Bone Marrow Transplantation (2012) 47, 236–242
© 2012 Macmillan Publishers Limited All rights reserved 0268-3369/12
www.nature.com/bmt

ORIGINAL ARTICLE

Clinical features and outcome of 2009-influenza A (H1N1) after allogeneic hematopoietic SCT

B Mohty[1,5], Y Thomas[2,3], M Vukicevic[1,5], M Nagy[1,5], E Levrat[1,5], M Bernimoulin[1,5], L Kaiser[2,3,4], E Roosnek[1,5], J Passweg[1,5] and Y Chalandon[1,5]

[1]*Division of Hematology, University Hospital, Geneva, Switzerland;* [2]*Laboratory of Virology, University Hospital, Geneva, Switzerland;* [3]*Swiss National Centre for Influenza, University Hospital, Geneva, Switzerland;* [4]*Division of Infectious Diseases, University Hospital, Geneva, Switzerland and* [5]*Division of Hematology, Geneva University Hospital Blood and Marrow Transplant Program, Geneva, Switzerland*

The impact of the 2009 H1N1-Influenza A (H1N1) pandemic in allogeneic hematopoietic SCT recipients (allo-HSCT) is not yet well defined. Between May 2009 and May 2010, all allo-HSCTs who presented with respiratory symptoms were screened for the presence of the H1N1 virus. Oseltamivir resistance was assessed and chart reviews were performed for all cases. In all, 51 of 248 (20%) allo-HSCT recipients followed at our outpatient clinic were screened. We identified 10 patients with H1N1 infection. Close contact with children was the most commonly suspected mode of transmission. Upper and lower respiratory tract infections were present in eight and five patients, respectively. Lymphopenia (<1 G/L) was the most frequent biological abnormality. High immunosuppression was responsible for severe infection requiring mechanical ventilation associated with prolonged viral shedding in three patients who had significant comorbidities and GvHD. Two of them developed an oseltamivir-resistant strain and both patients died subsequently despite intensive therapy, resulting in a case fatality rate of 20%. In conclusion, although most allo-HSCTs had mild symptoms from H1N1 infection, severe immunosuppression and emergence of oseltamivir resistance were likely responsible for a substantial morbidity, further supporting the need for vaccination and monitoring of close contacts, especially children.
Bone Marrow Transplantation (2012) **47,** 236–242; doi:10.1038/bmt.2011.57; published online 21 March 2011
Keywords: influenza A H1N1; infection; allogeneic hematopoietic SCT; swine flu; oseltamivir

Introduction

Respiratory virus infections (RVIs) are common after allogeneic hematopoietic SCT (allo-HSCT),[1–3] and influenza may account for up to 30% of all RVIs.[4,5] Influenza pneumonia-related mortality can reach 25%, particularly in those patients with chronic GvHD.[1,2] Recently, a new type of influenza A (H1N1) virus, characterized by antigenically distant surface Ags compared with human viruses,[6] has been involved in a worldwide pandemic outbreak that began in Mexico in March 2009.[7] On 11 June 2009, WHO (World Health Organization) declared it as the first pandemic of the twenty-first century and >17 700 deaths were reported as of March 2010.[8]

Although several large studies have characterized 2009-H1N1 as a novel infection in the general population,[9–11] the true extent of 2009-H1N1 infection is not yet well defined in allo-HSCT recipients. To better define H1N1 infection in this highly immunocompromised patient population, we reviewed our recent experience at the Geneva University Hospital. This observational study describes the incidence, clinical features and outcome of H1N1 infection among allo-HSCT recipients seen in our department during the pandemic.

Patients and methods

Study population

The Hematology Division at the Geneva University Hospital (Geneva, Switzerland) is a referral center for adults receiving allo-HSCT (population 1.8 million) and patients are closely followed up for many years post transplant. Between May 2009 and May 2010, 248 adult allo-HSCT recipients were followed up. Overall, 19 (8%) patients were within 6 months post transplant and 33 (13%) within 1 year. A total of 46 had an active GvHD (acute grade ⩾2 or chronic extensive). According to predefined institutional guidelines, all allo-HSCT recipients who presented with respiratory symptoms (such as sore throat, cough, rhinorrhea, nasal congestion or dyspnea) with or without fever were investigated for the presence of

Correspondence: Dr B Mohty, Service d'Hématologie, Hopital Universitaire de Genève, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva-14, Switzerland.
E-mail: bilal.mohty@hcuge.ch
Received 18 October 2010; revised 28 January 2011; accepted 30 January 2011; published online 21 March 2011

H1N1 and other community-acquired respiratory viruses (such as adenovirus, metapneumovirus, seasonal influenza A and B, parainfluenza, picornavirus, respiratory syncytial virus). All specimens for microbiological confirmation were taken from combined nasopharyngeal and throat swabs at the time of initial screening. In addition, bronchoalveolar lavages were performed in patients requiring mechanical ventilation. Serial specimens were collected at the discretion of the treating physician. All patients gave their informed consent and the study was approved by the Institutional Review Board.

