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Emerging Human Papillomavirus Vaccines against Cervical Cancer

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Abstract: Cervical cancer has been a huge health problem in our society for a long time. It has become as much an economic problem in addition to being a health problem. There are over one-half of a million cases of this disease occurring worldwide and more than one-half of these patients die from the disease. In 1976, Harald Zur discovered human papillomavirus as the aetiological agent of this disease. Initially, the HPV type 16 and 18 were implicated. Since then over 50 human papillomavirus types have been associated with the aetiology of cervical cancer. The introduction of the HPV vaccines has become a great source of hope for the possible elimination of cervical cancer. During the 1990s, some researchers found that inoculation a person with virus-like particles (VLP) that were developed from an L1 protein of the papillomaviruses could protect against the infection, but the protection is not universal for all HPVs. In 2006, the Food and Drug Administration (FDA) approved the quadrivalent vaccine by Merk & Co called Gardasil. Cervarix, the bivalent vaccine against HPV 16 and 18 by GlaxoSmithKline, was initially approved in 2009 by the Food and drug administration to protect girls and women against HPV 16 and 18. In 2014, the food drug administration approved a 9-valent human papillomavirus vaccine against HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58. The advantages from the discovery of these vaccines include possible elimination of cervical cancers, other anogenital cancers and benign human papillomavirus- related lesions such as condylomata accuminata and long-term economic benefits. There are some disadvantages like severe adverse effect associated with the use of the HPV vaccines occurring in less than 8% of patients who receive these vaccines. To do a review of the emerging human papillomavirus vaccine against cervical cancer. Scholarly journal articles/literature was extensively searched for with google search using keywords like human papillomavirus, emerging, vaccine and cervical cancer. These articles were studied and the information was used to write this review. Cervical cancer obviously has turned out to be a huge economic and public health menace globally. The advent of these HPV vaccines such as the bivalent vaccine, quadrivalent vaccine and the 9-valent vaccine has brought great relief to us all. However, these vaccines have their advantages, disadvantages and limitations generally. We look forward to the future with lots of hope for the emergence of a more effective and 'friendly' human papillomavirus vaccine against cervical cancer.
Keywords: Human, Papillomavirus, Vaccine and Cervical cancer

INTRODUCTION

Cervical cancer has been a huge health problem in our society for a long time. It has become as much an economic problem in addition to being a health problem. There are over one-half of a million cases of this disease occurring worldwide and more than one-half of these patients die from the disease. In 1976, Harald Zur discovered human papillomavirus as the aetiological agent of this disease [1]. Initially the HPV type 16 and 18 were implicated. Since then over 50 human papillomavirus types have been associated with the aetiology of cervical cancer. Nineteen of these HPV types have been classified as high-risk Human papillomavirus which include HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73 and 82[2]. There is a higher risk of developing the cancer when infected by these high-risk human papillomaviruses. There are also several low-risks HPV(such as 6,11, 40, 42, 43, 44, 54, 55, 57, 61, 62, 70, 70, 71, 72, 74, 81, 83, 84 and 89) and HPV with undetermined-risk(such as 2a, 3, 7, 10, 13, 27, 28, 29, 30,34, 86, 87, 90 and 91)[3-5]. These viruses are transmitted by sexual contact and the infect the cervical epithelium. Persistent infection with the virus

causes premalignant changes in the cervical epithelium referred to as intraepithelial lesions (high-grade or low-grade) characterized by atypical koilocytic changes. These premalignant lesions may progress in years to decades into malignant cervical lesions[5]. Human papillomavirus 16 is the most common type of virus isolated from cervical cancer in women worldwide and together with human papillomavirus types 18, 31, and 45 account for about eighty percent of invasive cervical cancer globally [5]. Since cervical cancer is caused by a sexually transmitted virus, the risk factors are early age at first sexual contact, immunosuppression (such as human immunodeficiency virus/acquired immunodeficiency syndrome), multiple sexual partners, multiple pregnancies, smoking, and use of oral contraceptive [6-10].

