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Original research

Association between ibrutinib treatment and hypertension

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ABSTRACT

Background Ibrutinib is a tyrosine kinase inhibitor most commonly associated with atrial fibrillation. However, additional cardiotoxicities have been identified, including accelerated hypertension. The incidence and risk factors of new or worsening hypertension following ibrutinib treatment are not as well known.

Methods We conducted a retrospective study of 144 patients diagnosed with B cell malignancies treated with ibrutinib (n=93) versus conventional chemoimmunotherapy (n=51) and evaluated their effects on blood pressure at 1, 2, 3 and 6 months after treatment initiation. Descriptive statistics were used to compare baseline characteristics for each treatment group. Fisher's exact test was used to identify covariates significantly associated with the development of hypertension. Repeated measures analyses were conducted to analyse longitudinal blood pressure changes.

Results Both treatments had similar prevalence of baseline hypertension at 63.4% and 66.7%, respectively. There were no differences between treatments by age, sex and baseline cardiac comorbidities. Both systolic and diastolic blood pressure significantly increased over time with ibrutinib compared with baseline, whereas conventional chemoimmunotherapy was not associated with significant changes in blood pressure. Baseline hypertensive status did not affect the degree of blood pressure change over time. A significant increase in systolic blood pressure (defined as more than 10 mm Hg) was noted for ibrutinib (36.6%) compared with conventional chemoimmunotherapy (7.9%) at 1 month after treatment initiation. Despite being hypertensive at follow-up, 61.2% of patients who were treated with ibrutinib did not receive adequate blood pressure management (increase or addition of blood pressure medications). Within the ibrutinib group, of patients who developed more than 20 mm Hg increase in systolic blood pressure, only 52.9% had hypertension management changes.

Conclusions Ibrutinib is associated with the development of hypertension and worsening of blood pressure. Cardiologists and oncologists must be aware of this cardiotoxicity to allow timely management of blood pressure elevations.

INTRODUCTION

Ibrutinib is a Bruton's tyrosine kinase inhibitor (TKI) that is used to treat chronic lymphoid leukaemia, Waldenstrom's macroglobulinaemia, as well as other conditions such as mantle cell lymphoma and marginal zone lymphoma.[1–6] Its mechanism of action is through blocking B cell signalling and targeting other downstream transcription factors, resulting in reduced expression of CD20 and ultimately promoting apoptosis and reducing cell proliferation.[4 7–9] However, ibrutinib has known cardiotoxicities, including atrial and ventricular arrhythmias as well as hypertension.[10–15] Unlike various other TKIs, the mechanism of ibrutinib blood pressure (BP) elevations is not due to inhibition of the vascular endothelial growth factor (VEGF) pathway and is yet to be fully elucidated.[16]

While initial reports suggested the incidence of ibrutinib-related hypertension was relatively modest (5%–18%),[1 2 6 17] more recent studies suggest a much higher burden.[10 16] In fact, a recent study by Dickerson *et al*[16] reported new or worsening hypertension in 78.3% of patients treated with ibrutinib. Our study compared the incidence of new or worsening hypertension for ibrutinib therapy versus conventional chemoimmunotherapy regimens for B cell malignancies and to assess the management of hypertension associated with these therapies.

METHODS

Study population

The patient population was derived from our previously described cohort of 137 patients diagnosed with B cell malignancies treated with ibrutinib therapy and 107 patients with conventional chemoimmunotherapy (lenalidomide/rituximab, fludarabine/cyclophosphamide/rituximab or bendamustine/rituximab) between 1 January 2010 and 31 December 2017.[15] In the original cohort, patients in the treatment groups (ibrutinib therapy vs conventional chemoimmunotherapy) were frequency-matched on age and sex to ensure no significant differences and to eliminate potential confounding from these covariates. The subcohort was not frequency-matched by age and sex.

Inclusion criteria were patients ≥18 years with documented vital signs at baseline, at 1 month and at least one additional assessment at 2, 3 and/or 6 months after initiation of cancer therapy. Patients

(ibrutinib group n=137, conventional chemoimmunotherapy group n=107) from the original publication[15] were excluded from this analysis if they did not have the requisite vital sign measurements recorded in the electronic medical record. The final analytical sample size was 144 patients (93 patients treated with ibrutinib therapy and 51 treated with conventional chemoimmunotherapy).

