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# Oseltamivir prophylaxis during the influenza season in a paediatric cancer centre: prospective observational study

# 流感高峰期在兒童癌病中心採用oseltamivir預防流感：預期觀察研究

**Objective.** To determine the role of oseltamivir prophylaxis for immunocompromised patients.
**Design.** Prospective, non-blinded, non-controlled observational study.
**Setting.** A paediatric cancer centre, Hong Kong.
**Participants.** Thirty-two patients, immunocompromised by chemotherapy or bone marrow transplantation during an influenza season in 2001.
**Intervention.** Oral oseltamivir prophylaxis 75 mg/d for 8 weeks.
**Main outcome measures.** Laboratory-confirmed influenza infection, symptoms of influenza, drug compliance, and any side-effects from oseltamivir treatment. Laboratory monitoring included virological surveillance for influenza A and B, blood counts, and renal and liver function tests.
**Results.** Patients' median age was 14.3 years (range, 6.3-23.4 years). Underlying conditions included malignancy (n=29) and other haematological diseases (n=3). No documented influenza infection according to serological tests was present throughout the study period. Five patients with symptoms of upper respiratory tract infection did not have any influenza infection detected by rapid virological assay and viral culture. For 16% of patients, the main side-effect in the study was gastro-intestinal upset.
**Conclusions.** Oral oseltamivir 75 mg once daily for 8 weeks may be useful in the prevention of influenza infection in patients immunocompromised by chemoradiotherapy; side-effects are few and acceptable.

**目的：**就免疫力弱的病人，確定 oseltamivir 預防流感的作用。
**設計：**非盲及沒有對照組的預期觀察研究。
**安排：**香港一所兒童癌病中心。
**參與者：**在2001年流感高峰期，32位接受化療或骨髓移植而導致免疫力減弱的病人。
**療法：**每天口服 oseltamivir 一次，劑量為 75 mg；連續服用 8 星期。
**主要結果測量：**實驗確診感染流感、流感症狀、服藥依從性及施用oseltamivir而造成的任何副作用。通過實驗監測的項目包括對甲型和乙型流感進行病毒學監察、血細胞數目記錄、腎和肝功能測試。
**結果：**病人的年齡中位數為 14.3 年 (分佈域為 6.3 至 23.4 年)，病人所患病症分別為惡性腫瘤(n=29) 及其他血液疾病(n=3)。在整個研究期間，血清測試紀錄並無顯示有病人感染流感。有5位病人出現上呼吸道感染的症狀，但經過病毒快速檢定和病毒培養的檢測後，發現並無感染流感的跡象。在研究期間，16% 的病人服藥後的主要副作用是腸胃不適。
**結論：**因化療而引致免疫力減弱的病人，每天口服劑量為 75 mg 的 oseltamivir 一次，連服 8 星期，可以預防感染流感。藥物的副作用不多，屬可接受程度。

***Key words:***
*Acetamides;*
*Antiviral agents;*
*Influenza;*
*Neuraminidase/antagonists & inhibitors*

***關鍵詞：***
*乙酰胺；*
*抗病毒劑；*
*流感；*
*神經氨酶 / 拮抗劑及抑制劑*

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## Introduction

Influenza infection is more common among children with cancer.[1,2] Influenza, however, complicates the clinical treatment of children undergoing chemotherapy or bone marrow transplantation.[3] Because influenza is highly contagious, preventing nosocomial spread through close contact demands extra isolation

facilities during the influenza season. Initial clinical manifestations of influenza infection may be indistinguishable from febrile neutropenia, thereby leading to unnecessary treatment and hospitalisation. Vaccination against the influenza virus is generally recommended, although the efficacy of the vaccine is lower among children with cancer than among healthy children because of concurrent high-dose chemoradiotherapy.[1] Yearly influenza vaccinations for hospital staff and care-givers help prevent outbreaks in high-risk medical units. However, the probability of exposure to the influenza virus remains substantial in the overcrowded living environment of Hong Kong during seasonal epidemics.

Oseltamivir, a neuraminidase inhibitor, is effective in reducing the severity and duration of infection with influenza A and B viruses in immunocompetent individuals.[4-6] Effective prophylactic use of oseltamivir has been demonstrated in adult and adolescents older than 13 years, and several randomised controlled trials of influenza prevention in adults during the peak influenza season have yielded promising results.[7-9] The drug has also been well tolerated without dosage adjustment in individuals with multiple medical problems.[8] Nausea and vomiting were the main reported adverse effects in 10% of patients.[8] Furthermore, oseltamivir is active against influenza B infection, which is common locally.[10]

In this study, we investigated oseltamivir prophylaxis against influenza infection in a young, immunocompromised population in Hong Kong.

