Gynecologic cancer in HIV-infected women: treatment and outcomes in a multi-institutional cohort

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Objective: To evaluate gynecologic cancer treatments in HIV-infected women for adherence to National Comprehensive Cancer Network (NCCN) guidelines and to describe survival by adherence to guidelines.

Design: Beyond cervical cancer, there are little data on treatment and outcomes for these women. This is a retrospective cohort study of HIV-infected women with gynecologic cancers.

Methods: HIV-infected women with gynecologic cancers from 2000 to 2015 were identified at two urban, comprehensive cancer centers. Chart reviews extracted demographic, HIV, and cancer-related variables. Cancer treatment was evaluated for adherence to NCCN guidelines. Overall survival was compared between those who received NCCN adherent and nonadherent cancer care.

Results: Fifty-seven women were identified; 15 vulvar (26%), 26 cervical (46%), nine ovarian (16%), and seven endometrial (12%) cancers. Median time from HIV to cancer diagnosis was 8.5 years, and 88% of women were black. Thirty patients (53%) had stage I, and 27 (47%) had stage II–IV disease. Overall, 28 women (49%) received NCCN-adherent care; 22 of 30 stage I (73%) and six of 27 stage II–IV patients (22%). Among 29 women not receiving NCCN-adherent care, 69% were due to patient-related factors or toxicity. Among women with II–IV cancers, 48-month survival was higher in women who received NCCN-adherent care than those who did not (60 versus 28%).

Conclusion: Most HIV-infected women with advanced gynecologic cancers did not receive NCCN-adherent care and had worse survival compared to those who did. Focus on treatment-related toxicities and patient-related barriers to cancer care are necessary in this population.

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Keywords: HIV, ovarian neoplasms, practice guideline, survival, uterine cervical neoplasms, uterine neoplasms, vulvar neoplasms

Introduction

The widespread adoption of combination antiretroviral therapy (cART) has dramatically reduced mortality rates among individuals living with HIV such that US and international guidelines recommend cART for all HIV-infected individuals to reduce the risk of disease progression [1]. As the life expectancy for individuals living with HIV continues to rise, these individuals will increasingly need to be treated for gynecologic

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malignancies [2]. Whereas large population studies have determined that individuals living with HIV are not at an increased risk of many non-AIDS-defining gynecologic malignancies (NADMs) [3], it is known that these cancers are increasing due to growth and aging of this population [4]. As the life expectancy of HIV-infected women continues to improve, and NADMs are the cause of increasing morbidity and mortality [5], it is critical to examine the treatment and outcomes of HIV-infected women with gynecologic cancers in order to improve the outcomes for this growing population.

Whereas some new data have emerged regarding cancer treatment for HIV-infected patients [6], there are few studies focused upon women with gynecologic malignancies, particularly non-AIDS-defining gynecologic malignancies [7,8]. As treatment options continue to broaden and advance with improvements in chemotherapeutic and other therapies [9,10], and also immunologic and targeted therapies, our understanding of outcomes, even with standard guideline-driven treatments, remains limited in this population. Previous work has demonstrated that HIV-infected patients are less likely to receive cancer treatment in general, and also guideline-concordant cancer care [11–14]. The National Comprehensive Cancer Network (NCCN) guidelines are evidence-based, consensus-driven guidelines that are the standard for treatment of gynecologic cancers. NCCN guidelines for gynecologic cancers do not separately address women with HIV status, and the ability to meet this standard practice guideline for HIV-infected women are currently poorly understood [15]. As this population continues to grow, our ability to measure outcomes based on standard treatment practices are increasingly important. Therefore, the study objectives are to evaluate adherence to NCCN guidelines in a cohort of HIV-infected women with gynecologic cancers, and to describe outcomes for women who were and were not treated according to NCCN guidelines. Furthermore, this study identifies the reasons for failure to meet NCCN guideline-adherent care.

Methods

We conducted a retrospective cohort study of HIV-infected women diagnosed with gynecologic cancers from 2000 to 2015 at two urban, high-volume comprehensive cancer centers: The Johns Hopkins Hospital and the University of Maryland, both in Baltimore, Maryland, USA. After Institutional Review Board (IRB) approval was obtained at both institutions, cancer registry data, HIV clinic records, and billing diagnostic codes were used to identify HIV-infected women with gynecologic cancers including cervical cancer, vulvar cancer, ovarian cancer, and endometrial cancer. Women diagnosed with HIV were identified by a diagnosis of 'HIV' or 'AIDS' recorded in the past medical history of the patient's chart, a laboratory result indicating a positive HIV test result, or positive HIV viral load.

