Esthesioneuroblastoma (ENB) is a rare malignancy arising from the olfactory epithelium of the nasal vault. ENB accounts for 3% to 6% of all intranasal tumors and has the best prognosis among sinonasal malignancies with neuroendocrine differentiation. The optimal treatment continues to be controversial, but the benefit of adjuvant therapy, particularly radiotherapy, has been well described in the literature. The largest reported series evaluated neoadjuvant radiotherapy of 50 Gy, with or without neoadjuvant chemotherapy, and found improved resectability with improved patient survival. We present two cases of advanced ENB at our institution treated with a preoperative concurrent radiochemotherapy in a manner akin to that of small-cell carcinoma of the lung.

Case Reports

A review of patient charts and electronic records was conducted. Histopathologic slides were reviewed, and the diagnosis of high-grade esthesioneuroblastoma was confirmed. Complications of adjuvant therapy were scored using the National Cancer Institute Common Terminology Criteria of Adverse Events (CTCAE) version 3.0.

Case 1. A 38-year-old male patient presented with anosmia and nasal fullness. A nasal endoscopy with biopsies demonstrated ENB in the right nasopharynx, Hyams grade 3. Figure 1 shows tumor cells positive for Synaptophysin immunohistochemical staining, at magnification. The staging work-up, including magnetic resonance imaging (MRI) and positron emission tomography (PET)/computed tomography (CT) scan, revealed the primary tumor involving bilateral cribriform plates, bilateral ethmoid sinuses, and right maxillary sinus, as well as bilateral neck metastases, making this Kadish stage C (Fig 2). After multidisciplinary discussion, treatment was to be neoadjuvant radiochemotherapy followed by a craniofacial resection and bilateral neck dissections. The preoperative regimen was to include two cycles of cisplatin (60 mg/m² on days 1 and 23) and etoposide (120 mg/m² on days 1 through 3 and 23 through 25) with 50 Gy of radiation in 25 fractions of 2 Gy per fraction beginning day 1. The radiotherapy target volume encompassed the primary disease and nodal drainage areas, covering the bilateral cervical chains down to the suprACLavicular fossa. Treatment toxicity included neutropenic fevers after both cycles of cisplatin and etoposide, as well as grade 2 dermatitis and grade 4 mucositis requiring temporary hyperalimentation. This patient elected to discontinue radiotherapy after 46 Gy in 23 fractions were delivered. However, these complications did not delay surgery, which was performed 12 weeks after the completion of neoadjuvant therapy. A craniofacial resection, medial orbital wall excision, total ethmoidectomies, and delayed bilateral level 2 to 5 neck dissection revealed no residual malignancy. Postoperatively, he experienced right shoulder pain and weakness. However, surgical re-exploration...
revealed the accessory nerve to be intact. He continues to have difficulty with grade 1 xerostomia and hypogeusia, as well as intermittent mild diplopia. With a follow-up of 30 months, including periodic imaging using MRI and PET/CT and direct visualization via nasal endoscopy, he continues to be disease free.

**Case 2.** A 66-year-old male patient presented with recurrent epistaxis and was found to have a mass involving the bilateral nasal cavities superiorly. A biopsy revealed a Hyams grade 4 ENB, with necrotic foci seen on hematoxylin and eosin stains at ×125 magnification (Fig 3). The staging work-up, including MRI and PET/CT imaging, revealed intracranial extension into the bilateral frontal lobes (Fig 4). There was no evidence of regional or distant metastases outside of the locally advanced primary tumor. The planned treatment was neoadjuvant radiochemotherapy followed by a craniofacial resection. The preoperative regimen was to include two cycles of cisplatin (60 mg/m² on days 1 and 23) and etoposide (120 mg/m² on day 1s through 3 and 23 through 25) with 50 Gy of radiation in 25 fractions of 2 Gy per fraction beginning day 1. The radiotherapy target volume encompassed the primary disease and nodal drainage areas, covering the bilateral cervical chains down to the supraclavicular fossa. After his first cycle of chemotherapy, he was admitted with hyponatremia from syndrome of inappropriate antidiuretic hormone hypersecretion. The cisplatin was then switched to carboplatin (target area under the curve of 6.0 mg/mL/min on day 23) for the second chemotherapy cycle, without delay in administration of the dose. He also developed a soft tissue infection around his G-tube site, which required a hospitalization for less than 1 week with intravenous antibiotic treatment. He also experienced grade 1 dermatitis and grade 4 mucositis, the latter necessitating near total nutritional intake via a gastric tube. After his second round of chemotherapy, the patient had neutropenic sepsis secondary to pneumonia and required admission to the intensive care unit, with intubation and mechanical ventilation for 4 days. Respiratory cultures revealed *Klebsiella* species. He fully recovered and proceeded to surgery without delay, 8 weeks after completion of neoadjuvant therapy. The procedure performed included craniofacial resection, ethmoidectomy, and right medial orbital wall excision. The specimen revealed no evidence of residual malignancy. After craniofacial resection, the patient was found to have pneumocephalus and meningitis, requiring endoscopic repair of the skull base defect. Follow-up scans showed resolution of pneumocephalus, and the patient’s neurocognitive function continues to improve to baseline. He continues to work full time as a financial planner. An MRI 13 months after treatment revealed osteonecrosis of the craniotomy bone flap. He began hyperbaric oxygen for this, with plans for surgical reconstruction. He also continues to have intermittent mild diplopia. With a follow-up period of 24 months, including periodic MRIs and nasal endoscopies, he continues to be disease free.

