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Intra-lesional Cidofovir injection to treat Recurrent Respiratory Papillomatosis: Review of literature.

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ABSTRACT:- ***Introduction****:* Recurrent respiratory papillomatosis(RRP) is a disease of the upper aerodigestive tract caused by infection with human papilloma virus(HPV) 6/11/16/18. Treatment involves surgical removal of the epithelial lesion in order to maintain airway patency and phonation.
Objective: Review of literature to analyse the effect and safety of intra-lesional Cidofovir injection in patients with RRP.
Method: Literature search done via Pubmed and NHS Athens using key words Cidofovir and RRP. Out of sixty two, thirty three articles studied consist of literature reviews and case series, systemic use and adverse effects of Cidofovir.
Result: The relapse-free duration increases and RRP gets less aggressive with intra-lesional Cidofovir which is a cytosine nucleoside analogue antiviral medication. Incidence of dysplasia or malignant degeneration which can occur with Cidofovir is the same as spontaneous malignant degeneration of RRP(2-3%).
Conclusion: Intra-lesional Cidofovir controls aggressive lesions of RRP without increasing the risk of laryngeal dysplasia. For evaluation of safety; further research is required to define adequate dose and frequency of treatment. Histology of the lesions at every procedure and assessment of HPV genotype would help to monitor response to treatment, detect dysplasia and progress of the disease.

Key words: *Recurrent respiratory papillomatosis, intra-lesional Cidofovir.*

I. INTRODUCTION

Recurrent respiratory papillomatosis is a disease of the upper aerodigestive tract caused by infection with HPV 6/11/16/18. Though it is benign, the disease process is unpredictable; ranging from mild disease and spontaneous remission to an aggressive disease with pulmonary spread and requirement for frequent surgical debulking procedures to maintain patent airway. It can present a protracted clinical course and cause potentially life-threatening compromise of the airways.[1] It is widely accepted that HPV may be transmitted from the mother's anogenital site to the infant's respiratory tract during and even before delivery through infected placenta and amniotic fluid, resulting in juvenile onset RRP after months or years, while in adults it may be transmitted through oral-genital sexual contact.[1,2] Rabah et al. found that HPV-11 infection confers a more aggressive course to RRP than HPV-6. Treatment involves surgical removal of the epithelial lesion in order to maintain airway patency and phonation. [3]

II. METHOD

A systematic review of the literature was undertaken, with articles describing the use of intra-lesional cidofovir for RRP. Literature search was made via Pubmed and NHS Athens using key words RRP and Cidofovir. Sixty two articles were identified. Out of those thirty three articles were included which were literature reviews, case series and articles on adverse effects of Cidofovir. Case reports from 1998 till 2016 were reviewed. The parameters taken into account were: concentration of infiltrated cidofovir (mg/ml), therapeutic response, relapse-free time (months), side effects, genotypes (HPV-6/11/16/18) and evolution of dysplasia.

III. RESULT

RRP is extremely difficult to treat and patients usually undergo multiple surgical procedures and are given toxic systemic medications to control the disease such as, acyclovir, ribavirin, isotretinoin, indol-3-carbinol and interferon.[4] Cidofovir was used intravenously, via nebulisation and most frequently as intra-lesional injection. Cidofovir is an acyclic nucleoside phosphonate analog. Cidofovir is active in vitro and in vivo against a broad range of DNA viruses.[5]The first report of successful intra-lesional injection of cidofovir directly into the respiratory papillomas was described in 1995 by Van Cutsem et al.[6] Cidofovir was described as the most used adjuvant therapy on a survey carried out with members of the American Society of Paediatric Otolaryngology. Sixty-one percent of the patients followed up in the services of the physicians included in the survey improved or were disease-free after treatment, against only four percent of cases in which the disease became more severe.[7]

3.1.Use of Intra-lesional Cidofovir: Concentration of cidofovir injected ranged from 0.0001mg/ml to 37.5mg/ml, recommended dose being 5 to 7.5mg/ml. Volumes up to 5ml per injection were routinely used. Total dose and frequency of cidofovir administration was highly variable. The need for repeat doses of cidofovir was judged on an individual basis.[8] One of the studies recommended, checking laboratory parameters like morphology with blood smear, urea, creatinine,ALT, AST, and bilirubin levels before the treatment,1 day and 4 weeks after the injection; due to high toxicity of cidofovir.[9]Because RRP can also be controlled with repeated microsurgery the use of cidofovir during pregnancy could be avoided.[1] Bielamowicz et al. reported a local inflammatory response after injection with cidofovir.[10] The findings of vocal fold or supraglottic scarring could be related to cidofovir or repeated microlaryngoscopy.[11]

