Acute Nonlymphocytic Leukemia Following Etoposide and Cisplatin Combination Chemotherapy for Advanced Non–Small-Cell Carcinoma of the Lung

By Mark J. Ratain, Lynne S. Kaminer, Jacob D. Bitran, Richard A. Larson, Michelle M. Le Beau, Consuelo Skosey, Sandy Purl, Philip C. Hoffman, James Wade, James W. Vardiman, Karen Daly, Janet D. Rowley, and Harvey M. Golomb

Combination chemotherapy is frequently used in the therapy of advanced non–small-cell lung cancer (NSCLC), but late complications are rarely recognized because of the short survival of most patients. Of 119 patients with advanced NSCLC treated with cisplatin and other drugs, four patients developed acute nonlymphocytic leukemia (ANLL). All four patients received etoposide and cisplatin with or without vindesine. Leukemia was diagnosed at 13, 19, 28, and 35 months after start of treatment. Three patients had morphologic and/or cytogenetic features of acute leukemia with significant monoblastic involvement; the fourth patient had trilineage dysplasia and cytogenetic abnormalities more commonly associated with therapy-related leukemia. Detailed analysis of the subgroup who survived longer than 1 year (24 patients) suggests that high cumulative doses of etoposide are leukemogenic; the median etoposide dose was 6,795 mg/m² (first year only) in the four leukemic patients compared with 3,025 mg/m² in the 20 nonleukemic patients (P < .01). The rate of ANLL was 0.30 per person-year after the first year (95% confidence limits 0.11 to 0.90), with a cumulative risk of 15% ± 11% at 2 years, and 44% ± 24% at 2.5 years. We conclude that high doses of etoposide are potentially leukemogenic, and can induce a syndrome with features of acute monoblastic leukemia de novo that is distinct from other secondary leukemias.

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A CUTE NONLYMPHOCYTIC LEUKEMIA (ANLL) is a known late complication of chemotherapy and/or radiotherapy.1-12 Most reports to date explicitly implicate alkylating agents as the leukemogenic factor,1,4,7 and the incidence of ANLL is higher in those patients treated with both alkylating agents and radiotherapy.1 Therapy-related ANLL (t-ANLL) may be morphologically1 and cytogenetically1,11 distinguishable from acute leukemia arising de novo. Initial reports of t-ANLL were primarily among long-term survivors after curative therapy for Hodgkin’s disease and non-Hodgkin’s lymphomas.1,2 More recently, this late complication of cytotoxic therapy has been reported in patients with small-cell carcinoma of the lung1,6 and other solid tumors.3,4,8,9,11,12

Combination chemotherapy (often containing alkylating agents) is frequently used in the management of patients with advanced non–small-cell lung cancer (NSCLC), but late complications of therapy are rarely recognized due to the short survival of most patients.14 Many recent studies have used cisplatin-based regimens, often in combination with etoposide and/or vindesine14,16 to exploit possible synergy.17

We recently suggested in a preliminary report that the combination of cisplatin, etoposide, and vindesine is highly leukemogenic, based on the development of ANLL in three of 24 lung cancer patients who survived 1 year or more.18 After further follow-up of this cohort of 24 patients, we now report a fourth case of ANLL. Analysis of these patients provides circumstantial evidence that etoposide may be the leukemogenic agent, and that etoposide may induce a leukemia with the morphologic and cytogenetic features of acute monoblastic leukemia (AMoL), rather than those more commonly seen in t-ANLL due to alkylating agents.

MATERIALS AND METHODS

From February 1981 to September 1984, 119 patients with stage III NSCLC were treated with cisplatin-containing regimens at the University of Chicago and Michael Reese Medical Centers. Patients with metastatic disease were entered into a phase III trial comparing three cisplatin-based regimens (Table 1) with a fourth arm using cyclophosphamide, doxorubicin, methotrexate, and procarbazine (CAMP).19 Patients with unresectable stage IIIb disease were entered in a phase II trial of vindesine, etoposide, and cisplatin (VEP) using the same schedule described in Table 1. The patients who received CAMP have been excluded from the present analysis, since they received cyclophosphamide, a known leukemogenic drug,14,15 although there were no patients with secondary leukemia in this cohort of 35 patients, of whom five survived at least 1 year.

