

# Combination Chemotherapy of Azacitidine and Cetuximab for Therapy-Related Acute Myeloid Leukemia following Oxaliplatin for Metastatic Colorectal Cancer

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## Key Words

Therapy-related leukemia · Colorectal cancer · Oxaliplatin · Azacitidine · Cetuximab

## Abstract

Therapy-related leukemia (TRL) has been reported to occur after treatment with alkylating agents and/or topoisomerase II inhibitors. Oxaliplatin (OXP) is used as a key drug for the treatment of colorectal cancer (CRC). Cisplatin and carboplatin have been linked with TRL, but the involvement of OXP is questionable. A 74-year-old male was diagnosed with peritoneal metastasis from CRC in July 2011. The patient received nine cycles of 5-fluorouracil (5-FU), leucovorin (LV), and OXP (mFOLFOX-6 regimen) and three cycles of 5-FU and LV only, resulting in a clinical complete response. However, recurrence of CRC was detected by CT within 3 months after the last course of chemotherapy. In April 2013, laboratory tests showed pancytopenia and 15% blast cells. A bone marrow examination revealed multilineage dysplasia and 20.4% myeloblasts. Cytogenetic analysis indicated a complex karyotype that included chromosome 5 and 7 abnormalities. The patient was diagnosed with TRL and treated with a combination of azacitidine (AZA) and cetuximab (Cmab) for both cancers. AZA might be useful in TRL when a patient needs to be treated simultaneously for more than one primary cancer because of its low toxicity. Moreover, Cmab

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is an effective therapeutic tool in TRL patients with metastatic CRC with the wild-type *K-ras* gene.

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## Introduction

Therapy-related leukemia (TRL) is a heterogeneous group of neoplasms that occur as a late consequence of exposure to certain cytotoxic agents and/or radiation therapy for a primary cancer or after immunosuppressive treatment [1]. Alkylating agents and topoisomerase II inhibitors have been implicated in the development of TRL [2]. Oxaliplatin (OXP) is a key drug for the treatment of colorectal cancer (CRC) [3, 4]. The incidence of TRL with the older platinum compounds, such as cisplatin and carboplatin, is well documented [5], but the association of OXP with TRL has not been established. Herein, we report a case of metastatic CRC complicated with OXP-related TRL treated with a combination of azacitidine (AZA) and cetuximab (Cmab).

## Case Presentation

A 74-year-old Japanese male was diagnosed with descending CRC with peritoneal metastasis in July 2011. Immunohistochemical analysis revealed that the resected primary tumor did not express the epidermal growth factor receptor (EGFR). The tumor harbored wild-type *K-ras*, detected by the allele-specific polymerase chain reaction assay. A hematologic examination revealed a white blood cell count of 6,700/ $\mu$ l, 177,000 platelets/ $\mu$ l, and a hemoglobin level of 10.4 g/dl. No atypical cells were seen on the peripheral blood smear examination. The patient was treated with nine cycles of 5-fluorouracil (5-FU), leucovorin (LV), and OXP (mFOLFOX-6 regimen). His peripheral neuropathy developed to grade 3 (CTCAEv4.0) due to OXP toxicity. Accordingly, we changed the regimen to 5-FU and LV only for three cycles, and he achieved a complete response. However, recurrence of CRC was detected by CT within 3 months of the last course of chemotherapy. At the same time, pancytopenia was noted, and he was referred to our department. Blood tests showed the following abnormalities: white blood cell count 2,000/ $\mu$ l with 15% blasts, platelet count 48,000/ $\mu$ l, and hemoglobin 8.8 g/dl. A bone marrow examination revealed a normocellular marrow with 20.2% myeloblasts, with an increased ratio between myeloid and erythroid cells, decreased erythropoiesis, and megakaryocytes. Morphologically, 10% or more of the cells in the three lineages were dysplastic. Bone marrow smears demonstrated a pseudo-Pelger nucleus, hypogranulated myelocytes, megaloblastic alteration, and micromegakaryocytes. Flow cytometry revealed an abnormal myeloid population expressing CD13, CD33, CD34, and human leukocyte antigen D-related. Chromosomal analyses revealed a complex karyotype, including 46,XY, inv(3)(q21q26.2), del(5)(q13q33), add(7)(q11.2), add(11)(q23), add(15)(p13), and del(16)(q11.1) [2, 4]. Based on these findings, the diagnosis was therapy-related acute myeloid leukemia (t-AML; M2 morphologic features) with multilineage dysplasia of the WHO classification system. Regarding his CRC, his serum carcinoembryonic antigen and carbohydrate antigen 19–9 levels had increased rapidly, and he was suffering from abdominal pain originating from peritoneal metastasis. The patient was given chemotherapy with AZA, a deoxyribonucleic acid methyltransferase-inhibiting cytosine nucleoside analogue, 75 mg/m<sup>2</sup> daily for 5 days every 28 days for t-AML. Moreover, in consideration of the patient's clinical presentation, we offered to use Cmab, an EGFR antagonist, combined with AZA, because his CRC harbored a wild-type *K-ras* gene. The

patient agreed to be treated with this combination therapy and received AZA subcutaneously on days 1–5 and Cmap (400 mg/m<sup>2</sup> for 1 week, followed by weekly doses of 250 mg/m<sup>2</sup>) intravenously on days 8, 15, and 22, administered every 28 days. He had developed grade 4 hematological toxicity, including neutropenia, anemia, and thrombocytopenia. These adverse effects (AE) were manageable with supportive treatments. Due to AZA administration, the absolute neutrophil count gradually increased. After four cycles of AZA, the patient had stable disease with less than 20% blasts in the bone marrow. The carcinoembryonic antigen and carbohydrate antigen 19–9 levels also decreased following the first Cmap infusion. This combination therapy achieved stable disease for 5 months (fig. 1). However, the level of the tumor marker began to increase gradually during the third course. The patient was complicated with postoperative adhesive intestinal obstruction and severe aspiration pneumonia after 4 months of this combination chemotherapy. Therefore, he was transferred to a palliative care hospital where he died 7 months later from TRL.