Data abstracted from the electronic medical records included patient demographics (age, race, BMI, comorbidities including psychiatric disease, and smoking, alcohol, and drug abuse history), HIV-related data (years since HIV diagnosis, $CD4^+$ cell count and HIV viral load within 30 days prior to cancer treatment, and treatment with cART at the time of cancer diagnosis), and cancer-related variables (disease type, grade, histology, stage, treatment history, and reasons for cancer treatment decisions).

Study outcomes

In order to evaluate adherence of treatment to NCCN guidelines, treatment for each patient was evaluated by cancer type and stage at presentation. For all patients, stage was categorized as stage I or stage II–IV due to major differences in guidelines with regards to the role of surgical treatment in stage I patients. Initial treatment strategies were categorized across cancer type (no treatment, surgery alone, surgery + radiation ± chemo, surgery + chemotherapy, lymph node assessment + chemoradiation, radiation alone, chemotherapy alone). Each treatment regimen was assessed as meeting or not meeting NCCN guidelines specific to each cancer type (see Appendix 1, http://links.lww.com/QAD/B172).

Reasons for non-NCCN-adherent care were categorized as practitioner-related (incorrect surgical procedure or adjuvant therapy chosen), patient-related (including loss to follow-up, social factors, refusal of therapy), treatment toxicity or medical comorbidities limiting therapy, and disease progression.

Statistical methods

Descriptive statistics were calculated to describe the patient population and cancer treatment-related information overall, and also by site of gynecological malignancy. Qualitative reasons why NCCN-adherent care was not provided are summarized. Overall survival was calculated, and Kaplan–Meier curves are presented to show differences across cancer type, NCCN treatment, and stage at diagnosis. Overall differences are noted when the chi-square P value was less than 0.05, and P values for individual comparisons were corrected for multiple comparisons. All statistical analyses were conducted using SAS v9.4 (Cary, North Carolina, USA).

Results

Fifty-seven HIV-infected women were diagnosed with gynecologic cancers during the study period: specifically, 15 (26%) vulvar cancers, 26 (46%) cervical cancers, nine

Table 1. Characteristics of HIV-infected gynecologic cancer patients.

	Vulvar ($n=15$) (26.3%)	Cervical ($n=26$) (45.6%)	Ovary ($n=9$) (15.8%)	Uterine ($n=7$) (12.3%)	Total ($N=57$)
Stage	Numbers (%)				
Stage I	8 (53.4%)	16 (61.5%)	1 (11.1%)	5 (71.4%)	30 (52.6%)
Stage II–IV	7 (46.6%)	10 (38.5%)	8 (88.9%)	2 (28.6%)	27 (47.4%)
Demographics	Median (IQR)				
Age	47 (38–50)	45 (35–46)	50 (44–51)	53 (44–68)	46 (38–50)
BMI	25.4 (23.1–30.2)	27.1 (21.5–28.9)	30.7 (25.2–33.6)	34.7 (29.6–38.2)	27.6 (23.1–32.0)
Race	Numbers (%)				
Black	12 (80.0%)	24 (92.3%)	7 (77.8%)	7 (100%)	50 (87.7%)
White	3 (20.0%)	2 (7.7%)	2 (22.2%)	0	7 (12.3%)
Comorbidities	Numbers (%)				
Hypertension	3/13 (23.1%)	6/23 (26.1%)	3/7 (42.9%)	4/7 (57.1%)	16/50 (32.0%)
Diabetes	1/13 (7.7%)	1/26 (3.8%)	1/7 (14.3%)	1/7 (14.3%)	4/54 (7.4%)
Illicit drug use (former or current)	4/14 (28.6%)	5/26 (19.2%)	2/9 (22.2%)	1/7 (14.3%)	12/56 (21.4%)
Hepatitis	6/14 (42.9%)	8/26 (30.8%)	1/9 (11.1%)	2/7 (28.6%)	17/56 (30.4%)
Psychiatric disease	3/14 (21.4%)	7/26 (26.9%)	1/9 (11.1%)	2/7 (28.6%)	13/56 (23.2%)
HIV factors	Median (IQR)				
Years from HIV diagnosis	9.5 (6–13)	4.5 (1–10)	12 (5–15)	11 (5–17)	8.5 (3–12)
$CD4^+$ cell count (cells/μl)	284 (50–494)	256 (110–400)	403 (326–683.5)	667 (100–865)	315 (110–494)
Viral load (copies/ml)	400 (20–32,233)	8,796 (1,045–21,791)	357 (20–400)	40 (20–115)	400 (43.5–15,723.5)
	Numbers (%)				
On cART	12 (85.7%)	13 (50%)	7 (77.8%)	6 (85.7%)	38 (67.9%)

