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CASE REPORT

Disease stabilization of progressive olfactory neuroblastoma (esthesioneuroblastoma) under treatment with sunitinib mesylate

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Abstract Olfactory neuroblastoma (esthesioneuroblastoma) is a rare neoplasm of the olfactory epithelium in the upper nasal cavity. Here, we report the case of a 69-year-old man who presented with massive progression of a metastatic esthesioneuroblastoma after endonasal resection, functional neck dissection, and radiotherapy of local and distant tumor relapses. After exhaustion of all conventional therapeutic options, we initiated treatment with the oral multityrosinekinase inhibitor sunitinib mesylate. Using this drug, significant improvement of clinical symptoms, disease stabilization, and recovery from Karnofsky index of 40% to 70% could be achieved in the absence of significant adverse drug effects. The patient died 15 months after initiation of sunitinib therapy due to complications of a traumatic femoral neck fracture without evidence of tumor progression. Immunohistochemical analysis of tumor tissue specimens obtained at initial surgery revealed ample expression of platelet-derived growth factor receptor (PDGFR)-b on stromal and endothelial cells. Sunitinib should be considered for palliative therapy of advanced esthesioneuroblastoma.

Keywords Olfactory neuroblastoma · Esthesioneuroblastoma · Sunitinib · Palliative

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Introduction

Olfactory neuroblastoma (esthesioneuroblastoma) is an uncommon neoplasm of the olfactory epithelium in the upper nasal cavity. The clinical course of esthesioneuroblastoma is highly variable. Some patients experience an aggressive disease course with early metastatic spread and die a few months after diagnosis. Other patients survive many years after diagnosis of esthesioneuroblastoma. A meta-analysis reported 5-year overall and disease-free survival rates of 45% and 41%, respectively [1]. Due to the rarity of the disease there is a lack of prospective randomized studies to guide therapy of esthesioneuroblastoma based on a high level of evidence [1]. Maximum surgical resection and postoperative radiotherapy are commonly considered part of the standard therapy. The role of systemic antineoplastic therapy for esthesioneuroblastoma is unclear. In a small retrospective patient series, Porter et al. [2] described that adjuvant therapy with cisplatin and etoposide for patients with Kadish stage C esthesioneuroblastoma may be of benefit following complete resection. In recurrent esthesioneuroblastoma, some small patient series and case reports have suggested limited efficacy of systemic antineoplastic therapy with cytotoxic agents including cisplatin [3], irinotecan and docetaxel [4], and temozolomide [5]. To our knowledge, there is no documented experience

with biologically targeted agents for the treatment of esthesioneuroblastoma in the literature so far. Here, we report our favorable single-patient experience with sunitinib mesylate in the palliative treatment of recurrent esthesioneuroblastoma. Sunitinib mesylate is an oral multityrosinekinase inhibitor targeting vascular endothelial growth factor receptor (VEGFR)- 1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-a, PDGFR-b, c-kit, fms-like tyrosine kinase receptor (FLT) 3, colony stimulating factor (CSF) 1R, and rearranged during transfection tyrosine kinase receptor (RET) [6]. Sunitinib mesylate has shown favorable antineoplastic activity in renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumor (GIST) and has been approved for these indications by the US Food and Drug Administration (FDA) [7–9]. Sunitinib is generally well tolerated. Serious (grade 3 or 4) adverse events occur in $\leq$10% of patients and include hypertension, fatigue, asthenia, diarrhea, hand–foot syndrome hypothyroidism, cardiac dysfunction and hematological toxicities (leucopenia, anemia, thrombocytopenia).

