Immunogenicity of an Inactivated Monovalent 2009 Influenza A (H1N1) Vaccine in Patients Who Have Cancer

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Key Words. Immune response • Vaccination • H1N1 • Myelosuppression • Immunosuppression

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Cite the primary concerns of oncologists regarding influenza vaccination for their cancer patients.
2. Describe research showing that cancer patients, whether taking myelosuppressive chemotherapy or not, are able to generate an immune response to the H1N1 vaccine similar to that of healthy controls.

CME

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ABSTRACT

Background. The immune response of patients who have cancer, who may be receiving immunosuppressive therapy, is generally considered to be decreased. This study

aimed to evaluate the immune response of cancer patients to the 2009 influenza A (H1N1) vaccine.

Patients and Methods. We conducted a prospective sin-

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gle site study comparing the immune response after H1N1 vaccination of healthy controls (group A), patients who had solid tumors and were taking myelosuppressive chemotherapy (group B), patients who had solid tumors and were taking nonmyelosuppressive or no treatment (group C), and patients who had hematologic malignancies (group D).

Results. At 2–6 weeks after vaccination, seroconversion was observed in 80.0% of group A (95% confidence interval [CI], 65.0%–89.7%), 72.2% of group B (95% CI, 55.9%–84.3%), 87.0% of group C (95% CI, 72.2%–94.7%), and 75.0% of group D (95% CI, 52.8%–89.2%) ($p = \text{NS}$). The geometric mean titer ratio, that is, geometric mean factor increase in antibody titer after vaccination,

was 12.6 (95% CI, 7.9–19.9), 12.7 (95% CI, 7.3–22.1), 23.0 (95% CI, 13.9–38.2), and 12.1 (95% CI, 5.3–27.9) ($p = \text{NS}$), and the seroprotection rates were 95.5% (95% CI, 84.0%–99.6%), 79.0% (95% CI, 63.4%–89.2%), 90.5% (95% CI, 77.4%–96.8%), and 90.0% (95% CI, 71%–98.7%) in the corresponding groups ($p = \text{NS}$). Immune responses were robust regardless of malignancy, or time intervals between the use of myelosuppressive or immunosuppressive medications and vaccination. No participants developed clinical H1N1 infection.

Conclusion. Cancer patients, whether taking myelosuppressive chemotherapy or not, are able to generate an immune response to the H1N1 vaccine similar to that of healthy controls. *The Oncologist* 2012;17:125–134

INTRODUCTION

Patients who have malignancies are at increased risk of contracting influenza, [1] and have higher complication and mortality rates [2–5]. The Centers for Disease Control and Prevention (CDC) has recommended annual vaccination against seasonal flu [6] and more recently against H1N1 [7] for patients who have a malignancy; however, it warns that those patients may have a decreased response secondary to immunosuppression [7]. This recommendation and accompanying warning is based upon the limited, outdated, and conflicting information on the efficacy of influenza vaccination in this population [8, 9]. Most have reported low response rates in cancer patients, particularly muted humoral response in patients who have lymphoproliferative disorders [10–14]. Some have reported that the response is delayed [11]. In addition, there is inadequate evidence concerning the best time to vaccinate patients who are actively receiving chemotherapy.

Although some reports have suggested similar immune response in patients who had solid tumors [15] or lymphoproliferative malignancies [16], the uncertainty about both the value and timing of influenza vaccine administration to cancer patients receiving immunosuppressive treatment may lead some oncologists unnecessarily to delay, or defer entirely, potentially useful vaccination [17, 18].

We hypothesized that factors which may potentially decrease immune response in cancer patients could include (a) disease-related factors, such as the immunosuppressive effect of the underlying active solid tumors or hematologic malignancies, or (b) treatment-related factors, such as the use and timing of myelosuppressive and/or immunosuppressive chemotherapy. Herein, we report our results from a prospective study evaluating the immunogenicity of the 2009 H1N1 vaccine in cancer patients with special attention to those factors.

METHODS

Study Design

This was a prospective study conducted at the Cancer Center of Maimonides Medical Center, Brooklyn, New York. The study was approved by the Maimonides Institutional Review Board

(IRB). Written informed consent was obtained from all participants.

