

USE OF AN INACTIVATED VARICELLA VACCINE IN RECIPIENTS OF HEMATOPOIETIC-CELL TRANSPLANTS

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ABSTRACT

Background The reactivation of varicella-zoster virus from latency causes zoster and is common among recipients of hematopoietic-cell transplants.

Methods We randomly assigned patients who were scheduled to undergo autologous hematopoietic-cell transplantation for non-Hodgkin's or Hodgkin's lymphoma to receive varicella vaccine or no vaccine. Heat-inactivated, live attenuated varicella vaccine was given within 30 days before transplantation and 30, 60, and 90 days after transplantation. The patients were monitored for zoster and for immunity against varicella-zoster virus for 12 months.

Results Of the 119 patients enrolled, 111 received a transplant. Zoster developed in 7 of 53 vaccinated patients (13 percent) and in 19 of 58 unvaccinated patients (33 percent) ($P=0.01$). After two patients in whom zoster developed before transplantation were excluded, the respective rates were 13 percent and 30 percent ($P=0.02$). In vitro CD4 T-cell proliferation in response to varicella-zoster virus (expressed as the mean stimulation index) was greater in patients who received the vaccine than in those who did not at 90 days, after three doses ($P=0.04$); at 120 days, after all four doses ($P<0.001$); at 6 months ($P=0.004$); and at 12 months ($P=0.02$). The risk of zoster was reduced for each unit increase in the stimulation index above 1.6; a stimulation index above 5.0 correlated with greater than 93 percent protection. Induration, erythema, or local pain at the injection site was observed in association with 10 percent of the doses.

Conclusions Inactivated varicella vaccine given before hematopoietic-cell transplantation and during the first 90 days thereafter reduces the risk of zoster. The protection correlates with reconstitution of CD4 T-cell immunity against varicella-zoster virus. (N Engl J Med 2002;347:26-34.)

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VARICELLA-ZOSTER virus causes chickenpox and becomes latent in sensory ganglia, with an estimated 250 genome equivalents per 100,000 ganglial cells.¹⁻⁷ When latency is disrupted, the virus is transported along neuronal axons to the skin, resulting in zoster. Since immune surveillance is critical for maintaining latency, zoster is common among immunocompromised patients, including recipients of hematopoietic-cell transplants.⁸⁻¹⁶ The increased risk of zoster in these patients

is associated with diminished T-cell immunity against varicella-zoster virus^{14,16,17} but not with low titers of IgG antibodies to varicella-zoster virus.¹⁸ T-cell immunity against varicella-zoster virus recovers slowly after hematopoietic-cell transplantation and often does not occur without reactivation of the virus,^{14,16} which usually induces a T-cell response and reestablishment of latency.²

Live varicella vaccines have been licensed for the prevention of varicella.¹⁹ These vaccines, as well as a heat-inactivated formulation, have also been found to enhance immunity against varicella-zoster virus in healthy persons.^{20,21} The inactivated varicella vaccine was immunogenic when three doses were given to a heterogeneous group of patients who had undergone allogeneic or autologous hematopoietic-cell transplantation, but the incidence of zoster was not reduced.²² In this study, we added a fourth dose, given within 30 days before transplantation, and tested only patients with lymphoma who received an autologous hematopoietic-cell transplant. The rationale for this dosing schedule was that T cells specific for varicella-zoster virus might persist, despite the preparatory regimen, if a dose of vaccine was given immediately before transplantation.²³⁻²⁵

METHODS

Population

Enrollment was offered to male and female patients 18 to 60 years old who were seropositive for varicella-zoster virus and who had lymphoma and were scheduled for autologous hematopoietic-cell transplantation within the upcoming 30 days. Eligibility criteria included lack of a response, at least once, to standard treatment for Hodgkin's disease or non-Hodgkin's lymphoma or a high risk of early recurrence. Exclusion criteria were a history of zoster within 12 months before the transplantation, exposure to varicella-zoster virus within 4 weeks, administration of another vaccine within 4 months, or neomycin sensitivity.