**Discussion**

A multimodal approach to the treatment of advanced ENB has been postulated to increase overall and recurrence-free survival. In the neoadjuvant setting, Polin et al showed significant tumor reduction (> 50% in tumor volume or > 90% regression of intracranial extension) in two thirds of patients treated with preoperative radiation with or without chemotherapy (not given concurrently) and increased recurrence-free survival in those responders. Although there is no standard chemotherapy regimen used for ENB, the agents used are chiefly cisplatin and etoposide, and doxorubicin and vincristine with an alkylating agent. In 1990, Polonowski et al reported complete pathologic response to induction treatment with four cycles of cisplatin and fluorouracil. Chao et al reported that one of eight patients receiving neoadjuvant treatment achieved complete response. This
Table 1. Preoperative Radiochemotherapy Regimens in the Literature

<table>
<thead>
<tr>
<th>First Author and Reference</th>
<th>Chemotherapy</th>
<th>Radiotherapy</th>
<th>Sequence</th>
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<tbody>
<tr>
<td>Bhattacharyya et al12</td>
<td>cisplatin (33 mg/m² per day for 3 days) and etoposide (100 mg/m² per day for 3 days), 2 cycles</td>
<td>68 Gy, composed of 70% morning photon (48 Gy) and 30% afternoon photon (20 Gy)</td>
<td>Chemotherapy followed by radiotherapy, followed again by chemotherapy</td>
</tr>
<tr>
<td>Resto et al11</td>
<td>cyclophosphamide, doxorubicin, and vincristine alternating with etoposide and cisplatin flouorouacil and cisplatin</td>
<td>53.60 Gy (mean dose, without chemotherapy), postchemotherapy doses unspecified</td>
<td>Chemotherapy alone, or radiotherapy followed by chemotherapy, chemotherapy followed by radiotherapy</td>
</tr>
<tr>
<td>Polin et al4</td>
<td>cyclophosphamide (650 mg/m²) and vincristine (1.5 mg/m²; maximal dose, 2 mg) administered every 3 weeks for 6 cycles; doxorubicin used with cyclophosphamide in 2 patients; methotrexate used with vincristine in 1 patient</td>
<td>50 Gy, fractionated</td>
<td>Unspecified</td>
</tr>
<tr>
<td>Fitzek et al20</td>
<td>cisplatin and etoposide (repeated after radiotherapy in responders)</td>
<td>high-dose proton-photon radiotherapy to 89.2 cobalt-Gray equivalents (CGE) using 1.6-1.8 CGE per fraction twice daily in a concomitant boost schedule</td>
<td>Chemotherapy followed by radiotherapy followed by chemotherapy in responders</td>
</tr>
<tr>
<td>Eich et al7</td>
<td>cisplatin, cyclophosphamide, dacarbazine, etoposide, ifosfamide, teniposide, vincristine, and vindesine used in no standard regimen</td>
<td>Target dose 50-60 Gy (range, 32-70 Gy) dose, fraction range 1.8-3 Gy, number of fractions range 16-36</td>
<td>Chemotherapy alone preoperatively; radiotherapy alone or followed by chemotherapy without surgery</td>
</tr>
<tr>
<td>Argiris et al10</td>
<td>cisplatin and etoposide</td>
<td>50-60 Gy</td>
<td>Unspecified</td>
</tr>
<tr>
<td>Chao et al10</td>
<td>cyclophosphamide and vincristine (doxorubicin or dacarbomycin added in 2 regimens), cisplatin and etoposide</td>
<td>40-50 Gy (mean 1.8-2 Gy fraction size, median 29 fractions)</td>
<td>Unspecified</td>
</tr>
<tr>
<td>Mishima et al14</td>
<td>chemotherapy consisting of cyclophosphamide, doxorubicin, and vincristine with continuous-infusion cisplatin and etoposide (with or without peripheral-blood stem-cell transplantation), range 2-7 cycles</td>
<td>40-50 Gy</td>
<td>Chemotherapy followed by radiotherapy</td>
</tr>
<tr>
<td>Sohrabi et al (current study)</td>
<td>cisplatin (80 mg/m² on days 1-23) and etoposide (120 mg/m² on days 1-3, 23-25) cisplatin changed to carboplatin (target AUC of 6.0 mg/mL/min on day 23) in patient 2</td>
<td>Target dose 50 Gy (25 fractions of 2 Gy starting day 1); treatment stopped after 46 Gy in patient 1</td>
<td>Concurrent</td>
</tr>
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Abbreviation: AUC, area under the curve.