The introduction of the HPV vaccines has become a great source of hope for the possible elimination of cervical cancer. During the 1990s, some researchers found that inoculation a person with virus-like particles (VLP) that were developed from an L1 protein of the papillomaviruses could protect against the infection, but the protection is not universal for all HPVs[11].

In 2006, the Food and Drug Administration (FDA) approved the quadrivalent vaccine by Merk & Co called Gardasil. This drug is administered to protect girls/women age 9 through 26 against cervical cancers that is caused by HPV type 6, 11, 16, and 18. It also contains sodium borate, amorphous aluminum hydroxyphosphate sulfate (adjuvant), sodium chloride, polysorbate 80, L-histidine and water[11,12] Cervarix, the bivalent vaccine against HPV 16 and 18 by GlaxoSmithKline, was initially approved in Europe and Australia and licensed in 2009 by the Food and drug administration to protect girls and women against HPV 16 and 18. Cervarix contains aluminum hydroxide, sodium chloride, 3-O-desacyl-4'monophosphoryl lipid A (adjuvant), water and sodium dihydrogen phosphate. Both vaccines are recommended to be administered in three doses at 0, 2 and 6 months. These vaccines are capable of preventing about 70% of all cervical cancers in women worldwide [11,12].

In December 2014, the food drug administration approved Gardasil 9 by Merk & Co, a 9-valent human papillomavirus vaccine against HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58. Human papillomavirus types 16 and 18 have been implicated as the cause of 70% of cervical cancer and types 31, 33, 45, 52 and 58 have been implicated in the aetiology of an additional 20% of cervical cancer globally [13]. The introduction of this vaccine has been exciting in the medical community generally as this may be the beginning of the end of cervical cancer in our society [14].

ADVANTAGES OF HPV VACCINES

There are obvious advantages from the discovery of these vaccines. They include possible elimination of cervical cancers, other anogenital cancers and benign human papillomavirus-related lesions such as condylomata accuminata, long-term economic benefits and possible elimination of the cervical cancer screening programmes.

Several anogenital cancers including cervical cancers, vaginal cancers, vulva cancers, anal cancers and penile cancers have been known to be caused by the human papillomavirus. The use of these vaccines have the potential of eliminating these diseases after some years if the vaccine is administered to male and female before their debut of sexual intercourse.

The introduction of this vaccine into the national immunization programmes has gone a long way in the effort to eliminate cervical cancer. Over 67 million doses of Gardasil were administered nationally in the US since the HPV vaccine was licensed in June 2006 until March 2014[14]. More than 92% of persons who were administered these vaccines do not develop any adverse effect [14,15]. The most common adverse effect following the administration of these vaccines includes dizziness, headache, syncope, local reaction and nausea [15]. Millions of doses of Gardasil have been administered in Australia and the most serious adverse effect reported is an allergic /anaphylactic reaction. The recently estimated rate of anaphylaxis in Australia is about 1.7 cases per a million doses [16, 17]. The use of this vaccine has been thought to reduce the incidence of sexually transmitted infection [15]. There has been a high rate of acceptance of this vaccine especially from parents of male children [18]. The HPV vaccine is capable of eliminating 90 to 100% of cervical cancer worldwide [19].

Apart from being a health problem, cervical cancer is also an economic problem because it affects young women, cutting their life short in their prime. The study by Tsuchiya et al in Brazil enumerated the economic loss from cervical cancer to include direct and indirect cost such as outpatient cost, productivity loss amounting to BRL 71 million and income loss due to premature death estimated to be BRL 917 million annually[20]. The administration of these vaccines appropriately would prevent such huge economic loss.

DISADVANTAGES OF HPV VACCINES

There are some disadvantages associated with the use of the HPV vaccines. Less than 8% of patients who receive these vaccines would develop severe adverse effect [14,15]. From June 2006 to June 2014 about 85 deaths were reported from the use of Gardasil [20, 21]. The few reported deaths from the clinical trial studies show that causes of death were consistent with what is expected in the general population and were not considered to be vaccine-associated [21] Two

females have been reported to have suffered from Amylotrophic lateral sclerosis following the administration of HPV vaccine[14]. Also some parents mostly those of female children have found it difficult to accept the administration of the HPV vaccines to their children making it hard to completely administer these vaccines to children from 9 years of age[18].

