Capecitabine Induces Rapid, Sustained Response in Two Patients with Extensive Oral Verrucous Carcinoma

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Abstract

Purpose: Oral verrucous carcinoma (VC) has been traditionally treated with surgery or radiation with frequent recurrences and significant morbidity. We describe rapid and dramatic response to oral capecitabine in two patients with advanced refractory VC.

Experimental Design: VC is a rare tumor of the oral cavity. It does not metastasize but over time causes morbidity and mortality through local invasion. Radiation and surgery have been the main treatment modalities but are plagued by mutilating effects, recurrences, and possibly malignant degeneration in some cases. To date, no effective chemotherapy regimens have been described in the international literature. The clinical records of two elderly females with extensive oral VC are described. Both patients were prescribed one cycle of capecitabine, 1000 mg bid for 14 days. Response was documented by photography in one patient. Immunohistochemical evaluation of three 5-fluorouracil metabolizing enzymes on pretreatment biopsies from both patients was also performed. A review of the literature with emphasis on treatment of oral VC is presented in view of our findings.

Results: Examination of the oral cavity before treatment revealed extensive involvement with an evenly spreading, exophytic, warty, whitish lesion in both patients. Microscopic examination of H&E-stained slides from biopsies of these lesions confirmed the clinical suspicion of VC. Both patients underwent treatment with oral capecitabine for one cycle (2 weeks on/1 week off) at a reduced dose of 1000 mg, p.o., bid. Both had a dramatic response with near complete resolution of their lesions within 3 weeks of initiating therapy. A durable partial response was documented at 1 year in the first patient and 6 months in the second. Immunohistochemical evaluation of pretreatment biopsies from both patients revealed a high level of expression of thymidine phosphorylase, a key enzyme in the metabolism of capecitabine.

Conclusions: Oral VC is a rare entity with a progressive course over years and limited options in terms of treatment. Preliminary observations in two elderly patients demonstrate that capecitabine, an oral fluoropyrimidine, is well tolerated and may induce rapid, clinically significant response. Although not curative, it may provide a cost-effective alternative for elderly patients with a significant improvement in their quality of life.

Introduction

Verrucous carcinomata are rare tumors of the oral cavity, representing anywhere from 1 to 10% of all oral squamous malignancies (1–5). Although oral presentations are most common, VC1 may also be present in the larynx or elsewhere in the aerodigestive tract (6). Similar lesions may be present elsewhere in the body as well. The most common sites of involvement in the mouth are the buccal mucosa and gingiva, the alveolar ridge, the palate, and the tongue. Compared with conventional squamous cell tumors of the head and neck, they tend to present at an advanced age, with a higher proportion of female patients. Although these tumors are classified as carcinomata, they are extremely well-differentiated rare variants of squamous carcinoma with little or no metastatic potential. However, they cause significant morbidity because of their local invasiveness and their pattern of stubborn recurrence with the currently acceptable modalities of radiation and surgery (7, 8).

We present two cases of VC of the oral cavity in elderly females that have responded dramatically to Capecitabine (Xeloda), an oral fluoropyrimidine that has been shown to be very effective against advanced colorectal cancer (9). These rapid responses occurred with a reduced dose during the first cycle of administration in both cases. To date, there has been no systematic published evaluation of the use or efficacy of chemotherapy in VC with published retrospective series rarely mentioning this treatment modality. An exception to that is a Japanese study that mentions an elaborate chemoradiation scheme with combination chemotherapy that includes i.v. drugs (10). We also discuss all relevant literature.

