mainly located within the cell processes but not within perikarya. The findings thus mimicked those of classic, pediatric neuroblastomas.[9] In contrast, dense core or neurosecretory-type granules in SITA resemble those of enterochromaffin (endocrine) cells of the digestive tract. They are aggregated within the perikarya, are often pleomorphic in shape, and are larger in size.[5-7] Considering its immunophenotype and the ultrastructural findings, we consider Case 26 to have a biphasic tumor composed of epithelial and genuine neuroblastic cells rather than a purely epithelial nature tumor such as a SITA.

In addition to this tumor, we had another biphasic tumor in the study (Case 25), one exhibiting ganglioneuroblastoma-like and epithelial (tubular, papillary, and rosette structures) features.[1] The epithelial differentiation exhibited by these two ONB could be regarded as differentiation toward the supporting cells of the olfactory epithelium, but not toward the mucosal epithelium of the nasal and paranasal sinus (Schneiderian membrane). Taking into account the wide morphologic variety of ONB, which ranges from neuronal to epithelial features, the finding of epithelial differentiation does not exclude the diagnosis of ONB. We do, however, agree with Dr. Vartanian that SITA should be distinguished from ONB in that the two lesions may have different etiologies and biologic behavior.

REFERENCES

1. Hirose T, Scheithauer BW, Lopes MBS, Gerber HA, Altermatt HJ, Harner SG, et al. Olfactory neuroblastoma: an immunohistochemical, ultrastructural, and flow cytometric study. *Cancer* 1995;76:4–19.
2. Sanchez-Casis G, Devine KD, Weiland LH. Nasal adenocarcinomas that closely simulate colonic carcinomas. *Cancer* 1971;28:714–20.
3. Barnes L. Intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. *Am J Surg Pathol* 1986;10:192–202.
4. Franquemont DW, Fechner RE, Mills SE. Histologic classification of sinonasal intestinal-type adenocarcinoma. *Am J Surg Pathol* 1991;15:368–75.
5. Schmid KO, Auböck L, Albegger K. Endocrine-amphicrine enteric carcinoma of the nasal mucosa. *Virchows Arch A Pathol Anat Histol Pathol* 1979;383:329–43.
6. Mills SE, Fechner RE, Cantrell RW. Aggressive sinonasal lesion resembling normal intestinal mucosa. *Am J Surg Pathol* 1982;6:803–9.
7. Batsakis JG, Mackay B, Ordonez NG. Enteric-type adenocarcinoma of the nasal cavity. An electron microscopic and immunocytochemical study. *Cancer* 1984;54:855–60.
8. McKinney CD, Mills SE, Franquemont DW. Sinonasal intestinal-type adenocarcinoma: immunohistochemical profile and comparison with colonic adenocarcinoma. *Mod Pathol* 1995;8:421–6.
9. Erlandson RA. Diagnostic transmission electron microscopy of tumors: with clinicopathological, immunohistochemical, and cytogenetic correlations. New York: Raven Press, 1994.

Takanori Hirose, M.D.
Bernd W. Scheithauer, M.D.

MBS Lopes, M.D.
Division of Anatomic Pathology
Mayo Clinic
Rochester, MN

Prospective Study of Combination Chemotherapy with Cyclophosphamide, Doxorubicin, and Cisplatin for Unresectable or Metastatic Malignant Pleural Mesothelioma

The study by Dr. Shin and colleagues on chemotherapy for advanced malignant pleural mesothelioma was interesting and informative.[1] The authors pointed to the antitumor activity of platinum analogues which led them to incorporate cisplatin with doxorubicin and cyclophosphamide. In this regard, we would like to draw their attention to some additional data on cisplatin efficacy in malignant mesothelioma.

Stewert and colleagues presented an intriguing report of 4 patients with unresectable mesotheliomas treated with high doses of doxorubicin (90 mg/m^2) and cisplatin (105–120 mg/m^2).[2] Two of the 4 patients achieved a complete response (CR) (1 persisting at more than 4 years), 1 had a partial response, and 1 stable disease (SD) with excellent symptomatic palliation. While the group was small and toxicity substantial, further study is certainly warranted.

Another recent report of the combination of cisplatin, interferon-α, and tamoxifen yielded a 19% objective response rate with a median survival of 14.7 months, toxicity being minimal.[3] Another group of 20 patients treated with cisplatin and vinblastine had a 25% objective response rate (10% CR), median survival being 19.3 months.[4] Nine other patients had SD (median survival: 15.7 months) and toxicity was acceptable.

Finally, Lerza and associates reported the use of high doses of intrapleural cisplatin (2 courses of 120 mg/m^2) on patients with inoperable malignant pleural mesothelioma.[5] This regimen was well tolerated, had not systemic toxicity, and achieved complete local control without recurrence of the pleural effusion.

These reports, in addition to the authors' study, provided increasing evidence for the efficacy of cisplatin in the management of unresectable malignant pleural mesothelioma.

