Secondary acute myeloid leukemia following treatment with VP16-containing regimens for non-Hodgkin's lymphoma

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We report on two patients who developed a secondary acute myeloid leukemia (sAL) after treatment for non-Hodgkin's lymphoma (NHL) with regimens containing low to intermediate doses of VP16. Clinical and hematologic features in these two patients were consistent with epipodophyllotoxin-associated sAL. In one case, a rearrangement of chromosome band 11q23 was detected.

Etoposide or VP16 is an epipodophyllotoxin-derivate targeting the enzyme topoisomerase II. In the last few years, a number of reports have focused on the risk of secondary acute myeloid leukemia in patients treated with regimens including epipodophyllotoxins for prior independent malignancy.[1,2] The risk of sAL is related both to the cumulative dose and to the schedule of administration.[3,4]

Among 89 adult patients with NHL treated at our Institution with regimens containing low to intermediate cumulative doses of VP16, two cases developed acute myeloid leukemia.

Patient #1. A 41-year-old woman with diffuse large cell NHL stage IVA, received VACOP-B[5] for 12 weeks. Because of disease progression, she underwent salvage therapy with VIM-Ara-C (VP16 + ifosfamide + mitoxantrone + cytosine arabinoside) plus G-CSF. Seventeen months from diagnosis, the patient developed acute leukemia with central nervous system involvement. Bone marrow blasts showed a myelomonocytic morphology. Blast cells were positive for CD34, CD33, HLA-DR, and CD11c. Cytogenetic analysis on marrow cells revealed 46,XX, t(9;11)(p22;q23). The patient died after a salvage attempt high-dose Ara-C. The cumulative doses of drugs administered prior to leukemic evolution were: VP16 2,130 mg/m^2, doxorubicin 300 mg/m^2, mitoxantrone 40 mg/m^2.

Patient #2. A 67-year-old man with a peripheral T-cell non-Hodgkin's lymphoma, stage IV A (PCR assay positive for TCR-γ), was treated with P-VEBEC[6] plus G-CSF. Total exposure to VP16 was 400 mg/m^2 and to epirubicin 200 mg/m^2. At disease progression, he was treated with vincristine plus cyclophosphamide. Twelve months from diagnosis, he developed an acute monoblastic leukemia with skin and gum involvement. Marrow cells were positive for CD13, CD11c, and HLA-DR. PCR assay on cutaneous biopsy failed to show any rearrangement of TCRγ. The patient died one week after the diagnosis of leukemia.

The clinical and molecular findings in these two patients are consistent with epipodophyllotoxin-related sAL.[7,8] In both patients leukemia developed after a short latent period without a detectable preleukemic phase and the phenotype was monocytic. In patient #1 marrow blasts showed a t(9;11)(p22;q23) at cytogenetic analysis. The strong association between rearrangement at chromosome band 11q23 and previous therapy with topoisomerase II inhibitors, primarily epipodophyllotoxins, has been extensively elucidated at the molecular level.

Thus far, no cases of sAL with features of topoisomerase-associated leukemia have been reported in NHL patients treated with chemotherapy containing standard doses of VP16. The development of VP16-related sAL has been recently observed following exposure to low doses of VP16 in one patient with Hodgkin's disease and one with virus-associated hemophagocytic syndrome.[9] In our patients, the leukemogenic potential of VP16 may have been enhanced by the concomitant use of other potentially leukemogenic agents such as anthracyclines and mitoxantrone (intercalative agents acting on topoisomerase II), and cyclophosphamide. On the other hand, anthracyclines are administered to relatively low cumulative doses because of their cardiac toxicity, and cyclophosphamide was associated with a nonsignificant increased risk of secondary leukemia in NHL patients.[10] In addition to antineoplastic drugs, our two patients received G-CSF. To date, it is unknown whether this drug may accelerate the development of acute leukemia after genetic damage of hemopoietic stem cells by epipodophyllotoxins.

In conclusion, our data show that VP16-containing regimens currently used in the treatment of NHL may carry a risk of secondary acute leukemia, even after relatively low cumulative exposure to VP16. Although sAL seems an infrequent event, this complication should be considered because of the increasing use of VP16 in the chemotherapy of NHL.