Virological methods

All analyses were performed according to standardized protocols[12] running in our virology laboratory, which is a WHO referral center for influenza. In brief, H1N1 virus was detected in samples using a real-time reverse transcription-PCR assay in accordance with the protocol from the US Centres for Disease Control and Prevention.[13] Whenever possible, H1N1 virus isolates were analyzed to determine the presence of the H275Y NA (neuraminidase) mutation using a nucleic acid sequencing assay.

Data collection and analysis

Chart review was performed for all patients who received a PCR-documented diagnosis of H1N1 infection during the study period. Transplant-related characteristics, immunosuppressive medication regimen, H1N1 infection-related features, copathogens and outcomes were assessed. Death due to H1N1 infection was defined as patients dying of respiratory failure after H1N1 infection or its complications. Respiratory tract infections were classified according to Ljungman *et al.*[2]: upper respiratory tract infection (URTI) was defined as detection of H1N1 from upper respiratory secretions together with symptoms from the upper respiratory tract. Lower respiratory tract infection (LRTI) was defined as hypoxia, pulmonary infiltrates or new abnormal chest auscultation findings, together with identification of the H1N1 virus in bronchoalveolar lavage or upper respiratory secretions. Hospital-acquired infection was defined as symptom onset >7 days after admission. The immunodeficiency status was graded as published elsewhere,[4] either as severe (SID) or MID (moderate). Lymphopenia was defined by lymphocyte counts <1 G/L. Data were analyzed with descriptive statistics and proportions were compared with a Fisher's exact two-tailed test using SPSS Statistics 13.0 software (SPSS, Chicago, IL, USA).

Results

Baseline characteristics

During the study period, 51 (20%) of 248 allo-HSCT recipients followed up at our outpatient clinic were screened. We identified 10 patients with H1N1 infection between 18 August 2009 and 29 December 2009, giving a frequency of 20% (10/51) (95% confidence interval, 9–30%) based on the number of patients screened or 4% (10/248) (95% confidence interval, 2–7%) based on the total number of patients followed up. Close contact with children $\leqslant 12$ years or adolescents in the previous 7 days was the most frequently suspected mode of transmission (50% of cases), whereas one case was considered nosocomial (UPN 10).

The median age of H1N1-infected patients was 50.5 (range, 23–62) years, and the median time since transplant was 15 (range, 6–109) months. Eight donors were HLA-identical siblings and all patients, but one (UPN 9), received PBSCs. Half of the patients received a so-called reduced-intensity conditioning regimen. At the time of infection, all patients were in CR for their underlying disease. Six patients had received a partial T cell-depleted transplant and four an unmanipulated graft. Most of the patients were heavily pre-treated before allo-HSCT, and one patient (UPN 4) was on lenalidomide as post-transplant maintenance therapy for multiple myeloma. Four patients had a Karnofsky score $\leqslant 80\%$ and presented various comorbid conditions. With respect to their immunodeficiency status, five patients were classified as having SID and five as MID. Five patients had GvHD (one acute grade 4 and four chronic extensive) and were receiving immunosuppressive drugs and corticosteroids at a mean dose of 46 mg prednisone equivalent daily (range, 30–80). Immunological reconstitution was incomplete in most of the patients as assessed by mean CD3, CD4 and CD8 lymphocyte count measured within few weeks before diagnosis: 0.7 G/L (range, 0.037–1.4), 0.26 G/L (0.011–0.74) and 0.43 G/L (0.02–1.07), respectively (UPN 9 had large granular lymphoproliferation (LGL) and was not included). All patients, except UPN 4, had been immunized against seasonal influenza and three patients had been vaccinated against H1N1 within a median of 19 days (range, 10–24) before symptom onset (UPN 2 and 3 were vaccinated 1 and 7 days, respectively, after the onset of symptoms) (Table 1).

Clinical features

All patients presented with fever and cough. Eight patients presented an URTI and five an LRTI (three patients had concomitant URTI and LRTI). The median duration of symptoms before virological diagnosis was 2.5 (range, 1–15) days. Commonly reported clinical manifestations were runny nose ($n=8$, 80%), myalgia ($n=6$, 60%) and dyspnea ($n=6$, 60%). Less common signs included sore throat (40%), gastrointestinal symptoms (20%), rarely sweating and fatigue. Abnormal physical examination findings were wheezes or rales on pulmonary auscultation (UPN 4, 5, 7, 8 and 10) and pharyngeal erythema (40% of patients). Chest X-rays were performed in seven patients. Alveolar or interstitial infiltrates were detected in two patients at presentation. Complete blood counts and serum chemistries were drawn in all patients at diagnosis, and revealed normal neutrophil counts in all cases and lymphopenia (<1 /L) in six patients. Associated respiratory pathogens were present at diagnosis or developed during the disease course in six patients as shown in Table 1.

