New Strategies In The Prevention And Treatment Of Cervical Cancer
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Citation

Abstract
Across the world, carcinoma of the uterine cervix is the second most common malignancy in women, and is a major cause of morbidity and mortality (1) (Table 1 and Fig.1 and 2). In the United States, the incidence of invasive cervical cancer has steadily decreased over the last several decades due to the early detection and treatment of pre-invasive disease. In 2002, there were approximately 12,800 new cases of invasive cervical carcinoma, and despite the fact that this disease is largely preventable, 4,600 U.S. women died (2). Data derived from the Surveillance, Epidemiology, and End Results (SEER) database (1992 through 1996) indicate that population-based cervical cancer mortality rates in the United States declined by 2.1% per year. Despite the widespread availability of cervical cytologic screening in the United States, approximately 20-30% of adult women no longer continue to undergo routine pelvic examinations and cytological screening [Papanicolaou (PAP) smears] after completion of childbearing. In this country, about half of cervical carcinomas develop after suboptimal screening, and another 25% are diagnosed following incorrect interpretation of an antecedent PAP smear. Thus, up to 30% of cases, particularly adenocarcinomas, develop despite good preventive surveillance. Adenocarcinomas usually develop within the endocervical canal, and because adenocarcinoma incidence rates relative to squamous cell carcinomas are increasing (3), it is possible that routine cervical cytological screening is less effective at detecting adenocarcinoma precursor and early invasive adenocarcinomas (4). A recent analysis of U.S. trends (SEER 1973-1998) indicated a 32.4% (1.63% per year) and 32.9% (1.57% per year) increase in incidence of adenocarcinoma and adenosquamous cell carcinoma, respectively (5). In a recent study from the United Kingdom, the risk of adenocarcinoma in women born in the early 1960s was 14 times greater than for women born before 1935 (3).

Figure 1
Table 1: Cervical Cancer: A Worldwide Disease Burden

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>900,000 cases/year with 400,000 new cases/year worldwide; &gt;200,000 deaths each year Cervical carcinoma is the 3rd leading malignancy among women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>Wide geographic variations: 4 - 45 / 100,000 women (Africa &gt; Latin America &gt; Asia &gt; Europe &gt; USA; rates increase coincident with HIV prevalence); 80% are reported from developing countries</td>
</tr>
<tr>
<td>Major Problem</td>
<td>Lack of access to effective screening</td>
</tr>
</tbody>
</table>

Figure 2
Figure 1: Annual Incidence and Mortality Rates per Region (Per 100,000 Women)
Because cervical cancer is related to HPV infection acquired early in life through sexual contacts, patients with cervical cancer tend to be younger than those with other gynecologic cancers (6). Using highly specific polymerase chain reaction techniques, HPV DNA was found to be present in 99.7% of cancers (7). All the papillomaviruses share a similar genomic organization, which consists of approximately 8000 base pairs in a double DNA strand. All the open reading frames (ORFs) that could encode proteins for these viruses are located on the one viral strand that is transcribed. The HPV genome has three distinct regions. The “early” region encodes the viral proteins involved in viral DNA replication, transcriptional regulation, and cellular transformation (E oncogenes). The “late” region encodes the viral capsid proteins (L1 and L2 genes). The third region, called the long control region, or also called the upstream regulatory region, does not contain any ORFs but contains cis-regulatory elements (Fig 3). HPV infection is prevalent worldwide, and in developing countries, where this disease is a social catastrophe, women are more likely to develop an invasive cancer after infection (6). Although some strains have a higher oncogenic potential than others (Table 2), only a minority of infected patients will develop cancerous lesions (Fig 4). Infections with HPV are extremely common, and usually transient.

**CARCINOGENESIS**

Depending upon the viral strain, and among women infected with the same strain, the biological course of HPV infection is quite variable. The viral subtypes most commonly associated with malignant tumors are HPV 16 and 18, with a preponderance of HPV 18 in adenocarcinoma and HPV 16 in squamous cell lesions (8). Although some strains have a higher oncogenic potential than others (Table 2), only a minority of infected patients will develop cancerous lesions (Fig 4). Infections with HPV are extremely common, and usually transient.

