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【 ORIGINAL ARTICLE 】

Bortezomib-thalidomide-dexamethasone-cisplatin-doxorubicin-cyclophosphamide-etoposide as a Salvage and Bridging Regimen before Hematopoietic Stem Cell Transplantation for Relapsed or Refractory Multiple Myeloma

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Abstract:

Objective Currently, treatment of relapsed or refractory multiple myeloma is challenging. Although bortezomib-thalidomide-dexamethasone-cisplatin-doxorubicin-cyclophosphamide-etoposide (VTD-PACE), a potent combination of a proteasome inhibitor, immunomodulatory drug, and conventional chemotherapeutics, is a widely used regimen, its efficacy and safety are unclear.

Methods We retrospectively analyzed the clinical data of 35 patients treated with VTD-PACE.

Results The overall response rate was 65.7% (complete response, 5.7%). The median progression-free survival (PFS) and overall survival (OS) were 8.0 [95% confidence interval (CI), 0.9-15.0] and 20.0 (95% CI, 17.5-22.5) months, respectively. Twenty-two (62.9%) patients developed grade 3-4 infections, and no therapy-related deaths occurred. Sixteen of 25 patients (64%) underwent stem cell harvest successfully with more than 2.0×10^6/kg of CD34 cells after VTD-PACE. Twenty-two patients underwent autologous or allogeneic stem cell transplantation (SCT). The response and survival durations were short in patients without SCT after VTD-PACE [median PFS: 4.0 (95% CI, 2.7-5.3) months; OS: 14.0 (6.9-21.0) months]; however, these responses significantly improved with SCT following VTD-PACE. The PFS was 8.0 (NA) months (p=0.024), and the OS was 21.0 (19.1-22.8) months (p=0.019).

Conclusion VTD-PACE is an effective and tolerable salvage regimen and feasible bridging therapy for SCT.

Key words: VTD-PACE, relapsed or refractory myeloma, bridging therapy, salvage therapy, stem cell mobilization

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Introduction

Recent advances in the development of anti-myeloma agents have led to improvements in the therapeutic response and survival of patients. However, treatment of relapsed or refractory myeloma remains challenging (1, 2), and effective strategies are needed.

Bortezomib-thalidomide-dexamethasone-cisplatin-doxorubicin-cyclophosphamide-etoposide (VTD-PACE) is a potent combination regimen consisting of a proteasome inhibitor, immunomodulatory drug, and conventional chemotherapy agents (3, 4). This primary regimen is used in transplant candidates (4) and previously treated patients (2). It may be an option for newly diagnosed patients with a high-risk and aggressive extramedullary disease, plasma cell leukemia, or aggressive relapse (5). However, few studies have examined the benefits of VTD-PACE (3, 4, 6), and its clinical utility is not well-understood.

In this study, we retrospectively analyzed the efficacy and safety of VTD-PACE as a therapy for patients with relapsed/refractory multiple myeloma.

Materials and Methods

Patients

We reviewed the medical records of patients with relapsed or refractory myeloma who were treated with VTD-PACE from August 2010 to September 2016 at the Center Hospital of the National Center for Global Health and Medicine (Tokyo, Japan).

Treatment

The patients were treated with one to five courses of VTD-PACE. The detailed regimen has been described by Barlogie et al. (4). In brief, this treatment consisted of 1.0 mg/m^2 bortezomib on days 1, 4, 8, and 11; 200 mg thalidomide on days 1-4; 40 mg dexamethasone on days 1-4; 10 mg/m^2 cisplatin on days 1-4; 10 mg/m^2 doxorubicin on days 1-4; 400 mg/m^2 cyclophosphamide on days 1-4; and 40 mg/m^2 etoposide on days 1-4. This regimen was approved by the National Center for Global Health and Medicine hospital cancer chemotherapy regimen review committee.

Assessment of efficacy and safety

The primary end-point was the overall response rate (ORR) to VTD-PACE, which was defined as a partial response or improvement (including a complete response, very good partial response, and partial response) after the last cycle of VTD-PACE. The secondary end-points were the overall survival (OS), progression-free survival (PFS), and adverse events (AEs). The OS was defined as the duration from the initiation of VTD-PACE to death, and patients were censored if they were known to be alive at the latest follow-up. The PFS was defined as the time from the initiation of VTD-PACE to disease progression or death, whichever occurred earlier. The response to therapy was assessed after each VTD-PACE cycle in accordance with International Myeloma Working Group uniform response criteria 2016 (7). AEs were graded using the Common Terminology Criteria for AEs version 4.0.

