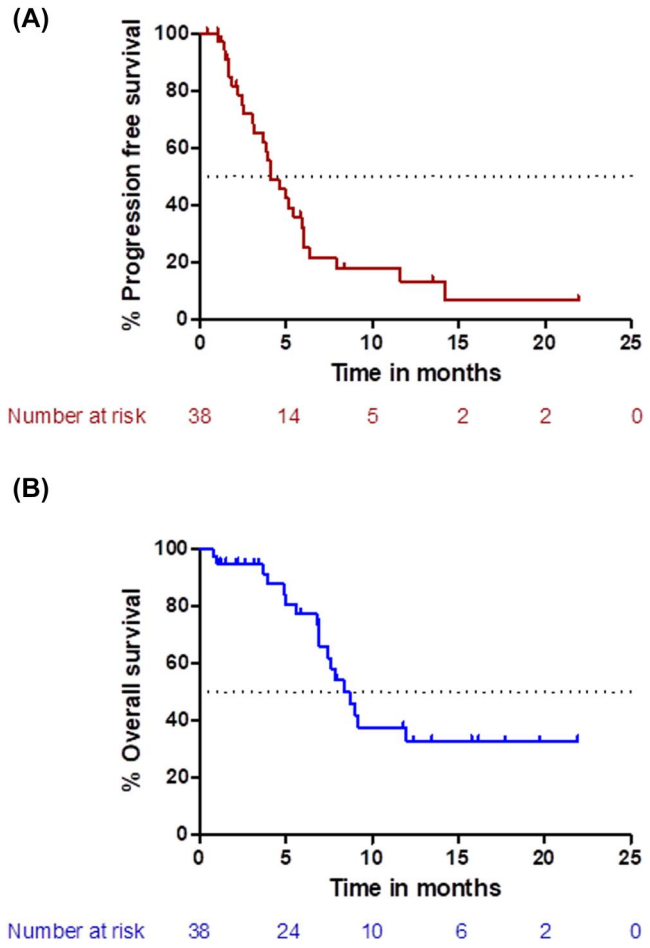

FIGURE 2 Progression-free survival (PFS) (A) and overall survival (OS) (B) of the entire group ($n = 34$). The median PFS and OS were 4.1 (95% CI 2.7–5.4) and 8.4 (95% CI 6.7–10.0) months, respectively

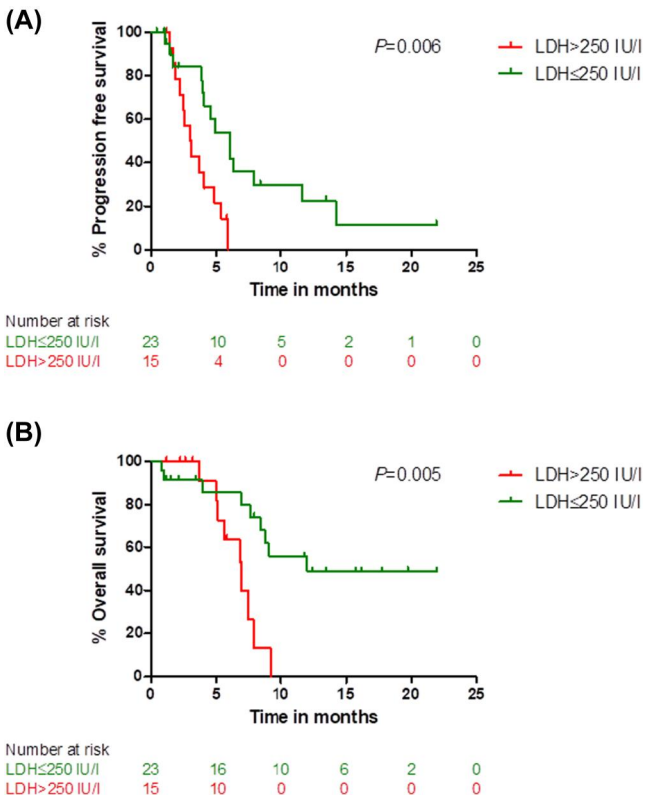

FIGURE 3 Patients with elevated lactate dehydrogenase (LDH) level (>250 IU/L) showed significantly inferior progression-free survival compared to those with normal LDH level (≤250 IU/L) (A). LDH >250 IU/L indicated a significantly inferior overall survival of patients (B)

