Unexpectedly durable palliation of metastatic olfactory neuroblastoma using anti-angiogenic therapy with Bevacizumab

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Abstract

Olfactory neuroblastomas (ONBs) are rare malignant tumors that arise from olfactory epithelium and typically present with symptoms attributable to locally invasive disease. Kadish radiographic staging and Hyams' histopathologic grading are prognostic. Overall survival rates, averaging 60-70% at 5 years, remain limited by high rates of delayed locoregional and distant progression. At initial presentation, the available evidence supports the use of multimodality therapy, historically surgery and radiation, to improve disease-free and overall survival. At recurrence/progression, the available evidence supports the use of therapy to improve disease control and symptoms (palliation), but patient heterogeneity dictates individualization of modalities. Although the ideal use of chemotherapy as a modality remains undefined, the available evidence supports it use, historically platinum-based, for palliation. However, recent insights into the molecular-genetic aberrations of ONBs, coupled with the emergence chemotherapeutic agents capable of targeting such aberrations, suggest an expanded role. The authors report a case of a 60 years-old man, heavily pre-treated for metastatic ONB, presenting with profound central-nerve-system and head-and-neck symptoms. He experienced unexpectedly durable palliation with Bevacizumab anti-angiogenic therapy. Additionally, he experienced localized palliation with an Ommaya reservoir. The authors review the literature regarding historical and emerging therapies for ONB to emphasize the needs for individualization and translational-clinical studies.

Introduction

Olfactory neuroblastomas (ONBs), also formerly known as esthesioneuroblastomas, olfactory placode tumor, esthesioneurocytoma, esthesioneuroepithelioma, and esthesioneuroma, originate from olfactory neuroepithelium, represent ~2% of sinonasal tract tumors and have median onset of 53 years.[1,2] Clinical presentation includes symptoms of a sinonasal mass. This may be accompanied by symptoms of invasion to the brain parenchyma and leptomeninges (LMs), or, more rarely, paraneoplastic syndromes. Differential diagnosis includes other sinonasal, skull-based or other small round blue cell tumors, including chordoma, chondrosarcoma, rhabdomyosarcoma, sinonasal undifferentiated carcinoma, squamous cell carcinoma, melanoma, Ewing sarcoma, extranodal NK/T cell or other lymphomas, and neuroendocrine carcinomas.[1,2] Given the non-specific presentation and wide differential diagnosis, late diagnosis is common.

Definitive diagnosis includes radiography, most commonly with computed tomography (CT), detailing bony erosion, invasion and destruction, and magnetic resonance imaging (MRI), detailing tumor extension within adjacent tissue. Definitive diagnosis involves radiographic staging, most commonly with the retrospectively and prospectively validated Kadish staging system. Kadish Stage A tumors are confined to the nasal cavity. Stage B tumors involve one or more paranasal sinuses. Stage C tumors involve beyond the nasal cavity and paranasal sinuses. Stage D tumors involve the lymph nodes or beyond.[3] Stages C and D presentations are common at both diagnosis and progression and, as expected, portend an inferior prognosis. For instance, Dulguerov *et al.*, reported on a meta-analysis of 57 ONB publications between 1990 and 2000 in which the 5 year (yr) survival for patients with metastases the involving cervical lymph nodes (LNs) was 29% *versus* (*vs.*) 64% for those who did not.[4] Other authors report similarly.[5]

Definitive diagnosis also includes histopathology, most commonly with Hematoxylin and Eosin (H&E), immuno-histochemistry, and occasionally, with special stains or electron microscopy. H&E details small, round cells with scant cytoplasm, organized in sheets, nests or lobules, and surrounded by fibrous septa. Nuclei are hyperchromatic, with uniform chromatin, rare mitoses, and unremarkable nucleoli. Homer Wright pseudorosettes, representing tumor cells centered around pink fibrillar material, are common.[6,7] Special stains distinguish ONBs from other tumors, including positively staining for neuron-specific enolase, synaptophysin, and less commonly chromogranin, neurofilament and cytokeratin.[7] Due to the rarity and complexity of ONB histo-pathologic diagnosis, consultation at academic centers is recommended.