Statistical analyses

The comparisons between patient groups were analyzed using Fisher's exact test and Mann-Whitney U test. The median OS and PFS were estimated using the Kaplan-Meier method. In general, the survival of relapsed or refractory myeloma patients is relatively short. We performed the generalized Wilcoxon test, which is sensitive to early occurring events, to compare the survival difference between patients treated with stem cell transplantation (SCT) and those who were not. All statistical analyses were performed using the SPSS Statistics 25.0 software program (SPSS, Chicago, USA).

Results

Patients

A total of 35 patients was included in the study. The patients' characteristics are summarized in Table 1. The median follow-up duration was 20.0 (range, 4-92) months. The median age was 54.0 (range, 34-66) years old. The median time to initiate VTD-PACE from the first-line treatment was 16.0 (range, 2-164) months. At the start of VTD-PACE, 23 of 35 patients (65.7%) had extramedullary disease. Twenty-four patients (68.6%) were categorized as revised international staging system (R-ISS) II or III, and 32.3% of patients had adverse cytogenetic abnormalities, which were defined as t(4;14), t(14;16), or del(17p) by an interphase fluorescence *in situ* hybridization analysis. One case had both t(14;16) and del(17p). The patients were previously treated with a median of 2 (range, 1-8) lines of therapy. Seventeen patients (48.6%) previously received at least 1 session of autologous SCT. All patients were previously treated with a bortezomib-containing regimen. The median number of VTD-PACE cycles was 2 (1-5); the reasons for discontinuing or switching to the other treatments are described in Supplementary material 1.

SCT following VTD-PACE was considered for patients in this cohort; however, those with liver dysfunction, renal failure, heart failure, active infection, and an inadequate number of stem cells or donors were excluded (Supplementary material 2). Prior to SCT, written informed consent was obtained from the patients.

Efficacy and outcome

The clinical course of the patients is described in Fig. 1. In all patients, the ORR was 65.7%, and 5.7% of patients achieved complete remission. However, the ORR of patients previously treated with ≥2 lines was 52.3%. In patients with

Table 1. Characteristics of Patients at Initiation of VTD-PACE Regimen (n=35).

Factor	Total	SCT (n=22)	Others (n=13)	p value
Gender, male/female, no. (%)	22 (62.9)/13 (37.1)	14/8	8/5	ns
Age at starting VTD-PACE, years, median (range)	54.0 (34-66)	52.5 (34-66)	54.0 (34-64)	ns
Time from initial therapy to VTD-PACE, month, median (range)	16.0 (2-164)	13.0 (2-122)	19.0 (2-164)	ns
Cycle number of VTD-PACE, median (range)	2 (1-5)	2 (1-6)	2 (1-4)	ns
Extramedullary disease, no. (%)	23 (65.7)	14 (63.6)	9 (69.2)	ns
ISS I/II/III stages, no. (%)	13 (37.1)/18 (51.4)/ 4 (11.4)	10 (45.5)/6 (27.3)/ 6 (27.3)	6 (46.2)/5 (38.5)/ 2 (15.2)	ns
R-ISS I-II/III stages, no. (%)	11 (31.4)/22 (62.9)/ 2 (5.7)	6 (27.3)/15 (68.2)/ 1 (4.5)	4 (30.8)/8 (61.5)/ 1 (7.7)	ns
High risk cytogenetics, no. (%)				
t(4;14) (n=34)	6 (17.6)	4 (18.2)	2 (15.4)	ns
Deletion (17p) (n=33)	4 (12.1)	4 (18.2)	0 (0.0)	ns
t(14;16) (n=31)	1 (3.2)	1 (4.5)	0 (0.0)	ns
Number of prior lines, no. (%)				
1	14 (40.0)	11 (50.0)	3 (23.1)	
2	9 (25.7)	6 (27.3)	3 (23.1)	
≥3	12 (34.3)	5 (22.7)	7 (53.8)	ns
Prior agents, no. (%)				
Lenalidomide	16 (45.7)	7 (31.8)	9 (69.2)	p=0.043*
Thalidomide	14 (40.0)	9 (40.9)	5 (38.5)	ns
Pomalidomide	2 (5.7)	1 (4.5)	1 (7.7)	ns
Bortezomib	35 (100)	22 (100)	13 (100)	ns
Carfilzomib	0 (0.0)	0 (0.0)	0 (0.0)	ns
Chemotherapeutics	15 (42.9)	7 (31.8)	8 (61.5)	ns
Autologous transplant	17 (48.6)	7 (36.4)	10 (76.9)	p=0.015$
Overall response	65.7%	77.3%	46.2%	ns
Stem cell harvest after VTD-PACE (%)		19 (86.4)	6 (46.2)	p=0.020*
Harvested CD34+cells ×10E6/kg, median (range)		4.7 (0-10.3)	0.08 (0-2.97)	p=0.005**
Transplant after VTD-PACE, no. (%)		22 (62.9)		
Single autologous transplant, no. (%)		11 (31.4)		
Tandem autologous transplant, no. (%)		7 (20.0)		
Single autologous and allogeneic transplant, no. (%)		3 (8.6)		
Allogeneic transplant, no. (%)		1 (2.9)		

