Centro Nacional para la Salud de la Infancia y la Adolescencia

PROPUESTA DE ACTUALIZACIÓN DEL MANUAL DIRIGIDO A TUTORES MENORES DE 18 AÑOS CON CÁNCER

PROPOSITO DEL PROYECTO

Contar con material didáctico actualizado en los temas de oncología que se utilicen para proporcionar la información a los padres de pacientes menores de 18 años con diagnóstico de cáncer

OBJETIVO GENERAL

Contribuir en proporcionar información a los tutores de pacientes menores de 18 años con diagnóstico de cáncer, fortalecer el conocimiento y entendimiento de la enfermedad de los pacientes para mejorar el tratamiento y disminuir las complicaciones, así como favorecer la atención oportuna de las mismas, disminuir abandonos a tratamiento

OBJETIVOS ESPECIFICOS

Generar una propuesta de reforzamiento de la información para tutores de menores de 18 años con diagnóstico de cáncer, con la finalidad de que cuenten con información de la enfermedad, el tratamiento, las complicaciones del tratamiento, que hacer en caso de presentarse alguna complicación, para disminuir los riesgos de los pacientes y favorecer los tratamiento oportunos de las posibles complicaciones y auxiliar en los problemas sociales de los tutores y pacientes

Se anexan las propuestas y bibliografía

En la página 15 introducir:

1.1.1 La sangre y sus componentes

La sangre está formada por tres tipos de células: los glóbulos blancos (linfoides y mieloides y son los que nos defienden de las infecciones virales, bacterianas, hongos y parásitos), glóbulos rojos (que son los que llevan la hemoglobina a todo el cuerpo, oxígeno y nutrientes) y las plaquetas (que nos ayudan a la coagulación, evitar sangrados).

Las tres líneas celulares son producidas por las células madre que se encuentran en la médula ósea, la cual se encuentra situada en el hueso esponjoso que se encuentra principalmente en huesos planos (cadera, esternón) y huesos largos (fémur, tibia, etc.), ahí crecen y maduran y posteriormente salen a las venas y arterias para irse al sitio correspondiente y realizar las funciones para las que fueron elaboradas

Los ganglios linfáticos son las casas de los linfocitos o glóbulos blancos y se encuentran en el cuerpo distribuidos en cuello, axilas, tórax, abdomen, íngles y las extremidades superiores e inferiores (brazos y piernas) y se observan como pequeñas bolitas que de forma normal pueden no palparse o ser menores a 1cm, crecen cuando hay un proceso infeccioso o por cáncer

En el apartado 2.2.4 Tumor de Wilms es conveniente mencionar que generalmente son niños previamente sanos, sin ataque al estado general, que el diagnostico se realiza por la persona que cuida al niño, al observar o palpar el aumento de volumen a nivel abdominal por la presencia del tumor, incluso antes de presentar manifestaciones clínicas como dolor o disminución del apetito o alteraciones gastrointestinales

Capítulo 4

4.2 Quimioterapia: puntos a considerar al administrarse quimioterapia.

"los efectos negativos de la quimioterapia desaparecen gradualmente al suspender el tratamiento. Aunque algunos efectos pueden tardar meses o años en desaparecer.

Hay efectos negativos de la quimioterapia que no desaparecen, estos son debidos al daño que producen en algunos órganos, como la miocardiopatía dilatada secundaria a antraciclinas, la fibrosis pulmonar secundaria a bleomicina o radioterapia, falla renal por metotrexate a altas dosis, hipotiroidismo posterior a radioterapia en cuello y tórax, esterilidad posterior a radioterapia en testículos.

Por lo anterior es importante llevar a cabo estudios y seguimiento estrecho de los pacientes aún posterior a finalizar el tratamiento con quimioterapia o radioterapia

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Assessment of hepatitis B immunization status after antineoplastic therapy in children with cancer

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Abstract

BACKGROUND AND OBJECTIVES:

Hepatitis B is a disease that is preventable with vaccination. Antibody levels after vaccination may be affected by suppression of the immune system due to cancer therapy. Children with cancer have a high risk of hepatitis B virus (HBV) infection. We aimed to assess the pretreatment immunization status against HBV infection and the rate of continuity of immunization after therapy in children with cancer.

DESIGN AND SETTING:

Retrospective case review of patients treated from 2004 to 2008.

PATIENTS AND METHODS:

We reviewed the medical records of patients treated in the departments of pediatric hematology and oncology and collected data on immunization history and hepatitis B serology. Anti-HBs antibody titers were compared before and after treatment.

RESULTS:

This study included 159 (99 males, 60 females) children who had a serologic examination. Antineoplastic therapy had been given for acute leukemia (n=66), non-Hodgkin lymphoma (n=27), Hodgkin lymphoma (n=20), and solid tumors (n=46). Fifty-one patients had not been immunized against HBV prior to the therapy; HBV serology was negative in 49 of these patients and HBsAg was positive in 2 patients. Anti-HBs antibody positivity was present in 99 of 108 patients with an immunization history, whereas no vaccination response was present in 9 patients. The titer of anti-HBs antibody was decreased below the protection level in 33 (33%) patients with positive anti-HBs antibody, whereas the protection level was found to be maintained in 66 (67%) patients. The most significant decrease (63.6%) was observed in leukemia patients. Posttreatment HBsAg and HBV DNA positivity was detected in two of the patients with negative pretreatment serology, whereas no HBV infection developed in the group with positive anti-HBs antibody.

CONCLUSIONS:

This study demonstrated the importance of routine childhood vaccination in reducing the risk of HBV infection in patients with cancer.

Intensive therapy performed on patients with cancer suppresses the immune system and makes patients vulnerable to infections. Surgical intervention and transfusion of blood products also increase the risk for hepatitis B virus (HBV) infection. HBV infection is a vaccine-preventable disease. Although children who have not received routine childhood vaccination can be immunized during cancer therapy, vaccination may not be sufficient, as cancer therapy can cause loss of acquired vaccination status. The type of cancer and the therapy applied may influence the level of antibody titer.[1] In Turkey, HBV vaccination has been given in accordance with the government vaccination program since 1998. In this study, we aimed to assess the pretreatment immunization status of patients against HBV infection, as well as the pretreatment and posttreatment antibody titers in immunized children.

PATIENTS AND METHODS

The files of all patients treated in the Departments of Pediatric Oncology and Hematology (Sisli Etfal Education and Research Hospital Clinic of Pediatrics, Istanbul, Turkey) between January 2004 and December 2008 were retrospectively examined in terms of history of HBV vaccination and serology (HBsAg, anti-HBs antibody, and anti-HBc antibody). Hepatitis B surface antigen (HBsAg), as well as the antibodies against HBsAg (anti-HBs) and HBc (anti-HBc), was examined using enzyme-linked immunosorbent assay methods. Antibody titers >10 mIU/mL were considered anti-HBs positive, and neither pretreatment nor posttreatment additional vaccination was applied. The pretreatment and posttreatment titers were compared; the effects of age, gender, antibody titer, and diagnosis on the level of antibody were evaluated in patients whose antibody titers decreased below the protection levels after the treatment. The prevalence of HBV infection among children with and without childhood vaccination was investigated. Institutional Review Board approval was not necessary since the study was restropective.

