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ORIGINAL RESEARCH

Patient-reported outcomes of brentuximab vedotin in Hodgkin lymphoma and anaplastic large-cell lymphoma

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Robert Chen[1]
Suzanne Allibone[2]
Nancy L Bartlett[3]
Pauline Brice[4]
Andy Chen[5]
Katrina Pose[6]
Lynn Rich[7]
Vijay Bonthapally[8]
Phillip M Garfin[9]
Michelle Fanale[10]

[1]Department of Hematology & Hematopoietic Cell Transplantation, City of Hope, Duarte, CA, USA; [2]The Lymphoma Service of the Christie NHS Foundation Trust, Manchester, UK; [3]Department of Medical Oncology, Washington University School of Medicine, St Louis, MO, USA; [4]Department of Hemato-Oncology, Hôpital Saint-Louis, Paris, France; [5]Knight Cancer Institute, Oregon Health & Science University, Portland, OR, [6]Lymphoma and Cancer Survivorship Stanford Comprehensive Cancer Center, Stanford, CA, [7]Lymphoma Program, James P. Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY, [8]Millennium Pharmaceuticals Inc., Cambridge, MA, [9]Seattle Genetics, Inc., Bothell, WA, [10]Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Correspondence: Robert Chen
City of Hope, 1500 East Duarte Road, Duarte, CA 91010, USA
Tel +1 626 359 8111
Email rchen@coh.org

Background: Patients with relapsed/refractory (R/R) Hodgkin lymphoma (HL) or R/R systemic anaplastic large-cell lymphoma (sALCL) treated with brentuximab vedotin (BV) experienced high remission rates in two Phase II trials. With increased response rates and survival times, patient-reported outcomes (PROs) and health-related quality of life (HRQoL) are becoming increasingly important and can help inform treatment decisions to enhance care of cancer patients.

Objective: The objective was to qualitatively assess HRQoL in long-term survivors treated with BV.

Methods: An eight-question survey assessing PRO-related aspects was developed and fielded to a subset of patients with HL or sALCL who remained in long-term follow-up after completing BV treatment in the two pivotal studies.

Results: The survey was completed by 25 of 38 patients (12 with HL, 13 with sALCL). The majority of patients reported that their energy level, outlook on life, difficulties with daily activities, ability to participate in physical activities, and overall HRQoL improved compared to those before BV treatment.

Limitations: Small sample size and lack of a baseline questionnaire or validated assessment instrument limit broad applicability of these findings to large populations of patients with HL or sALCL.

Conclusion: This is the first report of BV PRO data in R/R HL and sALCL. Given the patients' poor prognostic outcomes before stem cell transplant, these encouraging results warrant formal evaluation of PRO end points in BV trials.

Keywords: patient well-being, brentuximab vedotin, health-related quality of life, pilot study, activities of daily living

Introduction

Assessment of the long-term effects of cancer and its treatment is essential to patient care.[1,2] Although overall survival and disease-free survival remain as key end points for randomized clinical trials in oncology,[3] patient-reported outcomes (PROs) are increasingly used to inform treatment decisions and enhance quality of care.[4] As a result, PRO assessments are incorporated more frequently into randomized controlled trials in oncology.[5] PROs describe physical, emotional, functional, and psychosocial well-being and can provide help to assess the cumulative impact that cancer and its treatment have on patients. PRO data are also valuable to health care policy makers, regulatory organizations, and payers to help determine the worthiness of a therapy. For example, the US Food and Drug Administration has provided guidance on the incorporation and evaluation of PRO measures in clinical trials, and both the National

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Cancer Institute and American Cancer Society have stated goals to ensure improvement in quality of life (QoL) in patients with cancer and cancer survivors.[6–8] Several research and policy efforts in the USA reflect the growing emphasis placed upon PROs in decision making surrounding the care of patients with cancer.[2–4]

Treatments for Hodgkin lymphoma (HL) and systemic anaplastic large-cell lymphoma (sALCL) can be effective and impart relatively high survival rates for those who experience one of these lymphomas; most patients with HL or sALCL have disease that responds to therapy, and they have a good chance of being cured by first-line multimodal therapy.[9–11] Nevertheless, 15%–20% of patients with HL and 36%–60% of patients with sALCL fail first-line therapy and have relatively poor outcomes, particularly if relapsed prior to stem cell transplant (SCT), despite aggressive therapy.[10–15]