ISS: international staging system, R-ISS: revised-international staging system, VTD-PACE: bortezomib-thalidomide-dexamethasone-cisplatin-doxorubicin-cyclophosphamide-etoposide

*p<0.05, **p<0.01 by Fisher's exact test

$ p<0.05 by Mann-Whitney U test

extramedullary disease, the ORR was 60.9%, and all patients with adverse cytogenetic abnormalities achieved a partial response or better. The median PFS of all patients was 8.0 [95% confidence interval (CI): 0.9-15.0] months, and the median OS was 20.0 (95% CI: 17.5-22.5) months (Fig. 2).

In 25 patients, stem cell harvest was attempted during the hematological recovery phase after VTD-PACE. Harvest was successful in 16 patients (64%), with more than 2.0×10^6/kg of CD34 cells collected. Four patients had previously undergone stem cell collection, and one had cells collected from autologous bone marrow. Patients from whom an adequate number of autologous stem cells were able to be collected or for whom a source of allogeneic transplantation was available underwent SCT. Twenty-two patients received SCT (11 single autologous, 7 tandem autologous, 2 autologous SCT followed by allogeneic SCT, and 2 single allogeneic SCT) after VTD-PACE.

The differences in clinical backgrounds between the patients treated with SCT following VTD-PACE and those without SCT were analyzed (Table 1). The rates of prior exposure to lenalidomide and autologous SCT were more frequent among patients who were not treated with SCT than among those treated with SCT.

A comparison of the survival of patients with and without SCT is shown in Fig. 3. The median PFS of patients treated with SCT after VTD-PACE and those without SCT was 8.0 (95% CI: not applicable) months and 4.0 (95% CI: 2.7-5.3) months, respectively. The median OS of patients with SCT was 21.0 (95% CI: 19.1-22.8) months, whereas that without SCT was 14.0 (95% CI: 6.9-21.0) months. The PFS and OS were significantly longer in patients who underwent SCT than in those who did not (p=0.024, 0.019, respectively).

Four patients were treated with allogeneic SCT. Three achieved partial remission, and one achieved stable disease