3.2.Systemic use of cidofovir: Apart from the articles that describe the use of intra-lesional cidofovir, four articles had been published that described the use of intravenous cidofovir as treatment for RRP.[12-15] The four reported cases had pulmonary extension of their RRP. They received the intravenous injections with cidofovir at a dose of 5 mg/kg. In all cases the intravenous injections were associated with hyperhydration and probenecid in order to diminish nephrotoxicity.From the four patients with RRP that had been treated with intravenous cidofovir one displayed side-effects. She developed leukopenia and partial alopecia on her combination therapy of cidofovir and interferon.[13] At that time she had received 34 intravenous injections with cidofovir in a period of 16 months. The therapy was well tolerated in the other three patients. They received total of 27, 23 and 37intravenous injections in period of 14, 12 and 27 months, respectively.[12,14,15] One case report described nebulisation with cidofovir to reach the pulmonary lesions, the only complication reported was haemoptysis which was resolved by reducing the dose.[16]

3.3Dysplasia in RRP lesions: It was reported that malignant transformation happens more often in patients who have a history of smoking or radiation.[17] HPV-types 16 and 18 are considered high-risk types because they are frequently associated with severe atypia and invasive carcinoma in uterine cervical epithelium.[18] The reported incidence of spontaneous malignant degeneration of RRP is 2–3%.[1,19,20] One of these studies showed 2.7% of the patients treated with cidofovir had dysplasia or malignant degeneration. This percentage was concurrent with the incidence of spontaneous malignant degeneration of RRP (2–3%).[21] This review showed that cidofovir does not seem to induce dysplastic changes in HPV-infected laryngeal epithelium, and its use has shown promising results in treatment of RRP.[21] A retrospective study of 159 cases of RRP,Karatayli-Ozgursoy et al. Concluded that, adjunctive therapy with cidofovir, was not statistically associated with dysplasia or carcinoma-ex-papilloma.[22]

3.4Adverse effects of cidofovir: Systemic use of Cidofovir was associated with nephrotoxicity and neutropenia. These adverse effects were preventable with proper hydration and Probencid.[1] Intra-lesional use of Cidofovir was documented relatively safe. No effect was noted of intra-lesionally injected cidofovir on haematological and chemical parameters in blood.[19,23,24] The recommended dose of intra-lesional cidofovir is 3mg/kg, to reduce toxicity.[25]

IV. DISCUSSION

Studies included were mainly case series and literature reviews. The cases included were both Juvenile onset respiratory papillomatosis(JORP) as well as Adult onset repiratory papillomatosis(AORP). Intra-lesional cidofovir was effective in both. Duration of therapy and frequency of use of cidofovir were variable in every study, there were no standard criteria mentioned to decide those. The controversy of dysplastic changes caused by cidofovir could not be ruled out convincingly as no study provides data regarding regular biopsies of the papilloma lesions as well as it was difficult to rule out if the changes were spontaneous or due to use of cidofovir. Reported adverse effects of cidofovir were mostly related to its systemic use. As per the multiple previous studies its intra-lesional use is safe, though recommended dose is less than 3mg/kg. Cidofovir in combination with surgical debulking reduces the viral load in patients with RRP.[26] No histology evidence suggests that intralaryngeal cidofovir or bevacizumab alone or in combination resulted in significant changes to the porcine vocal fold.[27]

V. CONCLUSION

Cidofovir, has a good adjuvant action in RRP. The drug shows a high efficiency by increasing the relapse-free time and decreasing the number of surgeries required. Further research is necessary to define the most adequate doses, frequency of administration and duration of therapy. Simultaneously its adverse effects should be monitored by blood tests to monitor renal function. Studies done so far revealed that, the risk of dysplasia does not increase with the use of intra-lesional Cidofovir. As the response to treatment depends on HPV genome, identification of viral genome is necessary. Biopsy of the lesions at every surgical debulking is advisable to rule out dysplasia.

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