Owing to its uniform expression on malignant cells in HL and sALCL, CD30 has emerged as an attractive target for the treatment of these lymphomas. The antibody-drug conjugate brentuximab vedotin (BV) delivers the potent microtubule-disrupting agent monomethyl auristatin E to CD30-positive cells.[14,15] Two pivotal Phase II multicenter, open-label trials evaluated the safety and efficacy of BV in patients with relapsed/refractory (R/R) HL (NCT00848926) or sALCL (NCT00866047).[14,15] BV was associated with manageable toxicity and high objective response rates (75% HL; 86% sALCL).[14,15] The most common treatment-related adverse events (>15% in either study) in both studies included peripheral sensory neuropathy, nausea, fatigue, pyrexia, diarrhea, and neutropenia.[14,15]

As the number of survivors of HL and sALCL continues to grow, it will be increasingly important to understand the long-term disease- and treatment-related effects on survivor QoL. To understand the impact that BV might have on the QoL of patients who have survived HL or sALCL, we developed a brief eight-question survey to collect patient reports of QoL in the posttreatment setting for R/R HL or sALCL. The survey was fielded to patients who continued to return for long-term follow-up visits following therapy on either of the two Phase II trials described previously. This publication, the first PRO survey in R/R patients treated with BV, reports the results and discusses the impact this type of information may have on long-term patient care.

Methods

Participants

Detailed methodology used in the two pivotal Phase II studies of BV as well as the demographic and clinical characteristics of the patients with R/R HL or sALCL have been previously published.[14,15] Briefly, inclusion criterion for the sALCL trial included R/R sALCL after treatment failure of ≥1 prior therapy with curative intent and CD30-positive disease.[14] Patients in the HL trial had to have R/R HL after high-dose chemotherapy and autologous stem cell transplantation (ASCT) and CD30-positive disease.[15] Briefly, 102 and 58 patients were included in the R/R HL and sALCL trials, respectively. In the HL trial, 47% of patients were male, patients had a median age of 31 years (range: 15–77), 71% had primary refractory disease, patients had received a median of 3.5 prior chemotherapy regimens, and all patients underwent ASCT.[15] Of the 58 patients in the sALCL study, 57% were male and had a median age of 52 years (range: 14–76), 62% had primary refractory disease to front-line treatment, and patients had received a median of two prior lines of therapy.[14] Patients in both studies were treated with BV at 1.8 mg/kg intravenously over 30 minutes every 3 weeks on an outpatient basis for up to 16 cycles. Clinical response was determined by both investigators and by an independent central review facility according to revised response criteria for malignant lymphoma.[16]

During the long-term follow-up period, all patients who received one or more dose of study drug were evaluated for survival and disease status every 3 months during years 1 and 2, every 6 months during years 3–5, and annually thereafter.

Survey design and administration

Seattle Genetics, Inc., designed a pilot survey to assess PROs and provided the survey to study sites that participated in the two Phase II trials described earlier. The survey consisted of a series of ranked, close-ended questions with the opportunity to provide additional details to support their responses (Table 1). Surveys were offered to patients who returned for long-term follow-up visits and consented to participate in the study. Surveys were completed during the clinic visit and/or at the patient's convenience. Results were compiled, analyzed, and interpreted by Seattle Genetics, Inc. Patients were allowed to complete the survey only once. The pilot survey was approved by each study site's Institutional Review Board or Ethics Committee, and all patients provided written informed consent.