RESULTS

The median age of the 159 patients was 5 years. Sixty were male and 99 were female. Sixty-six of these patients had been treated for leukemia, 27 for non-Hodgkin lymphoma, and 46 for advanced-stage solid tumors (Table 1). Fifty-one patients had not been immunized with hepatitis B vaccine prior to treatment; HBV serology was negative in 49 of these patients, whereas HBsAg was positive in 2 of them. Anti-HBs antibody was positive in 99 of 108 patients with a history of immunization, whereas HBV serology was found to be negative in 9 patients (Table 2). Anti-HBs antibody titer results of 33 (33%) patients decreased below the protection level after treatment, whereas the protection level of anti-HBs antibody titer was found to be maintained in 66 (67%) patients. It was determined that age, gender, and pretreatment antibody titers had no influence on the posttreatment antibody titers in patients who had protective antibody levels prior to therapy. It was found that the antibody titers decreased below the protection levels in 63.6% of leukemia patients and in 15% of the other patients. In the regression analysis, having leukemia was found to be a predictive factor for the alteration of vaccination from positive responses to negative ones after treatment (P=.0001; odds ratio, 9.8). Whereas posttreatment HBsAg and HBV DNA levels were found to be positive in two of the patients with negative pretreatment serology, no HBV infection was found to have developed in the group with positive anti-HBs (Table 3).

DISCUSSION

National immunization programs play a significant role in reducing the prevalence of HBV infection, which is a vaccine-preventable disease. In Turkey, HBV vaccination has been part of the routine childhood immunization schedule since 1998. In previous years, the prevalence of HBV infection among children was approximately 5% to 14% and was remarkably higher than the prevalence shown in other developed countries.[2,3] In studies performed during that period, the prevalence of HBV infection among children with cancer was reported to be as high as 20% to 65%.[4,5] In a previous study that we performed in our clinic that examined the years between 1995 and 1998, none of the patients had received childhood immunization, and the prevalence of HBV infection was 9.4% at the time of diagnosis, whereas it was 35.8% during or after their treatment.[6] Although none of the patients had been immunized before the diagnosis of cancer in our previous study, in our present study, 68% of the patients had received childhood immunization. In the present study, we found the seroprevalence of HBV during the initial screening to be 1.3% and HbsAg to be positive in only two patients. Because vaccination for hepatitis B was started routinely in 1998 as part of the national vaccination program and because the median age of patients in our study group was 5 years, the patients in our study were vaccinated in the infantile period for hepatitis B. Despite the increase in the prevalence of pretreatment immunization in our hospital, which provides service to patients of very low socioeconomic status, 32% of the patients had not received childhood immunization and two of them had been treated for being HBV carriers. Surgical procedures and blood transfusions, in addition to immunosuppressive therapies, increase the risk of infection for hepatitis B during cancer chemotherapy.[1] Two patients who were HBsAg positive after chemotherapy were not vaccinated during the infantile period, and these patients had undergone surgical procedures during diagnosis and had multiple blood transfusions during chemotherapy. Although no problems related to HBV infection appeared in these patients during treatment, it is known that progression of HBV infection is serious in patients with cancer and the likelihood of becoming chronic is high; thus these considerations could lead to delay in cancer therapy.[1,7,8]

Immune system suppression may lead to a decrease in vaccine-mediated protection in patients who are immunized before therapy and have had a sufficient antibody titer.[1] Information about the effect of cancer therapy on vaccine-mediated immunization is not clear. There may be different factors that affect the antibody titers. Vaccine-mediated antibody titers of hepatitis B, measles, mumps, rubella, tetanus, and polio were determined to be negative by 46%, 25%, 26%, 24%, 14%, and 7%, respectively. It was found that the negativities of rubella, mumps, and tetanus antibodies were significantly influenced by age, whereas the negativity of measles antibody was significantly influenced by age and gender. The loss of antibody was more remarkable in younger patients and in girls.[9] In the present study, it was determined that age and gender had no effect on posttreatment antibody titers.

In a study performed on more homogenous types of cancers, it was determined that the decrease in vaccine -mediated antibody titers for hepatitis B was highest in patients with sarcoma and that the posttreatment antibody titers decreased below the protection level in 64% of the patients.[10] In the present study, we investigated antibody titers in a heterogeneous group of patients, including those with leukemia, lymphoma, and solid tumors. The loss of antibody titers after therapy was determined to be the highest in patients with leukemia (63.6%), and diagnosis of the disease was the unique factor that statistically significantly affected the antibody titers. In a study performed on leukemia patients only, it was determined that the vaccine-mediated immunization had been lost by 56% of patients, which is in agreement with the present study.[11] It was demonstrated that the antibody response, particularly with vaccination during intensive therapy, was shorter in children with leukemia than in those with solid tumors.[12] An anti-HBs antibody titer above 10 IU/L is considered protective for hepatitis B infection.[13] There are studies suggesting that the antibody titer should be elevated in patients with immune deficiency.[14] In the present study, a protective anti-HBs antibody titer was considered to be above 10 IU/L, and vaccination was not repeated in such patients. No statistical difference in post-treatment antibody loss was found between those with anti-HBs antibody titer above 10 IU/L and those with anti-HBs antibody titer above 100 IU/L; HBV infection did not develop in either of these groups.

Memory cells exist years after the primary immunization and protection continues, even though the level of antibody titer decreases in time in healthy children immunized with hepatitis B vaccine.[15] There are no adequate data for immune-deficient patients, and generally repeated vaccination is recommended during and after therapy in patients whose antibody levels decrease below protection levels.[1] The prevalence of infection in immunized patients and the antibody titer may also be important in the evaluation of vaccine protection. In a study performed in patients with leukemia, patients who had been immunized during therapy were compared with patients who had not been immunized in terms of the prevalence of HBV infection. A remarkable decrease was demonstrated in HBV infection in immunized patients, even though the antibody titer had not reached the protection level.[16] In the present study as well, despite the loss of antibody, we did not observe hepatitis B infection in any of the patients who received pretreatment immunization. HBV infection was observed in two patients in the group without immunization. Re-vaccination is recommended after chemotherapy, along with control of antibody levels, in all patients, especially in those with leukemias who have been prescribed chemotherapy, as not enough studies show a continuation of protectivity when antibody loss has occurred after chemotherapy.[1]

In conclusion, it may be stated that one-third of our study patients were not immunized before treatment and that HBV infection was found to have developed in two patients during therapy. In those who had received routine immunization, protection continued in 67% despite immunosuppressive therapy. No HBV infection developed in the immunized group, including those with antibody titers that had decreased below the protection levels. It is thought that routine childhood immunization is important in reducing the risk for HBV infection in patients with cancer.

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Figures and Tables

Table 1

Characteristic	Number of patients
Age	
1-16 years (median, 5 years)	159
Gender	
Female	60
Male	99
Primary disease	
Acute lymphoblastic leukemia	66
Non-Hodgkin lymphoma	27
Hodgkin-lymphoma	20
Solid tumor	46

Characteristics of the patients

Table 2

Hepatitis B serology	Number of patients		
	Not immunized	Immunized	Total
HBsAg, anti-HBs, anti-HBc (–)	49	9	58
Anti-HBs (+)	0	99	99
HbsAg (+)	2	0	2

–, Negative; +, positive.

Hepatitis B serology at the time of presentation at hospital

Table 3

Primary disease	Number of patients			
	Total	Anti-HBs (+)	Anti-HBs (−)	HBsAg (+)
Acute lymphoblastic leukemia	38	14	24	0
Non-Hodgkin lymphoma	16	13	3	0
Hodgkin lymphoma	10	6	4	0
Solid tumors	35	33	2	0

−, Negative; +, positive.

