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ORIGINAL ARTICLE

Outcome of Restarted Sunitinib Treatment in Patients with Metastatic Renal Cell Carcinoma: a Retrospective Trial and Combined Case Reports from Literature

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Abstract In practice it is still not clear whether a drug holiday in sunitinib (Su) treatment can be safety, without impairing the overall outcome of patients with metastatic renal cell carcinoma (mRCC). The aim was to retrospectively evaluate the outcome in patients who restarted Su after an interruption of ≥3 months and a combined analysis of case studies from literature. From 556 patients treated between January 2006 and March 2016 a group of 38 patients were selected whose treatment was interrupted for other reasons than disease progression. During interruption Su was restarted in case of RECIST-defined progression. The primary objective was the objective response (OR) and progression free survival (PFS) of baseline and restarted therapy. The secondary objective was the overall survival (OS) calculated from the start of baseline treatment. Multivariate survival analysis was also applied. The major causes of interruption were toxicity (39%) and patient' choice (24%). Median duration of interruption was 7 (range 3–41) months. The OR of baseline and restarted treatment was 63% and 39%, respectively. After a median follow-up of 76 (95% CI 65–79) months the median PFS of baseline and restarted treatment was 21 (18–27) and 14 (10–18) months, respectively. The median OS was 61 (56–80) months. In multivariate analysis the lack of OR of restated treatment was an independent predictor of shorter PFS of restarted Su. According to our findings and also on combined case studies from literature restarted Su can be effective in selected cases of patients who progressed during treatment holiday.

Keywords Drug holiday · Overall survival · Patient's choice · Progression-free survival · Toxicity

Introduction

Vascular endothelial growth factor receptor tyrosine kinase inhibitors (TKIs) are still the standard frontline therapy for patients with metastatic renal cell carcioma in the good and intermediate Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups [1].

Sunitinib (Su) was approved in 2006 as a treatment for mRCC in second-line and in 2007 for the first-line treatment and has become a reference standard of care by the international treatment guidelines. In mRCC Su therapy leads to progression-free survival (PFS) of 11.5 months and an overall survival (OS) of 26 months, which may extend up to 4 years with adequate sequential treatment [2].

The current practice is the continuous treatment until disease progression (PD) or unacceptable toxicity. In clinical practice a significant proportion of subjects temporarily discontinue cancer therapy because of complete response (CR), stable disease (SD), recurrent adverse events (AEs), concomitant comorbidities or patients' desire to have a break.

It is still not clear whether continuous therapy with TKIs or treatment with drug holiday can be safety, without impairing the overall outcome. Some studies reported that the majority of patients who had interrupted the therapy had favorable responses after treatment resumption with the same TKI [3, 4].

The aim of the present retrospective study was to analyze the efficacy and outcome of patients who restarted Su

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treatment after treatment interruption for at least 3 months treated for mRCC in a single institution cohort.

Patients and Methods

The medical records (electronic database of institute) of 556 patients with mRCC treated with Su as a first- or second-line therapy between January 2006 and March 2016 were retrospectively reviewed. Patients who achieved SD or better response with Su therapy and later discontinued the treatment for any reason with exception of PD were included. For the final analysis only those patients were selected, who restarted Su treatment because of tumor progression during the treatment holiday (≥3 months).

From patients' medical records demographic data, tumor characteristics, the history of treatments prior to restarted Su, date of progression and patients' status at the end of follow-up were extracted.

Patients were stratified according to the MSKCC risk criteria. Tumor response was classified according to the response evaluation criteria in solid tumors (RECIST) 1.1 guide-lines. Tumor response was assessed every two cycles of treatment, based on imaging with computed tomography (CT). AEs were assessed according to the National Cancer Institute – Common Toxicity Criteria (v.3.0).

Su was administrated orally at a dose of 50 mg daily, consisting of 4 week on treatment followed by a 2 week rest period in cycles of 6 weeks. The daily dose was reduced to 37.5 or 25 mg in case of severe AEs.

This investigation was approved by the Medical Research Council of Hungary and the Ethical Committee of the institute.