Case 1. A 71-year-old Argentinean female presented to her doctor with a 1 × 1-cm erythematous plaque in the palate in June 1988. Posterior to that lesion, a 0.5-cm whitish raised circumscribed papule was also discovered that was subsequently biopsied and called squamous/keratinized papilloma. Up to that point, she had an unremarkable medical history except for an

1 The abbreviations used are: VC, verrucous carcinoma; DPD, dihydro- pyrimidine dehydrogenase; TP, thymidine phosphorylase; TS, thymi- dine synthetase; SCC, squamous cell carcinoma; 5-FU, 5-fluorouracil.
appendectomy and a prolapsed uterus repair. She had never been a smoker or drinker, and her family history was significant for gastric cancer in her brother. Within months, new exophytic lesions appeared and were similar to the original papule under both gross and microscopic examination. Three separate excisions were performed, but a recurrence was noted in the first half of 1990. Histological examination again revealed papillomatosis. In September 1990, she underwent electrocoagulation and then received IFN A, vitamin A, and vitamin C. Soon afterward in 1991, a recurrence in the left buccal mucosa was again treated with electrocoagulation. An excisional biopsy in 1992 demonstrated the same histology. The lesions continued to spread in the mouth gradually.

In January 1993, the patient was evaluated in the United States, and a biopsy was taken and read as hyperkeratosis. She returned to Argentina where in April 1993, a surgical excision was performed followed by repair of the oral deficit with a skin graft from the leg. The histology of the excised lesion was again read as papillomatosis. The patient was then treated with electrocoagulations, vitamins, and IFN A intermittently with temporary remissions.

In April 1996, chemotherapy was started with single agent methotrexate given 50 mg i.v. and 0.05 mg intravenously every 20 days for a period of 12 months. An excellent response was noted with almost total disappearance of all lesions. A residual lesion together with the entire palate mucosa was excised, and again a skin graft was placed to close the gap in July 1997. Despite this treatment in March 1998, a recurrence was noted and its biopsy was shown to be consistent with dysplasia. Soon afterward, a large verrucous lesion was excised and read as VC. The patient received i.v. methotrexate at a dose of 75 mg intermittently until July 2000, with little response. The lesions continued to spread throughout the oral cavity. In August 2000, a thrombocytopenia detected on routine blood analysis prompted an extensive work-up, which led to the diagnosis of cirrhosis. Despite this treatment in March 1998, a recurrence was noted and its biopsy was shown to be consistent with dysplasia. Soon afterward, a large verrucous lesion was excised and read as VC. The patient received i.v. methotrexate at a dose of 75 mg intermittently until July 2000, with little response. The lesions continued to spread throughout the oral cavity. In August 2000, a thrombocytopenia detected on routine blood analysis prompted an extensive work-up, which led to the diagnosis of hepatitis C. Liver biopsy in September 2000 revealed hepatic cirrhosis.

The patient presented to our institution in January 2001. At that time, examination revealed extensive involvement of the oral cavity with ~50% of the mucosa replaced by tumor, primarily involving buccal mucosa, palate, and floor of mouth. The patient complained of significant pain and was confined to a liquid diet. Review of her previous biopsy specimens confirmed the diagnosis of VC.

Case 2. The second patient is a 75-year-old Caucasian female with multiple medical problems who presented with similar complaints especially on the right side of her oral cavity. The patient was diagnosed with an in situ carcinoma of unspecified histology in the left lateral mandibular ridge (third molar) in 1999 for which she underwent a wide excision. Afterward, she had what was felt to be recurrent leukoplaikia on the right mandible and soft palate which necessitated four additional laser-assisted excisions. The lesions continued to recur and get worse with time. She, too, however, had an unremarkable medical history. She had never been a smoker or drinker, and her family history was noncontributory. She presented to our institution in January 2002. Evaluation by an otolaryngologist revealed extensive tumor involving the floor of mouth, lateral tongue, buccal mucosa, and palate. A biopsy was performed that was consistent with VC. Her head and neck surgeon felt that, although resection with reconstruction in stages was technically feasible, it would be associated with marked morbidity and referred the patient to the medical oncology service for a consultation.

These two patients represent the only cases of VC treated at our center since 1998.

