Gynecologic Oncology Reports 33 (2020) 100608

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Review article

Topical therapies for the treatment of cervical intraepithelial neoplasia (CIN) 2–3: A narrative review

Nerlyne Desravines[a], Kate Miele[a], Rebecca Carlson[c], Carla Chibwesha[a,d], Lisa Rahangdale[a,b,*]

[a] University of North Carolina School of Medicine, Department of Obstetrics and Gynecology, Chapel Hill, NC, USA
[b] University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA
[c] University of North Carolina Health Sciences Library, Chapel Hill, NC, USA
[d] South Africa University of the Witwatersrand, Clinical HIV Research Unit, Department of Internal Medicine, Johannesburg-Braamfontein, Gauteng, ZA, South Africa

ARTICLE INFO

Keywords:
Cervical intraepithelial neoplasia (CIN) 2/3
Cervical dysplasia
Medical management
Topical therapy
Dysplasia treatment review
Excision alternatives

ABSTRACT

Current management of Cervical Intraepithelial Neoplasia (CIN), caused by high-risk human papillomavirus (hr-HPV), is based on surveillance and surgical therapy. Procedures carry potential risks such as preterm birth, and access remains limited throughout the world. However, there are no medical therapies recommended to promote the clearance of hr-HPV infection or CIN. Ultimately, even if less efficacious than excision procedures, medical therapies have the potential to decrease cervical cancer by eliminating barriers to treatment, such as access to treatment, or serving as an adjunct to surgical treatment in both high- and low-resource settings.

This review describes current research on topical therapies with the potential for self-application for the treatment of HPV or CIN. Therapies included are immune-modulators, anti-proliferative medications, antivirals, hormones, and herbal/alternative therapies. Randomized trials of immune-modulating (imiquimod), anti-proliferative (5-fluorouracil), and anti-viral (cidofovir) therapies have had the most promising results. However, no option has sufficient clinical trial evidence to be recommended as treatment for CIN 2–3 and surgery remains the standard of care.

The research described in this review serves as a guide for the development of future trials in the burgeoning arena of topical therapies for CIN 2–3.

1. Introduction

Persistent high-risk human papillomavirus (hr-HPV) infection is a necessary, but not always sufficient precursor to cervical cancer, the leading gynecologic cancer worldwide. (Ferlay et al., 2012) It is estimated that 80% of sexually active women will contract genital HPV by 50 years of age. (Dunne et al., 2007) Persistent hr-HPV infections are the most significant risk factors for the development of high-grade cervical dysplasia (also known as Cervical Intraepithelial Neoplasia or CIN 2–3) and cancer (Koshiol et al., 2008).

Standard-of-care management for CIN 2–3 consists of surgical therapy, which ablates or excises the cervical transformation zone. (Saslow et al., 2012) Ablative procedures consist of cryotherapy, thermal ablation or laser therapy. Excisional options include a loop electrosurgical excision procedure (LEEP) or cold knife cone (CKC), which remove one to three centimeters of cervical tissue. Although surgical therapy is highly successful in the majority of people, 5–16% of people with CIN 2–3 will have a recurrence of disease within 5 years of an excisional procedure; most recurrences will be within two years. (Katki et al., 2013; College, 2013) In high-risk people, such as those living with HIV in low- or middle-income countries, the risk can be as high as 19–37% (Smith et al., 2017; Greene et al., 2017).

The overall success of excisional treatments is high, and the immediate post-procedure risks, which are few, are minor. These include bleeding, infection and pain. However, there are long-term risks to consider, particularly in people of childbearing age. People who undergo excisional procedures for cervical dysplasia have an increased risk of preterm delivery, 1.56 relative risk for loop excision to 2.70 relative risk with a cold knife cone. (Krygiou et al., 2016) A systematic review and *meta*-analysis which included 65,082 treated women reported that this risk increases as more cervical tissue is removed through depth of excision or repeated treatments. (Krygiou et al., 2016) There is also psychological distress associated with the need for invasive procedures, (Kola and Walsh, 2009; Rogstad, 2002) as well as

* Corresponding author at: Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, 3027 Old Clinic Building, CB 7570, Chapel Hill, NC 27516, USA.
E-mail address: lisa_rahangdale@med.unc.edu (L. Rahangdale).

https://doi.org/10.1016/j.gore.2020.100608
Received 16 April 2020; Received in revised form 23 June 2020; Accepted 27 June 2020
Available online 02 July 2020

Table 1
Summary of Topical Therapies for the treatment of Cervical Intraepithelial Neoplasia (CIN) 2/3.

Study	Study Type	Dysplasia	Regimen	Sample Size	Diagnostic Testing	Findings
IMMUNE MODULATORS						
Imiquimod						
Lin 2012	Prospective Cohort	CIN or VAIN	Twice weekly for 12 doses	72	Histology 6 months post-treatment	51.4% with histological regression while 8.3% had progressive histology
Grimm 2012	RCT	CIN 2/3	Titrating 1–3 vaginal suppositories over 16 weeks	24(per group)	4 quadrant colposcopic-guided biopsies at 20 weeks	73% regression to low grade or normal vs. 39% in the placebo group
Diaz-Arrastia 2001	Prospective Case series	HSIL of vulvar, vagina or cervix	Application three times weekly for 6–16 weeks	8(2 cervical dysplasia)	Histology by 1 month	50% with complete resolution, 25% with regression to low grade
(Chen, 2013)	Retrospective case series	CIN or VAIN already treated with surgery	Twice weekly for 8 weeks	76	Repeat cytology/HPV 3 mos. after treatment	76.3% with normal pap smear. No histology performed.
Pachman 2012	RCT	CIN 2/3, recur or pers CIN I	1 packet every 4 days for 5 application then ablative vs. excisional therapy	56	Cytology +/- histology at 4 mos then q4-6 mos. Endpoint: persis/recur CIN by 2 years	No difference dysplasia (CIN2/3 or recurrent CIN with same HPV type) between 2 groups (25% vs. 21% in control)
Trans retinoic Acid						
Weiner 1986	Prospective cohort	Mild, mod, sev dysplasia	Daily for 4 days; 2 different concentration cohorts	42	Histology at 5 – 18 months	14% (2/14) and 45% (10/22) with resolution in the low and high concentration
Meyskens 1983	Phase I prospective cohort	Mild or mod CIN	Escalating doses of TRA for 4 consecutive days	35	Clinical and colposcopic examination of side effects	No systemic effects, mild cervical inflammation at higher doses, high vaginal toxicity at 0.484%
Graham 1986	Phase II prospective cohort	Mild, mod, sev dysplasia	Cervical cap for 4 days then 2-days every 3 months for one year	25	Cytology and Histology	50% (10/20) histologic and cytologic repression regression of disease
DiSilvestro 2001	Prospective cohort	CIN 2/3	Gel on sponge inside cervical cap for 4, 8 or 14 days	52	Colposcopic directed histology 90 days after treatment	46.9% regression. 53.1% with no change.
[a]Chen 1994	RCT	NR	Once daily for 50 days		NR	74.3% regression after two-courses of treatment
Surwit 1982	Prospective Cohort	CIN 2/3	Daily applications for 4 days	18	Conization of cervix 4 weeks post-treatment	Reduced lesion size in 33% and complete regression in 11%
Meyskens 1994	Phase III RCT	CIN 2/3	Cervical sponge daily for 4 days then 2 days at 3 and 6 mos.	301	Cytology and colposcopic guided histology at 15 months	Histologic resolution in 43% vs. 27% in CIN 2 placebo group. No difference in the CIN3 group.
Ruffin 2004	Prospective cohort	CIN 2/3	4 doses daily at different dosages	175	Histology at 12 weeks	Response to therapy not statistically significant in all 4 dose groups
Interferon						
Krause 1987	Prospective Cohort	CIN 3	Interferon gel in vaginal cup for 4 consecutive weeks	9	Conization after 4 weeks	22% (2/9) with complete resolution
Moller 1983	Prospective Cohort	CIN 2/3, CIS	Interferon gel via cervical cap2 times per week for 6 weeks	6	Histology at 6 and 12 wks	50% (3/6) with “light dysplasia”
Schneider 1995	Phase II RCT	CIN 2/3	3 concentrations of interferon gel for 28 days via diaphragm	33(24 therapy vs 9 laser)	Cytology and histology with HPV typing after 6 months	42% (10/24) vs 89% (8/9) with resolution and 42% (10/24) vs 11% (1/9) with regression
Yliskoski 1990	RCT	CIN or VAIN	Vaginal gelnightly for 2 weeks, multiple courses over 1 year	19(9 interferon vs 10 placebo)	HPV genotyping at 16 months	67% (6/9) HPV negative
Choo 1985	Prospective cohort	Mod, sev dysplasia, CIS	Twice daily application of gel via vaginal applicator	7 patients	Colposcopy – no histology	28% (2/7) resolution, 43% (3/7) regression and 28% (2/7) with no response on colposcopy
Granulocyte-macrophage colony stimulation factor (GM-CSF)						
Hubert 2010	RCT	CIN 1	Gel applied every 3 days for 4 doses with applicator	26 (15 CIN 1 and 11 controls)	Plasma HPV viral load and histology at 26–30 months	Decreased HPV viral load; no clinical response based on histology.
ANTIPROLIVERATIVE						
5-Fluorouracil (5FU)						
Maiman 1999	RCT	CIN 2/3	Cream applied once every 2 weeks for 6 months after excision	101 (50 therapy and 51 controls)	Histology at up to 18 mos	28% (14/50) vs. 47% (24/51) with recurrent CIN 2/3
(Barten, 1987)	Prospective Cohort	CIN 1,3	Cervical cap daily for 7 days	10	Histology at 6–12 mos	20% (2/10) resolution, 40% (4/10) with regression to CIN1, and 40% (4/10) with persistent CIN1/CIS
Sillman 1981	Prospective cohort	Vulvar, vaginal,cervical mod, sev dysplasia	Cream applied nightly for 2 weeks then once monthly	16	Histology	100% (16/16) with resolution
Rahangdale 2014	RCT	CIN 2	Cream every 2 weeks for 16 weeks	60 (31 treatment vs 29 placeb0)	Histology at 6 months	93% (26/28) vs. 56% (15/27) with regression