Definitive diagnosis also involves histopathologic staging, most commonly with the retrospectively and prospectively validated Hyams' system. Grade I tumors have prominent fibrillary matrix and tumor cells having an absence of nuclear pleomorphism, mitoses, or necrosis. Grade II tumors have some fibrillary matrix and tumor cells having a presence of moderate nuclear polymorphism, some mitoses, but no necrosis. Grade III tumors have negligible fibrillary matrix, the presence of Flexner type rosettes, and tumor cells having prominent mitoses, nuclear polymorphism, and some necrosis. Grade IV tumors have no fibrillary matrix or rosettes and tumor cells having striking nuclear pleomorphism, mitoses and prominent necrosis.[5] Higher Hyams' grade portend an inferior prognosis. For instance, the Dulguerov meta-analysis reported the 5 yr survival for patients with Hyams' I and II was 56% *vs.* 20% for Hyams' III and IV.[4] In another instance, the Kane *et al.* retrospective review reported the respective 5 yr and 10 yr survival for patients with Hyams' III was 47 *vs.* 31% for Hyams' IV, as well as a hazard ratio of death for III and IV grade tumors at 4.83 (P<0.001). Kane, as well as other authors, report high-grade tumors may portend increased response to chemotherapy.[8,9]

Prognostic factors at initial presentation include extension of disease and histo-pathologic grade. However, other possible prognostic and/or predictive factors include age,[1,8,10] and recently identified molecular-genetic aberrations.[1] In a collective review across albeit very heterogeneous ONB studies, prognosis at 5 yrs and 10 yrs are commonly reported as between 45-70% and 35-60%, respectively.[4,5,8] The prognostic influence of surveillance is undefined, and in the absence of consensus guidelines for ONB, much is extrapolated from other head-

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and-neck tumors. Given common reports of recurrence or progression >10 yrs after initial presentation, lifelong surveillance should be considered.[2]

Treatment at initial presentation of ONBs remains highly individualized, secondary to their rarity and heterogeneous presentation, most commonly extrapolated from predominantly single-institution series and always integrating patient and provider preferences. Current practice involves maximal safe resection by otolaryngologists and/or neurosurgeons and/or fractionated radiation therapy (RT) by either intensity modulated radiation therapy with photons or proton beam. To-date, the best reported results involve strategies combining surgery and RT at initial presentation and reserving chemotherapy for recurrence and/or progression (*e.g.* where surgery and/or RT are either undesirable or unachievable). For instance, the Dulguerov meta-analysis reported on a heterogeneous patient population where the 5 yr survival was 48% for surgery alone, 37% for RT alone, 65% for RT and surgery, 51% for RT and chemotherapy, and 47% for all three modalities.[4] Other authors report similarly.[5,11,12] For the initial presentation of Kadish A-C stage, surgery followed by RT is the historically preferred treatment. Most series report this combination results in better prolonged progression-free (PFS) and overall survival (OS) than either surgery or RT alone. Some series suggest that surgery alone may be sufficient for initial presentation, especially in Kadish A and/or with lower Hyams' grades.[8] If surgery is undesirable or unachievable, RT alone is most commonly utilized.[8] For the initial presentation of Kadish A-C stage, symptomatically debulking surgery followed by RT is the historically preferred treatment. More recently, the incorporation of chemotherapy at various times has been investigated.

For the recurrent/progressive presentation of Kadish C, especially with cervical LN or other loco-regional involvement, aggressive local therapy with surgery and/or RT is the historically preferred treatment. Available series report prolonged PFS and improved symptoms in a subset of patients.[4] For the recurrent/progressive presentation of Kadish D, symptom-specific palliation is the historically preferred treatment. Although the available literature is heterogeneous, this is clearly a situation where chemotherapy has been most investigated and holds the most promise. Predominantly generated from retrospective reviews, when recurrence or progression is solely loco-regional, meaningful clinical responses with surgery +/- RT range around 50% *vs.* chemotherapy alone around 30%.[4,13]

This case report will highlight the unexpectedly prolonged palliation of a patient with multiply recurrent/progressive Kadish D disease using an anti-angiogenic agent, Bevacizumab (Avastin), and the localized palliation with an Ommaya resevior.

