

Treatment Outcomes and Toxicity Profile of Carfilzomib in Multiple Myeloma: A Single Institution Experience

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Abstract

Carfilzomib is an irreversible proteasome inhibitor (PI), first approved in 2012 for treatment of relapsed refractory multiple myeloma (RRMM). The real-world use of carfilzomib in treatment of RRMM is important to assess. The objectives of this study are to evaluate the real-world outcome in overall response rates (ORR), progression-free survival (PFS), and adverse drug events (ADEs), including cardiotoxicity and nephrotoxicity for RRMM patients treated with carfilzomib. We retrospectively analyzed the charts of patients with a diagnosis of MM treated with carfilzomib between January 2013 and December 2018. Demographics, cytogenetics, fluorescence in situ hybridization (FISH), and treatment history were collected. Sixty-six patients fit the study criteria, with median age of 65 years (range 48 - 84). Using the Revised International Staging System (R-ISS), 7 (10.6%) patients were stage I, 28 (42.4%) stage II, and 31 (47.0%) stage III. Cytogenetics showed 33 (48.5%) were high risk. Eight (12.12%) patients were pretreated with more than 4 treatment lines and 27 (40.95) had an autologous stem cell transplant (ASCT) prior to carfilzomib. Prior treatments included lenalidomide, bortezomib, and cyclophosphamide-based regimens. The ORR was 77.2%, with 4 (6.2%) complete responses (CR). Ten patients (15%) received ASCT after carfilzomib for progression of disease (POD). The majority with POD received daratumumab (40%) or pomalidomide (46%). Grade 2 hypertension was noted in 9 (13.6%) patients, acute renal failure (ARF) in 11 (16.7%) and heart failure (HF) in 12 (18.2%). The median PFS on Carfilzomib was 6.96 months. This study showed carfilzomib improved PFS in patients with RRMM; however, there is increased risk for cardiac and renal toxicity, greater than previously reported in the literature. This study reinforces the importance for oncologists to be aware of these toxicities. Astute awareness, early monitoring, and prevention may favorably impact outcomes with use of carfilzomib.

Keywords: Multiple myeloma • Carfilzomib • Kyprolis • Proteasome inhibitor • Cardiotoxicity • Nephrotoxicity

Abbreviations: ADEs: Adverse Drug Events; ARF: Acute Renal Failure; ASCT: Autologous Stem Cell Transplant; CR: Complete Response; CTCAE: Common Terminology Criteria for Adverse Events; CyBORd: Cyclophosphamide, Bortezomib, and Dexamethasone; ECOG: Eastern Cooperative Oncology Group; FDA: Food and Drug Administration; FISH: Fluorescence in Situ Hybridization; HF: Heart Failure; IMiDs: Immunomodulatory Agents; IMWG: International Myeloma Working Group; Kd: Carfilzomib-dexamethasone; MM: Multiple Myeloma; NR: Non-Response; ORR: Overall Response Rate; OS: Overall Survival; PFS: Progression-Free Survival; PI: Proteasome Inhibitor; POD: Progression of Disease; PR: Partial Response; R-ISS: Revised International Staging System; RRMM: Relapsed/Refractory Multiple Myeloma; Vd: Bortezomib-Dexamethasone

Introduction

Multiple myeloma (MM) is a plasma cell dyscrasia characterized by bone marrow infiltration of malignant clonal plasma cells that proliferate in the bone marrow. This manifests as both medullary and extramedullary symptoms including hypercalcemia, anemia, bone lesions, and renal insufficiency (Slim-CRAB criteria) [1]. Several therapies are currently available for treating MM, but none have resulted in a cure. Nearly all patients will relapse after their initial treatment. The course of the disease further progresses through multiple cycles of relapses and remissions, with each time to relapse being consecutively shorter.

Survival outcomes of MM patients have increased with recent advances in treatment [2]. In the last few years, several drugs have been Food and Drug Administration (FDA) approved based on improvement of PFS and OS. Patients with MM are living longer and consequently receiving multiple

treatment lines. Examining the long-term effects of treatments has become increasingly important, as more patients are surviving the early part of their disease. Therefore, understanding treatment outcomes and toxicity profile of these novel medications is essential to optimizing patient outcomes, minimizing toxicities, and delivering personalized care.