(*continued on next page*)

Table 1 (*continued*)

Study	Study Type	Dysplasia	Regimen	Sample Size	Diagnostic Testing	Findings
Pride 1982	Prospective Cohort	Vaginal/Cervical dysplasia	Nightly for 10 nights via diaphragm	11	Conization or hysterectomy	55% (6/11) with resolution
Sidhu 1997	RCT	CIN 1/2	Bio-adhesive film using applicator	104 (51 with therapy vs 53 with placebo	Histology at 6 months	67% (32/48) and 72% (33/46) regression or resolution in the treatment and placebo group.
Cisplatin						
[a]Nakayama 1992	Prospective cohort	mild/mod/sev and "microinvasive ca"	Daily placement via gauze tampon for 10 days.	12	Histology at day 10	100% with resolution in CIN group (10/10) and 50% (1/2) regression in microinvasive ca group
Iodosteric Acid						
†Gleeson 1992	RCT	CIN 2/3	Application with pessary vs. placebo for 30 nights	NR	Histology at 30 days	No clinically significant difference in the 2 groups
ANTIVIRALS						
Cidofovir						
VanPachterbeke 2009	RCT	CIN 2,3	Gel via cervical cap once 6 weeks prior to conization	48 (23 treatment vs 25 placebo)	Conization	61% (14/23) cidofovir vs 20% (5/25) placebo with resolution
Snoeck 2000	Prospective Cohort	CIN 3	Gel applied every other day for 3 applications	15	Histology within 1 month	47% 7/15 with resolution, 7% (1/15) with regression to CIN I, 33% (5/15) with persistent CIN 2/3
Bossens 2018	Prospective cohort	CIN 2,3	Gel applied once per week for 3 weeks for 5 or 10 h	9	N/A	No clinically significant adverse events
Lopinavir and Ritonavir						
Hampson 2016	Prospective Cohort study	HSIL	Vaginal pessary twice daily for 2 weeks	23	Cytology at 12 weeks	63.6% with no dysplasia, 18.2% with low grade
Vidarabine						
†Okamoto 1999	Cohort study	CIN I and 2	Vidarabine ointment and/or podophyllin	21	Cytology and Histology	81% (17/21) with regression
Niwa 2003	Cohort study	CIN and Stage IA1 cervical cancer	Regimen not described	30	HPV typing by PCR	10% (1/10) with resolution of HPV infection
Terameprocol						
Khanna 2007	Phase I/II clinical trial	CIN 1 and 2/3	Direct cervical application once weekly for 3 weeks	7	N/A	No serious adverse events noted
HORMONALS						
Progesterone						
Hefler 2010	Phase II clinical trial	CIN 1	10 days month for 6 months	40	Cytology and histology	30% regression vs 38.3% in the placebo
Dehydroepiandrosterone (DHEA)						
Suh-Burgmann 2003	Prospective Cohort study	LSIL	Daily for up to 6 months	12	Histology	83% (10/13) with no dysplasia
HERBAL AND ALTERNATIVE REMEDIES						
Alternative Remedies						
Joshi 2011	Prospective cohort	LSIL	Capsules twice daily for 12 weeks	21	Histology	76% (16/21) with resolution to normal and 19% (3/21) unchanged.
Ahn 2003	RCT	Cervicitis, CIN 1, 2 and 3	4 groups (1 topical). Ointment twice weekly for 12 weeks	27 (topical group)	Histology	74% (20/27) topical vs. 10% (4/39) control with regression
Ashrafian 2015	RCT	CIN 1 and 2	3 groups (high dose, low dose, placebo) daily application for 180 days	25 high dose vs 24 low dose vs 23 placebo	Histology	100%, 90.5% and 61% regression in high dose, low dose and placebo
Shukla 2009	RCT	HPV 16 infection +/- LSIL	Praneem tablet vaginally daily for 30 days	20 (10 treatment vs 10 placebo)	HPV 16 PCR	Elimination of HPV 16 in 60% (6/10)
Swanick 2009	Case Report	CIN 2/3	Escharotic treatment 2x/weekly for 5 weeks	1	Cytology and colposcopy	NILM pap smear at 4 and 10 mos and satisfactory colposcopy at 10 mos
Valencia 2011	Prospective Cohort	LSIL cytology	Oral or topical spray for 8 weeks minimum.	62	Treatment until improvement per cytology and colposcopy	Improvement in colposcopic appearance in 74% at 12 weeks
Laccetta 2015	Prospective Cohort	ASCUS or LSIL cytology	Two cycles of daily application for 20 days	356 (176 treatment vs 180 placebo)	Cytology and Colposcopic evaluation at 6 and 12 mos.	83.5% vs. 60% of controls with negative pap smear. 55.4% vs. 24.7% of controls with no colpo lesions
Stentella 2017	Retrospective case-control	CIN 1/2	Carbodymethyl beta-glucan gel	999	Cytology, histology, colposcopic changes	Nonsignificant regression of CIN 2