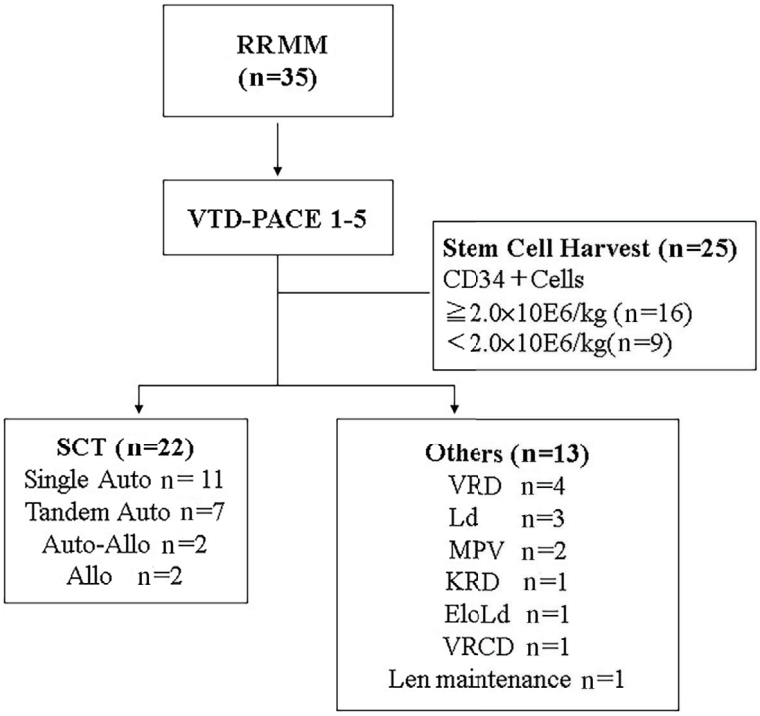

Figure 1. **Clinical course of the patients with relapsed or refractory multiple myeloma (RRMM).**

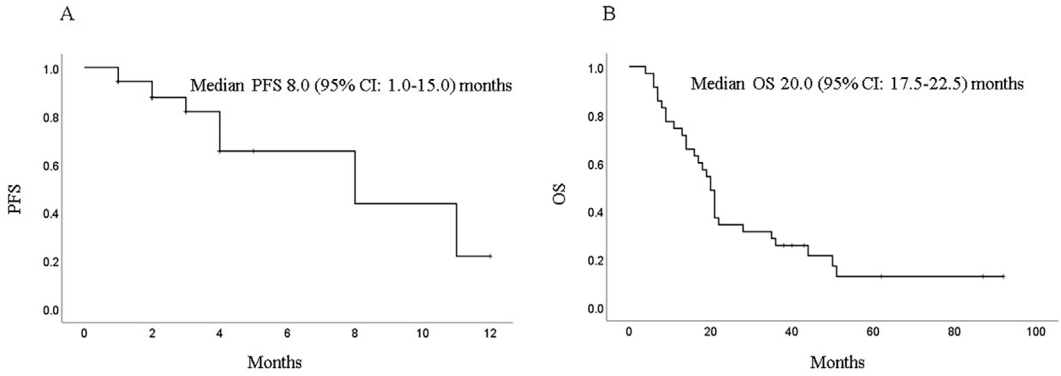

Figure 2. **Kaplan-Meier estimate of the progression-free survival and overall survival of all patients.**

after transplantation. The survival after allogeneic transplantation was relatively short (Supplementary material 3) at a median of 11 (95% CI: 5.1-16.9) months.

AEs

The details of the AEs related to VTD-PACE are described in Table 2. Grade 3-4 hematological AEs included neutropenia, anemia, and thrombocytopenia and were observed in most patients. Twenty-two patients (62.9%) developed grade 3-4 infection: 57.1% febrile neutropenia, 14.3% pneumonia, and 8.6% sepsis. Although 3 patients (8.6%) experienced tumor-lysis syndrome and one developed acute kidney injury, these conditions were reversible. Therapy-related death was not observed; however, the regimen was interrupted because of infection in two cases.

Discussion

We demonstrated the safety and efficacy of the VTD-PACE regimen for patients with relapsed or refractory multiple myeloma. In addition, our results suggested that SCT following VTD-PACE can improve patient outcomes. Novel agents (proteasome inhibitors, immune-modulating drugs, and monoclonal antibodies) are highly effective against myeloma cells (1, 2, 8). Nevertheless, myeloma cells tend to acquire various mechanisms to evade the actions of these drugs (9). The treatment of patients with adverse cytogenetic abnormality and extramedullary disease and those previously treated with two or more lines remains challenging (2, 10, 11). However, conventional cytotoxic drugs might be useful for conquering resistance. Cyclophosphamide has often been incorporated into newer agent-based regi-

