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ORIGINAL RESEARCH

Chemotherapy Induced Neutropenia, Febrile-Neutropenia and Determinants Among Solid Cancer Patients Attending Oncology Unit of a Tertiary Care Teaching Hospital in Ethiopia

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Background: Globally the incidence of cancer is about 19.3 million new cases per year. Chemotherapy is among the standard treatments for cancer but neutropenia and febrile neutropenia are the most common side effects.

Objective: To assess the incidences of chemotherapy-induced neutropenia, febrile-neutropenia and associated factors in solid cancer patients attending Oncology unit of St. Paul Hospital Millennium Medical College in Addis Ababa, Ethiopia.

Methods: In this institution-based longitudinal study conducted from February to September, 2020 at one of the largest teaching and referral hospitals of Ethiopia, 101 patients who were diagnosed with any type of solid cancer were recruited using convenience sampling method. Patients were followed-up until they completed five cycles of chemotherapy. Data were analyzed using SPSS version 23 software. Paired sample *t*-test was used to compare the pre- and post-treatment results. Chi-squared test was employed to determine associated factors of neutropenia, and p-values less than 0.05 were taken as statistically significant.

Results: Of the total 101 participants, 98 were eligible per inclusion criteria and 6 (6.1%) of them died during the study period. The age of the participants ranged from 16–84 years with a mean age of 45. Of them, 48 (49.0%) were in the age group of 16–44 years, 73 (74.5%) were female, 66 (67.3%) were married, and 42.9% attained primary education. Among 92 patients, the incidence of neutropenia was 65 (70.7%) and the incidence of febrile neutropenia was 46 (50.0%). Adriamycin + cyclophosphamide and Adriamycin + cyclophosphamide + paclitaxel were the most commonly used anti-cancer treatments in this study. None of the tested factors were associated with chemo-induced neutropenia.

Conclusion: More than two thirds of the patients had chemotherapy associated neutropenia while half of the patients had febrile neutropenia; close monitoring of such patients is warranted.

Keywords: solid tumors, cancer, chemotherapy, neutropenia, febrile neutropenia

Introduction

Cancer continues to be a significant public health problem and a leading cause of mortality all over the world.[1] In 2020 the occurrence of cancer incidence and death was 19.3 million and 10 million respectively.[2] Cancer is the second leading cause of death globally after cardiovascular illness.[3,4]

Chemotherapy is among the standard treatments for cancer patients.[5,6] One of the major side effects of anticancer regimen is myelosuppression.[7] Potentially life-threatening febrile neutropenia (FN), intravenous antibiotic treatment and prolonged hospitalization might be a consequence of chemotherapy. Chemotherapy dose reductions and delays are common consequences and may affect treatment outcomes adversely.[6]

One of the major hematotoxicities in anticancer treatments is neutropenia.[8,9] It is one of the main dose-limiting toxicities in clinical trials and is a common complication in cancer treatments.[9] Chemotherapy induced neutropenia (CIN) may also

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necessitate chemotherapy dose reductions, delays or even discontinuation,[10,11] all of which can lead to reduced treatment response and lower survival.[10] Febrile neutropenia is associated with increased mortality,[7,9,10] treatment costs,[7,9,10,12] and morbidity.[9,10,12] Therefore, febrile neutropenia is a clinically relevant problem that affects the patient's quality of life.[7,9]

There are varying degrees of neutropenia and FN reported by different studies. For example, the study conducted in South Korea and Turkey showed that the incidence of FN was 18% (15/82)[7] and 49.1% (81/165)[13] respectively. Where as in Nigeria the incidence of neutropenia and FN among the patients was 31.9% and 5.3%, respectively.[14]

Data are scant in our country regarding chemotherapy induced neutropenia. Hence, we planned to assess the incidence of chemotherapy-induced neutropenia, febrile neutropenia and the determining factors in solid cancer patients at a tertiary care teaching and referral hospital in Ethiopia.

Materials and Methods

Study Design and Population

An institution-based longitudinal study was performed at St Paul's Hospital Millennium Medical College (SPHMMC) Oncology unit from February to September 2020 using convenience sampling technique. The hospital was established in Addis Ababa, the capital city of Ethiopia in 1968 by the late Emperor Haile Selassie. SPHMMC oncology unit was established on August 1, 2018. It was the second hospital offering cancer treatment in the country.

