Can Routine Posttransplant HPV Vaccination Prevent Commonly Occurring Epithelial Cancers after Allogeneic Stem Cell Transplantation?

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Abstract

The association between squamous cell carcinoma (SCC) of the oral cavity, female genital tract, and skin with human papilloma virus (HPV) subtypes is well established in the general population and in solid organ transplant recipients, but no consistent link has been reported between HPV infection and SCC after allogeneic stem cell transplantation (allo-SCT). Studies are needed to determine if SCC, the most common secondary malignancy after allo-SCT, which is linked to chronic graft versus host disease and immunosuppressive therapy, is HPV related. Consideration should be given to assessing pretransplant HPV antibodies to identify patients at risk for HPV reactivation. If a strong relationship between HPV and second malignancies after SCT exists, studies to evaluate the immunogenicity and efficacy of quadrivalent HPV vaccine (subtypes 6, 11, 16, and 18) should be considered in both male and female long-term survivors after allo-SCT.

Relative mortality decreases with time from allogeneic stem cell transplantation (allo-SCT), but remains significantly elevated (1, 2). One of the most devastating long-term complications is the development of a second cancer that has a significantly higher incidence than in the general population (3–8). In a large multicenter, European study, the actuarial risk of second malignances at 15 years was 11.5 ± 2.3% (3). In the largest study of over 28,000 patients after allo-SCT, the risk for squamous cell carcinomas (SCCs) was five times higher than in the general population in patients with a history of chronic graft versus host disease (cGVHD) (ref. 4). A recent study showed late mortality attributed to treatment-related causes in 25% of the cases; in 7%, mortality was due to secondary cancer in long-term survivors after allo-SCT (2). Individuals in this large study were 3.6 times more likely to have died of a new malignancy. In this review, we discuss the common secondary solid cancers associated with immunosuppression, their link with human papilloma virus (HPV), and the implications for HPV vaccination in long-term allo-SCT survivors.

Common Secondary SCC after Allo-SCT

Solid cancers have a long latency period, but they are increasingly encountered because long-term survival after SCT has improved (3–6). In a recently published multi-institutional cohort of 28,874 allo-SCT recipients, the risk of secondary solid cancer risk rose three-fold among patients followed for longer than 15 years after transplant (4). Radiation was a significant risk factor for the development of mainly non-SCC (breast, thyroid, brain and CNS, bone and connective tissue, and melanoma), whereas cGVHD and immunosuppressive therapy (IST) were shown to contribute to an excess risk of SCC (4, 9, 10). Occurrence of cGVHD was associated with a five-fold increased risk of SCC (4), confirming earlier reports (7, 9). Importantly, in this large series, there was no association between SCC risk and radiation exposure. Both the duration of IST and the use of particular immunosuppressive agents have been shown to contribute to secondary cancers, especially SCC (3–5, 7, 9, 10). Head and neck, female genital tract, and skin are frequently reported SCCs after allo-SCT (3–6). The median time from allo-SCT to diagnosis of solid malignancy was 3.3 to 6.8 years (6), but a plateau has not yet been reached in long-term follow-up, and the cumulative incidence continues to rise.

Head and neck SCC. There is an increased risk of tumors of the oral cavity after allo-SCT (3–5). Bhatia and colleagues (5) reported a 17 times higher risk of cancer of the oral cavity in long-term survivors. In this study, all patients with SCC of the oral cavity (excluding salivary gland tumors) also had cGVHD, as did the patient who developed SCC of the esophagus. The Center for International Blood and Marrow transplant Research (CIBMTR) and investigators from the Fred Hutchinson Cancer Research Center reported a six-fold higher risk both for oral and skin SCCs after allo-SCT (7).

Female genital cancer. Cervical SCC is a frequent second solid tumor in long-term SCT survivors (3–5, 7). A 13-fold increased risk compared to the general population has been reported (5). Older age at transplantation was associated with an increased risk of cervical cancer (>34 years; 18.5× higher risk). We reported a higher prevalence of cervical dysplasia in long-term survivors after allo-SCT (occurring in more than one-third of patients). Prolonged IST for cGVHD was an independent factor associated with cervical dysplasia (11). Lower
Human papillomavirus (HPV) has been linked to cervical, skin, and oral cavity cancer. These are also common second malignancies in long-term survivors after allogeneic stem cell transplantation (allo-SCT). Here, we present data linking squamous cell cancer (SCC) occurring after SCT with immunosuppression predisposing to reactivation human papilloma virus. This association is of clinical importance because it is now possible to vaccinate SCT recipients against HPV16 and HPV18, which account for the majority of HPV types detected in SCC occurring in the general populations and after solid organ transplantation. Our data provide a strong rationale for HPV vaccination in males and females since SCC occurs equally in both sexes after allo-SCT. To reduce late morbidity and mortality from secondary SCC in long-term survivors after allo-SCT, it would therefore be timely to establish a multicenter, randomized study of the safety and effectiveness of HPV vaccination.

Skin SCC. Skin cancers, especially SCC, are the most common IST-related tumors (13, 14). Depending on the intensity of IST, their prevalence varies from 40% to 70% (13−15). Many publications excluded skin cancer during their analysis for second malignancies, but in those studies that included it, an association was demonstrated between SCC of skin and cGVHD/IST (3−5).