cART, combination antiretroviral therapy; IQR, interquartile range.

(16%) ovarian cancers, and seven (12%) endometrial cancers (Table 1). Of these, 30 women were diagnosed with stage I disease, and 27 with stage II–IV disease. Most women with vulvar (53%), cervical (62%), and endometrial (71%) cancers presented with stage I disease, whereas 89% of ovarian cancer patients presented with stage II–IV disease. The median age at diagnosis was 46 [interquartile range (IQR) 38–50], the median BMI was 27.6 (IQR 23.1–32.0), and 88% of patients were black. Medical comorbidities included hypertension (32%), diabetes (7%), hepatitis B and/or C (30%), reported history of illicit drug use (21%), and history of psychiatric diagnosis (23%) including anxiety, depression, and/or bipolar disease (Table 1).

The median time from HIV to cancer diagnosis was 8.5 years (IQR 3–12) (Table 1). Eight women were diagnosed with HIV within the same year as their gynecologic cancer diagnosis. The median $CD4^+$ cell count at cancer diagnosis was 315 cells/μl (IQR 110–494); 21% of women ($n=12$) were reported to have normal $CD4^+$ cell counts (>500 cells/μl), whereas 31.6% ($n=18$) had severely compromised $CD4^+$ cell counts (<200 cells/μl); $CD4^+$ cell count at cancer diagnosis was unavailable for six women (10%). The median viral load in this cohort was 400 copies/ml (IQR 43.5–15,723.5) at cancer diagnosis. Eighteen women had undetectable viral load (defined as <75 copies/ml), and eight women had viral loads that were detectable, but less than 1000 copies/ml. Viral load ranged from 1000 to 10 000 copies/ml in eight women, was above 10 000 copies/ml in 14 women, and was unavailable for nine women. A majority of women were receiving cART at the time of their cancer diagnosis ($n=38$, 67%). Receipt of cART was unknown for one woman. Notably, women diagnosed with cervical cancer were less likely to be receiving cART and had higher viral loads ($P<0.05$) than women diagnosed with the other gynecological malignancies, with nonsignificantly lower $CD4^+$ cell counts (Table 1).

NCCN-adherent treatment and survival

A total of 28 women (49%) received NCCN-adherent care. Of the 30 stage I patients, a majority ($n=22$, 73%) received treatment according to NCCN guidelines; five of eight vulvar cancer patients, 11 of 16 cervical cancer patients, one of one ovarian cancer patients, and five of five uterine cancer patients. Twenty-five of these women

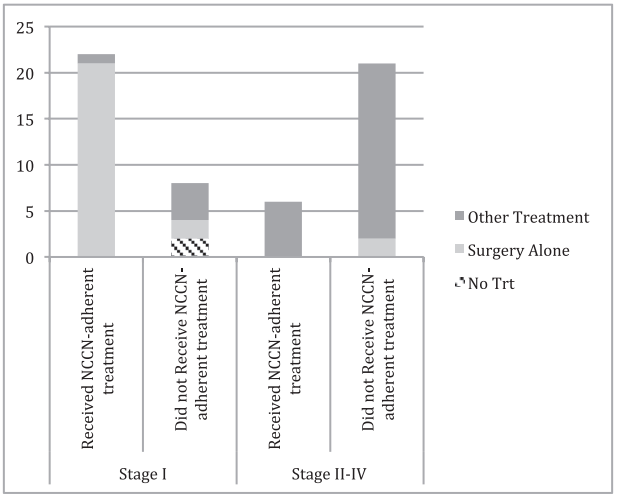

Fig. 1. NCCN-adherent versus nonadherent treatment by stage and treatment type. NCCN, National Comprehensive Cancer Network.