**Table 2: HPV Associated with Genital Lesions**

<table>
<thead>
<tr>
<th>Strain</th>
<th>Cervical Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>SIL(CIN), condyloma acuminatum, verrucous carcinoma</td>
</tr>
<tr>
<td>11</td>
<td>SIL(CIN), condyloma acuminatum</td>
</tr>
<tr>
<td>16</td>
<td>SIL(CIN), cervical cancer</td>
</tr>
<tr>
<td>18</td>
<td>SIL(CIN), cervical cancer</td>
</tr>
<tr>
<td>30</td>
<td>SIL(CIN)</td>
</tr>
<tr>
<td>31</td>
<td>SIL(CIN), cervical cancer</td>
</tr>
<tr>
<td>33</td>
<td>Mainly SIL(CIN)</td>
</tr>
<tr>
<td>35</td>
<td>Mainly SIL(CIN)</td>
</tr>
<tr>
<td>39</td>
<td>Mainly SIL(CIN)</td>
</tr>
<tr>
<td>40</td>
<td>SIL(CIN)</td>
</tr>
<tr>
<td>42</td>
<td>PIN, SIL(CIN)</td>
</tr>
<tr>
<td>43, 44</td>
<td>SIL(CIN)</td>
</tr>
<tr>
<td>45</td>
<td>SIL(CIN), cervical cancer</td>
</tr>
<tr>
<td>51-53</td>
<td>SIL(CIN), cervical cancer</td>
</tr>
<tr>
<td>56</td>
<td>SIL(CIN), cervical cancer</td>
</tr>
<tr>
<td>59</td>
<td>SIL(CIN), cervical cancer</td>
</tr>
<tr>
<td>61</td>
<td>SIL(CIN)</td>
</tr>
</tbody>
</table>

70% of cancers are caused by HPV 16 and 18 in the USA. There are geographical differences in the prevalence of HPV subtypes. SIL, squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; PIN, penile intraepithelial
neoplasia.

**Figure 6**
Figure 4: Natural history of Cervical Intraepithelial Neoplasia

HPV, human papilloma virus; SIL, squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; IVAS, invasive; CIS, carcinoma in situ.

Low-grade lesions caused by HPV infection tend to regress or persist, whereas untreated high-grade lesions (those with integrated HPV DNA) tend to progress. Recent large-scale epidemiologic studies encompassing women from throughout the world have implicated infection with high-risk HPV subtypes as a necessary precursor (9,10). Despite this, the vast majority of infected women do not develop cervical cancer, which indicates that one or more co-factors are also necessary for malignant transformation (table 3). On a molecular level, it appears that the transformation of a normal cell into a malignant cell requires at least two mutations involving tumor suppression. There is usually a 10 to 20 year “latent” period from the times of infection (usually around the onset of active sexual life) to the time of clinically detectable preinvasive or invasive disease. In addition to HPV infection, cofactors associated with cervical cancer development include cigarette smoking, oral contraceptive use, and multiparity. Cigarette smoking has been more commonly linked to squamous cell carcinoma, whereas oral contraceptive use has been implicated as a risk factor for invasive adenocarcinoma in young women, and the relative risk increases with the number of years of exposure (11). Higher rates of adenocarcinoma, and adenocarcinoma in situ have been reported among women who tested positive for HPV infection, and who reported long-term oral contraceptive use (12). These data indicate that the cofactors involved in squamous and adenocarcinoma development are somewhat different.