## Methods

### *Study design and participants*

This prospective open-label clinical study was performed in the Children's Cancer Centre at the Prince of Wales Hospital during the seasonal epidemic of influenza in 2001. The study was approved by the local ethics committee and each participant or parent provided written consent. Before the influenza season, patients older than 5 years who had received chemotherapy or bone marrow transplant in the past 1 year were recruited into the study. Patients were given oseltamivir prophylaxis (oral oseltamivir 75 mg/d for 8 weeks) at the onset of the influenza epidemic on 1 March 2001—that is, when our hospital laboratory detected 10 virologically confirmed cases for 2 consecutive weeks. The study period ended on 31 May 2001, making a total of 8 weeks because previous surveillance data showed that the seasonal epidemic of influenza A in Hong Kong usually lasts for 8 weeks early in the year.[10]

Patients who experienced an episode of influenza-like illness in the 2 weeks before the study were excluded, as were those who had previously received an influenza vaccination and those with significant renal impairment (creatinine clearance of <10 mL/min). We compared our findings with those from a retrospective review of laboratory-confirmed influenza infection between 1998 and 2000 in our centre.

**Table 1. Demographic characteristics of participants**

| Characteristic | No. (%)* |
|---|---|
| *Patients enrolled* | |
| Female | 17 (53) |
| Male | 15 (47) |
| *Age (years)* | |
| 5-9 | 8 (25) |
| 10-14 | 11 (34) |
| 15-19 | 12 (38) |
| 20-25 | 1 (3) |
| Median (range) | 14.3 (6.3-23.4) |
| *Diagnosis* | |
| Leukaemia | 19 (60) |
| Solid tumour | 10 (31) |
| Others† | 3 (9) |
| *Treatment* | |
| Chemotherapy‡ | 29 (91) |
| Bone marrow transplantation | 3 (9) |

* Or median (range) where indicated
† Langerhans' cell histiocytosis (n=1) and aplastic anaemia (n=2)
‡ 13 patients had completed treatment (10 within 3 months), seven received maintenance chemotherapy, and nine received intensive chemotherapy

### *Clinical and laboratory assessment*

Patient monitoring included weekly telephone interviews, a patient diary, and attendance of out-patient visits from the start of the study until 1 month after stopping oseltamivir treatment—12 weeks in total. Outcome measures included symptoms of influenza (fever, cough, runny nose, sore throat, headache, fatigue, and muscle ache), side-effects (nausea, vomiting, and diarrhoea), and compliance to oseltamivir. Laboratory monitoring included the influenza serological titre (an elevation of the influenza A or B haemagglutinin antibody titre of at least four times confirmed infection), complete blood picture, and renal and liver function at the time of recruitment, 1 month after prophylaxis, and at the end of the study in week 12. Participants with influenza symptoms submitted a nasal secretion sample or throat swab sample within 48 hours of the onset of symptoms for detection of influenza infection using a rapid virological assay.

## Results

### *Participant characteristics*

In the study period, 32 participants were recruited into study: 17 females and 15 males (Table 1). The median age was about 14 years. Sixty percent of the patients had leukaemia and approximately one third had a solid tumour. Twenty-nine patients belonged to the chemotherapy group and the remainder bone marrow transplant group. Because a fixed dose of oseltamivir of 75 mg was given, the highest daily dosage was 4 mg/kg in the youngest subject. Other subjects received a recommended prophylactic dose of oseltamivir, which varies according to the body weight of the subjects at different ages, as described in previous studies.[6]

### *Clinical response*

No laboratory-confirmed cases of influenza infection were present throughout the study period among the participants. Ten (31%) patients had a runny nose and cough in the first month of the study, and these symptoms became less frequent in the following month. Eleven (34%) patients had contracted an upper respiratory tract infection from another member of their household, and three (9%) patients had a sore throat, headache, and muscle ache during the study period. Eight requests were made for rapid influenza assay, which was performed for five patients with influenza symptoms: all tests were negative for virus, including influenza A and B. The other five patients did not return to the hospital for specimen collection. Three patients had vomiting related to oseltamivir initially, which resolved completely later during the study. All patients had satisfactory compliance to oseltamivir; missing doses were evident from the diaries of 20% of patients. On average, these participants missed a median of 2 days' drug therapy per week. No side-effects were detectable 1 month after completion of the study.

Nine patients received concurrent intensive chemotherapy with agents such as vincristine, cyclophosphamide, ifosfamide, carboplatin, etoposide, cytarabine, and high-dose methotrexate. Seven patients received maintenance chemotherapy with 6-mercaptopurine and methotrexate for acute lymphoblastic leukaemia. The three patients who received bone marrow transplants were receiving cyclosporin and prednisolone. Thirteen patients in the chemotherapy group had completed treatment, 10 of whom had done so within 3 months at the time of study. There was no abnormality due to oseltamivir administration in the complete blood picture and in renal and liver function test results at week 4 and at the end of the study.

