Acute Nonlymphocytic Leukemia, Preleukemia, and Solid Tumors Following Intensive Chemotherapy of Small Cell Carcinoma of the Lung

By Jens Pedersen-Bjergaard, Kell Østerlind, Mogens Hansen, Preben Philip, Anders G. Pedersen, and Heine H. Hansen

Six of 796 patients treated with intensive combination chemotherapy for small cell carcinoma of the lung developed overt acute nonlymphocytic leukemia (ANLL) (three patients) or preleukemia with severe refractory cytopenia and clonal cytogenetic abnormalities in bone marrow cells (three patients). The latent period to development of preleukemia or leukemia was less than two years in four of the six patients. The cumulative risk of preleukemia and leukemia according to a Kaplan-Meier estimate was 14.0% ± 6.9% (mean ± SE) four years after the start of treatment. The relative risk of overt ANLL was 77, since three cases were observed vs 0.039 cases expected, based on the age- and sex-specific incidence of acute nonlymphocytic leukemia in the general Danish population. The risk of secondary solid tumors was not increased. The possible causes of the exceptionally early appearance and very high cumulative risk of leukemic complications found in the present study, as compared to previous experience in other malignant diseases, is discussed, including the implications for future therapy of patients with small cell lung cancer.

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During the last decade, intensive chemotherapy of small cell lung cancer has resulted in a 70% to 80% frequency of objective tumor regression, a prolongation of median survival from three to four months in untreated patients to 12 to 14 monthes, and a 5% to 15% chance of long-term survival.1-4 Until now, few and most often single cases of secondary or treatment-related acute nonlymphocytic leukemia (ANLL) have been reported in this type of cancer.5-11 Nevertheless, due to the already poor survival from the primary tumor, these leukemias exert a marked negative effect on the possibility of long-term survival from small cell lung cancer.6,9,11

Cytogenetic investigation of bone marrow cells in ANLL following other types of primary tumor has revealed a characteristic pattern with partially or totally missing chromosomes No. 5 or No. 7.12-15 In previously reported patients with secondary leukemia following treatment for small cell lung cancer, however, only one patient possessed these characteristics,8 whereas three others showed uncharacteristic findings.7,8,10

Among a total of 796 consecutive patients treated with intensive chemotherapy for small cell carcinoma of the lung in two Copenhagen centers, we have recently observed three cases of overt ANLL and three cases of preleukemia with severe refractory cytopenia and characteristic chromosome abnormalities of the bone marrow. As these cases imply an extraordinarily high risk and an accelerated development of preleukemia and leukemia following current regimens for chemotherapy of small cell lung cancer, and as cytogenetic investigations were carried out successfully in all six patients, we found it justifiable to present these data.

PATIENTS AND METHODS

During the period April 1978 to October 1984, a total of 796 consecutive patients with newly diagnosed small cell carcinoma of the lung received combination chemotherapy in four prospective randomized studies. After admission, patients were informed of procedures and risks related to investigations and therapy according to Danish regulations for informed consent. This was followed by clinical staging, after which all patients received a combination of lomustine (70/mg² orally every fourth or seventh week), cyclophosphamide (1,000 mg/m² intravenously (IV) every fourth or seventh week), and vincristine (1.3 mg/m² IV weekly for five weeks, followed by 1.3 mg/m² IV every third or fourth week) combined with one or three of the drugs vepesid (etoposide), methotrexate, and doxorubicin. Radiotherapy was only used in a few patients for palliation in the terminal phase of the disease.

Patients were treated for a total period of 18 months or until progression of the disease or death. Patients alive at 18 months from the start of chemotherapy were restaged, and if they were found to be in complete remission, they were observed without further therapy. Preliminary results of these studies have been presented elsewhere.16-20 The courses of all patients were followed until death or Oct 1984.

In patients suspected to have preleukemia or ANLL, bone marrow cytology including cytochemistry was carried out for classification according to the French-American-British (FAB) proposals,21 together with cytogenetic studies as previously described.13,16 Preleukemia was diagnosed in patients with severe, refractory, and unexplained cytopenia, with <10% blasts plus promyelocytes in a hypocellular, normocellular, or hypercellular bone marrow and at least one of the clonal cytogenetic abnormalities 5q- or 7, or 7q-, or subsequent evolution to overt leukemia. Overt leukemia was diagnosed in patients with a hypercellular bone marrow with blasts plus promyelocytes >30%.

Risks of leukemic complications were evaluated in two ways. The cumulative risk of preleukemia and leukemia was estimated according to the method of Kaplan and Meier.22 The relative risk was assessed by comparing the observed number of overt secondary leukemias with the expected number of de novo ANLL calculated on the basis of person-years of observation and the age- and sex-specific incidence rates of ANLL for the general Danish population between 1973 and 1977.23 The relative risk of a secondary solid tumor was calculated in the same way, comparing observed with expected numbers of tumors.