Case Report

17 years prior to this report, a 42-year-old Hispanic male with refractory epistaxis was diagnosed with Kadish C (involving the ethmoid sinuses and frontal lobe LMs (T4, N0, M0) and Hyams' II (retrospectively estimated). He underwent aggressive resection, followed by external beam RT (5,600 cGy in 42 fractions) to the ethmoid sinuses. Six years later he underwent six cycles of Cisplatin and Etoposide for asymptomatic non-invasive frontal lobe LM progression with a maximal response of partial response (PR). Four years later, he presented with epistaxis, partial seizures and transient aphasia. He underwent a bifrontal craniotomy for debulking for progression involving the forehead skin, bifrontal sinuses, bifrontal LMs, right temporal lobe, internal auditory canal, and cavernous sinus (no cervical or systemic progression). Pathology confirmed ONB but Hyams' grading was not performed. Post-operatively, he underwent 24 cyles of Temozolomide for further asymptomatic LM and right frontal lobe progression with a maximal response of stable disease (SD). Three years later, he presented to one of the authors (EMD) with fatigue and worsening partial seizures. He underwent consultation for palliative chemotherapy for progression involving the LM, right frontal lobe, cavernous sinus (including complete encasement of the vessels and nerves), mid skull bones between the right temporal lobe and the orbit and development of encephaloceles (cystic dilations caused by obstruction of Virchow-Robbins spaces) (Figure 1).

Initial consultation revealed numerous sequela from his disease and treatment, including bilateral cataracts, altered lacrimation, posterior capsular fibrosis, right optic neuropathy without papilledema, abnormal visual field testing, tinnitus, sensorineural hearing loss, partial seizures, abnormal taste, and fatigue. Pertinent co-morbidities included diabetes mellitus II, diabetic retinopathy, hypertension, obesity, hypercholesterolemia, and anxiety.