Patients and Methods

These patients were seen at the Lombardi Cancer Center, Georgetown University. A complete history was obtained, and a physical was performed on the initial visit. Photographs of the oral lesions were taken during the initial visit for the second patient. Chemotherapy consent was obtained from both patients and routine chemistries were drawn. We reviewed all biopsy specimens with our staff pathologists and confirmed the diagnosis of oral VC. Capecitabine was prescribed at 1000 mg/day for 2 weeks. The patients were instructed not to take the capecitabine during the first week. They were seen at the end of the first week. Again a brief history was taken with special emphasis on side effects of capecitabine. A focused physical followed, and photographs of the oral cavity were taken and compared with the pretreatment photographs. No pretreatment photographs were available for the first patient.

Immunohistochemistry was performed in the laboratory of Dr. Robert B. Diasio at the University of Alabama at Birmingham. Five-μm paraffin sections were cut and stained immunohistochemically to evaluate DPD, TP, and TS with commercially available antibodies from Roche Diagnostics (Indianapolis, IN). Staining reagents were obtained from Dako, Inc. (Glostrup, Denmark). Antigen retrieval and immunohistochemical staining were performed according to protocols recommended by the manufacturer. The biopsy from the first patient was from a previous procedure in Argentina which was obtained previously. The biopsy from the second patient was obtained a few weeks before initiation of treatment at Georgetown University Hospital.

Results

The first patient presented to us in January 2001 for treatment options. We reviewed her slides from Argentina and confirmed the diagnosis of VC. Her main complaint was burning on swallowing and mouth sores. Her physical exam was remarkable in her oral cavity for a whitish, exophytic, fungating, and irregular mucosal lesion extending from the left side of the tongue to the anterior portion of the hard palate and into the internal surface of the upper lip. The lesion covered >50% of her oral mucosa. There was no cervical or supraclavicular or infraclavicular lymphadenopathy. The patient was given capecitabine at a dose of 1000 mg bid for 14 days. This dose was selected because of her history of hepatitis C and cirrhosis. She developed grade III mucositis from day 10 to day 20 of treatment but denied other symptoms, including diarrhea or hand/foot syndrome. After resolution of her mucositis, >90% of her disease had resolved with several small (<1 cm) patches of disease remaining on the buccal mucosa. Her pain had resolved, and she was able to eat more solid foods. More than 90% of the previously involved buccal mucosa remained disease free on visual inspection 6 months later.
The patient subsequently returned to Argentina and did well with much improved symptoms for 18 months after her initial therapy. She then developed gradually worsening dysphagia and returned for to our clinic for an evaluation. Work-up at that time revealed that an extensive tumor recurrence involving the floor of the mouth, tonsil pillar, and lateral pharyngeal wall. Two 2-cm left level II cervical lymph nodes were also observed. Because the clinical appearance at that time was more consistent with invasive squamous carcinoma, repeat biopsies were performed. A biopsy of the floor of the mouth was characteristic of her previous verrucous cancer, whereas deeper biopsies of the pharyngeal wall mass revealed verrucous cancer with areas of invasive squamous carcinoma. She is currently undergoing combined chemotherapy and radiation.

The second patient presented with a complaint of burning on swallowing and mouth sores. Her physical exam was remarkable in her oral cavity for a whitish, exophytic, fungating, and irregular mucosal lesion extending from the right side of the tongue and adjacent buccal mucosa and floor of mouth into the soft and hard palate crossing the midline (Fig. 1). There was no cervical or supraclavicular or infraclavicular lymphadenopathy. This patient too was given capecitabine at a dose of 1000 mg bid for 14 days starting on February 14, 2002. She also had a rapid and complete response after the first cycle of administration as evidenced on March 6, 2002 (Fig. 1). Unlike the first patient, she did not complain of significant mucositis but stated that the verrucous lesions began to slough off the basal mucosa at approximately day 7 of treatment. Her pain was significantly improved after her treatment but did not entirely resolve. Although >90% of the previously involved buccal mucosa re-
mained disease free on visual inspection, evidence of early recurrence was obvious at the floor of the mouth 1 month later.

