doi:10.4149/neo_2018_170519N363

Retreatment with lenalidomide is an effective option in heavily pretreated refractory multiple myeloma patients

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Received May 19, 2017 / Accepted September 27, 2017

The combination of lenalidomide and dexamethasone is the current gold standard for treatment of relapsed multiple myeloma. This study analyzes the efficiency of repeated lenalidomide treatment in patients with relapsed and refractory multiple myeloma. A total of 41 patients were prospectively evaluated at the University Hospital Brno. Lenalidomide was administered at standard dosing and in combination with corticosteroids and/or chemotherapy. The maximum cumulative dose of lenalidomide was limited to 4,200 mg because of Czech health insurance rules. Before the second lenalidomide treatment, all patients were refractory to the last treatment; previously, 95% of patients had bortezomib treatment, 48% had autologous transplantation and the median number of prior therapy lines was three. A partial 14.2% or better response was achieved with the second lenalidomide treatment. The median progression-free survival was 4.8 months, and median overall survival was 11.9 months. Unfortunately, predicting risk factors in lenalidomide retreatment proved unsuccessful. Although our treatment results were significantly affected by limited Czech health care system coverage for lenalidomide, we established that its repeated treatment is an effective therapeutic alternative for heavily pretreated patients with relapsed and refractory multiple myeloma.

Key words: multiple myeloma, lenalidomide, retreatment

Multiple myeloma (MM) is caused by uncontrolled proliferation of malignant plasma cells in the bone marrow, and it is the second most common hematological malignancy. Its prognosis in the era of conventional chemotherapy was not good, with median overall patient survival not longer than 30 months. Introduction of immunomodulatory drugs (lenalidomide, pomalidomide) and the proteasome inhibitors (bortezomib and carfilzomib) provided fundamental improvement in prognosis of newly diagnosed and relapsed MM patients [1]. Although it is generally accepted that relapsed MM is incurable [2], the efficiency of these drugs made it possible that a specific group of MM patients may even be cured. Relapsed and refractory MM patients have poor prognosis and their treatment options are often limited [3, 4]. Bortezomib-based regimen is a current standard treatment for newly diagnosed MM patients, and its combination with lenalidomide is widely used in the Czech Republic for initial relapse [5–9]. Lenalidomide is an immunomodulatory drug with high effectiveness in both primotherapy and in relapsed MM [7–10]. Retreatment with lenalidomide has not been widely reported, especially in case of refractory patients [11]. This study analyzes the lenalidomide retreatment in relapsed and refractory MM patients.

Patients and methods

We prospectively analyzed 41 patients repeatedly treated by lenalidomide-containing regimen. All patients were eligible for this treatment. Before the second lenalidomide treatment, other option was only palliative care. The patients were treated at the Brno University Hospital from June 2009 to December 2015, and all signed informed consent before entering this study. The study was approved by the Hospital Ethics committee in accordance with the current Helsinki Declaration.

The primary endpoint of this analysis was progression-free survival (PFS) and overall survival (OS) for lenalidomide retreatment. Response was assessed according to the 2014

International Myeloma Working Group (IMWG) criteria [12]. A total of 22 women and 19 men were included in the study with median age at first-line lenalidomide therapy of 67 years (range 53–78) and 69 years in the second line (range 55–81). The median of prior lines of therapy at the time of first-line lenalidomide treatment was 1 (range 0–3) and 3 (range 2–6) at the second-line treatment. Before second-line lenalidomide treatment; (1) 95.1% (39/41) of patients were pretreated with bortezomib and 61.0% (25/41) with thalidomide. (2) 48.7% (20/41) underwent high dose chemotherapy followed by peripheral blood stem cell transplant (PBSCT) and (3) all patients were refractory to their last line of treatment. There was no difference in the number of extramedullary disease between the first and second lines of lenalidomide treatment (12.2% vs. 14.6%, p=1.000), nor was there any significant difference in the ISS or DS stage of disease. Table 1 contains further characteristics. Lenalidomide was primarily administered orally at 25 mg/day dosage for 21 days in a 28-day cycle. This was reduced, as recommended, to 10 mg or 5 mg when necessary [13]. The median number of administered lenalidomide cycles was 8 (range 1–14) in the first lenalidomide treatment, and 4 (range 1–11) in the second treatment. The Czech health insurance system ruled that lenalidomide was not reimbursed if the patient had not achieved at least partial response after 4 cycles. Further, lenalidomide cost was only reimbursed until the total cumulative dose of 4,200 mg was reached in one line of treatment.