For patients with non-Hodgkin's lymphoma, the preparatory regimen included total-body irradiation and chemotherapy, whereas patients with Hodgkin's lymphoma received only myeloablative chemotherapy.²⁶⁻²⁹ Autologous hematopoietic-cell grafts were obtained by apheresis except in four patients with non-Hodgkin's lymphoma, from whom bone marrow was harvested. The grafts were purged with monoclonal antibodies against CD9, CD10, CD19,

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and CD20 plus rabbit complement.³⁰ The study was approved by the Stanford University institutional review board. Written informed consent was obtained from all the participants.

Study Design

In this randomized trial, the primary end point was the development of zoster within 12 months after transplantation. Eligible patients were enrolled, assigned an anonymous study number, and randomly assigned to receive vaccine (the vaccine group) or no vaccine (the control group). Placebo injections were not used in the control group because the development of zoster is a well-defined clinical end point. Randomization was performed in blocks according to the date of enrollment, and adjustment was made for covariates, including age, diagnosis, health status, and transplantation protocol. The participants and medical personnel were blinded to the randomization process, which was performed by members of the biostatistics core staff at Stanford University.

The study was designed to detect an absolute difference of 20 percentage points (30 percent vs. 10 percent) between the groups in the incidence of zoster; the necessary sample size was calculated to be 58 patients per group to detect such a difference at a one-sided alpha level of 0.05, with 80 percent power. Reconstitution of immunity against varicella-zoster virus was a secondary end point. The severity of zoster was not an end point, because patients received antiviral therapy for episodes of zoster. Our transplantation protocols did not include prophylaxis against varicella-zoster virus; acyclovir prophylaxis was given to patients with antibodies to herpes simplex virus who were given total-body irradiation. Enrollment, data collection, and outcomes were monitored by a data and safety monitoring committee.

Vaccination Regimen

The investigational heat-inactivated varicella vaccine was made from live attenuated varicella vaccine containing 6115 plaque-forming units per 0.5 ml (Varivax, lot no. 1458/W-C471, Merck). The vaccine was stored at -70°C , reconstituted with sterile diluent, and administered as a 0.5-ml dose by subcutaneous injection into the upper arm. A dose was given to patients in the vaccine group within 30 days before hematopoietic-cell transplantation, regardless of the apheresis schedule, and then again 30, 60, and 90 days after transplantation.

The occurrence of local pain, swelling, induration, redness, erythema, bruising, or pruritus was recorded for 21 days. The patients were monitored for survival and disease-related events.

Evaluation for Zoster and Immune Reconstitution

Symptoms of zoster were explained to the patients with the use of pictures of typical rashes. The patients were instructed to report symptoms and were interviewed monthly for four months and then every two months. Zoster was diagnosed if a painful, vesicular rash with a dermatomal distribution developed. The following features were documented: the onset, location, and duration of the lesions; cutaneous dissemination; systemic symptoms; and pain.

Patients in both groups were tested for immunity against varicella-zoster virus within 30 days before transplantation (before the first dose of the vaccine was given) and then again at 30 days after transplantation (before the second dose), at 90 days (after the third dose), at 120 days (after the fourth dose), and at 6 and 12 months. Immunity against varicella-zoster virus was reevaluated after an episode of zoster. The proliferation of T cells specific for varicella-zoster virus was assessed by measuring the uptake of tritiated thymidine by peripheral-blood mononuclear cells and expressed in terms of the stimulation index; the stimulation index was the ratio of mean counts per minute in antigen-containing wells to mean counts per minute in control wells.^{22,31} The inactivated varicella-zoster virus antigen used for stimulation caused proliferation of CD4 T cells.²² T cells exposed to varicella-zoster virus in vitro

were evaluated for the expression of intracellular interferon- γ and tumor necrosis factor α (TNF- α) and for the expression of CD4 and CD69, which is a marker of activated T cells, by flow cytometry (FACS-Calibur, Becton Dickinson Immunocytometry Systems).³² IgG antibodies to varicella-zoster virus were measured by enzyme-linked immunosorbent assay.²²

Statistical Analysis

Clinical and immunologic data were reported to the biostatistics core staff according to the patients' study numbers. Immunologic responses and the presence or absence of zoster were monitored for 12 months after transplantation (12.5 months after enrollment); overall survival was recorded until October 31, 2001. The probability of the development of zoster and the probability of survival were estimated with the use of the product-limit method of Kaplan and Meier; the probabilities in the two groups were compared with the use of the log-rank statistic. The unpaired t-test was used to compare the means of logarithms of stimulation indexes; stimulation indexes were reported as means \pm SE. The paired t-test was used to compare the pretransplantation and post-transplantation stimulation indexes and titers of IgG antibodies to varicella-zoster virus. All reported P values are two-sided. Local reactions were compared between the groups by means of Fisher's exact test.