In this study all volunteer solid cancer patients, who started chemotherapy at SPHMMC oncology unit during the study period, were included. Hematological analysis was done before and after chemotherapy at five time points to determine chemotherapy associated neutropenia and febrile neutropenia. Data on demographic variables such as sex, age, educational level and marital status were collected using structured format and clinical data including ECOG/PS score and type of cancer were extracted from patient charts.

Sample Size Determination and Sampling Method

Sample Size Determination

Since the study followed patients until they finished 5 cycles of treatment, all voluntary patients who started chemotherapy during the study period were included using convenience sampling technique. Accordingly, 101 patients were initially recruited to the study.

Sampling Method

The research was conducted by using convenience sampling technique. After obtaining consent and assent from children aged 16–17 years, eligible patients who were willing to participate were identified by oncology unit nurses. Socio-demographic and clinical data were collected by using standardized pretested questionnaire and from the patients' charts.

Specimen Collection and Laboratory Processing

About 5mL of venous blood was collected using ethylenediaminetetraacetic acid (EDTA) tubes. Hematological analysis was performed by using automated Beckman coulter DxH 800 analyzer in the laboratory of SPHMMC.

Data Analysis and Interpretation

Data were entered, cleaned, and analyzed by using SPSS version 23 software. The result was presented in table. Chi-squared test was used to determine association between developments of chemo induced neutropenia, febrile neutropenia and associated factors. Level of statistical significance was determined at p-value less than 0.05. Based on common toxicity criteria of the National Cancer Institute of America, neutropenia was defined as a decrease in the absolute number of neutrophils count (ANC) in the blood and was graded as follows.[6,15,16]

Grade 1, ANC 1.5–2.0 $x10^9$/l

Grade 2, ANC 1.0–1.5$x10^9$/l

Grade 3, ANC 0.5–1.0 $x10^9$/l and

Grade 4, ANC <0.5$x10^9$/l

The European Society of Medical Oncology (ESMO) and the European Organization for Research and Treatment of Cancer (EORTC) guidelines define FN as an oral temperature > 38.5°C or two consecutive readings of > 38.0°C for 2 h and an ANC < 500 cells/mm3 or expected to fall below this threshold.[8]

Results

Socio-Demographic Characteristics

A total of 101 newly diagnosed solid cancer patients were enrolled in the study. Because of incomplete information, three patients were excluded. Of the total participants, 98 were eligible per inclusion criteria. Six (6.1%) patients died during the study period. The age of the participants ranged from 16–84 years with a mean age of 45. From the total patients, 73 (74.5%) were females, 48 (49%) were in the age group of 16–44 years, 66 (67.3%) were married, and 42.9% attained primary education (Table 1).

Table 1 Baseline Socio-Demographic Characteristics of Solid Cancer Patients at St. Paul's Hospital Millennium Medical College Oncology Unit, Addis Ababa, Ethiopia from February to September, 2020

Variables		N	%
Age (Years)			
	16–44	48	49.0
	45–64	41	41.8
	65–74	6	6.1
	75–84	3	3.1
Sex			
	Male	25	25.5
	Female	73	74.5
Residence			
	Urban	76	77.6
	Rural	22	22.4
Educational Status			
	Cannot read and write	17	17.3
	Primary (1–8)	42	42.9
	Secondary (9–12)	11	11.2
	Diploma/Degree	26	26.5
	MSc and above	2	2.0
Marital status			
	Married	66	67.3
	Unmarried	20	20.4
	Divorced	5	5.1
	Widowed	7	7.1

(*Continued*)

Table 1 (Continued).

Variables		N	%
Occupation			
	Employed	36	36.7
	Merchant	14	14.3
	House-wife	37	37.8
	Student	2	2.0
	Farmer	9	9.2

Abbreviation: MSc, Masters of Science.

Clinical chart review revealed 43(43.9%) patients had Eastern Corporation Oncology Group/Performance Status (ECOG/PS) of 0, 53(54.1%) patients were found within the normal range of body mass index (BMI), 85(86.7%) patients were free from other chronic disease and 83(84.7%) did not use substances (Table 2).