Patients and Study Groups

Participants were enrolled into four prespecified groups according to their diagnosis and treatment: Group A, a control group of health care staff members in the Cancer Center; group B, patients who had a diagnosis of a solid tumor, who were receiving myelosuppressive chemotherapy (either in the adjuvant setting or for metastatic disease), and had chemotherapy within 28 days either before or after vaccination; group C, patients who had a diagnosis of a solid tumor and were receiving nonmyelosuppressive care, such as endocrine (hormonal) therapy or biologic therapy or no therapy, any myelosuppressive chemotherapy that would be >28 days away from vaccination; and group D, patients who had a diagnosis of a hematologic malignancy (including myeloproliferative and myelodysplastic diseases), excluding those with a history of autologous or allogeneic transplant. Eligible patients had an initial diagnosis of malignancy within the preceding 5 years, irrespective of the state of activity of their disease at the time they enrolled in the study.

Definitions of Myelosuppressive and Immunosuppressive Therapies

Traditional cytotoxic chemotherapy agents were all classified as myelosuppressive agents in this study. Among the targeted, biologic drugs, imatinib [19], sorafenib [20], and sunitinib [21] were classified as myelosuppressive, whereas erlotinib [22], bevacizumab [23], cetuximab [24], and trastuzumab [25] were classified as nonmyelosuppressive when used as single agents. Immunosuppressive therapy included glucocorticosteroids [26], fludarabine [27], rituximab [28], and other cytotoxic chemotherapy agents considered to have immunosuppressive potential: Cyclophosphamide, 5-fluorouracil, 6-mercaptopurine, Cytarabine, L-asparaginase, and vinca alkaloids [26]. Endocrine (hormonal) therapies were considered to have no myelosuppressive or immunosuppressive potential.

Figure 1. Participant disposition. *, This patient was treated with cyclophosphamide for mixed connective tissue disease. **, Those are the numbers used for calculation of seroconversion rate and the geometric mean titer ratio results at the initial postvaccination sampling time. ***, Those are the numbers used for calculation of seroconversion rate and the geometric mean titer ratio results at the repeat postvaccination sampling time.

Vaccine and Vaccination

A commercially available Influenza A (H1N1) 2009 Monovalent unadjuvanted vaccine produced by Sanofi Pasteur Inc. (Swiftwater, PA) [29] was used, and one single dose of vaccination was given to all participants. Group A participants received H1N1 vaccination in November 2009, whereas all other participants received vaccination between November 2009 and January 2010.

Laboratory Studies

Blood was drawn at baseline, at 2–6 weeks after vaccination, and 6–12 weeks after vaccination to test for anti-H1N1 antibody titers. A hemagglutination-inhibition (HI) assay using a standard method was performed at the University of Rochester Microbiology Research Laboratory to estimate the anti-H1N1 antibody titers [30].

Study Endpoints

Three immunogenicity endpoints were chosen for examination based on international guidelines [31, 32] and on similar H1N1 vaccination studies on healthy individuals [33–35]. They were as follows: (a) the seroconversion rate, the proportion of participants who had a fourfold increase in their antibody titer to 1:40 or greater after vaccination over baseline; (b) the geometric mean titer ratio, which is the geometric mean factor increase in antibody titer after vaccination over baseline; (c) the

seroprotection rate, the proportion of participants who had an antibody titer of 1:40 or greater at any test point (a titer of 1:40 or greater has been considered to be protective from infection in previous studies [36]). An antibody titer of < 1:10 was considered as 1:5, whereas an antibody titer of > 1:1280 was considered as 1:1280 for calculation of the geometric mean titer.

Timing of Vaccination

It was strongly recommended, but not required, that the H1N1 vaccine be given between intravenous chemotherapy treatment cycles, at least 7 days after the last and 7 days before the next chemotherapy infusion, at the discretion of the treating physician. Patients taking oral chemotherapy or biologic targeted therapy could continue therapy without interruption for the vaccination.

