Palliative Chemotherapy for Malignant Pheochromocytoma: Symptomatic Palliation of Two Cases

Masayasu Iwabuchi, Yutaka Oki and Hirotoshi Nakamura

Malignant pheochromocytoma is a rare tumor with a poor prognosis because excess production of catecholamines leads to potentially lethal complications. Several chemotherapy regimens have been reported to be effective against this tumor, but a standard form of chemotherapy has not been established. We treated two patients with histologically confirmed pheochromocytoma after surgical removal of the primary lesion. Non-cardiogenic pulmonary edema was resolved and bone metastases were controlled by individualized chemotherapy that decreased the catecholamine levels, and the performance status was improved in both cases. Palliative chemotherapy should be designed to improve the quality of life of cancer patients.

(Key words: pulmonary edema, bone metastasis, cytosine arabinoside, individualized modification, quality of life)

Case Reports

Case 1

A 35-year-old woman with malignant pheochromocytoma was admitted with dyspnea, hypertensive attacks, constipation, and a sensation of impending doom in 1993. Her blood pressure was 176/118 mmHg and heart rate, 110 bpm. The oxygen saturation was 90%. Abdominal X-ray films showed constipation and computed tomography showed pulmonary edema. Echocardiography showed a normal ejection fraction.

In 1988, she had undergone surgical treatment of a pheochromocytoma in the bladder wall and angiography had shown multiple lymph node metastases in the pelvis, indicating the malignancy of her disease.

Investigations revealed elevated catecholamine levels and disease progression. However, no mass lesions were found except for equivocal swelling of lymph nodes in the pelvis. The plasma norepinephrine level was 41 ng/ml (normal: 0.05–0.40) and 24-hour urinary norepinephrine was 17,100 μg/day (normal: 29–120). There was no uptake of 131-metaiodobenzylguanidine (MIBG) on scanning, suggesting that MIBG therapy was not indicated. Adrenergic blockade did not relieve her symptoms, so cytoreductive therapy was tried. The chemotherapeutic regimen, consisting of 750 mg/m² of cyclophosphamide on day 1, 1.4 mg/m² of vincristine on day 1, and 600 mg/m² of dacarbazine on days 1 and 2 (CVD), has been reported to be effective against malignant pheochromocytoma (1, 2). Due to her poor general condition, we modified the CVD regimen to VdsD; cyclophosphamide was not administered, 6 mg/m² of vindesine was given in place of vincristine on day 1, and dacarbazine was given according to the original schedule. She received chemotherapy at approximately 10-day intervals with careful observation of toxicity. Her pulmonary edema was resolved (Fig. 1A, B) and bowel function improved, with a decrease of 24-hour urinary catecholamines (Fig. 1C). The sensation of impending doom also diminished. According to the Eastern Cooperative Oncology Group, her performance status was improved from grade 3 to 1. She was discharged and continued to receive chemotherapy for 15 months as an outpatient. In 1995, seven years after the diagnosis of malignant pheochromocytoma, she died of cerebral hemorrhage due to disease progression.

Case 2

A 67-year-old man underwent resection of a pheochromocytoma of the right adrenal gland in 1986. Malignancy was diagnosed after multiple metastases to the paraaortic nodes were detected in 1992. Three courses of CVD did not produce improvement of catecholamine levels. He was followed as an outpatient, and lumbar vertebral metastases were treated with 40 Gy of radiation in 1995. In 1996, he was admitted because of persistent back pain and aspiration pneumonia due to recurrent laryngeal nerve paralysis caused by disease progression. A Tc-99m bone scan showed abnormal hot spots in L5 and the right fifth rib (Fig. 2A). Metastases were also observed in the
Figure 1. Improvement of pulmonary edema and 24-hour urinary norepinephrine excretion. Chemotherapy was performed with 6 mg/m² of vindesine on day 1, and 600 mg/m² of dacarbazine on days 1 and 2 (VdsD) at approximately 10-day intervals. A) Before chemotherapy, pulmonary edema is evident on computed tomography. B) Three weeks after starting chemotherapy, pulmonary edema has resolved. C) Twenty-four-hour urinary norepinephrine excretion was decreased by treatment.

lung field and the paraaortic region. Pain control with morphine was attempted, but failed. Subcutaneous administration of 20 mg of cytosine arabinoside was performed twice a week (1 mg/kg/week) under Adrenergic blockade. Four weeks later, his bone pain was resolved, and a repeat Tc-99m bone scan showed improvement (Fig. 2B). The 24-hour urinary norepinephrine excretion was decreased by 90% (from 22,600 µg/day to 2,140 µg/day; Fig. 2C). Low-dose cytosine arabinoside was continued for 6 months and his performance status improved from grade 3 to 2. In December 1996, he died of respiratory failure at 4 years after the diagnosis of malignant pheochromocytoma.