Eligibility criteria included: histologically confirmed NSCLC of stage IIIb, or stage IIIbM₁ with either malignant pleural effusion or T₄ lesions with mediastinal involvement; no prior chemotherapy; creatinine clearance >70 ml/min; and a Zubrod performance status ≤3. All patients were advised of procedures and attendant risk, and gave informed consent, in accordance with federal and institutional guidelines. Patients were hospitalized for administration of cisplatin to ensure adequate hydration. Cisplatin was administered over six to eight hours with mannitol diuresis. Etoposide and vindesine were administered in the outpatient clinic, using a 30 to 60...
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Table 1. Dose Schedules for VP, EP, VEP Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs</th>
<th>Dose</th>
<th>Schedule and Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>VP</td>
<td>Vindesine</td>
<td>3 mg/m²</td>
<td>Weekly IV for 12 weeks, then biweekly</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td>120 mg/m²</td>
<td>Every 3 weeks IV for 12 weeks, then every 6 weeks</td>
</tr>
<tr>
<td>EP</td>
<td>Etoposide</td>
<td>300 mg/m²</td>
<td>Weekly IV for 12 weeks, then biweekly</td>
</tr>
<tr>
<td>VEP</td>
<td>Vindesine</td>
<td>3 mg/m²</td>
<td>As per VP</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td>120 mg/m²</td>
<td>As per VP</td>
</tr>
<tr>
<td></td>
<td>Etoposide</td>
<td>300 mg/m²</td>
<td>As per EP</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td>120 mg/m²</td>
<td>As per VP and EP</td>
</tr>
</tbody>
</table>

Abbreviation: IV, intravenously.

Table 2. Summary of Clinical, Morphologic, and Cytogenetic Features of Leukemic Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Radiotherapy</th>
<th>VDS</th>
<th>VP16</th>
<th>DDP</th>
<th>Time to ANLL (mo)</th>
<th>Morphologic Classification</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57/F</td>
<td>No</td>
<td>0</td>
<td>7,350</td>
<td>603</td>
<td>28</td>
<td>t-ANLL</td>
<td>46,XX(22%)/45,XX,-5,-7,+der (5)t(5;7)(q12;p11) (56%)/45,XX, same, del(12)(p11p13) (11%)/45,XX,-5,-7,+der(5)t(17;?)q25,?q22.</td>
</tr>
<tr>
<td>2</td>
<td>58/F</td>
<td>No</td>
<td>77</td>
<td>7,950</td>
<td>590</td>
<td>19</td>
<td>AML;</td>
<td>46,XX(27%)/46,X,t(X;10)(p11p11)(70%)/SCA;46,X.t(X:10);t(17;?)q27;2;?(3)%</td>
</tr>
<tr>
<td>3</td>
<td>59/M</td>
<td>Yes</td>
<td>35</td>
<td>4,382</td>
<td>120</td>
<td>13</td>
<td>AML;</td>
<td>46,XY(53%)/46,XY,t(9;11)(p22;q23;2;?)q21(47%)/46,XX(56%)/46,XX,t(9;11)(p22;2;?)q21(95%)</td>
</tr>
<tr>
<td>4</td>
<td>70/F</td>
<td>No</td>
<td>0</td>
<td>6,240</td>
<td>120</td>
<td>35</td>
<td>AML;</td>
<td>46,XX(56%)/46,XX,t(9;11)(p22;2;?)q21(95%)</td>
</tr>
</tbody>
</table>

Abbreviations: VDS, vindesine; VP16, etoposide; DDP, cisplatin; t-ANLL, therapy-related acute nonlymphocytic leukemia; AML, acute myeloblastic leukemia; AMML, acute myelomonocytic leukemia; SCA, single cell abnormality.

*First year only.

