Second Lung Adenocarcinoma after Combination Chemotherapy in Two Patients with Primary Non-Hodgkin’s Lymphoma

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We report a rare complication of a secondary malignant solid tumor in two patients with non-Hodgkin’s malignant lymphoma who developed lung adenocarcinoma after treatments with combination chemotherapies. The first was a case of primary malignant lymphoma of the cervical spinal cord which had been previously treated with radiation to the spinal lesion and combination chemotherapies and entered complete remission. The patient was further treated for relapse with autologous bone marrow transplantation preconditioned with high-dose chemotherapy. Lung adenocarcinoma developed 5.5 years after the initial diagnosis. The second case of malignant lymphoma of lymph nodes did not respond to conventional combination chemotherapies and did not enter remission. Lung adenocarcinoma developed 1 year after the initial diagnosis. The two patients died of lung carcinoma. The clinical profiles of these cases are presented and the causal relationship of primary malignant neoplasms to the second malignant neoplasms is discussed.

Key words: malignant lymphoma – combination chemotherapy – second malignant neoplasm – lung adenocarcinoma

INTRODUCTION

An initial malignant lymphoma can be cured by an intensive combination of chemotherapy and radiation therapy, extending many patients’ lives. However, the emergence of second malignant neoplasms several years after initial treatment has been increasing recently. These treatments appear to be associated with an increase in second hematological malignancies, such as acute non-lymphocytic leukemia and myelodysplastic syndrome (1). A variety of solid tumors such as osteosarcoma, thyroid carcinoma, lung carcinoma, Wilms’ tumor, retinoblastoma, malignant lymphoma and central nervous system tumor have been reported as second malignant solid tumors (2–12). However, their association with solid tumors is very rare and the causal relationship is unclear.

We report two cases of second lung adenocarcinoma in primary non-Hodgkin’s malignant lymphoma and the causal relationship of the treatments and the second neoplasms is discussed.

CASE REPORT

Case 1

A 47-year-old male developed primary central nervous system (CNS) tumor of the cervical spine at the C3 level in April 1991. A biopsy specimen revealed diffuse small cleaved cells of B-cell type non-Hodgkin’s malignant lymphoma. He was treated with radiation to the spinal lesion with 44Gy, two courses of combination chemotherapy with M-BACOD (methotrexate, bleomycin, adriamycin, cyclophosphamide, vincristine, dexamethasone) and six intrathecal injections of MTX (methotrexate) and Ara-C (cytosine arabinoside). The tumor disappeared and complete remission was achieved. The patient complained of a cough and bone pain in October 1996. A chest X-ray revealed pleural effusion of the right lung. Computed tomography (CT) of the lungs revealed pleural effusion of the right lung and ipsilateral hilar lymph node swelling. A Ga
scintigram revealed accumulation in the right lung and a bone scintigram revealed multiple metastatic lesions. A cytological microscopic examination of the pleural fluid revealed adenocarcinoma. TNM staging revealed T4 N1 M1, stage IV. Chemotherapy with cisplatin, VP-16 and vindesine was ineffective. The patient died in September 1997. Autopsy revealed adenocarcinoma of the lung (Fig. 1), with metastasis to liver and bones. Recurrence of malignant lymphoma was not observed.

CASE 2

A 68-year-old female complained of lymph node swelling of the left neck in April 1996. CT revealed swelling of lymph nodes in the upper mediastinum, para-pancreatic and aortic regions of the abdomen. A biopsy specimen revealed non-Hodgkin's malignant lymphoma, diffuse, large, immunoblastic of B-cell type. Clinical staging was III. She did not have a tobacco smoking habit. The patient was treated with two courses each of the following three varying combination chemotherapies: (1) pirarubicin, cyclophosphamide, vindesine and prednisolone, (2) CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) and (3) DHAP (carboplatin, Ara-C and dexamethasone). The malignant lymphoma did not respond to the treatments and did not enter remission. The total doses of chemotherapeutic agents were pirarubicine 100 mg, cyclophosphamide 3.8 g, vincristine 6 mg, adriamycin 160 mg, carboplatin 900 mg and cytosine arabinoside 4.8 g. The patient complained of dyspnea and fever in February 1997. Chest X-ray revealed a pleural effusion and CT revealed a tumor shadow 4 cm in diameter at S10 of the right lung. A cytological microscopic examination of the pleural effusion and sputum revealed adenocarcinoma (Fig. 2). TNM staging revealed T4 N0 M0, stage IV. The patient died in May 1997. An autopsy was not performed.

DISCUSSION

The causative factors in the second malignant neoplasm suggest a relationship with radiation therapy, chemotherapy, a genetic predisposition to malignancy and finally immunosuppression (2-16). As for chemotherapy, it was suggested previously that certain alkylating agents were responsible for the pathogenesis of second malignant neoplasms (7,8). However, since most cases have recently been treated with combination chemotherapy, an increasing number of second malignant neoplasms are possibly attributable to the various chemotherapeutic agents, including topoisomerase II inhibitors.