Serial virological testing was performed in three patients who required mechanical ventilation and in one patient who had persistent respiratory signs for 23 days, despite having received oseltamivir treatment (UPN 4, 5, 6 and 7).

Table 1 Baseline and clinical features of H1N1-infected patients at presentation

Patients	*Sex/age malignancy*	*Donor type Cond Reg*	*Karnofsky score/chronic conditions*	*GvHD IS/Cs*	*Baseline CD3/CD4/CD8 (μL)*	*Sampling site/H1N1 immunization-to-symptoms onset interval (D)*	*Time since transplant (M)/symptom duration before diagnosis (D)*	*Rhinorrhea/sore throat/dyspnea/ myalgia*	*URTI/ LRTI*	*Associated respiratory copathogens*	*LOS (D)/ mechanical ventilation duration (D)*	*Oseltamivir/ zanamivir duration (D)*	*H275Y mutation/ viral shedding (D)*	*Outcome*
UPN 1	F/23 HL	Sib RIC/UM	100/None	None	1423/310/1076	NPS/−	8/4	Y/N/N/Y	Y/N	None	5/−	5/−	NA	Full Recovery
UPN 2	M/26 ALL	MUD MAC/T-dep	100/None	None	399/164/246	NPS/+1	6/1	Y/N/N/Y	Y/N	RSV Adenovirus	—	5/−	N/NA	Full Recovery
UPN 3	F/32 CML	Sib MAC/T-dep	100/None	None	1039/744/264	NPS/+7	109/2	Y/Y/N/Y	Y/N	None	—	5/−	N/NA	Full Recovery
UPN 4	M/49 MM	MUD MAC/UM	70 /None	Extensive Y/30	37/11/22	NPS+BAL/−	12/4	Y/N/Y/Y	Y/Y	Klebsiella Oxytoca	50/43	15/15	Y/12	Expired D+54
UPN 5	F/62 AML	Sib RIC/T-dep	80/Diabetes	Extensive Y/80	718/352/381	NPS/−24[a]	8/15	N/N/Y/N	N/Y	None	20/6	13/8	N/19	Full Recovery
UPN 6	M/57 NHL	Sib RIC/UM	100/Esophageal cancer	None	NA	NPS/−19	86/3	Y/Y/Y/Y	Y/N	Picornavirus	—	6/−	N/23	Full Recovery
UPN 7	M/40 AML	Sib MAC/T-dep	70/Diabetes, Renal, pulmonary	Extensive Y/30	861/121/691	NPS+BAL/−	52/1	Y/N/Y/N	Y/Y	CMV EBV	90/70	20/20	Y/21	Expired D+94
UPN 8	M/56 ALL Phi+	Sib RIC/UM	80/pulmonary	Extensive Y/30	1005/376/646	NPS/−10[a]	22/4	Y/Y/Y/N	Y/Y	None	—	5/−	N/NA	Full Recovery
UPN 9	M/52 CMML	Sib MAC/T-dep	100/LGL, splenectomized	None	6630/580/5967	NPS/−	18/2	Y/Y/Y/N	Y/N	RSV	—	7/−	NA	Full Recovery
UPN 10	M/53 AML	Sib RIC/T-dep	70/Diabetes, renal, pulmonary	Acute Y/60	141/16/115	NPS/−	8/2	N/N/N/Y	N/Y	Picornavirus	15/−	15/15	NA	Full Recovery

Abbreviations: ALL Phi+ = ALL Ph positive; BAL = bronchoalveolar lavage; CMML = chronic myelo-monocytic leukemia; Cond Reg = conditioning regimen; D = days; F = female; HL = Hodgkin's lymphoma; IS/C = immunosuppressive drug/corticosteroid (prednisone equivalent mg/day); LOS = length of stay; LRTI = lower respiratory tract infection; M = male; M = months; MAC = myeloablative conditioning; MM = multiple myeloma; MUD = matched unrelated donor; N = no; NA = not available; NHL = non-Hodgkin's lymphoma; NPS = nasopharyngeal swab; RIC = reduced-intensity conditioning; RSV = respiratory syncytial virus; Sib = identical sibling; T-dep = T-cell depletion; URTI = upper respiratory tract infection; UM = unmanipulated graft; Y = Yes.
[a]UPN 5 and 8 had 2 vaccine doses (only time since first dose is specified).

The median period of symptomatic viral shedding in those four patients was 22 (range, 19–81) days. Sequencing of the NA gene was performed on seven patients (not possible on the three remaining isolates mainly because of low viral loads). An oseltamivir-resistant strain appeared 7 and 6 days after initiation of oseltamivir in two patients (UPN 4 and 7), respectively, who later expired despite mechanical ventilation and i.v. zanamivir (Table 1).

Treatment and outcome

All patients were treated with oseltamivir at a dose of 75 mg two times a day. Treatment was started within a median of 3 (range, 0–8) days from symptom onset for a median duration of 6.5 (range, 5–20) days. Eight patients (80%) received broad spectrum antibiotics in addition to antiviral treatment.