Frequency of Solid Cancer

During the study period we observed that the most common solid cancer was breast cancer 42(45.2%) followed by adenocarcinoma 12(12.9%) (Table 3).

Anticancer Treatments

In this study, different anticancer treatments were prescribed by the oncologists based on the type and performance status or Eastern Cooperative Oncology Group (PS/ECOG) grading of the disease. The most common anti-cancer treatments used in this study were combinations of Adriamycin + Cyclophosphamide 30(32.6%), Adriamycin + Cyclophosphamide + Paclitaxel 12(13%) and Cisplatin + Paclitaxel 12 (13%) (Table 4).

Table 2 Baseline Clinical Characteristics of Cancer Patients Attending St. Paul Hospital Millennium Medical College Oncology Unit, Addis Ababa, Ethiopia from February 2020 to September 2020

Variables		N	%
ECOG/PS -Eastern Corporation Oncology Group/Performance Status	0.00	43	43.9
	1.00	30	30.6
	2.00	15	15.3
	3.00	7	7.1
	4.00	3	3.1
Body Mass Index (kg/m^2)	< 18.5 Under-weight	23	23.5
	18.5–24.9 Normal	53	54.1
	25–29.9 Over-weight	12	12.2
	≥30 Obese	10	10.2
Other chronic disease	Yes	13	13.3
	No	85	86.7
Substance use	Yes	15	15.3
	No	83	84.7

Table 3 Number of Patients with Solid Cancer at St. Paul's Hospital Millennium Medical College Oncology Unit, Addis Ababa, Ethiopia from February to September, 2020

Type of Cancer (ca)	Frequency	
	N	(%)
Breast ca	42	(45.2)
Pancreatic ca	5	(5.4)
Gastric ca	4	(4.3)
Adeno ca	12	(12.9)
Colorectal ca	5	(5.4)
Esophageal ca	4	(4.3)
Lung ca	4	(4.3)
Cervical ca	4	(4.3)
Liver ca	3	(3.2)
Seminoma ca	2	(2.2)
Nasopharyngeal ca	2	(2.2)
Liposarcoma ca	2	(2.2)
Others	4	(4.3)

Table 4 Chemotherapeutic Regimen Type Prescribed for Solid Cancer Patients at St. Paul's Hospital Millennium Medical College Oncology Unit, Addis Ababa, Ethiopia from February to September 2020

Regimens	Frequency	%
Adriamycin + Cyclophosphamide	30	32.6
Cisplatin + Gemcitabine	8	8.7
Adriamycin + Cyclophosphamide + Paclitaxel,	12	13.0
Cisplatin + Paclitaxel	12	13.0
Cisplatin + Capecitabine	9	9.8
Capecitabine + Oxaliplatin	8	8.7
Carboplatin + Paclitaxel	4	4.3
Others	9	9.7
Total	92	100

Magnitude of Neutropenia and Febrile Neutropenia

The magnitude of neutropenia in the first cycle was 25%, second cycle 27.2%, third cycle 31.5%, in the fourth and fifth cycles it was 28.3% and 35.9%, respectively. High grades of neutropenia were recorded in the third and fifth cycles. The

magnitude of febrile neutropenia (FN) continuously increased up to the 4th cycle of chemotherapy. The highest rate of febrile neutropenia was recorded in the fourth cycle which was 19(20.7%).

All patients who developed FN were admitted to SPHMMC emergency unit and the highest mean duration of FN was 6.57 (range 3–9) and 6.5 (range 4–12) days (Table 5).

Considering the incidence in each cycle, the overall incidences of neutropenia and febrile neutropenia in the whole cycle were 65(70.7%) and 46(50%), respectively.

We also observed that high rate of neutropenia and febrile neutropenia were recorded in patients who were treated with Adriamycin + cyclophosphamide.

Grading of Neutropenia

Grading of neutropenia on the basis of absolute neutrophil count (ANC) as shown in Table 6 revealed that most of the patients had ANC within the normal range and regardless of treatment cycle most patients were found to have Grade one neutropenia (Table 6).

