CARCINOMA OF UNKNOWN PRIMARY SITE—A COMPLETE AND SUSTAINED RESPONSE WITH INTERLEUKIN-2, ALPHA INTERFERON AND 5-FLUOROURACIL/LEUCOVORIN

The patient with carcinoma of an unknown primary site (CUPS) represents a major challenge to oncologists with 10–15% of patients referred to a solid tumor oncology service falling into this category (1). Patient prognosis is dismal and is little improved by conventional chemotherapy (2). The treatment approach is a careful anatomic evaluation to determine the primary site. Failure to identify the primary site requires a meticulous histopathological examination of the tissue sample to exclude the more readily treatable malignancies such as lymphoma, breast, prostate and germ-line tumors (3). The probability of antemortem diagnosis, however, is small. Response to empiric chemotherapy has been less than 30% (2) with median survivals of less than one year. The toxicity of chemotherapy in these patients with a limited life-span may be considerable and negatively affects the quality of life.

We are evaluating the role of immunochemotherapy for the treatment of solid malignancies that have failed to respond to conventional chemotherapy. We report a complete and sustained response of CUPS to immunochemotherapy in a man who had progressive disease after an initial response to chemotherapy alone.

Case report. A 48-year-old man (ex-smoker) was found to have bilateral multiple adenocarcinoma pulmonary nodules in October 1988. Evaluation failed to reveal the primary tumor and he was empirically treated with 3 cycles of VP-16 and cis-platinum. Initial tumor regression was noted one month after starting treatment with stable disease for a further 4 months. Disease progression then occurred despite a change in his chemotherapy to cyclophosphamide, doxorubicin and vincristine (CAV) alternating with VP-16 and cis-platinum. He was subsequently referred to the Mount Vernon Cancer Institute in April 1989.

A chest CT-scan (Fig. 1A) showed extensive bilateral nodular abnormalities with hilar and mediastinal adenopathy. He had dyspnea on minimal exertion and his Karnofsky score was 70%. He was treated with outpatient immunochemotherapy. His treatment consisted of cyclophosphamide 350 mg/m^2 p.o. followed 4 days later by recombinant human interleukin-2 (rh-IL-2, Hoffman-LaRoche) at 1×10^6 units/m^2 by intravenous bolus on days 1–5 and concomitant recombinant human alpha-interferon (rh-αIFN, Hoffman-LaRoche) at 9×10^6 units/m^2 i.m. on days 3 and 5. Following a one month break, he received leucovorin 500 mg/m^2 i.v. and 5-fluorouracil (5-FU) 375 mg/m^2 on days 1–5 every 21 days for two cycles. His subsequent treatment courses have been with continuous infusion rh-IL-2 at 1×10^6 units/m^2 on days 1–5 repeated weekly for 4 weeks with concurrent rh-αIFN 9×10^6 units/m^2 i.m. TIW. This course of rh-IL-2 and rh-αIFN combined with the chemotherapy has now been repeated three times.

Within two months of strating treatment, he was able to resume full-time work and to play golf. Repeat chest CT-scans have shown a progressive reduction of tumor burden with a partial response evident at 3 months and a complete response at 15 months after starting immunochemotherapy (Fig. 1B). Several new lung nodules appeared during treatment only to regress later. No metastatic disease has been detected outside the chest since the beginning of treatment. He remains well and continues on treatment two years after the initial diagnosis of CUPS, currently without demonstrable disease.

Discussion. Patients with CUPS have a median survival of only 4–5 months (4) when untreated and have response rates of less than 30% (2) to empiric combination chemotherapy. Responses, when seen, are of short duration. The chemotherapy regimens may be associated with significant toxicities (5, 6) with a concurrent decrease in the quality of life in this group of patients. The absence of effective chemotherapy for these patients led us to examine the use of immunochemotherapy. Immunotherapy is now a form of treatment for neoplastic disorders. Responses have been demonstrated in both animal models and in human trials using biologics either alone or in combination (7–10). There is also experimental animal and human data to suggest an additive or synergistic effect between immunotherapy and chemotherapy, often with response of the tumor to previously ineffective chemotherapy (7, 10).