PIs are one class that has changed the landscape of treatment options for MM. Carfilzomib is a second-generation irreversible PI first approved in 2012 for treatment of RRMM for patients who received at least 2 prior therapies, including bortezomib and immunomodulatory agents (IMiD) [3]. Since then, carfilzomib has been shown to be very effective in combination as well as a single agent for improving PFS in RRMM [4-7].

The endeavor study, a head-to-head comparison between carfilzomib-dexamethasone (Kd) and bortezomib-dexamethasone (Vd), showed clinically meaningful improvements in OS, PFS, and ORR favoring the carfilzomib arm. The median treatment time on carfilzomib was almost twice as long as bortezomib (48 weeks vs 27 weeks). After adjusting for years of exposure, the rates of grade 3 or worse ADEs between these two regimens were identical, with heart failure (HF) (8 / 2%) and ARF (5 / 1%) being among the most common reasons for treatment discontinuation [8]. In the ASPIRE study, the addition of carfilzomib to lenalidomide and dexamethasone was shown to have a higher ORR and CR rates in RRMM patients. Of note, cardiovascular ADEs (including hypertension, HF, pulmonary edema, and ischemic heart disease) occurred more frequently in the subgroup that was older 70 with 34.0% discontinuing carfilzomib [9]. As more patients are exposed to carfilzomib and for longer treatment times, there have been increasing reports of cardiovascular toxicity

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and nephrotoxicity [10-12]. These effects were noted in clinical trials however the real-world effects of this treatment are also important to assess.

The aim of this study was to analyze real-world outcomes in patients with RRMM treated with carfilzomib, in combination or as a single agent, at a single center site in the Northwell Health Cancer Institute. The ORR, PFS, and OS were assessed in association with baseline demographics. Additional outcomes measured included ADEs of carfilzomib, especially cardiotoxicity and nephrotoxic effects.

Research Methodology

This study is a retrospective chart analysis of subjects with a diagnosis of RRMM treated with a carfilzomib containing regimen between January 1, 2013 and December 31, 2018 at Monter Cancer Center. The study was approved by the Northwell Health Cancer Institute Institutional Review Board (IRB). The patient population was limited to individuals over the age of 18 with RRMM as defined by IMWG criteria. All patients had measurable disease at the time of starting therapy with carfilzomib. Seventy-seven RRMM patients were identified, with 66 patients fitting the specified criteria. Data was obtained through the electronic medical record (EMR), de-identified, collected, and recorded in REDCaps. Baseline demographics including age, gender, race, stage at diagnosis based on R-ISS criteria, including cytogenetics and FISH were collected [13]. Patients were categorized as high risk if pathology showed t, del (17p), or t [4,14-16]. The prior treatment regimens and history of ASCT were collected in relation to pre- or post- carfilzomib exposure. Toxicities, patient reported side effects, and reasons for terminating carfilzomib were recorded both from inpatient and outpatient chart review. Laboratory data and ADEs were collected up to December 31, 2019.

The aim of this study was to determine whether the baseline patient demographics and clinical characteristics for patients with RRMM treated with carfilzomib correlate with response. Additional goals were to describe the treatment course of RRMM patients who received carfilzomib, including ADEs, reasons for early termination of carfilzomib treatment, and safety outcomes. The ADEs documented were grade II or higher as defined by the Common terminology criteria for adverse events Version 5.0, (CTCAE v5.0) [13].

Data were summarized using descriptive statistics with frequencies, percentages, means, and standard deviations. OS was measured from start of treatment with carfilzomib to death. PFS was measured from the start of treatment with carfilzomib to disease progression or death. Patients who were alive at their last follow-up were considered censored, and time to last follow-up was used. Patients with a PR or better who were alive at their last follow-up were considered censored and the time to their last follow-up was used.

For both OS, PFS and each categorical factor, time to the event of interest was estimated using the product-limit method and compared using the log-rank test. For age, a Cox proportional hazards model was used to examine the association between age and the event of interest. Response to treatment was classified according to IMWG criteria, and dichotomized as CR, PR, or non-response (NR) [14]. For each categorical explanatory variable, the association between response and that variable was examined using the Fisher's exact test. The association between age and response was examined using the Mann-Whitney test.