(*continued on next page*)

Table 1 (*continued*)

Study	Study Type	Dysplasia	Regimen	Sample Size	Diagnostic Testing	Findings
Stefani 2014	Prospective Cohort	CIN 1	Bovine colostrum containing vaginal tablets	256	Histology at 6 months	75.5% regression
†Bottino 1991	RCT	NR	Cream applied vaginally	40 in dysplasia group	NR	70% (28/40) efficacy in dysplasia patients

[a]In these studies, only an abstract was available in English.
†In these studies, only an abstract was available for review.
RCT = randomized controlled trial; CIN = Cervical Intraepithelial Neoplasia, VAIN = Vaginal intraepithelial neoplasia, HSIL = High grade intraepithelial lesion, LSIL = Low grade intraepithelial lesion, CIS = carcinoma in situ, ASCUS = atypical squamous cells or unknown significance, mos = months, ca = carcinoma, NR = not reported.

significant individual and infrastructure costs. (Insinga et al., 2005; Shireman et al., 2001) The estimated cost of the common excisional procedures (cryotherapy, LEEP and cold knife cone) was estimated to cost $112, $407 and $3,739) with a projected annual cost of $75–91 million per 100,000 patients from LEEPs alone, based on 2001 US dollars. (Kleinberg et al., 2003) In a more contemporary analysis, the cost of cervical HPV-related disease is estimated to cost the US $4 billion annually, as adjusted to 2004 US dollars. The development of nonsurgical, noninvasive, and patient-controlled modes of treatment have the potential to decrease the long-term morbidity and cost of treatment.

Cervical cancer is a cancer of economic, social, and educational disparities. A medical therapy option could overcome many of the barriers to surgical therapy – desire for child-bearing, cost, health provider skill, equipment, geography, and patient fear. (Yabroff et al., 2005) Ultimately, even if less efficacious than excision procedures, medical therapies have the potential to decrease cervical cancer by eliminating barriers or as an adjunctive to surgical treatment to increase the efficiency of therapy. (Desravines et al., 2020; Maiman et al., 1999) Additionally, primary medical therapies would address a treatment bottleneck in both high- and low-resource settings, by allowing people to begin treatment immediately.

There are currently no topical therapies recommended to promote the clearance of hr-HPV infection or CIN however this is in large part due to the paucity of available data on the subject. This systematic review will discuss the published literature on topical therapies, exclusively those with the potential for patient self-application as a medical therapeutic alternative for the treatment of CIN 2/3.

2. Methods

2.1. Search methods

A medical librarian developed search strategies using a combination of keywords and MeSH and Emtree subject headings. As for the therapies, the search terms utilized were:" fluorouracil", "5-FU", "5-fluorouracil", "adrucil", "carac", "efudix", "efudex", "fluoro-uracile", "fluoro aracile", "fluoroplex", "fluorouracile", "tolak", "neofluor", "cidofovir", "imiquimod", "flurorophyrimidine", "curcumin", "interferon-alpha", "interferon", "antimetabolites", and "antineoplastic". For disease site and status, the search terms were "cervix uteri","cervical", "cervix", "uterine", "uterus", "endocervix", "endocervical", "intra-epithelial", "intraepithelial", "dysplasia", "cervical intraepithelial neoplasia", or "uterine cervical dysplasia". Additional keywords and Mesh terms were used for drug formulation and application method. The complete search terms included in the query are noted in Supplemental Figure 2. These were used to search PubMed via NLM, Embase via Elsevier, Web of Science, and ClinicalTrials.gov from the date of database inception to September 21, 2018, when all searches were completed.

2.2. Inclusion and exclusion

Articles were reviewed according to prospectively determined inclusion and exclusion criteria. Treatments with the potential for self-application were chosen for inclusion. In instances in which the topical therapy was applied by a medical provider, these studies were excluded. Treatments requiring or including provider-administration (injections, ablative therapies, excisional procedures, and photodynamic therapy) were excluded from the review. Animal and *in-vitro* studies were also excluded along with conference reports, conference abstracts, and editorials.

2.3. Data extractions

Citations were exported to Endnote and evaluated for duplicity. An

initial review of all abstracts and titles were completed by two independent gynecologists that evaluated for pertinence and applicability. Any conflicts between the two reviewers were resolved by a third gynecologist. Remaining abstracts were then be reviewed in its entirety for appropriateness based on the aforementioned inclusion and exclusion criteria. All studies that were determined applicable to the topical therapies for the treatment of CIN 2/3 were utilized for the completion of this review. We followed a systematized process, based on the PRISMA reporting standards for systematic reviews. The nature of these studies were heterogenous and lacked high quality studies. Study authors determined that this information was not amenable to a quantitative synthesis and thus the results of this research are presented as an expert narrative synthesis. The final studies included in this narrative review are outlined in Table 1.

3. Results

The collective database searches yielded a total of 1,043 citations, with an additional 13 citations found by searching ClinicalTrials.gov. The 1056 total citations were exported to Endnote and 288 duplicates were removed, leaving 768 unique citations found in all searches. Two reviewers (LR, ND) screened titles and abstracts for relevance, excluding 579 irrelevant studies. A third reviewer (KM) reviewed any conflicts. The full text of the remaining 189 papers were then reviewed for relevance and a further 145 studies were exclude for wrong study designs, interventions, outcomes, or patients. Ultimately, 41 studies were included in the review and data extracted. Fig. 1 provides a PRISMA diagram showing the process of study inclusion. Table 1 summarizes the types of therapies that have been studied to date.

3.1. Immune-modulators

Imiquimod functions at the TLR7 receptor to stimulate the innate immune system and increase production of the cytokines interferon α, interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α). Imiquimod is used to treat genital warts and vulvar/vaginal dysplasia. It has also been studied as a medical therapy for high-grade squamous intraepithelial lesions of the cervix. (Grimm et al., 2012; Pachman et al., 2012; Lin et al., 2012; Chen, 2013) Imiquimod is typically used as a topical cream with concentrations from 1% to 5% applied three to seven times per week for eight to 16 weeks. Local reactions can include erythema, pruritis, excoriation, erosion, edema, scabbing, or crusting. Though used topically with minimal systemic absorption, imiquimod therapy can produce systemic reactions such as myalgia, headache, fatigue, and nausea. (Grillo-Ardila et al., 2014) A review of its use in cervical, vulvar, and vaginal dysplasia also described mild to moderate local and systemic side effects but overall it was well-tolerated. (de Witte et al., 2015) In a review of 3 studies in which imiquimod was utilized for the treatment of CIN, side effects were well tolerated by patients; only 2 out of 132 patients discontinued therapy due to side effects. (de Witte et al., 2015)

De Witt et al reviewed 3 studies and only one was a randomized controlled trial. This randomized controlled trial was conducted by Grimm et al and showed that a 16-week course of self-applied dose escalating intravaginal imiquimod treatment of CIN 2–3 led to histologic regression and HPV clearance (73% versus 39%, $p < 0.05$ for histologic regression and 60% versus 14%, $p < 0.05$ for HPV clearance). (Grimm et al., 2012) More than 90% of participants in the imiquimod arm reported both local and systemic (flu-like symptoms and fatigue) symptoms however no participants experiences high-grade side effects and only one discontinued therapy (Grimm et al., 2012).