This is the first reported case of a complete and durable response to immunochemotherapy in CUPS. Our patient had a poor performance status and had already developed progressive disease in the face of initially effective chemotherapy. Unlike the severe toxicities seen with the use of high dose rh-IL-2 ± lymphokine-activated killer (LAK) cells (9), the toxicities with our low-dose treatment were well tolerated enabling the therapy

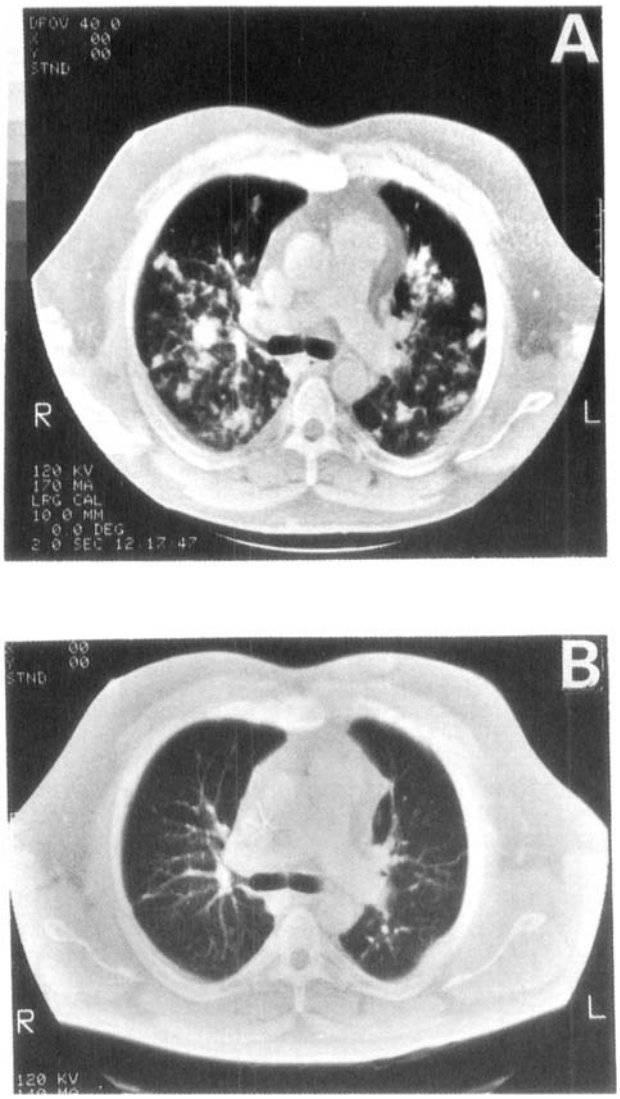

Fig. 1. Chest CT-scan, A) at presentation, and B) 15 months after starting treatment.

to be given in an outpatient setting. The success with this patient is exciting and warrants further investigation.

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REFERENCES

1. Moertel CG, Reitmeier RJ, Schutt AJ, Hahn RG. Treatment of the patient with adenocarcinoma of unknown origin. Cancer 1972; 30: 1469–72.
2. Sporn JR, Greenberg BR. Empiric chemotherapy in patients with carcinoma of unknown primary site. Am J Med 1990; 88: 49–55.
3. Greenberg BR, Lawrence HJ. Metastatic cancer with unknown primary. Med Clin North Am 1988; 72: 1055–65.
4. Altman E, Cadman E. An analysis of 1 539 patients with cancer of unknown primary site. Cancer 1986; 57: 120–4.
5. Goldberg RM, Smith FP, Ueno W, Ahlgren JD, Schein PS. 5-fluorouracil, Adriamycin, and mitomycin in the treatment of adenocarcinoma of unknown primary. J Clin Oncol 1986; 4: 395–9.
6. Woods RL, Fox RM, Tattersall MHN, Levi JA, Brodie GN. Metastatic carcinoma of unknown primary site: A randomized study of two combination chemotherapy regimens. N Engl J Med 1980; 303: 87–9.
7. Papa MZ, Yang JC, Vetto JT, Shiloni E, Eisenthal A, Rosenberg SA. Combined effects of chemotherapy and interleukin-2 in the therapy of mice with advanced pulmonary turmors. Cancer Res 1988; 48: 122–9.
8. Wadler S, Schwartz EL, Goldman M, et al. Fluorouracil and recombinant alpha-2a-interferon: An active regimen against advanced colorectal carcinoma. J Clin Oncol 1989; 7: 1769–75.
9. Rosenberg SA, Lotze MT, Yang JC, et al. Experience with the use of high-dose interleukin-2 in the treatment of 652 cancer patients. Ann Surg 1989; 210: 474–85.
10. Schulof R, Goldberg S, Holmlund J, Mehlman T, White C, Avis F. Outpatient recombinant interleukin-2 + alpha-interferon alternating with 5-fluorouracil/leukovorin for metastatic colorectal and breast cancer. Society for Biotherapy, 1990.