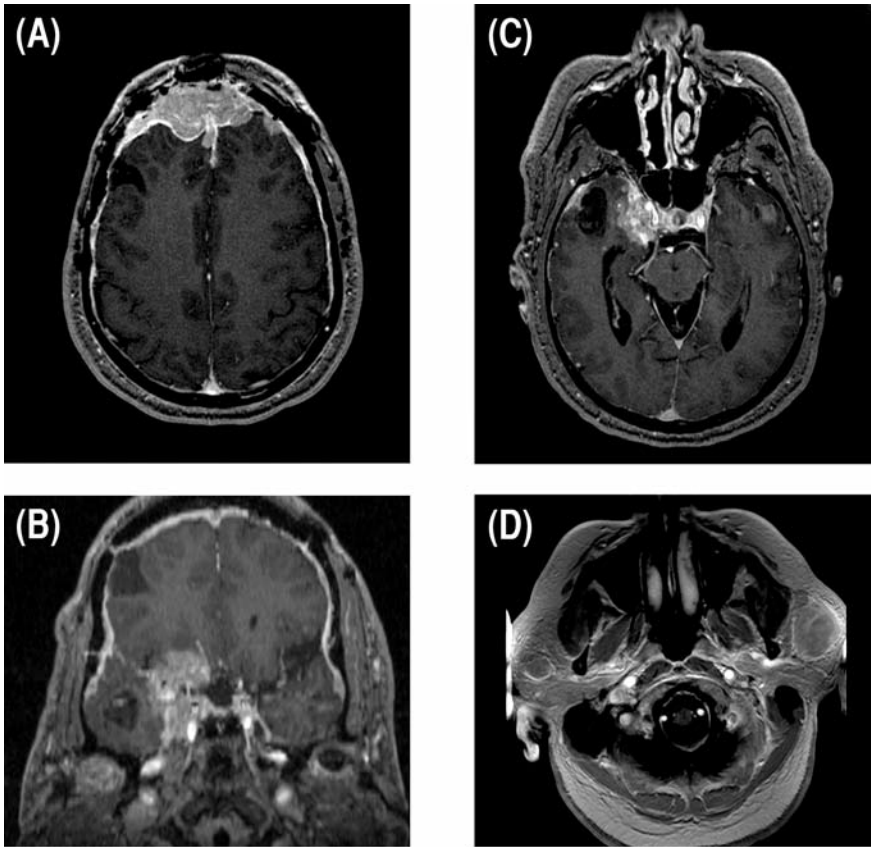

Figure 1. The composite Figure 1 demonstrates the pre-treatment maximal disease at the frontal lobes (A), cavernous sinus (B, C), and parotid lymph node (D), best imaged on T1-w gadolinium magnetic resonance imaging.

Pertinent exam findings included mild prominence of the forehead but no discrete masses, cranial neuropathies of bilateral VIII (sensory) and R VII (motor), but no palpable LNs or HSM. ECOG performance status (PS) was 0 and Karnofsky PS (KPS) was 100. FDG-PET/CT was negative for systemic disease. Multidisciplinary review determined no role for surgery or RT and recommended consideration of palliative chemotherapy. He declined available trials in favor of agents less likely to exacerbate existing sequela and co-morbidities (specifically, non-platinum agents). He initiated five cycles of Docetaxel and Irinotecan,[10] with a maximal response of SD. This was complicated by diarrhea alternating with constipation, dehydration, electrolyte abnormalities, neutropenic fever with bacteremia and upper respiratory infection that required inpatient management on several occasions. One year later, he elected serial surveillance for minimal asymptomatic progression involving the LM and bifrontal lobes. The following year, he presented with dizziness, slurred speech, word-finding abnormalities, worsening fatigue and neck fullness causing obstructive sleep apnea (OSA). He had diffuse progression involving the LM/dura and skull-base, surrounding but not compressing/invading blood vessels, new LNs (cervical, parotid, parapharyngeal and supraclavicular), worsening encephaloceles (especially the L frontal lobe) and new bifrontal vasogenic edema (Figures 1A-D and 2A). KPS was 80. Dexamethasone did not provide meaningful improvement. Following review of the available literature and intra/extramural multidisciplinary recommendations, he underwent anti-angiogenic therapy with Bevacizumab, a monoclonal antibody against the vascular endothelial growth factor (VEGF) receptor at 10 mg/kg q 2 weeks. He underwent ~24 months, the latter half at 15 mg/kg q 3 weeks for convenience. Within the first two months, his KPS improved to 90, he reported palliation of his fatigue, neuro-cognitive deficits, aphasia, and seizures, and he was able to discontinue Dexamethasone. Subsequently, and after a >30-day safety hold of Bevacizumab, he underwent Ommaya reservoir placement to attempt further localized palliation of the dominant L frontal lobe encephalocele. Fluid removal from the Ommaya provided dramatic neuro-cognitive improvement initially, with smaller improvements subsequently. No grade III or higher adverse event (AE) events occurred. The only AE attributable to treatment was grade II fatigue, which slightly improved with q 3 week Bevacizumab. Radiographic response to Bavacizumab included a partial response by month 2, followed by SD for ~22 months, followed by asymptomatic progression of the parotid, cervical, and supraclavicular LNs by month ~24 (Figures 2B and 3A-D). Radiographic response to tapping the Ommaya included a partial response and variable time to re-accumulation (Figure 2B). Ultimately, he presented with symptoms attributable to progressive LNs, including presumed OSA, and underwent palliative RT to involved sites. Following RT, he elected to Hospice. He passed ~2 months later from combined sequela if his disease, treatment, and co-morbidities. This was ~17 yrs from initial presentation and ~28 months after palliation with Bevacizumab and Ommaya reservoir drainage.