Posttreatment hepatitis B serology of the patients with positive anti-HBs antibody

Haemophilus influenzae Type b in an Immunocompetent, Fully Vaccinated ALL Survivor

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KEY WORDS

leukemia, cancer, chemotherapy, *Haemophilus influenzae* type b, vaccine, infectious disease

ABBREVIATIONS

ALL—acute lymphoblastic leukemia
Hib—*Haemophilus influenzae* type b
IV—intravenous
VZV—varicella-zoster virus

Dr Nevin acquired data, wrote the initial draft of the manuscript, made substantial contributions to subsequent revisions, and approved the final manuscript; Dr Kanter Washko provided substantial review and revision of the manuscript and approved the final manuscript; and Dr Arnold acquired data, reviewed and revised the manuscript, and approved the final manuscript.

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abstract

A 7-year-old boy with a history of recurrent acute lymphoblastic leukemia (ALL), in remission, presented to primary care clinic after 2 days of progressive right hip pain with weight-bearing activities. He was otherwise asymptomatic at the time of presentation. Blood cultures revealed Gram-negative diplococci, which prompted an MRI that was significant for a hip joint effusion and femoral head bone marrow edema. The patient had no sick contacts and no significant past medical history other than ALL. The patient had been given all recommended childhood vaccinations. Arthrocentesis and needle biopsy of the femoral neck were not diagnostic for malignancy and revealed only mild hip joint inflammation, leading to a diagnosis of osteomyelitis. The organism in the original blood culture was identified as *Haemophilus influenzae* type b, β-lactamase negative. Review of the patient's medical records showed a history of complete immunization to *Haemophilus influenzae* type b. An immunologic evaluation was made to determine if the patient retained immunity from his other vaccinations. Pathogen-specific antibody testing revealed detectable antibodies to polio but not measles, mumps, rubella, varicella-zoster virus, tetanus, diphtheria, pertussis, or hepatitis B. This loss of immunologic memory appears to be a rarely described side effect of ALL chemotherapy. There is currently no protocol to evaluate the immunologic memory of patients who underwent chemotherapy for ALL or to revaccinate them after their treatment. It is unclear whether the loss of immunologic memory is genuinely rare or is underdiagnosed because affected patients are protected by herd immunity. *Pediatrics* 2013;131:e1639–e1642

DISCUSSION

ALL is the most common cancer of childhood.[3] Over the past several decades, multidrug, combination chemotherapy regimens have become the standard of care for both initial and recurrent ALL, which has been related to a significant improvement in the 5-year survival rate for pediatric leukemia.[4] Whereas aggressive therapy has drastically reduced the recurrence of childhood leukemia, aggressive suppression of the patients' immune systems may cause a loss in humoral immunity among children who have survived ALL.[5] Multiple studies show various suboptimal levels of antibodies against routine childhood vaccines among ALL survivors.[5–10] The mechanisms of defects after chemotherapy may include a deficiency of both naive and memory T-helper cells, as well as a lack of circulating antibodies. The intensity of chemotherapy also seems to be an important factor in loss of immune memory. Ek et al[7] described a cohort in which 33% of patients undergoing standard therapy retained antibodies to tetanus, whereas no patients had detectable antibodies after high-intensity chemotherapy. There is also some evidence that revaccination is effective at restoring protective levels of antibodies among primary ALL survivors whose adaptive immunity was compromised after chemotherapy, suggesting a revaccination protocol may be warranted.[11] Although revaccination protocols already exist for bone marrow transplant recipients,[12] there are currently no widely accepted protocols for testing humoral immunity in ALL survivors, revaccinating survivors, or instructing survivors to avoid exposure to possible sources of infection.[5] In addition, no currently available data address the loss of immune memory or revaccination of survivors of relapsed ALL, for which higher cumulative doses of chemotherapy are given.

The possible defective humoral immunity in ALL survivors is of concern due to the recent reemergence of pathogens that had been largely eliminated in the United States, including Hib, pertussis, and measles.[5,13,14] Vaccination rates for Hib remains high among children aged 19 to 35 months, with >90% of children in California completing their full course of vaccinations from 1999 to 2009.[15] However, vaccination rates are not homogenous throughout states and exhibit both temporal and geographic clustering, which can leave some populations at especially high risk of local outbreaks.[16] Therefore, at-risk children may not be able to rely on herd immunity for protection against vaccine-preventable diseases.[17] Waning herd immunity is particularly worrisome for Hib, which, despite the existence of a vaccine that induces protective levels of antibodies in >99.5% of children younger than 5 years after 3 doses, continues to cause >8 million cases of serious illness and an estimated 370 000 deaths worldwide annually.[18,19] Meningitis, the most common manifestation of invasive Hib, has an average case mortality of 5%, with 10% of survivors manifesting permanent neurologic sequelae.[14] In the United States, however, the current Hib vaccination schedule has reduced the incidence of invasive Hib from 806 of 100 000 children under the age of 5 years in the prevaccination era to only 2.64 of 100 000 children in the postvaccination era.[20] These high rates of morbidity and mortality for Hib, paired with a high global disease burden, leads to a vital concern that ALL survivors be revaccinated if they lack humoral immunity from prechemotherapy vaccinations.

CONCLUSIONS

We present the first case we are aware of in which a fully vaccinated ALL relapse survivor presented with invasive Hib. This case prompted an evaluation revealing a lack of humoral immunity to nearly all previous vaccinations. Recent advances in the standard chemotherapy regimen for childhood ALL have significantly improved its 5-year survival rate. However, more aggressive chemotherapy regimens can compromise patients' humoral immunity and can leave them without antibodies from previous vaccinations.

Physicians treating survivors of ALL should consider the possibility of vaccine-preventable infections in their patient population. The case presented also indicates that additional research into the immunocompetence of ALL survivors may be indicated to determine if humoral immunity testing or revaccination should be routine practice.

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Haemophilus influenzae Type b in an Immunocompetent, Fully Vaccinated ALL Survivor

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Safety and immunogenicity of the live attenuated varicella vaccine following T replete or T cell depleted related and unrelated allogeneic hematopoietic cell transplantation (alloHCT)

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Abstract

There are limited studies assessing the live attenuated varicella vaccine following alloHCT. Due to the morbidity of varicella acquired after childhood, we immunized and retrospectively analyzed the safety and immunogenicity of this vaccine in 46 VZV seronegative patients <20 years old at HCT who achieved a CD4 cell count ≥200/ul, were off immunosuppression, and responded to ≥1 post HCT vaccines. Two vaccinated patients lacking follow-up titers were excluded from analysis. Stem cells were derived from an HLA-matched sibling (n=18) or an alternative (HLA MM related or unrelated) donor (n=26). Median time to vaccination was 4 years. Sixty-four percent of patients seroconverted following one immunization. There was no significant difference in response between recipients of a matched related or alternative donor graft (p=0.2) or between those given a TCD or T-replete alternative donor graft (p=0.27). Three of 44 patients developed a self-limited varicella-like rash within 2.5 weeks of immunization. With a median follow-up of 29.1 (range: 6.9-167.1) months, there were no subsequent cases of varicella-like rashes. No patient developed shingles. This study suggests that this vaccine is safe and immunogenic when given according to pre-set clinical and immunologic milestones, warranting larger prospective studies in patients ≥24 months following HCT as outlined in current post HCT vaccine guidelines.