Statistical Analysis

On the basis of previous reports, we estimated that the seroprotection rate would be 95% in the control group, 60% in group B, 70% in group C, and 50% in group D [15, 34, 37–39]. Using SPSS version 19.0 (SPSS Inc., IBM Corporation, Armonk, NY) for sample size determination, we estimated that the smallest number of participants in each group required to detect a significant difference among groups as stated above with a power of 80% and an α error of 0.05 (two sided) would be 36 participants in the control group A, 22 in group B, 36 in group C, and 15 in group D. However, as the true seroprotection rates could be higher than previously thought in patient groups, to increase statistical power to detect a smaller difference, we kept the study open for enrollment beyond these minimum requirements.

The 95% confidence intervals (CIs) for geometric mean titer values were estimated by calculating normal-based CIs for sample log-means and then making exponentiation of these numbers; Kruskal-Wallis tests were used to assess differences among patient groupings in the distribution of titer or titer ratio scores. Ninety-five percent CIs for prevalence of seroprotection and seroconversion were estimated using the method of Agresti and Coull [40]. Generalized Fisher's exact tests were used to assess differences among patient groupings in prevalence. When significant, post hoc tests between pairs of groups were conducted and the resulting p -values were bootstrap-adjusted to allow for multiple testing. All tests were two-sided with significance level of .05. SAS release 9.2 software (SAS Institute, Cary, NC) was used.

RESULTS

Study Patients

One hundred forty-six patients were eligible for the study (Figure 1). The median age in the control group was younger (46 years) than that in the patient groups (62 years); other demographics of the participants are shown in Table 1. The cancer diagnoses, treatment characteristics, and chemotherapy agents used are included in Table 2.

Table 1. Participant demographics

	Group A (n = 44)	Group B (n = 38)	Group C (n = 42)	Group D (n = 22)
Gender, no. (%)				
Male	18 (40.9)	14 (36.8)	17 (40.5)	15 (68.2)
Female	26 (59.1)	24 (63.2)	25 (59.5)	7 (31.8)
Age (years)				
Mean $\pm$ SD	45.8 $\pm$ 10.3	59.3 $\pm$ 12.9	65.2 $\pm$ 13.3	62.8 $\pm$ 13.3
Median	46.5	61.5	62.5	61.5
Range	27–67	31–82	36–95	35–86
Race, no. (%)				
Caucasian	29 (65.9)	13 (34.2)	10 (23.8)	12 (54.5)
Non-Caucasian	15 (34.1)	25 (65.8)	32 (76.2)	10 (45.5)
African American	10 (22.7)	9 (23.7)	10 (23.8)	2 (9.1)
Asian	5 (11.4)	14 (36.8)	17 (40.5)	6 (27.3)
Hispanic	0 (0)	2 (5.3)	5 (11.9)	2 (9.1)
Seasonal influenza vaccine received, no. (%)	43 (97.7)	18 (47.4)	27 (64.3)	17 (77.3)

Immunogenicity

Baseline seroprotection against H1N1, with an antibody titer of 1:40 or greater, was detectable in 59.0% of participants in group A and 21.1%, 38.1%, and 22.7% of participants in groups B, C, and D, respectively (Table 3). The difference between group A and group B and that between group A and group D were statistically significant ($p = .001$ and $p = .019$, respectively). The geometric mean titers (GMTs) at baseline followed the same pattern ($p < .001$).

H1N1 vaccination produced a robust immune response in the majority of patients in all groups (Table 3, Figure 2). The initial postvaccination sampling was performed between 2 and 6 weeks after vaccination (median of 28–29 days in all patient groups and 16 days in the control group). Seroconversion was observed in 80.0% (95% CI, 65.0%–89.7%), 72.2% (95% CI, 55.9%–84.3%), 87.0% (95% CI, 72.2%–94.7%), and 75.0% (95% CI, 52.8%–89.2%) of participants in groups A, B, C, and D, respectively, and there was no significant difference among the groups ($p = .512$, generalized Fisher's exact test). Similarly, there was substantial rise in GMTs after vaccination and the geometric mean titer ratios were 12.6 (95% CI, 7.9–19.9), 12.7 (95% CI, 7.3–22.1), 23.0 (95% CI, 13.9–38.2), and 12.1 (95% CI, 5.2–27.8) in the four groups, with no statistical difference among the groups ($p = .279$, Kruskal-Wallis test).

At the repeat postvaccination sampling (between 6–12 weeks), which was purposely chosen to capture potential delayed immune response, seroconversion rates and geometric mean titer ratios in the patient groups (groups B, C, and D) again showed no statistical difference to those in the control group A (Table 3, Figure 2).