### *Patient withdrawal*

Six patients withdrew from the study because of various reasons: one patient developed fever and upper respiratory tract infection without a defined infective source on the first day of the study; one had a sore throat with no defined infective organism, as well as vomiting, and stopped taking prophylaxis voluntarily by week 3; one stopped because of sickness from concurrent chemotherapy; one stopped because of epigastric discomfort due to prophylaxis; one withdrew because of admission to the bone marrow transplant unit after 1 month's prophylaxis; and one withdrew voluntarily after recruitment. Hence, two patients withdrew because of side-effects—vomiting and epigastric discomfort. In total, 16% (5/32) of the recruited subjects have gastro-intestinal side-effects.

### *Impact on hospitalisation*

Tables 2 and 3 summarise our retrospective review of the confirmed cases of influenza at our centre during previous influenza seasons in Hong Kong from 1998 to 2000. Four of 33 influenza cases were managed empirically as cases of febrile neutropenia. Twenty-five (76%) patients with documented influenza infection received systemic antibiotics. These findings contrasted with our result that there was no documented influenza infection in 2001.

**Table 2. Virologically documented influenza infection between 1998 and 2000 at the Children's Cancer Centre**

| Year | No. of cases | |
|---|---|---|
| | Influenza A | Influenza B |
| 1998 | 7 (H3N2 strain) | 2 |
| 1999 | 14 (H3N2 strain) | 3 |
| 2000 | 5 (H1N1 strain) | 2 |

**Table 3. Demographic characteristics of patients with influenza infection between 1998 and 2000 at the Children's Cancer Centre**

| Clinical feature | Influenza A | Influenza B |
|---|---|---|
| Sex ratio (M:F) | 12:14 | 3:4 |
| Median age (range) [years] | 7.0 (1.0-19.0) | 6.0 (0.4-10.0) |
| Diagnosis | | |
| Leukaemia | 14 | 3 |
| Solid tumour | 3 | 1 |
| Others* | 9 | 3 |
| Treatment | | |
| Chemotherapy† | 8 | 2 |
| Bone marrow transplantation | 6 | 3 |

* Haematological-related conditions during regular treatment (n=6) and haematological conditions after bone marrow transplantaion (n=6)
† Eight patients had completed treatment

## Discussion

Influenza infection affects the general health as well as treatment schedule of children with malignancy. Admitting influenza patients to an in-patient institution that cares for immunocompromised children is another important infection-control problem. Prevention of influenza infection is generally recommended in health care facilities. Treatment of influenza infection with oseltamivir is approved in Hong Kong in children aged 1 year or older. Oseltamivir is also approved for the prevention of influenza in adults and adolescents older than 13 years only. Previous studies of oseltamivir prophylaxis were mainly conducted among healthy adults and elderly persons.[7-9] The role of oseltamivir prophylaxis is an important issue among sick children. This study includes 59% of patients who were younger than 15 years, and provides clinical data on this younger group of patients. Our result agrees with the results of studies conducted among adults.[7-9] This observational study, however, is limited by its small sample size and by the absence of a control group for assessment of drug efficacy.

The severity of influenza appears to be similar in normal and immunocompromised children, although the clinical course could be longer.[11] Preventing influenza with

the use of influenza vaccine among children with cancer has been proposed.[12,13] Chisholm et al[12] reported that two thirds of patients made some protective response to the vaccine. To be protective, a timely vaccination—before the influenza season—is needed; administration of two doses 1 month apart. Generally speaking, children would be regarded as immunocompetent 3 months after completion of chemotherapy for immunisation against influenza. The main concern is the decreased immunogenicity in patients with cancer who are undergoing intensive chemotherapy and in recipients of bone marrow transplants, when compared with healthy individuals. Influenza vaccination of medical staff is mostly a personal decision among hospitals in Hong Kong. At the time of the study, vaccination against influenza A was not a standard practice. The mutation of the circulating strain of influenza virus, which may be substantially different from that occurring in previous years (ie antigenic drift), would result in vaccine failure.

Data from previous years (1998-2000) demonstrated the burden of influenza infection in our series of patients with cancer. The influenza epidemic in Hong Kong in 2001 was milder than in earlier years; the absence of influenza infection in our series of immunocompromised patients after oseltamivir prophylaxis would minimise the risk of nosocomial spread of influenza, as well as systemic antibiotic treatment and hospitalisation. Immunocompromised patients represent a substantial inpatient service load for paediatric units. Prophylaxis that targets a specific population during the influenza season appears to be beneficial as well as cost-effective.[14] Oral oseltamivir is active against both influenza A and B, with low incidence of side-effects and acceptable tolerability during long-term use (ie during 8 weeks). The most significant side-effect was nausea, which resolved gradually after the first week of the introduction of prophylaxis. The favourable drug compliance in our study suggests the practicability of oseltamivir administration during the influenza season.

In conclusion, the results of this pilot study should lead us to conduct a multicentre prospective randomised controlled trial with sufficient power to define the role of oseltamivir prophylaxis.

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