Introduction

Although varicella in childhood is generally a mild disease, immunocompetent individuals who develop chickenpox later in life develop a more serious infection, associated with an increased risk of visceral disease and need for hospitalization (1,2). In individuals >20 years of age, fatal varicella is 13 times higher than that observed in children (2). Studies have documented the safety and efficacy of the live attenuated varicella vaccine in healthy children (3) and patients with a history of impaired cellular or humoral immunity (4,5), such as children with acute lymphoblastic leukemia on maintenance therapy (6), pediatric solid organ transplant recipients on chronic immunosuppressive therapy (7,8), and treated

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fiber filter paper, and counted in a liquid scintillation counter. The absolute proliferative response was calculated as the median counts per minute (cpm) of triplicate wells minus the unstimulated medium control. Each day all assays performed on patients were run in parallel with a normal control and compared to values derived from 60 normal controls evaluated every 2 years.

Statistical Analysis

Fisher's exact test and the Wilcoxon rank sum test was used to examine covariate differences between responders and non-responders. The statistical packages SAS (9.2) was used to generate the test statistics. Only p values less than <0.05 were considered statistically significant.

Patient and transplant characteristics

Patient and donor characteristics are shown in Table 1. The majority of patients were transplanted for a hematologic malignancy (57%) or primary immunodeficiency disease (23%). The stem cell donor was an HLA-A, B, DRβ1 identical sibling, a haplo-identical family member, or an unrelated donor in 41%, 14%, and 45% of cases, respectively. Seventy percent of patients received an unmodified HCT. Of the remaining thirteen patients, 8 received a bone marrow transplant T cell depleted by either soybean lectin agglutination followed by rosetting with sheep erythrocytes (n=6) (20) or treatment with the T10B9 monoclonal antibody plus complement, n=2 (21) and 5 received a a peripheral blood stem cell graft T cell depleted by CD34 positive selection followed by rosetting with sheep erythrocytes (22). Eight-nine percent of patients received myeloablative cytoreduction which contained either hyperfractionated total body irradiation (n=15) or >8 mg/kg busulfan (n=24). Three patients received non-myeloablative conditioning [(melphalan, fludarabine, anti-CD52 (n=2) or cyclophosphamide and anti-thymocyte globulin (n=1)]. Two patients with severe combined immunodeficiency disease (SCID) received an HLA matched sibling BMT without prior cytoreduction. Three patients received post transplant rituximab at 25, 49, and 50 months prior to vaccination for the treatment of a severe auto-immune hemolytic anemia following an unmodified unrelated BMT (n=1) or to prevent an Epstein Barr virus lymphoproliferative disorder following a T cell depleted unrelated peripheral blood stem cell transplant (n=2). Six patients had a history of grade II-III acute GVHD and 3 patients developed chronic GVHD, which had resolved in all patients prior to vaccination.

RESULTS

Prior to receipt of the LAVV, all patients were VZV seronegative and 42 of 44 patients lacked a T cell proliferative response against varicella antigen. The median age at vaccination was 9 years. The median time from transplant to vaccination was 4 years with a range of 0.92-14.04 years. The wide range between HCT and immunization was due to the time it took patients to discontinue immunosuppression, reach immunologic milestones, and/or physician comfort administering the LAVV. There was no significant difference in time to vaccine in recipients of T cell depleted or T-replete transplant. The median time to first LAVV was 3.9 (range: 0.92- 14.04) years following a T cell depleted HCT and 4.1(range: 1.67-9.13) years post unmodified HCT, p=0.64.

B and T cell specific responses

The median time to measure antibody levels following the initial vaccine was 108 days (range: 29-395 days). Overall, 64% (28/44) of patients seroconverted following one vaccine. There was no significant different in the proportion of responders in patients evaluated < or > 108 days post immunization (14/23 vs 15/22). Response was observed in 50% (7/14), 68% (13/19), and 73% (8/11) of patients immunized between 0.92 and 3, 3 and 5, and >5 years

>1000 cells/ul, serum IgG >500 mg/dL, and a positive skin test to a recall antigen. Of the four VZV seronegative allogeneic patients immunized, three of 4 seroconverted at 6 weeks post immunization. Kussmaul and colleagues (15) evaluated the safety of the LAVV in 18 autologous and 50 allogeneic HCT recipient, 25 of whom were evaluable for response. Eligibility for vaccination included a circulating CD4 count of ≥ 200 cells/ul, a PHA response at least 50% of the lower limit of normal, a humoral response to the inactivated polio vaccine, and specific T and B cell response to tetanus toxoid. The median time to the first LAVV was 32 months post HCT (range: 16-144 months). There were no serious vaccine related events. Although the study by Kussmaul et al did not stipulate the proportion of responders who received an autologous versus an allogeneic HCT, of the 25 patients clearly evaluable for response, seroconversion occurred in 40%, 8%, and 4% of patients after one, two, or three vaccines, respectively (16).

Our study, although retrospective, represents the largest series analyzing the response of VZV seronegative patients following HCT vaccinated with LAVV. Although an ELISA was used to assess response, the seroconversion rate following the LAVV in our study is not markedly different than the 74% conversion rate observed in healthy children when measured by the highly sensitive fluorescent antibody to membrane antigen (FAMA) (27). The latter assay requires viral propagation in tissue culture, is not commercially available, and requires considerable operator expertise. In view of this several studies ((7-9, 14,16), including ours have used an ELISA based method to measure response to the LAVV .

The risk of shingles following the LAVV has been one of the main concerns surrounding immunization of children against chickenpox particularly those with a history of or ongoing immunodeficiency (27,28) . This risk has been evaluated in children with a history of leukemia (29), pediatric recipients of solid organ transplants (7,8), and HIV infected children on retroviral therapy (9-11). Studies in these populations have not shown an increased risk of VZV . In 1989, Lawrence et al. compared the risk of shingles in children with ALL in remission who were immunized versus those with a history of natural infection (29). Of the 346 immunized children, the incidence of zoster was 0.552 cases/100 person-years. In a subset of 82 matched pairs, there was no significant difference in the incidence of shingles in patients who were vaccinated (1.23 cases per 100 person-years) compared to 3.11 cases in children with a history of varicella, respectively (p=NS). In 2009, Civen and colleagues demonstrated immunized children<10 years had a 4 to 12 times lower risk of developing shingles than children with a history of chickenpox (29).

Due to breakthrough cases of varicella in recipients of a single vaccine, the Advisory Committee on Immunization Practices (ACIP) currently recommends a two dose schedule in healthy children at 12-15 months and 4-6 years, a second dose in children, adolescents, and adults previously given only one vaccine, routine immunization of all healthy VZV seronegative individuals 13 years of age or older, and immunization of HIV-infected children and adults with circulating CD4+ T lymphocyte counts > 200 cells/ul (3). Our study supports the use of the live attenuated varicella vaccine in VZV seronegative patients. The dichotomy of T and B cell responses in some of our patients (ie seroconversion in the absence of concurrent T cell response) suggest that kinetics of recovery of lymphoid populations required for a full response may differ from patient to patients. Larger prospective trials assessing the safety, immunogenicity, protection against chickenpox, and subsequent risk of shingles following the live attenuated varicella vaccine in this population are needed. Ideally, trials should be designed to identify biological markers which might allow earlier re-vaccination of patients with the requisite T and B cell populations and prevent premature vaccination and/or risk in patients unable to respond.

