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Four Cases of Therapy-Related Leukemia

Combination chemotherapy and radiation therapy have contributed to the successful treatment of various cancer patients. But the development of second malignancies is an inevitable complication of long-term cytotoxic treatment. The most serious and frequent of such complications is acute myelogenous leukemia (AML). Therapy-related leukemia is generally fatal. Since the number of patients exposed to chemotherapy is increasing each year, the clinical significance of this entity cannot be underestimated. There have been many investigations of therapy-related leukemia, but in Korea published reports are rare. We describe four such cases, involving one older female with lung cancer and three children with acute lymphoblastic leukemia (ALL) and malignant lymphoma. Alkylating agents were used for chemotherapy, and in one case, topoisomerase II inhibitor. Irrespective of the causative agents, the latency periods were relatively short, and despite induction chemotherapy in two, all survived for only a few months. During the follow-up of patients treated for primary malignancies, the possibility of therapy-related leukemia should always be borne in mind.

Key Words: *Neoplasms, second primary; Therapeutics; Leukemia*

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INTRODUCTION

The widespread use of intensive combination chemotherapy regimens and megavoltage radiation therapy has dramatically enhanced the long-term survival of cancer patients who in previous decades would have died. On the other hand, long-term cytotoxic treatment has led to the emergence of complications such as secondary malignancies, of which the most serious and frequent is myeloid leukemia. This was first reported in 1970 (1) following the use of an alkylating agent and there have been many subsequent investigations. According to some reports, approximately 10-15% of all cases of acute myelogenous leukemia (AML) are considered to be secondary or therapy-related (2, 3). We report here four cases of AML that developed after the treatment of primary malignancies which were either solid tumors or hematologic malignancies, and include a review of the literature.

CASE REPORTS

Case 1

A 66-year-old woman was admitted to Seoul National University Hospital with pancytopenia. Small cell lung cancer with multiple lymph node metastasis had been diagnosed 33 months previously, and thereafter she underwent chemotherapy and radiotherapy. A standard chemotherapeutic regimen including etoposide, ifosfamide, and cisplatin was administered for nine cycles and she was then followed up regularly. On admission, she complained of dyspnea, dizziness, generalized weakness, and epistaxis. Complete blood cell count showed hemoglobin 5.7 g/dL, WBC 2,200/μL, platelet $76 \times 10^3/\mu$L and blasts accounted for 35.4% of all nucleated cells seen on marrow smears. According to FAB classification, the morphological diagnosis was AML, M2. The patient was placed in supportive care without further chemotherapy and was still alive four months after the diagnosis.

Case 2

A seven-year-old boy was brought to Seoul National University Hospital with blasts in the peripheral blood. At the age of three years, ALL, L1 was diagnosed and he underwent a standard chemotherapeutic regimen with vincristine, L-aspaginase, methotrexate, and daunorubicine. Four months before admission, a follow-up bone marrow examination prior to coming-off-therapy revealed

myelodysplastic features and an increase of blasts, which accounted for 18.8% of all nucleated cells. Myelodysplastic syndrome, refractory anemia with an excess of blasts (MDS, RAEB) was diagnosed and low-dose cytosine arabinoside regimen was started, but blasts in the peripheral blood persisted for several months. AML, M4 was eventually diagnosed, but standard induction chemotherapy, followed by high-dose cytosine arabinoside treatment, failed to induce remission. Two months after starting his last course of chemotherapy, the patient died.

Case 3

A 15-year-old boy visited the pediatric emergency department with fever and vomiting. Two years previously, B-cell immunoblastic lymphoma had been diagnosed by cervical lymph node biopsy and treated by chemotherapy with vincristine, methotrexate, daunorubicine, L-asparaginase, and prednisolone, and with radiotherapy for the mediastinal mass. Examinations of chest-radiograph and laboratory findings showed pneumonic infiltration of both lung fields and markedly increased WBC counts. To control the pneumonia, antibiotic therapy was started. AML, M5b was diagnosed by bone marrow biopsy, but because of his critical condition, chemotherapy was not possible. On the 60th day of hospitalization, the patient died of acute respiratory distress syndrome.

Case 4

A 15-year-old girl suffered vaginal bleeding and epistaxis and was diagnosed as having ALL, L1. After two years of chemotherapy including L-asparaginase, vincristine, methotrexate, and daunorubicine, which induced complete remission, she was under regular follow-up for further two years. In the fourth year, MDS, RAEB was diagnosed by peripheral pancytopenia and bone marrow findings: blasts in the bone marrow accounted for 18% of all nucleated cells. After two months, these had increased to 40% and AML, M2 was diagnosed. The patient was reluctant to undergo chemotherapy, so courses of adriamycin and high-dose cytosine arabinoside were not completed. Four months after the most recent chemotherapy, the patient died of septic shock.