**Figure 7**

Figure 8: Table 3: Risk Factors for Cervix Cancer

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No prior smear screening</th>
<th>History of cervical dysplasia or genital warts</th>
<th>Young age at first coitus</th>
<th>Multiple sex partners</th>
<th>High-risk male partner (e.g., multiple female partners)</th>
<th>Sexually transmitted diseases</th>
<th>Cigarette smoking</th>
<th>Increasing age</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grade CIN by Pap smear</td>
<td>34</td>
<td>41</td>
<td>25</td>
<td>16</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grade CIN by Pap smear and biopsy</td>
<td>45</td>
<td>21</td>
<td>23</td>
<td>14</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIS by biopsy</td>
<td>27</td>
<td>32</td>
<td>-</td>
<td>13</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN2</td>
<td>25</td>
<td>23</td>
<td>-</td>
<td>22</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN3</td>
<td>32</td>
<td>56</td>
<td>-</td>
<td>12</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall all grades of CIN</td>
<td>32</td>
<td>56</td>
<td>-</td>
<td>12</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PREVENTION STRATEGIES**

**SECONDARY PREVENTION**

**SCREENING PRINCIPLES**

In every country in which screening programs have been introduced (table 4), PAP smear screening has lowered the morbidity and mortality from cervical cancer. Colposcopic inspection and cervical biopsy is the gold standard for the evaluation of an abnormal Pap smear. Once cervical dysplasia is diagnosed, treatment options include ablation, cone biopsy, and pharmaceutical agents. Efficacy of loop excision, cryotherapy, laser, and conization are comparable, but the advantage of excision over ablation is the availability of excised tissue for histological assessment, and avoidance of cautery artifact at the cervical margins. The role of HPV DNA testing in screening or diagnosis may be promising, but remains experimental.
**B. CLASSIFICATION**

Cervical neoplasia is a term used to describe both premalignant (cervical intraepithelial neoplasia [CIN]) and invasive (including microinvasive) lesions of the uterine cervix. The pathologic diagnosis of cervical neoplasia is based on seven morphologic criteria: nuclear size, nuclear shape, nuclear stain uptake, nuclear pleomorphism, mitosis count, and aspect, and decreased cell maturation. The term CIN was proposed by Richart to define the spectrum of intraepithelial changes. CIN-1 consists of undifferentiated cells extending one third of the distance from the basement membrane to the surface epithelium (mild dysplasia); CIN-2 is characterized by extension to two thirds of this distance (moderate dysplasia); and CIN-3 by extension through more than two thirds of this distance (severe dysplasia and carcinoma in situ [CIS]). Once the malignant cells penetrate the underlying basement membrane and infiltrate the stroma, the lesion is called invasive cervical cancer.

The Bethesda classification system, first established in 1988 and recently revised in 2001, is used to report cervical smears. In this system, noninvasive squamous lesions are classified as either atypical squamous cells of undetermined significance (ASCUS), which usually signifies atypia and inflammation, low-grade squamous intraepithelial lesions (LGSIL), which usually is related to atypia due to HPV and CIN1, or high-grade squamous intraepithelial lesions (HGSIL), which typically correlates with cervical biopsies consistent with CIN2 or worse disease. A full description of the 2001 Bethesda System is found at [http://jama.ama-assn.org/cgi/content/full/287/16/2114?maxtoshow=10&hits=10&RESULTFORMAT=&searchi d=1052780735306_6249&stored_search=&FIRSTINDEX=0&minscore=50&journalcode=jama](http://jama.ama-assn.org/cgi/content/full/287/16/2114?maxtoshow=10&hits=10&RESULTFORMAT=&searchid=1052780735306_6249&stored_search=&FIRSTINDEX=0&minscore=50&journalcode=jama)

**C. SCREENING GUIDELINES**

The United States by the American Cancer Society and the National Preventive Services Task Force has recently updated PAP smear guidelines. It is currently recommended that the first PAP smear be performed at 21 years or 3 years after onset of sexual activity, and should be repeated at regular intervals until age 65. If the woman is immunosuppressed, or has a history of intraepithelial neoplasia, there is no upper age limit for screening. Intervals are yearly until age 30, and in unaffected women, interval screening every 2 to 3 years thereafter is considered sufficient. In patients who have undergone hysterectomy, routine screening is not indicated unless the cervix was not removed (subtotal hysterectomy), or the indication for hysterectomy was for the treatment of dysplasia, carcinoma in situ, or malignancy. There is some controversy on what test is the most appropriate. The American Cancer Society recommends a liquid base PAP, and the Task force a regular Pap smear. Liquid tests are more sensitive, but less specific. They are also more expensive. Physicians must consult with their pathology services for interpretation of PAP technology.