Discussion

For all presentations of ONB, the role of chemotherapy is undefined and under active investigation. It is important to note that the available reported use of chemotherapy in ONB is very heterogeneous in the clinical situation at use, the goals of use, the agents used and the design of the study aimed to analyze benefit. Furthermore, many series include ONB amongst other head-and-neck or refractory solid tumor cancers. Thus, comparisons between regimens, let alone between surgery/RT, are impossible. Situations were chemotherapy has the most theoretical benefit in ONB, as in all cancers, includes the neo-adjuvant (before the *definitive* surgery and/or RT) setting, where chemotherapy downsizes the tumor sufficiently to make aggressive resection more achievable, the adjuvant (after the *definitive* surgery and/or RT) setting, where chemotherapy treats residual tumor, and the palliative setting, where chemotherapy ameliorates symptoms. In addition, several series report that higher Hyams' grade predicts higher response to chemotherapy.[8] Historically, cytotoxic (where the predominant mechanism is cell-killing) chemotherapy has been most utilized in ONBs. However, newer *targeted* approaches (usually cytostatic, where the predominant mechanism is cell-modifying) are increasingly being considered options, especially as the knowledge of molecular/genetic aberrations in ONBs advances.

Adjuvant cytotoxic chemotherapy most commonly yields only modest efficacy at moderate toxicity. For instance, in a single institution Mayo Clinic retrospective series, McElroy *et al.*, reported on 10 patients initially treated for Kadish Stage C disease with a cisplatin-containing regimen where the survival of patients with high-grade tumors was 44.5 months *vs.* 26.5 months for low-grade tumors. Median time to progression of salvage chemotherapy was 9.3 months (range 2-13). Although the sample size only supported hypothesis-generation, they reported high-grade tumors more sensitive to platinum-containing regimens.[9] Other authors report similar efficacy and toxicity with platinum-containing regimens in ONB.[14,15] Non-platinum-containing regimens also appear to show modest efficacy and with possibly less toxicity. To-date, they are most used after platinum failure or in the setting of medically-needed alternatives. For instance, McElroy *et al.* also report on 3 patients treated with non-platinum regimens in the second-line setting.[9] Other authors report modest efficacy with different non-platinum combinations, including Irinotecan and Docetaxel or

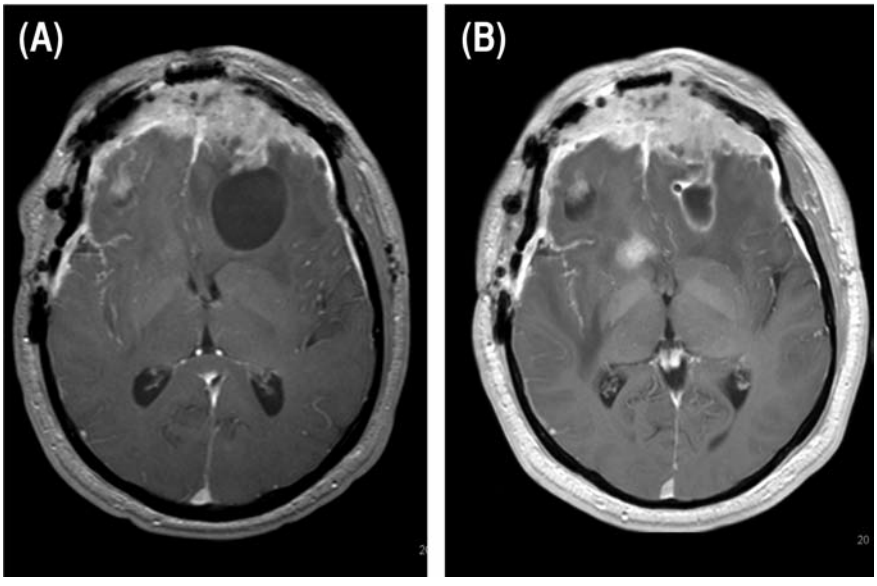

Figure 2. Pre- and post-placement of Ommaya reservoir demonstrating maximal encephalocele size (A) and representative minimization (B) after cerebrospinal fluid draw.

