**Prevention and treatment of pandemic influenza in cancer patients**

Every year influenza A epidemics cause numerous deaths and millions of hospitalizations, but the most important effects are generally seen when new viral strains emerge from different species.

In April 2009, for the first time in 41 years, a novel type of influenza A virus acquired the capacity for human-to-human transmission and caused a pandemic. This virus, ‘pandemic 2009 influenza A (H1N1) virus’, was derived from swine A (H1N1), which was a recombination of avian, human, and several swine influenza viruses [1].

Overall, the 2009 pandemic flu has been considered mild. In fact, most cases caused by the 2009 H1N1 virus were acute and self-limited, with the highest attack rates reported, as expected, among children and young adults. The relative sparing of adults is presumably due to the exposure of aged persons to antigenetically related influenza viruses earlier in life, resulting in the development of cross-protective antibodies [2]. The Center for Disease Control and Prevention estimates that about 59 million people were infected from April 2009 to mid-February 2010 in the United States; of these, about 265 000 were hospitalized and 12 000 died with an overall case fatality rate of 0.0203% [3].

Approximately one-quarter to one-half of patients with 2009 H1N1 virus infections who were hospitalized or died had no reported coexisting medical comorbidities. An Australian cohort study including all intensive care units identified 722 patients with confirmed pandemic H1N1 influenza during the winter of 2009: mean age was 40 years, 31.7% had not known predisposing factors, 48.8% were admitted with a viral pneumonia or acute respiratory distress syndrome (ARDS) and 20.3% had a bacterial pneumonia; the overall case fatality rate was reported to be 16.9% [4].

Among people with immunosuppression due to human immunodeficiency virus infection, organ transplantation, chemotherapy or corticosteroid treatment, high rates of influenza infection and related complications are frequently observed. Despite prevailing concerns regarding the risk of influenza infection in patients with impaired immune defenses, the actual rate and severity of infection in this vulnerable and heterogeneous population is not well defined.

Patients with cancer, whether receiving chemotherapy or not, are considered to be at a higher risk for influenza infection and its complications such as bacterial coinfection, with more protracted viral replication and shedding, higher progression to lower airway disease, more frequent need for mechanical ventilation and death compared with healthy persons [5]. Prior retrospective series have shown that seasonal influenza among cancer patients is associated with a frequency of pneumonia of 21%–80% and a case fatality rate from 4% up to 33% [6–8]. A large study regarding >64 000 hospitalized cancer patients between 1998 and 2001 showed that flu-related deaths occurred in about 9% of patients. People with lung carcinoma or hematological malignancies tended to have a more severe course and higher case fatality rate of 9% and 12%, respectively [9].

The more severe course in cancer patients can be due to several factors such as neutropenia as complication of chemotherapy, impaired immune function associated with disease or post-treatment impaired immune function (up to 12 months post chemotherapy), loss of immunity and concomitant use of corticosteroids [10].

However, to date, no comprehensive data have described whether clinical manifestations during the 2009 H1N1 influenza pandemic were different from those reported with seasonal epidemic influenza.

Among cancer patients, however, a few small studies have been published, some reporting severe diseases [11], other mild symptoms and a favorable clinical course [12].

Among these, the paper by Hajjar et al. [13] describes clinical and pathological findings of eight severe cases of laboratory-confirmed influenza A (H1N1); all presented an ARDS and five died. These were observed at an oncological intensive care unit in San Paulo, Brazil during the 2009 Southern Hemisphere H1N1 pandemics.

As the authors did not indicate the data regarding the incidence of flu cases in the general populations, in the oncology patients as well as the number of hospitalized cases in Brazil at that time, it is not possible to correctly estimate the prevalence and case-fatality rate.

Nonetheless, the description of these eight cases of severe influenza again highlights the importance of prevention and management of seasonal and pandemic flu in cancer patients.

The most important management step includes prevention by vaccination. Influenza vaccines are well tolerated in high-risk patients, and all adverse reactions are generally mild and similar to those observed in healthy people. Despite abnormalities in the immune function, there is evidence that patients with cancer, irrespective of chemotherapy regimen or timing, are able to respond to influenza vaccination in 70%–80% of cases [14, 15]. Yet, in the setting of hematological malignancies, patients with lymphoma and myeloma do not respond as well as those with solid cancers [14, 16]. Therefore, clinicians should ensure that patients with cancer are...
adequately immunized by adding a second dose of vaccine if indicated. Moreover, influenza vaccinations do not always ensure full protection. It is thus important that close contacts, in particular children, are appropriately immunized to prevent the spread of influenza within the family setting. Nevertheless, until now, influenza vaccinations have been underutilized (<45%) among family members of cancer patients [17]. Finally, all health care workers need to be vaccinated to protect vulnerable patients [18], in contrast to their currently low vaccination rates [19].

Another aspect to consider is bacterial complications. In the case records of Hajjar et al. [13], 87% of patients suffered from bacterial complications and 50% developed a *Streptococcus pneumoniae* pneumonia.