The analysis of duration of response was restricted to patients with a PR or better. Duration was measured as the time from documented response with carfilzomib to disease progression or death. Patients with stable, CR or PR at their last follow-up were considered censored and the time to their last follow-up was used.

The duration of time on carfilzomib was measured as the time from start of carfilzomib to discontinuation for any reason, and was estimated using the product limit method. Subjects who were still using carfilzomib as of the last follow-up were censored for this analysis. For each ADEs, the percent of subjects with that event was estimated, and the associated 95% exact binomial confidence intervals were calculated.

Results

Of the 66 patients, 28 patients lacked sufficient documentation to determine a response and were censored for the analysis. The cohort had a median age of 65 years (range 48 - 84 years) and was predominantly female (37, 56.1%). Racial demographics consisted of 23 (34.9%) White patients, 2 (3.0%) Hispanic, 19 (28.8%) Black, and 9 (13.7%) Asian patients. There were 13 (19.7%) patients who self-identified in the "other" category (Table 1). For R-ISS staging, 7 (10.0%) patients were stage I, 29 (43.9%) stage II, and 30 (45.5%) were stage III. Based on cytogenetic profiles, 32 (48.5%) patients were classified as high risk, with 9 (17.7%) positive for the t (4,14) mutation, 5 (9.8%) with the del 17p mutation, and 16 (31.4%) with the t (14,11) mutation. Of all patients, 30.3% were identified as having hyperploidy (Table 1).

The cohort was heavily pre-treated prior to carfilzomib initiation, with a mean of 2.3 treatment lines, median of 2 and a range of 0-6 treatment lines. These regimens included combination chemotherapy or immunotherapy for RRMM. Approximately 8 (12.1%) of patients received 4 or more treatment regimens; 21 (32.8%) of patients received 3 prior regimens, and 22 (33.3%) received 2 prior lines of MM-directed treatment. Prior treatments mainly included IMiDs, often lenalidomide, and PIs, frequently bortezomib. Cyclophosphamide in combination with bortezomib and dexamethasone (CyBorD) was also a frequently used upfront regimen. Regarding ASCT, 27 (40.9%) of patients had an ASCT prior to carfilzomib treatment. Thirty-five (54.7%) patients discontinued carfilzomib and were switched to another therapy. The most common treatment options post-carfilzomib were daratumumab 15 (22.7%) and a pomalidomide based regimen 17 (25.8%). Approximately 10 (15.0%) of patients required an ASCT post-carfilzomib in the setting of POD (Table 2).

Sixty-four of the 66 patients started on carfilzomib, discontinued the treatment. Approximately, 35.9% of patients reported ADEs resulting in discontinuing carfilzomib due to toxicity. Grade 2 or higher (by CTCAE v5.0) hypertension was noted in 9 (13.6%) of all patients, dyspnea in 15 (22.7%), 12 (18.2%) reported new onset cardiac failure, and ARF in 11 (16.7%) (Table 3).

Five of the 64 subjects who discontinued carfilzomib were lost to follow up. Of the patients that stopped carfilzomib, 29 (45.3%) had more than one reason for discontinuation of the treatment. There were 11 (17.2%) of patients

Table 1. Patient demographics.

Demographics, Baseline Disease, and Clinical Characteristics	
Age	
Median (Range) - yrs	65 (48-84)
Gender – no (%)	
Male	29 (43.9%)
Female	37 (56.1%)
Race – no (%)	
White	23 (34.9%)
Hispanic	2 (3.0%)
Black	19 (28.8%)
Asian	9 (13.7%)
Other	13 (19.7%)
R-ISS Stage – no (%)	
I	7 (10.0%)
II	29 (43.9%)
III	30 (45.5%)
Cytogenetics – no (%)	
High Risk	32 (48.5%)
Standard Risk	19 (28.8%)
Unknown	15 (22.7%)
Mutations – no (%)	
t(4,14)	9 (17.7%)
Del17p	5 (9.8%)
t(11,14)	16 (31.4%)

Table 2. Treatment lines before and after Carfilzomib.