LIMITATIONS OF HPV VACCINES

The normal HPV infection of the cervical epithelium stimulates a local immunologic response but the L1 viral-like particle is capable of stimulating a systemic immunologic response against HPV which is specific for the HPV type. The person is susceptible to infection by other HPV types not covered by the administered vaccine [22 – 26].

There are issues of the duration that these HPV vaccines can protect a person and possible administration of booster doses of the vaccine. Clinical trials show that Gardasil can protect against HPV for 5 years while Cervarix can do same for 8.4 years[25-30].

THE FUTURE

As we look into the future with so much hope. There are possibilities of developing chimeric L1- L2 VLP vaccines which would be able to stimulate a stronger immunologic response than the present L1 VLP vaccines. Also, there are possibilities of producing vaccines that are L3 VLP vaccines against oncogenic HPVs. Also, vaccines that target E5, E6 and E7 viral proteins have the potential of being effective vaccines.

CONCLUSION

Cervical cancer obviously has turned out to be huge economic and public health menace globally. The advent of these HPV vaccines such as the bivalent vaccine, quadrivalent vaccine and the 9-valent vaccine has brought relief to us all. However, these vaccines have their advantages, disadvantages and limitations generally. We look forward to the future with lots of hope for the emergence of more effective and 'friendly' human papillomavirus vaccine against cervical cancer.

REFERENCES

1. Zur Hausen H, Barré-Sinoussi F, Montagnier L. The Nobel Prize in Physiology or Medicine 2008. OF MEDICAL SCIENCES. 1992;15:25.
2. Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections. Journal of clinical virology. 2005 Mar 1;32:16-24.
3. Arney A, Bennett KM. Molecular diagnostics of human papillomavirus. Laboratory Medicine. 2010 Sep 1;41(9):523-30.
4. Schmitt M, Depuydt C, Benoy I, Bogers J, Antoine J, Arbyn M, Pawlita M, VALGENT Study Group. Multiple human papillomavirus infections with high viral loads are associated with cervical lesions but do not differentiate grades of cervical abnormalities. Journal of clinical microbiology. 2013 May 1;51(5):1458-64.
5. Munoz N, Castellsagué X, de González AB, Gissmann L. HPV in the etiology of human cancer. Vaccine. 2006 Aug 21;24:S1-0.
6. Food and Drug Administration. Highlights nof prescribing information. Gardasil 9 (Human Papillomavirus 9-valent Vaccine, Recombinant). Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2015. Available:http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457 (Accessed January 12, 2018)
7. Serwadda D, Wawer MJ, Shah KV, Sewankambo NK, Daniel R, Li C, Lorincz A, Meehan MP, Wabwire-Mangen F, Gray RH. Use of a hybrid capture assay of self-collected vaginal swabs in rural Uganda for detection of human papillomavirus. The Journal of infectious diseases. 1999 Oct 1;180(4):1316-9.
8. Kuhn L, Denny L, Pollack A, Lorincz A, Richart RM, Wright TC. Human papillomavirus DNA testing for cervical cancer screening in low-resource settings. Journal of the National Cancer Institute. 2000 May 17;92(10):818-25.
9. Bayo S, Bosch FX, de Sanjosé S, Muñoz N, Combita AL, Coursaget P, Diaz M, Dolo A, van den Brule AJ, Meijer CJ. Risk factors of invasive cervical cancer in Mali. International journal of epidemiology. 2002 Feb 1;31(1):202-9.
10. Chaouki N, Bosch FX, MUNoz N, Meijer CJ, El Gueddari B, El Ghazi A, Deacon J, Castellsague X, Walboomers JM. The viral origin of cervical cancer in Rabat, Morocco. International journal of cancer. 1998 Feb 9;75(4):546-54.
11. Schiller JT, Lowy DR. Papillomavirus-like particles and HPV vaccine development. Seminars in Cancer Biology. 1996;7(6):373–382.
12. Human papillomavirus vaccines, National cancer institute 2016. Available through https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-vaccine-fact-sheet. Accessed on 1/30/2018.
13. Joura EA, Guiliano AR, Iverson OE, Bouchard C, Mao C, Mehlsen, A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 2015: 19;372(8):711-23.
14. Human Papillomavirus (HPV) Vaccine. Available online: https: www.cdc.gov/vaccinesafety/Vaccines/HPV/jama.html. accessed 16/02/2018.
15. Mark Donald White Pros, cons, and ethics of HPV vaccine in teens—Why such controversy? Transl Androl Urol. 2014; 3(4): 429–434.
16. Backes DM, Kurman RJ, Pimenta JM, Smith JS. Systematic review of human papillomavirus