The time-varying Cox proportional-hazards model was used to estimate the relation between the occurrence of episodes of zoster and the stimulation index.³³ The stimulation index was used as the time-dependent covariate to obtain a risk ratio for zoster per unit increase in the stimulation index. For each patient with zoster, the stimulation index just before the onset of zoster was compared with that of patients without zoster at a similar time point; all the patients with zoster from both the vaccine group and the control group were included in this analysis. In separate analyses, a dichotomous variable was used to evaluate various cutoff values (e.g., a stimulation index of 3.0 or more) as predictors of the risk of zoster. Although the vaccine was supplied by Merck, the study design, accrual, data analysis, and manuscript preparation were carried out by the investigators under the aegis of competitive National Institutes of Health funding.

RESULTS

Characteristics of the Study Population

We enrolled 119 patients from March 1997 to June 2000; 59 patients were randomly assigned to a group that received the vaccine and 60 to a control group, which received no vaccine. Eight patients (six assigned to the vaccine group and two to the control group) did not undergo transplantation. The patients in the two groups were similar with respect to sex, age, diagnosis, and preparatory regimens (Table 1), and with respect to clinical indications for transplantation. Three patients in the vaccine group and two in the control group were given acyclovir as prophylaxis against herpes simplex virus infection. In addition, 29 patients in the vaccine group and 28 in the control group received intravenous or oral acyclovir for oral lesions, mucositis, or genital herpes during the first 120 days after transplantation; the dose of intravenous acyclovir ranged from 375 to 600 mg every eight hours, and that of oral acyclovir ranged from 200 to 800 mg five times a day. The average duration of treatment with intravenous or oral acyclovir was 10.8 days among the vaccinated patients

TABLE 1. CLINICAL CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	VACCINE GROUP (N=59)	CONTROL GROUP (N=60)	P VALUE*	RELATIVE RISK (95% CONFIDENCE INTERVAL)
Age (yr)				
Mean	44	44		
Range	20–60	19–60		
	no.			
Male sex	37	37		
Diagnosis				
Hodgkin's disease†	11	16		
Non-Hodgkin's lymphoma				
During first remission	5	5		
After first remission	43	39		
Transplantation not performed	6	2	0.16	
No. of patients with transplantation data	53	58		
Preparatory regimen‡				
Hodgkin's disease			0.43	
Lomustine (15 mg/kg of body weight), etoposide (60 mg/kg), cyclophosphamide (100 mg/kg)	6	5		
Carmustine (15 mg/kg), etoposide (60 mg/kg), cyclophosphamide (100 mg/kg)	5	10		
Non-Hodgkin's lymphoma			1.00	
Fractionated total-body irradiation (1200 cGy), etoposide (60 mg/kg), cyclophosphamide (100 mg/kg)	10	9		
Carmustine (15 mg/kg), etoposide (60 mg/kg), cyclophosphamide (100 mg/kg)	32	33		
Mitoxantrone (60 mg/m ²), melphalan (180 mg/m ²)	0	1		
Source of graft				
Hodgkin's disease				
Blood	11	15		
Non-Hodgkin's lymphoma			0.62	
Marrow	1	3		
Blood	41	40		
Zoster within 12 mo after transplantation				
All patients§	7	19	0.01	0.34 (0.14–0.80)
After exclusion of patients with zoster before transplantation¶	7	17	0.02	0.37 (0.15–0.90)

*Fisher's exact test was used for all the comparisons except the comparisons of rates of zoster, for which the log-rank test was used. All reported P values are two-sided.

†All the patients with Hodgkin's disease were enrolled after the first remission.

‡The preparatory regimens have been described by Stuart et al.,²⁶ Horning et al.,²⁷ Stockerl-Goldstein et al.,²⁸ and Johnston et al.²⁹

§Data are shown for 53 patients in the vaccine group and 58 patients in the control group who underwent transplantation.

