Prepoznavanje bolnic z visokim tveganjem za napredovanje ploščatoceličnih intraepitelijskih lezij materničnega vratu s ponavljajočo se oziroma trajno okužbo s HPV 16/18: kakšna je vloga biomarkerjev?

Determining high risk for squamous intraepithelial lesion progression in patients with recurrent or persistent HPV 16/18 infection: is there a role for biomarkers?

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Izvleček

Spremljanje ploščatoceličnih intraepitelijskih lezij nizke stopnje (PIL-NS) in zgodnje zdravljenje ponavljajočih se ploščatoceličnih intraepitelijskih lezij visoke stopnje (PIL-VS) predstavljata temeljena ukrepa pri preprečevanju raka materničnega vratu. Kljub temu da lahko na podlagi dosedanjih raziskav predvidimo, katera bolnica ima povišano tveganje za ponovni razvoj PIL-VS, ter identificiramo bolnice, ki imajo trajno okužbo s humanim papiloma virusom (HPV) 16 in 18, po konizaciji ostaja več dilem na področju zdravljenja. Ena izmed temeljnih dilem je, kako izbrati ženske, ki potrebujejo agresivno kirurško zdravljenje. Tovrstne ocene z dosedanjimi kliničnimi in patološkimi markerji je potrebno dopolniti z dopolnilno diagnostiko, ki zajema patobiologijo napredovanja bolezni. Na-

Abstract

Monitoring of low grade and early treatment of recurrent high grade squamous intraepithelial lesions (HSILs) are the cornerstones of cervical cancer prevention. Although current knowledge provides us with the ability to identify patients at risk for redeveloping HSIL, specifically patients with persistent human papilloma virus (HPV) 16 and 18 infection after conization, the danger of surgical overtreatment of these women with persistent infections remains. Complementary diagnostics encompassing the pathobiology of disease progression need to be evaluated. This perspective presents novel evidence that HPV methylation, c-MYC gene methylation, and co-expression of targeting protein for Xenopus kinesin-like protein and programmed death ligand 1 had a positive predictive value in determining

predek v našem razumevanju biologije bolezni kaže, da imajo HPV-metilacija, c-MYC metiliranje gena in ko-ekspresija TPX2 in PD-L1 pozitivno napovedno vrednost pri določanju, katere cervikalne lezije napredujejo v lezije visokega tveganja in katere spontano regresirajo.

which cervical lesions progress to high grade or spontaneously regress.

INTRODUCTION

Squamous intraepithelial lesion (SIL) and implementation of screening programs have dramatically reduced the number of cases of advanced cervical carcinoma (1). Regardless of success of current clinical treatment, prior to cervical cancer diagnosis, 16% of all carcinoma patients had undergone conization as a measure to eliminate high grade SIL but as the disease either recurred or progressed, the measures taken to prevent malignoma failed to detect them (2). In addition, studies show that even after conization, 5%–15% of patients were left with persistent or recurrent high grade lesions (2–5). In 2004, Paraskevaidis et al. (6) examined the role of HPV testing within the post-conization follow-up system to identify, as early as possible, treatment failure and persistent HPV leading to the recurrence of SIL 2+. At that time the assumption based on the heterogeneous data was that there might be a predictive value in HPV testing after conization. In 2016, Onuki and colleagues conducted a pooled analysis and found that positive surgical margins and testing for high risk HPV enable a high discrimination rate of the cases leading to SIL treatment failure (7). In order to prevent overtreatment in women, efforts have been made in the past to find other complementary methods of diagnosing high grade SIL (HSIL) or potential HSIL cases. In 2011, Martin et al. identified some biomarkers for diagnosis of specific patients with the potential for progression of SIL stage (8). This work was therefore built on the findings of these authors and offers a further outlook on the possibility of more accurate diagnosis of recurrent HSIL after conization.

EVIDENCE SELECTION

A Medline search with the combined keywords "HPV persistence," "conization," and "biomarker" led to four results in the database (from 2004 to 2015). For this reason we expanded our search and included the keywords "SIL persistence" and "marker." By adjusting the search to language (English) and species (human), we were left with 38 results. The evidence presented in this commentary does not touch upon all search results, but focuses on the new emerging or intriguing knowledge to serve for further investigation, and discovery of diagnostics.

TREATMENT FAILURE AND HPV INFECTION

In 2004, Paraskevaidis and colleagues identified the factors leading to failure of conization for SIL. Among those were: i) excision margins, ii) satellite HPV infections outside the transformation zone, iii) higher age, and iv) the extension of SIL to the endocervical glands (6). Advances in clinical research further pointed out that epidemiological data identified patient age, gravidity, and parity as contributing factors to patients with the risk of residual SIL 2+. Positive surgical margins have a special impact (4,9). Ayhan et al. pointed out that positive surgical margins, arising from a widespread disease (>50% volume), have a positive predictive value for treatment failure (9). This is especially important when taking into consideration that lesion size has been indicated to be an important consequence of infection with HPV 16 (10). Taking all this into consideration, we can establish a primary high risk group for the recurrence of HSIL. The chal-

lenge, therefore, is how to determine which patients of the group present a further risk for lesion progression or spontaneous regression.

