Auris Nasus Larynx 43 (2016) 541–545

Contents lists available at ScienceDirect

Auris Nasus Larynx

journal homepage: www.elsevier.com/locate/anl

Intralesional cidofovir injection for recurrent respiratory papillomatosis in Japan

Shigeyuki Murono *, Yosuke Nakanishi, Akira Tsuji, Kazuhira Endo, Satoru Kondo, Naohiro Wakisaka, Tomokazu Yoshizaki

Department of Otolaryngology, Head and Neck Surgery, School of Medicine, Kanazawa University, Japan

ARTICLE INFO

Article history:
Received 9 October 2015
Accepted 11 January 2016
Available online 6 February 2016

Keywords:
Recurrent respiratory papillomatosis
Cidofovir
Intralesional injection

ABSTRACT

Objective: The treatment of recurrent respiratory papillomatosis (RRP) continues to be difficult. Adjuvant pharmacological treatment is increasingly being used, and intralesional cidofovir injection remains the leading option. Almost all papers regarding the treatment come from the United States and Europe. The present study demonstrated it for the first time from Asia.

Methods: Ten patients with RRP were treated with intralesional cidofovir injection. The severity of papillomatosis and adverse events including blood leukocytes, blood neutrophils, and serum creatinine were evaluated before and after the completion of treatment.

Results: Human papillomavirus (HPV) type 6 was detected in nine patients, and no types of HPV were detected in a remaining patient. Severity scores significantly improved after treatment ($p = 0.005$). However, complete resolution was achieved in only one patient. No significant differences were observed between before and after treatment with respect to adverse events ($p = 0.866$ for blood leukocytes, $p = 0.866$ for blood neutrophils, and $p = 0.933$ for serum creatinine). Squamous cell carcinoma occurred three and half years after the completion of treatment in a patient without HPV detection. However, the link between cidofovir and the occurrence of carcinoma in the case remains questionable.

Conclusion: This initial report of intralesional cidofovir injection for RRP from Asia demonstrated acceptable efficacy without obvious adverse events. However, the uncontrolled spread of this treatment should be avoided, and eighteen statements approved by the task force of the United States should be referred to while planning this treatment.

1. Introduction

Recurrent respiratory papillomatosis (RRP) is a chronic disease characterized by papillomatous growths of the airway predominantly affecting the larynx and trachea. The condition is caused by the human papillomavirus (HPV), a small DNA virus, especially types 6 and 11 [1]. As RRP is most often located in the larynx, it is sometimes a debilitating disease compromising the voice and airway. The therapy focuses on surgical removal of the mucosal lesions in order to keep the airway open and maintain the voice satisfactorily. However, adjuvant pharmacological treatment, in addition to surgery, is increasingly being used [2].

Cidofovir, a cytosine nucleoside analogue that is incorporated into the growing DNA chain of both viruses and mammals, inhibits the viral DNA polymerization process and

* Corresponding author at: Department of Otolaryngology, Head and Neck Surgery, School of Medicine, Kanazawa University, 13-1 Takaramachi, Kanazawa, Ishikawa 920-8640, Japan. Tel.: +81 76 265 2413; fax: +81 76 234 4265.
E-mail address: murono@med.kanazawa-u.ac.jp (S. Murono).

http://dx.doi.org/10.1016/j.anl.2016.01.005
0385-8146/

has potent antiviral activity against a broad spectrum of herpes viruses and HPV [3,4]. Currently, the intralesional injection of cidofovir is the most widely used adjuvant therapy for RRP [1,2,5]. The majority of published reports come from the United States and Europe, while some come from other areas including Canada and Mexico [5,6]. However, there have been no publications from Asia, including Japan. This is the first report from Asia with respect to the intralesional injection of cidofovir for RRP.