¶Data are shown for 53 patients in the vaccine group and 56 patients in the control group who underwent transplantation. In two of the patients in the control group, zoster developed between the time of enrollment and the time of hematopoietic-cell transplantation.

and 9.8 days among those who were not vaccinated; one patient in each group was treated for more than 21 days. Twelve vaccinated patients and 14 unvaccinated patients died within 12 months after transplantation. Survival in the two groups was similar at a median follow-up time of 24.2 months (range, 0.9 to 56.0) (Fig. 1).

Tolerability of the Vaccine

All the patients in the vaccine group received the first dose of vaccine before the scheduled transplantation (mean, 13 days before transplantation; range, 2 to 34). Of the 53 patients in the vaccine group who underwent transplantation, 45 received three doses of the vaccine and 43 received four doses. Two

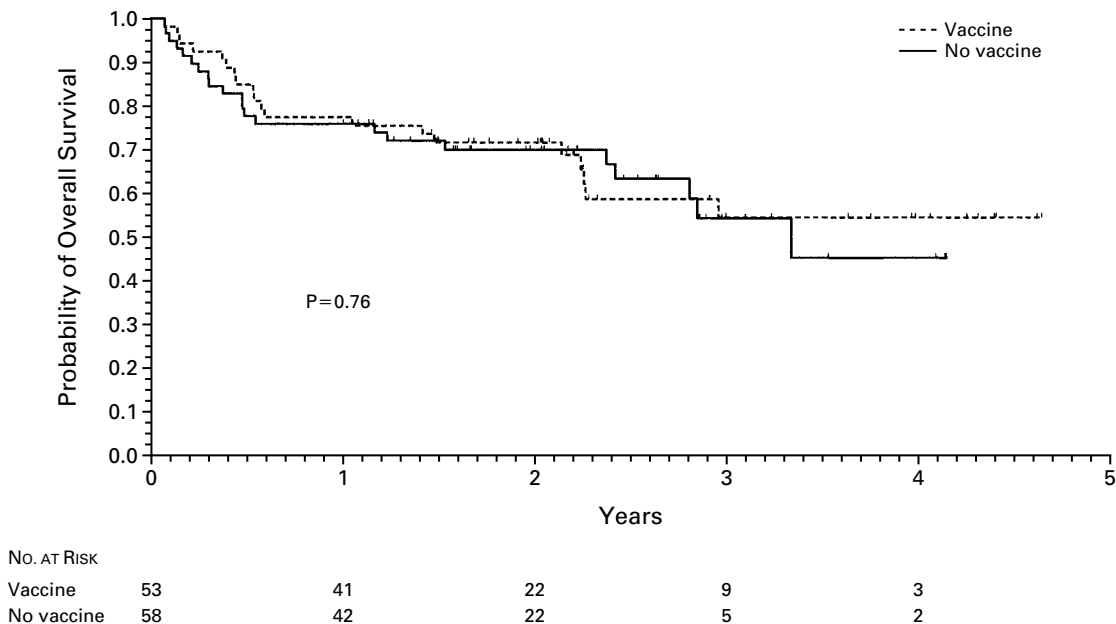


Figure 1. Probability of Overall Survival among Recipients of Autologous Hematopoietic-Cell Transplants Who Were Randomly Assigned to Receive Inactivated Varicella Vaccine or No Vaccine.

The Kaplan–Meier plot shows the probability of overall survival in the two groups from the time of enrollment until the most recent follow-up after hematopoietic-cell transplantation. Cumulative data are shown and indicate the percentage of participants surviving in each cohort at each time point until October 2001. The tick marks on each curve indicate the points at which patients’ data were censored.

patients in this group withdrew at 30 days for unexplained reasons, and 1 withdrew because of disease progression; 10 other patients in this group with disease progression continued to participate in the study. Twelve patients had local symptoms at the site of vaccination on at least one occasion, and one patient reported headache. Adverse reactions occurred with 20 of 198 doses of the vaccine (10 percent); local pain, induration, and erythema were the most common reactions.