REFERENCES

1. Shin DM, Fossella FV, Umsawasdi T, Murphy WK, Chasen MH, Walsh G, et al. Prospective study of combination chemotherapy with cyclophosphamide, doxorubicin, and cis-

platin for unresectable or metastatic malignant pleural mesothelioma. *Cancer* 1995;76:2230–6.
2. Stewert DJ, Gertler SZ, Tomiak A, Shamji F, Goel R, Evans WK. High dose doxorubicin plus cisplatin in the treatment of unresectable mesotheliomas: report of four cases. *Lung Cancer* 1994;11:251–8.
3. Pass HW, Temeck BK, Kranda K, Steinberg SM, Pass HI. A phase II trial investigating primary immunochemotherapy for malignant pleural mesothelioma and the feasibility of adjuvant immunochemotherapy after maximal cytoreduction. *Ann Surg Oncol* 1995;2:214–20.
4. Tsavaris N, Mylonakis N, Karvounis N, Bacoyiannis C, Briasoulis E, Skarlos D, et al. Combination chemotherapy with cisplatin-vinblastine in malignant mesothelioma. *Lung Cancer* 1994;11:299–303.
5. Lerza R, Esposito M, Vannozzi M, Bottino GB, Bogliolo G, Pannacciulli I. High doses of intrapleural cisplatin in a case of malignant pleural mesothelioma. Clinical observations and pharmacokinetic analyses. *Cancer* 1994;73:79–84.

Ajay Anand, M.D.
Division of Hematology and Oncology
Deaconess Hospital, Harvard Medical School
Boston, MA
Abhay Anand, M.D.
Division of Hematology and Oncology
New England Baptist Hospital
Boston, MA
Namrata Anand, M.D.
Department of Pathology
Deaconess Hospital, Harvard Medical School
Boston, MA

Recombinant Human Erythropoietin for the Correction of Cancer Associated Anemia with and without Concomitant Cytotoxic Chemotherapy

The article by Dr. Ludwig and associates provided further evidence for the efficacy of recombinant human erythropoietin (rHuEPO) in cancer patients with anemia, leading not only to an increase in hematocrit levels, but also to an improved performance status and quality of life.[1]

The authors point to cisplatin nephrotoxicity as being a contributor to anemia in cancer patients receiving this drug. However, cisplatin selectively damages renal tubules,[2] which are not a site for erythropoietin production. Besides, in large double-blind and open-label follow-up studies, patients receiving chemotherapy with or without cisplatin had comparable levels of anemia, need for transfusion, response rate, and extent and time to response to rHuEPO.[3]

The authors did not report any hypertensive episodes and suggested that hypertension in patients on rHuEPO is specific only for those with anemia related to end-stage renal disease.[1] We would like to caution that hypertension, seizures, and venous thromboses have all been encountered in rHuEPO treated cancer patients, usually in the setting of an inappropriate rise in red cell mass.[4] It appears prudent to avoid excessive increases in hemoglobin values and to monitor blood pressure initially, particularly in the setting of preexisting hypertension. Furthermore, as increased red cell mass due to exogenous erythropoietin is associated with reduced plasma volume, care must be exercised in treating patients with multiple myeloma or Waldenstrom's macroglobulinemia[5] to achieve benefit without complications.

The data presented, in addition to the authors' study, would perhaps further clarify the role of rHuEPO in the management of anemia in cancer patients.

REFERENCES

1. Ludwig H, Sundal E, Pecherstorfer M, Leitgeb C, Bauernhofer A, Beinhauer A, et al. Recombinant human erythropoietin for the correction of cancer associated anemia with and without concomitant cytotoxic chemotherapy. *Cancer* 1995;76:2319–29.
2. Anand A, Bashey B. Newer insights into cisplatin nephrotoxicity. *Ann Pharmacoth* 1993;27:1519–25.
3. Henry DH, Abels RI. Recombinant human erythropoietin in the treatment of cancer and chemotherapy-induced anemia: results of double-blind and open-label follow-up studies. *Semin Oncol* 1994;21(2Suppl3):21–8.
4. Abels RI, Larholt KM, Krantz KD, Bryant EC. Recombinant human erythropoietin (rHuEPO) for the treatment of the anemia of cancer. Murphy MJ Jr, editor. Blood Cell Growth Factors: Their Present and Future Use in Hematology and Oncology. *Alpha Med* 1991:122.
5. Eckardt KU, Dittmer J, Neumann R, Bauer C, Kurtz A. Decline of erythropoietin formation at continuous hypoxia is not due to feedback inhibition. *Am J Physiol* 1990;258:F1432.

Ajay Anand, M.D.
Division of Hematology and Oncology
Deaconess Hospital, Harvard Medical School
Boston, MA
Abhay Anand, M.D.
Division of Hematology and Oncology
New England Baptist Hospital
Boston, MA
Namrata Anand, M.D.
Department of Pathology
Deaconess Hospital, Harvard Medical School
Boston, MA