There are active studies evaluating the use of imiquimod. The "Topical Imiquimod treatment of high-grade Cervical intraepithelial neoplasia" (TOPIC) trial was a 2015 study designed to randomize patients into an imiquimod arm and an immediate treatment arm with excision however was prematurely stopped in 2017 due to poor enrollment. The study design was then converted to a non-randomized efficacy trial entitled TOPIC-3. A related study, TOPIC-2, is a non-inferiority randomized single blinded study in women with recurrent/persistent CIN after previous excisional treatment. (van de Sande et al., 2018) The study anticipates recruiting 433 patients to establish non-inferiority to recurrent excisional procedure. It is estimated to complete in 2020.

Other immune-modulating approaches have included *trans*-retinoic acid or interferon with both being used to treat viral infections and cancers. Trans-retinoic acid is a metabolite of Vitamin A and plays a key role in mucosal immune responses. Interferons are cytokines produced by the immune system when triggered by viral infection or other immune processes. They have both been studied on low-grade and high-grade CIN since the 1980s with little progress in the development of a viable agent. (Weiner et al., 1986; Meyskens et al., 1983; Krause et al., 1987; Meyskens et al., 1994; Ruffin et al., 2004; Graham et al., 1986; Choo et al., 1985; Yliskoski et al., 1990; Schneider et al., 1995) A Cochrane review of 5 studies utilizing retinoids (given orally and topically) for the treatment of CIN showed that retinoids are not effective in preventing progression in any grade of CIN (Helm et al., 2013).

Studies are notable for the delivery of medication through sponges in cervical caps and vaginalettes (delivery agents soaked in gel) which may be useful in the development of self-applied therapies. (Graham et al., 1986; Surwit et al., 1982; DiSilvestro et al., 2001; Singer et al., 1993) Additionally, a new approach has been the local application of GM-CSF (granulocyte–macrophage colony-stimulating factor), a cytokine produced in response to immune stimuli, in order to increase numbers of antigen-presenting cells (APCs) in CIN lesions. A Phase 1b study of 15 people with CIN 1 reported favorable toxicity, and significant increases in APCs and cytotoxic T-lymphocyte infiltration of cervical biopsies (Hubert et al., 2010).

3.2. Anti-Proliferative therapies

5-fluorouracil (5-FU) is an anti-metabolite which has been used widely to treat malignancies such as colon cancer as well as dermatologic conditions. (Ashton et al., 1970; van de Nieuwenhof et al., 2008; Stanley, 2013) The primary mechanism of 5-FU is to block synthesis of thymidine and prevent DNA replication. For decades, observational studies have demonstrated efficacy in using topical 5-FU for treatment of HPV-related diseases (e.g., genital warts, and vulvar and vaginal dysplasia). (van de Nieuwenhof et al., 2008; Weis, 2013; Stanley, 2003) Previously, 5-FU topical treatment was limited by side effects, including burning, erythema, erosion, pain, and chronic ulceration, because standard treatment regimens required multiple daily applications. (Krebs and Helmkamp, 1991) However, limiting the application of 5-FU to biweekly dosing or decreasing the concentration of 5-FU has shown improved tolerance. (Maiman et al., 1999; Rahangdale et al., 2014)

Small proof-of-concept studies of 5-FU for treatment of CIN were initiated in the 1980s. (Silman et al., 1981; Barten, 1987) Subsequently, Maiman et al. studied intravaginal 5-FU to prevent recurrence of CIN 2–3 after excisional treatment in HIV-infected people. (Maiman et al., 1999) People who self-applied 2 g of 5% intravaginal 5-FU every two weeks for up to six months were less likely to develop a CIN 2–3 recurrence at 18 months than those in the observation arm (31% vs. 8%, $p = 0.014$). (Maiman et al., 1999) Rahangdale et al used a similar dose schedule (2 g every two weeks) for 16 weeks for primary treatment of CIN 2. (Rahangdale et al., 2014) (Table 1) In this study, 60 people without HIV were randomly assigned to self-applied 5-FU (8 total doses) versus observation. Those in the 5-FU group were more likely to experience disease regression (CIN 1 or normal) (93% 5-FU versus 56% control; $p = 0.01$). The composite outcome of histology, Pap smear, and hr-HPV results was more likely to be normal in the 5-FU group than the observation arm (RR 2.25, 95% CI 1.05–5.09). In both studies people tolerated the biweekly dosing, and although mild side effects (e.g. bleeding, irritation, and discharge) were common, no moderate or

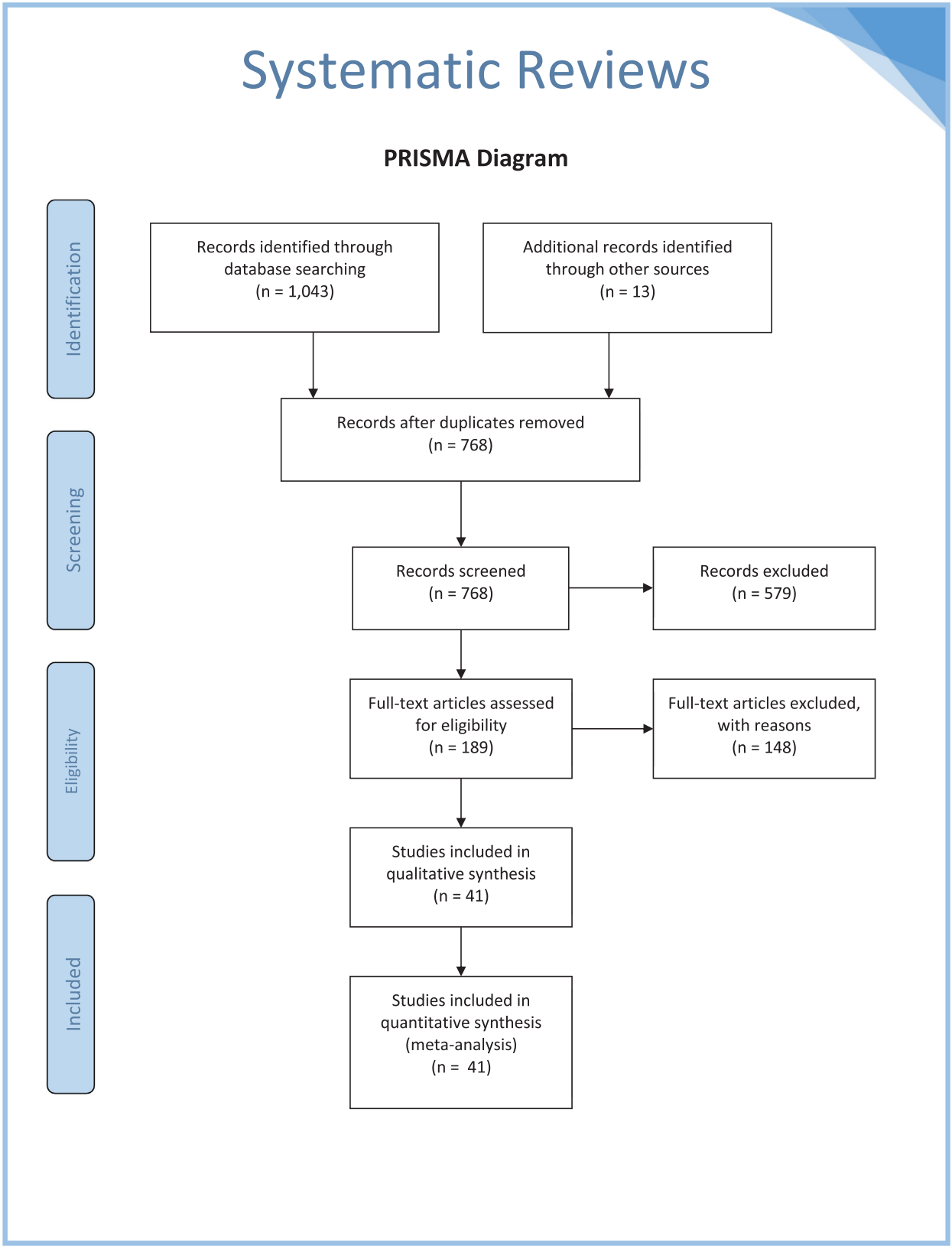

Fig. 1. The PRISMA diagram for database search results of topical therapies for the treatment of Cervical Intraepithelial Neoplasia (CIN) 2/3.

severe side effects were reported (Rahangdale et al., 2014).