Statistics

The primary objective was the clinical response and progression-free survival (PFS) of baseline and restarted Su treatment. The secondary objective was the overall survival (OS). The AEs of sunitinib treatment were registered as shown in our previously published report [5]. PFS was calculated from the start of sunitinib administration until disease progression, death from any cause or end of follow-up. OS was considered from the start of baseline sunitinib until death from any cause or end of follow-up. Multinomial logistic regression was used to find predictors of response. Multivariate Cox regression analysis was performed to find independent variables, which may significantly influence survivals. Correlation analysis between variables used in the multivariate analysis was performed to avoid multicollinearity. NCSS statistical software was used for all statistical analyses. $P > 0.05$ was considered statistically significant.

Results

Among 556 mRCC patients treated with Su as first or second line therapy 38 subjects were eligible for this analysis. The patient characteristics were typical of an mRCC population, with a male predominance (n = 29) and a median age of 63.5 years (range 38–92) at the beginning of baseline Su treatment. All patients had undergone prior nephrectomy. The histologic diagnosis of tumors were pure clear (n = 33) or mixed (dominantly clear cell) RCC (n = 5). Twenty one patients showed favorable risk on the basis of MSKCC criteria and 17 had intermediate risk. Almost all patients (n = 32) presented asynchronous metastases. The most common site of metastasis was lung (n = 30), followed by the mediastinal lymph nodes (n = 9).

Twenty-one patients had not received systemic therapy before baseline sunitinib treatment, while 15 patients had a history of prior cytokine (interferon ± IL-2) treatment, for one patient was administered cytokine and chemotherapy, and one patient was treated with sorafenib in first line. The clinicopathologic characteristics of patients are summarized in Table 1. The most common cause of Su discontinuation was toxicity (n = 15) and patient's choice (n = 14). Treatment characteristics of baseline and restarted Su are shown in Table 2. The best response of baseline Su treatment is presented in Table 3. The median PFS of baseline Su was 21 (95% CI 18–27) months.

The median duration of Su cessation was 7 months (range 3–41 months). During treatment break metastasectomy was performed in 5 patients and one of them also received radiotherapy, which was applied in other 2 patients as well (Table 3). New metastatic site(s) occurred in 11 patients (data not shown). In all cases, at the time of disease progression the Su was restarted. The median duration of restarted treatment was 11.5 (range 1–48) months. At the end of follow-up (31 March 2016) 5 subjects were on active Su treatment. The best response of restarted Su therapy was CR in one patient (3%) and PR in 14 (37%) patients, while 19 patients (50%) had SD and in 4 (11%) patients the disease progressed (Table 3). During the follow-up 31 patients had disease progression and nearly three-quarter of them (23 patients) died. In 12 cases new locations of metastases occurred during restarted treatment. The causes of discontinuation of restarted treatment are presented in Table 2. After a median follow-up of 76 months the median PFS of restarted treatment was 14 (95% CI 10–18) months and the median OS calculated from the start of baseline Su treatment was 61 (56–80) months (Figs. 1 and 2). The most frequent side-effects are shown is Table 4. There was no statistically significant difference between AEs of baseline and restarted treatment. An accumulation of adverse events was present in the majority of patients (n = 29), who had 4 or more different side effects, but only 2 of them had 2 different side effects of grade 3/4 (data not shown).

Table 1 Patients' characteristics at start of baseline and restarted sunitinib treatment

Parameters	Baseline N (%)	Restarted N (%)
Mean age (range) years	63.5 (38–91)	66 (42–93)
Number of metastasized organs		
One	18 (47)	12 (32)
Multiple	20 (53)	26 (68)
Site of metastasis		
Lung	30 (79)	33 (87)
Mediastinal lymph node	9 (24)	10 (26)
Adrenal gland	7 (18)	7 (18)
Retroperitoneal lymph node	5 (13)	7 (18)
Liver	4 (11)	4 (11)
Bone	4 (11)	6 (16)
Local recurrence	4 (11)	5 (13)
Brain	2 (5)	2 (5)
Contralateral kidney	0	2 (5)
Peritoneum	0	2 (5)
Pre-sunitinib treatment		
Nephrectomy	38 (100)	
Metastasectomy	0	5 (11)
Radiotherapy	4 (11)	3 (8)
Only immunotherapy	15 (39)	0
Immunotherapy + chemotherapy	1 (3)	0
Sorafenib	1 (3)	0