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<th>4</th>
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<tr>
<td>Type of primary treatment and duration (mo)</td>
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<td>CCNU, ADM, VCR, CTX, VP16 (13)</td>
<td>CCNU, VCR, CTX, VP16 (18)</td>
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<td>3*</td>
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<td>—</td>
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<td>45, XY, –13, del 7(q22)</td>
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**Final stage of lung cancer**

**PD†**

**PD**

**PD**

**CR**

**CR**

**CR**

**CR**

Abbreviations: E, extensive disease; L, limited disease; CCNU, lomustine; VCR, vincristine; CTX, cyclophosphamide; VP16, vepesid; ADM, doxorubicin; MTX, methotrexate; NR, no response; PD, progressive disease; CR, complete remission.

* Died in the preleukemic phase.

† Clinically in CR, but brain metastases were found at autopsy.
RESULTS
Among a total of 796 patients treated for small cell lung carcinoma and observed for a total of 618.7 years, three cases of overt acute nonlymphocytic leukemia (ANLL) and three cases of preleukemia with severe refractory cytopenia and characteristic cytogenetic abnormalities in the bone marrow were observed. The clinical, cytologic, and cytogenetic characteristics for these six patients are shown in Table 1. One male and five females developed leukemic complications, three patients after chemotherapy with four drug combinations and three patients after six drug combinations. The latent period from the start of chemotherapy to development of preleukemia or overt leukemia varied between 11 and 43 months and was less than 24 months in four of the six patients. In five of the six patients (cases No. 2 through 6) there was a preleukemic phase, and two of these patients progressed to overt leukemia of the FAB type M2 (myeloblastic with maturation) during observation. The five patients with preleukemia all disclosed chromosome abnormalities characteristic of secondary leukemia with a partially or totally missing chromosome No. 7. Patient No. 1, however, showed several findings uncharacteristic for secondary ANLL. Thus, the leukemia in this patient developed with a latent period of only 11 months after the start of chemotherapy of lung cancer, there was no preleukemic phase, and the leukemia was of FAB type M5 (monocytic) with a normal karyotype in bone marrow cells.

At the time of diagnosis of preleukemia or overt leukemia, four patients were clinically in complete remission for the lung cancer (cases No. 1, 4, 5, and 6), whereas recurrent carcinoma was present in cases No. 2 and 3. At autopsy, however, an unexpected pituitary metastasis from the lung carcinoma was found in case No. 1. Following development of overt leukemia, two patients (cases No. 4 and 5) received intensive antileukemic chemotherapy, daunorubicin plus cytosine arabinoside and aclacinomycin A, respectively, but without obtaining remission, as they both died of complications one week after start of treatment. Three patients (cases No. 2, 3, and 6) with preleukemia and severe cytopenia died of complicating infections.

The cumulative risk of preleukemia or leukemia in all 796 patients was estimated as 4.4% ± 2.4% (mean ± SE) two years after the start of treatment and 14.0% ± 6.9% at four years (Fig 1). Excluding the atypical case No. 1, values of 4.0% ± 2.4% at two years and 13.6% ± 6.9% at four years were obtained. The relative risk of overt ANLL was 77, since three cases were found v 0.039 expected in the 796 patients observed, for a total of 618.7 years.

Secondary neoplastic disease other than leukemia was observed in four additional patients. These included non-Hodgkin's lymphoma (nodular, poorly differentiated lymphocytic), carcinoma of the uterine cervix, adenocarcinoma of the contralateral lung, and cerebral astrocytoma, diagnosed 26 to 65 months from start of chemotherapy for small cell lung cancer. The risk of developing a solid tumor was not increased, since four cases were observed v 5.9 cases expected (relative risk, 0.7).

DISCUSSION
Various observations indicate that the extraordinarily high risk of secondary preleukemia and ANLL found in the present study of patients treated intensively for small cell lung cancer is realistic, and not a statistical contingency or an accidental accumulation of random cases of de novo leukemia. In other and smaller series of similar patients, and in a somewhat larger study from Stanford University comprising 158 patients, including three cases of leukemia, even higher cumulative risks of secondary ANLL have been suggested or observed. Thus, in the Stanford study, the cumulative risk of secondary leukemia reached 25% three years after the start of chemotherapy for small cell lung cancer. In three of the studies, the combination chemotherapy administered included lomustine and cyclophosphamide.