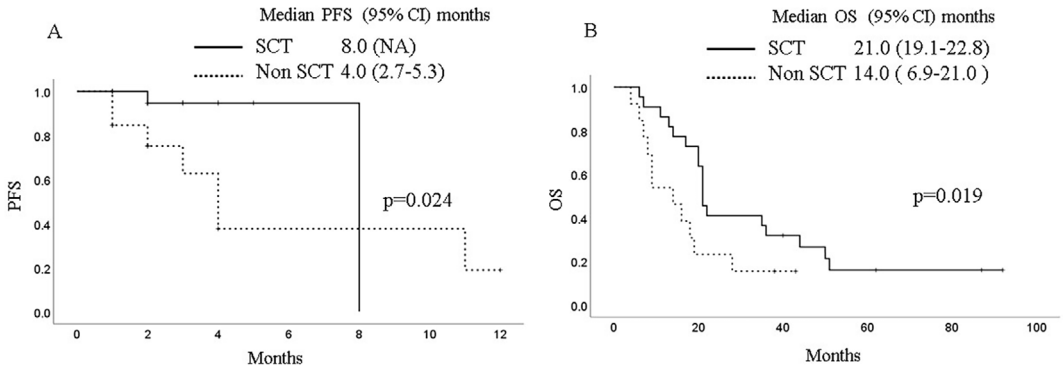

Figure 3. **Kaplan-Meier estimate of the progression-free survival and overall survival of patients with or without stem cell transplantation. The p value is based on the generalized Wilcoxon test.**

Table 2. **Grade 3 to 4 Adverse Events.**

Factors	n (%)
Hematological AEs, no. (%)	
Neutropenia	35 (100)
Anemia	28 (80.0)
Thrombocytopenia	33 (94.3)
Non-hematological AEs, no. (%)	
Electrolyte disturbance	**22 (62.9)**
Hypophosphatemia	16 (45.7)
Hypokalemia	11 (31.4)
Hyponatremia	6 (17.1)
Infection	**22 (62.9)**
Febrile neutropenia	20 (57.1)
Lung infection	5 (14.3)
Sepsis	3 (8.6)
Other	**5 (14.3)**
Tumor lysis syndrome	3 (8.6)
Oral mucositis	2 (5.7)
Nausea	2 (5.7)
Acute renal injury	1 (2.9)

AEs: adverse events

mens. carfilzomib, cyclophosphamide, and dexamethasone (KCD) and pomalidomide, cyclophosphamide, and dexamethasone (PCD) show efficacy against relapsed/refractory myeloma (12, 13). Furthermore, the combination of chemotherapeutic agents, such as with dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP), is an effective treatment option for patients with a history of exposure to novel agents (14).

In this study, VTD-PACE induced partial remission or a better response in more than half of patients who had previously been treated with two or more lines of treatment. This result suggests that the salvage regimen is effective for heavily pre-treated multiple myeloma. Furthermore, patients with adverse cytogenetic abnormalities and extramedullary disease responded well to VTD-PACE; however, the duration of the response was relatively short. Therefore, intensification therapy following VTD-PACE was necessary. Patients who underwent SCT showed a favorable survival. Several authors have reported that SCT is an effective salvage treatment for relapsed or refractory multiple myeloma (15, 16).

Fourteen cases were treated with VTD-PACE as the second line (six cases showed recurrence after autologous stem cell transplantation). All aimed for transplantation, with 10 undergoing harvest after VTD-PACE and eight successfully completing harvest. Eleven cases underwent SCT, including three using previously preserved stem cells. Barlogie et al. reported that VTD-PACE as the first-line treatment in Total Therapy 3 resulted in harvest with a high success rate of 87% (4). VTD-PACE can be used as a potent salvage regimen and an effective mobilizer, and it might be helpful as an alternative treatment to plerixafor.

The incidence of regimen-related AEs was compatible with previous reports. In several studies of VTD-PACE-like regimens, most patients developed neutropenia, thrombocytopenia, and anemia. Infection was observed in 16-49% (3, 6, 17, 18), with the frequency being higher in bortezomib-including regimens than in those without bortezomib (17). In our study, only one patient developed an acute renal injury; however, cisplatin-related nephrotoxicity is relatively common, being reported in 14-15% of patients (17, 18). Although no patient experienced thrombosis in our study, therapy-associated thrombosis has been reported in 10-11% of cases (4, 17). Anti-thrombotic prophylaxis should be considered. The age of the cohort in this study was relatively young (34-66 years old); however, the incidence of infection was higher than in previous studies (3, 6, 17, 18). Thus, careful discussion is needed when considering the indication of VTD-PACE for elderly patients or those with active infection.