patient had stage B disease and received two cycles of cyclophosphamide, doxorubicin, vincristine, and dacarbomycin, with 45 Gy of radiotherapy and no surgery. In the same series of eight patients, the four patients receiving cisplatin and etoposide in two or three cycles with approximately 60 Gy of radiotherapy showed less than 50% or no response. The sequence of radiotherapy and chemotherapy was not specified in the report. In 1997, Bhattacharyya et al12 reported nine successful treatments of ENB using two cycles of induction cisplatin (33 mg/m²) and etoposide (100 mg/m²), followed by 68 Gy of radiotherapy, followed by another two cycles of the same chemotherapeutic regimen. Of these nine patients, two patients underwent craniofacial resection, which revealed no tumor in the surgical specimen. The stage and grade for these tumors were not identifiable in the report. Mishima et al14 reported complete response by radiologic evaluation in eight of 12 patients treated with two cycles of combination chemotherapy consisting of cyclophosphamide, doxorubicin, and vincristine with continuous-infusion cisplatin and etoposide, with or without peripheral-blood stem-cell transplantation, followed by radiotherapy with 40 to 60 Gy. Ten of 12 patients had advanced disease by Kadish staging. Of note, one of these 12 patients showed complete response radiographically after the completion of chemotherapy alone.15 Kim et al16 evaluated the neoadjuvant regimen of chemotherapy alone, consisting of etoposide (75 mg/m² on days 1 through 5) ifosfamide (1,000 mg/m² on days 1 through 5), and cisplatin (20 mg/m² on days 1 through 5), and they reported complete response radiographically in two of 11 patients. These patients were diagnosed with Kadish stage B and C disease and received six cycles of the above regimen. Table 1 summarizes reported preoperative radiochemotherapy regimens.

There is evidence supporting concurrent radiochemotherapy with platinum-based chemotherapeutic agent in treatment of head and neck squamous cell carcinoma.17-20 Concurrent radiochemotherapy with cisplatin and etoposide has also been used in treatment of small-cell lung cancer.21-23 Considering the reported successes of platinum-based agents and University of Virginia’s experience with preoperative radiotherapy of 50 Gy, we used cisplatin (60 mg/m²) with etoposide (120 mg/m²) with concomitant radiotherapy of 50 Gy for the preoperative treatment of Kadish stage C and Hyams grade 3 and 4 tumors. Both patients experienced significant complications from the preoperative treatment, requiring hospitalizations and nutritional support via gastric tubes and minor changes from the original plan. However, these hospitalizations lasted less than a week each and required only intravenous antibiotic administration. During these hospital stays, radiotherapy treatments were continued. Perhaps most importantly, these complications did not delay surgery and have been associated with minimal late sequelae after a year of follow-up.

To our knowledge, this is the first report of treating high-grade, stage C ENB with neoadjuvant concurrent radiochemotherapy. Both patients enjoyed complete pathologic responses. Although the follow-up is only 30 and 24 months currently, these initial results are promising and warrant further study.
In conclusion, this regimen of preoperative concurrent radiochemotherapy for locally advanced disease is promising in terms of pathologic complete response and hence deserves further study in a prospective trial.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The author(s) indicated no potential conflicts of interest.

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DOI: 10.1200/JCO.2010.30.9278; published online ahead of print at www.jco.org on January 31, 2011