(83%) required surgery alone to treat their cancer, whereas five required surgery and adjuvant therapy. Overall, 21 of 25 (84%) who required surgery alone received NCCN-adherent care (Fig. 1).

Of 27 women with stage II–IV disease, only six (22%) received treatment according to NCCN guidelines. Four of 17 women (24%) with stage II–IV vulvar or cervical cancers received NCCN-adherent care (four of seven vulvar cancer patients and none of ten cervical cancer patients). Fourteen of these 17 women had locally advanced disease and were not surgical candidates; only two of 14 (14%) received NCCN-adherent chemoradiation and both had significant delays in therapy (no distinct timeline is cited for vulvar cancer treatment and therefore both met NCCN-adherent care). Two of 10 women with stage II–IV ovarian or uterine cancers received NCCN-adherent care (one of eight ovarian cancer patients, and one of two uterine cancer patients) (Fig. 1).

Among the 29 women who did not receive NCCN-adherent care, reasons were toxicity-related for 38% ($n = 11$), patient-related for 31% ($n = 9$), related to comorbidities in 17% ($n = 5$), practitioner-related for 10% ($n = 3$), and due to cancer progression in 3% ($n = 1$). Of 21 women with stage II–IV disease who received nonadherent care, nine (43%) were due to toxicity from treatment. Toxicity was more common for women with stage II–IV disease, whereas comorbidity-related reasons were more common in women with stage I disease.

Overall survival differed by specific site of the gynecological malignancy ($P = 0.04$) overall, but differences were particularly pronounced for ovarian cancer, with only 21% survival at 48 months compared to uterine cancer with 100% survival ($P < 0.01$). Overall survival after cervical cancer diagnosis was similar to vulvar cancer (79 and 77%, respectively) (Fig. 2). However, differences by stage and type of treatment, which differed by cancer type, were also found. Nearly all women with stage 1 cancer were alive at 48 months, irrespective of NCCN adherence (94 versus 100% not NCCN; $P > 0.05$). For women with stage II–IV disease, overall survival at 48 months among those who received NCCN-adherent care was 60%, whereas survival was 28% among those who did not receive NCCN-adherent care ($P = 0.05$) (Fig. 3). Overall survival was not associated with the median time from HIV diagnosis ($P = 0.92$), the median $CD4^+$ cell count ($P = 0.13$), or the median viral load ($P = 0.08$).

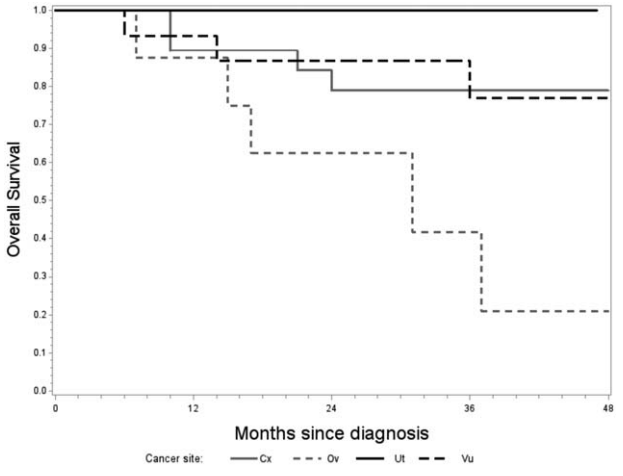

Fig. 2. Overall survival for HIV-infected with gynecologic malignancies, by gynecologic cancer type.