Table 1. Patient demographic and baseline characteristics.

Basic characteristics (N=41)	First treatment with lenalidomide	Second treatment with lenalidomide
Myeloma type, n (%)		
IgG	26 (63.4)	
IgA	8 (19.5)	
LC only	4 (9.8)	
Nonsecretory	3 (7.3)	
Durie-Salmon stage, n (%)		
I	4 (9.8)	3 (7.3)
II	5 (12.2)	5 (12.2)
III	32 (78.0)	33 (80.5)
Durie-Salmon substage A/B, n (%)	41/0 (100/0)	39/2 (95.1/4.9)
ISS stage, n (%); **N=40**		
Stage 1	17 (42.5)	13 (32.5)
Stage 2	14 (35.0)	15 (37.5)
Stage 3	9 (22.5)	12 (30.0)
Line of treatment, n (%)		
primotherapy	5 (12.2)	0 (0)
2nd	19 (46.3)	0 (0)
3rd	12 (29.3)	10 (24.4)
4th and more	5 (12.2)	31 (75.6)
7th and more	0 (0)	8 (19.5)

Count (relative frequencies) for categorical variables and median (5^{th}–95^{th} percentiles) for continuous variables

Patients received low molecular weight heparin or aspirin as prophylaxis for thromboembolic complications according to risk stratification [14]. Lenalidomide was most often administered with cyclophosphamide and corticosteroids (55%, 22/41), or only with corticosteroids (30%, 12/41) in first-line treatment. In the second-line therapy, lenalidomide was most often administered with corticosteroids (70.7%, 29/41). The first lenalidomide treatment was followed by PBSCT in 14.6% (6/41) of patients and by a second treatment with lenalidomide in 9.8% (4/41) of patients. Adverse events (AEs) were graded as established in the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 and safety was evaluated both throughout the study and during long-term follow-up.

Statistical analysis Data was described by absolute and relative frequencies for categorical variables and median supplemented by 5^{th}–95^{th} percentile range for continuous variables. The differences in basic characteristics for first and second lenalidomide treatments were tested by the McNemar paired test for categorical variables and the Wilcoxon paired signed-rank test for continuous variables. The univariate Cox proportional hazards model evaluating the association of predictors with PFS and PFS and TTP in both first and second treatments were visualised by Kaplan-Meier methodology and compared using the log-rank test. Two-sided tests were used with significance level of 0.05 and analysis was conducted in SPSS software (IBM Corp. Released 2013 IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). Finally, figures were plotted using R version 3.3.0 (www.r-project.org).

Results

Treatment response. Treatment response could be evaluated in 85% of patients (35/41), and overall response rate (ORR – partial response or better) was achieved by significantly more patients in the first line of lenalidomide treatment than in the second – 68.6% (24/35) vs. 14.2% (5/35), p<0.001.

The following responses were achieved; (1) complete response (CR) and stringent complete response (sCR) was achieved in the first line of treatment in 14.2% (5/35) of patients, but not in the second line; (2) very good partial response (VGPR) occurred significantly more often in the first treatment than in retreatment – 25.7% (9/35) vs. 5.7% (2/35), p=0.039; (3) partial response (PR) was significantly more often registered in the first line of treatment than in retreatment – 28.6% (10/35) vs. 8.6% (3/35), p=0.039 and (4) minor response (MR) was achieved equally in both lines of treatment – 5.7% vs. 5.7% (2/35), p=1.00.

