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Time to consider HPV vaccination after allogeneic stem cell transplantation

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Abstract

Squamous cell carcinoma (SCC) is among the most common secondary cancers after allogeneic stem cell transplantation (allo-SCT). Several types of human papillomavirus (HPV) are causally linked with SCC of the genital tract and head & neck, and the incidence of these cancers is higher among immunosuppressed patients compared to immunocompetent patients. In June 2006, a quadrivalent HPV vaccine was approved by the Food and Drug Administration (FDA) for females aged 9–26 to prevent cervical warts and vulvar, vaginal, and cervical cancer. FDA approval was granted in October 2009 for males aged 9–26 to prevent genital warts. The quadrivalent HPV vaccine is now available for off-label use and may be beneficial to patients after allo-SCT. It is time to evaluate the immunogenicity and efficacy in preventing HPV-related squamous cell carcinoma in this population.

Keywords

HPV; vaccination; secondary cancer; squamous cell carcinoma; transplantation

Human papilloma virus and squamous cell cancer in immunosuppressed patients

The incidence of virus-related malignancies is increasing among immunosuppressed populations, such as transplant recipients receiving immunosuppressive therapy and HIV-infected patients. The increased incidence of cancer in these two populations suggests that

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immunodeficiency is the common risk factor predisposing to the heightened risk of malignancy. As the life expectancy for chronically immunosuppressed patients continues to rise, malignancy will likely become an increasingly common complication for these patients. Studies of cancer epidemiology among transplant recipients can potentially inform our understanding of which viruses are associated with malignancy in this population.

Among immunosuppressed patients, the risk for developing squamous cell carcinoma (SCC) is 64–250 times greater than among the general population.[1–3] Several oncogenic types of human papillomavirus (HPV) have been implicated in the etiology of SCC of the female genital tract and head & neck; of these, HPV 16 and 18 are most frequently cited.[1;2;4] Significantly higher levels of HPV DNA have been reported in SCC from immunocompromised versus immunocompetent patients, possibly due to higher HPV viral loads in the former. A recently published meta-analysis showed that HIV-infected patients and solid organ transplant recipients had an increased incidence of HPV-related cancers, including those of the uterine cervix, vulva, vagina, penis, anus, oral cavity and pharynx.[2] The strikingly increased risk of HPV-related cancers seen in long-term transplant survivors suggests that even a modest level of immune suppression, if present for enough time, could increase the risk of those cancers.[1;2;4;5] Other factors playing a role in the onset of HPV-related benign and malignant tumors include the degree and duration of immunosuppression, age of transplant recipient, and immune system recovery after transplantation.

Approximately 70% of HPV infections in immunocompetent women are eventually cleared in one year. Natural immunity against HPV involves innate and adaptive immune responses, predominated by a robust, local cell-mediated immunity, which is associated with lesion regression and generation of serum neutralizing antibodies.[6;7] Clearance of HPV infection is diminished among immunocompromised individuals, and reactivation and progression to neoplastic lesions become more likely.[7–9]

Reactivation of latent DNA viruses has been well documented in immunocompromised hosts. A large proportion of these are herpes viruses, such as herpes simplex, varicella zoster, human herpes virus 6, Epstein-Barr, and cytomegalovirus. Hepatitis B virus has also been found to reactivate following allogeneic stem cell transplantation (allo-SCT). By extension, we hypothesize that HPV may reactivate and eventually lead to SCC in long-term survivors of allo-SCT. In over 90% of HPV-infected healthy individuals, anti-HPV antibodies develop and the virus is cleared from the serum, indicating resolution of infection. However, many patients in whom HPV has been eliminated from the serum still have detectible HPV DNA in tissues such as the female genital tract and oral mucosa. After allo-SCT, renal transplantation, HIV infection, or intensive chemotherapy, dormant HPV may reactivate in those sites. Late-onset HPV reactivation may be predicted by monitoring the progressive disappearance of anti-HPV antibodies.[1;4;10;11] While it is possible that a new HPV infection could occur in an immunocompromised host, reactivation of latent HPV may be an important cause of HPV-related malignancies in this population.[1;4]