RESULTS

Of the 24 1-year survivors, 17 were men and seven were women. The median age was 56 years (range, 38 to 69 years). Eighteen patients had metastatic disease, and six were stage IIIM0. Twelve patients had adenocarcinoma, eight patients had squamous cell carcinoma, and four patients had large cell undifferentiated carcinoma. Three patients received only vindesine and cisplatin, nine patients only etoposide and cisplatin, and 12 patients received all three drugs. Nineteen patients received radiotherapy to limited fields, usually in the thorax. Only two patients received pelvic radiation. The median dose in the 19 patients was 30 Gy (range, 12 to 60 Gy).

Nineteen patients died after a median survival of 15 months (range, 12 to 26 months) without evidence of ANLL, one patient is alive (for 32 months) without evidence of ANLL, and four patients developed ANLL. The clinical and pathologic features of the latter group are summarized in Table 2, and their individual case reports follow.

Patient No. 1

A 57-year-old woman presented in September 1981 with bilateral pulmonary nodules. Bronchoscopy was positive for adenocarcinoma. In November 1981, she began therapy with cisplatin and etoposide. A partial response was documented in December 1981. cisplatin was discontinued in April 1983 due to mild renal insufficiency, but etoposide was continued until March 1984. Blood counts at that time were hemocrit 22%, WBC count 1,700/μL, and platelets 65,000/μL. In April 1984, bone marrow aspiration and biopsy demonstrated a normocellular marrow with myelodysplasia but <5% myeloblasts. She was treated with cis-retinoic acid for 3 months without improvement. A second bone marrow examination in November 1984 was hypercellular with trilineage dysplasia and 25% to 30% myeloblasts. Cytogenetic analysis demonstrated a mosaic female karyotype characterized by three related abnormal clones, each with abnormalities of chromosomes 5 and 7 (Table 2). No further therapy was administered, and the patient died in November 1984.

Patient No. 2

A 58-year-old woman presented in May 1982 with a right lung mass and pleural effusion. Sputum cytology and thoracentesis were positive for adenocarcinoma. A bone scan showed increased uptake in the thoracic spine and right femur consistent with metastases. In June 1982, she began receiving VEP therapy with stabilization of her disease. In December 1983, she presented with dementia and ataxia. Lumbar puncture revealed malignant cells consistent with adenocarcinoma in the spinal fluid. An Ommaya shunt was implanted, and intraventricular methotrexate therapy (with oral minute infusion of etoposide and a rapid bolus for vindesine. Patients received at least two cycles (6 weeks) of therapy before re-evaluation. The therapy was discontinued in the event of progressive disease, unacceptable toxicity, or patient request. Palliative radiotherapy was allowed at any time. Twenty-four patients survived for more than 1 year after initiation of therapy (either chemotherapy or radiotherapy), and these patients were analyzed further for risk factors for ANLL. Patients who survived <1 year were not considered to be at risk of developing ANLL because the reported latent period for this complication is rarely this short. In fact, none of these 95 patients were noted to develop ANLL. The observation period was defined as time from start of therapy to death, ANLL (or the preleukemic phase), or September 18, 1986. The risk period was defined as the observation period following the first year. Risk estimates were determined by dividing the number of failures by the total person-years of risk, and an asymptotic maximum likelihood estimation was used to determine 95% confidence limits. The cumulative risk of ANLL was also estimated according to the method of Kaplan and Meier. The Mann-Whitney test was used to detect differences between the leukemic and nonleukemic patients.

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folinic acid) was administered weekly. In January 1984, her WBC count was noted to be 64,000/μL, mostly monoblasts. The bone marrow was hypercellular with ~80% monoblasts and promonocytes, consistent with AMoL. Cytochemical staining supported the monocytic origin of the leukemic cells, as the alpha naphthyl esterase reaction was strongly positive in 89% of the marrow blasts and was completely inhibited by sodium fluoride. Cytogenetic analysis demonstrated a reciprocal translocation of the short arms of chromosome 10 and the X chromosome (Table 2). Treatment was begun with low-dose subcutaneous cytosine arabinoside (10 mg/m² twice daily), but the patient died ten days later of acute renal failure.

