Oxaliplatin-Related Acute Myelogenous Leukemia

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ABSTRACT

A 56-year-old woman diagnosed with a poorly differentiated cecal adenocarcinoma with metastases to ovaries, omentum, and sigmoid colon went into remission after 12 cycles of infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX-4 regimen). Thirteen months later, a pelvic recurrence was diagnosed, and the patient received nine cycles of FOLFOX-6 plus bevacizumab, resulting in a clinical complete response but the development of pancytopenia. Bone marrow biopsy was consistent with therapy-related acute myelogenous leukemia. Chromosome analysis showed structural rearrangements with partial deletions of the long arms of chromosomes 5, 7, 20, and 21, as well as trisomy of chromosome 8 and losses of chromosomes 3 and 11. Induction chemotherapy led to remission, but the patient died two months later from complications of colon cancer progression. It is likely that the leukemia was related to the oxaliplatin administration. The Oncologist 2006;11:261–262

In August 2002, a 56-year-old woman was diagnosed with a cecal adenocarcinoma on screening colonoscopy. Exploratory laparotomy revealed a 2.5-cm grade 3 poorly differentiated signet ring–type adenocarcinoma with metastasis to the ovaries, omentum, sigmoid colon, and 4 of 21 regional lymph nodes (T4N2M1). The tumor was microsatellite stable. The patient was treated with 12 cycles of infusional 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin (the FOLFOX-4 regimen) over 6 months (last cycle in February 2003) with no clinical evidence of disease at the end of treatment. She remained in remission until March 2004, when a surveillance computed tomography (CT) scan showed a new 3 × 3 cm pelvic lesion consistent with recurrence. No other metastatic lesions were seen on CT scans of the chest, abdomen, and pelvis. The patient received nine cycles of FOLFOX-6 plus bevacizumab and tolerated it well except for minimal peripheral neuropathy and mild thrombocytopenia that caused a 1-week delay in therapy during cycle 9 in August 2004. At the end of cycle 9, a CT scan documented complete resolution of the pelvic metastatic lesion. Given persistent thrombocytopenia, oxaliplatin was held and the patient received only 5-FU, LV, and bevacizumab during cycle 10. Chemotherapy was then discontinued. In addition to the thrombocytopenia, leukopenia and anemia also developed during the next 2 months, leading to a bone marrow biopsy in November 2004 that showed a hypercellular marrow with 48.5% myeloblasts, increased ratio between myeloid and erythroid cells, decreased erythropoiesis, and megakaryocytes. A flow cytometry analysis showed 30% monocytes, 21% lymphocytes without abnormal cell popu-
lation, and 11% blasts positive for CD45, CD7, CD13, CD33, CD45, CD117, and human leukocyte antigen DR. Multiple related clones with complex karyotypic abnormalities were identified. Structural rearrangements with partial deletions of the long arms of chromosomes 5, 7, 20, and 21 were noted, as well as trisomy of chromosome 8 and losses of chromosomes 3 and 11 (Fig. 1). The karyotype was 46;XX,-3,add(5)(q13),add(7)(q32)[7]/46, idem,+8[2]/45, idem, add(20)(q13.3)[2]/44, idem,-11,+0.2mar,+1-2r[cp7]/45, idem, del(21)(q22)[cp2]. These findings were consistent with therapy-related leukemia (TRL). Induction therapy with cytosine arabinoside and mitoxantrone resulted in remission in December 2004, but the patient developed multiple complications from progression of colon cancer thereafter and died in early February 2005 (30 months after the initial diagnosis of metastatic colon cancer).

The present case had characteristics of both the major groups of TRL [1]. The chromosome 5 and 7 abnormalities were compatible with acute myelogenous leukemia (AML) induced by alkylating agents, but the short latency period after starting chemotherapy (28 months), the absence of documented preceding myelodysplastic syndrome, and monocytic phenotype are more common with topoisomerase II inhibitor–related AML [2]. This patient had received no prior topoisomerase inhibitors nor had she been exposed to environmental carcinogens, suggesting that her leukemia represented either a coincidental de novo event or, more likely, was related to oxaliplatin. Cisplatin and carboplatin have been widely associated with TRL, but this is only the second report linking oxaliplatin to TRL. Oxaliplatin, a third-generation platinum analogue, has a distinct spectrum of activity and toxicity profile from those of cisplatin and carboplatin. A case of acute promyelocytic leukemia in a patient with metastatic colon adenocarcinoma treated with 46 cycles of leucovorin plus 5-FU followed by three cycles of irinotecan was recently published [3]. The karyotype [45,XX,der(6)t(6;17)(p25;q22),-13,der(14)t(14;16)(p11;p11),-16,der(17)(dup12q21),i(21)(q10),+i(21)(q10)] was distinct from our case and likely related to the use of irinotecan, a topoisomerase I inhibitor with mutagenic effects comparable with those of topoisomerase II inhibitors classically associated with TRL [2, 4]. It is unlikely that 5-FU played a role in the present TRL given the absence of a definitive 5-FU leukemogenic effect despite its use for almost 50 years. It is noteworthy, however, that anecdotal cases of 5-FU–related leukemia have been reported [5, 6]. It is unlikely that bevacizumab played a significant role in the pathogenesis of this leukemia given that it has no direct DNA effects. The genetic basis of TRL was recently reviewed [2]. In summary, the excitement brought by the greater survival and response rates of metastatic colon cancer with the incorporation of oxaliplatin to the treatment armamentarium [7] needs to be tempered by vigilant monitoring of long-term serious side effects. Confirmation and better characterization of oxaliplatin-related AML warrants further investigation.

**Disclosure of Potential Conflicts of Interest**

Dr. Locker has been a member of the speakers bureau for sanofi-aventis and Genentech.

**REFERENCES**


