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BRIEF REPORT

Antiviral Prescribing Among Patients at an Ambulatory Cancer Center With Laboratory-Confirmed Influenza

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Among 133 cancer outpatients diagnosed with influenza between 2016 and 2018, 110 (83%) were prescribed oseltamivir. Among 109 with a known symptom onset date, 53% presented for care and 31% were prescribed oseltamivir within 48 hours. Patient/provider education and rapid diagnostics are needed to improve early oseltamivir use among cancer patients with influenza.

Keywords. ambulatory setting; antibiotic prescribing; cancer patients; influenza; oseltamivir prescribing; rapid diagnostics.

Influenza causes significant morbidity and mortality, with an increased risk of complications, hospitalization, and mortality among cancer patients when compared with the general population [1–3]. Neuraminidase inhibitors (NAIs) such as oseltamivir shorten the disease course and reduce the risk of complications particularly when administered within 48 hours of symptom onset [4–6].

Early NAI therapy is especially important in populations at increased risk of influenza complications including cancer patients and hematopoietic cell transplantation (HCT) recipients [7, 8]. National guidelines recommend empiric therapy with NAIs for all high-risk patients presenting with acute respiratory infection (ARI) during influenza season [9]. A major obstacle to early treatment with NAI is delayed presentation to care by symptomatic patients. NAI therapy is most effective when started within 2 days of symptom onset, yet a study of high-risk outpatients with an acute respiratory illness found that less than half presented for care within 48 hours of symptom onset [10]. Additionally, high-risk outpatients with laboratory-confirmed influenza are twice as likely to be prescribed antibiotics as antivirals [11].

Limited data exist on timing of presentation to care and management of cancer outpatients diagnosed with influenza. In this study, we aim to characterize clinical presentation, antimicrobial prescribing, and outcomes among patients with influenza at an ambulatory cancer center.

METHODS

Study Design

We conducted a retrospective cohort study of consecutive outpatients presenting to care at Fred Hutchinson Cancer Center from January 1, 2016, to December 31, 2018, and diagnosed with laboratory-confirmed influenza. Electronic data capture was used to identify patients diagnosed with influenza A or B by polymerase chain reaction (PCR). Patients diagnosed with influenza in the emergency department (ED), inpatient setting, or outside facility were excluded. Patient demographics and clinical information including influenza vaccination history and antimicrobial prescriptions were extracted from the electronic medical record (EMR). Chart review was conducted to identify the index date of the first clinical encounter for influenza symptoms and collect antibiotic indication and clinical outcome data.

Patient Consent

The Fred Hutch Institutional Review Board approved the study with a waiver of informed consent.

Definitions and Laboratory Methods

Symptom onset date was defined as the first day of new symptoms consistent with respiratory tract infection. The date of first clinical encounter (day 0) was the first clinic visit or telephone encounter at which the patient reported new respiratory symptoms to a provider or nurse. Influenza testing was performed at the provider's discretion using a laboratory-developed multiplex PCR capable of detecting 12 respiratory viruses with a turnaround time of 24 hours [12–14]. Patients were considered to have been vaccinated if they received an influenza vaccine between September 1 and April 30 of the corresponding influenza season and before their positive influenza test.

Antibiotic and antiviral prescription data were collected between days −7 and +7. Antibiotic indications were classified as upper respiratory infection (URI)–related if the antibiotic was prescribed for treatment of respiratory symptoms without

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Table 1. Baseline Characteristics According to Antiviral Prescription Status Among Cancer Outpatients With Laboratory-Confirmed Influenza

