Effective Eradication of Oral Verrucous Carcinoma with Continuous Intraarterial Infusion Chemotherapy

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Abstract: Background. We evaluated the effectiveness of intraarterial methotrexate infusion as a primary therapy for oral verrucous carcinoma (VC).

Methods. Fifteen male patients (mean age, 55 years) were included. By using an implantable port-catheter system and a portable pump, methotrexate was continuously infused to the external carotid artery for a mean period of 7.5 days (50 mg/day), followed by weekly bolus of methotrexate (25 mg) via intraarterial route for a mean period of 10 weeks.

Results. The tumor regressed dramatically and disappeared completely after treatment within a mean period of 2.5 months. All patients obtained complete remission and recovered without disfigurement. All patients were alive without disease recurrence at a median follow-up of 43 months. The side effects were tolerable.

Conclusions. The results of our treatment modality for oral VC appear to compete favorably with the results of surgical series and even more with those of radiotherapy series.

Keywords: oral cavity; verrucous carcinoma; intraarterial chemotherapy; continuous infusion; methotrexate

Verrucous carcinoma (VC), characterized by distinguished clinical and pathologic features, represents a distinct extremely well-differentiated and low-grade malignant variant of squamous cell carcinoma (SCC). It arises most commonly from the oral cavity1 and larynx2 and may involve anatomic sites.2–5 The pathogenesis of VC is poorly understood, and VC may cause significant morbidity with repeated recurrence and local invasion, although it does not metastasize.

Various treatment regimens, including laser surgery, photodynamic therapy, cryosurgery, immunotherapy, retinoid therapy, and chemotherapy, have been used for the management of VC, but the response to these treatments remains a matter of debate.5–7 Surgery has been advocated as the treatment of choice. However, wide involvement often makes total excision difficult, and extensive surgical resection may lead to cosmetic and functional disability. Radiotherapy is an alternative option, usually resulting in poorer local control compared with surgery.7 It has been reported that the potential for anaplastic transfor-
information and metastasis of the existing VC might develop in patients with VC after radiation therapy. A high recurrence rate has been noted in patients with VC treated with either radiation or surgery alone. The literature on the role of chemotherapy for VC is limited to case reports, and we are aware of no systematic published evaluation on the efficacy of chemotherapy for VC in head and neck region.

Our favorable clinical results were obtained through the use of intraarterial infusion chemotherapy. This treatment modality offered not only better prognosis but also satisfactory cosmetic and functional results without resorting to complicated surgery. We consider that intraarterial infusion chemotherapy for oral VC has the potential to improve outcome while preserving the organ. In this study, we evaluated the effectiveness of intraarterial methotrexate infusion as a primary therapy for patients with oral VC.

MATERIALS AND METHODS

Patient Characteristics. A total of 15 patients with various stages of oral VC who underwent continuous intraarterial chemotherapy were recruited for this study during the past 6 years (see Figure 1). Of these 15 patients, 8 had large T3-4 tumors and 7 had T1-2 tumors. Two of the 15 patients were previously treated by local excision, whereas the others had no treatment prior to this admission.

The demographic characteristics and the clinical features of the patients are listed in Table 1. Staging was performed according to the TNM classification of the Union Internationale Contre le Cancer (UICC), sixth edition. For staging, detailed physical examination, chest radiograph, and routine biochemical and hematologic tests were performed. In addition, bone scintigraphy and imaging studies (ultrasonography, CT, and MRI) were performed to assess the progression of VC and exclude the possibility of distant metastasis. None of the patients were seen with clinically evident regional lymphadenopathy. All patients were treated with curative intent.

Patient Selection Criteria. Inclusion criteria were as follows: (1) age older than 18 years; (2) previously untreated or recurrent VC without distant metastases; (3) Karnofsky performance status score greater than 60; (4) histologically proven diagnosis of VC by biopsy; (5) adequate hematologic and renal function; and (6) acquisition of written informed consent for this treatment. This study was reviewed and approved by the Human Investigation Review Committee at the KMUH.