A recent case series highlights the role of 5-FU in clinical practice for patients seeking a LEEP alternative in both recurrent and primary CIN 2/3. (Desravines et al., 2020) A Phase 1 study of feasibility of combination therapy with topical 5-FU with imiquimod for women with CIN 2–3 is estimated to complete in 2020 (ClinicalTrials.gov Identifier: NCT03196180).

3.3. Antivirals

Cidofovir is an acyclic nucleoside phosphonate derivative with broad-spectrum anti-DNA virus activity and an extended half-life, allowing for infrequent application. It is used as treatment for vulvar and non-genital HPV lesions as well as for viruses such as herpes, Mollusca contagiosa, and adenovirus. Studies of cidofovir gel have shown promising results for clearance of CIN with minimal toxicity. (Snoeck et al., 2000; Van Pachterbeke et al., 2009; Bossens et al., 2018) Previous dosing regimens have ranged from three times every other day to three times per week to once per week. Van Pachterbeke, et al, reported a randomized, placebo-controlled trial of 2% cidofovir gel applied three times in one week in 48 people with CIN 2–3. Subsequent cervical biopsy demonstrated that 61% cidofovir versus 20% placebo ($p < 0.01$) demonstrated regression or clearance of CIN 2–3 (Van Pachterbeke et al., 2009) (Table 1).

Lopinavir and ritonavir, a combination oral HIV protease inhibitor (Lopimune) has been studied as potential treatment for CIN. (Hampson et al., 2006; Lahiri et al., 2015; Batman et al., 2011) Hampson, et al conducted an exploratory study of 23 HIV-uninfected people with hr-HPV and HSIL cytology. (Hampson et al., 2016) Each person self-inserted one lopinavir/ritonavir combination capsule per vagina twice a day for two weeks. Cytology and hr-HPV testing at 12 weeks showed 82% regression in cytology results from HSIL to either low grade or no dysplasia; 78% of these were confirmed by histology. The therapy was well-tolerated with local side effects of vaginal discharge and irritation, and systemic side effects of headache, nausea, and abdominal pain. (Hampson et al., 2016)

Other antivirals being studied include Vidarabine and Terameprocol. Vidarabine, a DNA polymerase inhibitor used for treatment of HSV, has been applied successfully as an ointment in conjunction with podophyllin or compared to 5-FU for treatment of HPV infection in studies of ten to 28 people. (Niwa et al., 2003; Okamoto et al., 1999) Terameprocol (*meso*-tetra-o-methyl nordihydroguaiaretic acid, EM-1421) is a transcription inhibitor that selectively interferes with HPV viral genes E6 and E7. A phase 1 study of people with CIN 1–3 treated with terameprocol demonstrated safety and a maximum tolerated dose of 1% and 2% ointments (Okamoto et al., 1999; Khanna et al., 2007).

3.4. Hormonal

Hormones have been studied as topical therapy for CIN 1. Though there is growing interest in developing treatment for CIN 1, these HPV-related lesions are usually observed and not routinely treated with surgical therapy. (Saslow et al., 2012) Vaginal progesterone has previously been shown to increase the vaginal presence of Langerhans cells, which are critical to the local immune response to HPV. People with CIN 1 were treated with intravaginal micronized progesterone suppositories (400 mg) inserted daily for ten days per month for six months. The progesterone group experienced less histologic regression (30%) than the control group (38%) (HR 3.8, 95% CI 1.8–8.3). (Hefler et al., 2010) Dehydroepiandrosterone (DHEA) is an adrenal steroid with immune modulation and tumor inhibition functions. A pilot study of 12 people with CIN 1 treated with intravaginal DHEA for three months reported regression in 83% (10/12) and was well-tolerated. (Suh-Burgmann et al., 2003) No hormonal therapies have been studied as alternative therapies for CIN 2–3.

3.5. Herbal/alternative

A variety of alternative herbal or non-pharmacologic options have been studied for treatment of HPV and CIN with mixed results. A prospective randomized placebo controlled trial study of CIN 1–2 treated with self-applied diindolylmethane vaginal suppositories found that treatment groups at 100 mg/day and 200 mg/day reported regression of 91% (95% CI 70–99%) and 100% (95% CI 82–100%), respectively, compared to placebo 61% (95% CI 36–83%). (Ashrafian et al., 2015) However, the distribution of CIN 1 and CIN 2 was not described. Histologic regression was not defined, and participants with normal appearing colposcopy were not biopsied. (Table 1) A case report of use of *Sanquinaria canadensis* (bloodroot) used as escharotic treatment has described successful treatment of CIN 2–3 in a 20-year old (Swanick et al., 2009) A retrospective study of beta-glucan included CIN 2–3 lesions and did not show benefit (Stentella et al., 2017).

Studies of green tea extract, *Azadirachta indica* (neem), beta-glucan, bovine colostrum, curcuma (tumeric) and glucyrrhizinic acid (licorice root) have demonstrated tolerability and possible efficacy in treatment of HPV infections or CIN 1. (Stentella et al., 2017; Ahn et al., 2003; Joshi et al., 2011; Shukla et al., 2009; Laccetta et al., 2015; Stefani et al., 2014; Valencia et al., 2011) Ahn et al. in 2003 in an RCT found that application of a green tea cervical ointment twice weekly for 12 weeks results in the regression of 74% (20/27) of those in the treatment group versus 10% (4/39) in the control group however, the cohort contained with cervicitis, CIN 1, 2 and 3 thus limiting the inferences on efficacy that could be made from this group. (Ahn et al., 2003) The prospective study of glycyrrhizinic acid had participants using an oral or topical spray until there was improvement as noted on pap smear and colposcopy but not necessarily histology. (Valencia et al., 2011) There next two studies utilizing beta glucan with mixed results. (Stentella et al., 2017; Laccetta et al., 2015) Laccetta et al. described women with ASCUS and LSIL cytology and found a significant regression of visual colposcopic lesions (55% v. 25%) meanwhile Stentella et al. found a nonsignificant difference in a group of women with CIN 1 or 2. (Stentella et al., 2017; Laccetta et al., 2015)

A 2009 study of praneem, the seed extract of *Azadirachta indica,* reported high risk HPV 16 elimination in 60% (6/10) in the treatment compared to 10% (1/10) in the placebo group. (Shukla et al., 2009) A single study evaluating the effect of curcuma (tumeric) vaginal capsules in women with LSIL cytology found 76% resolution of dysplasia (16/21) however, there was no control group for comparison. (Joshi et al., 2011) A pilot study of bovine colostrum tablets in women with CIN 1 found 75% regression of lesions based on histology. Studies of herbal remedies were either small pilot, feasibility, or proof of concept studies that demonstrated possible efficacy but conclusions remain elusive.