Baseline Characteristic[a]	Antiviral Prescribed (n = 110)	No Antiviral Prescribed (n = 23)	Total (n = 133)
Age, median (IQR), y	57 (40–66)	47 (29–66)	56 (40–66)
Sex			
Male	65 (89)	8 (11)	73 (55)
Female	45 (75)	15 (25)	60 (45)
Race			
White	86 (85)	15 (15)	101 (76)
Asian	15 (79)	4 (21)	19 (14)
Black or African American	4 (80)	1 (20)	5 (4)
American Indian or Native Alaskan	1 (50)	1 (50)	2 (2)
Hawaiian or Pacific Islander	1 (100)	0 (0)	1 (1)
Unknown	3 (60)	2 (40)	5 (4)
Ethnicity			
Hispanic or Latino	6 (60)	4 (40)	10 (8)
Not Hispanic or Latino	100 (86)	16 (14)	116 (87)
Unknown	4 (57)	3 (43)	7 (5)
Diagnosis			
Hematologic	93 (85)	16 (15)	109 (82)
Leukemias	48 (86)	8 (14)	56 (42)
Lymphomas	21 (91)	2 (9)	23 (17)
Multiple myeloma	14 (88)	2 (13)	16 (12)
Other hematologic	10 (71)	4 (29)	14 (11)
Solid tumor	11 (73)	4 (27)	15 (11)
Genitourinary	2 (67)	1 (33)	3 (2)
Gastrointestinal	2 (67)	1 (33)	3 (2)
Lung	2 (100)	0	2 (2)
Breast	0	1 (100)	1 (1)
Head and neck	1 (100)	0	1 (1)
Other solid tumor	4 (80)	1 (20)	5 (4)
Other	6 (67)	3 (33)	9 (7)
Influenza vaccination status			
Currently vaccinated	37 (90)	4 (10)	41 (31)
Unknown	73 (79)	19 (21)	92 (69)
Absolute neutrophil count,[b] median (IQR)	2.7 (1.6–4.9)	2.9 (1.7–5.2)	2.7 (1.6–5.0)
Absolute lymphocyte count,[b] median (IQR)	0.8 (0.5–1.4)	1.2 (0.7–1.7)	0.8 (0.5–1.5)
Previous hematopoietic cell transplant			
Yes	59 (86)	10 (14)	69 (52)
No	51 (80)	13 (20)	64 (48)
Influenza type			
A	69 (82)	15 (18)	84 (63)
B	41 (84)	8 (16)	49 (37)
Symptoms documented			
Cough	97 (87)	14 (13)	111 (83)
Fever	45 (82)	10 (18)	55 (41)
Rhinorrhea	43 (81)	10 (19)	53 (40)
Sputum production	37 (82)	8 (18)	45 (34)
Nasal congestion	31 (91)	3 (9)	34 (26)
Fatigue	23 (82)	5 (18)	28 (21)
Myalgia	23 (88)	3 (12)	26 (20)
Sore throat	19 (83)	4 (17)	23 (17)
Chills	16 (84)	3 (16)	19 (14)
Headache	16 (89)	2 (11)	18 (14)
Dyspnea	14 (88)	2 (13)	16 (12)
Initial encounter type			
Provider visit	72 (80)	18 (20)	90 (68)
Nurse visit or phone call	38 (88)	5 (12)	43 (32)
Days from symptom onset to clinical encounter[c]			
0–2	52 (90)	6 (10)	58 (44)
3–7	30 (81)	7 (19)	37 (28)
8+	10 (71)	4 (29)	14 (11)
Unknown symptom onset	18 (75)	6 (25)	24 (18)
Days from clinical encounter to influenza test			
0	93 (86)	15 (14)	108 (81)
1	10 (100)	0	10 (8)
2+	7 (47)	8 (53)	15 (11)

Abbreviation: IQR, interquartile range.

[a]Values are in No. (%) unless otherwise specified. Percentages for the Antiviral Prescribed and No Antiviral Prescribed columns are row percentages, and those for the Total column are column percentages.

[b]In units of 10^3 cells/μL.

[c]Twenty-four patients had no documented symptom onset date.

physical exam or radiographic signs of lower respiratory tract infection or without documented concern for a bacterial infection. Remaining antibiotic prescriptions were classified as non-URI-related and by specific indications, including lower respiratory tract infection (LRTI) and antibiotic prophylaxis. LRTI-related antibiotics were defined as prescription of an antibiotic for treatment of respiratory symptoms with physical or radiographic signs of LRTI or with documented suspicion of a bacterial infection.