Previous Treatment Lines – no (%)	
Median (Range)	2 (0-6)
0	2 (3%)
1	13 (19.7%)
2	22 (33.3%)
3	21 (31.8%)
4 or more	8 (12.1%)
Treatments Prior to Carfilzomib Lines – no (%)	
Revlimid/Velcade /Dexamethasone (RVD)	30 (45.5%)
Cyclophosphamide + Bortezomib + Dexamethasone (CyBORd)	25 (37.9%)
Dexamethasone + Cyclophosphamide + Etoposide + Cisplatin (DCEP)	6 (9.1%)
Daratumumab (based regimens)	9 (13.6%)
Treatments after Carfilzomib	
Dexamethasone + Cyclophosphamide + Etoposide + Cisplatin DCEP	7 (10.6%)
Daratumumab (based regimens)	15 (22.4%)
Pomalidomide based regimens	17 (25.85%)
ASCT	10 (15.2%)

Table 3. Toxicity frequency Carfilzomib.

Adverse Event	N	% (95% Exact Binomial Confidence Interval)
Dyspnea	15	22.7% (13.3%, 34.7%)
Hypertension	9	13.6% (6.4%, 24.3%)
Heart Failure	12	18.2% (9.8%, 29.6%)
Acute Renal Failure	11	16.7% (8.6%, 27.9%)
GI Toxicity	8	12.1% (5.4%, 22.5%)
Fatigue	22	33.3% (22.2%, 46.0%)
Cough	7	10.6% (4.4%, 20.6%)
Pyrexia	6	9.1% (3.4%, 18.7%)
URI	16	24.2% (14.5%, 36.4%)
Thrombosis	2	3.0% (0.4%, 10.5%)

Table 4. Reason for stopping Carfilzomib.

Reason for Stopping	Number/Percent of Patients
Medication No Longer Effective	12 (18.8%)
Continued Different Treatment	35 (54.7%)
Side Effects Intolerable	23 (35.9%)
Hospice	11 (17.2%)
Death	9 (14.1%)
Lost to Follow Up	5 (7.8%)

that stopped treatment to pursue hospice and 9 (14.1%) who died while on the treatment (Table 4).

We found 30 (79.9%) subjects had documented response, with 26 (68.4%) subjects achieving PR and 4 (5.9%) achieving a CR, as defined by IMWG response criteria [14]. The ORR was 79.9%, with 70.0% of patients having POD during the timeframe of this study. Median OS for the entire cohort was 16.1 months (95% CI: 10.7 months, 32.7 months). Patients with wildtype 17p were more likely to respond to carfilzomib than those with del 17p, this was found to be statistically significant ($P < 0.007$). There was no statistically significant association between age and response, PFS, and ORR. The median age for those who with a PR or better was 67 years (Range: 37 to 88 years), and the median age for those who had no response was 59.5 years (Range: 47 to 81 years).

wenty-nine of the 66 (43.9%) patients studied were alive at their last follow-up. These patients were censored for the survival analysis and the time to their last follow-up was used. The median OS for females was 17.3 months (95% CI: 10.7 - 63.1) and for males 16.1 months (95% CI: 4.5 - 54.4). We found

no statistical difference in median OS of patients when compared with age, gender, number of previous treatment regimens, and chromosomal analysis.

Fifty-nine patients had POD during the course of study. The median PFS on carfilzomib was 6.5 months for males (95% CI: 2.8 - 23.2) and 5.3 months for females (95% CI: 2.3 - 11.3). There was no statistically significant difference in age, number of previous treatment lines, patients with high-risk mutations, or patients with hyperploidy and PFS. One exception was patients with the t (4,14) mutation showed a statistically significant lower PFS than patients with standard risk cytogenetics ($P < 0.0213$). The median PFS in patients with the t (4,14) mutation was 1.7 months (95% CI: 0.5 - 12.4) while those without the mutation had a median PFS of 8.2 months (95% CI: 3.3 - 15.7)).