Technique of Catheter Placement. A totally implantable port-catheter system (Jet Port Plus Allround; PFM, Cologne, Germany) consisting of an injection port and a detachable catheter was used for catheterization. In our department, this technique of continuous intraarterial infusion chemotherapy used for treatment of patients with cancer has been previously reported. With the patient under local anesthesia, the catheter was inserted through the superficial temporal artery of the affected side and moved in a retrograde manner into the external carotid artery. The tip of the catheter was placed proximal to the branching of the feeding artery of the tumor. The distal end was embedded subcutaneously along the lateral neck and connected to the port, which was implanted subcutaneously near the infraclavicular region. The same procedure could be also performed in the opposite side. The proper location was confirmed by patent blue V (Guerbet Co, France) infusion through the catheter. The distribution of the dye could be observed, and the proposed therapeutic field for drug infusion was thus confirmed (Figure 2). A previous study indicated that well-stained areas were considered as profusely perfused areas, whereas poorly stained areas were considered as poorly perfused areas.

Chemotherapy Regimen. Methotrexate 50 mg was infused continuously to the external carotid artery every 24 hours using a portable pump (CADD-1; Deltec, St. Paul, MN). Folinic acid 6 mg was given intramuscularly every 6 hours during the period of methotrexate infusion. The end point of continuous methotrexate administration was determined by the white blood cell (WBC) and platelet counts, which were less than 3000/μL and 10 × 10^3/μL, respectively. Methotrexate was given continuously for a mean period of 7.5 days (range, 5–10 days). After completion of infusion therapy, the regimen was changed to weekly bolus of a low dose (25 mg) of methotrexate via the intraarterial route, and folinic acid was not given at our outpatient clinic. The total administered dose of methotrexate for intraarterial infusion ranged from 250 to 500 mg (mean, 375 mg) in these 15 patients. A weekly bolus of methotrexate was given in these patients for a mean period of 10 weeks (range, 8–
12 weeks) (Table 1). After complete disappearance of the gross lesion, no further anticancer therapy was given.

**Assessment of Therapeutic Effect.** The change of clinical condition was recorded at weekly interviews during the treatment period. Treatment results were evaluated 1 month after discontinuation of treatment. Visual examination, palpation, CT, and MRI were performed, and the effects were recorded according to the World Health Organization (WHO) response criteria. A complete response (CR) was defined as the absence of tumor for 4 consecutive weeks or more, and a partial response (PR) was defined as a reduction in a cross-section of the tumor to 50% or smaller. No change (NC) was defined as a tumor cross-section reduction rate of smaller than 50% or an increase in the tumor diameter. For statistical analysis, the local control rate and overall survival rate were analyzed with use of the Kaplan–Meier method. After the treatment was completed as determined by impalpable tumor and gross disappearance of the lesion, the regional lymph nodes

![FIGURE 1. Case 14. An exophytic verrucous carcinoma from right buccal mucosa before treatment. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]](image1)

![FIGURE 2. Case 14. The distribution of the dye and the proposed therapeutic field for drug infusion were observed in the same patient. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]](image2)

**Table 1.** The demographic characteristics of patients with oral verrucous carcinoma.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age, y</th>
<th>Tumor location</th>
<th>TNM stage</th>
<th>Tumor size, cm</th>
<th>MTX, mg*</th>
<th>Weekly bolus</th>
<th>Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>57</td>
<td>Right bucca</td>
<td>T2N0M0</td>
<td>2 × 2</td>
<td>350</td>
<td>9</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>52</td>
<td>Bil bucca</td>
<td>T1N0M0</td>
<td>1 × 1</td>
<td>400</td>
<td>8</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>52</td>
<td>Right bucca</td>
<td>T2N0M0</td>
<td>2 × 2</td>
<td>500</td>
<td>8</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>65</td>
<td>Right bucca</td>
<td>T3N0M0</td>
<td>5 × 3.5</td>
<td>250</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>51</td>
<td>Left palate</td>
<td>T4N0M0</td>
<td>3 × 3</td>
<td>400</td>
<td>10</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>52</td>
<td>Right palate</td>
<td>T3N0M0</td>
<td>4 × 3</td>
<td>300</td>
<td>9</td>
<td>43</td>
</tr>
<tr>
<td>7</td>
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<td>Right bucca</td>
<td>T2N0M0</td>
<td>4 × 2.5</td>
<td>500</td>
<td>8</td>
<td>44</td>
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<tr>
<td>8</td>
<td>M</td>
<td>43</td>
<td>Right bucca</td>
<td>T3N0M0</td>
<td>5 × 2</td>
<td>450</td>
<td>10</td>
<td>44</td>
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<tr>
<td>9</td>
<td>M</td>
<td>62</td>
<td>Right bucca</td>
<td>T4N0M0</td>
<td>6 × 4</td>
<td>400</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>53</td>
<td>Left bucca</td>
<td>T4N0M0</td>
<td>8 × 10</td>
<td>400</td>
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<td>43</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>59</td>
<td>Left lower gum</td>
<td>T2N0M0</td>
<td>3 × 3</td>
<td>400</td>
<td>8</td>
<td>38</td>
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<tr>
<td>12</td>
<td>M</td>
<td>52</td>
<td>Right upper lip</td>
<td>T2N0M0</td>
<td>3 × 3</td>
<td>300</td>
<td>8</td>
<td>69</td>
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<tr>
<td>13</td>
<td>M</td>
<td>55</td>
<td>Right bucca</td>
<td>T2N0M0</td>
<td>4 × 3</td>
<td>300</td>
<td>9</td>
<td>36</td>
</tr>
<tr>
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<td>Palate</td>
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<td>63</td>
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<td>T4N0M0</td>
<td>5 × 3</td>
<td>300</td>
<td>12</td>
<td>24</td>
</tr>
</tbody>
</table>