Due to the reduced sample size from our original publication, we performed post-hoc power calculations[18] to detect a significant difference in mean vital sign measurements between the two treatment groups. The post-hoc power calculations were based on the main effects of an overall mean change and not based on repeated measures. Based on an alpha of 0.05, and assuming a mean systolic blood pressure (SBP) of 130 mm Hg, diastolic blood pressure (DBP) of 90 mm Hg, and heart rate of 80 beats per minute and SD of 10 for all measurements, we have at least 82% power to detect a statistically significant mean difference of 5 mm Hg or beats per minute for each measure.

Data collection

The electronic medical records were evaluated to abstract baseline characteristics including demographics, cardiovascular comorbidities, cardiovascular medications and hospitalisations. BP was recorded at baseline and at 1, 2, 3 and/or 6 months time points after cancer treatment initiation or until treatment was stopped. All BP measurements were obtained from outpatient clinic visits at Moffitt Cancer Center. Hypertension was defined as BP ≥130/80 mm Hg or use of antihypertensive medications based on 2017 American Heart Association/American College of Cardiology hypertension criteria. Over the course of cancer treatment, initiation or discontinuation of antihypertensive medications or dose adjustments were recorded. The data set was reviewed for accuracy by a second, independent investigator.

Data analysis

Data are presented as count and percentage for categorical data and mean with SD for continuous data. Fisher's exact test was used to test for differences between the two patient groups for categorical covariates and Student's t-test was used to test for differences for continuous covariates. Repeated measures analysis using a fixed effects general linear model with baseline BP included as a covariate and a variance components covariance was conducted to assess changes in SBP and DBP over three time points with assessment of the main interaction effect. We have performed post-hoc Bonferroni test. In addition to the baseline and 1-month follow-up BP measurements, we also generated a third time point summary measurement which combined BP measures at 2, 3 or 6 months using the earliest available time points. The third time point summary measurement was generated because BP measurements were not uniformly assessed after the 1-month measurements. As such, this ensured at least two sets of vital signs were evaluated after the initiation of cancer therapy as described in the Study population section. SPSS V.24.0 was used for statistical analysis. A p value of less than 0.05 was considered statistically significant.

Patient and public involvement

Patients and the public were not involved in the development of question, design, recruitment, conduct or outcome measures of the current research study.

RESULTS

From the original cohort, 93 patients treated with ibrutinib and 51 patients treated with conventional chemoimmunotherapy met the inclusion criteria for the current analysis. Baseline patient demographics are presented in table 1. The two groups were well matched without significant differences in baseline comorbidities or medications. Compared with conventional chemoimmunotherapy group, more patients treated with ibrutinib demonstrated a significant increase in BP over time. Between baseline and 1 month, 18.3% of patients treated with ibrutinib had an increase in their SBP of between 10 mm Hg and 19 mm Hg, and an additional 18.3% experienced an increase in SBP of ≥20 mm Hg. In contrast, only 7.9% of patients in the conventional chemoimmunotherapy group experienced an SBP increase of more than 10 mm Hg from baseline.

The mean baseline SBP and DBP were significantly higher in the conventional chemoimmunotherapy group (129/77 mm Hg) compared with the ibrutinib-treated group (122/72 mm Hg). However, there was no significant difference in the number of patients meeting the study definition of hypertension (ibrutinib 63.4%, conventional chemoimmunotherapy 66.7%, p=0.720). The lower baseline BP in the ibrutinib group was not driven by excess antihypertensive therapy; in fact, baseline BP was actually higher in patients taking antihypertensive medications at baseline (125/74 mm Hg vs 117/70 mm Hg, p=0.008 and p=0.055 for SBP and DBP, respectively). Of note, when the criteria for hypertension were used based on prior guidelines (BP ≥140/90 or use of antihypertensive medications), the number of patients with hypertension at baseline was lower (ibrutinib 51.6%, conventional chemoimmunotherapy 56.9%, p=0.547).

