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Editorial

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Therapeutic vaccination using HPV 16 E7 to eradicate CIN3

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▸ See the article "A phase 1/2a, dose-escalation, safety and preliminary efficacy study of oral therapeutic vaccine in subjects with cervical intraepithelial neoplasia 3" in volume 30, e88.

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The cervical cancer epidemic continues with approximately 569,847 new cases and 311,394 deaths reported worldwide annually [1]. Unique among human malignancies, invasive disease is typically diagnosed between the ages of 35 and 44 years, when young children are in the home and patients are in the midst of their careers. While early stage carcinomas (up to 2018 International Federation of Gynecology and Obstetrics [FIGO] IB_{1-2}) can often be cured via radical surgery with lymphadenectomy and adjuvant therapy as indicated by surgico-pathologic findings, locally advanced disease (FIGO stages IB_3-IVA) lends itself to platinum-based chemoradiation followed by high dose rate intracavitary brachytherapy [2]. Patients with central, isolated recurrence following definitive radiotherapy may be salvaged through pelvic exenteration, but in the era of chemoradiation, local recurrences are often accompanied by distant failure. Integration of the fully humanized monoclonal antibody, bevacizumab, with chemotherapy doublets to sequester vascular endothelial growth factor and prevent tumor angiogenesis, confers a statistically significant and clinically meaningful survival benefit, which is modest at best [3]. Interestingly, despite having been studied in many solid tumors, bevacizumab has only demonstrated a survival advantage in cervical cancer, 2 (of 7) trials in colorectal cancer, and in a single study of unresectable pleural mesothelioma. Given that prevention of the development of invasive carcinoma will always be preferable to treatment, there has been renewed focus on precancerous lesions (e.g., cervical intraepithelial neoplasia [CIN] 3) which often require invasive surgical techniques to eradicate (e.g., surgical excision or ablation using cryotherapy or CO_2 laser).

The scientific advances in our understanding of cervical neoplasia can be traced back through the centuries beginning over 2000 years ago when Hippocrates the Asclepiad (460–375 BCE) of the Greek Island of Kos originally described the disease as being so destructive "it is better to be left uncured than treated" [4]. The Italian cancer epidemiologist and physician Domenico Antonio Rigoni-Stern (1810–1855) analyzed death certificates of women in Verona during the period of 1760–1839 and recorded a high frequency of cervical cancer in married women, widows, and prostitutes; rarely did the disease manifest in virgins and nuns [5]. Accordingly, he postulated that the disease may arise through sexual contact. Before his theory would be validated, another Greek physician, Georgios Nikolaou Papanicolaou (1883–1962) embarked on his own odyssey which brought him to Cornell University in New York where he developed cytologic screening for cervical cancer [6], perfecting the technique by

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often practicing on Mrs. Andromahi Mavrogeni Papanicolaou. Following its introduction into clinical practice in the 1950s, the Pap smear has saved thousands of lives, further cementing the disease's novelty through cost-effective, non-invasive, reliable screening. Finally, from 1976–1984, the German virologist Harald zur Hausen (1936–) identified the etiologic role of human papillomavirus (HPV) subtypes 16 and 18 in the development of cervical cancer [7], leading directly to high risk HPV DNA detection assays to augment cytologic screening through increased sensitivity. zur Hausen would ultimately receive the Nobel Prize in Physiology or Medicine in 2008 for this discovery. Not only has the identification of relevant viral DNA sequences allowed for the development of prophylactic HPV vaccination using virus-like particle technology incorporating a cDNA of the highly antigenic L1 HPV capsid protein, but the molecular cascade which governs virus-induced carcinogenesis has also been elucidated. Specifically, the HPV oncoproteins E6 and E7 degrade and inactivate the cellular tumor suppressor gene products, p53 and pRb, respectively, leading directly to dysregulation of the cell cycle [8]. Inflamed tumors develop through infection by high risk HPV subtypes and viral integration into host DNA which disrupts the viral regulatory E2 reading frame, resulting in loss of the negative feedback loop which otherwise prevents viral oncogene expression. With continued understanding of the immunologic tolerance taking place in the tumor microenvironment, we are finally in a position to consider therapeutic vaccination for this disease based on HPV oncogene expression. In a randomized, placebo-controlled phase 2 trial involving 129 women with CIN2–3 using the HPV 16 E6 and E7-based therapeutic vaccine, tipapkinogen sovacivec, complete resolution among vaccine-recipients with CIN3 was 21% (compared to 0% in the placebo arm) [9].

In the September 2019 issue of the *Journal of Gynecologic Oncology*, Park and colleagues [10] have reported data from a phase 1/2a dose-escalation study of BLS-M07 to treat CIN3. The vaccine is novel and is orally administered five times each week (on weeks 1, 2, 4, and 8) at a dose of 1,000 mg. By embedding the HPV 16 E7 antigen on the surface of the *Lactobacillus casei* vaccine construct, the investigators were able to monitor disease regression using the Reid Colposcopic Index grading system and measure serum HPV 16 E7 antibody production. There were no grade 3 or 4 treatment-related adverse events or deaths observed among the 19 patients enrolled with CIN3. Importantly, not only did vaccination induce protective humoral immunity, but in phase 2a, six of eight subjects (75%) were cured at 16 weeks' follow-up [10]. This contrasts favorably with what is observed in clinical practice during which time regression rates of 25% may require up to 1 year or even longer.

The oral schedule, high efficacy, absence of notable side effects, and position during the preinvasive course of the disease represent clear advantages of this vaccine strategy. However, because the trial was not placebo-controlled and the investigators performing colposcopic-directed biopsies after vaccination may not have been blinded to the participation by the patients on the trial, the efficacy results will need further validation in a double-randomized, placebo-controlled trial. In addition, in designing a confirmatory trial, a strong consideration for excisional biopsy (cold knife cervical conization or large loop excision of the transformation zone) should be made so as to pathologically confirm complete tumor regression induced by recipients of study vaccine. A revision of the administration schedule to fewer days and/or fewer weeks may have a positive impact on compliance in a real world setting, provided that efficacy is not compromised. Finally, applicability of this novel technology to patients with non-HPV 16 CIN3 along with analysis of viral DNA clearance through hybrid capture will also need to be addressed.

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