4. Discussion

There has been a long-standing and continued interest in the development of a safe, effective topical therapy for treatment of CIN and HPV. A medical therapy option could overcome many of the barriers to surgical therapy – desire for child-bearing, cost, health provider skill, equipment, geography, and patient fear. (Yabroff et al., 2005) In this review, we have summarized the available data on immune modulators (imiquimod, transretinoic acid, interferon and GM-CSF), anti-proliferative therapy (5-Fluorouracil), antivirals (cidofovir, lopinavir/ritonavir, vidarabine and terameprocol), hormonals (progesterone, DHEA) and herbal supplements. Overall, the randomized trials of immune-modulating (imiquimod), anti-proliferative (5-FU), and anti-viral (cidofovir) therapies have had the most promising results, but there is still more need for study.

Of the immune modulators, there has been little progress with transretinoic acid and interferons for a viable agent. The metanalysis of the 5 retinoids have not found them to effective. The GM-CSF study is in its infancy as a Phase 1b study. Imiquimod shows the most promise in this group. There is no conclusive data at this time but multiple studies using imiquimod for the treatment of CIN 2–3 as primary therapy or in conjunction with HPV vaccines are ongoing, specifically the TOPIC-2 and TOPIC-3 trial. (Koeneman et al., 2016) The results of both of these studies will better inform our knowledge of imiquimod as topical therapy in primary and recurrent cervical dysplasia compared with excision therapy.

5-FU, an antiproliferative agent, has been limited by its side effect profile in the treatment of other sites. Modified regimens have shown better patient tolerance in the treatment of recurrent and primary cervical dysplasia. (Desravines et al., 2020;36.; Maiman et al., 1999; Rahangdale et al., 2014) There is interest from patients in using this therapy as evidenced by the recent case series featuring 25 women. There is also a phase I study of feasibility using combination therapy of topical 5-FU with imiquimod. However, more research is still needed to understand the potential of this agent as a treatment for CIN 2/3.

Of the antivirals, cidofovir has demonstrated the most promising results largely based on the van Pachterbeke randomized control trial which demonstrated regression of CIN 2–3. The work on terameprocol is early with information arising from a Phase 1 trial. Vidarabine at this time has only been used in conjunction with other topical treatments. Only an exploratory analysis is available for lopinavir and ritonavir and more research is needed on this modality.

No conclusions can be made regarding utility of hormonal and herbal therapies due to study design, inclusion criteria or limited sample size. The progesterone and DHEA studies enrolled participants with low grade dysplasia (CIN 1) where standard of care is observation. This was a similar concern in the diindolylmethane, an herbal therapy, where participants had either CIN I or 2 and the distribution of disease was not described. Beta gluten is not effective and there is only a singular report of using sanquinara canadensis.

Limitations of this review include the low quality of clinical studies, few randomized controlled trials, and small sample sizes showing nonsignificant results. Regimens and inclusion criteria often varied so results were not comparable or generalizable. Strengths of this paper include that this was a standardized review using reproducible methods on a unique contemporary topic. The review highlights our current understanding of the topic in order to guide future directions for research on topical therapies for HPV or CIN.

Important aspects of a topical therapy to consider in the development of future therapies for treatment of HPV or CIN are safety, efficacy, delivery, and accessibility. Ideally, a topical therapy would be patient-controlled though either provider- or self- administered methodologies continue to be studied. All studies must have rigorous assessment of safety including monitoring for local and systemic adverse events and consideration of fetal risk with unplanned pregnancy. An observation period of six months with careful screening and follow up is considered reasonable when considering risk of progression. (Silverman et al., 2002) Sample size calculations must consider a threshold for efficacy which allows topical therapy to be comparable with current standard surgical options. Delivery methods ranged from a capsule or suppository to inserting the cream via vaginal applicator, sponge, pessary, or ring. As topical therapies are developed, the ease of administration and feasibility of the delivery method is critical to patient acceptance. A final consideration is accessibility. Any product in development will require extensive study including cost in order to achieve regulatory approval for sale in the market. This cost may make topical therapy unfeasible for high-risk, under-insured individuals who are most at risk for developing cervical cancer. Of the therapies described, imiquimod and 5-FU are already in use as topical therapies, have generic formulations, and have been studied as self-applied preparations. There may be an advantage to exploring therapies that can be procured at a lower cost for ease of scale up.

5. Conclusion

At this time, there is no option with sufficient clinical trial evidence or proven efficacy to recommend topical therapy as a primary treatment for HPV infection or CIN. Unanswered questions about topical therapies include effectiveness outside of the research setting, patient acceptability, and long-term efficacy. But there is potential that by combining differing mechanisms of action (e.g. immune modulation and anti-proliferative therapy), neoadjuvant or adjuvant approaches to surgery, and/or in conjunction with HPV vaccines, more effective and accessible treatment regimens will be created with a lower risk profile. This approach may also be useful for providing options to people desiring alternative or less-invasive management, and be readily available in settings where there are treatment delays or limited access. While surgical therapy is the gold standard and is highly effective in treating CIN 2–3, an effective topical therapy may provide an accessible additional option in our cancer prevention toolkit.

6. Contribution to authorship

ND participated in the carrying out, analysis, and writing of the paper. KM participated in the planning, carrying out, analysis, and writing of the paper. RC created the search strategies and participated in the planning, carrying out, and writing of the paper. CC participated in the analysis and writing of the paper. LR led the conception, planning, carrying out, analysis, and writing of the paper. All authors have provided substantial contribution and are in agreement with all aspects of the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2020.100608.

References

Ahn, W.S., Yoo, J., Huh, S., et al., 2003. Protective effects of green tea extracts (polyphenon E and EGCG) on human cervical lesions. Eur. J. Cancer Prev. 12, 383–390.

Ashrafian L, Sukhikh G, Kiselev V, et al. Double-blind randomized placebo-controlled multicenter clinical trial (phase IIa) on diindolymethane's efficacy and safety in the treatment of CIN: implications for cervical cancer prevention. EPMA J. 2015;6:doi: 10.1186/s13167-13015-10048-13169.

Ashton, H., Beveridge, G.W., Stevenson, C.J., 1970. Topical treatment of skin tumours with 5-fluorouracil. Br. J. Dermatol. 82 (2), 207–209.

Barten, G., 1987. Local treatment of cervical intraepithelial neoplasia using 5 percent 5-fluoruracil cream. Zentralbl. Gynakol. 109, 1510–1516.

Batman, G., Hampson, L., Hampson, I.N., 2011. Lessons from repurposing HIV drugs: a prospective novel strategy for drug design. Future Virology. 6, 1021–1023.

Bossens, M., Van Pachterbeke, C., De Maertelaer, V., et al., 2018. Safety and tolerance of cidofovir as a 2% gel for local application in high-grade cervical intraepithelial neoplasia: A phase 1 investigation. Int. J. Clin. Pharmacol. 56, 134–141.

Chen, F.P., 2013. Efficacy of imiquimod 5% cream for persistent human papillomavirus in genital intraepithelial neoplasm. Taiwanese J. Obstetrics Gynecol. 52 (4), 475–478.

Choo, Y., Hsu, C., Seto, W.H., et al., 1985. Intravaginal application of leukocyte interferon gel in the treatment of cervical intraepithelial neoplasia (CIN). Arch Gynecol. 237, 51–54.