Results

Patients

Surveys were fielded to 38 patients who met the criteria for long-term follow-up. Long-term follow-up was defined as the time to earliest progressive disease per investigator assessment, death, or last contact. Twenty-five patients

Table 1 Patient questionnaire

1. Have you had an SCT following completing treatment in the brentuximab vedotin clinical study? Yes/No
a. If yes, allogeneic or autologous
i. If allogeneic, are you currently experiencing any GVHD complications? Yes/No.
If yes, please describe
2. Are you working (includes working at home, childcare, volunteering, etc)? Yes/No a. If yes, full time or part time
3. Are you a student? Yes/No. If yes, full time or part time
4. Currently my energy level is (circle one)
Great compared to before/Good compared to before/About the same as I was before/Worse than I was before
5. My general outlook on life is (circle one)
Very positive compared to before/Positive compared to before/About the same as I was before/Negative compared to before
6. Do you have any issues or difficulties with your activities of daily living compared to your level of activity previously? Yes/No. If yes, please describe. (Please limit to 100 words or less.)
7. Are you able to participate in physical activities (ie, regular exercise, running, biking, walking)? Yes/No
8. How is your life today compared to prior coming on to the brentuximab vedotin clinical trial (please limit to 100 words or less)?

Notes: For questions 4–8 the following instructions was provided. "Your response to the following questions should be your perception of how your status is now compared to that before your clinical trial therapy with brentuximab vedotin".
Abbreviations: GVHD, graft-versus-host disease; SCT, stem cell transplant.

(66%) completed the survey (12/19 from the HL study and 13/19 from the sALCL study). Demographic information and clinical characteristics of patients who completed the survey are presented in Table 2. The median age of the survey respondents was 41 years (27 years HL; 53 years sALCL). At the initiation of treatment with BV, participants had an Eastern Cooperative Oncology Group performance status of 0 (40%) or 1 (60%). The most common stage at diagnosis was stage II for patients with HL (75%) and stage IV for patients with sALCL (46%). At baseline, 36% of participants had baseline B symptoms, fever and night sweats being the most common symptoms.

The median follow-up from the first dose of BV for all study participants was ~5 years (60.2 months; range: 37.7–66.5; Table 2). Clinical benefits as assessed per investigator and according to the responding population are listed in Table 3. The overall objective response rate of the survey participants was 100% (92% complete remission and 8% partial remission). The median duration of response has not been achieved (range: >9.9 months to >64.7 months). No patients have died since completing the survey, and only one participant from the sALCL study had subsequent progressive disease.

Survey responses

Of the survey participants, 13 (52%) responded that they had undergone an SCT after treatment with BV. Of the patients who specified the type of SCT they received (n=12), seven had an allogeneic SCT (four patients with HL and three with sALCL) and five patients (all sALCL) reported receiving an autologous SCT. For those receiving allogeneic SCT, five participants (three patients with HL and two with sALCL) reported experiencing graft-versus-host disease (GVHD) complications, including mouth and leg sores, scleroderma, worsened diabetes, shortness of breath, diarrhea, skin allergies, and rosacea.

More than half (56%) of all respondents reported that they were currently working or going to school (66% HL and 46% sALCL); the proportion of survey responders who reported not working or going to school had a higher mean age (33 vs 52 years old, respectively). Of all study participants who were able to work, eight and four participants reported working full time and part time, respectively. When examined by study, five and two participants with HL reported working full time and part time, respectively, and three and two participants with sALCL reported working full time and part time, respectively.

The majority of survey participants from both studies (17/25; 68%) reported that their energy level was good or great compared with before the treatment with BV (Figure 1A); the majority of participants in the HL study (10/12; 83%) responded that their energy level was good or great compared with before the treatment with BV, and seven of 13 participants (54%) of the sALCL study responded similarly. The six remaining patients from the sALCL study (6/13; 46%) responded that their energy level was about the same or worse compared with that before the treatment with BV. One patient with sALCL reported an energy level worse than prior to BV treatment due to GVHD complications.

All survey respondents reported that their general outlook was the same or improved compared to their outlook before starting treatment with BV (Figure 1B). Most patients (20/25 [80%]) reported having a positive or more positive outlook

