Letter to the Editor

Bcr-abl positive blast crisis of chronic myeloid leukemia emerging in a case of metastatic colorectal cancer 3 months after completion of an 8-month course of cetuximab and irinotecan

To the Editor:

Cetuximab, the anti-EGFR (epidermal growth factor receptor) chimeric monoclonal antibody C225, has recently been approved for therapy of advanced colorectal cancer (1). Side effects merely consist of skin reactions and digestive symptoms. A leukemic potential has not been reported.

Case report

Colorectal cancer (CRC) was diagnosed in a 56-yr-old male patient in December 1999. Carcinoembryonic antigen (CEA) level was not elevated. After sigmoid resection for a stage II CRC (UICC, pT3pN0M0) adjuvant treatment was not given. In January 2001, a solitary liver metastasis was surgically resected. In July 2003 lung, hilar and mediastinal lymph node metastases were detected. Therapy with capcitabine and oxaliplatin was started. After eight cycles the patient entered partial remission in December 2003 and therapy was stopped. Because of rapid progression the patient was accrued to the international study protocol EMR 62 202-025 (Companies Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, CT, USA and Merck, Darmstadt, Germany) and randomized to the cetuximab-arm in March 2004. Therapy consisted of cetuximab 250 mg/m²

Fig. 1. Units for cells of differential counts are on the primary y-axis (left). Only units for complete white cell counts are on the secondary y-axis (right). Diff.count, differential count of white cells; Ch.th., chemotherapy with capcitabine and oxaliplatin; Progr.disease: progressive disease.
(day 1, 8 and 15) and irinotecan 350 mg/m^2 (day 1). Filgrastim was not given. Therapy was finalized in November 2004 after 11 cycles. Computed tomography (CT) scan revealed only persistence of one solitary mediastinal lymph node metastasis. The complete blood and differential counts were normal. Five weeks later the white cell count was slightly increased to 16,900/mm^3 and another 6 wk later to 28,900/mm^3. Twenty weeks after end of cetuximab the white cell count reached 100,000/mm^3 with 15% blasts (Fig. 1). A CT scan revealed progression of intrapulmonary metastases. The bone marrow showed primary, biphenotypic blast crisis of Philadelphia-chromosome positive chronic myeloid leukemia (CML): 30% blasts: CD34+, CD117-, CD13+, CD33+, CD19+, CD10+; 46,XY, t(9;22)(q34;q11); BCR-ABL positive (Multiplex RT-PCR, Major breakpoint). Therapy with imatinib was started. Three weeks later the white cell count returned to normal.

To our knowledge this is the first report of a biphenotypic blast crisis of Philadelphia-chromosome positive CML after treatment for CRC with cetuximab.

CML is a rare event as secondary malignant neoplasm (2). However, large epidemiological studies failed to disclose a higher incidence of CML in patients who have previously been treated for a primary cancer (3). There are two reports on CML in patients with gastrointestinal cancers (4, 5). Capecitabine and oxaliplatin reportedly have never induced CML. The leukemic potential of topoisomerase II inhibitors (e.g. etoposide) mainly applies for the Philadelphia chromosome carrying leukemias (6). A leukemic potential of the topoisomerase I inhibitor irinotecan has not been reported. The incidence of CML is about 2/10^5 inhabitant per year in central Europe. Primary blast crisis is a rare event and primary biphenotypic blast crisis is a rarity (7). Leukemia induction has not been reported after the new immunotherapies for CRC. Clinicians should closely observe blood cell dyskrasias and hemopoietic chromosomal aberrations in the course of the new, highly efficacious antibody therapies.

References