Overall, the seroprotection rate was 95.5% (95% CI, 84.0%–99.6%), 79.0% (95% CI, 63.4%–89.2%), 90.5% (95% CI, 77.4%–96.8%), and 90.1% (95% CI, 71.0%–98.7%) in groups A, B, C, and D, respectively (Table 3). These rates

again did not vary significantly ($p = .133$, generalized Fisher's exact test).

We performed additional analyses focusing on one single disease or treatment-related factors at a time in all patients (combining participants in groups B, C, and D) and compared the results to those in the control group A.

First, we examined the effect of the presence of active malignancy. Seroconversion rates in the face of active tumor and in the absence of tumor were 75.5% (95% CI, 62.3%–85.2%) and 82.9% (95% CI, 68.4%–91.8%), respectively. Neither was statistically different from the normal control group rate of 80.0% (95% CI, 65.0%–89.8%) ($p = .691$, Fisher's exact test) (Table 4).

Second, we examined the use of myelosuppressive chemotherapy and its timing in relation to vaccination. We subgrouped patients receiving myelosuppressive chemotherapy into (a) treatment received ≤ 7 days before or after vaccination; (b) treatment received between 8 and 28 days before or after vaccination; (c) treatment received 29–90 days from vaccination and compared these outcomes to those observed in the (d) control group A. Thirty patients were found to have received myelosuppressive regimens within 7 days of vaccination, and their seroconversion rate was 73.3% (95% CI, 55.4%–86.0%), not statistically different from that in the control group (80.0%, 95% CI, 65.0%–89.8%), or that in the patients who received treatment between 8 and 28 days ($n = 17$, 76.5%, 95% CI, 52.2%–91.0%) or between 29 and 90 days ($n = 47$, 83.0%, 95% CI, 69.6%–91.4%) ($p = .757$, Fisher's exact test). Similar results were observed in the geometric mean titer ratio among these subgroups ($p = .936$, Kruskal-Wallis test) (Table 4).

Third, we examined the effect of immunosuppressive medications. We subdivided patients into those (a) receiving immunosuppressive chemotherapy with or without steroids, (b) receiving steroids without immunosuppressive chemotherapy,

Table 2. Tumor and treatment characteristics in cancer patients

	Group B (n = 38)	Group C (n = 42)	Group D (n = 22)
Tumor types			
Breast	9	15	N/A
Lung	7	4	N/A
Esophageal/stomach	4	3	N/A
Hepatocellular/pancreas/gall bladder	1	4	N/A
Colorectal	4	6	N/A
Ovarian/endometrium	7	0	N/A
Cervical	2	2	N/A
GIST tumor	2	0	N/A
Bladder/prostate/renal	1	4	N/A
Brain	1	0	N/A
Head and neck	0	4	N/A
Plasma cell malignancies	N/A	N/A	5
Lymphoma	N/A	N/A	8
MDS + AML	N/A	N/A	5
Myeloproliferative disorders	N/A	N/A	4
Treatment purpose			
Adjuvant (tumor not present)	12	27	7
Neoadjuvant/palliative (tumor present)	26	15	15
Treatment type			
Myelosuppressive chemotherapy	38	0	10
Targeted therapy (including Rituximab)	8	8	3
Hormonal treatment	0	10	N/A
Chemotherapy regimens used (within 28 days before or after the vaccination)	Doxorubicin and cyclophosphamide Paclitaxel, carboplatin Paclitaxel, carboplatin, trastuzumab Docetaxel, carboplatin Cisplatin, etoposide Cisplatin, irinotecan Cisplatin, doxorubicin Docetaxel, cyclophosphamide Epirubicin, oxaliplatin, capecitabine Oxaliplatin, 5FU, leucovorin Irinotecan, 5FU, leucovorin Bevacizumab, navelbine Cetuximab, irinotecan Liposomal doxorubicin, carboplatin Trastuzumab, paclitaxel Trastuzumab, ixabepilone gemcitabine, erlotinib Single agents: pemetrexed, cisplatin, docetaxel, paclitaxel, gemcitabine, topotecan, temozolomide, imatinib	Tamoxifen, letrozole, anastrozole, cetuximab, erlotinib, goserelin acetate, trastuzumab, leuprolide	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone Fludarabine, cyclophosphamide, rituximab Tretinoin, 6-mercaptopurine, methotrexate Single agent: hydroxyurea, lenalidomide, anagrelide, dexamethasone, cytarabine, imatinib, light treatment
Abbreviations: AML, acute myelogenous leukemia; GIST, gastrointestinal stromal tumor; MDS, myelodysplastic syndrome; N/A, not applicable.			

