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Adjuvant therapy for recurrent respiratory papillomatosis

Terapie adjuwantowe w nawracającej brodawczakowatości krtani

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Keywords

respiratory papillomatosis, JoRRP, cidofovir, bevacizum, HPV vaccine

Summary

Recurrent respiratory papillomatosis (RRP) is a relatively rare disease with potentially devastating consequences for the patient. Its course is unpredictable, ranging from mild disease and spontaneous remission to aggressive disease with pulmonary dissemination and the need for frequent surgery. It can also have a chronic clinical course and cause potentially life-threatening airway damage. A number of alternative medical therapies to standard surgical treatment have been investigated in recent decades, but the results of these studies remain moderate. Recent years have brought significant changes in the incidence of the disease due to breakthroughs in vaccination and prevention of human papillomavirus (HPV) or related pathology. In Poland and many other countries, RRP is not a notifiable disease, hence current data is very limited. It has been accepted to refer to RRP as Juvenile-onset papillomatosis (JoRRP) when the disease occurs in childhood, otherwise it is Adult-onset RRP (AoRRP). This review will present the most promising directions in the fight and prevention of this disease.

Słowa kluczowe

nawracająca brodawczakowatość krtani, JoRRP, cydofowir, bewacizumab (Avamys), szczepionka p/HPV

Streszczenie

Nawracająca brodawczakowatość układu oddechowego (RRP) jest stosunkowo rzadką chorobą o potencjalnie wyniszczających konsekwencjach dla pacjenta. Jej przebieg jest nieprzewidywalny, od łagodnej choroby i spontanicznej remisji do agresywnej choroby z rozsiewem płucnym i koniecznością częstych zabiegów chirurgicznych. Może mieć również przewlekły przebieg kliniczny i powodować potencjalnie zagrażające życiu uszkodzenie dróg oddechowych. W ostatnich dekadach badano wiele alternatywnych terapii medycznych w stosunku do standardowego leczenia chirurgicznego, jednak wyniki tych badań pozostają umiarkowane. Ostatnie lata przyniosły znaczące zmiany w zapadalności na tę chorobę ze względu na przełom w szczepieniach i profilaktyce wirusa brodawczaka ludzkiego (HPV) czy związanej z nim patologii. W Polsce i wielu innych krajach RRP nie jest chorobą podlegającą obowiązkowi zgłaszania, stąd aktualne dane są bardzo ograniczone. Przyjęto określać RRP mianem brodawczakowatości o początku w wieku młodzieńczym (JoRRP), gdy choroba pojawia się w dzieciństwie, w przeciwnym razie jest to RRP o początku w wieku dorosłym (AoRRP). W niniejszym przeglądzie zostaną przedstawione najbardziej obiecujące kierunki w walce i prewencji tej choroby.

Introduction

Recurrent respiratory papillomatosis (RRP) is a benign disease of the airway caused by low-risk human papillomavirus (HPV), most commonly with subtypes 6 and 11 (1-3). HPV is thought to infect the stem cells within the basal layer of the epithelium and either cause active disease or remain dormant (4, 5). The disease is characterized by the development of exophytic proliferative lesions of connective

tissue covered by epithelium which affect the mucosa of the airways. RRP has usually been subdivided into juvenile-onset RRP (JoRRP; age at onset, < 18 years) and adult-onset RRP (AoRRP; age at onset, ≥ 18 years) (6, 7). Juvenile-onset recurrent respiratory papillomatosis (JoRRP) is a rare but morbid disease characterized by multiple upper airway lesions that lead to dysphonia and potential airway obstruction. As a result of an aggressive course of the disease, the squamous papillomas spread in the aerodigestive tract finally causing respiratory failure related to colonization of the lung parenchyma. Because of its recurrent nature, multiple surgical excisions are required to manage RRP. Surgery is the mainstay of treatment, but numerous adjuvant therapies have been applied to improve surgical outcome. Medical treatment alone is currently unable to control or eradicate the disease. The aim of this review is to present an overview on current and future perspectives in the management of RRP.

Management of RRP

Surgery

Traditional management of RRP has been surgical excision in the operating room (OR) under general anesthesia. Various surgical modalities appear to be equally effective treatments for RRP (8). Most commonly with potassium-titanyl-phosphate (KTP) lasers or microdebriders, but also using CO_2 lasers or cold steel instruments.

Indications for surgery are based on the presence of warts that causes symptoms. The urgency of intervention depends on the severity of symptoms and is divided into scheduled, elective, urgent or emergent (9). Laryngeal lesions, if present, cause number of symptoms such as low-pitched, coarse, fluttering voice, aphonia or breathy voice, or cough, pneumonias, even dysphagia. Signs of severe airway obstruction include tachypnea, stridor, retractions (suprasternal, substernal, intracostal), flaring of the nasal ala, and use of accessory neck or chest muscles. It is necessary to remember that in a patient undergoing multiple surgeries a year not every lesion needs to be removed in every surgical procedure. Surgical excision is still the current, gold standard of care in the treatment of recurrent respiratory papillomatosis (RRP). Special care must be taken during surgical removal of lesions either to spare all vital and functional structures or prevent iatrogenic scarring of the larynx or trachea.