Since this study was a retrospective study and the number of patients involved was relatively small, there may be some bias. Measurement bias in reviewing medical records and selection bias in comparing transplanted and non-transplanted cases cannot be ruled out. Therefore, the results cannot be directly generalized. However, our real-world analysis suggests that VTD-PACE salvage and bridging therapy prior to SCT is feasible for relapsed/refractory multiple myeloma. A further prospective investigation is warranted.

The study was conducted in accordance with the ethical guidelines for clinical research in Japan and the Declaration of Helsinki and was approved by the Centre Hospital of the National Centre for Global Health and Medicine Review Board.

The authors state that they have no Conflict of Interest (COI).

References

1. Nooka AK, Kastritis E, Dimopoulos MA, Lonial S. Treatment options for relapsed and refractory multiple myeloma. Blood **125**: 3085-3099, 2015.
2. Moreau P, Kumar SK, San Miguel J, et al. Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. Lancet Oncol **22**: e105-e118, 2021.
3. Lee CK, Barlogie B, Munshi N, et al. DTPACE: an effective, novel combination chemotherapy with thalidomide for previously treated patients with myeloma. J Clin Oncol **21**: 2732-2739, 2003.
4. 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 **138**: 176-185, 2007.
5. NCCN Guidelines® Insights. Multiple Myeloma, Version 3.2022. J Natl Compr Canc Netw **20**: 8-19, 2022.
6. Lakshman A, Singh PP, Rajkumar SV, et al. Efficacy of VDT PACE-like regimens in treatment of relapsed/refractory multiple myeloma. Am J Hematol **93**: 179-186, 2018.
7. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol **17**: e328-e346, 2016.
8. Gulla A, Anderson KC. Multiple myeloma: the (r)evolution of current therapy and a glance into future. Haematologica **105**: 2358-2367, 2020.
9. Botta C, Mendicino F, Martino EA, et al. Mechanisms of immune evasion in multiple myeloma: open questions and therapeutic opportunities. Cancers (Basel) **13**: 3213, 2021.
10. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood **127**: 2955-2962, 2016.
11. Rosinol L, Beksac M, Zamagni E, et al. Expert review on soft-tissue plasmacytomas in multiple myeloma: definition, disease assessment and treatment considerations. Br J Haematol **194**: 496-507, 2021.
12. Pennipede D, Mohyuddin GR, Hawkins R, et al. Carfilzomib, cyclophosphamide, and dexamethasone (KCd) for the treatment of triple-class relapsed/refractory multiple myeloma (RRMM). Eur J Haematol **107**: 602-608, 2021.
13. Rodriguez-Otero P, Sirvent M, Gonzalez-Rodriguez AP, et al. Pomalidomide, cyclophosphamide, and dexamethasone for the treatment of relapsed/refractory multiple myeloma: real-world analysis of the pethema-GEM experience. Clin Lymphoma Myeloma Leuk **21**: 413-420, 2021.
14. Park S, Lee SJ, Jung CW, et al. DCEP for relapsed or refractory multiple myeloma after therapy with novel agents. Ann Hematol **93**: 99-105, 2014.
15. Hagen PA, Stiff P. The role of salvage second autologous hematopoietic cell transplantation in relapsed multiple myeloma. Biol Blood Marrow Transplant **25**: e98-e107, 2019.
16. Dhakal B, D'Souza A, Kleman A, Chhabra S, Mohan M, Hari P. Salvage second transplantation in relapsed multiple myeloma. Leukemia **35**: 1214-1217, 2021.
17. Abdallah AO, Sigle M, Mohyuddin GR, et al. Outcomes of VD-PACE with immunomodulatory agent as a salvage therapy for relapsed/refractory multiple myeloma. Clin Lymphoma Myeloma Leuk **21**: e220-e226, 2021.
18. Gerrie AS, Mikhael JR, Chen L, et al. D(T)PACE as salvage therapy for aggressive or refractory multiple myeloma. Br J Haematol **161**: 802-810, 2013.