Estimated rates of a second malignant neoplasm occurring were 12% after 5-24 years (2), 3.3% after 29 years (3) and 2.53% after 15 years (9), from the initial diagnosis. These represent a 20-fold (2) and 10-fold (3) increase in second malignant neoplasms compared with the expected rate for the general population. Neglia et al. (9) found 24 neoplasms of the central nervous system, 10 leukemias, 10 lymphomas and nine other neoplasms among 9720 children who had previously received chemotherapy during 4.7 years of follow-up. This represented a 7-fold increase in all cancers and a 22-fold increase in neoplasms of the central nervous system. In addition, a variety of solid tumors such as osteosarcoma, thyroid carcinoma, lung carcinoma, Wilms' tumor, retinoblastoma, malignant lymphoma and central nervous system tumor have been reported (2-12). These reports examined the long-term follow-up of the primary malignant neoplasms especially during childhood. There are a few reports of long-term follow-up in adults. More cases of second malignant neoplasms in adults should be collected.

The reported cases of lung cancer as the second malignant neoplasm were previously believed to be rare. However, Konits et al. (4) found six cases of lung carcinoma among 655 patients with Hodgkin's and non-Hodgkin's malignant lymphoma. Five of the six cases of lung carcinoma occurred in patients older than 45 who received follow-up check-ups for more than 4 years. Van
Leeuwen et al. (8) reported an increased risk of lung carcinoma in a study of Hodgkin's disease (HD) in 744 patients whose condition had been followed up for 17 years and the 15-year estimated cumulative risk of lung carcinoma was 6.2%. The report noted 14 cases of lung carcinoma, nine cases of non-Hodgkin's malignant lymphoma, 16 cases of leukemia and six cases of myelodysplastic syndrome. As for pathology, Konits et al. (4) reported three cases of adenocarcinoma, one case of squamous cell carcinoma and two cases of small cell carcinoma in six cases with lung carcinoma. List et al. (5) reported that small cell carcinoma appeared to be the predominant cell type (42%), followed by adenocarcinoma (31%), large cell carcinoma (14%) and squamous cell carcinoma (10%). Our two cases were adenocarcinoma. It is unclear whether our results indicate a high risk of adenocarcinoma as a second malignant neoplasm or if the occurrence is accidental. More cases need to be studied before a hypothesis can be reached. It has been reported that lung carcinoma predominantly occurred in previously irradiated areas (5,8). In contrast, twice the risk of developing lung cancer had been reported with chemotherapy than with radiotherapy in patients with HD (10). However, more recently, numerous patients received combination chemotherapy in addition to radiation therapy (11). In the present report, the first patient was treated with a combination chemotherapy in addition to radiation to the spinal cord. Lung carcinoma appeared outside the radiation field and the effect of radiation is unlikely to be related to the development of a second lung carcinoma. The second patient was treated solely by combination chemotherapy. These results suggested that the effects of varying chemotherapeutic agents are possibly related to the pathogenesis of second malignant neoplasms, although we could not specify any agent. The intervals from the diagnosis of malignant lymphoma and HD to the development of lung carcinoma ranged from 4.5 to 10 years (4) and that from HD was 8.1 years (8). In the first patient in our study, the interval was 5.5 years. However, it was shorter in the second patient, only 1 year, and the reason is unclear.

The occurrence of a second hematological malignancy caused by chemotherapeutic agents such as myelodysplastic syndrome and acute non-lymphocytic leukemia appears to be associated with both unbalanced and balanced chromosomal translocations (1). The effects of various chemotherapeutic agents on the chromosomes in secondary solid tumor has not been well studied.

Immunosuppression may occur within a malignant lymphoma itself, as malignant lymphoma of the central nervous system frequently occurs in patients with acquired immune deficiency (13) and our first patients had primarily malignant lymphoma of the central nervous system. Immunosuppression may also be caused by chemotherapy. Both causes of immune suppression may contribute to the pathogenesis of a second malignant neoplasm.

The genetic predisposition of the patients may also be responsible for the pathogenesis of a second malignant neoplasm. The mutations of the p53 tumor suppressor gene is frequently observed in a cancer-prone family with Li–Fraumeni syndrome (14). Recent studies have identified germline mutations of p53 gene found in blood leukocytes of patients with second malignant neoplasms (15,16). These results suggest that inactivation of the p53 gene may be involved in the development of second malignant neoplasms (15,16). However, we have not studied the mutation of p53.

The effect of high-dose chemotherapy on secondary malignancy should be considered (17). A French group reported 18 cases of new malignancy with an incidence of 8.9% at 5 years in 467 autologous transplant recipients, including eight cases of solid tumor (18). A study in Minneapolis reported seven solid tumors in 750 autologous transplant recipients (19). The kinds of tumor were not described in these reports.

Ongoing accurate long-term follow-up of patients who receive chemotherapy and/or radiation therapy is necessary for the early detection and treatment of second hematological and non-hematological malignancies.

References