prevalence in invasive penile cancer. Cancer Causes & Control. 2009 May 1;20(4):449-57.
17. Liddon N, Hood J, Wynn BA, Markowitz LE. Acceptability of human papillomavirus vaccine for males: a review of the literature. Journal of Adolescent Health. 2010 Feb 1;46(2):113-23.
18. Cutts FT, Franceschi S, Goldie S, Castellsague X, De Sanjose S, Garnett G, Edmunds WJ, Claeys P, Goldenthal KL, Harper DM, Markowitz L. Human papillomavirus and HPV vaccines: a review. Bulletin of the World Health Organization. 2007 Sep;85(9):719-26.
19. World Health Organization, editor. Global tuberculosis report 2013. World Health Organization; 2013.
20. Tsuchiya CT, Pepe C, Alves MR. The Societal and Economic Impact of Cervical Cancer in Brazil. Value in Health. 2015 Nov 1;18(7):A447.
21. Gee J, Naleway A, Shui I, Baggs J, Yin R, Li R, Kulldorff M, Lewis E, Fireman B, Daley MF, Klein NP. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. Vaccine. 2011 Oct 26;29(46):8279-84.
22. Future I/II Study Group. Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial. The BMJ. 2010;341.
23. Paavonen J, Naud P, Salmerón J, Wheeler CM, Chow SN, Apter D, Kitchener H, Castellsagué X, Teixeira JC, Skinner SR, Hedrick J. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. The Lancet. 2009 Jul 25;374(9686):301-14.
24. Herrero R, Wacholder S, Rodríguez AC, Solomon D, González P, Kreimer AR, Porras C, Schussler J, Jiménez S, Sherman ME. Prevention of persistent human papillomavirus infection by an HPV16/18 vaccine: a community-based randomized clinical trial in Guanacaste, Costa Rica. Cancer Discov 2011; 1: 408-19; PMID: 22586631.
25. McKeage K, Romanowski B. AS04-Adjuvanted Human Papillomavirus (HPV) Types 16 and 18 Vaccine (Cervarix®). Drugs. 2011 Mar 1;71(4):465-88.
26. Schiller JT, Castellsagué X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. Vaccine. 2012 Nov 20;30:F123-38.
27. Ma B, Maraj B, Tran NP, Knoff J, Chen A, Alvarez RD, Hung CF, Wu TC. Emerging human papillomavirus vaccines. Expert opinion on emerging drugs. 2012 Dec 1;17(4):469-92.
28. Hung CF, Ma B, Monie A, Tsen SW, Wu TC. Therapeutic human papillomavirus vaccines: current clinical trials and future directions. Expert opinion on biological therapy. 2008 Apr 1;8(4):421-39.
29. World Health Organization. Global Advisory Committee on Vaccine Safety Statement on the continued safety of HPV vaccination. 2014.
30. Skinner SR, Szarewski A, Romanowski B, Garland SM, Lazcano-Ponce E, Salmerón J, Del Rosario-Raymundo MR, Verheijen RH, Quek SC, da Silva DP, Kitchener H. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. The Lancet. 2014 Dec 20;384(9961):2213-27.