To the Editor:

Therapy-related myelodysplasia (t-MDS) and acute myeloid leukemia (t-AML) are strongly correlated with exposure to alkylating agents and to large field radiation therapy, especially to active marrow. The syndrome is characterized by a latent period of 3 to 8 years, a preleukemic phase with pancytopenia lasting on average 6 months, increasingly severe trilineage dysplasia, and clonal cytogenetic abnormalities usually involving loss of all or part of chromosomes 5 and/or 7.

More recently, we and others have described a less common therapy-related leukemia syndrome associated with exposure to high doses of epipodophyllotoxins or DNA intercalating agents such as doxorubicin. These drugs are known to inhibit topoisomerase II activity. The risk of leukemia after etoposide is dose-related and is more commonly seen at cumulative doses greater than 2,000 mg/m². These leukemias tend to have a much shorter latent interval and a short or undetected preleukemic phase; most of them have a monoblastic phenotype and cytogenetic abnormalities involving chromosome band 11q23. We have also studied five therapy-related leukemia patients with a different structural rearrangement, a balanced translocation, t(3;21)(q26;q22); all five patients had received classical alkylating agents in addition to doxorubicin in three and etoposide in only one of the latter three.

In a recent letter in Blood, Drs Pedersen-Bjergaard and Philip have drawn attention to the close association of exposure to agents that inhibit topoisomerase II activity and balanced translocations involving bands 11q23 and 21q22 in their series of 91 patients with t-MDS/t-AML. In Table 1 we display our own data on 132 similar patients using the same format and nomenclature. The patients classified as balanced translocations of 11q23 or 21q22 had recurring translocations typical of AML, such as the t(9;11) in four patients or the t(3;21) in five patients, whereas patients with unbalanced rearrangements had nonrecurring abnormalities that generally resulted in loss of chromosomal material. As in Pedersen-Bjergaard and Philip’s analysis, we have not considered cisplatin as a classical alkylating agent; its use is included as other treatment, as is radiation therapy alone. The agents that target topoisomerase II include etoposide, teniposide, and doxorubicin. Many of our patients received a variety of chemotherapy agents in multiple sequences as well as in combination with radiation therapy, making it difficult to incriminate a single leukemogenic exposure. Among the 10 patients who had balanced translocations involving either band 11q23 or 21q22, eight had received a topoisomerase II inhibitor, with or without an alkylating agent, and two had received...
only alkylating agents. Four patients had also received radiation therapy. Only 1 of 10 patients with an unbalanced translocation had received a topoisomerase II inhibitor, and that patient had also received alkylating agents. Balanced translocations involving band 11q23 or 21q22 were significantly associated with prior exposure to agents that inhibit topoisomerase II activity (P = .003, Fisher's exact test, two-sided). The breakpoints in the balanced translocations have been or are close to being cloned. Thus, the relationship between the position of the breakpoints in the balanced and unbalanced translocations will be determined in the near future.

Our data support Pedersen-Bjergaard and Philip's observation that balanced translocations involving 11q23 or 21q22 in therapy-related leukemia are associated with agents that inhibit topoisomerase II rather than with alkylating agents. Using the combined data from both series, 19 of 21 patients with balanced translocations had received a topoisomerase II inhibitor alone or in combination with alkylating agents. In contrast, only 3 of 16 patients with unbalanced translocations received topoisomerase II inhibitors and all three had also received alkylating agents. However, it may be important that abnormalities of chromosomes 5 and/or 7 also occurred in patients treated solely with etoposide or doxorubicin as well as among those who received topoisomerase II inhibitors plus alkylating agents. Of our 132 patients, 97 (73%) had a clonal abnormality of chromosome 5 and/or 7; 26 of these patients had received topoisomerase II inhibitors with (24 patients) or without (two patients) alkylating agents. As high-dose etoposide therapy is incorporated into more combination chemotherapy regimens, we may find an increasing fraction of t-MDS/t-AML patients with balanced recurring translocations. These observations provide a further focus for continued investigation into the molecular and genetic mechanisms of leukemogenesis.

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Balanced translocations involving chromosome bands 11q23 and 21q22 in therapy-related leukemia [letter]

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