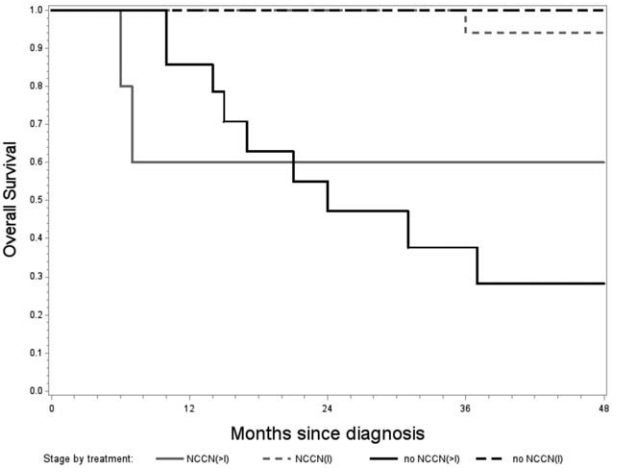

Fig. 3. Overall survival for those with NCCN-adherent versus nonadherent care, by cancer stage at diagnosis. NCCN, National Comprehensive Cancer Network.

Vulvar cancer treatment

Of the 15 HIV-infected women with vulvar cancer, nine (60%) received NCCN-adherent care. For stage I patients, seven required surgery alone, and five (71%) received NCCN-adherent surgery (one received no treatment and the other did not have appropriate lymph node assessment). One woman underwent surgery and chemoradiation; however, she did not complete chemotherapy due to toxicity. For stage II–IV patients, three had significant radiation toxicity and were unable to complete treatment. Additionally, two women had significant delays in chemoradiation; however, this did not exclude them from being NCCN-adherent. Therefore, only two of seven women (28.6%) with advanced-stage disease received NCCN-adherent care without delays (i.e. chemoradiation completed within 8 weeks).

Cervical cancer treatment

Eleven of 26 patients (42%) with cervical cancer received NCCN-adherent care. Twelve of 16 women with stage I disease required surgery alone, and 11 (92%) received NCCN-adherent surgical treatment (one patient was not treated due to comorbidities). Two women with stage 1 disease required adjuvant treatment; one received only one week of radiation, and the other received insufficient dose due to noncompliance. The other two stage I

patients received upfront radiation with no chemotherapy, and one received no brachytherapy. Ten women presented with advanced stage disease and none received NCCN-adherent care due to insufficient doses of radiation ($n=4$), failure to receive chemo-sensitization ($n=1$), delays in therapy ($n=4$), progression of disease ($n=1$), or incorrect treatment (surgery despite metastatic disease) ($n=1$).

Ovarian cancer treatment

There were nine women in the cohort diagnosed with ovarian cancer, and only one (11%) received NCCN-adherent care. There was only one stage I patient in this cohort with the potential for surgery alone; however, this patient was not staged as per NCCN guidelines and therefore did not receive adherent care. Eight women had advanced disease. Four underwent upfront surgical resection, and three of four (75%) received optimal debulking surgery; however, none ultimately received NCCN-adherent adjuvant chemotherapy. Four women were treated with chemotherapy alone; three of these women did not receive adherent care due to lacking surgical assessment or appropriate chemotherapy. The fourth women received NCCN-adherent care with the appropriate regimen and number of cycles of chemotherapy, and also appropriate assessment for surgery by a gynecologic oncologist.

Uterine cancer treatment

Of seven women with uterine cancer, five were diagnosed with stage IA endometrial cancer, and all five received appropriate surgery with lymph node assessment. One woman with advanced disease underwent appropriate surgical staging and required adjuvant chemotherapy with appropriate regimen and cycles received. One woman received only one cycle of chemotherapy and died of complications.

Discussion

The population of HIV-infected women is increasing over time, and a recent study showed that while the incidence of AIDS-defining cancers decreased by threefold from 1991–1995 to 2001–2005, the incidence of non-AIDS-defining cancers is increasing by almost the same amount [4]. Historically, multiple studies have focused on AIDS-defining diseases, such as cervical cancer; however, there are significantly less data on HIV-infected women with vulvar cancer [16–18], and only limited reports on HIV-infected women with ovarian and endometrial cancers [19–23]. To our knowledge, there is no case series describing guideline-specific care and outcomes of HIV-infected women with gynecologic cancers.