American College of Obstetricians and Gyncologists. Management of abnormal cervical cancer screening test results and cervical cancer precursors. Practice Bulletin No. 140. Obstet Gynecol. 2013;122:1338-1367.

de Witte, C.J., van de Sande, A.J.M., van Beekhuizen, H.J., Koeneman, M.M., Kruse, A.J., Gerestein, C.G., 2015. Imiquimod in cervical, vaginal and vulvar intraepithelial neoplasia: a review. Gynecol. Oncol. 139, 377–384.

Desravines N, Chibwesha CJ, Rahangdale L. Low dose 5-fluorouracil intravaginal therapy for the treatment of cervical intraepithelial neoplasia 2/3: A case series. J. Gynecol. Surg. 2020;36.

DiSilvestro, P.A., DiSilvestro, J.M., Lernhardt, W., Pfahl, M., Mannel, R.S., 2001. Treatment of cervical intraepithelial neoplasia levels 2 and 3 with adapalene, a retinoid-related molecule. J. Low Genit Tract. Dis. 5, 33–37.

Dunne, E.F., Unger, E.R., Sternberg, M., et al., 2007. Prevalence of HPV infection among females in the United States. JAMA 297, 813–819.

Ferlay J., Soerjomataram I., Ervik M., et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 1International Agency for Research on Cancer. http://globocan.iarc.fr. Published 2013. Accessed Jan 9, 2014.

Graham, V., Surwit, E.S., Weiner, S., Meyskens, F.L., 1986. Phase II trial of beta-all-transretinoic acid for cervical intraepithelial neoplasia via a collagen sponge and cervical cap. West. J. Med. 145, 192–195.

Greene SA, Nyongesa-Malava E, Richardson BA, et al. Randomized trial of LEEP vs cyrotherapy to treat CIN2/3 in HIV-infected women. Conference on Retroviruses and