*Methotrexate (total dose administered by intraarterial infusion).*
of the neck were checked for any sign of metastasis by clinical examination or image studies at regular intervals of every 2 months for the first 2 years and thereafter every 3 months for the next 3 years.

**Adverse Side Effects.** Adverse side effects were assessed according to the standard WHO criteria. The evaluation parameters were peripheral blood cell count, liver function, renal function, oral mucositis, and nausea/vomiting. Blood biochemical examination was performed once weekly, and peripheral blood counts were measured twice weekly. Any side effects such as lesion pain, swallowing problems, or skin rash were noted by weekly interview and clinical examination. Complications due to the catheter placement were also evaluated.

**RESULTS**

All 15 patients with pathologically confirmed VC were men, with an age range of 43 to 65 years (mean, 55 years) at diagnosis. The most common site of VC within the oral cavity was the buccal mucosa, followed by the palate. The details are listed in Table 1.

**Survival.** All tumors began to decrease in size in the first week of infusion therapy. The period of hospitalization ranged from 10 to 14 days (mean, 12 days). In every case, the tumor regressed dramatically and disappeared completely after treatment within a mean period of 2.5 months (range, 2–3 months) (Figure 3). Pathologically, all patients demonstrated a pure VC before treatment (Figure 4). All patients obtained complete remission and achieved good cosmetic and functional preservation after the end of infusion therapy. All 15 patients are still alive with no recurrence of the lesion at a mean follow-up period of 42 months (range, 24–69 months).

**Complications.** No catheter-related complications occurred. According to the manufacturer’s instructions, the silicon membrane of the injection port is designed to withstand about 2000 punctures using a 22G Huber needle, and all material components are implantation-tested. In this study, although the infusion port was frequently accessed during the period of infusion therapy, no major complications such as extravasation and catheter- or port-related sepsis were found. After completion of methotrexate therapy, the intraarterial catheter and injection port remained in place. However, no significant side effects were found during follow-up.

The side effects due to infusion chemotherapy were mild and tolerable. The major complication was bone marrow suppression of grade I to II toxicity based on WHO classification. No patients experienced vomiting. Mild and transient local toxicity such as pain or mucositis of the infused
area was relatively common. The median time for occurrence of mucositis was 6 days (range, 5–7 days) after infusion chemotherapy, whereas the mean time for mucositis healing was 8 days (range, 7–10 days) after discontinuing therapy. Seven patients had elevated serum transaminase levels, which were noted up to 600 IU/mL. However, levels returned to normal within 3 weeks after discontinuation of infusion therapy. Neurological or vascular events were not observed in any cases. A summary of the toxicities is shown in Table 2.

## DISCUSSION

In Taiwan, oral cancer is a significant health problem and in 2001 was the fourth most common cancer in males. VC of the oral cavity is an unusual neoplasm, accounting for 1% to 10% of all oral squamous malignancies. VC is recognized as a variant of the conventional squamous cell carcinoma because of its local invasiveness, nonmetastasizing behavior, and special clinical appearance. It most often arises from the upper aerodigestive tract, with the oral cavity being the most common site of origin. The incidence is highest in the cheek mucosa, gingivae, and retromolar areas. A significant finding in our study was that VC of the oral cavity tends to be seen at a younger age (mean, 55 years) with an overwhelming predominance of male patients compared with a national survey in the United States. These differences in demographic features likely reflect different mechanisms of carcinogenesis between different geographic areas.