Finally, Chi-squared test analysis showed no significant association between the occurrence of neutropenia and sex (p = 0.264), age group (p=0.216), residence (p=0.209), educational status (p=0.340), marital status (p= 0.546) and

Table 5 Distribution of Chemotherapy Induced Neutropenia and Febrile Neutropenia in the Whole Cycle in Patients Attending St. Paul's Hospital Millennium Medical College Oncology Unit, Addis Ababa, Ethiopia from February to September 2020

Variables	Treatment-Cycle				
	1 (n=92)	2 (n=92)	3(n=92)	4 (n=92)	5 (n=92)
	N (%)	N (%)	N (%)	N (%)	N (%)
Neutropenia	23(25)	25(27.2)	29(31.5)	26(28.3)	33(35.9)
Febrile- Neutropenia	8(8.7)	9(9.8)	14(15.2)	19(20.7)	17(18.5)
Mean duration of FN in days	5.88	6	6.57	6.5	5.94
Minimum duration of FN	3	3	3	4	2
Maximum duration of FN	14	9	9	12	9

Abbreviation: FN, febrile neutropenia.

Table 6 Grading of Neutropenia in Patients Attending St. Paul's Hospital Millennium Medical College Oncology Unit, Addis Ababa, Ethiopia from February to September 2020

Neutropenia Grading*	Treatment Cycle				
	1st	2nd	3rd	4th	5th
	N (%)	N (%)	N (%)	N (%)	N (%)
Grade one	14(15.2)	11(12.0)	15(16.3)	11(12.0)	14(15.2)
Grade two	10(10.9)	10 (10.9)	11(12.0)	6(6.5)	13(14.2)
Grade three	11(12.0)	3(3.3)	3(3.3)	8(8.7)	5(5.4)
Grade four	1(1)	0%	0%	2(2.2)	3(3.3)

Notes: *Based on common toxicity criteria of the National Cancer Institute of America ANC grading: grade 1, ANC 1.5 to 2.0x10^9/l; grade 2, ANC 1.0 to 1.5x10^9/l; grade 3, ANC 0.5 to 1x10^9/l; grade 4, ANC <0.5x10^9/l.

occupational status (p= 0.115). Similarly, no significant association was observed between the occurrence of febrile neutropenia and the socio-demographic variables (p>0.05), as shown in Table 7.

There was also no significant association between the occurrence of neutropenia and ECOG/PS (p = 0.414), BMI (p=0.064), other chronic disease (p=0.393), and substance use (p=0.381). Similarly, no significant association was observed between the occurrence of febrile neutropenia and the clinical characteristics variable (p>0.05), as shown in Table 8.

Table 7 Baseline Socio-Demographic Characteristics by Incidence of Neutropenia and Febrile Neutropenia Among Patients at St. Paul Hospital Millennium Medical College Oncology Unit, Addis Ababa, Ethiopia from February to September, 2020

Variables		N (%)	Neutropenia N (%)	P-value	F. Neutropenia N (%)	P-value
Age (Years)				0.216		0.194
	16–44	48(49)	34(52)		25(54.3)	
	45–64	41(48.1)	26(40)		18(39.1)	
	65–74	6(6.1)	2(3.1)		1(2.2)	
	75–84	3(3.1)	3(4.6)		2(4.3)	
Sex				0.264		0.543
	Male	25(25.5)	17(26.2)		12(26.1)	
	Female	73(74.5)	48(73.8)		34(73.9)	
Residence				0.209		0.169
	Urban	76(77.6)	50(77.0)		35(76.1)	
	Rural	22(22.4)	15(23.1)		11(23.9)	
Educational Status				0.340		0.292
	Cannot read and Write	17(17.3)	10(15.0)		7(15.2)	
	Primary (1–8)	42(42.9)	29(45.0)		22(47.8)	
	Secondary (9–12)	11(11.2)	8(12.3)		6(13.0)	
	Diploma/Degree	26(26.5)	17(26.0)		10(21.7)	
	Master of Science and above	2(2)	1(1.5)		1(2.2)	
Marital status				0.546		0.688
	Married	66(67.3)	42(65.0)		30(65.2)	
	Unmarried	20(20.4)	15(23.0)		11(23.9)	
	Divorced	5(5.1)	4(6.0)		2(4.3)	
	Widowed	7(7.1)	4(6.0)		3(6.5)	
Occupation				0.115		0.148
	Employed	36(36.7)	27(41.5)		20(43.5)	
	Merchant	14(14.3)	10(15.0)		4(8.7)	
	House-wife	37(37.8)	22(34.0)		18(39.1)	
	Student	2(2.0)	1(1.5)		0(0.0)	
	Farmer	9(9.2)	5(8.0)		4(8.7)	