Key words

VP16, secondary leukemia

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Pulmonary multinodular relapse of non-Hodgkin's lymphoma

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We describe here a case of pulmonary multinodular relapse of non-Hodgkin's lymphoma following autologous stem cell transplantation.

A 44-year-old patient was admitted for autologous peripheral stem cell transplantation. His diagnosis was diffuse large cell B lymphoma, stage II with bulky disease. After an initial complete remission he had relapsed and a second partial remission was achieved with ESHAP chemotherapy.

Transplantation was performed without incidences; in computerized tomography (CT) revealed two small para-aortic lymph nodes, which were evaluated by gallium scan showing their residual nature, thus the patient was considerd to have achieved complete remission. Radiotherapy was administered to the bulky zone and a new CT showed no change in the size of residual nodes, but small nodular images appeared in the lung parenchyma. Chest radiography showed a pattern of small, ill-defined nodular images (Figure 1). At this point, six months after transplantation, the patient's only complaint was mild cough, with no dyspnea or fever. Physical examination yielded no significative findings. The platelet count was 35×10^9/L, attributed to delayed recovery of platelets after transplantation. Several tests were performed in order to determine the nature of the pulmonary disease.

Except for the platelet count, the rest of the blood count was within normal ranges as were the lactate dehydrogenase concentration and arterial O_2 saturation. Mantoux test and serology for *Aspergillus* were negative and so, too, was cytomegalovirus antigen detection. Fibrobronchoscopic findings were nonspecific; cytological analysis of bronchoalveolar lavage (BAL) specimens demonstrated a hemorrhagic background and the presence of hemosiderin-laden macrophages. Bacteriologic cultures and fluoroscopy for *Mycobacteria* were negative. This led to the diagnosis of alveolar hemorrhage, prompting an intensive schedule of platelet support in order to maintain the platelet count above 50×10^9/L.

Three weeks later, the patient's status remained unchanged, and a new radiograph showed the growth of nodules. In view of this progression, regardless of the patient's good status, an open lung biopsy was performed. Histopathologic findings led to the diagnosis of lung infiltration by lymphoma, with a nodu-

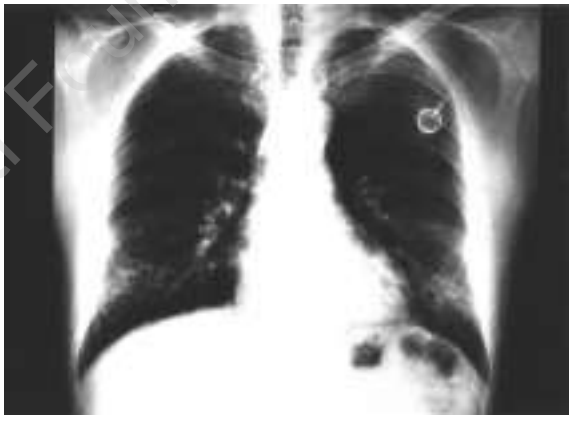

Figure 1. Chest radiography: nodular opacities, predominantly in basal zones.

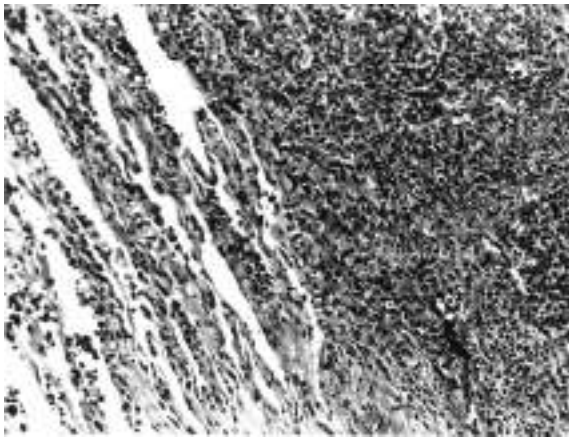

Figure 2. Lung biopsy: diffuse large cell B lymphoma, nodular infiltration (200 x).