Five patients of whom four (UPN 4, 5, 7 and 10) had significant comorbidities and active GvHD were hospitalized for a median of 20 (range, 5–90) days. Of the latter, three patients (UPN 4, 5 and 7) required mechanical ventilation for a median time of 43 (range, 6–70) days. Zanamivir was administered i.v. for these four patients (UPN 4, 5, 7 and 10) in addition to oseltamivir for a median duration of 15 (range, 8–20) days. Patients UPN 4 and 7 died of respiratory failure within 54 and 94 days of symptom onset, respectively, resulting in a case fatality rate of 20%. All patients tolerated oseltamivir and zanamivir, and none discontinued treatment because of adverse effects (Table 1).

Discussion

Several studies have described H1N1 infection in allo-HSCT (Table 2),[14–19] but its clinical spectrum is still being defined. Here, we report the impact of the H1N1 epidemic in a population of allo-HSCT recipients who were followed up in the long term in a clinic using standardized guidelines.[20]

H1N1 incidence peaked in November 2009, similar to the general Swiss population.[21] Overall, 4% of our total patient population had a proven H1N1 infection. When considering only those screened for a respiratory illness, ~20% were infected. Redelman-Sidi *et al*.[17] found that 22% of their screened patients were positive for H1N1 during the New York city outbreak. In fact, the denominator of H1N1-infected patients is difficult to establish.[22,23] Whereas a frequency of 20% is most likely too high, 4% is certainly an underestimate if patients with mild illness may not have sought medical care and therefore may not have been diagnosed.

Nosocomial infection rates may range from 11 to 19% in allo-HSCTs.[15,18] Close contact with children was the most common presumed mode of transmission in our series, which is not surprising as this has been previously reported as the most significant risk factor of developing RVIs.[1] Indeed, approximately one child in every three was infected with H1N1 in England,[24] whereas in the United States, the rate of secondary outbreaks in households was 13% with children at increased risk for infection by a factor of 4.[25] Similarly, Kumar *et al*.[26] reported that pediatric solid organ transplant recipients were substantially more likely to have fever, rhinorrhoea, sore throat and headache at presentation than were adult patients. Notably in this study, 31% of patients had ill household contacts.[26] Taken together, these observations should alert physicians involved in the care of HSCT patients about the high risk of viral transmission through close contact with children, underlining the importance of education and vaccination of patients and their family households. Close contact with symptomatic children should be avoided whenever possible during periods of RVI epidemics.

Fever and cough were the most common symptoms observed. H1N1-related LRTI developed in 50%, of patients, which is in the range of 31–68% of almost all other series.[14–16,18,19,26,27] The 30% mechanical ventilation and 20% case fatality rates observed in our study correspond to those found in other small series,[16,18,19,27–29] but are higher than the frequencies reported in larger series (4.0–13.5% and 3.0–7.3%, respectively).[14,22,26] Although this may reflect a reporting bias if patients with more severe illness were more likely to come to medical attention, we believe that allo-HSCT recipients are at higher risk for severe complications, notably in case of development of H1N1 oseltamivir-resistant strains[15,19] or concomitant respiratory pathogens.[16,19,26,27,30–32]

The average duration of H1N1 viral shedding in the general population was ~6 days.[9–11] Redelman-Sidi *et al*.[17] failed to demonstrate a significant prolonged viral shedding in HSCT patients. However, we along with others[18,19,30] have found evidence of prolonged viral shedding in severely immunosuppressed allo-HSCTs and in patients with oseltamivir resistance. Although it remains uncertain whether these are representative of the entire population of allo-HSCTs, protracted infections are expected to occur in this patient population.

Half of our patients were classified as SID. Interestingly, LRTI, prolonged viral shedding, hospitalization, longer antiviral treatment, ventilator requirement and H1N1 resistance were documented only in SID patients. Lymphopenia, which has been previously reported as a risk factor for LRTI, both for community-acquired RVI[1–4,33] and for H1N1 influenza[9,14–18,26] was observed in six patients at the time of diagnosis. Chronic GvHD and its corollary of long-term immunosuppression has also been associated with the risk of developing RVI and LRTI.[1] Recently, Taplitz *et al*.[18] showed that the use of >20 mg of prednisone equivalent daily was significantly associated with the development of LRTI and with 30-day mortality. In our study, 11% (5/46) of patients with active GvHD contracted an H1N1 infection as compared with 2.5% (5/202) of patients without GvHD ($P<0.03$). Furthermore, 5 of 33 (15%) patients within the first year post transplant had an H1N1 infection, whereas only 5 of 215 (2.3%) patients after the first year were infected ($P<0.005$). Taken together, these observations suggest that highly immunocompromised allo-HSCT recipients are at risk for severe complications from influenza and deserve close monitoring.