Opportunistic Infections; 2017; Seattle, WA.
Grillo-Ardila, C.F., Angel-Muller, E., Salazar-Diaz, L.C., Gaitan, H.G., Ruiz-Parra, A.I., Lethaby, A., 2014. Imiquimod for anogenital warts in non-immunocompromised adults. Cochrane Database Syst. Rev. 11.
Grimm, C., Polterauer, S., Natter, C., et al., 2012. Treatment of cervical intraepithelial neoplasia with topical imiquimod: a randomized controlled trial. Obstet. Gynecol. 120 (1), 152–159.
Hampson, L., Kitchener, H.C., Hampson, I.N., 2006. Specific HIV protease inhibitors inhibit the ability of HPV 16 to degrade p53 and selectively kill E6-dependent cervical carcinoma cells in vitro. Antivir. Ther. 11, 813–825.
Hampson, L., Maranga, I., Masinde, M.S., et al., 2016. A single-arm, proof-of-concept trial of lopimune (lopinavir/ritonavir) as treatment for HPV-related pre-invasive cervical disease. PLoS ONE 11, e0147917.
Hefler, L., Grimm, C., Tempfer, C., Reinthaller, A., 2010. Treatment with vaginal progesterone in women with low-grade cervical dysplasia: a phase II trial. Anticancer Res. 30, 1257–1261.
Helm C.W. et al. Retinoids for preventing the progression of cervical intra-epithelial neoplasia. Cochrane Systematic Review. 2013.
Hubert, P., Doyen, J., Capelle, X., et al., 2010. Local applications of GM-CSF induce the recruitment of immune cells in cervical low-grade squamous intraepithelial lesions. Am. J. Reprod. Immunol. 64, 126–136.
Insinga, R.P., Dasback, E.J., Elbasha, E.H., 2005. Assessing the annual economic burden of preventing and treating anogenital human papillomavirus-related disease in the US. Pharmacoeconomics. 23, 1107–1122.
Joshi, J.V., Paradkar, P.H., Jagtap, S.S., Agashe, S.V., Soman, G., Vaidya, A.B., 2011. Chemopreventative potential and safety profile of curcuma longa extract in women with cervical low-grade squamous intraepithelial neoplasia. Asian Pac. J. Cancer Prev. 12, 3305–3311.
Katki, H.A., Schiffman, M., Castle, P.E., et al., 2013. Five-year risk of recurrence after treatment of CIN 2, CIN 3, or AIS: performance of HPV nd Pap cotesting in post-treatment management. J. Low Genit. Tract. Dis. 17, S78–S84.
Khanna, N., Dalby, R., Tan, M., Arnold, S., Stern, J., Frazier, N., 2007. Phase I/II clinical safety studies of terameprocol vaginal ointment. Gynecol Onc. 107, 554–562.
Kleinberg, M.J.S.J.J., Stringer, J.S., Partridge, E.E., 2003. A cost-effectiveness analysis of management strategies for cervical intraepithelial neoplasia grades 2 and 3. Am. J. Obstet. Gynecol. 1186–1188.
Koeneman MM, Kruse AJ, Kooreman LFS, et al. TOPical Imiquimod treatment of high-grade Cervical intraepithelial neoplasia (TOPIC trial): study protocol for a randomized controlled trial. BMC Cancer. 2016:doi: 10.1186/s12885-12016-12187-12883.
Kola, S., Walsh, J.C., 2009. Patients' psychological reactions to colposcopy and LLETZ treatment for cervical intraepithelial neoplasia. Eur. J. Obstet. Gynecol. Reprod. Biol. 146, 96–99.
Koshiol, J., Lindsay, L., Pimenta, J.M., Poole, C., Jenkins, D., Smith, J.S., 2008. Persistent human papillomavirus infection and cervical neoplasia: a systematic review and meta-analysis. Am. J. Epidemiol. 168, 123–137.
Krause, S., Phillipsen, T., Rank, F., Stroyer, I., 1987. Interferon and cervical dysplasia: CIN III treated wtih local interferon application. Colposcopy Gynecologic Laser Surgery 3, 195–198.
Krebs, H.B., Helmkamp, B.F., 1991. Chronic ulcerations following topical therapy with 5-fluorouracil for vaginal human papillomavirus-associated lesions. Obstet. Gynecol. 78 (2), 205–208.
Krygiou, M., Athanasiou, A., Paraskevaidi, M., et al., 2016. Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis. BMJ 354, i3633.
Laccetta, G., Carrone, A., Burratti, M., Mancino, P., 2015. Effect of the treatment with beta-glucan in women with cervical cytologic report of atypical squamous cells of undetermined significance (ASCUS) and low-grade intraepithelial lesions (L-SIL). Minerva Ginecol. 67, 113–120.
Lahiri, C.D., Dugan, K.B., Xie, X., et al., 2015. Oral lopinavir use and human papillomavirus infection in HIV-positive women. J. Acquir. Immune Defic. Syndr. 70, e63–e66.
Lin, C.T., Qiu, J.T., Wang, C.J., et al., 2012. Topical imiquimod treatment for human papillomavirus infection in patients with and without cervical/vaginal intraepithelial neoplasia. Taiwanese J. Obstetr. Gynecol. 51 (4), 533–538.
Maiman, M., Watts, D.H., Andersen, J., Clax, P., Merino, M., Kendall, M.A., 1999. Vaginal 5-fluorouracil for high-grade cervical dysplasia in human immunodeficiency virus infection: a randomized trial. Obstet. Gynecol. 94 (6), 954–961.
Meyskens, F.L., Graham, V., Chvapil, M., Dorr, R.T., Alberts, D.S., Surwit, E.A., 1983. A phase I trial of beta-all-transretinoic acid delivered via a collagen sponge and a cervical cap for mild or moderate intraepithelial cervical neoplasia. J. Natl Cancer Inst. 71, 921–925.
Meyskens, F.L., Surwit, E., Moon, T.E., et al., 1994. Enhancement of regression of cervical intraepithelial neoplasia II (moderate dysplasia) with topically applied all-trans-retinoic acid: a randomized trial. J. Natl Cancer Inst. 86, 539–543.
Niwa, K., Tagami, K., Lian, Z., Gao, J., Mori, H., Tamaya, T., 2003. Topical vidarabine of 5-fluoruracil treatment against persistant HPV in genital (pre)cancerous lesions. Oncol Reports. 10, 1437–1441.
Okamoto, A., Woodworth, C.D., Yen, K., et al., 1999. Combination therapy with podophyllin and vidarabine for human papillomavirus positive cervical intraepithelial neoplasia. Oncol Rep. 6, 269–276.
Pachman DR, Barton DL, Clayton AC, et al. Randomized clinical trial of imiquimod: an adjunct to treating cervical dysplasia. Am. J. Obstet. Gynecol. 2012;206(1):42 e41-47.
Rahangdale, L., Lippmann, Q., Garcia, K., Budwit, D., Smith, J.S., Van le, L., 2014. Topical 5-fluorouracil for treatment of Cerivcal Intraepithelial Neoplasia 2: a randomized controlled trial. Am. J. Obstet. Gynecol. 210, e1–e8.
Rogstad, K.E., 2002. The psychological impact of abnormal cytology and colposcopy. Br. J. Obstet. Gynecol. 109, 364–368.
Ruffin, M.T., Bailey, J.M., Normolle, D.P., et al., 2004. Low-dose topical delivery of all-trans retinoic acid for cervical intraepithelial neoplasia II and III. Cancer Epidemiol Biomarkers Prev. 13, 2148–2152.
Saslow, D., Solomon, D., Lawson, H.W., et al., 2012. American cancer society, American society for colposcopy and cervical pathology, and american society for clinical pathology screening guidelines for prevention and early detection of cervical cancer. J. Low Genit. Tract. Dis. 16, 175–204.
Schneider, A., Gruber, T., Kirchmayr, R., Wagner, D., Papendick, U., Schlunk, G., 1995. Efficacy trial of topically administered Interferon gamma-1beta gel in comparison to laser treatment in cervical intraepithelial neoplasia. Arch. Gynecol Obste. 256, 75–83.
Shireman, T.I., Tsevat, J., Goldie, S.J., 2001. Time costs associated with cervical cancer screening. Int. J. Technol. Assess. Health Care 17, 146–152.
Shukla, S., Bharti, A.C., Hussain, S., et al., 2009. Elimination of high-risk human papillomavirus HPV 16 infection by “Praneem” polyherbal table in women with early cervical intraepithelial lesions. J. Cancer Res. Clin. Oncol. 135, 1701–1709.
Silman, F.H., Boyce, J.G., Macasaet, M.A., Nicastri, A.D., 1981. 5-fluorouracil/chemosurgery for intraepithelial neoplasia of the lower genital tract. Obstet. Gynecol. 58, 356–360.
Silverman MH, Hedley ML, Petry KU, JS W. Clinical trials in cervical intraepithelial neoplasia: balancing the need for efficacy with patient safety. J Low Genit Tract Dis. 2002;6:206-211.
Singer, Z., Soos, E., Feichter, G., 1993. Treatment of cervical intraepithelial neoplasia associated with human pappilomavirus by interferon vaginalettes. Radiation Oncol. 27, 321–325.
Smith, J.S., Sanusi, B., Swarts, A., et al., 2017. A randomized clinical trial comparing cervical dysplasia treatment with cryotherapy vs loop electrosurgical excision procedure in HIV-seropositive women from Johannesburg, South Africa. Am. J. Obstet. Gynecol.
Snoeck, R., Noel, J.C., Muller, C., Clercq, De, Bossens, M., 2000. Cidofovir, a new approach for the treatment of cervix intraepithelial neoplasia III (CIN III). J. Med. Virol. 60, 205–209.
Stanley M. Chapter 17: Genital human papillomavirus infections–current and prospective therapies. J Natl Cancer Inst Monogr. 2003(31):117-124.
Stefani, C., Liverani, C.A., Bianco, V., et al., 2014. Spontaneous regresson of low-grace cervical intraepithelial lesions is positively improved by topical bovine colostrom preparations (GINEDIE (R)). A multicentre, observational, Italian pilot study. Eur. Rev. Med. Pharm. Sci. 18, 728–733.
Stentella, P., Biamonti, A., Carraro, C., et al., 2017. Efficacy of carboxymethyl beta-glucan in cervical intraepithelial neoplasia: a retrospective, case-control study. Minerva Ginecol. 69, 425–430.
Suh-Burgmann, E., Sivret, J., Duska, L.R., Del Carmen, M., Seiden, M.V., 2003. Long-term administration of intravaginal dehydroepiandrosterone on regression of low-grade cervical dysplasia - a pilot study. Gynecol. Obstet. Invest. 55, 25–31.
Surwit, E., Graham, V., Droegemuller, W., et al., 1982. Evaluatiom of topically applied trans-retinoic acid in the treatment of cervical intraepithelial lesions. Am. J. Obstet. Gynecol. 143, 821–823.
Swanick, S., Windstar-Hamlin, K., Zwickey, H., 2009. An alternative treatment for cervical intraepithelial neoplasia II, III. *Integr. Cancer Ther.* 8, 164–167.
Valencia, M.H., Pacheco, A.C., Quijano, T.H., Giron, A.V., Lopez, C.V., 2011. Clinical response to glycyrrhizinic acid in genital infection dueto human papillomavirus and low-grade squamous intraepithelial lesion. Clin. Pract 1(e93).
van de Nieuwenhof, H.P., van der Avoort, I.A., de Hullu, J.A., 2008. Review of squamous premalignant vulvar lesions. Crit. Rev. Oncol. Hematol. 68 (2), 131–156.
van de Sande, A., Koeneman, M., Gerestein, C., Kruse, A., van Kemenade, F., van Beekhuizen, H., 2018. TOPical Imiquimod treatment of residual or recurrent cervical intraepithelial neoplasia (TOPIC-2 trial): a study protocol for a randomized controlled trial. BMC Cancer. 18, 4510–4517.
Van Pachterbeke, C., Bucella, D., Rozenberg, S., et al., 2009. Topical treatment of CIN 2+ by cidofovir: Results of a phase II, double-blind, prosective, placebo-controlled study. Gynecol Onc. 115, 69–74.
Weiner, S.A., Surwit, E.A., Graham, V.E., Meyskens, F.L., 1986. A phase I trial of topically applied trans-retinoic acid in cervical dysplasia-clinical efficacy. Invest. New Drugs 4, 241–244.
Weis, S.E., 2013. Current treatment options for management of anal intraepithelial neoplasia. Onco. Targets Ther. 6, 651–665.
Yabroff, K.R., Lawrence, W.F., King, J.C., et al., 2005. Geographic disparities in cervical cancer mortality: what are roles of risk factor prevalence, screening, and use of recommended treatment? J. Rural. Health. 21, 149–157.
Yliskoski, M., Cantell, K., Syrjanen, K., Syrjanen, S., 1990. Topical treatment with human leukocyte interferon of HPV 16 infections associated with cervical and vaginal intraepithelial neoplasias. Gynecol Onc. 36, 353–357.