Patient No. 3
A 59-year-old man presented in February 1984 with a left pleural effusion. Thoracentesis and pleural biopsy were both positive for adenocarcinoma. Radiotherapy to the left hemithorax (30 Gy in 15 fractions) was administered in March 1984. He began receiving VEP therapy in April 1984, which was complicated by acute renal failure. In May 1984, therapy was restarted using only etoposide and vindesine. He continued without evidence of disease progression until January 1985 when a complete spinal cord compression (at T-8) was diagnosed. A laminectomy was performed, followed by an additional 20 Gy (10 fractions) to the thoracic spine. In April 1985, the patient complained of severe fatigue, and a complete blood count revealed a hematocrit of 21%, WBC count of 1,100/μL, and a platelet count of 218,000/μL. A bone marrow biopsy demonstrated total replacement of the marrow by malignant cells, initially felt to be metastatic adenocarcinoma, but later confirmed as poorly differentiated AMoL. Cytogenetic analysis demonstrated a reciprocal translocation involving the short arm of chromosome 9 and the long arm of chromosome 18 (Table 2). The patient was treated with cyclophosphamide 1,000 mg/m² and doxorubicin 40 mg/m² monthly for four cycles, and had no residual leukemia in September 1986. A follow-up bone marrow exam 2 months later also showed no evidence of leukemia, but the patient died of progressive carcinoma in January 1986.

Patient No. 4
A 70-year-old woman presented in August 1983 with a right lung mass. Needle aspiration of the mass was positive for adenocarcinoma. Chest computed tomography (CT) scan demonstrated bilateral hilar and mediastinal adenopathy, a right middle lobe mass, and an enlarged left adrenal gland. In October 1983 she was begun on etoposide and cisplatin but received only one dose of cisplatin because of nephrotoxicity. In fact, this allowed these patients to receive higher doses of etoposide. As shown in Fig 2, there appears to be a relationship between the total dose of etoposide during the first year of therapy and the development of ANLL. Other reports have suggested a similar dose effect for the alkylating agents. However, we cannot exclude the possibility that the other known leukemogenic factors present in these patients (ie, smoking, radiation therapy, cisplatin), or even unknown factors such as the Tween 80 required for formulation of the etoposide, were contributory to the development of ANLL, especially in patients no. 2, 3, and 4. The risk of ANLL in our patient population probably exceeds 11% per person per year with a cumulative risk of 44% ± 24% at 2.5 years, which is much higher than that during the same period was 1.42 per person-year (95% confidence limits are 0.91 to 2.23). The cumulative risk of ANLL by Kaplan-Meier analysis was 15% ± 11% at 2 years and 44% ± 24% at 2.5 years (Fig 1).

Comparison of Leukemic and Nonleukemic Patients
Nonparametric testing (Mann-Whitney) was used to compare the leukemic (n = 4) and nonleukemic patients (n = 20). There were no significant differences in the cumulative vindesine or cisplatin doses during the first year of observation (Table 3). However, the patients who eventually developed ANLL had received significantly more etoposide than the nonleukemic patients (Table 3, Fig 2).

DISCUSSION
This is the first report of ANLL following combination chemotherapy with cisplatin and etoposide. None of the leukemic patients ever received classical alkylating agents that have previously been associated with the development of t-ANLL. Also, radiotherapy does not appear to be causative in these cases, since only patient no. 3 received radiotherapy and only to a limited thoracic port, not to the pelvis as has previously been associated with t-ANLL.