Secondary malignancies in allogeneic stem cell transplant recipients

Currently, more than 15, 000– 20, 000 patients undergo an allo-SCT annually throughout the world, with the number of long-term survivors increasing rapidly. As stem cell transplantation becomes safer, more than 80% of patients living 2 years after allo-SCT will become long-term survivors. As patients age after transplantation, the focus of care moves beyond cure of the original disease to the identification and treatment of chronic complications that can affect quality of life. Chronic graft-versus-host disease (cGVHD) has attracted the most attention, but large database analyses have identified other problems that occur in sizeable numbers, such as hypothyroidism, secondary malignancies, pulmonary

complications, congestive heart failure, metabolic syndrome, infertility, and premature menopause. Large population-based studies in transplant recipients have shown that a wide range of cancers could be associated with immune deficiency. Compared to recipients of autologous SCT, recipients of allo-SCT are at increased risk for chronic sequelae of transplantation for two reasons: complications from the immunosuppression needed to prevent GVHD, and the immunosuppressive effect of GVHD itself.

Relative mortality decreases with time from allo-SCT but remains significantly elevated. One of the most devastating long-term complications is the development of a second cancer, which occurs more frequently than in the general population. In the largest study of over 28,000 patients after allo-SCT, the risk for SCC was 5 times higher in patients with a history of cGVHD than in the general population.[12] In a recent study, 25% of late mortality after allo-SCT was attributed to treatment-related causes, including 7% due to secondary cancers in long-term survivors.[13] The association between HPV and SCC of the oral cavity, female genital tract, and skin is well established in the general population and immunosuppressed populations like HIV patients and solid organ transplant recipients.

HPV vaccine in immunosuppressed patients, safety among males, and clinical data

Reported prevalence of genital HPV infection in the general population ranges from 20% to 46%, and is as high as 64% in clinic-based populations.[1;14–16] Although HPV infection is common, studies suggest approximately 90% of infections clear within 2 years. Interestingly, a study investigating asymptomatic HPV infection of the oral cavity, using consensus PCR to detect HPV in oral brushings, revealed HPV DNA in 18% of samples from renal transplant patients versus 1% of samples from control patients ($P<0.001$).[17] The fact that HPV 16 and 18 predominate in SCC of the uterine cervix and head & neck suggests that the newly developed prophylactic HPV vaccines for cervical cancer might be useful to prevent SCC. The success of this strategy would depend upon the proportion of cancers that are HPV 16- or 18-positive and therefore preventable by HPV vaccination. The prevalence of HPV-related SCC in HIV patients and organ transplant recipients provides a strong rationale for HPV vaccination in both male and female recipients of allo-SCT. Vaccination might result in a substantially decreased incidence of SCC and benign HPV-related lesions after allo-SCT. Validation of this approach would require long-term follow up in a large patient population. An important first stem is to document the immunogenicity of HPV vaccinations in allo-SCT recipients.

HPV-quadrivalent vaccine is comprised of virus-like particles (VLP), which are the L1 capsid proteins from HPV types 6, 11, 16, and 18. When given according recommended schedule: 0.5 ml intramuscularly in 3 doses, 0, 2 and 6 months, the vaccine has shown efficacy in preventing persistent female genital HPV infection and HPV-related cervical dysplasia for up to 5 years. It is FDA-approved for use in females and males aged 9–26 for the prevention of cervical, vulvar and vaginal cancer and genital warts caused by the aforementioned HPV types. It is estimated that 25% of U.S. females aged 13–17 received the vaccine in 2007. Immunocompromised patients are at increased risk of latent HPV reactivation, new HPV infection, and rapid progression to pre-malignant and malignant lesions. Vaccination might halt or prevent serious sequelae of infection in this group. Since these vaccines are prophylactic, it is assumed that maximum effectiveness will be achieved by administration before exposure to HPV or viral reactivation. As HPV VLP vaccines are highly immunogenic—increasing antibody production as well as stimulating innate and cellular immunity—vaccinating individuals could offer a boosting effect of previously acquired natural immunity.[10;18;19]