Table 3 Clinical outcomes of baseline and restarted sunitinib

Parameters	Baseline N (%)	Restarted N (%)
Best response		
Complete response (CR)	9 (24)	1 (3)
Partial response (PR)	15 (39)	14 (37)
Stable disease (SD)	14 (37)	19 (50)
Progressive disease (PD)	0	4 (11)
Objective response (CR + PR)	24 (63)	15 (39)
Clinical benefit (CR + PR + SD)	38 (100)	24 (63)
Survival (95% CI) months		
Progression-free	21 (18–27)	14 (10–18)
Overall	61 (56–80)	
Pattern of progression		
Preexisting lesions	23 (61)	26 (68)
New lesions	15 (39)[a]	7 (18)
No progression	0	5 (13)
Systemic therapy after sunitinib	38 (100)	16 (42)[b]
Metastasectomy	5 (11)[a]	2 (5)
Radiotherapy	3 (8)[a]	8 (21)

Abbreviations: *CI* confidence interval, *CR* complete response, *PD* progressive disease, *PR*- partial response, *SD* stable disease

[a] during sunitinib discontinuation

[b] rechallenged sunitinib (7), everolimus (6), axitinib (3), nivolumab (3), cabozantinib (2) and pazopanib (1)

In order to determine the influence of different parameters on survivals univariate and multivariate analysis were performed. For baseline PFS gender, age, prognostic score, histology, metastasis synchronicity, multiple organ metastases, pulmonary metastasis, previous immunotherapy, Su dose reduction, best response were analyzed by Kaplan Meier method and log rank test. The older age (≥63 years), synchronous metastasis, lack of previous immunotherapy and PR resulted in statistically significantly shorter PFS of baseline treatment (Table 5). In multivariate analysis only those parameters were included, which proved to have significant effect on survival in univariate analysis. Based on multivariate Cox regression analysis older age, synchronous metastases and PR vs. SD (or CR) were independent factors of shorter baseline PFS. For restarted PFS gender, age, tumor histology, metastasis synchronicity, multiple metastases, pulmonary metastasis, previous immunotherapy, new metastasized organs, therapy during Su break, duration of break, baseline PFS duration, toxicity at cessation, restarted sunitinib dose reduction and the best response during restarted Su were analyzed by Kaplan Meier method and log rank test. Only the objective response rate of restarted treatment influenced the PFS of restarted Su (Table 5). None of the parameters had statistically significant effect on response in multinomial logistic regression.

Table 2 Treatment characteristics of baseline and restarted sunitib

Parameters	Baseline N (%)	Restarted N (%)
Median treatment duration (95% CI) months	15.5 (11–19)	11.5 (8–15)
Dose reduction	14 (37)	9 (24)
Cause of sunitinib discontinuation		
Toxicity	15 (39)	7 (16)
Patient's choice[a]	14 (37)	2 (5)
Other cause (other disease, surgery)	9 (24)	2 (5)
Progressive disease	0	21 (47)

Abbreviation: *CI* confidence interval

[a] patients with stable disease or clinically disease free

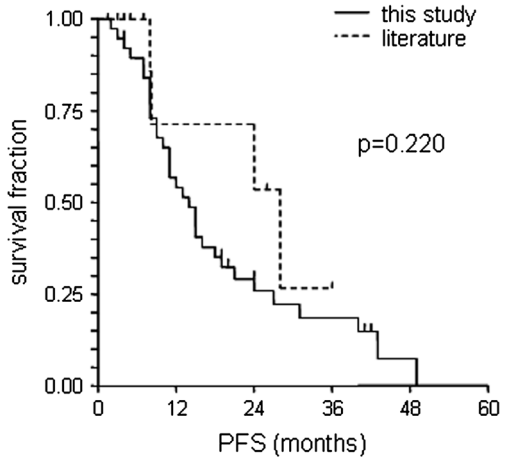

Fig. 1 Progression free survival (PFS) of restarted sunitinib treatment of mRCC patients from our study (—) and combined case studies from literature (—). The treatment break was ≥3 months

Similarly, no variable influenced significantly the OS in multivariate Cox regression (data not shown).