ACUTE CEREBROVASCULAR ACCIDENT AFTER TREATMENT WITH CISPLATIN

Acute cerebrovascular accidents (ACVA) constitute an important clinical problem in cancer patients. ACVA is the second cause of CNS pathology after metastasis. The mechanisms implicated are (1):

1) Direct effects of the tumor (tumor embolism, vascular infiltration).
2) Secondary effects of diagnostic procedures or treatment (lumbar puncture, radiotherapy, chemotherapy).
3) Septic complications.
4) Coagulopathy with disseminated intravascular coagulation, thrombocytopenia.

Vascular complications associated with antineoplastic agents are being reported with increasing frequency. Examples of vascular toxicity are small arterial lesions causing Raynaud's phenomenon (bleomycin, cisplatin) and thrombotic microangiopathy (mitomycin). Cisplatin has been associated with acute vascular ischemic events, such as myocardial infarction, arterial thrombosis and ACVA (2, 3). Cases of ACVA in patients treated with cisplatin combinations for different tumors have been published: germ cell tumor (4), ovarian cancer (5), sarcoma (6), lung, and head and neck cancers (7, 8). The pathogenesis of cisplatin-associated ACVA is unknown, but factors such as endothelial cell damage, clotting abnormalities, autonomic dysfunction, vasculitis and fibroblastic stimulation have been suggested (2).

We will report a case of arterial carotid occlusion and secondary ACVA after cisplatin treatment.

Case report. A 25-year-old female smoker of 10 cigarettes a day without other risk factors for cardiovascular disease (diabetes, hypertension, hyperlipidemia, contraceptives) had an osteosarcoma in the left maxillary bone and underwent radical surgery in November, 1987. Radiotherapy to the orbital region and surgical bed was completed in February, 1988. The patient remained asymptomatic until June 1990 when a solitary nodule in the left perihilar region was detected. A pneumonectomy was performed in July 1990 and histologic study confirmed pulmonary metastasis. The patient was then treated at 3-week intervals with four cycles of cisplatin 100 mg/m^2 on day 1 and doxorubicin 25 mg/m^2 on days 1 through 3. In November 1990 she decided to discontinue chemotherapy. Eighteen weeks after the first cisplatin dose (and six after cessation of chemotherapy), on December 29, 1990 the patient was readmitted due to confusion, headache and left-sided hemiplegia. Blood cells counts, clotting tests, biochemical screening, and serum electrolytes, including magnesium, were normal. A first CT scan of the brain without contrast was evaluated as

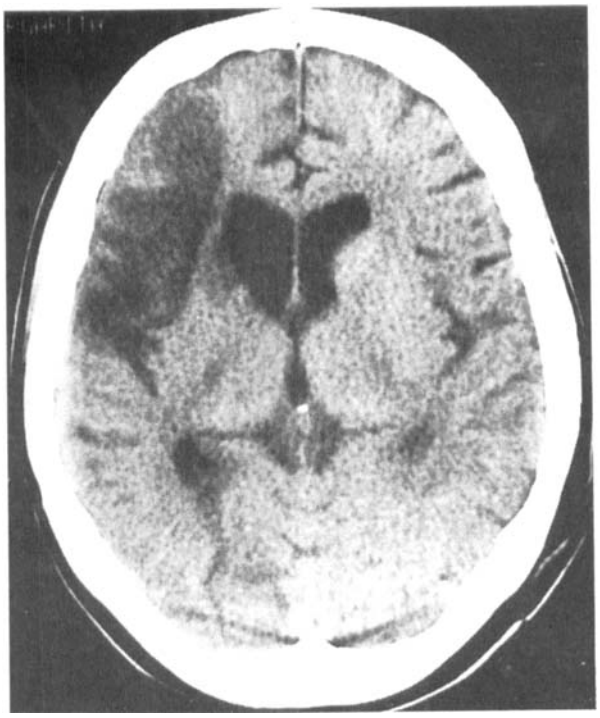

Figure. CT scan with contrast. Right ischemic lesion involving regions of the anterior and middle cerebral arteries.