Table 2 Survey respondent demographics and disease characteristics

Characteristic	HL study (n=12)	sALCL study (n=13)	All patients (N=25)
Median age, years	27.0	53.0	41.0
Min, max	21, 63	14, 76	14, 76
Sex, n (%)			
Male	5 (42)	9 (69)	14 (56)
Female	7 (58)	4 (31)	11 (44)
Race, n (%)			
Asian	1 (8)	0	1 (4)
Black or African American	0	2 (15)	2 (8)
White	11 (92)	11 (85)	22 (88)
Ethnicity, n (%)			
Hispanic or Latino	2 (17)	3 (23)	5 (20)
Not Hispanic or Latino	10 (83)	10 (77)	20 (80)
ECOG performance status, n (%)			
0	6 (50)	4 (31)	10 (40)
1	6 (50)	9 (69)	15 (60)
ALK status, n (%)			
Positive	NA	3 (23)	3 (12)
Negative	NA	10 (77)	10 (40)
Time from initial diagnosis to first dose, months			
Mean (STD)	47.76 (26.90)	34.18 (35.24)	40.70 (31.63)
Median	37.24	22.93	31.74
Min, max	11.8, 98.7	5.2, 113.2	5.2, 113.2
Baseline B symptoms, n (%)	3 (25)	6 (46)	9 (36)
Fever	1 (8)	4 (31)	5 (20)
Night sweat	2 (17)	3 (23)	5 (20)
Weight loss >10%	1 (8)	0	1 (4)
Follow-up time from first dose, months			
Mean (STD)	62.30 (3.28)	56.31 (7.05)	59.18 (6.25)
Median	62.93	58.05	60.16
Min, max	56.1, 66.0	37.7, 66.5	37.7, 66.5
Follow-up time from EOT, months[a]			
Mean (STD)	53.26 (4.18)	48.80 (9.24)	50.42 (7.64)
Median	53.49	46.42	52.30
Min, max	44.8, 59.6	25.2, 61.4	25.2, 61.4

Notes: [a]EOT visit date or last dose +30 days. Excludes patients with progressive disease before EOT.
Abbreviations: ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; HL, Hodgkin lymphoma; Min, minimum; Max, maximum; sALCL, systemic anaplastic large-cell lymphoma; STD, standard deviation.

Table 3 A summary of clinical responses of respondents per investigator

End point, n (%)	HL study (n=12)	sALCL study (n=13)	Both studies (N=25)
Best clinical response			
Complete remission, [95% CI[a]]	10 (83), [51.6–97.9]	13 (100), [75.3–100]	23 (92), [74–99]
Partial remission	2 (17)	0	2 (8)
Stable disease	0	0	0
Progressive disease	0	0	0
Objective response rate (CR + PR), [95% CI[a]]	12 (100), [73.5–100]	13 (100), [75.3–100]	25 (100), [86.3–100]
Number of patients with subsequent PD or death	0	1 (8)	1 (4)
Disease control rate (CR + PR + SD), [95% CI[a]]	12 (100), [73.5–100]	13 (100), [75.3–100]	25 (100), [86.3–100]

Notes: The duration of response was calculated from the earliest occurrence of either CR or PR. [a]Computed using the method of Brookmeyer and Crowley.
Abbreviations: CI, confidence interval; CR, complete remission; HL, Hodgkin lymphoma; PD, progressive disease; PR, partial remission; sALCL, systemic anaplastic large-cell lymphoma; SD, stable disease.