Similar number of patients in these lines had stable disease (SD) – 2.9% (1/35) versus 17.1% (6/35), p=0.125. In the retreated group, 14.2% (5/35) of patients achieved SD after only the fourth cycle of treatment; and this accounted for 83% (5/6) of all of patients with SD. Treatment in these

Table 2. Characteristics before second administration of lenalidomide. (patients with final treatment response PR or better in second therapy with lenalidomide; N = 5 patients). Previous treatment lines before lenalidomide retreatmetnt

Patient No.	1st line	2nd line	3rd line	4th line	5th line
1	BDD +PBSCT	CTD	**RAD**	PBSCT	BDD
2	CTD	BDD	**RCP**	VD	
3	**RD**	CVD + PBSCT	BDD		
4	**RP**	BDD			
5	CVD	RCP	VTP		

Abbreviations: **BDD**- bortezomib-doxorubicin-dexamethasone; **PBSCT** – peripheral blood stem cell transplant; **CTD** – cyclophosphamide-thalidomide-dexamethasone; **RAD** – lenalidomide-doxorubicin-dexamethasone; **RCP** – lenalidomide-cyclophosphamide-prednisone; **VD** – bortezomib-dexamethasone; **RD**- lenalidomide- dexamethasone; **CVD** – cyclophosphamide-bortezomib-dexamethasone; **RP**- lenalidomide-prednisone; **VTP** – bortezomib-thalidomide-prednisone

patients was stopped according to Czech health insurance rules. Significantly fewer patients progressed during treatment after the first treatment than after retreatment – 22.9% (8/35) vs. 62.9% (22/35); p=0.003. Only 4.9% (2/41) of patients in the first group and 19.5% (8/41) of patients in the second group progressed after the first 1–2 treatment cycles. Only 36% (8/22) of patients with disease progression progressed in the first two cycles of lenalidomide retreatment. From all patients who progressed after second lenalidomide treatment, 18% (4/22) achieved at least PR before treatment withdrawal. It was the same number of patients (9.8% (4/41), who achieved treatment response (PR or better), but progressed after treatment withdrawal. Patients who did not achieve at least PR had a median of 3 treatment cycles in both lines of treatment. Finally, Table 2 lists the previous lines of treatment for patients who achieved treatment response after the second lenalidomide treatment.

Survival intervals. Median PFS was statistically significantly longer in the first lenalidomide treatment at 15.2 months compared to 4.8 months in the second treatment (p<0.001). Unfortunately, 14.2% (5/35) of patients had to stop the second lenalidomide treatment after 4 cycles due to lenalidomide reimbursement rules, regardless of disease progression. The PFS at 12 months was also significantly longer in the first lenalidomide treatment (73.2% vs. 15.1%; p<0.001) (Figure 1, Table 3).

Time to progression (TTP) was significantly longer in the first lenalidomide treatment (median 15.2 months vs. 4.8 months, p<0.001), and duration of response (DOR) was longer in the first lenalidomide treatment (14.8 months vs. 10.6 months; p=0.042). Treatment response lasted in 66.7% of patients at 12 months compared to 20.5% without response, and the median OS in repeated lenalidomide treatment was 11.9 months [95% CI: 10.1–13.7].

Subgroup analysis. No risk factor predicting successful repeated lenalidomide treatment was found. Dependency on previous lenalidomide treatment response was not proven; HR 1.043 (95% CI: 0.495–2.200; p=0.912). Furthermore, no dependency was determined on the number of previous lines of therapy prior to first and second lenalidomide treatments or the time between lenalidomide treatments. Previous exposure to bortezomib, thalidomide or carfilzomib before the second lenalidomide treatment was not established as a risk factor for repeated lenalidomide treatment success.

Moreover, the outcome of second lenalidomide treatment was independent of all the following; gender, age, ISS or DS stage, Eastern Cooperative Oncology Group (ECOG) performance status, type and amount of paraprotein or light chains, the levels of beta2microglobulin, albumin, lactate dehydro-

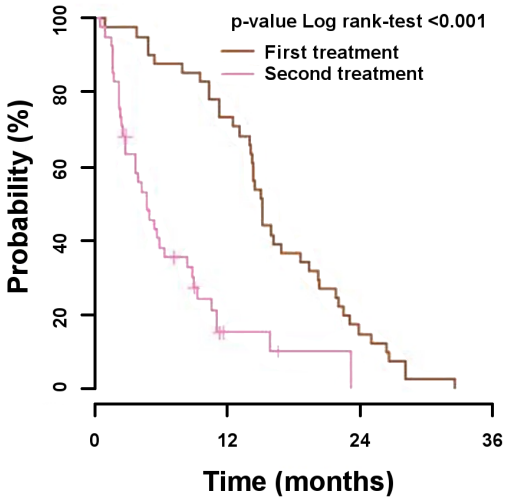

Figure 1. Progression free survival (PFS) for lenalidomide treatment (N=82 treatment lines). Kaplan-Meier curves of PFS for the first and second lenalidomide treatment. The Y axis presents patients surviving without progression in percent and the X axis gives time of follow-up in months. The first lenalidomide treatment is in dark grey and the second is in light grey. P-value is by Log rank-test

Table 3. Progression free survival (PFS) for lenalidomide treatment.