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Table 1

Patient and Donor Characteristics

	N=44
Age (range) at HCT	4.5 (0.1-19) yr
Sex (male/female)	25/19
Diagnosis:	
Hematologic malignancy	**25**
Immunodeficiency (SCID/WAS)	**10 (7/3)**
Other:	**9**
Hemoglobinopathy	
Hemophagocytic lymphohistiocytosis	2
Kostman's syndrome	1
Wolman's syndrome	1
Aplastic anemia	1
Time (median, range) from HCT to vaccine	4.0 (0.92-14.04) yr
Age (range) at vaccination	8.9 (2.48-31.3) yr
Transplant type	
Unmodified (n=31)	
HLA-Matched sibling	17
Unrelated Adult donor	8
Unrelated Cord blood (single/double unit)	5 (1/4)
T cell depleted (n=13)	
HLA Matched sibling	1
HLA Mis-matched Related	6
Unrelated	7

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Differential loss of humoral immunity against measles, mumps, rubella and varicella-zoster virus in children treated for cancer

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ABSTRACT

Background: Intensive chemotherapy in children with cancer results in long-term impairment of humoral immunity. Whereas most studies to date focused on children with acute lymphoblastic leukemia (ALL), little data have been published on patients suffering from Hodgkin disease or from solid tumors. We therefore analyzed the loss of protective immunity (defined as immunity at the time of diagnosis and lack of immunity after completion of therapy) against vaccine-preventable diseases in children treated for various malignancies.
Methods: Children and adolescents <21 years of age at diagnosis and treated between 2001 and 2010 for various malignancies in the Department of Pediatric Hematology and Oncology, University of Frankfurt, were included in the retrospective chart review. Antibody levels against measles, mumps, rubella and varicella-zoster-virus (VZV) were routinely assessed at the time of diagnosis and within 12 months after completion of therapy.
Results: The study population consisted of 195 children (122 male); 80 patients had ALL, 15 acute myelogenous leukemia (AML), 18 non-Hodgkin lymphoma (NHL), 22 Hodgkin disease, and 60 various solid tumors. Overall, 27%, 47%, 19%, and 17% of the patients lost their humoral immunity against measles, mumps, rubella, and VZV, respectively. The risk of losing protective antibody titers depended on age with a higher risk in younger children. The loss of protective humoral immunity occurred significantly more often in patients with ALL compared to patients with any other underlying malignant disease (hematological malignancies such AML and NHL, Hodgkin disease or solid tumors).
Conclusions: Our data demonstrate that a significant number of children lose pre-existing humoral immunity against measles, mumps, rubella, and VZV after completion of chemotherapy. This loss occurs more often in children with ALL than in children with AML, solid tumors and Hodgkin disease. Our results underline the need for post-chemotherapy revaccination of childhood cancer survivors.

1. Introduction

Over the last decades, the number of children and adolescents who survive their cancer has dramatically increased, which is the result of better treatment strategies and better supportive care. Currently, cure rates of 75% and higher are achieved in industrial countries [1]. Survivors of pediatric cancer, however, are at risk of potential long-term consequences of therapy, such as the risk of secondary malignancies, the impairment of organ function such as cardiomyopathy or hearing loss, and secondary immunodeficiency including the loss of pre-existing protective antibody titers [2,3]. The clinical implications of losing protection against vaccine-preventable diseases are serious, since these patients are not only at risk for a potentially life-threatening infection, but may also serve as a reservoir for additional spread of these pathogens in the population. Unfortunately, the compliance with revaccination of pediatric cancer survivors is poor, as reported recently [4].

Most analyses of both chemotherapy-induced impairment and reconstitution of the immune system after completion of therapy focus on children with acute lymphoblastic leukemia (ALL), whereas little data have been published on patients suffering from Hodgkin disease or from solid tumors. Although it has been demonstrated that vaccination influences various immune responses such

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Table 1
Number of patients with underlying malignancy according to age group.

Age group	Hematological malignancies			Hodgkin disease	Solid tumors						Total
	ALL	AML	NHL		Ewing Sarcoma	Osteo-sarcoma	Nephro-blastoma	Neuro-blastoma	Medullo-blastoma	Astro-cytoma	
<2 years	10	2	0	0	0	0	1	7	1	1	22
2–6 years	41	3	4	2	1	1	7	8	6	1	74
7–12 years	21	2	8	3	2	3	0	0	1	0	40
13–21 years	8	8	6	17	6	10	0	0	3	1	59
Total	80	15	18	22	9	14	8	15	11	3	195

ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia; NHL = non-Hodgkin lymphoma.

Table 2
Humoral immunity according to underlying malignancy. Presented are the numbers of patients with protective and non-protective humoral immunity at the time of diagnosis of the underlying malignancy and after completion of chemotherapy, respectively. −/− non protective immunity at the time of diagnosis/non protective immunity after completion of chemotherapy; −/+ non protective immunity at the time of diagnosis/protective immunity after completion of chemotherapy; +/− protective immunity at the time of diagnosis/non protective immunity after completion of chemotherapy; +/+ protective immunity at the time of diagnosis/protective immunity after completion of chemotherapy.

	Hematological malignancies			Hodgkin disease	Solid tumors	Total
	ALL	AML	NHL			
Measels	−/− 0/71 (0%)	−/− 1/12 (8.3%)	−/− 1/16 (6.3%)	−/− 0/14 (0%)	−/− 2/24 (8.3%)	−/− 4/137 (2.9%)
	−/+ 1/71 (1.4%)	−/+ 0/12 (0%)	−/+ 3/16 (18.6%)	−/+ 0/14 (0%)	−/+ 0/24 (0%)	−/+ 4/137 (2.9%)
	+/− 21/71 (29.5%)	+/− 1/12 (8.3%)	+/− 0/16 (0%)	+/− 1/14 (7.1%)	+/− 0/24 (0%)	+/− 23/137 (16.8%)
	+/+ 49/71 (69%)	+/+ 10/12 (83.3%)	+/+ 12/16 (75%)	+/+ 13/14 (92.9%)	+/+ 22/24 (91.6%)	+/+ 106/137 (77.4%)
Mumps	−/− 2/69 (2.9%)	−/− 2/12 (16.6%)	−/− 2/16 (12.6%)	−/− 1/14 (7.1%)	−/− 5/22 (22.7%)	−/− 12/133 (9%)
	−/+ 12/69 (17.4%)	−/+ 1/12 (8.3%)	−/+ 3/16 (18.8%)	−/+ 1/14 (7.1%)	−/+ 0/22 (0%)	−/+ 17/133 (12.8%)
	+/− 25/69 (36.2%)	+/− 1/12 (8.3%)	+/− 1/16 (6.3%)	+/− 1/14 (7.1%)	+/− 5/22 (22.7%)	+/− 33/133 (24.8%)
	+/+ 30/69 (43.5%)	+/+ 8/12 (66.6%)	+/+ 10/16 (62.5%)	+/+ 11/14 (78.5%)	+/+ 12/22 (54.5%)	+/+ 71/133 (53.4%)
Rubella	−/− 9/62 (14.5%)	−/− 0/7 (0%)	−/− 0/13 (0%)	−/− 0/13 (0%)	−/− 0/10 (0%)	−/− 9/105 (8.6%)
	−/+ 10/62 (16.1%)	−/+ 1/7 (14.2%)	−/+ 9/13 (69.2%)	−/+ 0/13 (0%)	−/+ 1/10 (10%)	−/+ 21/105 (20%)
	+/− 13/62 (20.9%)	+/− 0/7 (0%)	+/− 0/13 (0%)	+/− 0/13 (0%)	+/− 0/10 (0%)	+/− 13/105 (12.4%)
	+/+ 30/62 (48.4%)	+/+ 6/7 (85.7%)	+/+ 4/13 (30%)	+/+ 13/13 (100%)	+/+ 9/10 (90%)	+/+ 62/105 (59%)
VZV	−/− 5/53 (9.4%)	−/− 2/6 (33.3%)	−/− 0/8 (0%)	−/− 2/10 (20%)	−/− 6/28 (21.4%)	−/− 15/105 (14.3%)
	−/+ 13/53 (24.5%)	−/+ 0/6 (0%)	−/+ 8/8 (100%)	−/+ 0/10 (0%)	−/+ 6/28 (21.4%)	−/+ 27/105 (25.7%)
	+/− 9/53 (16.9%)	+/− 0/6 (0%)	+/− 0/8 (0%)	+/− 0/10 (0%)	+/− 2/28 (7.1%)	+/− 11/105 (14%)
	+/+ 26/53 (49%)	+/+ 4/6 (66.6%)	+/+ 0/8 (0%)	+/+ 8/10 (80%)	+/+ 14/28 (50%)	+/+ 52/105 (49.5%)