Discussion

Studies have clearly demonstrated favorable OR and PFS with carfilzomib based therapy use in RRMM [8,9,15]. The ENDEAVOR study showed patients treated with carfilzomib had improved and deeper responses compared to those

treated with bortezomib. These results translated to a longer PFS and OS. Of note, this trial also showed a small, but clinically significant rate of patients who experienced HF (22 / 5%), hypertension (41 / 9%), dyspnea (25 / 5%) and ARF (19 / 4%) out of a cohort of 464 [8]. In light of these clinical findings, frequent monitoring and active medical management is important to allow for safe and optimal administration of this medication. The ARROW study, evaluated different dosing administration of carfilzomib. This study showed substantial efficacy of once-a-week carfilzomib infusions with favorable toxicity profiles as opposed to twice weekly [16]. The ARROW study findings suggest that optimal dosing administration is also important in mitigating the adverse side effects for patients on carfilzomib. The ENDURANCE trial cautions selecting carfilzomib for newly diagnosed MM patients (NDMM), given PFS for the carfilzomib group was not superior to the standard-of-care group. However, one limitation was several high-risk patients were excluded from the trial [17]. On the other hand, carfilzomib-based regimens, to some degree, appear to overcome some of the adverse cytogenetic outcomes, based on the data seen in the ENDEAVOR study [18]. This study specifically focused on the t(4,14), t(14,16), and del(17p) mutations to risk-stratify. Patients and was able to find improved PFS, OS, and ORR in both the standard risk and high-risk groups. This suggests carfilzomib should be considered in high risk patients therefore additional research is necessary in high-risk MM exposed to carfilzomib [18].

Studies have shown significant cardiotoxicity and nephrotoxicity associated with carfilzomib [10-12,15,19]. The cardiotoxicity appears to be dose-dependent, while the renal toxicity has been difficult to predict [11,12,16]. A retrospective analysis by Palmieri et al. showed carfilzomib had high efficacy associated with higher cardiotoxicity in RRMM patients, with the incidence of hypertension of 35% [15]. A meta-analysis of the SEER database by Fakhria et al. showed the incidence of dyspnea to be 28%, 22% hypertension, 15% edema, and 14% HF [20]. In our study, no patient discontinued carfilzomib due to newly diagnosed hypertension and none required medication adjustment. While the patients in our study mostly remained at goal for their blood pressure, the rates of HF and other symptoms of cardiotoxicity secondary to carfilzomib may be underdiagnosed in many patients.

Further studies are necessary evaluate the progression of these side effects and ideal screening processes to identify patients at higher risk for developing cardiotoxicity. Early screening, frequent monitoring, and early discontinuation of carfilzomib in certain populations at higher risk for cardiotoxicity is warranted to allow for better patient outcomes. These toxicities are important for the community oncologist and primary care physicians to be aware of and optimally manage. Hypertension and dyspnea may be early signs of HF, and thus cardiotoxicity. Further investigation into the mechanism of injury and manifestation of these toxicities is important to predict and manage these complications.

We also found there were 11 (16.7%) (95% CI: 8.6%- 27.9%) of patients who developed acute renal failure during the course of their treatment. Of those that developed ARF, three of these patients had premature death secondary to a complication of renal failure. Four patients were dialysis-dependent prior to initiation of carfilzomib.

Our study showed improved PFS with the majority of patients achieving a PR or CR. The median PFS for men and women were 16.1 months (95% CI: 4.5- 54.4) and 17.3 (95% CI: 10.7- 63.1) respectively. No correlation between age, gender, history of prior treatment lines and correlation with PFS, OS and ORR were found. Our study supports use of carfilzomib in patients with RRMM regardless of risk stratification. Further data needs to be analyzed to identify which populations would be able to achieve the most benefit from these therapies. Previous studies, including the ENDEAVOR study have shown that carfilzomib is effective in certain high-risk RRMM patients at improving PFS and ORR [21]. The MANHATTAN trial was a nonrandomized clinical trial that assessed the effectiveness of daratumumab to weekly dosing of carfilzomib with lenalidomide and dexamethasone at minimal residual disease (MRD) for patients with NDMM. Of the forty-one enrolled patients, 29 were able to achieve MRD. The ORR was 100% with 95% achieving a complete response or a very good [22]. The unprecedented response to quadruplet therapy shows that there needs to be additional research in identifying not only the target populations, but also the ideal combination of medications to maximum

potency while still maintaining a tolerable side effect profile.

There was no difference in outcomes with patients that had received ASCT in terms of PFS, ORR, and OS. Furthermore, 15% of patients were able to continue to ASCT after treatment with carfilzomib. The improved outcomes in our study clearly show that carfilzomib is a potent medication with tolerable side-effect and toxicity profile. Prior studies with ASCT were mostly performed in an era without these novel anti-myeloma agents. The findings in this study suggest the role of ASCT should be re-evaluated in the setting of newer therapies like carfilzomib.