As these cancers increase, our ability to meet the standard of care and to understand the impact of standard-of-care treatment on this population is critical. In this retrospective cohort study of women with HIV infection and gynecologic cancers, we found that almost 50% of women did not receive optimal NCCN-adherent treatment. More than 60% of these women were unable to complete NCCN-adherent therapy due to either treatment-related toxicity or to social factors leading to delay, refusal, or barriers to care. Whereas most HIV-infected women who required surgery alone for stage I disease received guideline-adherent care, women with advanced-stage disease requiring treatment other than surgery were less likely to receive guideline-adherent care. Whereas treatment-related decisions are complex and often multifactorial, further investigation into toxicity and patient-related barriers to adjuvant treatment may help to improve survival in this population. Furthermore, it is important to recognize that there are no published cancer treatment guidelines and that HIV-infected patients have historically have been excluded from cancer treatment trials. There are no published cancer guidelines that specifically address HIV-infected patients, and it is unclear whether current national guidelines are appropriate for this population. Evidence also suggests that oncologists may not be comfortable treating HIV-infected patients, and this discomfort also may play a critical role in physician-related treatment decisions [24]. Particularly for those women who present with late-stage gynecologic cancers, addressing and further understanding these factors may play a critical role in improving survival.

Survival did not differ among women in this cohort with stage I disease who did or did not receive NCCN-adherent care, possibly due to the high rate of cure for stage I gynecologic cancers. For women with stage II–IV disease, however, 48-month overall survival was significantly lower for women who did not receive NCCN-adherent care, with only 28% survival. The 4-year overall survival reported by Surveillance, Epidemiology, and End Results (SEER) data is 76.3, 72.1, 49.7, and 83.9% for vulvar, cervical, ovarian, and endometrial cancer, respectively, versus 80, 78, 22, and 100% in this cohort [25]. Differences in these numbers are partially accounted for by stage distribution and sample size. However, in our cohort, the affect of toxicity and patient-related barriers to receiving guideline-adherent and NCCN-adherent care, particularly among advanced-stage ovarian cancer patients, likely play a prominent role in the lower survival compared to SEER data.

Although this study is the first multi-institutional study of HIV-infected women with gynecologic cancers evaluating guideline-specific treatment and survival, it is limited in several ways. The sample size for each of the gynecologic cancers was limited, with almost half of the patients having cervical cancer, reflecting the greatly

increased incidence of cervical cancer compared to other gynecologic cancers. Although two institutions were included, both were from the same state, and these data may therefore not be generalizable. The demographics of this population were also skewed in that the overwhelming majority of women were African American, and there was a significant proportion of women with a history of illicit drug use and psychiatric disease. This also may not be reflective of the larger population of HIV-infected women with gynecologic cancers. Additionally, although several different mechanisms were cross-referenced to identify all HIV-infected women with gynecologic cancers at these institutions, it is possible that some women were not identified for inclusion.

It is also critical to recognize that the natural history of HIV is extremely complex. This complexity limits the inference of this study design, given that data points in this study are from one point in the patient's history. Furthermore, whereas this study objectively determines NCCN adherence, the reasons for nonadherence are also complex and confounded by multiple factors, including the possibility that these patients may be more likely to have additional factors that limit the ability to receive NCCN-adherent treatment. Further studies are needed to help elucidate not only what is appropriate treatment for HIV-infected women (including investigation of possible increase in toxicity, interactions of various pharmacotherapies, etc.), but also physicians' perceptions and willingness to treat patients with HIV and other comorbidities. Despite these limitations, this cohort is the first of its kind to provide detailed treatment information on HIV-infected women with gynecologic cancers. This allowed us to not only examine the treatments received and their concordance with NCCN guidelines, but also to identify reasons why NCCN-adherent care was either not planned or not achieved.

Conclusion

As women with HIV infection continue to live longer and the proportion of women living with HIV continues to age [4], physicians will be faced with treatment-related issues that may greatly affect survival in this population. Our data suggest that whereas HIV-infected women may more often successfully receive surgical treatment, upfront radiation and chemotherapy, and also adjuvant treatment is more often not successfully realized. Although several social, medical, and disease-related factors contributed to this finding, our ability to recognize limitations to realizing appropriate guideline-adherent treatment is of growing importance. Further research is necessary to define treatment-related limitations and interactions for women receiving both cART and cancer-related treatments, and also to compare matched patients who are not infected with HIV. As treatment for gynecologic cancers continue to evolve, this will include not only chemotherapy, radiation, and surgery, but will incorporate targeted and immunotherapies. This study highlights the critical need to expand our understanding of best practices for the treatment of HIV-infected women with gynecologic cancers, particularly those with advanced disease.

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Conflicts of interest

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