VZV = varicella-zoster virus; ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia; NHL = non-Hodgkin lymphoma.

tumors (Table 2). Although the percentages of patients with the loss of humoral immunity differed considerably between patients with ALL and patients with AML or NHL, these differences did not reach statistical significance; only the risk of losing protection against measles and mumps significantly differed between patients with ALL and patients with NHL (21/70 versus 0/12, respectively, $P = 0.03$ for measles and 25/55 versus 1/11, respectively, for mumps, $P = 0.04$). None of the protection rates significantly differed between patients with AML, NHL, Hodgkin Disease, and solid tumors, respectively. However, when comparing patients suffering from ALL with patients suffering from other malignancies included in the current study (hematological malignancies such AML and NHL, Hodgkin disease or solid tumors), a loss of protective humoral immunity occurred significantly more frequently in patients with ALL. This trend was seen for measles: 21/70 versus 7/61 ($P = 0.003$), for mumps: 25/55 versus11/53 ($P = 0.008$), for rubella: 13/43 versus 0/41 ($P = 0.0001$), and for VZV: 9/35 versus 1/37 ($P = 0.006$), and was confirmed in the multivariate analysis for measles, rubella, and VZB ($P = 0.003$, $P = 0.0003$, and $P = 0.005$, respectively). Notably, among patients with ALL, standard- and medium-risk patients and patients treated according to the high-risk arm did not significantly differ regarding the loss of immunity against measles, mumps, and VZV, respectively. Only for rubella, patients in the high-risk arm had a higher risk of losing humoral immunity compared to standard/medium-risk patients (4/0 versus 9/30, $P = 0.002$).

At the time of diagnosis of the underlying malignancy, eight out of a total of 139 (6%), 28/136 (21%), 25/109 (23%), and 34/72 (32%) children were lacking humoral immunity against measles, mumps, rubella, and varicella, respectively. After completion of therapy, protective immunity unexpectedly appeared in three, six, eleven, and twelve of these unprotected patients, respectively.

4. Discussion

Our retrospective observational analysis of 195 patients demonstrated that a significant proportion of children and adolescents undergoing chemotherapy for cancer lost protective humoral immunity against vaccine-preventable diseases, namely against measles (loss of protection in 21% of the patients), mumps (33%), rubella (15%), and chickenpox (14%). Importantly, patients suffering from ALL lose their humoral protection significantly more frequently compared to children and adolescents who were treated for other malignancies. Although the reason for the loss of antibodies in blood acquired as a result of vaccination is not fully understood, the loss of humoral immunity has been demonstrated in a number of studies and has been linked to chemotherapy-induced alterations of the immune system [2,3,12]. In this regard, B cells seem to play a major role, since a quantitative loss of B cells is commonly accompanied by lower levels of immunoglobulins, and this problem lasts for months after cessation of treatment [13]. Although B-cell depletion in both bone marrow and in peripheral blood is a hallmark of intensive chemotherapeutic regimens, it also occurs as a result of less intensive anti-cancer treatment schedules, as in maintenance therapy of childhood ALL [14]. Whereas it is unlikely that physiological fluctuations in virus serum antibody levels and/or the reconstitution of the immune system after cessation of chemotherapy account for the present results [15–17], we recognize that there is a potential selection bias because the study does not include patients who

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Cancer Prevention Research

Risk Factors for Non-initiation of the Human Papillomavirus Vaccine among Adolescent Survivors of Childhood Cancer

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Abstract

Effective vaccination is now available to prevent human papillomavirus (HPV), the most common sexually transmitted infection and cause of cervical cancer. This study aimed to estimate the prevalence of HPV vaccination among childhood cancer survivors and identify factors associated with HPV vaccine initiation and completion. Mothers of daughters of ages 9 to 17 years with/without a history of childhood cancer ($n = 235$, $M_{age} = 13.2$ years, SD = 2.69; $n = 70$, $M_{age} = 13.3$ years, SD = 2.47, respectively) completed surveys querying HPV vaccination initiation and completion along with sociodemographic, medical, HPV knowledge and communication, and health belief factors, which may relate to vaccination outcomes. Multivariate logistic regression was used to identify factors that associate with HPV vaccination initiation and completion. Among cancer survivors, 32.6% initiated and 17.9% completed the three-dose vaccine series, whereas 34.3% and 20.0% of controls initiated and completed, respectively. Univariate analyses indicated no differences between cancer/no cancer groups on considered risk factors. Among all participants, multivariate logistic regression analyses found vaccine initiation associated with older age of daughter and physician recommendation, whereas increased perceived barriers associated with a decreased likelihood of initiation (all $P < 0.05$). Among those having initiated, risk factors for noncompletion included being non-White, increased perceived severity of HPV, and increased perceived barriers to vaccination (all $P < 0.05$). A minority of adolescents surviving childhood cancer has completed vaccination despite their increased risk for HPV-related complication. These results inform the prioritization of strategies to be included in vaccine promotion efforts. *Cancer Prev Res; 6(10); 1101–10. ©2013 AACR.*

Introduction

Genital human papillomavirus (HPV) is the most common sexually transmitted infection (1) and has a causal role in the expression of cervical and other cancers (2). Approximately, 80% of sexually active women are exposed to HPV during their lifetime (3), and HPV is most prevalent among females of ages 20 to 24 years (4). Rates increase sharply after the median age of sexual debut, 16.6 years for females in the United States (5). Recent efforts to reduce cervical cancer have led to the development of vaccines to protect against HPV, which are currently available and have been shown to be safe and effective (6–10). Quadrivalent HPV vaccination, approved in 2006 for females between 9 and 26 years of age (11) protects against HPV types 16 and 18 (which account for 70% of cervical cancers) and 6 and 11 (which account for 90% of genital warts; ref. 12). In 2009, HPV vaccination was also approved for males (13).

