Secondary acute promyelocytic leukemia following irinotecan and oxaliplatin for advanced colon cancer

The recent introduction of irinotecan and oxaliplatin has resulted in significant progress in the treatment of advanced colorectal cancer [1]. We report on a patient with possible treatment-related acute promyelocytic leukemia after sequential chemotherapy with these cytotoxic agents.

A 65-year-old woman underwent a left hemicolectomy for adenocarcinoma in December 1989. In February 1991, abdominal computed tomography scan revealed unresectable liver metastases and chemotherapy was decided upon. She received 46 cycles of the LVFU2 infusional regimen and remained in partial response for 18 months. In June 1995, the disease progressed; the patient received three cycles of irinotecan but her condition did not improve. She subsequently received three courses of a combination of LV5FU2 and oxaliplatin. In May 1996, multiple ecchymoses appeared. The platelet count was $18 \times 10^9/l$ and the white cell count $3.1 \times 10^9/l$ with 12% blasts. Bone marrow examination established the diagnosis of acute promyelocytic leukemia. Cytogenetic and fluorescence in situ hybridization (FISH) analyses were performed on bone marrow cells (Figure 1). The karyotype did not reveal a t(15;17)(q22;q21) translocation but indicated additional material on chromosomes 6 and 17. FISH showed no evidence of t(15;17) translocation or PML-RARA fusion but an amplification of the RARA gene. Death occurred rapidly before any specific treatment was started.

The occurrence of acute promyelocytic leukemia with such unusual and complex karyotypic pattern in a patient with advanced colon cancer raises the question of whether the disease is etiologically related to one or more cytotoxic agents. Single-agent fluorouracil has demonstrated no carcinogenic potential, either in animals or in humans. Although platinum derivatives like cisplatin and carboplatin have been shown to be leukemogenic [2], no data are available concerning the third-generation derivative oxaliplatin. Irinotecan belongs to

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**Figure 1.** Cytogenetic analysis and fluorescence in situ hybridization (FISH). The karyotype (46,XX,add(6)(p23),-13,add(14)(p11),-16, add(17)(q10),-21, +3mar) demonstrates no t(15;17)(q22;q21) translocation but indicates additional material on chromosomes 6 and 17 (arrows) (A). Double painting reveals a derivative chromosome 6 with material from chromosome 17 translocated to its short arm, but no material from chromosome 6 is found on chromosome 17 (B). Dual color FISH with PML-RARA sequences detect amplification of the RARA gene (eight copies) on the derivative chromosome 17 without PML-RARA fusion (C). Final karyotype after FISH investigation: 45,XX,der(6)(t(6;17)(p25;q22)), -13,der(14)(t(14;16)(p11;p11),-16,der(17)(dupq12q21),i(21)(q10),+i(21)(q10).
the class of topoisomerase I inhibitors the mutagenic properties of which \textit{in vitro} are similar to those induced by topoisomerase II inhibitors \cite{3}, and which are therefore expected to cause similar clinical manifestations, such as acute leukemia.

Irinotecan and oxaliplatin have become important components of our chemotherapeutic armamentarium against metastatic colorectal cancer. Moreover, oxaliplatin has recently been incorporated into adjuvant therapy regimens for high-risk colon cancer \cite{4}, and irinotecan is currently evaluated in this setting. We believe that epidemiological surveys with long-term hematological follow-up are needed to monitor carefully their potential for the development of secondary leukemias.

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