There are no standard guidelines regarding the role of HPV testing, as studies are on-going to validate this technique. The potential advantages of HPV testing include the rapid acquisition of a clinical result, the potential for mass screening, and its use to determine the need for colposcopic assessment in patients with ASCUS smears. Other tests, including image recognition and optical-probes are considered experimental.

**D. SCREENING TECHNIQUE**

PAP smears have to cover the entire cervix (360°) and the endocervix. The spatula is used to scrape the cervix and the brush to scrape the endocervical canal. Lubricant should not be used, but the speculum can be moistened with water. The spatula and brush scraping should be transferred to a microscope slide with immediate fixation. The smear should not be allowed to dry. (Fig 5).

Figure 5: PAP smear technique (courtesy of Catherine Burke, RN)
E. BARRIERS TO SCREENING

There are many potential barriers to effective cervical screening. The list includes, but is not limited to psychological, educational, and financial impediments to screening. Psychological barriers include embarrassment, unpleasantness, and modesty. Educational barriers include a lack of knowledge regarding the importance, implications, and recommended intervals for screening. Social barriers include financial burden, lack of medical insurance, and availability of childcare. In the United States, higher incidence of cervical carcinoma in blacks and other minority women has been linked to socioeconomic status (14).

F. TREATMENT APPROACH

Consensus guidelines for the management of women with cervical cytological abnormalities were published in 2001, after the publication of the Bethesda system update. These can be found at http://jama.ama-assn.org/cgi/content/full/287/16/2120

PRIMARY PREVENTION OR HPV VACCINATION

Given the global prevalence of HPV and its proven association with cervical cancer, research efforts have focused on the development of HPV-viral vaccines. The papillomaviridae comprise more than 200 types. All HPV subtypes structurally consist of a small, non-enveloped icosahedron with a circular double-stranded DNA of about 8 kB. The virus infects the basal epithelium of genital tract, skin and upper respiratory tract. Because it is primarily sexually transmitted, the risk for HPV genital tract infection is greatest with in women with multiple sexual partners, or who have partners with a promiscuous lifestyle. Worldwide, HPV infection is the most common sexually transmitted disease (STD). Approximately 7% to 15% of the population are affected, but rates in young women (50%), are especially high. In a study of the natural history of HPV infection in
males, performed at a STD clinic, 68% had HPV virus on the penile shaft, 48% on the coronal sulcus, 42% on the scrotum. The cumulative HPV point prevalence was 70% (Perez et al. 2002).

Current vaccine trials are directed to prevention and therapy of cervical cancer. Prevention vaccines are directed against capsular antigens (L1, L2), and therapeutic vaccines utilize nuclear antigens (E6, E7). Three major prevention vaccines are being tested in phase II and III trials, and include HPV 16 Monovalent, HPV Quadrivalent (HPV 6, 11, 16, 18), and HPV 16,18 Bivalent. Vaccines are made of virus-like particles (VLP) similar to the HPV outer capsid proteins, which are non-infectious, recombinant proteins produced in yeast and purified. Like hepatitis B vaccines, HPV vaccines are administered in 3 doses. The icosahedral form of the VLP may potentially help recipients to form protective antibodies.

As of today, no serious adverse experiences have been observed during clinical research with these vaccines. In a randomized, double-blinded, placebo controlled trial involving 2392 healthy women16 to 23 of age treated with HPV16 monovalent, there were no serious adverse events. The main undesirable effect was local reaction at the site of injection. The HPV 16 vaccine elicited a strong antibody response of neutralizing antibodies. Recipients of HPV 16 vaccine (N=768) had no HPV 16 DNA detected, whereas in patients who received a placebo (N=765), 41 cases of HPV 16 DNA infection were detected within 2 years of follow-up (15). A phase II study has also been completed using the quadrivalent vaccine, with comparable tolerability and immunogenicity results. Further studies will examine persistence of antibodies, long term protection from HPV infection, and prevention of cervical disease development. A 90% effective vaccine would reduce genital warts by about 80%, cervical cancer and anal cancer by 50% to 65%, intraepithelial neoplasia by 50%, and abnormal PAP smears by 40%. Important questions to be answered in further studies include the efficacy in young adolescents (10-15 years of age) and in males. Studies need to better define the ecology of HPV in various ethnicity and geographic locations. Since cervical cancer is a major cause of mortality in underdeveloped countries and HPV infection is a sexually transmitted disease, the acceptability of HPV vaccines among various ethnic groups in different cultures worldwide and the cost of these vaccines are major considerations.