Development of Zoster

Zoster was diagnosed within 12 months after transplantation in 7 of 53 patients in the vaccine group (13 percent) and in 19 of 58 patients in the control group (33 percent) ($P=0.01$) (Table 1 and Fig. 2). The difference remained significant when two patients in the control group in whom zoster developed before transplantation were excluded (leaving 17 patients with zoster of 56 [30 percent]) ($P=0.02$). The median interval between transplantation and the diagnosis of zoster was 92 days (mean, 129) in the vaccine group and 130 days (mean, 166) in the control group ($P=0.41$ for the comparison of the median inter-

vals). One vaccinated patient and two unvaccinated patients had a relapse of disease before zoster developed. All the patients, regardless of study group, in whom zoster developed received antiviral treatment for zoster. The severity of zoster did not differ between the two groups.

Immunity against Varicella–Zoster Virus

In vitro CD4 T-cell proliferation in response to varicella–zoster virus appeared earlier in peripheral-blood specimens from the vaccinated patients than it did in specimens from the unvaccinated patients. Since the proliferative response increased after an episode of zoster, any evaluations after such episodes were excluded from the analysis. Before transplantation, the mean (\pm SE) stimulation index was similar in the two groups (8.2 ± 1.65 in the vaccine group and 9.9 ± 2.32 in the control group, $P=0.39$), and responses remained similar and low 30 days after transplantation. By 90 days, the mean stimulation index was 15.7 ± 3.47 in the vaccine group and 8.0 ± 1.63 in the control group ($P=0.04$); the difference between the groups was significant 120 days ($P<0.001$) and 6 months ($P=0.004$) after transplanta-

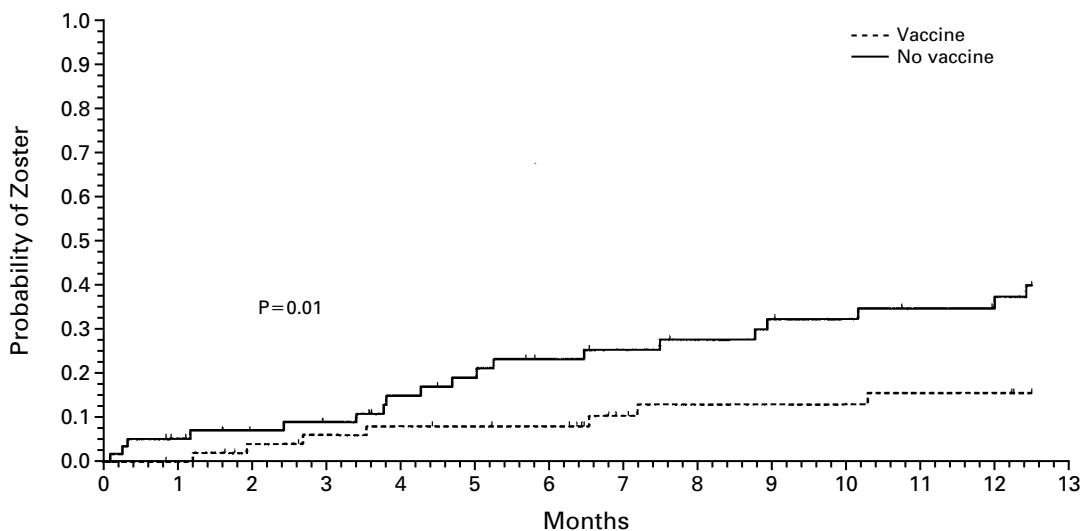


Figure 2. Probability of Zoster among Recipients of Autologous Hematopoietic-Cell Transplants Who Were Randomly Assigned to Receive Inactivated Varicella Vaccine or No Vaccine.

The Kaplan-Meier plot shows the probability of zoster in the two groups from the time of enrollment until 12.5 months after hematopoietic-cell transplantation. The incidence of zoster was significantly higher in the control group. When the two patients in the control group in whom zoster developed before transplantation were excluded from the analysis, the difference remained significant ($P=0.02$). The tick marks on each curve indicate the points at which patients' data were censored.

tion (Fig. 3). The patients in the vaccine group had significantly higher mean stimulation indexes at 6 months ($P=0.01$) and at 12 months ($P<0.001$) than they did before transplantation; among the patients in the control group the difference was not significant ($P=0.30$ for the comparison between pretransplantation values and the values at 6 months and $P=0.46$ for the comparison between pretransplantation values and the values at 12 months). At 12 months, the mean stimulation index was higher in the vaccine group than in the control group (42.8 ± 8.30 vs. 21.3 ± 5.91 , $P=0.02$).