Doxorubicin, Ifosfamide, and Vincristine. For instance, in a 2008 single institution retrospective series, Kiyoto *et al.*, reported on 12 patients with advanced or metastatic disease who received Irinotecan and Docetaxel (and RT if no prior RT), where partial responses was 25% (3), median PFS was 13.6 months and OS was 36.6 months. Response rates were higher in patients <50 years old (y.o.) (3 of 4 patients) *vs.* >50 y.o. (0 of 8 patients) and in patients with only loco-regional disease who also received RT.[10] Neo-adjuvant cytotoxic chemotherapy most commonly yields only modest efficacy at moderate toxicity. For instance, a 2011 case report by Aljumaily *et al.* detailed a patient with intracranial involvement of loco-regional disease who achieved a very good PR with neoadjuvant cisplatin and etoposide, allowing for definitive surgery and RT, and followed by adjuvant chemotherapy. At publication, PFS surpassed 8 months.[16] Palliative cytotoxic chemotherapy most commonly yields only modest and temporary symptom improvement and with the goal of less toxicity.[17,18]

Targeted therapy is under investigation for the theoretical possibilities of providing additional agents, less toxicity, and more efficacy, especially as insights at the molecular-genetic aberrations advance. For instance, a case report by Preusser *et al.*, detailed a patient whose ONB widely disseminated after surgery/RT and expressed platelet-derived growth factor receptor (PDGFR)-b on stromal and endothelial cells. After receiving the multi-tyrosine kinase inhibitor (TKI) sunitinib mesylate, the patient experienced significant improvement of symptoms, including recovery of KPS from 40 to 70, disease stabilization for 15 months, and no significant toxicity.[19] Other authors propose additional targets within the sonic hedgehog and anti-angiogenic pathways, already established in central nervous system, head-and-neck or other advanced refractory tumors, as potential targets in ONB.[20-23]

In our case, Bevacizumab was selected for the possible palliative effects documented in other central nervous system, head-and-neck and advanced refractory tumors, including: i) targeting of the anti-angiogenic pathway, ii) improving the therapeutic to toxicity ratio, and iii) targeting of the vascular permeability resulting in peri-tumoral vasogenic edema (and possibly encephaloceles).[21-27] Unfortunately, attempts to secure tissue to clinically correlate our patient's results with anti-angiogenic and other pathways were unsuccessful. Other chemotherapies documented in the literature to have a possible role in ONB, including Carboplatin, Methotrexate, Taxanes, Gemcitabine, mTor inhibitors, 5-flourouracil, as well as investigational agents, were declined by the patient in an effort to avoid exacerbating pre-existing treatment toxicities. The Ommaya reservoir was selected for its possible localized palliation of the profoundly disrupted cerebrospinal fluid flow at the L frontal lobe by the diffuse LM disease.

Acknowledging the limitations of a case report, the authors make the following observations regarding their criteria for selection of Bevacizumab targeted therapy. Although it is impossible to fully compare our patient against historical cohorts, it is informative that our patient's improvement in KPS, minimal adverse events, as well as protracted time to progression and survival appear to be at least as good as those of other systemic agents the existing literature - especially given the number of previous recurrences and burden of disease. Additionally, it is informative that our patient's ability to durably discontinue Dexamethasone appears to support its ability to modify vascular permeability in ONB. Lastly, although only hypothesis-generating, it is also informative that our patient's improvements appear to also provide rationale for consideration of an Ommaya reservoir when symptomatic encephaloceles exist.