**THERAPEUTIC STRATEGIES**

**STAGING**

The staging of cervical cancer is clinical, although newer technology such as magnetic resonance imaging, high-resolution computerized tomography, and surgical staging that consists of extraperitoneal common and paraaortic lymph node sampling and peritoneal washings are used to direct therapy in developed countries. Clinical staging, which consists of a pelvic examination, assessment of rectal and bladder involvement by cystoscopy and proctosigmoidoscopy, and ureteral integrity by intravenous pyelogram or computerized axial tomography, can be performed almost anywhere in the world, including developing countries and rural communities. To facilitate comparison of treatment outcomes worldwide, the International Federation of Gynecology and Obstetrics (FIGO) has chosen not to incorporate surgery or additional radiographic modalities into the staging system (http://www.figo.org/content/PDF/cervix-uteri_p7-9.pdf). Lymph node status, except for inguinal and supraclavicular nodes that are assessable by physical examination, does not affect FIGO stage, although node status for cervical carcinoma has been incorporated into TNM staging system. Of importance, once a patient has been clinically staged, the stage must not be changed.

**GENERAL TREATMENT RULES**

For stage 0 to IB1, the treatment may include surgery, radiation therapy, or both depending on patient and physician preference. For stage IB2 and above, the primary treatment consists of concurrent chemoradiation with platinum-based chemotherapy. Data from five phase III randomized trials, which together involve 1,912 patients with cervical cancer demonstrated that platinum-based chemotherapy given concurrently with radiation therapy prolongs survival in women with locally advanced cervical cancer, stages IB-IVA. Additionally, response rates and survival were improved in women with stage I-IIA disease who were found to have metastatic disease in the pelvic lymph nodes, positive parametrial disease, or positive surgical margins at the time of primary surgery. Concurrent radiotherapy and cisplatin-based chemotherapy reduced the risk of recurrence by 30-50% across a spectrum of chemotherapy prescriptions. Based on these data, in February 1999 the NIH issued summaries of these five trials with the current recommendation that “strong consideration should be given to incorporation of concurrent chemotherapy with radiation therapy in women who require...
radiation therapy for the treatment of cervical cancer” (http://www.nci.nih.gov/clinicaltrials/digestpage/cervical-cancer-announcement). The optimal chemotherapy regimen has not been defined, because significant results were seen using cisplatin alone or in combination with 5-flurouracil (5-FU) (Efudex, Fluoroplex) or 5-FU/hydroxyurea (Droxia, Hydrea). All of these regimens appear to be well tolerated, although long-term toxicity data are incomplete.

Neoadjuvant chemotherapy prior to surgery or radiation therapy is another treatment modality under investigation. An advantage of chemotherapy in this setting is the potential significant reduction in localized disease, which facilitates surgical excision, for example, in women with Stage IB2 lesions. Theoretically, the combination of chemotherapy and surgery may obviate the need for radiation therapy, and may be useful in regions where radiotherapy facilities are limited. A potential disadvantage, however, is the induction of added resistance to radiation therapy induced by chemotherapy, which may increase the likelihood of local failure in patients with positive surgical margins and/or pelvic lymph node involvement.

In patients with persistent or recurrent disease after radiation therapy treatment options include chemotherapy, radiation therapy, and/or surgery. Pelvic exenteration (anterior, posterior, total) is indicated only for those patients with localized disease without pelvic side-wall involvement. Palliative surgical procedures including urinary diversion or colostomy may be warranted for ureteral obstruction and fistula formation. Rare patients with isolated systemic disease (paraaoortic or supraclavicular lymph node involvement) may benefit from the combination of chemotherapy and radiation therapy. Under almost all other circumstances, treatment of recurrent or persistent cervical cancer is palliative, and chemotherapy is the best available alternative. (Table 5) (a).