LRTI and hospitalization outcomes were captured based on visits through day 14. LRTI was defined by physical exam signs (eg, rales or dullness to percussion) or radiographic findings (eg, consolidation, interstitial infiltrate, or ground-glass opacities) consistent with bacterial or viral lower respiratory tract infection in addition to documented suspicion of LRTI by the clinician. Deaths were captured through day 30.

Statistical Methods

Categorical variables were summarized using frequency counts and percentages. Continuous variables were summarized by median and interquartile range (IQR). For group comparisons of NAI prescribing, we used generalized estimating equations with the Poisson distribution to account for correlation among patients seen by the same provider.

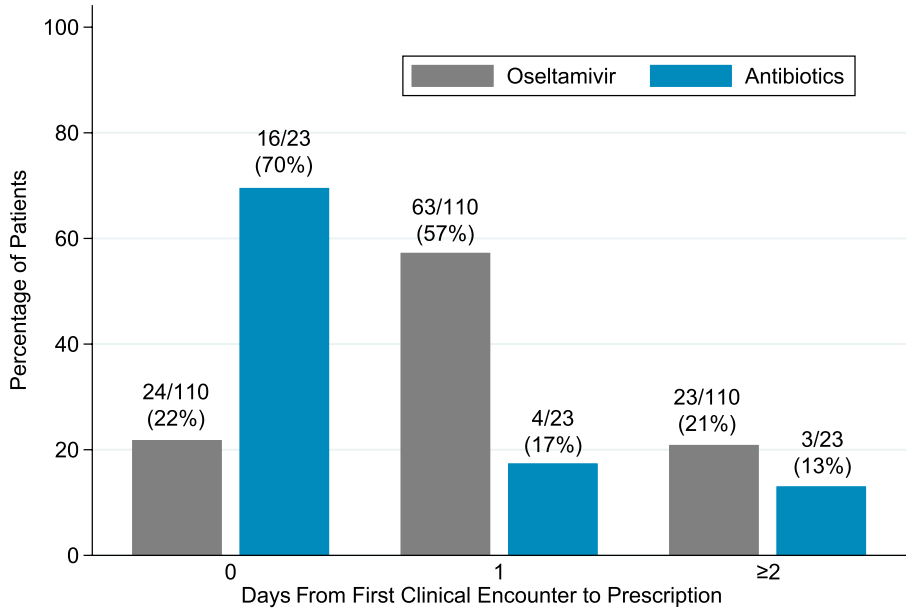

Figure 1. Time from First Clinical Encounter to Oseltamivir and Antibiotic Prescription

RESULTS

Of 139 patients with laboratory-confirmed influenza, 6 (4%) were excluded due to a prior diagnosis of influenza at an outside facility; 133 (96%) patients seen by 68 providers were eligible for analysis. Baseline characteristics are shown in Table 1. Among 133 patients, 109 (82%) had a diagnosis of hematologic malignancy, and 69 (52%) had a prior HCT. Date of symptom onset was known among 109 patients, of whom 58 (53%) presented to care within 48 hours. Cough was the most commonly reported symptom (111 [83%]); all other symptoms were documented in less than half of patients. The majority of patients (107 [80%]) had test orders placed on day 0, while the remaining 26 patients were tested a median (IQR) of 3 (1–6) days later. Test results were available on day 0 for 2 (2%) patients, day 1 for 98 (74%) patients, and for the remaining patients at a median (IQR) of 3 (2–7) days. Forty-one (31%) patients were known to be vaccinated.