KNOWN BIOMARKERS

Martin et al. identified the following markers for complementary diagnosis of cases leading to intraepithelial neoplasia progression: Ki-67, p16INK4a (CDKN2A), topoisomerase IIa (TOPO-IIa), minichromosome maintenance protein, and MYB proto-oncogene like 2 (8). In the years after this review, factors were tested regarding their prognostic value. Quint and colleagues tested the usefulness of the markers Ki-67, p16, retinoblastoma protein (pRb), and p53 for their prognostic value in determining which low grade SIL (LSIL) cases will progress to HSIL (11). However, the outcomes of the study in comparison to the promising nature of the markers showed no significant difference in expression of the named markers between patients. Regardless of the finding that a high percentage of recurrent lesions expressed p16INK4a, the predictive value of this marker for which lesions will progress to HSIL is low (11-13). A more promising emerging factor for determining the risk of low risk cervical lesions progressing to high risk lesions has been found in c-MYC gene amplification combined with HPV infection (14). Gimenes et al. were able to monitor disease progression efficiently by monitoring the presence of HPV-16/18 and c-MYC gene amplification. If both criteria were met (present infection and amplification) progression was highly likely (14).

Progression monitoring could also be possible with biomarkers presented by Zhang et al. in 2015 (4). They focused on programmed cell death-1 (PD-1), insulin-like growth factor II mRNA-binding protein 3 (IMP3), and targeting protein for Xenopus kinesin-like protein 2 (TPX-2). When staining TPX2 in pathological grade II and III samples, expression was significantly higher compared to that of grade I and samples from healthy women. Similarly, the PD-L1-positive rate was significantly higher in HSIL than in the LSIL healthy volunteer groups. In the persistence/recurrence groups, there was significant co-expression of TPX2 and PD-L1 in the HSIL group, suggesting that co-expression of TPX2 and PD-L1 could be a potential predictor for SIL progression. Howitt et al. showed that stathmin-1 (STMN-1) was overexpressed in cervical carcinoma and in SIL3 lesions (18). Staining for STMN-1 distinguished cases with HSIL and benign lesions. Although for STMN-1 the current body of evidence is low, there could be a predictive value with this marker. Therefore, further studies specifically targeting the potential of STMN-1 for diagnostic purposes are needed.

HPV GENE METHYLATION

The connection between HPV gene methylation and disease progression is especially intriguing. Increased methylation at the CpG sites in HPV52/58 L1 gene correlates with the severity of cervical neoplasia. HPV L1 gene methylation status could therefore be a potential biomarker for detecting HSIL (15). Lesions that undergo irreversible recombination can be detected by DNA methylation in high fractions. Kalantari et al. also concluded that the number of false-positive samples (methylated samples with episomal HPV-16 DNA) is small. HPV-16 was found to be chromosomally integrated in a fraction of precancerous infections in methylated samples and could be a marker for detection of cancer progression (16,17).

OTHER CLINICAL CONSIDERATIONS

HPV pathobiological mechanisms are not the origin of all clinical aspects of progression toward HSIL. During virus acquisition and persistence, the microbiome of patients has a potential role (19). A review by Mitra and colleagues points out that reduced Lactobacillus spp. in the vaginal flora is positively correlated with progression of SIL and cervical cancer. However, as the mechanisms of this disturbance in vaginal flora are not known yet; therefore, a greater base of knowledge needs to be built prior to an understanding of how microbiota determination could influence risk assessment in predicting cervical lesion progression (19).

With the exponential growth of personalized medicine, our paradigm of diagnosing patients and predicting their risk of developing malignant disease from benign SIL needs to be evolved. Therefore, a deep understanding is required of what turns some high risk patients with persistent HPV infection, but LSIL, into patients with HSIL. This commentary reports some of the knowledge gained on biomarkers in the last few years, showing that although promising, the progression cannot be determined with staining for the traditional markers that are believed to affect cell transformation (Ki-67, p16, pRb, and p53). There is a need for further examination of new markers (such as c-MYC, HPV methylation, STNM-1, and co-expression of TPX2 and PD-L1) as well as the microbiome of patients. A strong evidence base of which markers predict disease progression or regression in high risk HPV-16/18-infected patients can then lead us towards preventing the consequences of overtreatment (such as the risk of pre-term birth in consequent pregnancies, as well as providing rapid treatment to patients at risk of developing HSIL (20).

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