Table 8 Baseline Clinical Characteristics by Incidence of Neutropenia and Febrile Neutropenia Among Patients at St. Paul Hospital Millennium Medical College Oncology Unit, Addis Ababa, Ethiopia from February to September, 2020

Variables		N (%)	Neutropenia N (%)	P-value	F. Neutropenia N (%)	P-value
ECOG/PS				0.414		0.667
	0.00	41(44.6)	11(47.8)		3(37.5)	
	1.00	27(29.3)	7(30.4)		2(25.0)	
	2.00	15(16.3)	3(13.0)		2(25.0)	
	3.00	7(7.6)	2(8.7)		1(12.5)	
	4.0	2(2.2)	0(0.0)		0(0.0)	
Body Mass Index (kg/m^2)				0.064		0.207
	<18.5 Under-Weight	19(20.7)	9(39.1)		2(25.0)	
	18.5–24.9 Normal	52(56.5)	10(43.5)		6(75.0)	
	25–29 Over-weight	14(15.2)	3(13.0)		0(0.0)	
	≥30 Obese	7(7.6)	1(4.3)		0(0.0)	
OCD				0.393		0.891
	Yes	13(14.1)	2(8.7)		1(12.5)	
	No	79(85.9)	21(91.3)		7(87.5)	
Substance use				0.381		0.882
	Yes	13(14.1)	0(0.0)		2(22.2)	
	No	79(85.9)	0(0.0)		7(77.8)	

Abbreviations: ECOG/PS, Eastern Corporation Oncology Group/Performance Status, OCD, other chronic disease.

Discussion

In anti-cancer treatment, the most important concern is how to gain the maximal pharmacologic effect while avoiding, if not minimizing, the appearance of adverse effects. Adverse effects of anticancer agents may lead not only to patients' pain and anxiety but also to death in some cases.[17]

The development of prophylactic granulocyte colony stimulating factor (G-CSF) shortens the duration of neutropenia and reduces related infections.[18] It also reduces the incidence and severity of neutropenia in high-risk patients.[19] But G-CSF is not routinely prescribed to all patients. According to the current guidelines, the prophylactic use of G-CSF should be based on the evaluation of patients' overall risk for FN by two components: type of chemotherapy regimens[1,18] and patient-related factors.[18] Besides, factors like cost and paucity of conclusive studies showing efficacy in particular diseases could also limit its use.[1] However, hematotoxicities like neutropenia is still a dose-limiting factor.[17]

The current study aimed at assessing the incidence of chemotherapy induced neutropenia and febrile neutropenia with its determinants in solid cancer patients at St Paul's Hospital Millennium Medical College Oncology unit in Addis Ababa, Ethiopia. Among the total of 92 newly diagnosed patients aged from 16–84 years old, the magnitude of chemotherapy induced neutropenia and febrile neutropenia in the whole cycle was 65(70.7%) and 46(50%) respectively. Whereas the research conducted by Hashiguchi et al showed chemotherapy-induced neutropenia occurred in 147(50.5%) patients and febrile neutropenia occurred in 20 (6.9%) patients.[9]

In the present study, the most common chemotherapy regimen was Adriamycin + cyclophosphamide (AC) (32.6%). But research conducted by Hashiguchi et al showed that the most common chemotherapy regimen used in their patients was paclitaxel plus carboplatin (TC) therapy. In our case this combination was prescribed for 4/92 (4.3%) patients only. The reason might be that different regimens are used for different cancer types.[9]

