Treatment Response of Esthesioneuroblastoma to Neoadjuvant Chemotherapy

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Introduction
Esthesioneuroblastoma (olfactory neuroblastoma) is a rare nasal cavity tumor arising from the olfactory epithelium. Treatment consists of surgical resection with possible external beam radiation. The role of neoadjuvant chemotherapy has not yet been clearly identified in treatment. We present a case report of a patient with advanced Kadish stage C esthesioneuroblastoma that demonstrated a significant response to neoadjuvant chemotherapy allowing for surgical resection with negative margins.

Case Report
A 46 year old male presented to an outside clinic with nasal obstruction. He noted significant worsening of his symptoms over the last 6 months. Additionally there were new complaints of diplopia with lateral gaze, intermittent epistaxis, and anosmia.

• Rigid nasal endoscopy revealed a friable mass above the inferior turbinate obstructing the right nasal cavity and visualization of cephalad structures. (figure 1)
• CT & MRI demonstrated a large mass within the paranasal sinuses with extension into the brain and orbit (figure 2).
• Biopsy performed in the operating room revealed high grade esthesioneuroblastoma. Positive staining was reported for synaptophysin, Neuron specific enolase, S-100, pan Keratin, and Cam 5.2

Staging was determined as Hyams grade IV tumor, Kadish stage C (table 1) involving the right nasal cavity with extension into the anterior cranial fossa, ethmoid and sphenoid sinuses with compression of the medial wall of the right maxillary sinus with bony erosion.

The patient was treated with neoadjuvant chemotherapy consisting of two cycles of etoposide (100 mg/m²) and cisplatin (33 mg/m²). Imaging was repeated after each cycle (figure 3).

Repeat MRI following neoadjuvant chemotherapy revealed significant interval decrease in size of the complex sinonasal mass without persistent intracranial involvement, amenable to en-bloc surgical excision. Pathologic examination demonstrated a 1.2 x 0.6 cm tumor with negative margins representing a significant response of the tumor to neoadjuvant chemotherapy. Currently the patient 8 months status post anterior craniofacial resection, doing well with no evidence of recurrence or complication.

Table 1: Kadish Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Tumor confined to nasal cavity</td>
</tr>
<tr>
<td>B</td>
<td>Tumor confined to nasal cavity and paranasal sinuses</td>
</tr>
<tr>
<td>C</td>
<td>Tumor extent beyond nasal cavity and paranasal sinuses, involving involvement of cribiform plate, base of skull, orbit or intracranial cavity</td>
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Table 2: Hyams Staging

<table>
<thead>
<tr>
<th>Grade</th>
<th>Lobular Architecture</th>
<th>Mitotic Index</th>
<th>Nuclear Polymorphism</th>
<th>Fibrous Matrix</th>
<th>Rosettes</th>
<th>Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>Zero</td>
<td>None</td>
<td>Prominent</td>
<td>MW Rosettes</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>Low</td>
<td>Low</td>
<td>Present</td>
<td>MW Rosettes</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>+/-</td>
<td>Mod</td>
<td>Low</td>
<td>Low</td>
<td>FW Rosettes</td>
<td>Rare</td>
</tr>
<tr>
<td>4</td>
<td>+/-</td>
<td>High</td>
<td>Absent</td>
<td>None</td>
<td>Frequent</td>
<td></td>
</tr>
</tbody>
</table>

Follow-up by Loy et al at the same institution showed patients treated with vincristine and cyclophosphamide had disease free survival of 86.5% and 82.6% at 5 and 15 years, respectively. These rates were significantly higher than those cited for the combination of surgery and radiation alone, 65 to 68 percent at 5 years.

Similarly, M. D. Anderson reported using preoperative chemotherapy in 3 patients to reduce tumor burden in order to achieve surgical resection. Of the 3 patients, one patient responded to two cycles of cisplatin and etoposide while the others received different regimens.

McKelvy et al demonstrated high grade esthesioneuroblastoma response to cisplatin-based chemotherapy at the Mayo Clinic. McLean et al described 7 of 21 patients with Kadish B and C disease who were treated with postoperative carbo-or cisplatin plus etoposide following radiation.

Fitze et al concluded that neoadjuvant chemotherapy would be a beneficial treatment in patients with esthesioneuroblastoma. In this study, patients received two cycles of cisplatin (33 mg/m²) and etoposide (100 mg/m²) prior to surgical excision, followed by another two cycles post-operatively followed by proton radiation. Response was seen in 6 of 10 patients, and overall the subjects had a 5-year survival rate of 74% and a 5-year local control rate of 88%.

Kim et al found similar results using neoadjuvant etoposide, cisplatin, and ifosfamide, which led to objective responses in 9 of 11 patients without disease progression. However, median survival of 18 months was less than reported previously by Polin.

Discussion
Treatment for esthesioneuroblastoma is most often a combination of surgery and radiation. Survival rates range from 65% for surgery plus radiotherapy, the greatest of all the groups, 51% for radiotherapy and chemotherapy, 48% for surgery, 47% for surgery plus radiotherapy and chemotherapy, and 37% for radiotherapy alone. The histopathological grading according to Hyams and the presence of cervical lymph-node metastases are the most predictive prognostic factors. Due to the small numbers of cases, the exact role of chemotherapy in treatment protocols was found to be unclear.

The use of chemotherapy in treatment of esthesioneuroblastoma was first advocated in publications from the University of Virginia in 1998. Polin et al found that preoperative radiation and chemotherapy resulted in a reduced tumor burden, increasing the chances of total resection and long-term disease-free progression. In their protocol patients with advanced disease (Kadish stage C) were treated first with two cycles of cyclophosphamide (300-650 mg/m²) and vincristine (1-2 mg), followed by 50 Gy of radiotherapy prior to surgical resection of the tumor.

Conclusions
- Neoadjuvant chemotherapy consisting of etoposide and cisplatin is a potential effective therapeutic option in the treatment of esthesioneuroblastoma with significant extension to surrounding structures prior to surgical resection.
- Due to the rarity of this tumor larger, multi-institutional studies will be required to validate the efficacy of this treatment in comparison to current adjuvant chemotherapy protocols.

References