Despite the development of surgical techniques, up to 30% of patients who have undergone multiple surgical excisions of a papilloma in the anterior commissure of the larynx have developed scarring of the anterior glottis and web formation (10). Unless the surgeon can be assured that iatrogenic injury will not result from their technique, papilloma should be left in the anterior commissure in children requiring several surgeries a year. A small percentage of patients have been described to develop subglottic stenosis as a result of surgical interventions in the anterior commissure of the larynx (10).

Another surgical premise in RRP is to avoid tracheotomy at all costs. Frequent surgical procedures (i.e., twice a month) are favored over tracheotomy in children and adults with recurrent aggressive disease. Tracheotomy is believed to promote the spread of papilloma down the trachea, into the bronchi and lungs. There are no known contraindications to surgical removal of recurrent respiratory papillomatosis (RRP). If a child or adult's only presenting symptom is voice deterioration, the procedure can be scheduled as an elective. Airway obstruction is an absolute indication for immediate intervention.

Nonsurgical adjuvant treatment

In the context of identifying the viral etiology of RRP, several attempts have been made to treat RRP conservatively. Unfortunately, despite sound scientific theories, many treatments have proved ineffective, and in principle medical treatment can only be considered as an adjuvant to surgery.

Cidofovir, a cytosine analog, was investigated and developed with the premise of treating cancer; subsequently, its antiviral activity against DNA viruses was noted hence it is now the antiviral drug most commonly used in the medical adjuvant treatment of RRP. Cidofovir was first used in 1995, then the formulation was tested in patients with severe recurrent laryngeal papillomatosis (11). To date, the exact mechanism of action against HPV is not clearly defined. Induction of apoptosis and enhancement of the immune response are accepted as likely mechanisms of action (12).

Prospective studies of intraoperative, intradermal injections of cidofovir available in the literature indicate partial or complete regression of papillomas and a reduction in the frequency of debulking surgeries (12-17). Van Cutsem et al. (18) first suggested that injection of cidofovir into papillomas of the lower pharynx and esophagus resulted in remission of the disease, and Snoeck et al. (19) subsequently showed apparently complete remission of papillomas in 14 of 17 patients treated with direct intraoperative injections of cidofovir. Multicenter observations confirm that intradermal administration does not cause systemic toxicity or local side effects; measured plasma concentrations are below toxic values and are completely dose-dependent in children (17).

No definitive protocol has been developed regarding the dose, frequency of administration or concentration of the drug (20). However, because of the long-term effect, infrequent administration of cidofovir is indicated. Pransky et al. found that the greatest benefit can be achieved when repeated injections are given at short intervals (2-4 weeks) in an aggressive disease course (13). Naiman et al. confirmed that patients receiving injections less frequently than once a month showed less benefit from treatment (17). In addition, the number of injections required to achieve a clinically significant response is unclear. This probably indicates variability in the biology of the disease rather than the treatment protocol adopted, and suggests that treatment of this condition requires a patient-by-patient approach. Dosing of cidofovir is also controversial: a survey of 74 surgeons using cidofovir found that cidofovir should be started intradermally, at a dose of 3 mg/kg or less, if

surgical debulking is required more frequently than every 2-3 months (20).

A factor that may improve the response to treatment in pediatric patients, according to Akst et al., is the sequential increase in doses of topical cidofovir. The practice of increasing cidofovir concentrations from 5 to 10 mg/mL during step-dose protocol (RRP) treatment has been proposed (14). Similarly, Pransky et al. observed the need to increase drug concentrations in children as a consequence of initially small, acceptable volumes. In practice, submucosal injection may cause transient swelling of the vocal folds, with the risk of airway obstruction being greatest in infants and young patients (14). There have recently been reports of inhalation of cidofovir, which may provide further ground for clinical trials in the near future (21).

Bevacizumab is a recombinant humanized IgG1 monoclonal antibody that blocks angiogenesis by inhibiting human vascular endothelial growth factor-A (VEGF-A) (22). It is the first angiogenesis inhibitor approved by the FDA (23).

Rahbar et al., in their retrospective study, found strong expression of VEGF-A mRNA in the squamous epithelium of all RRP patients, and strong expression of VEGFR-1 and VEGFR-2 was noted in endothelial cells of papillary blood vessels (24). These observations formed the basis for the use of bevacizumab in the context of RRP. Several subsequent studies have shown that bevacizumab is relatively safe and active in both Jo-RRP and Ao-RRP. In their study, Sidell et al. achieved a 58% reduction in median Derkay scores by removing papillomas with KTP laser followed by intradermal administration of bevacizumab at a dose of 14.25 mg at intervals of four to six weeks (25). Additionally, the time between treatments more than doubled (25).

