CASE REPORT

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Abstract: Background. Adenoid cystic carcinoma (ACC) is a malignant neoplasia of the salivary glands that is treated primarily by surgery. Local control and survival are usually compromised despite surgery. Expression of KIT tyrosine kinase is involved in the pathogenesis of ACC. Imatinib mesylate is a potent inhibitor of KIT tyrosine kinase, so we explored the possibility that ACC could be a potential target for this drug.

Methods. We report two cases of unresectable ACC treated with imatinib mesylate in the context of recurrent disease (case 1) and locally advanced tumor at its initial presentation (case 2).

Results. Both patients responded well to treatment with imatinib mesylate. Significant regression of recurrent disease (case 1) resulted in a successful salvage surgical resection; the locally advanced tumor (case 2) had an excellent response to treatment, but, unfortunately, the patient refused salvage resection.

Conclusion. This is the first time ACC is reported to respond to imatinib mesylate. Studies in which more patients are enrolled in controlled clinical trials are needed to confirm this observation.

Keywords: adenoid cystic carcinoma; imatinib mesylate

Adenoid cystic carcinoma (ACC) is a malignant neoplasia of the salivary glands. It is characterized by a long disease-free interval after curative resection, only to recur regionally with persistent, relentless growth and a high rate of eventual metastasis. ACC may be located in major salivary glands, but it is more frequently located in minor ones. It has an exceptional ability to invade nerve tissue, and, specifically, it involves the nerve sheaths, with a typical pattern of skip metastasis, covering a wide locoregional area of the nerves peripheral to the primary tumor. With this natural history, even after adjuvant radiotherapy, local control and survival are usually compromised.

ACC is classically considered unresponsive to cancer chemotherapy, maybe because of its slow growth rate. When feasible, surgery followed by radiation therapy is the only curative treatment option. There is no effective therapy for advanced, recurrent, or metastatic disease.

Expression of KIT, a transmembrane receptor tyrosine kinase, has been reported to be present...
in ACC. This receptor, the product of the proto-oncogene c-kit, is detected by immunohistochemical staining for CD117. It has also been established that c-kit protein overexpression is involved in the pathogenesis of ACC, but no gene mutation has been clearly identified as the mechanism of c-kit activation in this neoplasm.1–3

Imatinib mesylate (Glivec, Novartis, Novartis Oncology, Basel, Switzerland) is a potent small molecule inhibitor of the platelet-derived growth factor receptor, ABL and KIT tyrosine kinases. Imatinib mesylate inhibits proliferation, causes apoptosis in KIT-expressing cells, or both. Because ACC’s pathogenesis is related to activation of a receptor targeted by imatinib (KIT), we thought ACC could respond to treatment with this drug.

**CASE REPORT**

**Case 1.** In April 2002, a patient sought salvage surgery for a locally recurrent ACC, which had been removed for cure 8 years previously. The index tumor had originated from the left submaxillary gland and had been treated by a submaxillary gland dissection, followed by a standard left radical neck dissection. Postoperatively, he received external beam radiation therapy to a total dose of 50 Gy.

The patient had noticed severe mandibular trismus and a slowly growing mass over the mandibular area for the previous 3 months. An incisional biopsy showed recurrent salivary gland ACC. Immunohistochemistry stains were reported positive for CD 117. His recurrent disease was considered inoperable, and the patient was started on conventional chemotherapy with cisplatinum and 5-fluorouracil, with no response at all after two cycles. He was then considered for palliative use of imatinib mesylate. A minimal response was observed initially after 2 weeks on 400 mg a day. The dose was therefore increased to 600 mg a day, and an objective partial response, with disappearance of the trismus, was achieved, which proved to be enough so that the patient was submitted for salvage surgical resection. He underwent a left composite resection of the mandible, in continuity with left total parotidectomy with sacrifice of the facial nerve, and resection of the retromolar structures, because the tumor had infiltrated the pterygoid muscle mechanism. The tumor was removed completely, and the pathology report revealed clear, although very close, surgical margins. Viable ACC cells were still present in the specimen.