In the ibrutinib group, 59 (63.4%) patients had baseline hypertension compared with 34 (66.7%) patients in the conventional chemoimmunotherapy group. The number of patients who had hypertension at 1 month increased to 67 (72%) patients in the ibrutinib group, while there was a decrease to 28 (54.9%) patients in the conventional chemoimmunotherapy group. From the 2–6 months summary data, there was no difference in the incidence of hypertension between the ibrutinib group (71%, n=66) and the conventional chemoimmunotherapy group (68.6%, n=35, p=0.849).

Repeated measures analyses demonstrated statistically significant difference in mean SBP and DBP (both p<0.010) over the three recorded time points within each treatment group (figure 1). Using post-hoc Bonferroni analysis to compare baseline, 1 month and 2, 3 or 6 months BP values, ibrutinib patients demonstrated a statistically significant change (p<0.001) for each comparison (baseline BP: 122/72 mm Hg; 1 month BP: 130/74 mm Hg; 2, 3 or 6 months BP: 133/76 mm Hg). Using the same method for the conventional chemoimmunotherapy group, there was a significant decrease in BP at 1 month (baseline BP: 129/77 mm Hg; 1 month BP: 123/73 mm Hg; p=0.006). However, there was no significant difference from baseline and at 2, 3 or 6 months time points (BP 127/75 mm Hg, p=0.923). In addition, there were no statistically significant changes in SBP between baseline/1 month (ΔA) and baseline/2–6 months (ΔB) (ΔA +8.4±16.4 mm Hg and ΔB 11.5±16.4 mm Hg, p=0.239) in the ibrutinib group (figure 1). In comparison, changes in SBP between baseline/1 month (ΔA) and baseline/2–6 months (ΔB) were statistically significant (ΔA −6.2±12.6 mm Hg and ΔB 0.0±15.6 mm Hg, p=0.003) in the conventional chemoimmunotherapy group. The BP change patterns were different between the ibrutinib and conventional

Table 1 Patient demographics by chemotherapy regimens

	Patients treated with ibrutinib (n=93)	Patients treated with conventional chemoimmunotherapy (n=51)	P value*
Age at onset of therapy, mean±SD	66.9±10.7	64.2±9.1	0.143
Sex, male, n (%)	64 (68.8)	34 (66.7)	0.853
BMI, mean±SD	27.6±5.3	28.4±5.8	0.374
Smoking history, n (%)	52 (55.9)	28 (54.9)	1.000
SBP at baseline	121±15	129±17	0.008
DBP at baseline	72±10	77±8	0.001
Heart rate at baseline	80±15	77±12	0.143
Baseline comorbidities, n (%)			
Hypertension†	59 (63.4)	34 (66.7)	0.720
Diabetes mellitus	20 (21.5)	11 (21.6)	1.000
Hyperlipidaemia	46 (49.5)	23 (45.1)	0.728
Coronary artery disease	16 (17.2)	12 (23.5)	0.384
Atrial fibrillation	10 (10.8)	8 (15.7)	0.435
Cardiomyopathy	6 (6.5)	3 (5.9)	1.000
Stroke	2 (2.2)	3 (5.9)	0.346
Baseline cardiovascular medications, n (%)			
ACEi	12 (12.9)	6 (11.8)	1.000
ARB	11 (11.8)	2 (3.9)	0.138
Beta blocker	22 (23.7)	10 (19.6)	0.677
CCB	14 (15.1)	6 (11.8)	0.626
Thiazide	10 (10.8)	5 (9.8)	1.000
Loop diuretics	5 (5.4)	1 (2.0)	0.423
Nitrates	0 (0)	0 (0)	
Statin	28 (30.1)	20 (39.2)	0.356
Aspirin	23 (24.7)	17 (33.3)	0.331
Malignancy type, n (%)			**<0.001**
Chronic lymphocytic leukaemia	70 (75.3)	27 (52.9)	
Mantle cell lymphoma	11 (11.8)	24 (47.1)	
Waldenstrom's macroglobulinaemia	10 (10.8)	0 (0)	
Other	2 (2.2)	0 (0)	

*P values were derived from Fisher's exact test for categorical variables and Student's t-test for continuous variables. All p values are two-sided, and p value in bold is statistically significant.
†Hypertension was defined by individual chart review through SBP ≥130 or DBP ≥80 or on antihypertensive medications.
ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.

chemoimmunotherapy group (p<0.001 for both SBP and DBP), with a trend towards an increase primarily in SBP in the ibrutinib group.