Discussion

In patients with pheochromocytoma, objective remission means the regression of measurable tumor lesions to less than 50% and a decrease in catecholamine concentration and disease-related symptoms (3). It has been reported that reducing the catecholamine level achieves palliation of malignant pheochromocytoma (4). The present two cases did not show significant regression of measurable tumors but did obtain symptomatic improvement. In case 1, modified CVD therapy controlled the pulmonary edema and other symptoms. An elevated level of catecholamines can cause pulmonary edema by increasing pulmonary capillary permeability and peripheral vasoconstriction, leading to a shift of extracellular fluid (5). In addition, catecholamines reduce bowel motility, leading to paralytic ileus. The chemotherapy regimen we used was modified to avoid hydration-induced heart failure and to reduce the risk of vinca alkaloid neuropathy (6); the vindesine dose was de-
Palliative for Malignant Pheochromocytoma
termined from the sensitivity testing of cultured human neuro-
blastoma cells (7), and the treatment schedule was derived from
a study of chemotherapy-induced bone marrow changes in a
neuroblastoma patient (8). There was a clear decrease of the
norepinephrine level in case 1, associated with symptomatic
improvement. Hypertensive episodes due to pheochromocy-
toma are sometimes accompanied by a sense of impending
doom, and control of such attacks gives the patient a sense of
well-being.

Starling and coworkers reported that neuroblastomas resis-
tant to cyclophosphamide and vincristine did not respond to
cytosine arabinoside (9). Our case 2 did not want to undergo
intensive chemotherapy, although morphine and radiotherapy
had not controlled his lumbar pain. Fortunately, low-dose cy-
tosine arabinoside achieved palliation without drug toxicity,
and he spent 6 more pain-free months with his wife after his
performance status was improved from grade 3 to 2. Single-
agent treatment of malignant pheochromocytoma has not pro-
duced survival longer than 4 years (10). The benefits of low-
dose cytosine arabinoside for hematologic disorders have been
reported (11, 12), this is the first report of malignant pheochro-
mocytoma treated with such therapy. Though it was reported
that more than 85% of the patients with malignant pheochro-
mocytoma die with a median survival of 16 months from diag-
nosis of metastases (13), our patients obtained longer survival
than has been reported. Moreover, they obtained improvement
in symptoms and performance status according to the Eastern
Cooperative Oncology Group, suggesting that individualized
chemotherapy is useful for palliation of malignant pheochro-
mocytoma, and that successful control of potentially lethal
complications may improve the prognosis of the tumor.

Acknowledgements: We would thank Dr. Toshifumi Katsuki (Yaizu Mu-
unicipal Hospital), and Dr. Toru Watanabe (National Cancer Center) for their
invaluable advice and the E10 staff for special nursing.

References

1) Keiser HR, Goldstein DS, Wade JL, Douglas FL, Averbuch SD. Treat-
2) Averbuch SD, Steakley CS, Young RC, et al. Malignant pheochromocy-
toma: Effective treatment with a combination of cyclophosphamide, vin-
3) WHO handbook for reporting results of cancer treatment. Geneva. World
4) Senan S, Reed N, Connell J. Palliation of malignant pheochromocytoma
cent concepts of diagnosis and treatment. Combined clinical staff con-
1326, 1966.
videsine sulfate. Changes in motor behaviors and muscle spindle
activities of the cat following chronic administration of videsine and
7) Hill BT, Whelan RD. Assessment of the sensitivities of cultured human
8) Shackney SE, Bunn PA, Ford SS, Erickson B, Ross WE, Levine AS. A
study of drug-induced kinetic perturbations in the marrow of a patient
9) Starling KA, Sutow WW, Donaldson MH, Land VJ, Lane DM. Drug tri-
als in neuroblastoma: cyclophosphamide (NSC-26271) alone; vincristine
(NSC-67574) plus cyclophosphamide; 6-mercaptopurine (NSC-755) plus
6-mercaptopurine riboside (NSC-40774); and cytosine arabinos-
10) Siddiqui MZ, Von Eyben FE, Spanos G. High-voltage irradiation and
combination chemotherapy for malignant pheochromocytoma. Cancer 62:
11) Baccarani M, Tura S. Differentiation of myeloid leukaemic cells: new
12) Housset M, Daniel MT, Degos L. Small doses of ARA-C in the treatment
of acute myeloid leukemia: differentiation of myeloid leukemia cells?
13) Schlumberger M, Gicquel C, Lumbruno J, et al. Malignant pheochro-
mocytoma: clinical, biological, histologic and therapeutic data in a series
of 20 patients with distant metastases. J Endocrinol Invest 15: 631–642,