**NEW CHEMOTHERAPY STRATEGIES**

The 1990s have seen the rapid development of new effective anticancer agents, a few of which have been tested in cervical cancer. Table 6 details the phase II studies of the many agents tested; however no specific drug or regimen has received FDA approval for the treatment of cervical cancer. Vinorelbine, gemcitabine, and the topoisomerase inhibitors, in particular, irinotecan are among the most promising new agents. As single agents, the response rate is around 20%. All of these drugs are now being investigated with cisplatin in phase III randomized studies. The Gynecologic Oncology Group (GOG) is planning a 4-arm randomized trial to test these three drugs with cisplatin versus the cisplatin and paclitaxel standard (GOG 204).

**Figure 13**

Table 5: Chemotherapeutic agents for recurrent cervical cancer

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>% Response Rate</th>
<th>Most Active Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents</td>
<td>15-29</td>
<td>Ifosfamide, Tirapazamine?</td>
</tr>
<tr>
<td>Platinum</td>
<td>15-23</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>Antitumor antibiotics</td>
<td>11-22</td>
<td>Mitomycin-C</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>5-20</td>
<td>5-Fluorouracil, Gemcitabine?</td>
</tr>
<tr>
<td>Plant alkaloids</td>
<td>0-18</td>
<td>Vincristine, Novobine?</td>
</tr>
<tr>
<td>Topoisomerase inhibitors</td>
<td>13-24</td>
<td>Irinotecan</td>
</tr>
<tr>
<td>Taxanes</td>
<td>0-17</td>
<td>Paclitaxel</td>
</tr>
</tbody>
</table>

**NEW CHEMOTHERAPY STRATEGIES**

Figure 14

Table 6: Clinical Studies of Chemotherapy in Cervical Cancer from 1997-2002

<table>
<thead>
<tr>
<th>Treatments</th>
<th>No studies</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroprusside</td>
<td>5</td>
<td>0-0%</td>
</tr>
<tr>
<td>with interferon alpha</td>
<td></td>
<td>18-21%</td>
</tr>
<tr>
<td>with chemotherapy</td>
<td></td>
<td>18-21%</td>
</tr>
<tr>
<td>Platinum-based combinations</td>
<td>13</td>
<td>28-67%</td>
</tr>
<tr>
<td>Single agents</td>
<td>9+5</td>
<td>26%</td>
</tr>
<tr>
<td>Cisplatin high dose</td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>JMV246</td>
<td></td>
<td>10-26%</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td></td>
<td>18%</td>
</tr>
<tr>
<td>Topotecan</td>
<td></td>
<td>18%</td>
</tr>
<tr>
<td>Irinotecan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td>Amscarlide</td>
<td></td>
<td>4.3%</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td></td>
<td>4.2%</td>
</tr>
</tbody>
</table>

Tirapazamine (SR4233, WIN59075) is a benzotriazine di-N-oxide. In preclinical testing, cytotoxicity is selectively directed toward hypoxic cells (Fig 6).
Cervical cancers are known to be hypoxic tumors because of early necrotic development. Drugs that are effective in hypoxic cells are especially attractive in the management of cervical cancer. In this setting, radiation and chemotherapy failures have been attributed to tumor hypoxia, because tumor oxygenation is critical for free radical formation that fixes DNA breaks after radiation therapy. In preclinical models, tirapazamine enhances both irradiation and chemotherapy effectiveness. In human non-small-cell lung cancer cells, NIH3T3 mouse cells, and in hamster CHO cells “in vivo” models, the addition of cisplatin has been tested under hypoxic conditions. Simultaneous administration of cisplatin induces an additive cytotoxicity. However, when tirapazamine precedes cisplatin administration there is synergistic activity (17). However, there is no interaction when the tirapazamine is given under aerobic conditions. A promising phase I study of tirapazamine and cisplatin in recurrent cervical carcinoma (18), and also its combination with radiotherapy for the primary treatment of cervical cancer have demonstrated safety and feasibility (19).