When adjusting for baseline hypertension, these changes were no longer statistically significant (figure 2). There were no statistically significant differences in BP changes after initiation of ibrutinib based on baseline hypertension status, with both baseline hypertension and no hypertension groups having increase in SBP (figure 2A) and DBP (figure 2B) at 1 month after initiation of ibrutinib.

Overall, patients with baseline hypertension did not get sufficient treatment for hypertension for both groups treated with ibrutinib or conventional chemoimmunotherapy. Among patients in the ibrutinib group who developed hypertension, 38.8% had management changes (increase or addition of antihypertensive medication), whereas 61.2% did not get management changes. Of the patients who developed an SBP increase of >20 mm Hg, only 52.9% had hypertension management changes. The degree of management changes for hypertension was similar in the conventional chemoimmunotherapy group (39.3% with management changes).

DISCUSSION

This study found that the incidence of new or worsening hypertension was greater in patients treated with ibrutinib compared with patients receiving conventional chemoimmunotherapy, with the largest increase occurring within the first month of therapy. These data are consistent with recent studies reporting a significantly elevated incidence of ibrutinib-related hypertension.[16] Longitudinal analyses demonstrated that ibrutinib use was consistently associated with increasing BP. Interestingly, the conventional chemoimmunotherapy group demonstrated a decline in BP at the 1-month time point, which may be attributed to a mild autonomic dysfunction which commonly occurs in the setting of cytotoxic chemotherapy.[19] Also, despite the lower average BP at baseline in the ibrutinib group compared with the conventional chemoimmunotherapy group, the ibrutinib group had greater increases in their BP (particularly SBP) from baseline values and a trend towards increased values over time.

Previous safety analyses of ibrutinib demonstrated a 3% incidence of developing hypertension compared with 1% with conventional chemoimmunotherapy.[20] However, subsequent studies have suggested a much higher incidence of developing new or worsening hypertension, up to 40% in one observational study.[10 21] Most recently, a retrospective study of 562 patients treated with ibrutinib