PFS	First treatment with lenalidomide (N=41)	Second treatment with lenalidomide (N=41)
Median (95% CI)	15.2 (14.2–16.2)	4.8 (3.0–6.6)
6 months (95% CI)	87.8 (73.2–94.7)	37.9 (23.2–52.5)
12 months (95% CI)	73.2 (56.8–84.2)	15.1 (5.8–28.6)
24 months (95% CI)	14.6 (5.9–27.0)	–

Table 4. Subgroup PFS analysis.

	HR (95% CI) for PFS from second treatment with lenalidomide	p-value
Characteristics associated with the first treatment with lenalidomide		
2nd line of therapy	0.852 (0.302–2.399)	0.761
3rd line of therapy	2.229 (0.753–6.599)	0.148
4th or higher line of therapy	1.631 (0.465–5.720)	0.445
Bortezomib in any previous therapy	2.016 (0.273–14.896)	0.492
Thalidomide in any previous therapy	0.891 (0.446–1.778)	0.743
Characteristics at second treatment with lenalidomide		
Age (years) (unit increase)	0.950 (0.905–0.998)	0.043
Sex: women	reference	
Sex: men	1.129 (0.800–1.592)	0.490
ISS: stage 1	reference	
ISS: stage 2	1.889 (0.801–4.453)	0.146
ISS: stage 3	1.807 (0.741–4.408)	0.194
Durie-Salmon: stage I	reference	
Durie-Salmon: stage II	1.230 (0.223–6.797)	0.812
Durie-Salmon: stage III	1.515 (0.359–6.384)	0.571
Durie-Salmon substage: A	reference	
Durie-Salmon substage: B	0.776 (0.377–1.597)	0.491
Performance status: 0	reference	
Performance status: 1	1.935 (0.652–5.742)	0.234
Performance status: 2–3	1.849 (0.593–5.769)	0.290
M-protein type: IgG	reference	
M-protein type: IgA	0.943 (0.381–2.334)	0.898
M-protein type: LC only	1.227 (0.421–3.572)	0.708
Nonsecretory	0.209 (0.028–1.577)	0.129
Light chain type: kappa	reference	
Light chain type: lambda	1.810 (0.884–3.707)	0.105
Beta2 microglobulin (mg/l)	1.092 (0.954–1.251)	0.203
Albumin level (g/l)	1.007 (0.949–1.069)	0.809
LDH level	1.129 (0.943–1.353)	0.188
Creatinine level (umol/l)	1.004 (0.993–1.015)	0.450
Calcium total level (mmol/l)	2.306 (0.206–25.817)	0.498
Hemoglobin level (g/l)	0.990 (0.968–1.012)	0.379
Thrombocyte count (10E9/l)	1.002 (0.997–1.006)	0.398
Serum M-protein level (g/l)	1.001 (0.984–1.019)	0.889
Bone marrow aspiration cytology: 10–20%	0.227 (0.010–5.369)	0.358
Bone marrow aspiration cytology: >20	0.376 (0.017–8.084)	0.532
Osteolytic lesions: more than 2	0.624 (0.164–2.379)	0.490
Extramedullary mass: yes	1.415 (0.536–3.731)	0.483

Univariate cox regression model for characteristics measured at second treatment with lenalidomide and PFS from this treatment line

genase, creatinine, calcium, hemoglobin, thrombocytes, infiltration of bone marrow, the number of osteolytic lesions or the presence of extramedullary disease. The dependence of treatment results on basic patients' characteristics before the second treatment is summarized in Table 4.

Table 5. Type of toxicity for the first and second treatment with lenalidomide.