There have been conflicting data as to the efficacy of influenza immunization.[34–36] In our study, three patients had H1N1 infection despite having been vaccinated. In

Table 2 Baseline and clinical features of H1N1-infected patients in the literature

Author country	*No. of patients (% of allo)*	*Donor type/ Cond Reg*	*Median time since transplant (range)*	*Median age (y) (range)*	*GvHD (%) IS or Cs*	*Vaccine*	*Rhinorrhea/ Sore throat/ dyspnea/ myalgia*	*Fever/ cough/GI symptoms/ CNS symptoms*	*URTI LRTI (%)*	*Antiviral treatment*	*Hospital/ mechanical ventilation*	*H275Y mutation/ PVS*	*Outcome/ mortality rate (%)*	*Comments*
This study	10 (100%)	2 MUD, 8 Sib/5 MAC, 5 RIC	15 M (6–109)	50.5 (23–62)	5 (50%) 5	H1N1: 5 Seasonal: 9	8/4/6/6	10/10/2/0	8 5 (50%)	O: 10 Z: 4	5 3	3 3	Two deaths (20%)	
Taplitz *et al.*,[18] USA	27 (80%)[a]	12 MUD, 10 Sib/NA	379 D (5–2895)	46 (20–67)	17 (63%) 12	H1N1: 3 Seasonal: NA	12/10/16/14	25/26/ 7/2	13 14 (52%)	O: 25 Z: 5, P: 2	NA 7	1[b] NA	Nine deaths (33%)	19% Nosocomial
Redelman-Sidi *et al.*,[17] USA	21 (57%)	NA/19 MAC, 2 RIC	44 M (5 M to 15 Y)	36 (5–72)	4 (19%) NA	NA	NA	NA	9[c] 6 (40%)	O: 19 Z: 1	8 0	0 0	Full recovery	None nosocomial and none <5 M
Tramontana *et al.*,[19] Australia	16 (50%)[d]	7 Sib, 1 MUD/NA	3 allo <100 D 8 auto >2 Y	56.5 (30–72)	5 (31%) 12	H1N1: 0 Seasonal: NA	NA	NA	16 11 (70%)	O:15 Z: 2	16 9	3 1	Six deaths (37,5 %)	Three nosocomial and four with copathogens (aspergilus, CMV, Staph, HSV, HHV6, EBV)
George *et al.*,[16] Australia	13 (92%)	3 MUD, 8 Sib, 1 Haplo/2 MAC, 10 RIC, 1 auto	425 D (2–1541)	53.6 (37–63)	7 (54%) 5	H1N1: NA Seasonal: 9	NA/13/5/NA	13/11/ NA/NA	13 5 (40%)	O: 13 Z: 1	5 4	NA	Four deaths (30%)	Five with copathogens and four had H1N1 before HSCT
Ditschkowski *et al.*,[28] Germany	10 (NA)	NA	10 M	NA	5 (50%) 10	NA	NA	NA	NA	O: 10	7 3	NA	Two deaths (20%)	
Garland *et al.*,[29] UK	9 (44%)	3 MUD, 1 Sib/1 MAC, 3 RIC, 5auto	4 M (8 D to 6 Y)	62 (35–75)	NA 3	H1N1: 1 Seasonal: NA	NA	NA	NA	O: 9 Z: 3	9 3	NA	Three deaths (20%)	No copathogen
Patel *et al.*,[27] USA	5 (80%)	1 MUD, 3 Sib/3 MAC, 1 RIC, 1 auto	12 M (3–19)	51 (23–56)	4 (80%) 3	H1N1: 0 Seasonal: NA	NA	NA	5 3 (60%)	O: 5 P: 1	1 1	NA 1	One death (20%)	One with parainfluenza, aspergillosis and rhizopus
Lalayanni *et al.*,[40] Greece	3 (100%)	NA	18 M (15 M to 5 Y)	40 (35–54)	1 NA	H1N1: 1 Seasonal: NA	NA	NA	3 2 (66%)	O: 3 Z: 1	3 2	NA 1	Two deaths (66%)	
CDC,[30] USA	2 (NA)	NA	24 D	10 and 40	NA	NA	1/NA/NA/NA	2/2/ NA/NA	2 NA	O: 2, Z:1 Rib: 1, R:1	2 1	2 2	Full recovery	One with pneumocystis and staph
Kharfan-Dabaja *et al.*,[31] USA	2 (100%)	2 MUD/ 2RIC	191 D (171–211)	46.5 (41–52)	2 2	NA	NA/1/1/2	2/2/ 1/NA	2 1	O: 2	2 1	NA 0	One death	One with Aspergillus
Bastos *et al.*,[41] Brazil	1 (100%)	CB/RIC	3 D	12	0 1	NA	1/NA/1/NA	1/1/ NA/NA	1 1	O and Z	1 1	NA 1	Full recovery	No copathogen
Rozovski *et al.*,[32] Israel	1 (100%)	1 Sib/RIC	118 D	62	1 1	NA	NA/NA/1/1	1/1/NA/1	1 1	O	1 1	NA	Death	Sepsis to Klebsiella pneumonia
Frangoul *et al.*,[42] USA	1 (100%)	CB/MAC	7 Y	9	1 1	NA	NA/NA/1/NA	No/NA/ 1 /NA	0 0	O	1 1	NA	Death	Infection mimicking gut GVHD
Campbell *et al.*,[43] USA	1 (0%)	1 Auto	2 D	40	0 0	NA	NA/NA/No/NA	1/1/ 1/NA	1 1	O, A, Rib, P	1 1	NA 1	Death	Extrapulmonary H1N1 RNA