Case report

Beginning in May 2002, a 64-year old, previously healthy man developed recurring epistaxis. Nasal endoscopy showed polypoid grey and fleshy tumor masses in the right nasal cavity. Cranial magnetic resonance imaging (MRI) revealed tumor tissue formations consuming the entire right ethmoid sinus and the right nasal cavity above the middle nasal concha with inhomogeneous contrast enhancement. Sonography of the neck did not reveal any enlarged lymph nodes. In December 2002 the tumor was subtotally resected via the endonasal route. The histological diagnosis was olfactory neuroblastoma (esthesioneuroblastoma) (Fig. 1). Tumor extent corresponded to Kadish stage B, as tumor tissue was confined to the nasal cavity and paranasal sinuses [10]. No adjuvant therapy was initiated and the patient was followed up by 3-monthly MRI investigations. In March 2004 (22 months after initial diagnosis), local tumor relapse at the right frontobasis with invasion of the right orbita was detected on follow-up MRI. The tumor relapse was treated by local fractionated radiation with single doses of 2 Gy up to a total dose 60 Gy. Radiotherapy was well tolerated apart from periorbital rash and conjunctivitis. The further clinical course was uneventful until September 2005 (40 months after initial diagnosis), when the patient noted swelling of a lymph node on the right side of his neck. Lymph node biopsy revealed tumor cell formations showing similar characteristics to the primary tumor, thus corresponding to metastasis of the esthesioneuroblastoma. The patient underwent radical functional neck dissection. Histopathological examination showed metastatic esthesioneuroblastoma in 5 of 31 removed lymph nodes and also in the right submandibular gland. Postoperatively, three-dimensional (3-D) planned local radiotherapy was performed with total

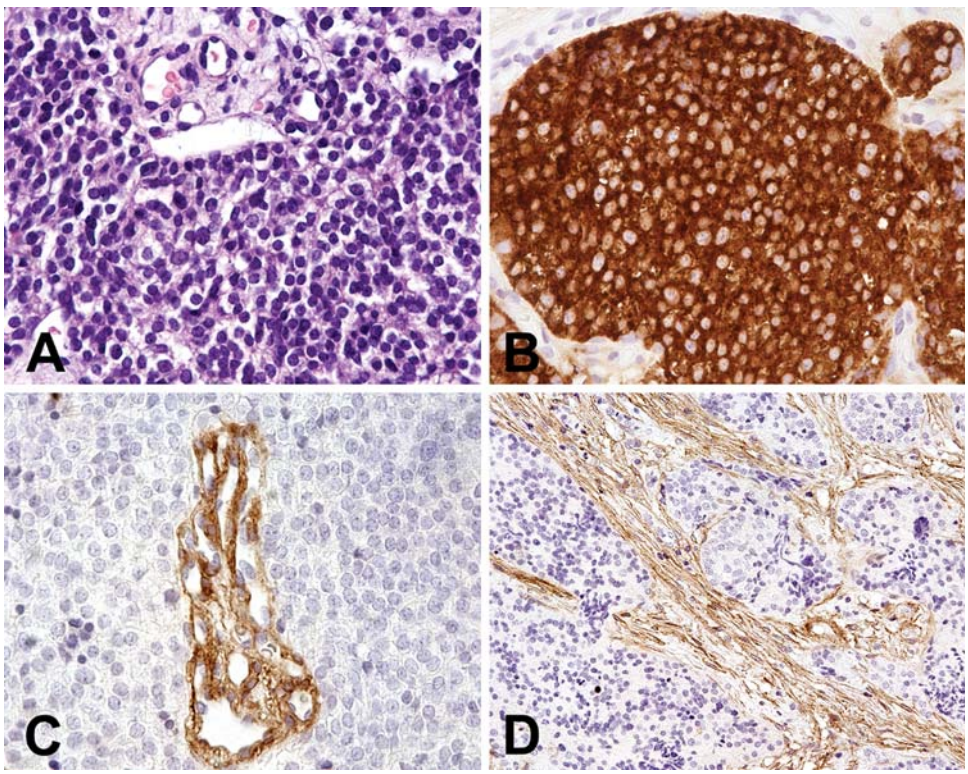

Fig. 1 **a** Histopathology shows a cellular tumor composed of uniform small cells with scant cytoplasm (hematoxylin and eosin, original magnification 400×). **b** Immunohistochemistry shows typical expression of the neuronal marker synaptophysin in tumor cells (antisynaptophysin, original magnification 400×). **c** and **d** Immunohistochemistry shows prominent expression of platelet-derived growth factor receptor beta (PDGFR-b) in endothelial cells (**c** anti-PDGFR-b, original magnification 400×) and stromal septae (**d** anti-PDGFR-b, original magnification 200×)