Toxicity, n (%) (N=41)		First treatment with lenalidomide	Second treatment with lenalidomide
Anaemia	grade 1	24 (58.5 %)	18 (43.9 %)
	grade 2	6 (14.6 %)	12 (29.3 %)
	grade 3	5 (12.2 %)	6 (14.6 %)
Neutropenia	grade 1	9 (22.0 %)	7 (17.1 %)
	grade 2	6 (14.6 %)	12 (29.3 %)
	grade 3	24 (58.5 %)	10 (24.4 %)
Thrombocytopenia	grade 1	20 (48.8 %)	17 (41.5 %)
	grade 2	5 (12.2 %)	2 (4.9 %)
	grade 3	8 (19.5 %)	8 (19.5 %)
Infection	grade 1	2 (4.9 %)	2 (4.9 %)
	grade 2	14 (34.1 %)	14 (34.1 %)
Fatigue	grade 1	14 (34.1 %)	9 (22.0 %)
	grade 3	5 (12.2 %)	10 (24.4 %)
Neuropathy	grade 1	13 (31.7 %)	7 (17.1 %)
	grade 2	5 (12.2 %)	5 (12.2 %)
	grade 3	2 (4.9 %)	0 (0.0 %)
Diarrhoea	grade 1	1 (2.4 %)	1 (2.4 %)
	grade 2	4 (9.8 %)	4 (9.8 %)
	grade 3	1 (2.4 %)	2 (4.9 %)
Constipation	grade 1	3 (7.3 %)	1 (2.4 %)
	grade 2	6 (14.6 %)	0 (0.0 %)
Nausea	grade 1	1 (2.4 %)	2 (4.9 %)
	grade 2	3 (7.3 %)	2 (4.9 %)
	grade 3	0 (0.0 %)	1 (2.4 %)
Anorexia	grade 1	2 (4.9 %)	0 (0.0 %)
	grade 2	3 (7.3 %)	1 (2.4 %)
	grade 3	1 (2.4 %)	0 (0.0 %)

Count (relative frequencies)

Adverse events. As expected, treatment toxicity was mainly haematologic. In the first lenalidomide treatment, the most common side effect was anemia – 73% (30/41), but at grades 1–2 this was not severe. Other less serious side effects of treatment were thrombocytopenia – 60.9% (25/41), infections – 39.0% (16/41) and neutropenia – 36.5% (15/41). The most common severe (grade 3) side effects of treatment were neutropenia – 58.5% (24/41) and infections – 22% (9/22).

In the second lenalidomide treatment, the most frequent side effect was also anemia – 73% (30/41). Other less serious adverse effects (grades 1–2) were thrombocytopenia – 46% (19/41), neutropenia – 46% (19/41) and infections – 39% (16/41); and the most common severe (grade 3) adverse effects of this treatment were neutropenia – 24.4%, 10/41) and thrombocytopenia – 19.5% (8/41). No grade 4 toxicity was observed during first or second lenalidomide treatments and no patients died due to the treatment: – results are summarized in Table 5.

Table 6. Comparison between lenalidomide retreatment, daratumumab monotherapy and pomalidomide dexamethasone.

	Lenalidomide retreatment	Daratumumab monotherapy [19]	Pomalidomide-dexamethasone [17]
Number of patients	41	106	302
Median previous treatment lines (range)	3 (2-6)	5 (2-14)	5 (2-14)
Previous bortezomib treatment	95.1%	99%	100.0%
Previous lenalidomide treatment	100.0%	100.0%	100.0%
Previous PBSCT	48.7%	100.0%	71.0%
Refractory to the last treatment line	100.0%	97.0%	82.0%
PFS median (months)	4.8	3.7	4.0
OS median (months)	11.9	17.5	12.7

Discussion

Advances in MM treatment have significantly extended patient survival [15–19], the number of pretreated and refractory patients has increased [3]. Despite expanding treatment options, in real-life clinical practice we are forced to choose between repeated cancer therapy and palliative treatment. Lenalidomide is an effective anti-myeloma drug standardly used to treat relapsed MM in the Czech Republic. Combined therapy with lenalidomide and dexamethasone achieved median PFS of 25.5 months in newly diagnosed MM patients [9] and 17.6 months in relapsed MM patients [18]. Lenalidomide retreatment has previously been described in only one study [11]. Therein, 48 patients were retreated with lenalidomide after first-line lenalidomide treatment. The median of treatment lines before the second treatment was 2; lenalidomide was used in newly-diagnosed disease in 42% of patients and only 24% had prior bortezomib treatment before second-line lenalidomide treatment. That study therefore had a considerably less pretreated group of patients than ours, and their median time of lenalidomide treatment was 7 months compared to 4 months for our group. This was most likely due to Czech health insurance rules which forced us to treat patients with only a limited dose of lenalidomide and to discontinue treatment in those who had not achieved partial response (PR) after 4 cycles. In second lenalidomide treatment, 54% of patients achieved PR and better response. The median PFS for the second lenalidomide treatment was 16.0 months. The ORR was only 25% in the subgroup that progressed after the first lenalidomide treatment, so PFS and other treatment results were not determined. [11].