Discussion

In this retrospective study 38 patients, who achieved SD or a better response under Su therapy and later discontinued treatment for any reason with the exception of disease progression were analyzed. After a median of 15.5 months receiving Su therapy, patients were observed on average 11.2 months until RECIST-defined PD. The reasons for drug holiday were diverse, 39% of patients interrupted the treatment because of adverse events, however, these toxicities were of low grade but the sustained presence worsened the quality of life. Some recent studies showed that intermittent breaks of Su (or other TKIs) treatment could decrease toxicity without compromising the efficacy, and most tumors responded after the reinitiation of the same therapy. The strategy of treatment break (interruption and resumption) could be an option for selected mRCC patients [6], which is demonstrated in our study.

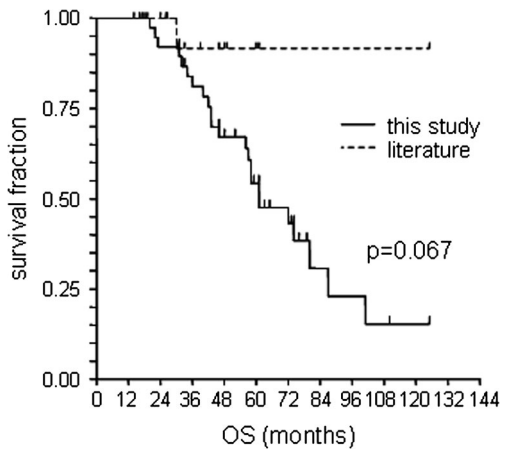

Fig. 2 Overall survival (OS) of sunitinib-treated mRCC patients from our study (—) and combined case studies from literature (—). After a ≥ 3 months treatment break the sunitinib was restarted

Table 4 Summation of treatment related side-effects

Side effects	Baseline N (%)		Restarted N (%)	
	All grades	Grade 3/4	All grades	Grade 3/4
Diarrhea	24 (63)		23 (61)	
Hypothyreosis	22 (58)		26 (68)	
Hypertension	21 (55)		18 (47)	
Anaemia	21 (55)	2 (5)	29 (76)	5 (13)
Mucositis	16 (42)		17 (45)	
Thrombocytopenia	15 (39)	5 (13)	15 (39)	4 (11)
Leukopenia	15 (39)		14 (37)	
Hand-foot syndrome	12 (32)		14 (37)	
Skin rash	11(29)		10 (26)	
Cardiovascular toxicity	9 (24)		8 (21)	
Renal disorder	9 (24)	1 (2)	15 (39)	4 (11)
Hepatic malfunction	3 (8)	3 (7)	5 (13)	2 (5)
Metabolic toxicity	2 (5)	1 (2)	5 (13)	2 (5)
Other	1 (3)		2 (5)	

Table 5 Univariate and multivariate survival analysis of baseline and restarted sunitinib treatment

Parameters	mPFS (95% CI)	p[a]	HR (95% CI)	p[b]
Baseline				
Age		0.042		
<63 years	25 (19–37)		1 (reference)	
≥63 years	19 (13–25)		2.39 (1.11–5.13)	0.026
Synchronicity		0.0004		
Asynchronous	25 (19–32)		1 (reference)	
Synchronous	16 (9–18)		5.42 (1.71–17.2)	0.004
Immunotherapy		0.043		
No	19 (17–23)		1 (reference)	
Yes	37 (19–45)		0.61 (0.29–1.28)	n.s.
Response		0.027		
CR	27 (23–39)		0.77 (0.28–2.14)	n.s.
PR	17 (13–21)		2.41 (1.09–5.37)	0.031
SD	20 (18–42)		1 (reference)	
Restarted				
Response		0.043		
CR + PR	18 (12–49)		0.47 (0.22–1.00)	0.051
SD + PD	11 (8–15)		1 (reference)	

Abbreviations: *CI* confidence interval, *CR* complete response, *HR* hazard ratio, *n.s.* statistically non-significant, *PD* progressive disease, *PR* partial response, *SD* stable disease