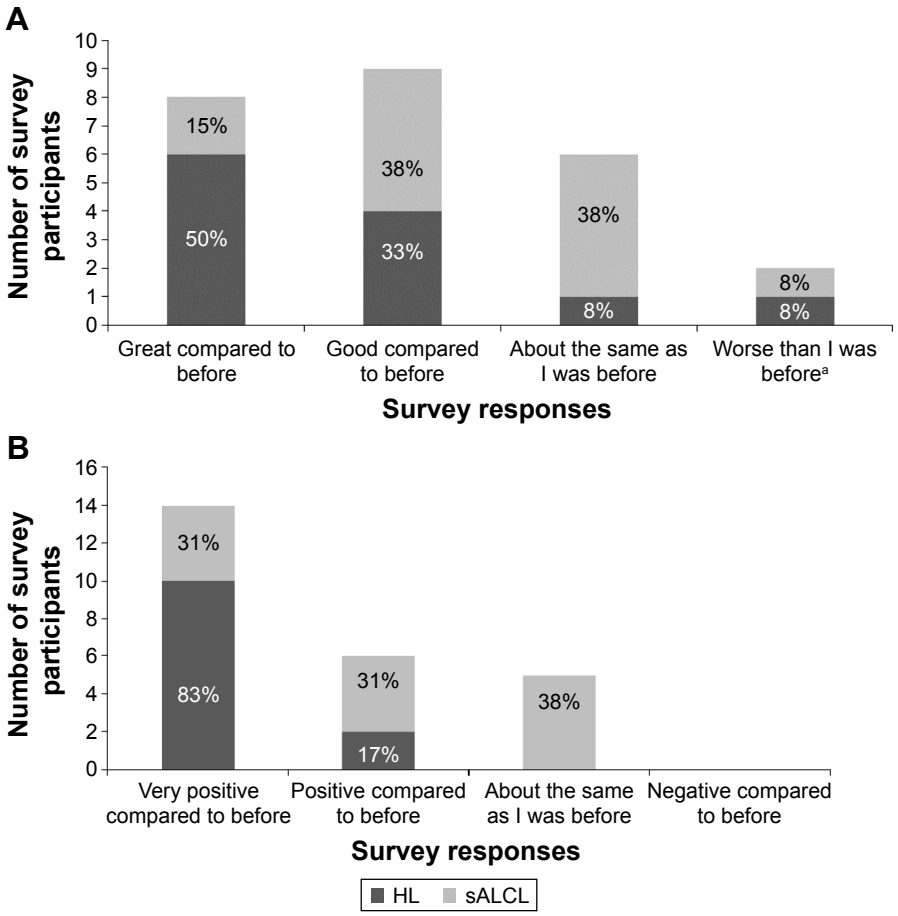

Figure 1 (**A**) Current energy level compared with that before the treatment with BV. (**B**) Current general outlook on life compared with that before the treatment with BV.
Note: [a]Both patients had graft-versus-host disease.
Abbreviations: BV, brentuximab vedotin; HL, Hodgkin lymphoma; sALCL, systemic anaplastic large-cell lymphoma.

on life (12 and eight participants from the HL study and the sALCL study, respectively), and 20% of participants (5/25), all with sALCL, reported that their general outlook was about the same as before the start of BV treatment.

Most of the patients who responded to the survey (22/25 [88%]) were able to participate in daily activities, and the majority (72%) reported no new issues or difficulties with activities of daily living compared with their previous level of activity. A few patients (6/25 [24%]; two from the HL study and four from the sALCL study) reported new issues with activities of daily life including numbness in toes (from neuropathy) sometimes affecting balance but not QoL, increased requirement for sleep including daytime sleep to stay active, leg pain and swelling from blood clot, flare in rheumatoid arthritis that hinders energy and function involving hands and feet, leg cramps, and impaired mobility hindering use of stairs.

In response to the survey question, "How is life today, compared to before coming on the BV clinical trial?", all patients with HL responded relatively positive (Table 4). Participants in the sALCL study had a mixed, but mostly positive, set of responses.

Discussion

BV is an important treatment option for patients with relapsed HL or sALCL who would otherwise have had limited therapeutic options and an unfavorable prognosis. The improved responses reported in key BV clinical trials[14,15,17] warrant consideration of health-related QoL (HRQoL) in the post-treatment setting as an important factor in maintaining patient treatment satisfaction and well-being. The prognosis for patients experiencing relapse is poor, and the QoL of patients who live with HL or sALCL is often compromised.[18,19] Therefore, it is critical for decision makers to evaluate both treatment outcomes and QoL. This is the first report of PRO data from a pilot survey of patients with R/R HL or sALCL treated with BV, the results of which provide encouraging insights into patient well-being after receiving BV therapy for

Table 4 Examples of responses to the question "How is life today, compared to prior to coming on the BV clinical trial?"

