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Short communication

Acute nonlymphocytic leukemia following chemotherapy with cisplatin and etoposide for non-small-cell carcinoma of the lung: case report

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Summary. A case of acute nonlymphocytic leukemia (ANLL) following chemotherapy with cisplatin (CDDP) and etoposide (VP16) for non-small-cell lung cancer (NSCLC) diagnosed 24 months before is reported. Although the fortuitous occurrence of two unrelated malignancies cannot be excluded, the hypothesis of secondary leukemia must be taken into account. The clinical and experimental data implying these agents, generally considered to be noncarcinogenic in man, in the occurrence of secondary malignancies are briefly discussed.

Introduction

Since the introduction of effective treatments for neoplastic diseases, various late complications of those treatments have been described. Among those complications, secondary malignancies and especially acute leukemias are probably the most dreadful. The secondary leukoses are principally observed after treatment with some chemotherapeutic agents, mainly alkylating agents, nitrosoureas and procarbazine, and after combined radio- and chemotherapy [4, 11]. Other agents, however, have the reputation of being only slightly leukemogenic, if at all, such as antimetabolites and plant alkaloids [4, 11]. We report a case of acute nonlymphocytic leukemia (ANLL) that occurred in a patient with non-small-cell lung cancer (NSCLC) who was treated with cisplatin (CDDP) and etoposide (VP16), two drugs considered to belong to the latter category above.

Case report

In September 1984, squamous-cell lung cancer with mediastinal involvement and carcinomatous lymphangitis of the left lung was diagnosed in a 64-year-old patient with no history of hematological disease or treatment with radiotherapy, chemotherapy or immunosuppressive drugs. Hematological data were normal.

The patient was given ten courses of chemotherapy consisting of 60 mg/m^2 CDDP on day 1 and 120 mg/m^2 VP16 on days 1–3, repeated every 3 or 4 weeks. The response was favourable and the patient remained untreated for 8 months, after which a local recurrence was demonstrated. The initial chemotherapy was then resumed at the same doses. The hematological data were normal at that time. However, after two courses, the VP16 dose was reduced to 90 mg/m^2 due to leukopenia and thrombocytopenia.

Since August 1986 chemotherapy had been stopped because of increasing pancytopenia (WBC, 2.93×10^9/l, with 31% neutrophils, 53% lymphocytes and 12% monocytes; platelets, 40×10^9/l; hemoglobin, 114 g/l). A bone marrow aspiration showed the presence of 8% myeloblasts (peroxidase- and chloroacetate esterase-positive) in poorly cellularized marrow and the absence of neoplastic cells.

Further marrow aspirates demonstrated an increasing percentage of myeloblasts, with numerous immature monocytes (acute nonlymphocytic leukemia (ANLL) type M4, according to the FAB classification [2] (after 1 month: 14% myeloblasts, 15% monocytes; after 2 months: 37% myeloblasts, 4% monocytes; peripheral blood after 1 month: WBC, 2.84×10^9/l, with 9% neutrophils, 56% lymphocytes, 29% monocytes and 2% blasts; platelets, 21×10^9/l; hemoglobin, 90 g/l; peripheral blood after 3 months: WBC, 1.97×10^9/l, with no neutrophils, 50% lymphocytes, 20% monocytes and 25% blasts; platelets, 8×10^9/l; hemoglobin, 66 g/l). A bone marrow biopsy did not show any neoplastic cells. A cytogenetic study conducted on the bone marrow blasts revealed complex abnormalities in the G band, with trisomy 8 and the presence of three additional nonidentified markers.

Treatment with low-dose cytosine arabinoside (10 mg/m^2 given subcutaneously every 12 h) [6] was given for 2 weeks, with no favourable response. The patient refused further intensive chemotherapy. On December 25, 1986, he died of gastrointestinal bleeding; he had received 15 courses of CDDP (total dose, 900 mg/m^2) and VP16

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(total dose, 5,130 mg/m^2). A myelodysplastic syndrome (refractory anemia with excess of blasts: RAEB) was diagnosed 24 months after the beginning of chemotherapy [3]; this syndrome underwent transformation into acute myelomonoblastic leukemia after 6 weeks.

Discussion

Although the drugs known to be leukemogenic principally include alkylating agents, nitrosoureas and procarbazine, CDDP has been demonstrated to be mutagenic and carcinogenic in animals [4, 5, 10]. Recently, Kempf and Ivankovic [9] observed the development of renal fibrosarcomas and leukemias of the myeloid lineage in rats treated with CDDP; 24% of the animals that survived for >100 days after chemotherapy with CDDP developed leukemia.

In humans, cases of leukemia secondary to treatment with CDDP, vinblastine and bleomycin for testicular tumors have been reported [8, 13, 17]. Bassett and Weiss [1] reported one case of acute leukemia after treatment with CDDP alone for carcinoma of the bladder. In 1987, Ratain et al. [15] reported an increased risk of ANLL in patients treated for NSCLC with CDDP, VP16 and vindesine. Of 24 patients surviving for >1 year after the onset of their disease, 4 presented with secondary leukosis; the leukemic risk was correlated with the total dose of VP16 and not with CDDP or vindesine (two patients developed leukosis after one dose of CDDP). The interval before the onset of secondary leukemia (13, 19, 28 and 35 months) was shorter than those usually described after the administration of alkylating agents (50.6 ± 17 months, with a range of 28–97 months in the review published by de Gramont et al. [7]; a median of 58 months, with a range of 11–192 months according to Michels et al. [12]).

As the epipodophyllotoxins – VP16 and teniposide – cause breaks in DNA strands by forming a ternary complex with topoisomerase II, they might be expected to be carcinogenic [16]. According to Pui et al. [14], treatment with epipodophyllotoxins may be a causative factor in the development of secondary acute myeloid leukemia in children previously treated for acute lymphoid leukemia. In our patient, the interval between the onset of chemotherapy and the appearance of secondary leukemia was also shorter (24 months) than those usually described after treatment with alkylating agents. This case must be related to the four patients reported by Ratain et al. [15] as well as to those reported by Pui et al. [14]. We cannot with certainty rule out the possibility that our patient successively presented with two unrelated malignant diseases, with a 2-year interval between their occurrences; however, the hematological data indicate secondary leukemia, beginning with a myelodysplastic syndrome (RAEB), followed by an acute leukemia characterized by severe cytopenia rather than hyperleukocytosis.

The cytogenetic findings do not enable us to determine whether this was a primary or secondary leukosis: trisomy 8 is one of the most often observed abnormalities in "de novo" acute myeloblastic leukemia, but it can also be seen in secondary leukemias and myelodysplastic syndromes, albeit less frequently than the abnormalities involving chromosomes 5 (5q- or -5) and 7 (-7) [4, 11, 18]. We think it important that such cases be reported so as to enable the confirmation or exclusion of a leukemogenic effect of the agents involved.

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