[a] Log rank test

[b] Wald test

In the literature there are some case reports and few reports with low number of patients investigating the efficacy of restarted Su in mRCC (Table 6). In investigations in which the treatment was interrupted because of surgical intervention on primary tumor (nephrectomy) were not considered. Johannsen et al. [7] studied the effect of TKI discontinuation in a cohort of 12 patients out of whom 5 were treated with Su. The readministration was effective in all cases and the outcome of each patient was detailed. In another publication Johannsen et al. [4] evaluated a larger cohort (n = 36) including all patients from the previous publication. At all 12 patients with mRCC were retreated with Su. The OR and clinical benefit rate (CBR) of restarted Su was 62% and 100%, respectively. Unfortunately, the PFS of restarted Su and the OS of patients were not reported, thus they were approximated assuming that the evaluation of best response of restarted treatment was performed 3 or more months after the resumption. Albiges et al. studied the effect of Su cessation exclusively on patients who reached CR with TKI alone (median break 5.6 months) or with Su and local treatment (median break 8.9 months) [3]. In total 24 patients progressed and 14 of them restarted Su (or max 2 of them sorafenib) resulting in 57% OR (71% CBR) and a mOS longer than two years. Koo et al. [1] analyzed 16 patients of whom treatment was interrupted (for a median of 11.8 months) and after progression they were subsequently treated (11 with TKIs (6 with Su)). The majority of patients achieved SD and the mPFS was 28 months. Miura et al. [8] followed 9 patients on Su treatment, which was ceased. In 4 patients after a break of median 6 months the treatment was recommenced with Su. The OR, CBR and mPFS was 50%, 100%, and 28 months, respectively, while mOS was not reached.

The other publications in which a Su holiday was applied were case reports. The duration of interruption of the available 32 cases varied in a broad range (from 10 days to 25 months, median 4.2 months). The efficacy of restarted Su treatment was calculated for all cases and for a subcohort of 22 patients who had a break of ≥3 months, which is the same as in our study. The difference between the response pattern in our study and that of 22 cases not reached the level of statistical significance (exact test p = 0.2). The mPFS of restarted treatment for the 22 cases seems to be longer than in our study (28 vs. 14 months), however the result of the log rank test was non-significant (p = 0.22) (Fig. 1). For mOS the same non-significant difference (p = 0.067) was observed (Fig. 2). The trend for longer survivals might be attributed to a shorter follow-up of the 22 cases (31 vs. 76 months in our study) and/or selection bias.

The mOS of restarted Su in our study and that from the literature can not be compared to the mOS of a continuous, randomized Su trial, because the median follow-up in our investigation was much longer than in published continuous Su trials. Molina et al. [23] evaluated 186 patients treated with first-line Su and after a median follow-up of 64 months (vs. 76 months in our study) the mOS was only 30.4 months (vs. 61 months in or study), − on the other hand our patients can be considered "selected" as they did not progressed during the baseline treatment, which lasted for a median of >15 months.

In the clinical practice, there is a concern that discontinuation of anti-cancer drug may increase the risk of rebound phenomenon or flare-up syndrome, which result in rapid clinical progression after stopping the effective treatment [24]. The rebound phenomenon may be rarely seen in clinical practice when VEGFR-TKI therapy is discontinued after a long duration of TKI treatment, especially when patients were responders before discontinuation. A clinical concern with observation of patients with mRCC would be occurrence of new sites of metastases that could lead to increased mortality, which might be avoided with continuous treatment. In our study, overall, 11 patients had new lesions during the expectant management, which means a median rate of 11/7 = 1.6 new lesions/months. This rate calculated for the restarted treatment is 12/11.5 = 1.0. Data suggest that the occurrence is partly due to break itself and does not reflect the course of disease while on treatment. In our study and in Table 6, the restarted Su regained the control of disease in 63 and >70% of patients, respectively.

The *de novo* onset of epithelial to mesenchimal transition (EMT)-like phenotype in RCC patients on Su treatment was reported. EMT can be associated with metastases, angiogenesis and resistance mechanism. The reversion of histological phenotype also suggests that this resistance may also be transient." According to this hypothesis patients who have initially received clinical benefit from treatment with TKIs and then developed resistant disease may respond again to TKIs following a break from anti VEGF therapies". The "holiday" period from anti VEGF therapies may lead to "reset" the tumor microenvironment and reestablish a primarily VEGF-driven tumor growth" [25].