Grading of neutropenia on the basis of absolute neutrophil count (ANC) revealed that most of the patients, regardless of treatment cycle, were Grade one. However after the initiation of chemotherapy the worst grade of neutropenia was observed. Among patients experiencing neutropenia, less incidence of worst grade neutropenia was seen during the first cycle 1(1%), in the fourth cycle 2(2.2%), and fifth cycle 3(3.3%). But Han et al 2012 reported that the worst grade was seen during the first cycle in 32(18.18%) patients, during the second cycle in 38(21.59%), during the third cycle in 32 (18.18%), during the fourth cycle in 31(17.61%), and during the fifth cycle in 22(12.5%). He also reported that mild neutropenia (grades 1–2) occurred in 139 (42%) patients and severe neutropenia (grades 3–4) occurred in 37 (11%). The other 159 patients (47%) did not experience neutropenia during treatment with cyclophosphamide, methotrexate and fluorouracil (CEF),[20] and similarly Salako et al reported that 6.6% of their patients had mild, 3.4% moderate, and 1.4% severe neutropenia.[14]

In the present study the magnitude of febrile neutropenia continuously increased while the patients were receiving chemotherapy: 8(8.7%) patients in the first cycle, 9(9.8%) in the second cycle, 14(15.22%) in the third cycle, 19(20.7%) in the fourth cycle, and 17(18.5%) in the fifth cycle. All of them were admitted to the SPHMMC emergency department and mean duration of FN was 5.87 days (range 3–14 days), 6 days (range 3–9 days), 6.57 days (range 3–9 days), 6.5 days (range 4–12 days), and 5.94 days (range 2–9 days) for cycle 1, 2, 3, 4, and 5 respectively.

But research conducted by Weycker et al and Philip et al showed different results than the present study.[21,22] According to Weycker et al's research, the overall risk of FN during any myelosuppressive chemotherapy regimen course was 16.8%, which is almost 3 times lower compared to our study finding of 50% FN. Risk of FN was 8.1% in cycle 1, 4.9% in cycle 2, and 3.8% in subsequent cycles.[21] Similarly, the research done by Philip et al showed that the incidence of chemotherapy induced febrile neutropenia (CIFN) in each cycle varied, 36.63% was encountered in cycle 1 followed by 22.72% and 18.18% in cycle 2 and cycle 6, respectively.[22] Moreover, the research conducted by Salako et al showed that the incidence of neutropenia decreased with increasing chemotherapy courses, with a rate of 14.2% and 4.9% after the first and last course, respectively.[14]

While in our case it was incremental starting from 8.7% in the 1st cycle to 20.7% in the 5th cycle. The mean duration of neutropenia and fever in the 3 cycles was 3.6 days (range 1–12 days), 3.4 days (range 1–9 days), and 8.4 (range 2–9) days, respectively. The source of fever was unexplained by examination in 14 (56.0%) patients.[21] Based on their study the magnitude of FN decreased with increasing chemotherapy cycles but the duration of FN was more or less similar to our study. The cause might be differences in care between a resource constrained setting and the US, though other factors like geographical location and race difference could play a role.

Limitations

Because of the short study period we could not recruit more study participants.

The effects of chemotherapy on other components of CBC were not analyzed.

Conclusion and Recommendation

We discovered that incidence of CIN and FN was 65(70.7%) and 46(50.0%) respectively in our study. However, no statistically significant correlations were discovered between the considered sociodemographic and clinical data. So, in addition to the factors examined in the current study which revealed no statistically significant connections, more research on the predicting factors of neutropenia and febrile neutropenia with a superior design, is advised.

Abbreviations

ANC, absolute neutrophil count; BMI, body mass index; CIN, chemotherapy induced neutropenia; ECOG/PS, Eastern Corporation Oncology Group/Performance Status; EDTA, ethylenediaminetetraacetic acid; FN, febrile neutropenia; G-CSF, granulocyte colony stimulating factor; SPHMMC, St Paul's Hospital Millennium Medical College.

Ethical Considerations

The study protocol was reviewed and approved by the Departmental Research and Ethics Review Committee of the Department of Medical Laboratory Sciences of Addis Ababa University. Official permission from the study site was obtained.

The researcher then informed the participants of the study in accordance with the Helsinki Declaration. They were informed that the aim of this study was to assess chemotherapy-induced neutropenia, febrile-neutropenia, and its determinants among solid cancer patients visiting St. Paul Hospital Millennium Medical College, Oncology Unit, Addis Ababa, Ethiopia. They also understood that supplying a modest amount of blood did not endanger their health. The participants were also informed by the investigator that they were free to withdraw their agreement at any time with no repercussions. After they provided their permission, they were asked to sign informed consent to confirm their willingness to take part in the study.

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Disclosure

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