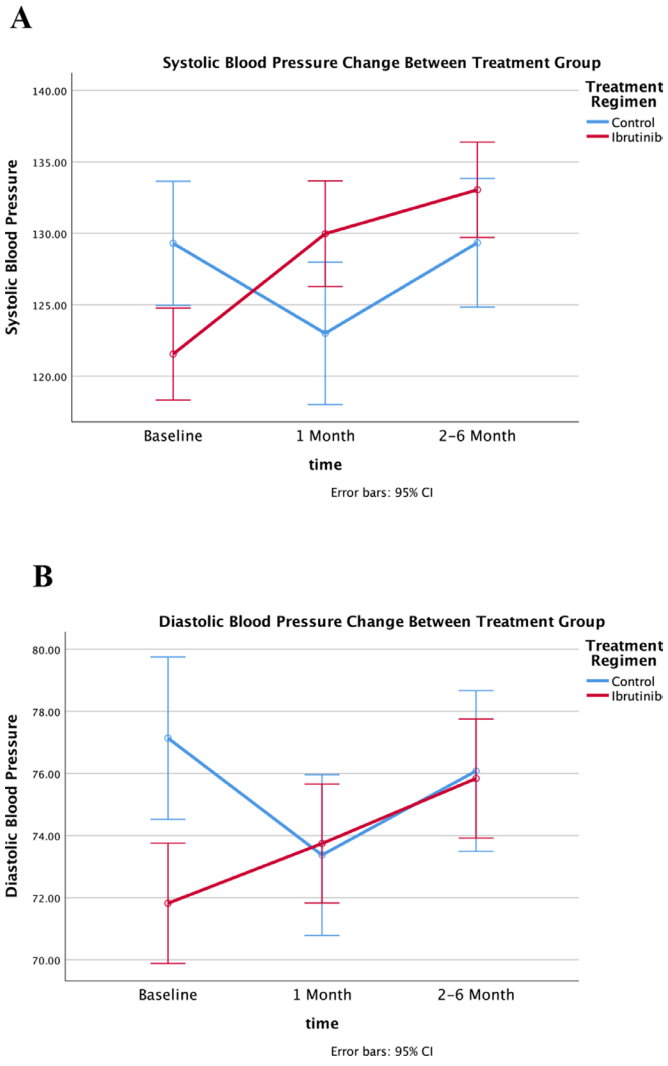
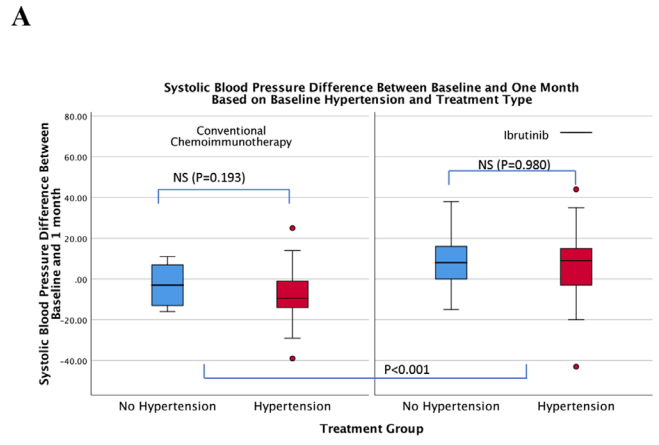
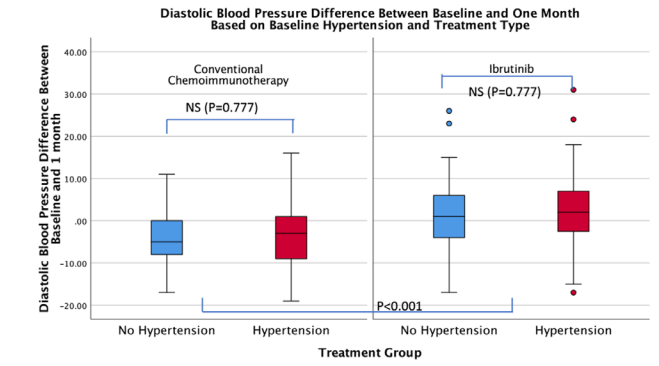


Figure 1 Changes in blood pressure over time based on treatment group. (A) Changes in systolic blood pressure over time based on treatment regimen. Ibrutinib treatment causes significant increase in systolic blood pressure over time compared with baseline. (B) Changes in diastolic blood pressure over time based on treatment regimen. In a repeated measure post-hoc Bonferroni test, there was statistically significant increase in blood pressure at 1 month and at 2–6 months summary data when compared with baseline (p<0.001) in the ibrutinib group.



	Conventional Chemoimmunotherapy		Ibrutinib	
	No HTN(N=17)	HTN (N=34)	No HTN (N=34)	HTN (N=59)
Δ SBP	-3.35±9.81	-7.76±13.64	8.47±13.35	8.39±18.07



	Conventional Chemoimmunotherapy		Ibrutinib	
	No HTN(N=17)	HTN (N=34)	No HTN (N=34)	HTN (N=59)
Δ DBP	-4.18±7.18	-3.55±7.44	1.44±9.60	2.20±8.77

Figure 2 Box plot for changes in blood pressure from baseline to 1 month by treatment and baseline hypertension status. Systolic (A) and diastolic (B) blood pressure changes from baseline and 1 month were not different between hypertension (red bar) and normotension (blue bar) in both ibrutinib and conventional chemoimmunotherapy groups. Changes in systolic and diastolic blood pressure were significantly different overall for ibrutinib versus conventional chemoimmunotherapy (p<0.001) in the ibrutinib group. Δ, change in blood pressure; DBP, diastolic blood pressure; HTN, hypertension; NS, not statistically significant; SBP, systolic blood pressure.

over a median follow-up of 30 months reported hypertension in 78.3%, with 71.6% developing new-onset hypertension and 82.4% worsening of their baseline high BP. The average time to developing ibrutinib-associated hypertension was 1.8 months (50% cumulative incidence). Treatment of ibrutinib-induced hypertension reduces the risk of subsequent major adverse cardiac events (defined as stroke, myocardial infarction, heart failure and cardiac arrhythmia, in addition to cardiovascular death); however, no specific antihypertensive class was more efficacious.[16] In our study, patients in neither treatment group were adequately initiated on antihypertensive medications when BP elevations were identified. It is essential to raise awareness on ibrutinib association with hypertension to allow for expeditious initiation of antihypertensives to avoid the adverse acute and chronic cardiovascular consequences associated with uncontrolled hypertension, including myocardial infarction, renal dysfunction and stroke.