Immunohistochemical evaluation of pretreatment biopsies of both patients (Fig. 2) revealed low staining of DPD (Fig. 2, left panels) as compared with high staining for TP (Fig. 2, middle panels) in both patients. DPD staining was low to moderate throughout both the basal and squamous cell layers and mostly cytoplasmic. More specifically, in both patients the basal and squamous cell layers showed intense cytoplasmic staining for TP. In addition, both patients had high nuclear TP staining in the squamous cell layer but not in the basal cell layer. There was a similar pattern for TS staining in the first patient’s biopsy (Fig. 2, right panels), whereas the second patient’s biopsy showed a weaker intensity and a reduction in nuclear expression.

Discussion

Verrucous hyperplasia (11) is a verrucous lesion that invariably leads to VC, which represents a distinct extremely well-differentiated and slow-growing variant of SCC. It is most common in the oral cavity and presents in patients who are older and more likely to be female than those with routine head and neck SCC. The first case report was published in 1941 by Friedell and Rosenthal (12) who described it as papillary verrucoid carcinoma. In 1949, Ackerman (13) reported a series of 31 similar oral cases and coined the term VC with characteristic clinical and histological findings. This type of SCC is fairly rare compared with the conventional form and, although it does not metastasize, is very difficult to eradicate because of its stubborn tendency to recur locally. The major treatment modalities have been surgery and radiation but their effectiveness has been a matter of debate over the years (14).

The pathogenesis of VC is poorly understood, and its origin, classification, and response to treatment are controversial. It is a distinct neoplastic entity of squamous origin that occurs in the oral cavity (14), larynx (15), penis (15), cervix (15), perianal area (15), esophagus (16), nose (17), and more rarely in any epithelium of squamous morphology (18). Larynx (35.2%) and oral cavity (55.9%) are the most common sites for head and neck cases (6). It has been associated with smoking but not drinking. Tobacco chewing has been implicated in verrucous lesions. About 30% of patients in Ackerman’s original report were tobacco chewers (13). Verrucous hyperplasia and verrucous leukoplakia have been shown to be likely precursor lesions (11). Controversy surrounds the etiologic role of human papilloma virus. DNA of noncarcinogenic strains 6 and 11 was frequently detected in archival tissue biopsies of cases of oral VC (19) both by PCR and in situ hybridization.

Tumors originally thought to be VC with features of SCC are a source of potential confusion. Recent reports classify these mixed cases separately as low-grade papillary SCC rather than VC (20). The formal definition (13) refers to a warty and densely keratinized surface. The lesion is contained within a sharply circumscribed deep margin. Close inspection reveals bulbous well-oriented rete ridges with well-keratinized squamous epithelium with no anaplasia. One of the most distinguishing features is a pushing rather than infiltrating type of advancing margin. There is associated inflammation in the adjacent stroma.

VCs neither fulfill the classical histological and cytological criteria of malignancy nor possess the capability to metastasize. The diagnosis is largely a clinical one and is most effectively achieved by persistent communication between the pathologist.
and the surgeon but usually only after multiple biopsies have been taken. Adjacent cervical lymph nodes are often enlarged, but this is generally secondary to inflammatory changes and not tumor spread (1, 2, 15). Ackerman pointed out that the lymphadenopathy was attributable to poor oral hygiene and coexistent infections (13). Imaging and cytopathological techniques can easily distinguish between these possibilities.

Surgery has been thought to be by far the preferred modality of treatment especially for smaller lesions, which are easy to localize (2, 3, 15). Excision aims at eradication and preservation of function. Radiation has reemerged recently as an acceptable alternative to surgery, especially for lesions that are more extensive (21). VC was initially thought to be somewhat radioresistant in the mouth or the larynx (22, 23). Local recurrence rate was reported as high as 57% in early studies. In addition, early studies suggested that radiation-induced dedifferentiation into anaplastic cancer in irradiated lesions. This transformation seems to occur in >10% of VC cases (24). In a series (2) of 104 patients treated from 1946 to 1980 with a minimum follow-up of 2 years, 20% of cases had SCC within VC lesions. A high incidence of multiple primaries with a higher tendency for local recurrence was noted. Surgery was considered as the primary treatment modality with 82% control after primary lesion excision and 94% after surgical salvage of recurrence. Radiation was deemed less effective but an acceptable alternative. A retrospective analysis of 2350 cases of VC of the head and neck between 1985 and 1996 (6) found an overall 5-year survival rate of 77.9%. For localized disease, survival after surgery was 88.9%, compared with 57.6% after irradiation, a modality generally applied to more advanced lesions.