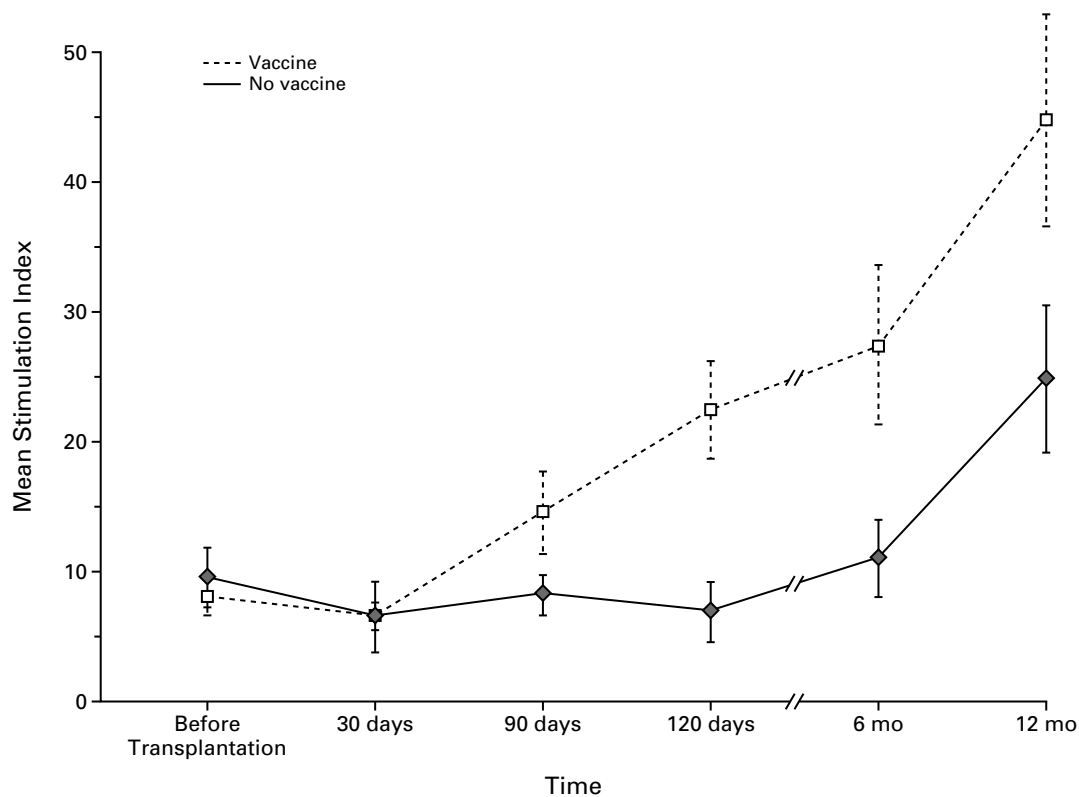
Immunity against varicella-zoster virus was evaluated by testing for intracellular cytokines in 19 patients in each group six months after transplantation. These two subgroups were balanced with respect to mean age (43 years [range, 21 to 58] in those who were vaccinated and 40 years [range, 19 to 59] in those who were not vaccinated), number of men (13 and 13), and diagnosis of Hodgkin's disease (5 and 6, respectively) and non-Hodgkin's lymphoma (14 and 13, respectively); all the patients survived for more than 12 months after transplantation. The proportion of CD4 T cells that produced TNF- α was 0.50 ± 0.12 percent in the subgroup of vaccinated patients and 0.19 ± 0.07 percent in the subgroup of unvaccinated patients ($P=0.03$) (Fig. 4). The pro-

portions of interferon- γ -positive CD4 T cells were 0.33 ± 0.11 percent and 0.11 ± 0.05 percent, respectively ($P=0.07$).