The mechanism by which ibrutinib exerts its hypertensive effects remains unclear, although one proposed mechanism is off-target downregulation of the VEGF pathway through Bruton's tyrosine kinase inhibition.[22] Hypertension is a common on-target cardiotoxicity of VEGF inhibitors, a class of TKIs including sunitinib, axitinib and pazopanib used to treat various solid and liquid tumours.[23] VEGF inhibitor hypertension may be related to decreased nitric oxide bioavailability, microvascular rarefaction, and/or production of endogenous vasoactive substances including endothelin-1 and sFlt-1, leading to increased systemic vascular resistance.[16 24 25]

We acknowledge some limitations to this study. First, this is a retrospective study from a single centre which may not be generalisable

to other institutions. The conventional chemoimmunotherapy group had fewer patients than the ibrutinib group due to lack of baseline vital signs available in the electronic medical record because many of the patients initiated therapy prior to establishing care at Moffitt Cancer Center. Nevertheless, the baseline clinical characteristics, including age, sex and comorbid conditions, were not significantly different between the two treatment groups, which should reduce the likelihood of biased results. Although the mean baseline BP was higher in the chemoimmunotherapy group (which may simply be due to chance), there was no significant difference in the prevalence of baseline hypertension between groups as defined by the study. This is an inherent limitation of a retrospective study that can be overcome by future prospective observational study. Future studies may also consider usage of 24-hour ambulatory BP measurements. In addition, 6 months is a relatively short follow-up period and a longer interval could yield different results. Our definition of hypertension included use of new or additional antihypertensive medications, which may have biased our baseline data and patient demographics. Next, we do not have information on dose adjustments of antihypertensive medications that may affect BP trends. However, there were no patients who had initiation or adjustment of antihypertension medications prior to 1-month follow-up visit (which showed the most elevation of BP with maintenance of elevated BP afterwards). Finally, our study was not designed to assess the efficacy of specific antihypertension medications, nor the associated adverse cardiac events. Further studies should be designed to assess for the efficacy of the various antihypertensive medications in patients with ibrutinib-induced hypertension.

In conclusion, patients treated with ibrutinib were more likely to develop new-onset hypertension or have worsening of their pre-existing hypertension, even when compared with comparative chemotherapy. Moreover, initiation of appropriate medical therapy was often delayed in both populations. Future prospective studies are necessary to better ascertain the incidence of ibrutinib-associated hypertension, as well as basic and translational studies to determine the mechanism of ibrutinib's vascular effects. With increased awareness and knowledge, along with collaboration with cardiologists and oncologists, management algorithms should be developed so patients can receive optimal treatment to prevent long-term cardiovascular complications from uncontrolled hypertension.

Key messages

What is already known on this subject?

- The Bruton's tyrosine kinase inhibitor ibrutinib is used to treat various B cell malignancies and is associated with various cardiotoxicities including arrhythmias.

What might this study add?

- The present study demonstrates that hypertension is also an important cardiotoxicity of ibrutinib when compared with conventional chemoimmunotherapy.
- A significant increase in blood pressure of more than 10 mm Hg was seen in 36% of patients on ibrutinib, with the majority of patients receiving inadequate treatment for their hypertension.

How might this impact on clinical practice?

- Both cardiologists and oncologists must be aware of this cardiotoxicity and aggressively manage blood pressure elevations in patients on ibrutinib to reduce long-term adverse cardiovascular outcomes.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Data were obtained by retrospective chart review; informed consent was not necessary.

Ethics approval This study was in accordance with the ethical standards of institutional/national research committee and with the Declaration of Helsinki 1964 and was approved by the University of South Florida IRB (#Pro00022060) and by Moffitt Cancer Center (MCC) Scientific Review Committee (MCC #18229).

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