While, Zeitels et al. determined the efficacy of bevacizumab in combination with KTP laser excision in 20 adult patients with bilateral vocal fold RRP to be 95% (19/20) (26). Patients had better control of vocal fold disease treated with bevacizumab and KTP laser than vocal fold disease treated with KTP laser alone (26). Consistent with these studies, other researchers have reported promising results using surgery and bevacizumab, with minimal complications (25, 27, 28).

The decision to undertake systemic treatment with bevacizumab is made by summarizing the frequency of surgical interventions, the load of the papilloma and its manifestation. Patients with an aggressive course of RRP with involvement of the lower respiratory tract (i.e. bronchioles, lungs) or patients suffering from RRP that is difficult to treat surgically or shows multiple recurrences are eligible for systemic bevacizumab therapy (27). It is widely accepted to use bevacizumab at a dose of 10 mg/kg mc in a 90-minute infusion. It is essential to monitor blood pressure before and after the infusion, as well as laboratory monitoring of calcium metabolism parameters.

In recent reports, systemic use of bevacizumab has been increasingly reported and effective in one in three case (28).

HPV vaccine

The idea of immunological treatment of RRP predates the isolation of human papilloma virus as the cause of the condition (1990). The first attempts at immunotherapy were made in the 1960s, using a vaccine against bovine warts (29). In the 1960s and 1970s, attention turned to autologous vaccines (30, 31), while a mumps vaccine was tested in 1990 (32). The breakthrough discovery of HPV enabled the development and dissemination of a quadrivalent vaccine in 2006. Originally for the prevention of cervical cancer. The year 2015 brings an expanded with 5 additional oncogenic subtypes product-a 9-valent vaccine against the most common HPV strains (33). As early as 2009, Gallagher and Derkay (34) highlight the therapeutic effect of the HPV vaccine on RRP. They put forward the thesis that the antibody-induced humoral immune response to the vaccine can inhibit latent, in the surrounding to overt mucosa, HPV infection. By the above mechanism, the vaccine reduces the risk of both recurrence and reinfection (35). In contrast, Goon et al. (36) suggested that in the adaptive immune response, the cellular response can also be activated by vaccination.

Recent reports show 9-valent Gardasil as a promising adjuvant therapy option for primary surgical removal of lesions. Extending the operative intervals has been suggested, especially in the case of recurrent disease in JoRRP (37). A systematic review and meta-analysis by Rosenfield and colleagues evaluates 12 publications and includes 63 RRP patients treated with Gardisil-9. The above meta-analysis showed a statistically significant reduction in the number of surgeries within one month after HPV vaccination. The mean interoperative interval (ISI) increased from 7.02 months pre-vaccination to 34.45 months post-vaccination, translating into significant improvements in the quality of life and cost of treatment for RRP in patients (6). Study limitations were variability in serology and DNA data collection HPV and measurement of results, however, this fact does not eliminate the role of vaccination in RRP therapy. It should be added that HPV vaccination has been studied as an adjunct to treatment for other HPV-related diseases, including genital warts and cervical cancer, with no statistically significant benefit in terms of secondary prevention (38).

Research is currently underway on the next generation of the HPV vaccine. Gardasil-9 targets the capsid protein L-1 of the virus, which leads to the production of neutralizing antibodies. In contrast, the new vaccines target the E6 and E7 oncoproteins (39). E6 and E7 have been found to be highly expressed in HPV-associated tumors and comorbidities (40). This observation suggests a benefit of the vaccine down to the ability to generate a stronger T-cell immune response. The new INO-3016 vaccine showed immunological activity both in vitro and in vivo. Clinically significant reductions in surgical interventions have been reported (40). Two studies of HPV-DNA vaccines are ongoing: study Inovio INO-3107 (NCT04398433) and an NIH-funded study by Clint Allen et al. (41). We do not know the final results of these studies.

In the cited studies, the adult population of the respondents is an undoubted limitation. The pediatric patient and YoRRP represent a different course and stage of the disease.

Conclusions

Various surgical modalities appear to be equally effective treatments for RRP. Adult and pediatric patients have decreased recurrent disease burden when receiving concurrent adjuvant therapy. There has been significant progress in the prevention and treatment of RRP over the past few years. Current data indicate that due to the increasing use of the HPV vaccine, there will be a significant decrease in the incidence of RRP. Healthcare providers can help reduce RRP cases by encouraging HPV-9 vaccination, which could lead to the eradication of this difficult disease. The addition of systemic medical treatment options, including secondary vaccinations, intravenous bevacizumab, and topical cidofovir, has expanded our arsenal to control resistant cases of RRP. Ongoing research into DNA vaccines and PD-L1 blockade may offer additional treatment options in the future.

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

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