DISCUSSION

In spite of many investigations into therapy-related AML (t-AML) in other countries, published reports in Korea are rare (4, 5). The only systematic study was by KSPHO (the Korean Society of Pediatric Hematology-Oncology) and involved secondary malignancies after the treatment of childhood cancer. Among 24 cases enrolled in that study, AML was the most prevalent form, accounting for seven (6).

The clinical significance of the development of t-AML cannot be understated, and it is one of the many prices of success that medicine now faces. Because the number of patients exposed to chemotherapy is increasing each year and treatment of t-AML is not usually successful, it has become more problematic than primary cancer. The clinician must balance, in a treatment plan, the risks associated with the administration of alkylating agents and topoisomerase II inhibitors with the benefits achieved by such regimens.

Both chemotherapeutic agents and ionizing radiation can result in the cellular DNA damage. It is more often lethal to cells, but nonlethal and heritable mutations in a single somatic cell are also possible. The carcinogenesis is dependent on numerous factors, including type and schedule of chemotherapy, intensity of carcinogenic exposure, primary cancer, and host characteristics.

The four patients reported here include one elderly female with small cell lung cancer and three children, two with ALL and the other with malignant lymphoma. It is known that older patients have increased risk of therapy-related leukemia and that the latency period is shorter than in younger patients (7), but even so, three of our four patients were children, and except case 4, their latency periods were similar to those seen in older patients. According to the literature, the latency period ranges from five to seven years with alkylating agents and from six months to five years with topoisomerase II inhibitors (8). These four cases showed relatively short latency periods, however, irrespective of the causative agents (Table 1).

Table 1. Clinical characteristics of therapy-related leukemia

Case	Age/sex	Initial diagnosis	Secondary diagnosis	Preleukemic phase	Latency (months)	Suspected agent	RT
1	66/F	Lung cancer	AML, M2	-	33	Etoposide	+
2	7/M	ALL, L1	AML, M4	RAEB	33	Cyclophosphamide	+
3	15/M	NHL	AML, M5b	-	24	Cyclophosphamide	+
4	18/F	ALL, L2	AML, M2	RAEB	51	Cyclophosphamide	+

RT, radiation therapy; NHL, non-Hodgkin's lymphoma

Table 2. Laboratory and therapeutic informations of therapy-related leukemia

Case	Hb (g/dL)	WBC (/μL)	Platelet (×10³/μL)	Blasts (%)	Induction treatment	Survival after diagnosis (months)
1	5.7	2,200	76	35.4	ND†	4, alive
2	9.9	5,100	568	70.2	+	5 (9*)
3	5.4	230,000	45	42.6	ND†	2
4	9.5	3,900	28	40.0	+ (incomplete)	9 (11*)

*Survival time since diagnosis of therapy-related MDS, RAEB
†ND: not done

If the patient is free of primary disease, the diagnosis of t-AML or MDS is straightforward, especially when therapy is not current. There was no confusion in diagnosing these cases, and the clinical and morphological features were consistent. For several months two patients went through the preleukemic phases of RAEB, and in all cases the final outcome was AML, M2, M4, and M5 by the FAB classification. These findings are typical of t-AML. Cytogenetic clonal abnormalities can be observed in about 90% of therapy-related leukemia and most are abnormalities of chromosome 5 and/or 7 (9). Cytogenetic data were available only in the second case and the normal chromosome pattern on initial diagnosis of ALL shifted to deletion of the long arm of chromosome 9. Although cytogenetic findings were not available in other cases, they are not the essential criteria for confirmation of a diagnosis of t-AML. It should be emphasized, however, that to obtain appropriate information, such as cytogenetic findings, clinical suspicion of t-AML is important.

Early studies showed that prognosis was dismal, with a remission rate of only 10% (8). The results of aggressive induction chemotherapy were more encouraging, however, with remission rates of 30-60% reported (10). The median duration of remission was only a few months, however, implying no survival gain. Two of the four patients described in this report underwent induction chemotherapy but showed discouraging results (Table 2).

In conclusion, therapy-related leukemia is generally a fatal disease. We report four cases of t-AML caused by chemotherapy with alkylating agents in three cases and topoisomerase II inhibitor in one case. Despite induction chemotherapy in two, however, none showed increased survival time. If patients treated for primary malignancies were followed up more closely, more patients with therapy-related leukemia would be detected. The challenge of understanding the pathogenesis of t-AML and defining the contributing risk factors requires continued studies.

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