(c) not receiving either immunosuppressive chemotherapy agents or steroids, and (d) normal controls. Of note, dexamethasone was used as an adjunct antiemetic premedication in 78.9% of patients in group B, and as part of the treatment in 9% of patients in group D. Again, there was no statistically signif-

icant difference in either the seroconversion rate ($p = .937$, Fisher's exact test) or geometric mean titer ratio ($p = .897$, Kruskal-Wallis test) among the subgroups (Table 4).

Fourth, we focused on patients who had active lymphoproliferative diseases and plasma cell malignancies and found that

Table 3. Immune responses after vaccination as measured by hemagglutination-inhibition (HI) assay

	Group A	Group B	Group C	Group D	<i>p</i> -value
Baseline					
Antibody titer $\geq 1:40$, % (95% CI)	59.1 (44.4–72.3)	21.1 (10.8–36.6)	38.1 (25.0–53.2)	23.0 (9.7–43.9)	.001 ^a
Geometric mean titer, value (95% CI)	34.7 (23.9–50.2)	11.4 (7.6–16.9)	15.4 (10.3–23.0)	18.2 (8.6–38.7)	<.001
Initial postvaccination test (weeks 2–6)					
Geometric mean titer, value (95% CI)	422.2 (272.7–653.7)	151.0 (81.6–279.4)	370.3 (223.3–614.0)	197.0 (86.5–448.5)	.279
Geometric mean titer ratio, value (95% CI)	12.6 (7.9–19.9)	12.7 (7.3–22.1)	23.0 (13.9–38.2)	12.1 (5.3–27.9)	.442
Seroconversion rate, % (95% CI)	80.0 (65.0–89.8)	72.2 (55.9–84.3)	86.8 (72.2–94.7)	75.0 (52.8–89.2)	
Repeat postvaccination test (weeks 6–12)					
Geometric mean titer, value (95% CI)	308.8 (198.2–481.1)	127.0 (70.7–228.0)	206.3 (116.1–366.5)	121.3 (54.6–269.2)	.791
Geometric mean titer ratio, value (95% CI)	9.9 (6.3–15.5)	11.5 (6.6–20.1)	12.7 (7.2–22.3)	8.6 (4.0–18.6)	
Seroconversion rate, % (95% CI)	76.9 (61.5–87.6)	69.4 (53.0–82.1)	76.7 (58.8–88.5)	65.0 (43.2–82.0)	.704
Postvaccination seroprotection rate (antibody titer equal or greater than 1:40), % (95% CI)	95.5 (84.0–99.6)	79.0 (63.4–89.2)	90.5 (77.4–96.8)	90.9 (71.0–98.7)	.133

^aWith use of bootstrap-adjusted *p*-value for pairwise comparisons, the *p*-value for the difference between group A and group B was .001 and between group A and group D was .019, whereas the difference between group A and group C was not statistically significant (*p* = .113).
Abbreviation: CI, confidence interval.

their seroconversion rate and geometric mean titer ratio were also not statistically different from those of the healthy controls in group A (Table 4). Five of those patients were also taking chemotherapy, including three patients taking a rituximab-containing regimen. One patient who received 6 cycles of R-CHOP, with the last treatment 10 days before vaccination, was able to generate a robust immune response. The other two patients failed to generate immunity, including one who received rituximab and bendamustine 47 days prior, and one who received rituximab and fludarabine 6 days prior.

Clinical Outcome

Six months after the start of the trial, 111 participants were questioned (in person or by telephone interview) for hospital admissions for severe influenza-like symptoms, and none reported such events.