Routine HPV vaccination is currently recommended by the Advisory Committee on Immunization Practices for adolescent girls of ages 11 and 12 years, with catch-up vaccination for women through 26 years of age (14). It is recommended that the vaccine be administered before sexual debut due to the mechanism of HPV transmission (11). With appropriate use of the vaccine, the American Cancer Society estimates a potential reduction of cervical cancer risk by more than 70% over the next decade (15, 16). HPV vaccine uptake is particularly important for females surviving childhood cancer, many of whom are at increased risk for HPV-related complications secondary to the direct and indirect effects of cancer treatment. Survivors at increased risk for HPV persistence and complications include those with a history of hematopoietic stem cell transplantation (17), Hodgkin lymphoma (18, 19), treatment with pelvic irradiation (20, 21), and those receiving other cancer treatments resulting in sustained immunosuppression (22–26). Survivors of childhood cancer seem to also be at increased risk for HPV infection/complication/escalation given the unique behavioral, cognitive, and

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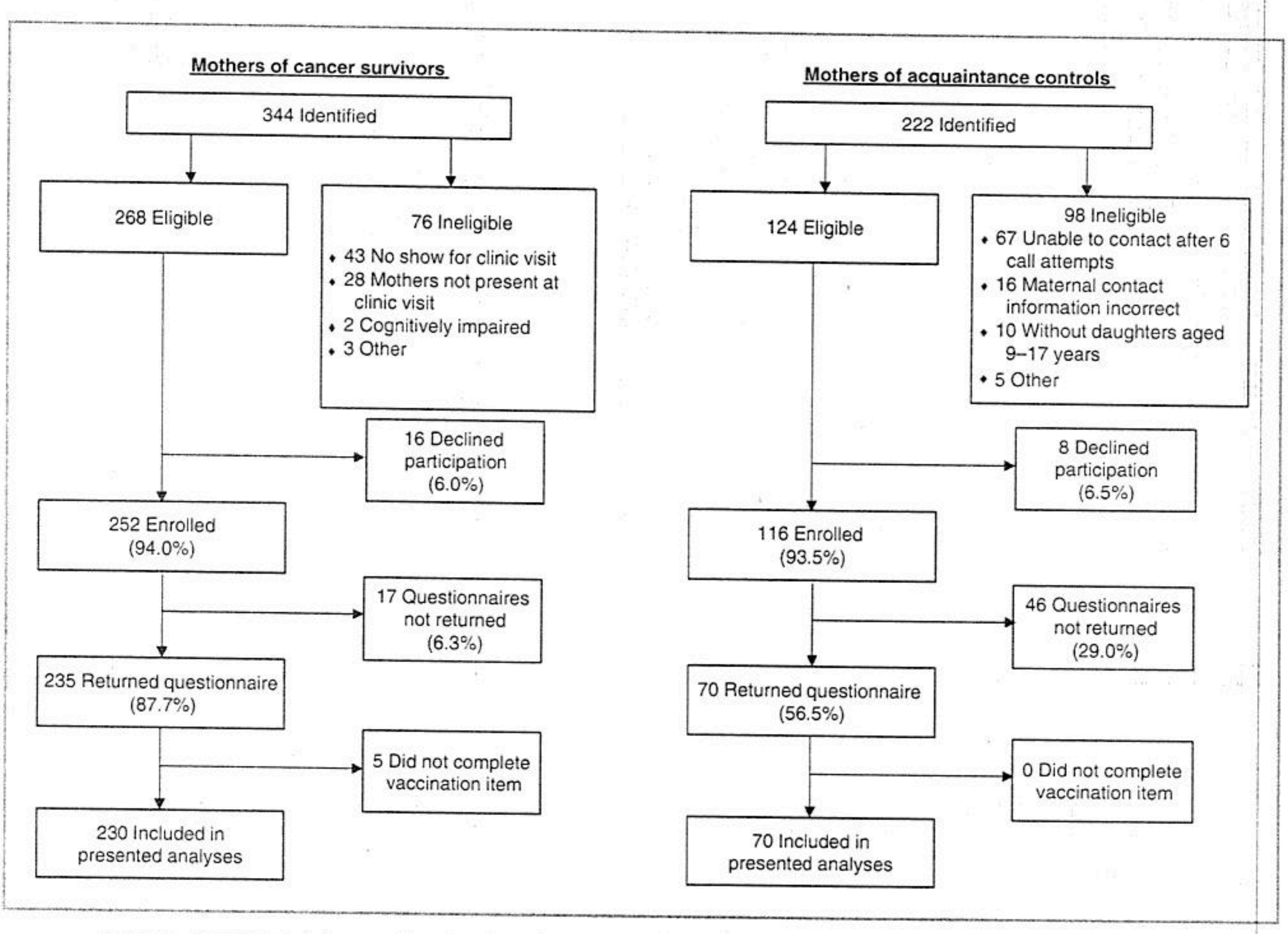

Figure 1. Flowchart depicting recruitment and questionnaire completion for mothers of cancer survivors and mothers of controls.

status, education level, and annual household income, along with medical history of gynecologic care and cervical cancer screening. Items were adapted from instruments previously used in the HPV vaccine literature (refs. 42–44; Table 1). Items measuring maternal perceptions of daughter's sexual activity and relationship status were also adapted from previous self-report questionnaires (41).

HPV knowledge and communication

Knowledge of HPV, cervical cancer, and HPV vaccination was measured by a scale adapted from Brabin and colleagues (42). Correct responses to 10 multiple-choice items were summed for a total knowledge score, with higher scores representing greater knowledge. The questionnaire content was abstracted from the Centers for Disease Control and Prevention (CDC) HPV vaccination information website as well as other sources (42, 45). Familial communication about the messages and purpose of HPV vaccination was assessed via a four-item scale also adapted from Brabin and colleagues (42). The 18-item Mother–Adolescent Sexual Communication Instrument assessed maternal–adolescent sexual behavior and development communication (46). Internal reliability in our sample was high ($\alpha = 0.92$) and convergent and discriminant validity have been previously established and described (46). Communication scores were recoded into binary variables (median splits) before model inclusion: HPV communication (Mdn = 14; range, 4–16), and sexual communication (Mdn = 68; range, 18–90).

Health beliefs

The HPV Vaccine Health Beliefs Questionnaire (47) is a validated instrument designed to measure maternal perceptions of daughters' vulnerability to HPV, severity of HPV, barriers to, benefits of, and self-efficacy for initiating/completing the vaccine. Internal reliability was acceptable for all subscales in our sample: vulnerability ($\alpha = 0.95$), severity ($\alpha = 0.87$), barriers ($\alpha = 0.81$), benefits ($\alpha = 0.82$), and self-efficacy ($\alpha = 0.91$). Cox and colleagues (47) also found the internal reliabilities of these factors to be robust, which contributed to establishing the predictive validity of health belief factors as it relates to HPV vaccination acceptability among mothers of girls of ages 11 to 16 years. Additional measures of vaccine-related Cues to Action and Social Environmental Influence were also considered with scales adapted from previously validated surveys (42–44, 47). Health belief scores were recoded into binary variables (median splits) before model inclusion: vulnerability (Mdn = 12.0;

Table 2. Univariate analysis for sociodemographic and medical factors by HPV vaccination status