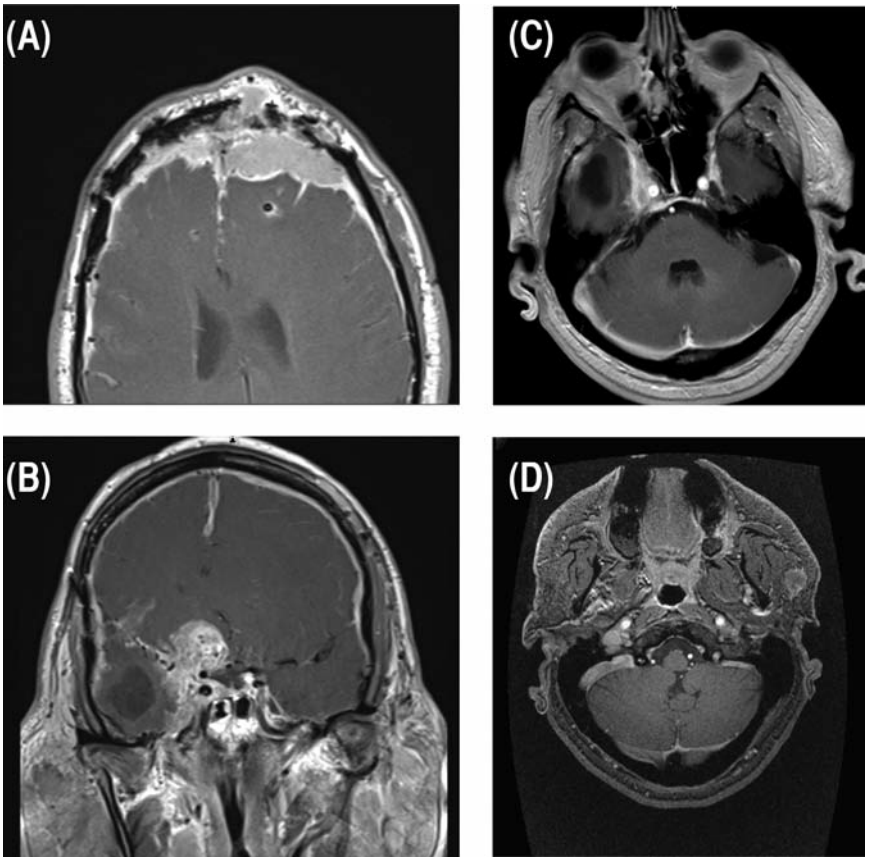

Figure 3. The composite Figure 3 demonstrates the post-treatment maximal response (seen within ~ 2 months) at the frontal lobes (A), cavernous sinus (B, C), and parotid lymph node (D), best imaged on T1-w gadolinium magnetic resonance imaging.

Conclusions

The authors report on the unexpectedly durable palliation of a heavily pre-treated man with diffuse metastatic CNS and H&N ONB with antiangiogenic therapy and the localized palliation with an Ommaya reservoir. They review the literature regarding historical and emerging therapies for ONB to emphasize the needs for individualization and translational-clinical studies. Anti-angiogenic therapy has palliative potential in ONB. However, larger, prospective, translational-clinical studies are needed to explore their optimal role.

References

1. Thompson LD. Olfactory neuroblastoma. Head Neck Pathol 2009;3:252-9.
2. Ward PD, Heth JA, Thompson BG, Marentette LJ. Esthesioneuroblastoma: results and outcomes of a single institu-