The pathogenesis of VC remains unclear, and the response to treatment is controversial. Verrucous hyperplasia and oral leukoplakia have been shown to be likely precursor lesions that may transform into a squamous cell carcinoma or VC. Some carcinogens, including tobacco, alcohol, cigarettes, and betel nuts, may cause leukoplakia that then proceeds toward the development of oral cancer. Although previous studies have indicated that tobacco chewing plays a significant role in the pathogenesis of VC, the habitual chewing of betel nut may be the most important etiologic factor in our patients. In this study, all patients had the habit of chewing betel nut. Recently, several investigators found that most patients with VC were positive for human papillomavirus (HPV). However, the results of various studies using different techniques to determine the etiologic role of HPV in VC are not in agreement.

Excision with and without radical surgery, chemotherapy, radiation, or a combination of modalities have all been used in the treatment of VC. Surgery alone has been considered to be by far the preferred modality of treatment, especially for smaller lesions, which are easy to localize. Surgery aims at complete eradication of the tumor and has the potential for cure. However, some patients underwent extensive surgery, compromising postoperative function and decreasing quality of life. Surgical treatment is confounded by a high recurrence rate and local recurrence rates ranging from 0% to 29% in surgically treated patients with VC of the head and neck. Ackerman reported 3 recurrences in 17 patients with oral VC, and Goethals et al. reported 10 recurrences in 45 patients treated with excision alone.

Controversy exists regarding the efficacy of radiotherapy for VC. The data from a previous survey identifies much worse outcome among the cases treated with irradiation. McClure et al. reported a high recurrence rate of verrucous carcinoma treated with radiation in 10 cases. It has been reported that local recurrence rates range from 38% to 46% in primarily irradiated patients. However, the concept of anaplastic transformation after radiotherapy has not been substantiated in more recent literature. Radiochemotherapy has been practiced recently as an acceptable alternative to surgery, especially for more extensive lesions.

To our knowledge, no effective chemotherapeutic regimen for VC has been reported in the literature, and in most patients, the agents have been given via systemic intravenous route. Our experience with intraarterial methotrexate infusion as the first-line treatment for VC is encouraging. In this study, a complete response rate for VC could be achieved using intraarterial methotrexate infusion.
infusion in all our patients. The rate of local tumor control is 100%. All patients remain alive and no evidence of recurrence of VC has been observed at a mean follow-up of 36 months.

The results of our study are consistent with previous findings that survival in patients with oral VC is generally favorable compared with that in patients with oral SCC. A contemporary survey of 2350 patients with head and neck VC showed a 5-year relative survival rate of 77.9%. For localized disease, survival after surgery was 88.9%, compared with 57.6% after irradiation, the modality generally used for more advanced lesions. Although the follow-up period might be considered relatively short, our treatment results appear to compete favorably with the results of surgical series and even more with those of radiotherapy series.

To the best of our knowledge, no similar studies of intraarterial methotrexate monotherapy for oral VC have been reported. This treatment seems to be highly effective with the simultaneous advantage of organ-sparing. It is an alternative option for patients with inoperable tumors or patients who have refused surgery, as well as for patients who are not candidates for major surgery or in whom surgery would cause an important functional and/or cosmetic impairment.

Intraarterial methotrexate infusion has an acceptable toxicity profile. The common toxicities of diarrhea and hand/foot syndrome did not occur with this infusion regimen. Most reported adverse effects were of local mucocutaneous lesions (stomatitis and skin rash), and gastrointestinal symptoms were less common than with systemic 5-fluorouracil (5-FU)/leukovorin. Intraarterial infusion therapy has theoretical advantages over intravenous systemic chemotherapy because of the higher concentrations of drug delivered to the tumor with minimal systemic toxicity. These characteristics of intraarterial chemotherapy demonstrate that greater and persistent exposure of the tumor to the drug might provide better local control with reduced systemic toxicity. Moreover, it has been shown that intraarterial chemotherapy via continuous infusion has the advantages of delivering a persistent and high concentration of anticancer drug to the tumor region, inducing a rapid shrinkage of the tumor and achieving local palliation within a relatively short time. Continuous intraarterial chemotherapy protocol has the potential to be an important treatment strategy for patients with an oral VC.

REFERENCES