dose of 60 Gy and single dose of 2 Gy, taking into account the tolerance dose of the spinal cord. Radiation therapy was well tolerated, apart from slight dysphagia, hoarseness, and rash. In October 2005, recurrent epistaxis occured, which was successfully treated by maxillary artery embolization. Periodical follow-up investigations showed stable disease until July 2007 (62 months after initial diagnosis), when the patient developed significant worsening of neurological symptoms including progressive gait disturbance and decline in cognitive function. At this time, he presented to our clinic with Karnofsky index of 40%. MRI showed massive tumor progression with tumor masses consuming the nasal cavity and the ethmoid and maxillary sinuses with infiltration of both orbitae and both frontal lobes with marked peritumoral edema (Fig. 2a, b). The tumor formations showed infiltration of the frontal bone and the subcutis of the forehead. Owing to the poor general medical condition and suboptimal compliance, we decided against cytotoxic chemotherapy. Further radiotherapy could not be performed because a cumulative dose of 60 Gy had already been applied at time of first relapse, because of the tumor size, and because of the vicinity of the tumor to organs at risk (optic chiasm, brain tissue). We initiated oral therapy with sunitinib mesylate. During the first cycle (one cycle = 4 weeks daily sunitinib mesylate and 2 weeks without sunitinib mesylate), the patient received 25 mg sunitinib mesylate per day. This dosage was well tolerated and the patient experienced significant improvement of symptoms. In the second cycle, we prescribed 50 mg sunitinib mesylate. However, as the patient developed grade 3 hypertension, we started oral antihypertensive medication and decreased the sunitinib mesylate dose to a daily dose of 37.5 mg for the third cycle. The hypertension subsided and sunitinib mesylate treatment was continued at a daily dose of 37.5 mg for all consecutive cycles. Further side-effects were mild and included hypothyroidism (maximal thyroid stimulating hormone level 45 mU/ml), grade 2 leukopenia, and grade 1 anaemia. These mild toxicities did not require discontinuation of sunitinib mesylate therapy or reduction of sunitinib mesylate dose. Soon after initiation of sunitinib therapy, there was significant and lasting improvement of clinical symptoms. For 15 months from initiation of sunitinib mesylate treatment, stable disease was documented on 3-monthly MRI investigations. For this entire time period, the patient was clinically stable, mobile, eloquent, and able to live at home and cope with activities of daily living with assistance by his family (Karnofsky performance score 70%). In total, the patient had completed ten cycles of sunitinib mesylate treatment before he was hospitalized due to a traumatic femoral neck fracture in December 2008. The patient received an hemiprothesis of the left hip. Postoperatively, there was progressive worsening of general condition and the patient died 3 days after the operation at an age of 71 years (6.4 years after initial diagnosis).

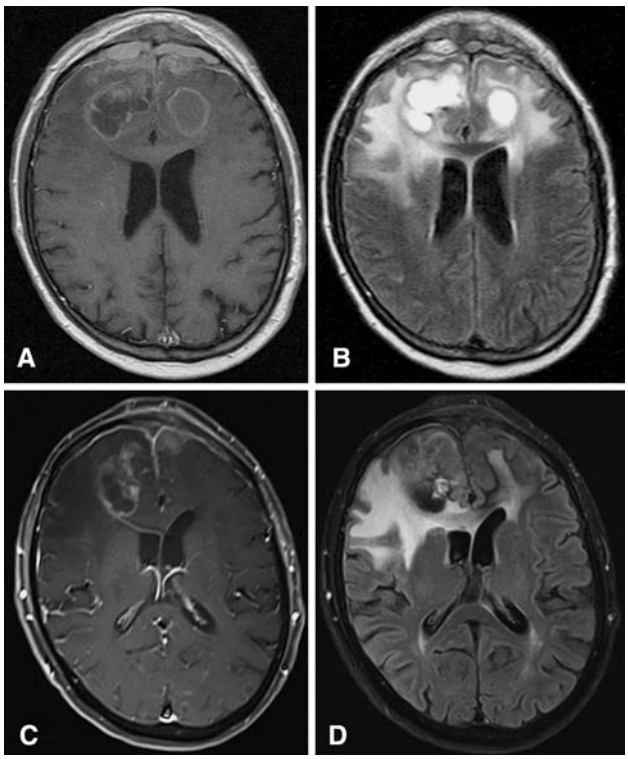

Fig. 2 **a** and **b** Magnetic resonance imaging (MRI) at initiation of sunitinib therapy. **a** Showing ring-shaped lesions in the frontal lone and dural enhancement. **b** Fluid-attenuated imaging recovery (FLAIR) images depicting the extent of perifocal edema. **c** and **d** MRI 15 months after initiation of sunitinib treatment. **c** T1-weighted contrast-enhanced image with regression of enhancing structures. **d** FLAIR images showing reduction of edema