Regarding cytogenetics, our study found no difference in PFS, ORR, and OS based on high-risk cytogenetics or hyperploidy. When each mutation was analyzed separately, patients with del(17p) mutation were 3 times less likely to be able to obtain CR or PR than patients without del(17p) ($P < 0.05$). Patients without a t(4,14) mutation had 4 times better PFS compared to those with the mutation ($P < 0.02$). Although patients with these mutations had worse outcomes compared to the remaining patient population, a notable number of these patients (12, 63.1% of high-risk patients) were still able to achieve a CR or PR complete. This illustrates that while carfilzomib should be considered in these high-risk cytogenetic groups, relapses are still common amongst the high-risk patients.

The ORR in our trial was similar to that in other published clinical trials, including the APSIRE and ENDEAVOR trials [8,9,23]. The PFS, however differed from those seen in the clinical trials. We had a lower PFS compared to the ASPIRE trial [9]. Multiple factors may have contributed to this observed deviation. The proportion of patients with high-risk cytogenetics, the Eastern Cooperative Oncology Group (ECOG) functional status prior to treatment, and the number of previous treatment lines differed substantially between our study and those reported in the ASPIRE trial. Nearly half of the patients (32, 48.5%) in our study had high-risk cytogenetics while in the ASPIRE trial only 12% were high-risk. Approximately 90% of the patients in the ASPIRE trial had an ECOG functional status of 0 or 1, considerably higher than seen in our patient population. Additionally, our patients were heavily pretreated, with about 70% having received > 2 lines of treatment prior to carfilzomib. These factors are surrogate markers for healthier/fitter patients in the clinical trials, which likely translated to the lower PFS and survival rates, observed in our study in comparison to ASPIRE [9].

The proportion of grade 2 ADEs and above in our study was comparable to the frequencies reported in the ASPIRE and ENDEAVOR trials [8]. A recent study by Fotiou et al. has shown that renal toxicity is a common and unpredictable adverse event from carfilzomib therapy. The majority of patients having ARF within 2-3 months of initiating treatment and the renal toxicities of carfilzomib extend beyond elevated creatinine levels [11]. Therefore, although our proportions of nephrotoxicity are comparable to other clinical trials, these results may underestimate the total incidence of nephrotoxicity.

When compared to a meta-analysis by Waxman et al, our rate of cardiac toxicity was higher [10]. Factors that may have contributed to this include the lower fitness of our patient population and higher doses of carfilzomib received by our patient population compared to the meta-analysis.

Limitations in this study include incomplete records for a portion of subjects. During the timeframe of this study, medical records were being transitioned from paper charts to EMR. Patient records prior to June 30, 2017 were incompletely transferred to the EMR system. This was most noticeable with pathology records including bone marrow biopsy results with cytogenetic analysis or FISH. Cause of death documentation was also limited, as many were documented by clinicians other than the subject's primary oncologist. In such cases, the causes of death were often listed as multiorgan failure, or cardiopulmonary arrest. Finally, this is a retrospective single center study, with known inherent biases that may result in additional variance.

Conclusion

Overall, our study shows that carfilzomib improved PFS and OS in patients with RRMM. The vast majority of our patients were able to obtain PR or better.

These patients were shown to be at increased risk for cardiac and renal toxicity higher than those reported in previous literature. The toxicities noted in this study reinforce the importance for oncologists to be aware of these issues. Early intervention and optimal management of these toxicities may favorably impact quality of life, response, or tolerance to carfilzomib therapy.

Key Points

1. Carfilzomib should be considered early in the course of treatment for patients with RRMM.
2. A notable number of patients experience cardiotoxicity or nephrotoxicity when treated with carfilzomib, a higher number than previously reported in literature.

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Authorship Contributions

RT and MHB analyzed the data and wrote the manuscript.

NK: Performed the biostatistical calculations.

Conflict of Interest

RT: No conflict of interests to disclose.

MHB: Consulting with Bristol Myers Squibb, GlaxoSmith Kline, Sanofi, Karyopharm, Guidepoint, Cardinal Health, Scientia CME and Janssen.

NK: No conflicts of interest.

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