such a patient cohort that was heavily pretreated with a median of five prior lines of therapy and enriched for high-risk cytogenetics and EMD. Currently, "VDT-PACE"-like regimens are well-established salvage therapies in patients with RRMM.[24] In a retrospective study of Lakshman et al., an ORR of 54.4% was demonstrated in RRMM patients treated with "VDT-PACE"-like regimens.[11] Additionally, "DTPACE" (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide) had shown an ORR of 32% in patients with previously treated MM.[25] Our results demonstrated that incorporation of more recent anti-MM agents such carfilzomib and daratumumab into "VDT-PACE"-like regimens could somewhat improve their efficacy. More recently, Harrell et al. reported on patients with aggressive RRMM treated with "KD-PACE"-like salvage therapy that achieved an ORR of 77%, with 64% of the patients receiving additional IMiD treatment including pomalidomide (31%), thalidomide (25%), and lenalidomide (7.7%). In their study, the patients had been treated with a median of three prior lines of therapy, and 54% of them had high-risk cytogenetics according to the same definition as in our study, with 19% and 10% of the patients showing plasma cell leukemia and EMD, respectively.[26] Our findings demonstrated a comparable ORR in RRMM patients who received "Dara-KDT-P(A)CE"-like regimens. However, in our cohort, the patients were more heavily pretreated with a median of five prior lines of therapy, and the proportion of patients harboring high-risk cytogenetics or EMD was higher. Of note, in the current study, subgroup analyses of patients with penta-refractory MM and high-risk cytogenetics yielded promising ORR of 65% and 79%, respectively, suggesting that "Dara-KDT-P(A)CE"-like regimens could achieve synergistic anti-MM effects and could overcome resistance to single-agent therapy in these heavily pretreated, multi-refractory, high-risk RRMM patients.

In the current study, the median PFS and OS from start of "Dara-KDT-P(A)CE" were 4.1 (95% CI 2.7–5.4) and 8.4 (95% CI 6.7–10.0) months, respectively. Comparably, a median PFS of 3.8 months (95% CI 2.83–4.87) and a median OS of 8.9 months (95% CI 5.06–11.14) were reported in RRMM patients who received "DCEP" (dexamethasone, cyclophosphamide, etoposide, and cisplatin) therapy.[27] Moreover, in RRMM patients treated with "VDT-PACE"-like regimens, Lakshman et al. have reported similar median PFS and OS of 3.1 (95% CI 1.9–3.9) and 8.1 months (95% CI 6.2–9.9), respectively.[11] Furthermore, comparable median PFS (4.6 months, 95% CI 3.2–7.5 months) and OS (11.2 months, 95% CI 6.1–14.5 months) were also shown in RRMM patients receiving "KD-PACE" salvage therapy.[26] As mentioned above, importantly, the patients in our cohort

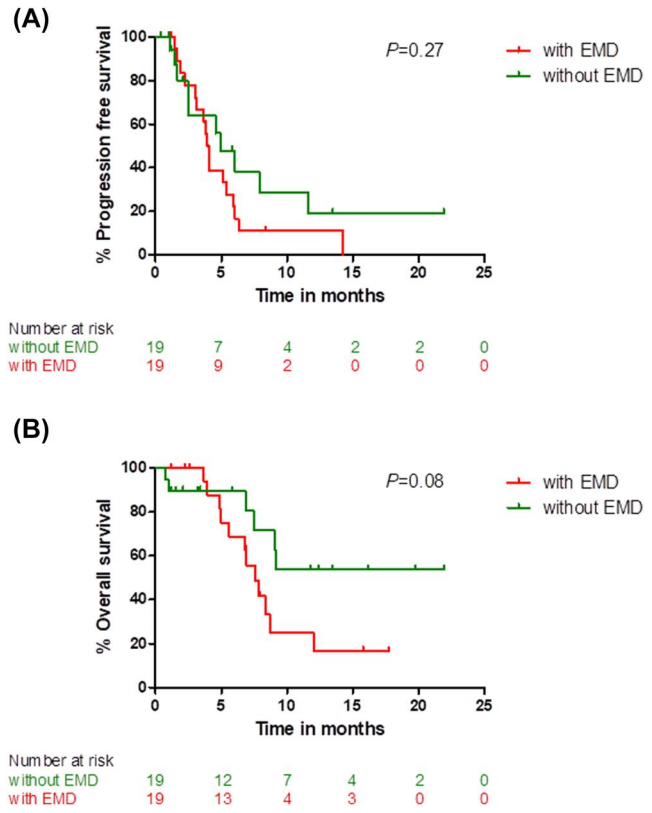

FIGURE 4 With regard to progression-free survival, there was no significant difference between patients with and without extramedullary disease (EMD) (A). Patients suffering from EMD showed a trend toward inferior overall survival compared with those without EMD (B)

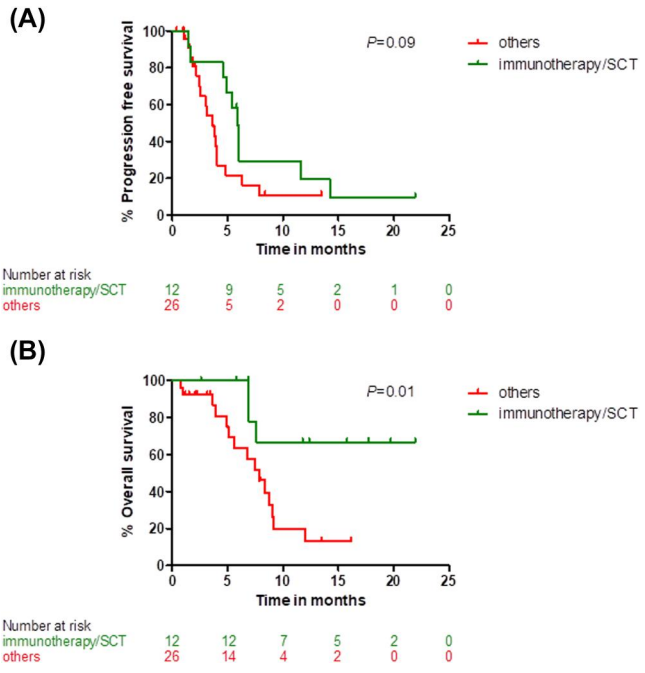

FIGURE 5 Patients who received immunotherapy within clinical trials (CAR T-cell and BiTE) or consolidation with autologous or allogeneic stem cell transplant (SCT) after "Dara-KDT-P(A)CE" showed a trend toward superior progression-free survival (A) and a significantly superior overall survival (B) in comparison with other patients