Our circumstantial data suggest that high cumulative doses of etoposide may be causative in the development of ANLL. All four leukemic patients received both cisplatin and etoposide, but patients no. 3 and 4 received only a single dose of cisplatin because of nephrotoxicity. In fact, this allowed these patients to receive higher doses of etoposide. As shown in Fig 2, there appears to be a relationship between the total dose of etoposide during the first year of therapy and the development of ANLL. Other reports have suggested a similar dose effect for the alkylating agents. However, we cannot exclude the possibility that the other known leukemogenic factors present in these patients (ie, smoking, radiation therapy, cisplatin), or even unknown factors such as the Tween 80 required for formulation of the etoposide, were contributory to the development of ANLL, especially in patients no. 2, 3, and 4. The risk of ANLL in our patient population probably exceeds 11% per person per year with a cumulative risk of 44% ± 24% at 2.5 years, which is much higher than that during the same period was 1.42 per person-year (95% confidence limits are 0.91 to 2.23). The cumulative risk of ANLL by Kaplan-Meier analysis was 15% ± 11% at 2 years and 44% ± 24% at 2.5 years (Fig 1).
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The median cumulative dose of etoposide received by these patients was 5,795 mg/m² for leukemic patients and 3,025 mg/m² for nonleukemic patients. This difference was statistically significant (P < .01, Mann-Whitney).

Although cisplatin and etoposide are often used in the management of germ cell tumors and small cell carcinoma of the lung, there have been no reports of this combination being leukemogenic. This may be due either to differences in scheduling, or to the relatively low cumulative doses of etoposide received by these patients. In four 3-week cycles of cisplatin/etoposide as usually administered to patients with germ cell tumors, only 2,000 mg/m² etoposide is administered, using 100 mg/m² daily doses. Similar schedules have been used in small cell carcinoma, with etoposide doses of 300 to 500 mg/m² per 3- to 4-week cycle. Thus, it is quite possible that the high incidence of ANLL in our patients is due to the unusual schedule and dose intensity of etoposide used in this study (Table 1). Our four leukemic patients received >4,000 to 8,000 mg/m² of etoposide in 1 year, and the nonleukemic patients received a median of 2,000 mg/m² for their NSCLC, usually 300 mg/m² per week.

Etoposide-induced ANLL may represent a new syndrome that differs from classical t-ANLL. Although the clinical features of three of these patients raise the question whether they actually represent ANLL de novo, this is statistically unlikely. Patient no. 1 had trilineage dysplasia and the cytogenetic abnormalities of chromosomes 5 and 7 frequently observed in t-ANLL, but the other three patients had the morphologic and/or cytogenetic characteristics usually seen with AMoL. Moreover, patients no. 2, 3, and 4 lacked a preleukemic phase, which was noted in 76% of the 63 patients with t-ANLL reported by Le Beau et al. Finally, the latency period from the start of therapy to overt leukemia in patients no. 2 and 3 was short, ie, 13 and 19 months. This compares with a median of 58 months in the study of Michels et al and to a median of 56 months in the 63 patients with t-ANLL in our previous series. However, Pedersen-Bjergaard et al recently reported four patients (of six) with small cell carcinoma of the lung who developed ANLL after a latency period of <2 years.

As noted earlier, most patients with t-ANLL secondary to alkylating agents have losses of all or part of the long arm of chromosomes 5 and 7, and these abnormalities were present in patient no. 1. Two of our patients, however, had chromosome abnormalities characteristic of AMoL, namely translocations involving chromosomes 9 and 11, with breakpoints at 9p22 and 11q23. AMoL has rarely been observed as a therapy-related leukemia; it did not occur in any of the 26 cases reported on by Rowley et al. It is of interest that we have also studied one other patient who developed secondary AMoL, but she had been treated for ovarian carcinoma with alkylating agents. Michels et al noted two cases of AMoL in their series of 65 patients with secondary leukemia. Two other patients with a secondary AMoL and a t(9;11) have been reported on separately by Weh et al and Dewald et al. The child described in the former report received combination chemotherapy including teniposide, another epipodophyllotoxin and a topoisomerase II inhibitor, and cisplatin, and AMoL was diagnosed 38 months after beginning therapy; there was no preleukemic phase. The patient reported on by Dewald et al also did not have a preleukemic phase before presentation with AMoL 7 years after therapy.