HL study
I have a better outlook. There isn't as much fear of relapse.
Great! No complaints!
I'm still alive and doing great!
My life is great. I am now a mother of two boys. I feel much healthier and my outlook on life is more positive.
Very good.
Much better because I'm in remission.
Very positive. I'm on the right side of the earth.
I feel wonderful, healthy, and great.
Life has been great after my remission as a result of the clinical trial. I am now back to my job, but in a different line of work because of my disability […] I and my family now feel that we are living a good life after merely surviving for 8 years due to my ailment.
Excellent. It was much easier. If not for this treatment I would have had to do brother/sister transplant and I don't feel I was strong enough to make it.
I get to have [sic] physical activities (tango, yoga, walking, cycling) with moderate rest time. Same for the intellectual effort that can not be too long.
I'm in a stage of acceptance of my very different state than the others but very valid. [sic]
sALCL study
Excellent, the drug has worked miracles.
Miracle.
Fantastic.
Good.
The same as before.
My life and activities are about the same as before my illness and treatment. I have experienced increased family stressors peripherally related to my illness (lost my home, credit issues).
Very tired, limited walking.
Better. Mostly feeling worse due to the GVHD and transplant recovery.
Before SGN35 had very low energy, didn't feel well, didn't have any hair and felt really sick. And now feels a lot better. Has a normal life.
Sometimes forgets has cancer.[a]
My life today is amazing. When I thought there was no hope of killing my cancer, I was offered this study and was soon put into my remission […] I've been here for my husband and teenage daughters.
I am retired so my activity level is rather low. I feel that cancer has not effected [sic] the way I have aged.
I had some difficult periods after the allogenic stem cell transplant due to GVHD but now everything is OK and I hope that it will continue.

Note: [a]Response entered on behalf of patient by evaluating physician.
Abbreviations: HL, Hodgkin lymphoma; GVHD, graft-versus-host disease; sALCL, systemic anaplastic large-cell lymphoma.

R/R HL or sALCL in the posttreatment setting. The majority of patients reported good or great energy levels and improved outlook on life, and the majority were working or attending school and able to participate in activities of daily living. Notably, five of the seven patients who underwent SCT also responded positively to the survey questions.

The symptoms of cancer and adverse events associated with its treatments can greatly impact patient QoL and the well-being of long-term survivors, and patients can still suffer from somatic and psychological concerns months or years into recovery.[18–20] HL is one of the more common cancers in young adults.[11] These patients can have many years of life ahead of them, and thus maximizing HRQoL for the survivors of this cancer should be an important goal as we evaluate new therapies for HL. Additionally, as survival rates increase with the advancement of therapies for HL or sALCL, the margin of improvement in survival provided by any new therapy will decrease. Thus, understanding the impact of novel therapies – as single agents or in combination with established regimens – on HRQoL may drive clinical decision making and changes to standards of care.

PRO data not only provide insight into patient well-being after therapy and are essential for the evaluation of cancer care,[21,22] but their importance is also reflected in the abundance of guidance for developing, assessing, implementing, and analyzing such data from regulatory agencies, publishing standards organizations, quality standards organizations, and professional associations.[2–5] PRO data are also important for payers and health technology assessments to understand the benefits and risks of treatments. However, the variety of satisfaction questionnaires used for patients with cancer has made comparisons and integration of results across studies challenging.[22] This highlights the need for a common set of PRO instruments across studies for guiding clinical practice and informing health policy.

The current pilot study has several limitations, including a small sample size, lack of a baseline questionnaire for comparisons, use of a nonvalidated assessment instrument, and patient recall bias over a median of 5 years from the

first dose of BV. Furthermore, patients in the long-term follow-up, to whom the pilot survey was offered, may be expected to report more positive outcomes by virtue of having no or minimal disease. Conversely, some patients who underwent an SCT may report a less-positive outlook and less energy due to symptoms associated with GVHD. Notably, five of the seven patients who received an SCT responded positively to the survey questions; the remaining two patients who reported negatively on energy levels before and after treatment experienced GVHD. Lastly, although therapy subsequent to BV could impact PROs, at the time the questionnaire was provided, patients had not received any other therapy other than SCT.

Conclusion

Despite the limitations of this study, the results showed that patients treated with BV self-reported positive QoL are leading their lives with few limitations to daily functioning, emotional well-being, and work life. These findings underscore the need to more formally characterize PROs with BV using validated instruments given the improvements in response and survival in these highly refractory patients and the promising signal reported herein. Selecting the most appropriate PRO tool(s) in ongoing and future BV trials will help guide physicians, caregivers, and patients through treatment and survivorship. Furthermore, the assessment of HRQoL with validated PRO instruments in future trials may help determine the value of BV in earlier lines of therapy, when current standards are effective at treating illness, but often at the expense of creating long-term complications of therapy.

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Disclosure

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