Most patients (110 [83%]) were prescribed an NAI, which was oseltamivir in all instances. Of these, 24 (22%) were prescribed on day 0, while 63 (57%) were prescribed on day 1; most prescriptions were ordered on or after the day test results became available (83/110; 75%) (Figure 1). Among 109 patients with a documented symptom onset date, 34 (31%) were prescribed oseltamivir within 48 hours of symptom onset. Sixty-two (91%) of the 68 providers prescribed oseltamivir to at least 1 patient, and the majority (50 [74%]) prescribed oseltamivir to every patient (Supplementary Figure 1).

Thirteen (10%) patients were prescribed an antibiotic for URI, of which azithromycin (6 [46%]) and levofloxacin (5 [38%]) were the most common. Ten patients (8%) were prescribed a total of 21 antibiotics for LRTI, of which vancomycin (6 [29%]), cefepime (5 [24%]), and levofloxacin (4 [19%]) were most common. Among 23 patients prescribed antibiotics for either URI or LRTI, the majority (16 [70%]) were prescribed on day 0 (Figure 1).

The characteristics of 58 patients who presented for care within 2 days of symptom onset are shown in Supplementary Table 1. Initial clinical encounters by telephone or with a nurse led to fewer patients (14 [48%]) receiving oseltamivir within 48 hours of symptom onset than initial encounters with a provider (20 [69%]; $P = .08$). A greater proportion of patients with a hematologic malignancy (29 [62%]) were prescribed oseltamivir within 48 hours compared with those with solid tumors (3 [43%]; $P = .28$).

Nine (6.8%) patients progressed to LRTI, 1 with methicillin-susceptible *Staphylococcus aureus* pneumonia. There were 11 patients (8.3%) with influenza-related hospitalizations, 1 (0.7%) admitted to the intensive care unit, and an additional patient died on day 20 due to progression of his underlying malignancy. Among patients with influenza-related hospitalizations, 10 (91%) were prescribed oseltamivir, of whom 5 were prescribed oseltamivir within 2 days of symptom onset. There were 5 patients with influenza-related hospitalizations that occurred on or after day 2, among whom 3 (60%) received oseltamivir before day 2.

DISCUSSION

Oseltamivir was frequently prescribed among cancer patients, but less than a third received treatment within 48 hours of

symptom onset. Most were prescribed oseltamivir only after test results were available, on the day after clinical presentation. Among those prescribed antibiotics, most were prescribed empirically at the first clinical encounter.

Roughly half of patients presented within 48 hours of symptom onset. This is consistent with the study by Stewart et al. [10], which found that 40% of high-risk patients with influenza presented within 48 hours of symptom onset, suggesting a need to improve patient awareness and understand drivers of delayed presentation to care. Increased utilization of telehealth services may enable earlier access to care [15].

Our study highlights an unmet need for accessible, reliable, rapid respiratory virus diagnostics, as providers appeared to rely on test results to guide antiviral decision-making despite empiric treatment being recommended among high-risk patients with suspected influenza [9, 16]. This is even more critical now in the era of coronavirus-19 (COVID-19) where patients with influenza and COVID-19 infection may present with overlapping symptoms.

Despite the fact that a minority received early treatment, there were few complications in our cohort, with 8% of patients requiring hospitalization and 1 death unrelated to influenza. This may reflect our selection of patients tested in the ambulatory setting and the overall high frequency of oseltamivir prescribing in this population, which may have provided some benefit even when prescribed late. Studies suggest that oseltamivir prescribed up to 5 days after symptom onset may still be of benefit [17, 18]. Additionally, at least one-third of patients were vaccinated for influenza, which may have offered additional protection.

A limitation of this study is the sampling bias inherent in restricting the study population to those tested in the ambulatory setting. As such, our data do not offer insight into the clinical course and outcomes of those who may have presented directly to the ED with more serious illness. By including only those with laboratory-confirmed influenza, we have a limited characterization of the clinical decision-making around those presenting with acute respiratory symptoms who were not tested at all.

CONCLUSIONS

Delayed presentation to care is an obstacle to early NAI use. Patient and provider education, along with rapid diagnostics, is needed to improve early NAI use among cancer patients with influenza.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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