	Not initiated $n = 201$[e] Freq (%)	Initiated $n = 99$ Freq (%)	Incomplete[d] $n = 43$ Freq (%)	Complete $n = 56$ Freq (%)
Health status				
Cancer survivor	155 (67.4)	75 (32.6)	33 (44)	42 (56)
Healthy control	46 (65.7)	24 (34.3)	10 (41.7)	14 (58.3)
Race of maternal caregiver				
White	160 (69.9)	69 (30.1)[c]	25 (36.2)	44 (63.8)[b]
Non-White	41 (57.7)	30 (42.3)	18 (60)	12 (40)
Age of daughter, y				
9–13	123 (81.5)	28 (18.5)[a]	15 (53.6)	13 (46.4)[b]
14–17	78 (52.3)	71 (47.7)	28 (39.4)	43 (60.6)
Daughter sees OB/GYN				
No	173 (72.7)	65 (27.3)[a]	28 (43.1)	37 (56.9)
Yes	24 (45.3)	29 (54.7)	12 (41.4)	17 (58.6)
Daughter gets yearly Pap test				
No	185 (70.9)	76 (29.1)[a]	32 (42.1)	44 (57.9)
Yes	10 (37.0)	17 (63)	7 (41.2)	10 (58.8)
Doctor recommended vaccine				
No	126 (88.7)	16 (11.3)[a]	10 (62.5)	6 (37.5)[c]
Yes	64 (45.1)	78 (54.9)	30 (38.5)	48 (61.5)
Allowed to date				
No	151 (76.6)	46 (23.4)[a]	24 (52.2)	22 (47.8)[c]
Yes	39 (45.3)	47 (54.7)	16 (34)	31 (66)
Current relationship				
No	174 (70.4)	73 (29.6)[b]	34 (46.6)	39 (53.4)
Yes	23 (52.3)	21 (47.7)	6 (28.6)	15 (71.4)
Past relationship				
No	172 (72.6)	65 (27.4)[a]	30 (46.2)	35 (53.8)
Yes	18 (40)	27 (60)	11 (40.7)	16 (59.3)
Sexually active, current				
No	185 (68.8)	84 (31.2)[c]	37 (44)	47 (56)
Yes	7 (46.7)	8 (53.3)	3 (37.5)	5 (62.5)
Sexually active, past				
No	179 (69.6)	78 (30.4)[a]	35 (44.9)	43 (55.1)
Yes	10 (38.5)	16 (61.5)	5 (31.3)	11 (68.8)
Predict sexual activity by high school graduate				
No	121 (70.3)	51 (29.7)[b]	20 (39.2)	31 (60.8)
Yes	27 (50.9)	26 (49.1)	12 (46.2)	14 (53.8)
Not sure	45 (72.6)	17 (27.4)	9 (52.9)	8 (47.1)

[a]$P < 0.01$; [b]$P < 0.05$; [c]$P < 0.10$; these P values are associated with χ^2 tests that examined group differences on the variables.
[d]Percentage based on number having received at least one dose of HPV vaccine.
[e]All n's may not equal 300 or 99 due to missing data.

combined in the presented multivariate models. Participant status (cancer vs. control) was also retained as a factor in both models.

Results

Univariate cancer/control comparisons

Univariate differences emerged between cancer/no cancer groups on risk factors including vulnerability to HPV infection and complication ($P = 0.04$) and prediction of daughter's sexual activity ($P = 0.09$). Specifically, mothers of daughters with a cancer history perceived their child to be more susceptible to HPV infection and complication, but were less likely to predict that their daughters would be sexually active by high school graduation. No other significant cancer/control differences were found on any other sociodemographic and medical history variables, HPV-specific knowledge and communication variables, or health belief variables.

Table 4. Multivariate logistic regression for factors associating with HPV vaccination initiation[a]

Variable	OR (95% CI)	*P*
Health status		
Cancer survivor	1.00	
Healthy control	1.14 (0.43–2.98)	0.796
Daughter's age, y		
Preadolescents, 9–13	1.00	
Adolescents, 14–17	5.82 (2.00–16.91)	0.001
Doctor recommended vaccine		
No	1.00	
Yes	6.54 (2.56–16.73)	0.000
Health belief factor: vulnerability		
Low	1.00	
High	0.45 (0.19–1.04)	0.062
Health belief factor: barriers		
Low	1.00	
High	0.26 (0.10–0.70)	0.008

[a]Only variables that were significant or marginally significant predictors in the multivariate analyses are included in this table, with the exception of the cancer/no cancer groups.

Table 5. Multivariate logistic regression for factors associating with HPV vaccine completion[a]

Variable	OR (95% CI)	*P*
Health status		
Cancer survivor	1.00	
Healthy control	1.13 (0.36–3.58)	0.839
Race of maternal caregiver		
White	1.00	
Non-White	0.26 (0.07–0.89)	0.032
Daughter's age, y		
Preadolescents, 9–13	1.00	
Adolescents, 14–17	4.83 (0.93–25.05)	0.061
Health belief factor: vulnerability		
Low	1.00	
High	0.27 (0.07–1.11)	0.069
Health belief factor: severity		
Low	1.00	
High	0.17 (0.05–0.61)	0.007
Health belief factor: barriers		
Low	1.00	
High	0.21 (0.06–0.74)	0.015

[a]Only variables that were significant or marginally significant predictors in the multivariate analyses are included in this table, with the exception of the cancer/no cancer groups.

Discussion

Advances in the treatment of childhood cancer have resulted in the majority of survivors living into adulthood (48, 49). Given the reduction of mortality associated with cancer treatment, increased attention has been placed on promoting health and quality of life in survivorship (29, 50). HPV vaccination is one tool to assist in these efforts, and as such, a need exists to better understand vaccine prevalence and determinants in this vulnerable group.

On the basis of maternal report, the results of our study found that 32.6% of cancer survivors have initiated the vaccine series, whereas 17.9% have completed it. No differences in vaccine rates were identified between cancer survivors and acquaintance control groups, but univariate differences in known risk factors for vaccine initiation and completion did emerge. Specifically, mothers of survivors perceived greater vulnerability to HPV-related complication upon patient exposure but were less likely to believe that their daughters would engage in sexual activity before high school graduation. Although survivors are at increased risk for HPV-related complication, they did not engage in higher rates of vaccination. Cancer survivors and control participants were similar on many risk factors previously identified as being predictive of vaccination status, including age (39) physician recommendation (51–54) and race (36, 38, 55). The similarities between groups are consistent with previous research that identified no differences in risky sexual behavior between adolescent childhood cancer survivors and healthy siblings (56). Conceivably, interventions designed to increase vaccine uptake in the healthy population may be generalizable for use among childhood cancer survivor populations as well based on these similarities.

Among the entire sample, the modeling of determinants associated with vaccine initiation found that older daughter age and physician recommendation were both related to increased vaccine uptake, whereas perceptions of high vaccine barriers were associated with decreased initiation. Our study aligns with previous research showing that physician recommendation for HPV immunization is a robust predictor of vaccine uptake (52, 57). It is interesting to note that only half of all mothers endorsed physician recommendation for HPV vaccination. Amidst the nonsignificant cancer/control differences described in the results, a trend was seen in which a minority of survivor families received a physician recommendation for vaccination, whereas a majority of controls reported receiving one. This is discouraging given survivors' frequency of medical encounters and their increased risk for HPV-related complication (58). These data suggest potential confusion in vaccine management in that some primary care physicians may assume that oncologists are managing this aspect of care and *vice versa*. This lack of clarity may account for these less than optimal vaccine rates in the cancer group, and physician communication/recommendation may be targets of future intervention, particularly in light of physician recommendation being predictive of vaccine initiation. Physician endorsement of HPV vaccination, as well as problem-solving specific to perceived barriers to vaccine initiation or

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Risk Factors for Non-initiation of the Human Papillomavirus Vaccine among Adolescent Survivors of Childhood Cancer

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