The results of a study reported in Morbidity and Mortality Weekly Report confirmed that bacterial coinfection with *Streptococcus pneumoniae* may have contributed to deaths during the recent H1N1 pandemic [20].

No evidence exists on the prophylactic use of antibiotics in immunocompromised patients. So, during influenza outbreaks, vaccines against *Streptococcus pneumoniae* may be useful in preventing secondary pneumococcal infections and in reducing illnesses and deaths.

Vaccination with the polysaccharide pneumococcal vaccine (23 valent pneumococcal vaccine) induced satisfactory serological response in cancer patients and controls [14]; however, responses in controls were generally stronger. On the other hand, conflicting results have also been published in hematological patients [21, 22]. In any case, the Centers for Disease Control and Prevention recommend that all people aged 65 years and older, as well as people with high-risk conditions, receive the 23-valent pneumococcal polysaccharide vaccine with a single revaccination within 5 years after initial dose.

Another management step to consider is the use of antiviral therapy during flu epidemics.

Due to resistance against the M2 inhibitors in 2009 H1N1 pandemic strains, amantadine and rimantadine should not be used as a single agent to treat or prevent influenza [23]. At present, two neuraminidase inhibitors (zanamivir and oseltamivir) are licensed for the treatment of influenza A. Oseltamivir is commercially available for oral administration and zanamivir is available as an inhalation powder. Currently, the circulating 2009 H1N1 virus is susceptible to the two neuraminidase inhibitors. Standard doses of oseltamivir or inhaled zanamivir can be used for the treatment of mild diseases. Intravenous administration of zanamivir is also possible and may be preferable for critically ill patients and for those with altered mental status or absorption problems. The neuraminidase inhibitors should be used when symptoms have occurred within the previous 48 h and best within 12 h [24]. In otherwise healthy adults, the treatment started within 36–48 h after the onset of illness, led to a decrease of 1–2 days of clinical courses and to a lower frequency of secondary complications than untreated patients. Moreover, therapy starting within the first 12 h after the onset of fever resulted in a shortened course by more than 3 days compared with 48 h.

Therefore, it is vitally important that family doctors are knowledgeable of the fact that antivirals, to be most effective, must be administered within the 12-h window when the flu is suspected. When it is not possible to respect the 12-h window, it is recommended that antiviral therapy be administered even past the 48-h window [25]. All the eight patients described by Hajjar et al. [13] received oseltamivir during hospitalization, seven of these within 24 h of admission. However, it was not stated how much time passed from symptoms onset to hospital admission.

In a report on 45 patients with hematological neoplasms and/or bone marrow transplants where deaths were not reported, the antiviral therapy was initiated on average 3.2 days after symptoms and in more than 50% of cases, within 2 days [12].

The risk of developing resistance to antivirals is increased in immunocompromised patients with prolonged viral shedding [26] especially in those who have received high doses of steroids (>2 mg/kg). In fact, most oseltamivir-resistant 2009 H1N1 viruses have been isolated from patients with immunosuppression who had received prolonged courses of treatment [27].

In hospitalized patients, intravenous zanamivir is, if available, the best option in suspected or confirmed oseltamivir-resistant H1N1 virus infection.

Some have suggested a more aggressive approach using high-dose oral oseltamivir (150 mg b.i.d.) or even triple combination therapy with oseltamivir, amantadine, and ribavirin [28]. Randomized trials are ongoing in both immunosuppressed and immunocompetent patients with severe infection to test these hypotheses. A novel neuraminidase inhibitor, peramivir, is presently in advanced clinical development, while other compounds targeting viral polymerase and hemaagglutinin are under investigation.

As regards the use of corticosteroids, in the patients described by Hajjar et al. [13], they were administered to all patients with ARDS. The role of corticosteroids remains controversial and no data from randomized trials are available yet. High-dose corticosteroids, as already stated here, prolong viral shedding, but there also seems to be an antiinflammatory effect with moderate doses (up to 1 mg/kg of prednisone) that may be beneficial in patients with acute lung injury and acute respiratory distress syndrome [23]. In Hajjar’s study, due to the seriousness and the rapid nature of hypoxemia progression, five patients required mechanical ventilation within 48 h, while the remaining three required noninvasive ventilation; none of the eight underwent extracorporeal membrane oxygenation (ECMO). In patients with a high Murray score and/or a pH < 7.2, an ECMO can be advised. In a study designed to determine the safety, efficacy, and cost-effectiveness of ECMO compared with conventional ventilation in the treatment of adults with severe acute respiratory failure, a Murray score > 3.0 and pH < 7.2, the 6-month survival was 57/90 (63%) for patients allocated to ECMO versus 41/87 (47%) for patients allocated to conventional treatment [29].

Worldwide, the incidence of cancer is on the rise but, due to the early diagnosis programs that have educated patients on the value of screening as well as the better results obtained by cancer therapies, mortality is decreasing. A correct approach to
the prevention and treatment of influenza A could further reduce cancer mortality.

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references