Titers of varicella-zoster virus IgG antibody before transplantation ranged from 1:256 to 1:16,384 on testing by enzyme-linked immunosorbent assay and did not differ between the two groups, according to the unpaired t-test. Six months after transplantation, the IgG titers had increased by a factor of four in 6 of the 106 patients who had not had zoster (3 in the vaccine group and 3 in the control group), and they had decreased by a factor of four in 7 patients (4 in the vaccine group and 3 in the control group); the titers did not change in the remaining 93 patients.

Risk of Zoster and Rate of Varicella-Zoster Virus-Specific CD4 T-Cell Proliferation

Cox proportional-hazards analysis with time-dependent covariate analysis was used to assess the relative risk of zoster as predicted by the stimulation index. Both vaccinated and unvaccinated patients were included in this analysis. Before the development of zoster, the stimulation indexes in patients in whom zoster subsequently developed were significantly different from the stimulation indexes in patients in whom zoster never developed and who were tested



NO. TESTED	Before Transplantation	30 days	90 days	120 days	6 mo	12 mo
Vaccine	53	49	42	39	34	33
No vaccine	58	50	43	34	30	27

Figure 3. CD4 T-Cell Proliferation in Response to Varicella–Zoster Virus Antigen among Recipients of Hematopoietic-Cell Transplants Who Were Randomly Assigned to Receive Inactivated Varicella Vaccine or No Vaccine.

In vitro T-cell proliferation in response to varicella–zoster virus antigen is shown as the mean stimulation index in relation to the time of hematopoietic-cell transplantation. Inactivated varicella vaccine was given to patients in the vaccine group before transplantation and 30, 60, and 90 days after transplantation. In the vaccine group, the stimulation index at 30 days represents the mean response after the pretransplantation dose of the vaccine; by 90 days, three doses had been given, and by 120 days the last dose had been given. The vertical bars represent the standard errors.

at the same interval after transplantation ($P=0.008$; relative risk of zoster, 0.81; 95 percent confidence interval, 0.69 to 0.95). Patients who had a stimulation index of 1.6 or above had a significantly lower risk of zoster than those with a stimulation index below 1.6 ($P=0.006$; relative risk of zoster, 0.32; 95 percent confidence interval, 0.14 to 0.70). A patient who had a stimulation index above 1.6 had a 68 percent lower probability of subsequently having zoster than a patient with a stimulation index below 1.6 (95 percent confidence interval, 0.32 to 1.0). If the stimulation index was greater than or equal to 3.0, the risk was 76 percent lower than it was with an index below

1.6; if the index was greater than or equal to 4.0, the risk was 83 percent lower; and if the index was greater than or equal to 5.0, the risk was 93 percent lower.

Immune Reconstitution

The mean stimulation index before the onset of zoster was 4.9 ± 1.18 in the 7 patients in the vaccine group in whom zoster subsequently developed and 2.2 ± 0.4 in 19 such patients in the control group ($P=0.01$). After the resolution of zoster, the stimulation index increased to 55.0 ± 20.76 and 28.1 ± 6.68 (in 18 patients in the control group), respectively ($P=0.34$).

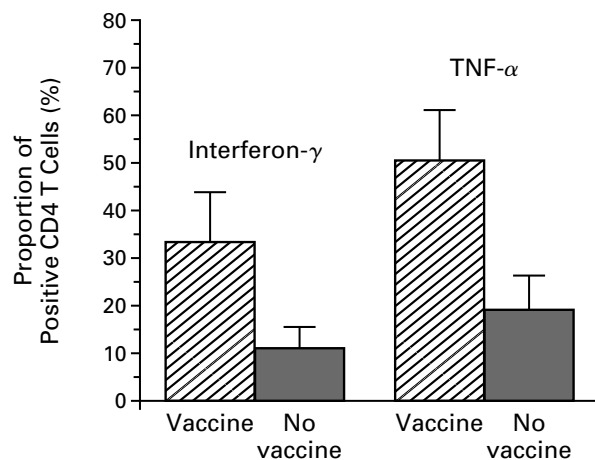


Figure 4. Expression of Interferon- γ and Tumor Necrosis Factor α (TNF- α) in CD4 T Cells Incubated with Varicella-Zoster Virus. The mean percentage of CD4 T cells that expressed CD69 and intracellular interferon- γ or TNF- α was determined six months after hematopoietic-cell transplantation in 19 patients in the vaccine group and 19 patients in the control group. The differences between these two subgroups were analyzed with the use of the unpaired t-test and were not significant with respect to the expression of CD69 and interferon- γ ($P=0.07$) but were significant with respect to the expression of CD69 and TNF- α ($P=0.03$). The vertical bars represent the standard errors.