Studies in male adolescents aged 9–15 years have shown immune responses to HPV vaccines similar to those in girls.[20] Giuliano and Palefsky presented data on the safety and efficacy of HPV-quadrivalent vaccine in decreasing the incidence of HPV infection and HPV-related genital disease among 4065 young men.[21] Guris, et al. showed that 7 months after receiving HPV-quadrivalent vaccine, seroconversion among young men was 98.9, 99.2, 98.8 and 97.4% against HPV 6, 11, 16 and 18, respectively.[22] A study by Reisinger, et al. showed no vaccine-related serious adverse events among male recipients of HPV-quadrivalent vaccine.[23]

Data about the safety of HPV vaccination in immunosuppressed persons is available for patients with HIV. Weinberg, et al. investigated the safety and immunogenicity of HPV-quadrivalent vaccine in HIV-infected children who were being treated with antiretrovirals.[24] Among 82 subjects who were HPV-seronegative at baseline, 98, 99, 100 and 95% of subjects seroconverted for HPV 6, 11, 16, and 18, respectively, 28 weeks after vaccination. Cell-mediated immunity, as determined by ELISPOT assays, was detected in 36 of 60 HIV-infected children at 28 weeks after immunization with HPV-quadrivalent vaccine. There was no significant difference in the proportion of grade ≥3 adverse reactions for vaccine and placebo.

Data on immunogenicity and clinical effectiveness of quadrivalent HPV vaccine in allo-SCT recipients are lacking. Despite the several-fold increase in the overall incidence of cervical dysplasia and squamous cell carcinoma in patients with SCT, optimal HPV screening strategies and the effect of HPV vaccination on transplant recipients are largely unknown. Experience with other vaccines is rather encouraging in allo-SCT, although increased dosages or altered administration schedules are occasionally required. Also, shorter intervals between booster vaccinations might be considered for this group of patients. Thus, although future recipients of SCT will likely have received the HPV vaccine at a younger age, boosters after SCT will likely still be required for optimal protection.

Despite the safety and theoretical efficacy of the vaccine, several questions remain before HPV vaccination can be proposed as the standard of care post-SCT: How long will the vaccine confer protection in immunosuppressed patients? How effective is the current vaccination schedule in immunosuppressed patients? To investigate whether the quadrivalent, recombinant HPV vaccine reduces late morbidity and mortality from secondary SCC in long-term survivors after allo-SCT, ideally a large, multicenter, randomized, placebo-controlled study would be conducted given the low absolute rate of secondary SCC. The protective effect against malignant and pre-malignant lesions will only be measurable 5–10 years after vaccination—the timeframe during which HPV-related cancers are likely to develop. Now is an opportune time to examine the immunogenicity and long-term efficacy of HPV vaccination in SCT recipients.

Reference List

1. Savani BN, Goodman S, Barrett AJ. Can routine posttransplant HPV vaccination prevent commonly occurring epithelial cancers after allogeneic stem cell transplantation? Clin.Cancer Res. 2009; 15:2219–2221. [PubMed: 19293253]
2. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet. 2007; 370:59–67. [PubMed: 17617273]
3. Dubina M, Goldenberg G. Viral-associated nonmelanoma skin cancers: a review. Am.J.Dermatopathol. 2009; 31:561–573. [PubMed: 19590418]
4. Savani BN, Stratton P, Shenoy A, et al. Increased risk of cervical dysplasia in long-term survivors of allogeneic stem cell transplantation--implications for screening and HPV vaccination. Biol.Blood Marrow Transplant. 2008; 14:1072–1075. [PubMed: 18721771]