The accelerated development of secondary leukemia observed in the present study supports the contention that the patients must have been subjected to an extraordinarily high leukemogenic exposure. In previous studies of other tumor types, only a minor fraction of patients who developed secondary leukemia had a latent period of less than two years from the start of treatment. Thus, in our own cumulative series of 55 patients with secondary leukemia, only nine (16%) (one of whom was case No. 4 in the present study) had a latent period below two years, as compared to four of six patients in the present study.

Very few cases of secondary ANLL following intensive chemotherapy of small cell lung cancer have previously been studied cytogenetically. The fact that five of six patients in the present study presented clonal cytogenetic abnormalities with a partially or totally missing chromosome No. 7, a highly characteristic feature in secondary preleukemia and secondary leukemia, strongly supports a causal relationship between the use of intensive chemotherapy and leukemic complications. We have previously shown that patients who develop leukemia with a very short or a very prolonged latent
period from the start of treatment for the primary tumor, often present clinical, cytologic, and cytogenetic features that are uncharacteristic for secondary ANLL. This suggests that such cases could represent "spontaneous" de novo leukemias, and therefore should be excluded from the risk calculations. Accordingly, patient No. 1 was excluded from the alternative calculation in the present study, but without any major influence on the overall risk of secondary leukemia.

As compared to most previous studies of patients with other types of tumors treated with alkylating agents, the present results indicate an approximately two- to ninefold higher risk per year of secondary leukemia. Thus, the cumulative risk in the present study was increasing by about 4.5% per year from one to four years after the start of treatment, whereas values in the range of 0.5% to 2% have been observed after chemotherapy of various other tumor types in other centers. In a recent comparative study from our institution, comprising patients with non-Hodgkin’s lymphomas treated with cyclophosphamide, patients with ovarian carcinoma treated with dihydroxybutylsulfan, and patients with Hodgkin’s disease treated with melphalan or nitrosoureas and chlorambucil, the cumulative risk of secondary preleukemia or overt ANLL was increasing by approximately 1% to 1.5% per year for all three types of tumor, from two to at least nine years after the start of chemotherapy.

Two circumstances may have contributed to the extraordinarily high risk of secondary ANLL observed in the present study. The first is a simultaneous administration of lomustine and cyclophosphamide; the second is the prolonged administration of chemotherapy for up to 18 months. In a previously published study from Canada of patients with multiple myeloma likewise treated with a nitrosourea, carmustine, and simultaneously or subsequently melphalan or cyclophosphamide, the cumulative risk of secondary ANLL was also very high: 17.4% at 50 months. This suggests that simultaneous treatment with two different alkylating agents may have an additive or even synergistic effect on leukemogenesis. As a significant alkylating agent dose-response relationship has previously been observed in secondary ANLL, the prolonged duration of chemotherapy may likewise have contributed to the high risk of secondary ANLL. However, chemotherapy of up to 18 months duration could hardly account for the accelerated development of leukemia observed in the present study.

No excess of secondary solid tumors was observed in the present study. We could therefore not confirm the highly increased risk of secondary solid tumors observed in another recently published study of long-term survivors of small cell lung cancer.

As in other series of small cell lung cancer, the general survival of patients in the present study was poor, with most patients dying of progressive carcinoma. Quantitatively, therefore, for the whole group of 796 patients, the secondary preleukemias and leukemias were a minor problem. Nevertheless, a cumulative risk of secondary leukemia of 14.0% within four years must cause serious concern for the small group of long-term survivors; especially so because other studies have shown that the risk of secondary leukemia is still continuously increasing for at least eight or nine years after the start of treatment with alkylating agents. Alkylating agents, which are among the most active drugs in the treatment of small cell lung cancer, have so far been considered almost indispensable for obtaining optimal results. However, regimens comprising only one alkylating agent or given for a shorter period of time may be equally effective but with a lower risk of leukemia. Recently, a new regimen of vepesid, cisplatinum, and radiotherapy has been introduced. If such types of treatment could replace the regimens containing alkylating agents, or if the load of alkylating agents could at least be reduced, the risk of secondary ANLL in patients with small cell lung cancer could possibly be eliminated or brought down to a more acceptable level.

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NOTE ADDED IN PROOF

Since the first submission of this manuscript, we have within a short period of time observed another three patients developing overt secondary ANLL after treatment with a combination of nitrosoureas and other alkylating agents. Two patients, one with an apudoma and another with planocellular lung cancer, developed secondary ANLL 13 and 63 months after the start of treatment with lomustine, cyclophosphamide, vincristine, and vepesid on the same regimen used for patients with small cell lung cancer. A third patient developed secondary ANLL 88 months after the start of treatment with lomustine, melphalan, methotrexate, and prednisone for breast cancer. These three cases further incriminate a combination of nitrosoureas and other alkylating agents as extremely leukemogenic.

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