DISCUSSION

This study demonstrates that one dose of H1N1 vaccination induces a robust immune response in cancer patients as measured by standard vaccination outcomes. The seroconversion rates in cancer patients taking cytotoxic myelosuppressive chemotherapy for solid tumors and hematologic malignancies (group B and group D) were 72% and 75%, respectively, congruent with the results seen in healthy individuals in our study of 80% (group A) and in previously published trials describing healthy individuals, in which approximately 70% was reported after one vaccination [33–35, 41]. The magnitude of response as measured by geometric mean titer ratio in cancer patients taking cytotoxic myelosuppressive chemotherapy was also similar to that of healthy individuals. In cancer patients taking other treatments without myelosuppressive potential, the vaccination outcomes were also as good as healthy controls. In ad-

dition, the response was not delayed; seroconversion was readily detectable at the 2–6 week time point in all groups of cancer patients, the same time point generally studied in healthy individuals [33, 35, 41].

To the best of our knowledge, this is the first contemporary study to demonstrate that cancer patients taking cytotoxic myelosuppressive chemotherapy can mount as strong an immune response to the H1N1 vaccine as do healthy individuals; three similar studies on the same theme have recently been published and, in contrast, showed decreased immune response rates in cancer patients to H1N1 vaccine [42–44]. Although the heterogeneity in the patient groups from different studies may account for the difference in response rate, the three other studies used adjuvanted vaccines made by GlaxoSmithKline Biologicals (Research Triangle Park, NC), whereas we used an unadjuvanted vaccine made by Sanofi Pasteur Inc. It is possible that the difference in the nature or potency of the vaccines contributed to the difference in immune response; studies would be required for direct comparison.

Another difference between our study and the other studies was the higher baseline seroprotection rate in our study (21%–35% in cancer patients and 59% in healthy controls) as compared with a 3%–15% rate in others [42–44]. The appearance of baseline seroprotective titer most likely reflected natural exposure. Before the start of the H1N1 vaccination in this study, by July 7, 2009, 996 hospitalized patients already had confirmed infections in New York City [45]. The possibility that natural subclinical exposure served as a “priming” procedure for patients, allowing them to develop a stronger immune response after vaccination, is a plausible hypothesis which will need further study. It is unlikely that the unexpectedly high rate of baseline seroprotection in the control group A was due to cross reactivity from previous exposures to swine influenza

Figure 2. Reverse cumulative-distribution curves of antibody titers in serum samples obtained on baseline (A), weeks 2–6 (B), or weeks 6–12 (C).

[46], as most of the participants in this group were too young to have had such exposure.

The relationship of cancer to an immunocompromised state is a complex subject. Cancer patients comprise an extremely heterogeneous group with numerous variations, including the presence or absence of disease, various solid tumor or hematologic diagnoses, chemotherapy for adjuvant use or palliative purposes,

treatment with cytotoxic chemotherapy having variable degrees of myelosuppression, or treatment with new targeted agents or biologic agents for which the myelosuppressive potential is not well-documented. In most of the previous studies on cancer and vaccination, those disease or treatment-related factors have not been individually studied and have proven to be very difficult to analyze. Some studies have assigned patients to arbitrarily defined groups based on one factor, but many other factors overlapped among groups [42]. In this study, we designed three patient groups first to separate hematologic malignancies from solid tumors and second to separate patients who were receiving myelosuppressive chemotherapy for a solid malignancy from those who were not. We further performed post hoc analyses looking at the effect of (a) the presence or absence of detectable tumor, (b) the timing of myelosuppressive chemotherapy with respect to vaccination, and (c) the use of agents with documented immunosuppressive potential. We also included a group of healthy control patients who received the same vaccination over the same time and all of our analyses were compared with this control group. The median age of the control patients was younger than that of the cancer patients, setting a higher bar for comparison. Therefore, we conclude with confidence that myelosuppressive and/or immunosuppressive chemotherapy in general does not hamper the ability of cancer patients to generate an anti-H1N1 immune response from the vaccine we used.

It has been suggested that vaccine given close to the administration of chemotherapy is associated with a lower response rate [39, 42, 47]. Therefore, it has been recommended that vaccination be given 2 weeks or more before initiation of chemotherapy [9, 48–53]. However, we observed that even when myelosuppressive treatment was given <7 days from the administration of the vaccine, the immune response was not muted. That finding is reassuring and has important clinical implications because some regimens require weekly chemotherapy.