We have found limited literature information on chemotherapy schemata applicable to this rare malignancy. A Japanese study reports a case of VC of the tongue that was treated with a concurrent chemoradiation regimen before surgery (10). A triple drug combination was used, including tegafur/uracil, an oral fluorinated pyrimidine. No evidence of tumor cells was found in the surgical specimen. No clinical evidence of recurrence was noted ~2 years after excision. Tegafur/uracil has been extensively studied in head and neck cancer (25). Its dose-limiting toxicities have been reported as diarrhea and stomatitis. It was shown to produce a partial response rate of 19% when used alone in a Phase II study involving 43 patients with previously treated head and neck cancer (26). In combination with cisplatin, it has comparable response rates to infusional 5-FU in combination with cisplatin as demonstrated in a small randomized trial involving 67 patients in the neoadjuvant setting (27). Other oral fluoropyrimidines such as capecitabine have not been adequately evaluated in head and neck cancer. Although response to capecitabine may be superior to infusional 5-FU in some malignancies, there are no data that allow such a comparison in head and neck cancer. As far as VC is concerned, most authors have more or less stated that VC is unlikely to benefit from chemotherapy because of the well-differentiated appearance and slow growing nature of the tumor.

Capecitabine is the first oral fluoropyrimidine with substantial activity in metastatic breast cancer (28) and colorectal cancer (29). The compound is inactive in its native form and is activated through a series of metabolic steps (30). It is absorbed through the gastrointestinal tract, undergoes the first metabolic conversion in the liver, and reaches both healthy and malignant cells through circulating blood. However, it is the last two metabolic steps, which occur primarily within cancer cells, which allow for selective activation and cytotoxicity. More specifically, capecitabine is converted to 5-FU via a three-step enzymatic process (31). It is absorbed intact in the gastrointestinal mucosa. It is converted to 5-deoxyxofluorocytidine through the action of carboxylesterase in the liver. Then, intratumoral cytidine deaminase and TP are required for activation. It is exactly this requirement for TP that is thought to contribute to its increased efficacy and reduced toxicity as compared with 5-FU because many types of cancer cells are believed to have higher levels of TP than normal tissues. Indeed, whereas 5-FU response has been associated with low levels of its metabolic enzymes, TP, TS, and DPD (32), response to capecitabine has been associated with a high TP:DPD ratio (33).

The immunohistochemical profile obtained in these patients agrees with the above observations and supports our hypothesis that VC selectively activates capecitabine and makes this new p.o. bioavailable drug a suitable option in the treatment of VC. Obviously a larger series of patients with oral VC is needed to assess the response rate of this cancer to capecitabine as well as duration of response, dosage, and number of cycles to achieve complete remission. In addition, an immunohistochemical evaluation similar to ours may establish predictive markers to help clinicians if this drug is suitable for a specific patient.

Capecitabine has an acceptable toxicity profile. Diarrhea and hand/foot syndrome are the dose-limiting toxicities (9). Most reported adverse effects are of gastrointestinal nature (diarrhea, stomatitis, and nausea) and are less common than with bolus 5-FU/leukovorin. The same conclusion applies to myelosuppression. Because capecitabine has such an acceptable toxicity profile, convenient dosing, and excellent activity in other major cancers, we hypothesized that contrary to conventional thinking it may show activity in VC. We used capecitabine at a reduced dose for a single cycle and obtained a rapid and dramatic response in two elderly patients with extensive oral VC. This response was associated with excellent palliation of symptoms with low morbidity. The role of capecitabine in the initial management of VC is not clear but given the morbidity and lack of long-term efficacy of existing therapies, this highly active drug may be an acceptable alternative to those treatments in selected patients.

References
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