Expression analysis of sunitinib mesylate target molecules in tumor tissue specimens

Methods

We assessed expression of sunitinib mesylate target molecules VEGF-receptor-1, -2, and -3, PDGFR-a, and PDGFR-b in formalin-fixed paraffin-embedded tumor tissue samples obtained at the primary surgery in 2002 using immunohistochemistry. For immunohistochemistry, 3- to 5-μm-thick tissue sections were deparaffinized in xylene (2 × 20 min). Heat-induced epitope retrieval was performed by boiling the slides in citrate buffer (pH 6.0) using a microwave (1 min × 350 W and 5 min × 90 W). Incubation with primary antibodies (VEGFR-1 and -3 and PDGFR-a at 1:200 dilution, VEGFR-2 at 1:100 dilution, and PDGFR-b at 1:50 dilution in 1% normal goat serum/0.3% PBS-Triton X-100) was carried out overnight at 4°C. Antibodies were purchased from the following suppliers: rabbit polyclonal

antibodies FLT-1/VEGFR-1 AB-1 (RB-1527, Labvision, Fremont, CA), FLK-1/KDR/VEGFR-2 Ab-1 (RB-1526, Thermo Scientific, Fremont, CA), FLT-4/VEGFR-3 (C20, sc-321, Santa Cruz Biotechnology, CA) PDGFR-a AB-1 (RB-1691 P1, Thermo Scientific), and rabbit monoclonal antibody PDGFR-b (28E1, 3169, Cell Signaling, Santa Cruz, CA). The bound primary antibody was detected by a biotinylated anti-rabbit (VEGFR-1, -2, -3 and PDGFR-alpha, -beta) secondary antibody (Vector Laboratories, Inc., CA; both made in goat; 60 min). Staining sensitivity was increased using the VECTASTAIN Elite ABC Kit PK-6100 Standard (Vector laboratories, Burlingame, CA) as described in the supplier's manual, and the reaction was visualized through incubation with liquid substrate DAB (3,3′-diaminobenzidine tetrahydrochloride, Sigma, St. Louis, MO) for 1–2 min. Afterwards the slides were counterstained with Mayer's hemalaun (Merck), mounted with Entellan (Merck, Darmstadt, Germany), and cover-slipped. Negative controls were included in each batch, replacing the primary or secondary antibody and staining with an isotype-matched IgG2 monoclonal antibody.

Results

We found ample expression of PDGFR-b in stromal and endothelial cells, but not in tumor cells (Fig. 1 c and d). We did not detect unequivocal expression of VEGFR-1, VEGFR-2, VEGFR-3, or PDGFR-a, in tumor, endothelial or stromal cells.

Discussion

Herein we report the case of a recurrent and heavily pretreated olfactory neuroblastoma (esthesioneuroblastoma). At the time of presentation with massive tumor progression, all radiotherapeutic options had been exhausted. Palliative therapy of esthesioneuroblastoma often includes cytotoxic agents such as cisplatin [3], irinotecan and docetaxel [4] or temozolomide [5]. However, due to poor general medical condition and suboptimal compliance we decided against therapy with cytotoxic chemotherapy in our patient and initiated sunitinib mesylate treatment. Using this drug, we were able to achieve improvement of clinical symptoms in the absence of significant adverse drug effects, which resulted in clear improvement of quality of life. Furthermore, radiological disease stabilization was documented for 15 months before the patient died without evidence of tumor progression. The lack of significant adverse effects and the advantage of an oral drug without the need for frequent follow-up visits to the hospital were valued by the patient and his family. Based on our single-patient experience, we feel that sunitinib should be considered as an alternative for palliative therapy of advanced esthesioneuroblastoma. However, it must be kept in mind that our experience could also have been a chance observation.

Immunohistochemical analysis of the tumor specimen obtained at initial tumor resection showed ample expression of PDGFR-b on stromal and endothelial cells. It may be hypothesized that inhibition of stromal and endothelial cell growth or function by PDGFR-b blockage may have contributed to the favorable clinical course under sunitinib observed in our patient.

Further studies are needed to substantiate our favorable experience with sunitinib mesylate treatment of olfactory neuroblastoma and to establish the pathobiological effect of sunitinib on tumor cells and the tumor microenvironment in esthesioneuroblastoma.

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