Abbreviations: ARDS = acute respiratory distress syndrome; ATG = anti-thymocyte globulin; Auto = autograft; CB = cord blood; Cond Reg = conditioning regimen; CNS = central nervous system; Cy = cyclophosphamid; D = days; Fluda = fludarabine; GI = gastrointestinal; Haplo = haplo-identical; HHV 6 = human herpes virus 6; HSCT = hematopoietic SCT; IS/C = immunosuppressive drug/ corticosteroid; LOS = length of stay; LRTI = lower respiratory tract infection; M = months; MAC = myeloablative conditioning; MMF = mycophenolate mofetil; MUD = matched unrelated donor; NA = not available; O = oseltamivir; P = peramivir; PVS = prolonged viral shedding; Rib = ribavirine; RIC = reduced-intensity conditioning; R = rimantadine; Ritux = rituximab; Sib = identical sibling; staph = staphylococcus; T-dep = T-cell depletion; URTI = upper respiratory tract infection; Y = year; y = years; Z = zanamivir.

Data are number of patients unless otherwise specified. Only data on HSCT patients (allo and auto) provided in the articles are reported in the table.

[a]Only 17 of 27 patients had a PCR-documented H1N1 infection (probable cases were defined as patients who had a positive test for influenza A in the context of widespread community H1N1 activity, without PCR confirmation).

[b]Only one patient has been tested for H275Y mutation in this study.

[c]Information on URTI or LRTI was lacking for six patients.

[d]Some patients reported in this study might be common to those reported in the study by George *et al.*[16]

healthy adults, a single dose of H1N1 vaccine was highly immunogenic.[37] Ljungman[22] failed to demonstrate any protective effect from either the seasonal or the H1N1 vaccines in HSCT patients. In contrast, in the Spanish series,[14] only one of the vaccinated patients against seasonal influenza was diagnosed with pneumonia compared with 41% who were not vaccinated ($P = 0.005$). Although it is not possible to draw definitive conclusions as to the protective effect of H1N1 vaccine in HSCT patients, preliminary results from a large study (http://ClinicalTrials.gov, ID: NCT01022905) conducted in our hospital suggest that severely immunocompromised allo-HSCT patients do not respond to H1N1 vaccination. Therefore, influenza vaccination of family members and close contacts, especially children, is strongly recommended to limit the risk of influenza exposure in HSCT recipients. Additional strategies such as post-exposure oseltamivir prophylaxis for high-risk patients may be warranted.[19,26,38]

Our study has several limitations. The number of H1N1-confirmed cases was low, making the reliable estimation of clinical outcomes, such as mechanical ventilation or mortality rates, difficult. Furthermore, only a limited number of allo-HSCT recipients within 6 months post transplant (19 patients) were included, precluding us to precisely analyze the impact of H1N1 infection in the early post-transplant period.

In conclusion, although most allo-HSCT recipients had mild symptoms from H1N1 infection as does the general population,[23] high immunosuppression and emergence of oseltamivir-resistant strains were responsible for a substantial number of deaths in the allo-HSCT setting. Complications included higher rates of LRTI, prolonged viral shedding and respiratory failure. Our study strongly supports the need for vaccination and monitoring of family households, especially children.[39]

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We thank our nurse staff of the transplant unit '5FL' and the outpatient clinic 'polyclinique d'oncologie' for excellent care given to patients.