HPV Infection in the Immunocompromised Host

The reported prevalence of genital HPV in the general population ranges from 20% to 46% (16−19), and in clinic-based populations, a prevalence as high as 64% has been reported (20) (an order of magnitude higher than the prevalence of N gonorrhea, Chlamydia trachomatis, T vaginalis, or M genitalium). Although HPV infection is common, studies suggest that ~90% of infections clear within 2 years (21).

Interestingly, a study investigating asymptomatic HPV infection in oral cavity brushes collected for HPV analysis by consensus PCR showed HPV DNA in 18% of renal transplant versus 1% control samples (P < 0.001) (ref. 22). In addition, in the renal transplant group, the risk of an HPV-positive sample was higher in older patients (P = 0.05). The high rate of HPV carriage is noteworthy; this study extends previous observations of asymptomatic infection and identifies IST and older age as risk factors for oral HPV infection.

Reactivation of latent DNA viruses has been well documented in immunocompromised hosts. Herpes viruses such as herpes simplex, varicella zoster, human herpes virus 6, Epstein-Barr, and cytomegalovirus reactivations are well recognized, and hepatitis B virus has also been found to reactivate after allo-SCT (23). Similarly, HPV may reactivate and lead to SCC in long-term SCT survivors. The appearance of anti-HPV antibodies and the clearance of HPV from the serum occur in over 90% of individuals and indicate resolution of infection. However, many patients in whom HPV has been eliminated from the serum still have detectable HPV DNA in tissues such as skin, oral cavity, and the female genital tract, as discussed above (13, 14, 16, 22, 24). After allo-SCT, renal transplantation, or intensive chemotherapy, dormant HPV may reactivate in these sites. Late-onset HPV reactivation can be predicted by monitoring the progressive disappearance of anti-HPV antibodies. Although it is possible that a new HPV infection in an immunocompromised host could occur, we found increased prevalence of cervical dysplasia in non-sexually active long-term survivors, suggesting that HPV reactivated from dormant virus (11).

Links between HPV and Commonly Occurring SCC after Allo-SCT

Head and neck SCC. HPV has been etiologically linked with head and neck SCC (HNSCC) (refs. 24, 25). Among HNSCC biopsies, the true prevalence of HPV DNA remains uncertain, yet studies have estimated that up to 70% of HNSCCs may be HPV positive (24, 25). In a recently published meta-analysis of 5,046 HNSCC cancer specimens from 60 studies, the overall HPV prevalence was 25.9%; however, HPV prevalence was significantly higher in oropharyngeal SCC (35.6%). HPV16 accounted for the majority of HPV-positive oropharyngeal SCCs (86.7%) (ref. 24). Although other oncogenic HPVs were detected in HNSCC, in a recent case-controlled study, HPV16 DNA predominated, occurring in 72% of 100 paraffin-embedded tumor specimens of oropharyngeal cancer (25).

Female genital cancer. The obligate cause of cancer of the cervix, and HPV16 is the most prevalent HPV type seen in cervical SCC (26). High-risk HPV types are detected in 99% of cervical cancers, and worldwide, ~70% of cervical cancers are due to HPV types 16 and 18. We also found HPV-related cervical dysplasia in 31% of long-term survivors, most with high-risk HPV16 and HPV18 subtypes (11). It would be important to study prospectively the prevalence of HPV-related cervical dysplasia in long-term SCT survivors by examining Pap smears for HPV DNA. Guidelines for the screening and prevention of second malignancies would be helpful in reducing the risk of cancer development.

Skin SCC. HPV also plays a role in SCC of the skin (13, 14). Among organ transplant recipients, HPV DNA was detected in more than 70% of SCC of the skin (13−15). The risk of skin SCC increases with the degree of immunosuppression (27, 28) Both UV radiation and immunosuppression may increase the activity of HPV, which may also contribute to cancer development.

Implications for HPV Vaccinations after Allo-SCT

The fact that HPV16 and HPV18 predominate in SCC of the cervix, HNSCC, and some skin cancer suggests that the newly developed prophylactic HPV vaccines for cervical cancer might be useful to prevent SCC occurring after allo-SCT. The success of this strategy would depend upon the proportion of cancers that are HPV positive and therefore preventable by HPV vaccination. The results reviewed here provide a strong rationale for HPV vaccination in both males and females since SCCs occur equally in both sexes after allo-SCT. Vaccination might result in a substantial reduction in the incidence of SCC expected after allo-SCT, but validation of the approach would require long-term follow-up in a large patient group.
Several questions remain to be answered by serial studies of HPV antibodies before definitive application of HPV vaccines after SCT. How long would the vaccine confer protection in immunosuppressed patients? How effective is the current vaccine schedule in immunosuppressed patients? To address these questions, we now plan to follow HPV antibodies in seropositive patients to determine the frequency of negative seroconversion and to vaccinate both pretransplant seropositive and sero-negative patients older than 12 years undergoing allogeneic SCT with the quadrivalent (types 6, 11, 16, 18) HPV recombinant vaccine. Three doses of vaccine (at 0, 2, and 6 months) will be given, starting 1 year after SCT, or as soon as the patient is no longer receiving systemic immunosuppressive agents. Additional doses of vaccine at 6-month intervals would be given for patients who do not seroconvert. HPV titers will be monitored prevaccine; at 2, 6, 7, and 12 months, and annually postvaccine, or every 6 months for non-seroconverters.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References
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