In conclusion, while cisplatin-based regimens are very active, no survival advantage has ever been shown for combination versus single agent cisplatin, and the toxicity of combination chemotherapy is usually worse. Single agent topoisomerase-I inhibitors have activity (10-25%), especially in non-radiated field recurrence. A randomized GOG trial of a topoisomerase-I inhibitor/cisplatin combination versus cisplatin has been completed (GOG 179). The role of vinorelbine and gemcitabine in the primary treatment of cervical cancer in the neoadjuvant setting or in combination with cisplatin and radiation therapy is also investigated. The role of tirapazamine with cisplatin in the primary treatment of cervical cancer needs to be evaluated in the Phase III setting.

BIOLOGICAL THERAPIES

THERAPEUTIC VACCINATIONS

Patients affected with cervix cancer are immunocompromised and usually lack T-cell-mediated immunoresponsiveness. There is a downregulation of HLA class I molecules in both preinvasive and invasive disease which may be peptide-mediated. Because of HPV infection, E6 and E7 HPV genes are retained in cervical cancer cells, and have become a target of therapeutic vaccination. Different techniques are being tested. Adoptive immunotherapy is a technique that uses systemic administration of immune effector cells into the host. Different effector cells have been tested in clinical trials, such as NK cells, LAK cells, tumor-infiltrating lymphocytes, and activated T-cells (20). Peptide-based vaccines of cervical carcinoma use small peptides derived from cervical cancer cells that theoretically are recognized by antigen presenting cells, and stimulate the production of T cells and NK cells (31,32,33). Specific dendritic cell stimulation is used to increase the immunity of the patient (24,25,26). Vaccination with vectors encoding for HPV (E6, E7) may build an immune reaction against the cancer cells (27,28). DNA vaccines utilize L1 or L2 for the same purpose. For example, a TA-HPV (therapeutic antigen-human papilloma virus), developed by Xenova, has an antigenic property that activates HPV-specific cytotoxic T-cells to attack tumor cells containing the viral antigen. Phase II trials in 60 patients with high-grade anogenital intraepithelial neoplasia are on-going (29). Immunomodulation with B7 co-stimulatory antigen could increase the immune recognition against the tumor (30). RNA silencing is the most recent gene therapy technique and is used to block the transcription of oncogenes in the cancer cell (31).

These techniques have not yet been tested in randomized trials and may require very specific eligibility criteria that may render their dissemination to the general cervix cancer population impractical.

BIOLOGICAL TREATMENTS

EPIDERMAL GROWTH FACTOR PATHWAY
The Epidermal Growth Factor Receptor (EGFR) has been found to be elevated in cervical cancer tissue. The E5 HPV gene has been linked to the expression of EGFR by abrogating degradation of the receptor by inhibiting the endosomal proton-ATPase. Therefore, HPV could induce upregulation of the EGF receptor network, and cause constitutive activation of this pathway in cervical cancer cells (32).

Many studies have looked at the value of EGFR expression as a prognostic factor. The reports are at times conflicting. Scambia et al studied 90 patients, but did not find a prognostic value to EGFR expression (33). Kimmig et al found a lower EGFR expression in cervix cancer in comparison to normal cervical tissue (34). However, Boiko et al found a spatial dysregulation of EGFR (35) and Kersemaekers and Mathur both found that the overexpression of EGFR is an independent predictor for prognosis in earlier stages (stage I and II) of cervical cancer and is expressed in about 50% of patients (36, 37). Serum EGFR level may also be useful as a biological marker of cervical carcinoma (38).

One important question is whether EGFR expression could be used for treatment purposes in women with cervical cancer. If the EGFR pathway is activated, either by EGFR overexpression, or by the presence of an abnormal tyrosine kinase molecule in the intracellular portion of the receptor molecule, inhibition of EGFR might inhibit cell proliferation. There may also be a correlation between EGFR expression and active DNA replication (35% in high EGFR-expressing vs 19% in non-EGFR-expressing) and EGFR expression correlated with chemosensitivity of cisplatin and topoisomerase I inhibitors, but not topoisomerase II inhibitors (39). This may have important implication for the design of clinical studies of chemotherapy in combination with biologic agents. It is possible that biologic agents such as EGFR inhibitors may desensitize the tumor cells from chemotherapy. Therefore, concurrent chemotherapy with cytotoxic and biologic agents may be less than additive. As an example, a phase III trial of chemotherapy plus Gefitinib for lung cancer did not show advantage over chemotherapy alone. Phase I and II trials of EGFR inhibition are on-going.