References

1 Martino R, Porras RP, Rabella N, Williams JV, Ramila E, Margall N *et al*. Prospective study of the incidence, clinical features, and outcome of symptomatic upper and lower respiratory tract infections by respiratory viruses in adult recipients of hematopoietic stem cell transplants for hematologic malignancies. *Biol Blood Marrow Transplant* 2005; **11**: 781–796.
2 Ljungman P, Ward KN, Crooks BN, Parker A, Martino R, Shaw PJ *et al*. Respiratory virus infections after stem cell transplantation: a prospective study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant* 2001; **28**: 479–484.
3 Nichols WG, Guthrie KA, Corey L, Boeckh M. Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality, and the effect of antiviral therapy. *Clin Infect Dis* 2004; **39**: 1300–1306.
4 Khanna N, Steffen I, Studt JD, Schreiber A, Lehmann T, Weisser M *et al*. Outcome of influenza infections in outpatients after allogeneic hematopoietic stem cell transplantation. *Transpl Infect Dis* 2009; **11**: 100–105.
5 Martino R, Ramila E, Rabella N, Munoz JM, Peyret M, Portos JM *et al*. Respiratory virus infections in adults with hematologic malignancies: a prospective study. *Clin Infect Dis* 2003; **36**: 1–8.
6 Garten RJ, Davis CT, Russell CA, Shu B, Lindstrom S, Balish A *et al*. Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. *Science* 2009; **325**: 197–201.
7 CDC. Outbreak of swine-origin influenza A (H1N1) virus infection—Mexico, March-April 2009. *MMWR Morb Mortal Wkly Rep* 2009; **58**: 467–470.
8 Bautista E, Chotpitayasunondh T, Gao Z, Harper SA, Shaw M, Uyeki TM *et al*. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. *N Engl J Med* 2010; **362**: 1708–1719.
9 Cao B, Li XW, Mao Y, Wang J, Lu HZ, Chen YS *et al*. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. *N Engl J Med* 2009; **361**: 2507–2517.
10 Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J *et al*. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. *N Engl J Med* 2009; **361**: 1935–1944.
11 Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, Hernandez M, Quinones-Falconi F, Bautista E *et al*. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. *N Engl J Med* 2009; **361**: 680–689.
12 Garbino J, Gerbase MW, Wunderli W, Kolarova L, Nicod LP, Rochat T *et al*. Respiratory viruses and severe lower respiratory tract complications in hospitalized patients. *Chest* 2004; **125**: 1033–1039.
13 World Health Organization. *CDC Protocol of Realtime RT-PCR for Swine Influenza A (H1N1)*. World Health Organization: Geneva, Accessed 30 November 2009, at http://www.who.int/csr/resources/publications/swineflu/realtimeptpcr/en. 2009.
14 De la Camara R, Cannata J, Nieto J, Gonzalez-Vicent M, Lassaletta A, Garcia-Noblejas A *et al*. Novel swine-origin influenza A (H1N1) in SCT and onco-haematological patients: clinical characteristics and outcome in 87 confirmed cases. *Bone Marrow Transplant* 2010; **45**(suppl 2): S35–S36. (Abstract 224).
15 Ljungman P. *H1N1 Infections In Hematopoietic Stem Cell Transplant Recipients: A Prospective Study*, ICAAC Meeting 2010. Abstract.
16 George B, Ferguson P, Kerridge I, Gilroy N, Gottlieb D, Hertzberg M. The clinical impact of infection with Swine flu (H1N1 09) strain of influenza virus in hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant* 2010; **17**: 147–153.
17 Redelman-Sidi G, Sepkowitz KA, Huang CK, Park S, Stiles J, Eagan J *et al*. 2009 H1N1 influenza infection in cancer patients and hematopoietic stem cell transplant recipients. *J Infect* 2010; **60**: 257–263.
18 Taplitz R, Espinosa-Aguilar L, Green J, Forrest G, Ball E, Maziarz R *et al*. Novel H1N1 influenza in hematopoietic stem cell transplant recipients: two center's experience. *Biol Blood Marrow Transplant* (e-pub ahead of print 10 August 2010).
19 Tramontana AR, George B, Hurt AC, Doyle JS, Langan K, Reid AB *et al*. Oseltamivir resistance in adult oncology and