were more heavily pretreated, and high-risk cytogenetic abnormalities and patients with EMD were more frequently observed than in the prior studies. Generally, "Dara-KDT-P(A)CE" seems to be feasible in RRMM patients waiting for a slot in a novel immunotherapy trial with competitive enrollment. As BCMA CAR T-cells have lately been approved for treatment of RRMM, "Dara-KDT-P(A)CE"-like regimen might be an option as bridging therapy prior to CAR T-cell infusion to reduce the tumor burden and to mitigate potential life-threatening toxicities of CAR T-cell therapy such as cytokine release syndrome (CRS) and neurotoxicity.[4]

Overall, hematological AEs grade ≥3 were documented in 34 (89%), with anemia, leukopenia, neutropenia, and thrombocytopenia grade ≥3 presenting in 25 (66%), 31 (82%), 27 (71%), and 29 (76%) patients, respectively. Besides, neutropenic fever (n = 10, 26%) was the most common non-hematological AE grade ≥3, and two (5%) patients died of neutropenic fever after one and four cycles. The spectrum of AEs was comparable to that in "VDT-PACE" and "KD-PACE"-like regimens.[11,26] Noteworthy, treatment related mortality rates of 5% and 6% were likewise reported in RRMM patients treated with "VDT-PACE" and "DCEP" regimens, respectively.[27] Unfortunately, we did not see any alternative therapy strategies for these heavily pretreated RRMM patients, as a treatment within a clinical trial was not available. In this context, in our cohort, the safety profile of "Dara-KDT-P(A)CE" was largely acceptable and manageable.

Lately, besides daratumumab and carfilzomib, several other novel anti-MM agents such as belantamab mafodotin and isatuximab were also approved for treatment of RRMM,[28,29] with some bi-specific antibodies being presently under clinical investigation. In principle, integration of these novel agents into the well-established regimens might be an option to further improve their efficacy. However, robust clinical data are currently not available, and this approach should be evaluated in clinical trials.

The major limitations of our current study include the retrospective, single-center design and limited number of patients. Hence, we have not performed a multivariate survival analysis using cox regression model. In addition, a significant proportion of our patients have received this therapy with dose modifications, which might result in some heterogeneity of the de facto administered treatments.

In conclusion, "Dara-KDT-P(A)CE" is feasible in heavily pretreated, multi-refractory, high-risk, aggressive RRMM without alternative therapy options. This regimen also represents an effective bridging therapy prior to novel cellular immunotherapies to reduce the tumor burden and to attenuate the potential life-threatening toxicities.

TABLE 3 Adverse events

	Any grade ≥2	Grade 3	Grade 4	Grade 5
Hematologic events, *n* (%)				
Anemia	36 (95)	25 (66)		
White blood cell decreased	34 (89)	11 (29)	20 (53)	
Neutrophil count decreased	31 (82)	14 (37)	13 (34)	
Platelet count decreased	31 (82)	12 (32)	17 (45)	
Non-hematologic events, *n* (%)				
Neutropenic fever	10 (26)	7 (18)	1 (3)	2 (5)
Pneumonia	6 (16)	3 (8)	3 (8)	
Heart failure	5 (13)	3 (8)	1 (3)	
Renal failure	4 (10)	2 (5)	2 (5)	
Tumor lysis syndrome	3 (8)	3 (8)		
Intracranial hemorrhage	1 (3)		1 (3)	
Seizure	1 (3)		1 (3)	
Diarrhea	1 (3)	1 (3)		
Esophageal infection	1 (3)	1 (3)		
Catheter associated infection	1 (3)	1 (3)		
Syncope	1 (3)	1 (3)		
Urinary tract infection	1 (3)	1 (3)		
Mucositis	1 (3)	1 (3)		
Discitis with epidural abscess	1 (3)	1 (3)		
Peripheral polyneuropathy	3 (8)			
Influenza	1 (3)			
Oral herpes	1 (3)			

CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest relevant to the submitted manuscript.

DATA AVAILABILITY STATEMENT

Data presented in this study are available in the Article or available from the corresponding author upon reasonable request.

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TRANSPARENT PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/hon.2949.

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How to cite this article: Zhou X, Ruckdeschel A, Peter J, et al. Salvage therapy with "Dara-KDT-P(A)CE" in heavily pretreated, high-risk, proliferative, relapsed/refractory multiple myeloma. *Hematol Oncol*. 2022;40(2):202-211. https://doi.org/10.1002/hon.2949