Photodynamic therapy of Cervical Intraepithelial Neoplasia using Hexylaminolevulinate

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Objective
Cervical intraepithelial neoplasia (CIN) is the precancerous lesion of invasive cervical cancer. As it was shown in the last years, infection with human papilloma virus (HPV) is a necessary cause for the development of cervical cancer and its precursors. Especially among younger women, the prevalence of CIN has increased during the last decades. Age-specific incidence curves show a peak between 25 – 29 years and then decrease with age.

So far, the established treatment consists of excision techniques such as loop electrosurgical excision procedure (LEEP), cold knife excision of the transformation zone or local destruction by laser- or cryotherapy. These treatment methods have been proven satisfactory efficacy and differ mainly in complication rates and costs. The major disadvantage common to all methods is the substantial excision or destruction of cervical stroma which may cause cervical insufficiency with premature delivery or low-birth-weight babies or cervical scar stricture, so that a method that preserves the cervix would be desirable.

Porphyrin-mediated photodynamic therapy (PDT) is a promising alternative procedure. After application of a photosensitizer, dysplastic cells may become susceptible to destruction by light of a certain wavelength mediated by local cytotoxic effects of reactive oxygen species, especially singlet oxygen. The tissue selectivity of the different photosensitizers currently under investigation and the laser irradiation restricted to the lesion area combined with the short half-life of the arising cytotoxic species ensure that the phototoxic damage is mainly localized to the lesion and spares normal surrounding tissue.

Photodetection of CIN lesions using 5-aminolevulinic acid (5-ALA) induced porphyrin fluorescence has been shown to be effective compared to conventional colposcopy, too. However, several studies examining the possible therapeutic use of ALA-based PDT for CIN reported equivocal results. Hexamethylaminolevulinate (HAL) and methylaminolevulinate (MAL) are esterified derivates of 5-ALA with substantially shorter half-lives, so that a method that preserves the cervix would be desirable.

Results
The mean age was 30.8 years (range 20 – 54 years). 4 of 56 patients were lost to follow up due to different reasons. Among the 52 evaluable patients, there were 13 patients with a histological diagnosis of a CIN 1, 20 with a CIN 2 and 19 with a transformation zone or local destruction by laser- or cryotherapy. These treatment electrosurgical excision procedure (LEEP), cold knife excision of the cervix between 25 – 29 years and then decrease with age.

The overall histologic response rate for complete or partial response was 63% (33/52).

Conclusion
PDT seems to be a non-invasive, repeatable procedure for CIN and cervical HPV infection with minimal side effects and preservation of cervical function which can be easily performed on outpatient basis.

Patients & Methods
The ethical committee of our institute endorsed the study design prior to patient acquisition and written informed consent was obtained from all women enrolled. We report data from two clinical studies were we included 24 and 32 non-pregnant women with a high-risk HPV test result, a histological diagnosis of a high-grade or a persistent (> 1 year) low-grade squamous intraepithelial lesion and consent to follow this procedure. Each patient had a complete history and gynecologic examination including cervical cytology, HPV DNA testing, colposcopy and biopsy confirming CIN 1 - 3.

The study drug hexylaminolevulinate was supplied as a powder by Photocure ASA, Norway. With a defined incubation time of 5 hours (first population) or 12 hours (second population), HAL was topically applied to the cervix for 12 hours using a cervical cap (Wisap, Sauerlach, Germany). Patients were counselled to stay supine during incubation.

After removal of the study solution, the portio uteri was illuminated by red coherent light of a wave length of 633 nm using a PDT laser and a special cylindrical light catheter with a backscattering surface for homogenous light distribution (both Bioline GmbH, Jena, Germany). This applicator illuminated both ecto- and endocervical canal homogenously for 17 minutes (= 1000 s), administering a light dose of 100 J/cm². After the intervention, we inquired for possible side effects.

At 1 month evaluation, we performed gynecologic examination, cervical cytology, colposcopy and HPV DNA testing. If the response was non-complete (cervical cytology, colposcopy and HPV DNA status), we offered a repeat PDT. Response evaluation was performed at 6 month follow-up and included gynecologic examination, colposcopy, cytology, histology and HPV DNA testing. A complete remission was defined as a histological regression of the CIN state from high-grade CIN to CIN 1.

Chart 1: Response and Non-Responder six months after PDT.

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<thead>
<tr>
<th>CIN 1</th>
<th>CIN 2</th>
<th>CIN 3</th>
<th>CIN 1-3</th>
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<td>n</td>
<td>Complete / Partial Remission</td>
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<td>52</td>
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Table 1: Response and Non-Responder six months after PDT.

References