tion's experience. Skull Base 2009;19:133.
3. Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma. A clinical analysis of 17 cases. Cancer 1976;37:1571.
4. Dulguerov P, Allal AS, Calcaterra TC. Esthesioneuroblastoma: a meta-analysis and review. Lancet Oncol 2001;2:683.
5. Ozsahin M, Gruber G, Olszyk O, et al. Outcome and prognostic factors in olfactory neuroblastoma: a rare cancer network study. Int J Radiat Oncol Biol Phys 2010; 78:992-7.
6. Hyams, VJ, Batsakis, JG, Michaels, L. Tumors of the upper respiratory tract and ear. Atlas of Tumor Pathology, Armed Forces Institute of Pathology 1988.
7. Hirose T, Scheithauer BW, Lopes MB, et al. Olfactory neuroblastoma. An immunohistochemical, ultrastructural, and flow cytometric study. Cancer 1995;76:4.
8. Kane AJ, Sughrue ME, Rutkowski MJ et al. Posttreatment prognosis of patients with esthesioneuroblastoma. J Neurosurg 2010; 113:340-51.
9. McElroy EA Jr, Buckner JC, Lewis JE. Chemotherapy for advanced esthesioneuroblastoma: the Mayo Clinic experience. Neurosurgery 1998;42:1023.
10. Kiyota N, Tahara M, Fujii S, et al. Nonplatinum-based chemotherapy with irinotecan plus docetaxel for advanced or metastatic olfactory neuroblastoma: a retrospective analysis of 12 cases. Cancer 2008;112:885-91.
11. Madani I, Bonte K, Vakaet L, et al. Intensity-modulated radiotherapy for sinonasal tumors: Ghent University Hospital update. Int J Radiat Oncol Biol Phys 2009;73:424.
12. Diaz EM Jr, Johnigan RH 3rd, Pero C, et al. Olfactory neuroblastoma: a 22 year experience at one comprehensive cancer center. Head Neck 2005;27:138-49.
13. Kim HJ, Cho HJ, Kim KS, et al. Results of salvage therapy after failure of initial treatment for advanced olfactory neuroblastoma. J Craniomaxillofac Surg 2008;36: 47-52.
14. Chamberlain MC. Treatment of intracranial metastatic esthesioneuroblastoma. Cancer 2002;95:243-8.
15. Kim DW, Jo YH, Kim JH, et al. Neoadjuvant Etoposide, Ifosfamide, and Cisplatin for the Treatment of Olfactory Neuroblastoma. Cancer 2004;101:2257.
16. Aljumaily RM, Nystrom JS, Wein RO. Neoadjuvant chemotherapy in the setting of locally advanced olfactory neuroblastoma with intracranial extension. Rare Tumors 2011;3:e1.
17. Sheehan JM, Sheehan JP, Jane JA Sr, Polin RS. Chemotherapy for esthesioneuroblastomas. Neurosurg Clin N Am 2000;11:693.
18. Turano S, Mastroianni C, Manfredi C, et al. Advanced adult esthesioneuroblastoma successfully treated with cisplatin and etoposide alternated with doxorubicin, ifosfamide and vincristine. J Neurooncol 2010;98:131.
19. Preusser M, Hutterer M, Sohm M, et al. Disease stabilization of progressive olfactory neuroblastoma (esthesioneuroblastoma) under treatment with sunitinib mesylate. J Neurooncol 2010;97:305.
20. Mao L, Xia YP, Zhou YN, et al. Activation of sonic hedgehog signaling pathway in olfactory neuroblastoma. Oncology 2009; 77:231.
21. Pastorino F, Di Paolo D, Loi M, et al. Recent advances in targeted anti-vasculature therapy: the neuroblastoma model. Curr Drug Targets 2009;10:1021-7.
22. Benesch M, Windelberg M, Sauseng W, et al. Compassionate use of Bevacizumab (Avastin) in children and young adults with refractory or recurrent solid tumors. Ann Oncol 2008;19:807-13.
23. Reardon DA, Turner S, Peters KB, et al. A review of VEGF/VEGFR-targeted therapeutics for recurrent glioblastoma. J Natl Compr Canc Netw. 2011;9:414-27.
24. Harris AL. Von Hippel-Lindau syndrome: target for anti-vascular endothelial growth factor (VEGF) receptor therapy. Oncologist 2000;5:32-6.
25. Mukherji SK. Bevacizumab (Avastin). Am J Neuroradiol 2010;31:235-6.
26. Nassehi D, Dyrbye H, Andresen M, et al. Vascular endothelial growth factor A protein level and gene expression in intracranial meningiomas with brain edema. APMIS 2011;119:831-43.
27. Machein MR, Plate KH. VEGF in brain tumors. J Neurooncol 2000;50:109-20.