Weh et al proposed that acute leukemias with a specific translocation be considered primary, not secondary, leukemias. This recommendation is based on their concern that such patients might otherwise not be treated in view of the generally poor response of patients with t-ANLL to therapy. Three of our own patients plus the other five cases noted had features usually associated with AMoL de novo, and these leukemias may have developed independent of the prior cytotoxic therapy received. A similar argument may be made for three other patients whom we have studied, each of whom developed acute promyelocytic leukemia with a t(15;17); two had received radiotherapy only, neither had a preleukemic phase, and the latent period was 23 and 56 months. However, it is equally plausible that these specific chromosomal rearrangements were induced by mutagenic treatment, and

Table 3. Comparison of Leukemic and Nonleukemic Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>VDS</th>
<th>VP16</th>
<th>DDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemic</td>
<td>4</td>
<td>21 (0-77)</td>
<td>6,795 (4,382-7,950)</td>
<td>355 (120-603)</td>
</tr>
<tr>
<td>Nonleukemic</td>
<td>20</td>
<td>17 (0-77)</td>
<td>3,025 (0-8,155)</td>
<td>485 (120-727)</td>
</tr>
</tbody>
</table>

Abbreviations: VDS, vindesine; VP16, etoposide; DDP, cisplatin.

*First year only.
†Range
‡P < .01 (Mann-Whitney).

Fig 2. Comparison of cumulative etoposide doses received by the leukemic and nonleukemic patients. The median cumulative etoposide dose (indicated by the bar) was significantly higher in the leukemic patients (P < .01, Mann-Whitney). The sole nonleukemic patient alive without ANLL received 2,005 mg/m² of etoposide. (VP-16, etoposide).
that once these genetic rearrangements had occurred, the subsequent leukemia manifest the same clinical features typically seen when that particular chromosomal abnormality occurs spontaneously. For reasons not yet clear, it seems likely that high doses of etoposide, and possibly teniposide, may induce genetic mutations that result in acute leukemia with a monoblastic phenotype.

The mechanism for malignant transformation by etoposide may differ from that of alkylating agents due to the different molecular pharmacology of these drugs. Alkylating agents are cytotoxic because of their ability to form cross-links with DNA. Etoposide also interacts with DNA, by forming a ternary complex with topoisomerase II, which blocks the catenation activity of the enzyme leading to DNA strand breakage. It has also been suggested that etoposide may cause DNA damage via a dehydrogenase-induced free radical intermediate. In addition, it is possible that cisplatin may have contributed to the leukemogenesis in these patients, since it also acts to cross-link DNA.

Although etoposide has not previously been demonstrated to be leukemogenic in humans, the topoisomerase II inhibitors are extremely potent clastogens in vitro, producing a high frequency of sister chromatid exchange and other chromosomal aberrations. The mutagenicity of the closely related drug teniposide appears to be highly site-specific, and thus teniposide-induced (or etoposide-induced) neoplasms might produce a unique clinical syndrome. Oncologists must be alert to the fact that increasing numbers of patients are being exposed to very potent mutagenic chemicals in an effort to treat malignant diseases effectively. The careful description of untoward consequences of some of these drugs, especially when used at high doses, will help to minimize these consequences. Thorough investigation of the few patients who unfortunately develop leukemia will provide critical insights into the mechanisms associated with leukemogenesis.

ACKNOWLEDGMENT

The authors thank Dr Richard Schilsky for his many helpful comments and Dora Currin for preparation of the manuscript.

NOTE ADDED IN PROOF

Fenaux et al recently reported a case of AML following combination chemotherapy for osteosarcoma, associated with t(9;11)(p21;q23). This case also had a short latency period of 11 months, but the patient did not receive either etoposide or cisplatin.

REFERENCES

19. Hoffman PC, Bitran JD, Golomb HM, Albain KS, Skosey CA: Do high dose cisplatin regimens add to the therapy of metastatic
Acute nonlymphocytic leukemia following etoposide and cisplatin combination chemotherapy for advanced non-small-cell carcinoma of the lung

MJ Ratain, LS Kaminer, JD Bitran, RA Larson, MM Le Beau, C Skosey, S Purl, PC Hoffman, J Wade and JW Vardiman