5. Villeneuve PJ, Schaubel DE, Fenton SS, et al. Cancer incidence among Canadian kidney transplant recipients. Am.J.Transplant. 2007; 7:941–948. [PubMed: 17331115]
6. Stanley M. Immune responses to human papillomavirus. Vaccine. 2006; 24(Suppl 1):S16–S22. [PubMed: 16219398]
7. De VH, Franceschi S. Human papillomavirus vaccines in HIV-positive men and women. Curr.Opin.Oncol. 2007; 19:470–475. [PubMed: 17762573]
8. Strickler HD, Palefsky JM, Shah KV, et al. Human papillomavirus type 16 and immune status in human immunodeficiency virus-seropositive women. J.Natl.Cancer Inst. 2003; 95:1062–1071. [PubMed: 12865452]
9. Moscicki AB. Human papillomavirus infection in adolescents. Pediatr.Clin.North Am. 1999; 46:783–807. [PubMed: 10494257]
10. Gillison ML, Chaturvedi AK, Lowy DR. HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women. Cancer. 2008; 113:3036–3046. [PubMed: 18980286]
11. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. J.Natl.Cancer Inst. 2009; 101:1120–1130. [PubMed: 19648510]
12. Rizzo JD, Curtis RE, Socie G, et al. Solid cancers after allogeneic hematopoietic cell transplantation. Blood. 2009; 113:1175–1183. [PubMed: 18971419]
13. Bhatia S, Francisco L, Carter A, et al. Late mortality after allogeneic hematopoietic cell transplantation and functional status of long-term survivors: report from the Bone Marrow Transplant Survivor Study. Blood. 2007; 110:3784–3792. [PubMed: 17671231]
14. Tarkowski TA, Koumans EH, Sawyer M, et al. Epidemiology of human papillomavirus infection and abnormal cytologic test results in an urban adolescent population. J.Infect.Dis. 2004; 189:46–50. [PubMed: 14702152]
15. Dunne EF, Unger ER, Sternberg M, et al. Prevalence of HPV infection among females in the United States. JAMA. 2007; 297:813–819. [PubMed: 17327523]
16. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. NEJM. 1998; 338:423–428. [PubMed: 9459645]
17. Rose B, Wilkins D, Li W, et al. Human papillomavirus in the oral cavity of patients with and without renal transplantation. Transplantation. 2006; 82:570–573. [PubMed: 16926603]
18. Barr E, Sings HL. Prophylactic HPV vaccines: new interventions for cancer control. Vaccine. 2008; 26:6244–6257. [PubMed: 18694795]
19. Kenter GG, Welters MJ, Valentijn AR, et al. Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia. N.Engl.J.Med. 2009; 361:1838–1847. [PubMed: 19890126]
20. Block SL, Nolan T, Sattler C, et al. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. Pediatrics. 2006; 118:2135–2145. [PubMed: 17079588]
21. Giuliano, A.; Palefsky, J. Efficacy against male genital disease and infection IPC 2009. 25t International Papillomavirus Conference & Clinical Workshop; Malmo, Sweden. May 8–14, 2009; p. 01-07.2009
22. Guris, D. The immunogenicity of Quadrivalent HPV (types 6/11/16/18) vaccine in young men. 25t International Papillomavirus Conference & Clinical Workshop; Malmo, Sweden. May 8–14, 2009; p. 5772009
23. Reisinger KS, Block SL, Lazcano-Ponce E, et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. Pediatr.Infect.Dis.J. 2007; 26:201–209. [PubMed: 17484215]
24. Weinberg, A.; Song, LY.; Handelsman, E. Safety and immunogenicity of a quadrivalent vaccine to prevent human papilloma virus infection in HIV-infected children: IMPAACT P1047. 15th Conference on Retroviruses and Opportunisitic Infections; Boston, MA. Feb 3–6 2008; p. 619a