**COX 2 PATHWAY**

The cyclooxygenase enzyme converts the arachidonic acid to prostaglandin. The cyclooxygenase COX-2 is specifically induced in response to inflammatory processes (Fig 7). The therapeutic action of nonsteroidal anti-inflammatory drugs (NSAIDs) is thought to be due to inhibition of COX-2, whereas their gastrointestinal toxicity is believed to be due to inhibition of COX-1. COX-1, a constitutive gene, fulfills a homeostatic function in the GI tract. COX-2, an inducible gene, is an immediate early response gene that is induced by growth factors, proinflammatory cytokines, carcinogens, oncogenes, and tumor promoters (Fig 7). COX-2 can convert tobacco procarcinogens into carcinogens. Further, high levels of COX-2 promote angiogenesis and inhibit apoptosis, leading to unregulated cell growth.

http://www.jbc.org/cgi/content/full/274/33/22903#F1

**Figure 6**

Figure 7: Arachidonic Pathway

COX-2 is overexpressed in at least 85% of colorectal cancers and in half of all premalignant adenomas. It is also overexpressed in malignancies of the breast, lung, liver, pancreas, skin, bladder, cervix, stomach, esophagus, and head and neck. Because of the markedly improved safety profile of selective COX-2 inhibitors over conventional NSAIDs, a number of new studies aimed at demonstrating their value as preventive or therapeutic agents are underway for a variety of cancers. In 1999, the FDA granted approval to use celecoxib for the treatment of familial adenomatous polyposis (FAP). In preapproval trials, celecoxib reduced overall tumor burden by an average of 31% over a 6-month course of treatment, with some FAP patients achieving as much as an 80% reduction and some as little as 10%. One of the main target of COX-2 inhibition is now prevention of sporadic colorectal adenomas. Other prevention trials are planned for premalignant states, such as Barrett’s esophagus, bladder cancer, and oral leukoplakia.

COX 2 expression has commonly been found in various cancers, including cervical cancer (40). A high tumor/stroma of COX2 expression level is a factor of poor prognosis for treatment response in patients diagnosed with cervix cancer.

Studies of inhibition of COX2 pathway in cervical cancer are now under way.
http://www.rtog.org/members/protocols/c0128/main.html and SWOG 0212

TUMOR SUPPRESSOR GENES

Tumor suppressor genes P53 and Retinoblastoma are both down regulated by HPV infection. E6 gene inhibits P53 and E7 gene, the retinoblastoma tumor suppressor gene product. Inactivation of p53 by E6 protein leads to the loss of functional p53, whereas somatic mutation results in the expression of an altered p53 protein, which can interfere with wild-type p53 and elicit positive transforming activity. This effect has been seen in HPV negative tumors (a). E6 oncoprotein binds the cellular p53 tumor suppressor protein, thereby marking it for degradation through the ubiquitin-mediated pathway. Therapeutic strategies have focused on increasing the expression of these downregulated tumor suppressor genes (a). No clinical trial has been completed in patients with cervical cancer.

CONCLUSIONS

Despite the known role for cell transformation by HPV, there is no specific inhibitory molecule of oncogenesis for cervical cancer treatment. When cervical cancer persists or recurs following definitive treatment, currently available single-agent and combination chemotherapy regimens are at best, palliative. Many biologic targets are currently under study. EGFR and COX-2 overexpression could be therapeutic targets. Given the almost obligatory role of HPV infection in the development of cervical carcinoma, the best strategies for prevention and treatment require a better understanding of HPV biology. In particular, preventive vaccines, but also HPV-targeted therapy warrants further investigation.

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