Patients who have hematologic malignancies are usually considered unlikely to generate an effective immune response [10–14]. Two recent studies on H1N1 response arrived at similar conclusions [43, 44]. In our study, patients who had hematologic malignancies achieved effective immunity. In particular, patients with lymphoproliferative and plasma cell malignancies with or without treatment achieved good response. It should be noted that our study, similar to previous studies, suffers from a relatively small sample size and a heterogeneous mixture of plasma cell malignancies, myeloid malignancies, and lymphoproliferative malignancies. Whether there is intrinsic disease-specific immunosuppression or treatment-induced immunosuppression will need further study. Rituximab treatment was associated with a lower seroconversion rate both in our study and in others [43, 44]. However, one of our three patients who received rituximab mounted a robust response, suggesting that not all patients are immunosuppressed to the same degree.

CONCLUSIONS

Our results strongly suggest that cancer patients, in general, can develop an effective, protective immune response to a current H1N1 influenza vaccine, despite underlying malignancies and/or immunosuppressive treatment. However, our conclu-

Table 4. Subgroup analysis on influence of disease and treatment-related factors on immunogenicity in cancer patients (groups B + C + D) compared with normal control (group A)

	Seroconversion rate % (95% CI)	Geometric mean titer ratio (95% CI)
Presence of active malignancy		
Active malignancy (<i>n</i> = 53)	75.5 (62.3–85.2)	13.5 (8.5–21.4)
Absence of active malignancy (<i>n</i> = 41)	82.9 (68.4–91.8)	19.9 (12.1–32.8)
Normal control (<i>n</i> = 40)	80.0 (65.0–89.8)	12.6 (7.9–19.9)
	<i>p</i> = .691	<i>p</i> = .103
Use of myelosuppressive chemotherapy		
Myelosuppressive chemo ≤7 days from vaccination (<i>n</i> = 30)	73.3 (55.4–86.0)	15.3 (7.9–29.6)
Myelosuppressive chemo 8–28 days from vaccination (<i>n</i> = 17)	76.5 (52.2–91.0)	10.2 (4.9–21.3)
Myelosuppressive chemo 29–90 days from vaccination (<i>n</i> = 47)	83.0 (69.6–91.4)	19.4 (12.1–31.1)
Normal control (<i>n</i> = 40)	80.0 (65.0–89.8)	12.6 (7.9–19.9)
	<i>p</i> = .757	<i>p</i> = .936
Use of immunosuppressive treatment		
Immunosuppressive chemotherapy ± steroids within 28 days (<i>n</i> = 16)	75.0 (50.0–90.3)	16.0 (7.0–36.3)
Steroid and without immunosuppressive chemotherapy within 28 days (<i>n</i> = 21)	76.2 (54.5–89.8)	17.1 (7.3–40.1)
No usage of either immunosuppressive chemotherapy or steroids within 28 days (<i>n</i> = 57)	80.7 (68.5–89.0)	15.6 (10.2–23.9)
Normal control (<i>n</i> = 40)	80.0 (65.0–89.8)	12.6 (7.9–19.9)
	<i>p</i> = .937	<i>p</i> = .897
Active lymphoproliferative and plasma cell malignancies (<i>n</i> = 9)	66.7 (35.1–88.3)	8.0 (2.1–31.1)
Normal control (<i>n</i> = 40)	80.0 (65.0–89.8)	12.6 (7.9–19.9)
	<i>p</i> = .400	<i>p</i> = .472

Abbreviation: CI, confidence interval.

sion must be tempered by the reality that this was a relatively small-scale study. In addition, naturally acquired immunity could be a confounding factor in assessing immune response to vaccination because our trial was conducted after the epidemic was established. Large-scale studies will be required to validate our results, focusing on the comparative potency of different vaccines, and the effect of vaccination in patients taking newer immunosuppressive medications such as rituximab.

On the basis of our results, we strongly recommend that influenza vaccination be offered to all cancer patients. Patients who are already fighting against cancer should be given the opportunity to be protected from H1N1 and other types of influenza by the simple administration of an available vaccine.

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See the accompanying commentary on pages 1–2 of this issue.