Our patient group was significantly more pretreated than in the quoted study and lenalidomide retreatment was the last-available treatment option for all our patients at the time. Only four lenalidomide cycles in case of insufficient response after four cycles and maximum cumulative dose of 4200 mg of lenalidomide were reimbursed. It is clear that these limitations had a significant impact on both our treatment length and results. We suggest that if prolonged administration of lenalidomide was reimbursed, therapeutic response could occur later, and we could achieve better treatment results. We also consider that the limitation of the cumulative dose of lenalidomide affected the number of patients who progressed after treatment withdrawal due to this rule. A maximum of eleven cycles in the second line was reached for the same reason. Hence, PFS and OS are clearly influenced by the length of lenalidomide dosing [9, 20].

Pomalidomide or daratumumab are current possible treatment choices for refractory and heavily pre-treated MM patients. In a randomized trial evaluating combined treatment with pomalidomide and dexamethasone [17], there was a similarly pre-treated group of patients to our group. All these had received previous bortezomib and lenalidomide treatment, 57% had received thalidomide and 71% underwent high-dose chemotherapy with autologous transplantation. Results highlighted that 82% of these patients were refractory to the last treatment, and the number of previous lines of therapy was 5. In another trial evaluating daratumumab monotherapy, 99% of patients were pre-treated with bortezomib, 100 % with lenalidomide and 44 % with thalidomide [19]. Further, 80 % underwent high dose chemotherapy followed by autologous stem-cell transplant. The median of prior treatment lines was 5, and 97% of patients were refractory to the last treatment line. It should be noted here that 63% of patients in this group were pretreated with carfilzomib and 50% with pomalidomide. Although our group differed in the number of previous therapy lines, our patients had similar resistance to previous treatment types, and all were refractory to the last administered therapy.

In a clinical trial with pomalidomide and dexamethasone [17], median PFS was 4.0 months and median OS was 12.7 months. Meanwhile, daratumumab monotherapy [19] achieved a median PFS 3.7 months and median OS of 17.5 months. These results are listed in Table 6. In those trials, both pomalidomide and daratumumab were administered until disease progression. Although treatment duration in our patients was limited by Czech health insurance rules, our analytic results are comparable with those from both the pomalidomide and daratumumab treatments [17, 19]. Moreover, our literature survey and this paper establish that

the direct comparison of repeated lenalidomide treatment with pomalidomide or daratumumab in a large randomized trial is obviously lacking. A surprising finding from our analysis is that PFS length in the second lenalidomide treatment is independent of response to its first treatment. This is explained by MM clonal theory [21]. We assume that even if the first lenalidomide treatment did not achieve treatment response, the second treatment can affect other plasma cell clones selected by previous non-lenalidomide therapy. The results of the second lenalidomide treatment did not depend on age or ECOG performance status. This might encourage use of repeated lenalidomide treatment in elderly and frail patients who can benefit from home-administered oral treatment. Toxicity of lenalidomide retreatment was tolerable and usually moderate at grade 1–2, and its incidence was comparable between the two treatment lines without clinical significance.

Results of our analysis demonstrate the effectiveness and usefulness of repeated lenalidomide treatment in a significantly pre-treated group of relapsed and refractory MM patients. In a broad spectrum of patients, repeated lenalidomide treatment is a comparable alternative to pomalidomide or daratumumab treatment, and its great advantage is its much lower cost.

Acknowledgments: The authors thank all patients and their caregivers for participating in this study, and also John B. Smith for proofreading the manuscript. This work was supported by The Czech Ministry of Health Grant No.AZV 15-29508A and specific research grant - MUNI/A/1106/2016

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