hematology patients infected with pandemic (H1N1) 2009 virus, Australia. *Emerg Infect Dis* 2010; **16**: 1068–1075.
20 Chalandon Y, Roosnek E, Mermillod B, Waelchli L, Helg C, Chapuis B. Can only partial T-cell depletion of the graft before hematopoietic stem cell transplantation mitigate graft-versus-host disease while preserving a graft-versus-leukemia reaction? A prospective phase II study. *Biol Blood Marrow Transplant* 2006; **12**: 102–110.
21 OFSP. Rapport de situation hebdomdaire de l'OFSP. http://www.bag.admin.ch/dokumentation/publikationen/01435/07914/index.html?lang=fr. Accessed online 9 September 2010.
22 Ljungman P. Solid-organ transplants and the risks of pandemic influenza. *Lancet Infect Dis* 2010; **10**: 506–507.
23 Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ *et al*. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med* 2009; **360**: 2605–2615.
24 Miller E, Hoschler K, Hardelid P, Stanford E, Andrews N, Zambon M. Incidence of 2009 pandemic influenza A H1N1 infection in England: a cross-sectional serological study. *Lancet* 2010; **375**: 1100–1108.
25 Cauchemez S, Donnelly CA, Reed C, Ghani AC, Fraser C, Kent CK *et al*. Household transmission of 2009 pandemic influenza A (H1N1) virus in the United States. *N Engl J Med* 2009; **361**: 2619–2627.
26 Kumar D, Michaels MG, Morris MI, Green M, Avery RK, Liu C *et al*. Outcomes from pandemic influenza A H1N1 infection in recipients of solid-organ transplants: a multicentre cohort study. *Lancet Infect Dis* 2010; **10**: 521–526.
27 Patel P, Sweiss K, Shatavi S, Peace D, Clark N, Rondelli D. The impact of novel influenza A (H1N1) after hematopoietic SCT. *Bone Marrow Transplant* 2010; **45**: 1756–1757.
28 Ditschkowski M, Elmaagacli AH, Beelen DW. H1N1 in allogeneic stem cell recipients: courses of infection and influence of vaccination on graft-versus-host-disease (GVHD). *Ann Hematol* 2010; **90**: 117–118.
29 Garland P, de Lavallade H, Sekine T, Hoschler K, Sriskandan S, Patel P *et al*. Humoral and cellular immunity to primary H1N1 infection in patients with hematological malignancies and following stem cell transplantation. *Biol Blood Marrow Transplant* (e-pub ahead of print 10 August 2010).
30 CDC. Oseltamivir-resistant novel influenza A (H1N1) virus infection in two immunosuppressed patients—Seattle, Washington, 2009. *MMWR Morb Mortal Wkly Rep* 2009; **58**: 893–896.
31 Kharfan-Dabaja MA, Velez A, Richards K, Greene JN, Field T, Sandin R. Influenza A/pandemic 2009/H1N1 in the setting of allogeneic hematopoietic cell transplantation: a potentially catastrophic problem in a vulnerable population. *Int J Hematol* 2010; **91**: 124–127.
32 Rozovski U, Herishanu Y, Gipstein L, Naparstek E. Fatal H1N1 influenza infection in an allo-SCT recipient. *Bone Marrow Transplant* 2010; **45**: 1572–1573.
33 Chemaly RF, Ghosh S, Bodey GP, Rohatgi N, Safdar A, Keating MJ *et al*. Respiratory viral infections in adults with hematologic malignancies and human stem cell transplantation recipients: a retrospective study at a major cancer center. *Medicine (Baltimore)* 2006; **85**: 278–287.
34 Engelhard D, Nagler A, Hardan I, Morag A, Aker M, Baciu H *et al*. Antibody response to a two-dose regimen of influenza vaccine in allogeneic T cell-depleted and autologous BMT recipients. *Bone Marrow Transplant* 1993; **11**: 1–5.
35 Pauksen K, Linde A, Hammarstrom V, Sjolin J, Carneskog J, Jonsson G *et al*. Granulocyte-macrophage colony-stimulating factor as immunomodulating factor together with influenza vaccination in stem cell transplant patients. *Clin Infect Dis* 2000; **30**: 342–348.
36 Avetisyan G, Aschan J, Hassan M, Ljungman P. Evaluation of immune responses to seasonal influenza vaccination in healthy volunteers and in patients after stem cell transplantation. *Transplantation* 2008; **86**: 257–263.
37 Plennevaux E, Sheldon E, Blatter M, Reeves-Hoche MK, Denis M. Immune response after a single vaccination against 2009 influenza A H1N1 in USA: a preliminary report of two randomised controlled phase 2 trials. *Lancet* 2010; **375**: 41–48.
38 Zaia J, Baden L, Boeckh MJ, Chakrabarti S, Einsele H, Ljungman P *et al*. Viral disease prevention after hematopoietic cell transplantation. *Bone Marrow Transplant* 2009; **44**: 471–482.
39 Ljungman P, Cordonnier C, Einsele H, Englund J, Machado CM, Storek J *et al*. Vaccination of hematopoietic cell transplant recipients. *Bone Marrow Transplant* 2009; **44**: 521–526.
40 Lalayanni C, Sirigou A, Iskas M, Smias C, Sakellari I, Anagnostopoulos A. Outbreak of novel influenza A (H1N1) in an adult haematology department and haematopoietic cell transplantation unit: clinical presentation and outcome. *J Infect* 2010; **61**: 270–272.
41 Bastos DA, Rodrigues CA, Patah P, Kallas EG, Rocha V, Novis Y. Pandemic influenza A H1N1/09 virus infection in hematopoietic SCT recipient. *Bone Marrow Transplant* 2010 (e-pub ahead of print 7 June 2010; doi:10.1038/bmt.2010.133).
42 Frangoul H, Domm J, Denison MR, Calder C, Black J. H1N1 infection mimicking the clinical presentation of gastrointestinal GVHD in a patient following allo-SCT. *Bone Marrow Transplant* 2010; **46**: 152–153.
43 Campbell AP, Jacob ST, Kuypers J, Wald A, Englund JA, Corey L *et al*. Respiratory failure caused by 2009 novel influenza A/H1N1 in a hematopoietic stem-cell transplant recipient: detection of extrapulmonary H1N1 RNA and use of intravenous peramivir. *Ann Intern Med* 2010; **152**: 619–620.