The patient underwent reconstructive surgery with a local musculocutaneous flap. He thereafter underwent re-irradiation of the area to the base of the skull, so as to cover a wide skip metastatic regional basin. As of today, more than 20 months later, his physical examination and his follow-up image studies are normal without evidence of disease.

**Case 2.** In September 2002, a 56-year-old man with a 3-month history of foreign body sensation in his throat, dysphagia, odynophagia, and blood streaks in his saliva was seen in consultation. On physical examination, a large friable mass in the base of the tongue extending posteriorly with local infiltration of parapharyngeal structures was seen. CT revealed a mass measuring $13 \times 5.3$ cm infiltrating the left tonsillar pillar, base of the tongue, the supraglottic larynx (epiglottis and vallecula), and invading the hypopharynx. Enlarged lymph nodes were also noted in the left side of the neck.

A biopsy of the mass revealed ACC, with a membranous pattern in tumoral cells. Staining for CD 117 was reported positive. With this locally advanced stage IVA disease, the patient’s disease was considered inoperable.

On November 2002, the patient began treatment with imatinib mesylate at 600 mg a day with palliative intent. Three weeks later, an important clinical improvement was noted, with resolution of his dysphagia and bleeding. A clinically objective partial response of 80% was estimated
on restaging with endoscopy and CT. No evidence of mass lesion in the hypopharynx, epiglottis, or valleculae was present. A recent endoscopy revealed the tumor was now confined to the base of the tongue, measuring $3 \times 3$ cm with no direct invasion to the previously involved structures.

The patient was advised to undergo salvage radical surgical resection, but he refused. We, therefore, have continued his palliative imatinib mesylate treatment. At 15 months, the same partial response persists, with stable clinical symptoms and imaging findings (Figure 1).

**DISCUSSION**

Our patients’ results indicate that inhibition of KIT tyrosine kinase by imatinib mesylate could be an effective therapeutic alternative for these tumors and represents the translation into clinical practice of a molecular biology concept.

It is known that cancer targets that will respond to KIT inhibition are those whose proliferation and/or survival are partially or completely dependent on KIT activation. It is not clear whether this activation needs to be the result of mutations of c-kit, or just the stimulation of the receptor by its ligand. No mutations have been identified as responsible for KIT activation in ACC, but it is possible to stop duplication, or even induce remission of tumor growth, as demonstrated in our two patients, with a KIT tyrosine kinase inhibitor. This observation confirms the important role of KIT tyrosine kinase activity in the pathogenesis of ACC, no matter which mechanism of activation is involved.

Disease in our patients was considered initially inoperable, one case in the common setting of recurrent ACC and the other involving initial presentation with locally advanced disease. No proven, effective treatment options were available for either case.

In the first case, imatinib mesylate achieved a significant reduction of tumor burden, making it amenable to surgical resection, the only actually effective curative treatment for this disease. The initial dose level used did not translate into a proper clinical response, so we decided to escalate it to a higher level, as recommended for other responsive neoplasms, namely, chronic myelogenous leukemia and gastrointestinal stromal tumor. Our second patient was initiated at this higher dose level. A dramatic reduction in tumor size was achieved and sustained with imatinib mesylate. The fact that this second patient was treatment-naive, with no compromise of his vascular supply secondary to surgery and/or radiation therapy, may account for a more significant response. This may be an important factor determining the quality of response, because it has been suggested by others that earlier treatment of tumors with molecular targeted therapies usually translates into better overall responses. The drug was well tolerated in both cases.

To our knowledge, this is the first time ACC has been reported to respond clinically to imatinib mesylate, and our results suggest that exploration of this venue of treatment for patients with this dismal prognosis is warranted. Larger series would be necessary in properly conducted, prospective, controlled clinical trials to confirm our findings. There is an ongoing phase II trial on the use of imatinib mesylate in advanced ACC, and we await its results in the near future.

On the basis of our observations, we propose a phase II trial in patients with unresectable ACC that uses imatinib mesylate in a neoadjuvant setting.

**REFERENCES**