DISCUSSION

Reactivation of varicella-zoster virus is a persistent source of illness in recipients of hematopoietic-cell transplants, despite antiviral therapy.^{2,12-15,34,35} We found that the administration of an investigational inactivated varicella vaccine, in a regimen in which one dose was given before transplantation and three doses were given after transplantation, offered substantial protection from zoster among patients with lymphoma who received an autologous transplant.

The risk of zoster is high among patients with impaired cell-mediated immunity against varicella-zoster virus.^{8-16,31,34,35} The relation that we observed between vaccine-induced reconstitution of T-cell immunity against varicella-zoster virus and a decreased incidence of zoster shows that cellular immunity modulates the capacity of latent herpesviruses to reactivate and cause disease. The proliferation of CD4 T cells specific for varicella-zoster virus was detected earlier in patients who were reexposed to varicella-zoster virus antigens by vaccination just before autologous transplantation; this finding suggests that mature, antigen-specific T cells may persist during the preparatory regimen.³⁶

Restoration of immunity against varicella-zoster virus was measured with the use of a simple in vitro assay of CD4 T-cell proliferation. Our evaluation of patients who were being monitored for zoster showed that a high stimulation index, as determined by this assay, was an immunologic correlate of protection. A stimulation index above 5.0 was highly predictive of protection from zoster. In healthy adults who have immunity to varicella-zoster virus, the stimulation index ranges from 5.0 to more than 20.0.³¹ The relation between a high stimulation index and a reduced risk of zoster may reflect the contribution of varicella-zoster virus-specific CD4 T cells to the control of viral replication, since these cells make interferon- γ and other cytokines and are cytotoxic to cells infected with the virus.^{14,17,31,32} Protection against zoster after immunization with inactivated varicella vaccine may be due to the early restoration of antiviral CD4 T cells to levels found in populations at low risk for zoster.^{32,37-40} Reconstitution of varicella-zoster virus-specific CD4 T cells by vaccination may provide helper functions necessary to expand varicella-zoster virus-specific CD8 T-cell populations that are essential to preserving the latency of the virus.^{14,31} In studies of immunity to human cytomegalovirus, another herpesvirus, the adoptive transfer of cytomegalovirus-specific CD8 T cells to patients who received bone marrow transplants resulted in effective antiviral immunity if the patient had anti-cytomegalovirus CD4 T cells.^{41,42}

Inactivated vaccines containing multiple viral proteins, like the vaccine we tested, or those formulated with viral protein subunits may be useful for accelerating the recovery of cellular immunity to other herpesviruses, especially human cytomegalovirus; infection with cytomegalovirus is more difficult to diagnose and treat in immunocompromised patients than infection with varicella-zoster virus.⁴³ The persistence of T-cell immunity against varicella-zoster virus for 12 months after transplantation and the higher stimulation index in vaccinated patients 12 months after transplantation than before transplantation suggest robust reconstitution, as has been observed in such patients with some bacterial vaccines.⁴⁴⁻⁴⁶ Although the use of a varicella vaccine after allogeneic hematopoietic-cell transplantation did not reduce the incidence of zoster,²² immunization before transplantation or immunization of the donor might enhance the effectiveness of the vaccine.⁴⁵ A regimen of vaccination both before and after transplantation might be particularly effective for patients with herpesvirus infections, because antiviral immunity may be stimulated further by subclinical reactivation of the latent virus. The use of fewer than three doses after transplantation might be sufficient, since the proliferation of T cells specific for varicella-zoster virus

was significantly enhanced at 90 days after transplantation, after three doses of inactivated varicella vaccine had been given, as compared with that in the control group. The principle of vaccination before transplantation to stimulate antigen-specific memory T cells in numbers sufficient to allow some T cells to survive the preparatory regimen, coupled with subsequent post-transplantation doses, should be generally applicable.

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