2. Materials and methods

2.1. Patients

In the present case study, ten patients, including eight men and two women, were treated from 2007 to 2013 at the Department of Otolaryngology, Head and Neck Surgery, Kanazawa University Hospital, Japan. All patients had histologically confirmed recurring laryngeal papillomatosis, and had previously received several surgeries. This study was approved by the Kanazawa University Hospital Institutional Review Board. Patients were comprehensively informed about this treatment, including the off-label use of cidofovir, and signed consent was obtained from all of them.

2.2. Procedures

Injection was performed using microlaryngoscopy under general anesthesia with a regular endotracheal tube. In the present study, no surgical procedures, including the removal or evaporation of lesions, were attempted prior to the injection, except for in one case with severe airway obstruction, as previously reported [7,8]. Cidofovir, at a concentration of 7.5 mg/mL, was injected into the mucosa surrounding the tumors with the use of a laryngeal injection needle (19-gauge, Nagashima Medical Instruments Co. Ltd, Tokyo), which subsequently infiltrated toward the lesions. A total of 1–4 mL of the agent, dependent on the extension of the disease, was introduced in one surgery. If extrusion from injected point was observed, we tried to minimize it with pinching the point with laryngeal forceps. Injection was scheduled three times every two weeks.

2.3. Evaluation

The severity of papillomatosis was evaluated before the first injection and one month after the third injection with a flexible laryngeal videoscope according to the published staging system [9]. Adverse events with respect to blood tests were evaluated using Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0), as typically done in cancer treatment. Values of blood leukocytes, blood neutrophils, and serum creatinine before and after the first cidofovir injection, which was referred to as ‘‘immediately after’’, as well as late after the third cidofovir injection ranging from 6 months to 3 years, which was referred to as ‘‘late after’’, were retrospectively collected.

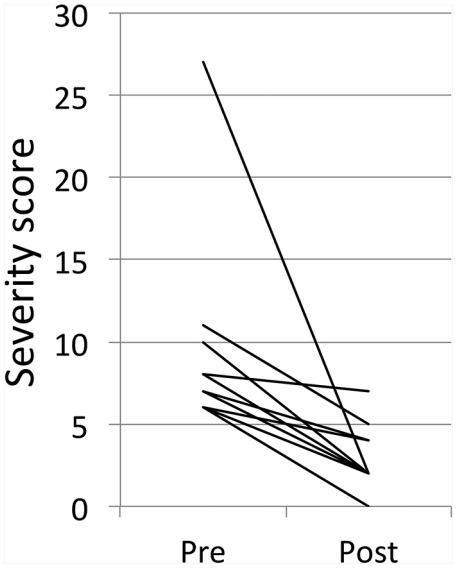

Fig. 1. Change of recurrent respiratory papillomatosis severity scores before (Pre) and after (Post) treatment in each patient.

2.4. Statistical analysis

A Wilcoxon signed-rank test was used to investigate the differences between parameters before and after treatment. All analyses were carried out using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). In all tests, $p < 0.05$ was considered significant.

3. Results

3.1. Effect of treatment

Mean and median ages of the ten patients were 44 and 42.5 years, respectively, ranging from 24 to 69 years old. Papillomatosis was limited within the larynx in all patients. HPV type 6 was detected in nine patients, while no types of HPV were detected in a remaining patient.

All patients completed the scheduled intralesional cidofovir injections. Pre-treatment and post-treatment severity scores of each patient are shown in Fig. 1. A patient with a pre-treatment severity score of 27 required surgical debulking at the initial treatment. Means ± standard deviations (SD) of pre-treatment and post-treatment severity scores were 9.60 ± 6.35 and 3.00 ± 2.00, respectively, showing significant improvement after treatment ($p = 0.005$) (Fig. 2). If the patient who required surgical debulking is removed from analyses, means ± SD of pre-treatment and post-treatment severity scores are 7.67 ± 1.80 and 3.11 ± 2.09, respectively, also showing significant improvement after treatment ($p = 0.007$).

A patient who achieved complete resolution after treatment remained free from disease for more than 5 years. However, most of the remaining patients required additional surgical procedures at some point, as shown in Fig. 3.