Our study has several limitations inherent to a retrospective design and analysis. There was no definitive indication for treatment cessation and the timing of the sunitinib holiday was not decided by a protocol, but sometimes by the patients' decision. In spite of limitations, the results of our study are strengthened by the results of the cohort trials and that of combined case reports (Table 6) from the literature.

In conclusion, based on our results and on combined case reports from the literature Su treatment could be

Table 6 Efficacy of restarted sunitinib according to the literature

Reference nr.	Treatment break [months]	Best response of restarted sunitinib	PFS (censor) [months]	OS (censor) [months]
[4]	6	SD	≥3 (0)	≥33 (0)
[4]	25	SD	≥3 (0)	≥31 (0)
[4]	6[a]	PR	≥3 (0)	≥19 (0)
[4]	9[a]	PR	≥3 (0)	≥19 (0)
[4]	1[a]	PR	≥3 (0)	≥20 (0)
[4]	7[a]	SD	≥3 (0)	≥17 (0)
[4]	1[a]	PR	≥3 (0)	≥12 (0)
[4]	8[a]	PR	≥3 (0)	≥14 (0)
[4, 7]	3	PR	3 (0)	18 (0)
[4, 7]	7	SD	1.5 (0)	26.5 (0)[b]
[4, 7]	6[a]	PR	1.5 (0)	26.5 (0)
[4, 7]	12[a]	SD	≥3 (0)	≥26 (0)
[8]	4.2	CR	28 (1)	61 (0)
[8]	8.6	SD	8.2 (1)	49 (0)[c]
[8]	2.2	PR	32 (0)	48 (0)
[8]	7.9	SD	26 (0)	46 (0)
[9]	3	CR	9 (0)	31 (0)
[10]	6	PR	8 (1)	39 (0)[c/b]
[10]	2	PD	2 (1)	19 (0)
[11]	12[a]	PR	≥3 (0)	≥31 (0)
[12]	3	SD?	24 (1)	125 (0)[c]
[13]	6	CR	4 (0)	24 (0)
[14]	4	SD	36 (0)	48 (0)
[15]	1[b]	SD	18 (1)	25 (0)
[15]	0.5[b]	SD	13 (0)	27 (0)
[16]	0.5	PD	6 (1)	8 (0)
[17]	0.7	SD	4 (1)	6 (1)
[18]	5	PR	7 (0)	16 (0)
[19]	0.7	CR	9 (0)	12 (0)
[20]	12	SD?	5 (0)	30 (1)[c]
[21]	3	SD	~5 (0)	~60 (0)
[22]	0.33	PR	22.7 (1)	≥31 (0)
Total n = 32	m 4.2 ([a/b] 34%)	53% OR, 94% CB	m 24	NR (5S 90%)
Total n = 22 (break ≥3 months)	m 6 ([a] 32%)	55% OR, 100% CB	m 28	NR (5S 92%)
Our study n = *38*	*m 7 ([a/b] 18%)*	*39% OR, 89% CB*	*m 14*	*m 61 (5S 72%)*
[3] (n = 11)	m 5.6	n = 14[s1]	≥3 (0)	m ≥ 24.2
[3] (n = 13)	m 8.9[a/d/b]	57% OR, 71% CB		m ≥ 29.3
[1] (n = 11[s2])	m 11.8[a/b, n]	18% OR, 100% CB	m 28	–

Abbreviations: *5S* 5-year survival rate, *CB* clinical benefit (OR+SD), *CR* complete response, *m* median, *NR* not reached, *OR* objective response (CR+PR), *OS* overall survival, *PD* progressive disease, *PFS* progression-free survival, *PR* partial response, *SD* stable disease

[a] metastasectomy

[b] radiotherapy

[c] systemic therapy

[d] nephrectomy

[s1] sunitinib n = 12, 13 or 14

[s2] sunitinib n = 6, other TKI n = 5

[n] TKI n = 11, other systemic therapy n = 5

interrupted when clinically warranted, but cessation should be approached with caution in older patients or patients having synchronous metastases at diagnosis or presenting partial response as best response of baseline Su treatment. Results of an ongoing prospective trial (STAR) [26] probably will give a better approach with new aspects to be used in the routine practice [27].

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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