## Discussion

Therapy-related myeloid neoplasms (t-MN) are defined by the WHO as clonal hematopoietic stem cell disorders related to previous exposure to chemotherapy and/or radiation therapy, including myelodysplastic syndromes, t-AML, and myelodysplastic/myeloproliferative neoplasms [6]. Based on the clinical manifestations and morphologic features, there are two subtypes of t-MN. The subtype associated with alkylating agents and/or radiation generally is thought to develop after a latency period of 5–10 years and is accompanied by MDS features and abnormalities of chromosomes 5 or 7 [2]. The other subtype is associated with topoisomerase II inhibitor treatment and presents with symptoms at about 1–3 years after treatment, with generally balanced chromosomal translocations related to 11q23 or 21q22, such as t(9;11), t(11;19), and t(6;11), and without MDS manifestations [2]. Platinum-based compounds are effective broad-spectrum anticancer drugs widely used in the treatment of various malignancies. It has been reported that cisplatin and carboplatin have been associated with TRL [5]. On the other hand, the risk of secondary carcinogenesis following treatment with OXP is unclear. In the present case, TRL developed 21 months after OXP administration and harbored a complex karyotype with abnormalities of chromosomes 5 and 7. These clinical manifestations have featured both types of t-MN. The clinical characteristics of 8 patients who developed TRL after treatment with OXP are summarized in table 1 [7–13]. There were 5 male and 3 female patients with a mean age of 64 years (range, 25–79). Regarding the periods of latency of OXP-related t-MN, these have been relatively shorter than those of alkylating agents/radiation and topoisomerase II inhibitor-induced t-MN. The median period of latency to diagnosis of TRL was 19 months (range: 12–29).

The prognosis of t-MN remains dismal. In particular, patients with OXP-related TRL died within 2 months of the diagnosis, except chronic myeloid leukemia cases (table 1). The only curative treatment for t-MN is hematopoietic stem cell transplantation (HSCT). However, t-MN patients undergoing HSCT have high treatment-related mortality rates [14]. Generally, HSCT is not feasible in t-MN patients, mostly because of their poor performance status and age. The randomized AZA-001 trial has shown that treatment with AZA significantly increases the overall survival (OS) of patients with higher-risk MDS, except for t-MN patients [15]. Recently, a cooperative Italian group reported a retrospective analysis of 50 t-MN patients treated with AZA. The study showed that the overall response rate was 42% and the median OS was 21 months from the start of AZA [16]. However, the median OS was 16.2

months for patients with complex karyotypes. These data indicated that AZA treatment might prolong the survival of t-MN patients. AZA is better tolerated than intensive chemotherapy in elderly patients with higher-risk MDS or AML [17, 18]. Accordingly, treatment with AZA rather than best supportive care should be considered for t-MN patients who are not eligible for HSCT.

The standard AZA administration schedule is 75 mg/m<sup>2</sup>/day for 7 days, repeated every 28 days (525 mg/m<sup>2</sup> total monthly dose). In the present case, we applied a 5-day AZA schedule (375 mg/m<sup>2</sup> total monthly dose) because of severe neutropenia and thrombocytopenia. This 5-day schedule delivers approximately 30% less than the standard dose (525 mg/m<sup>2</sup> total monthly dose). It has been reported that a 5-day dose-intensified (500 mg/m<sup>2</sup> total monthly dose) AZA schedule has similar efficacy to the standard AZA administration regimen [19]. A randomized trial by the Japan Adult Leukemia Study Group is currently in progress and is intended to compare a 5-day schedule of AZA treatment with a 7-day schedule for high-risk MDS. In our case, the patient did not meet the criteria for response, but absolute neutrophil count tended to increase gradually, and the blast count in the bone marrow decreased until the end of his life.

Cmab, a monoclonal antibody against EGFR, has activity against CRC with a wild-type *K-ras* gene [20]. A randomized trial (CO.17) showed that Cmab monotherapy as compared with supportive care alone significantly improves OS (median, 9.5 vs. 4.8 months) and progression-free survival (median, 3.7 vs. 1.9 months) in patients with *K-ras* wild-type CRC and in whom other treatments had failed [21, 22]. In addition, this therapy preserves the quality of life. Our case survived for 7 months receiving combination chemotherapy. This outcome supported the data of the previous study, showing that Cmab monotherapy improved OS compared with supportive care alone. The most common severe AE of Cmab are rashes and infections without neutropenia. Cmab does not increase the risk of hematologic AE [21]. Despite our patient suffering from pancytopenia due to TRL, we were able to treat him with Cmab combined with AZA, and he had no severe AE during this treatment. The efficacy of the combination chemotherapy of AZA and Cmab was limited; however, the toxicity was low and tolerable. This combination therapy might be a therapeutic option for pancytopenic t-MN patients with wild-type *K-ras* CRC.

t-MN has been recognized as one of the most serious late AE of cytotoxic therapies in clinical oncology and may be attributed to an improved OS following primary malignancies. Oncologists should carefully check the whole blood count analysis on routine follow-ups, even for asymptomatic patients who have undergone chemotherapy. The incidence and clinical features of OXP-related t-MN should be clarified. Furthermore, the development of effective treatments for t-MN is needed urgently.

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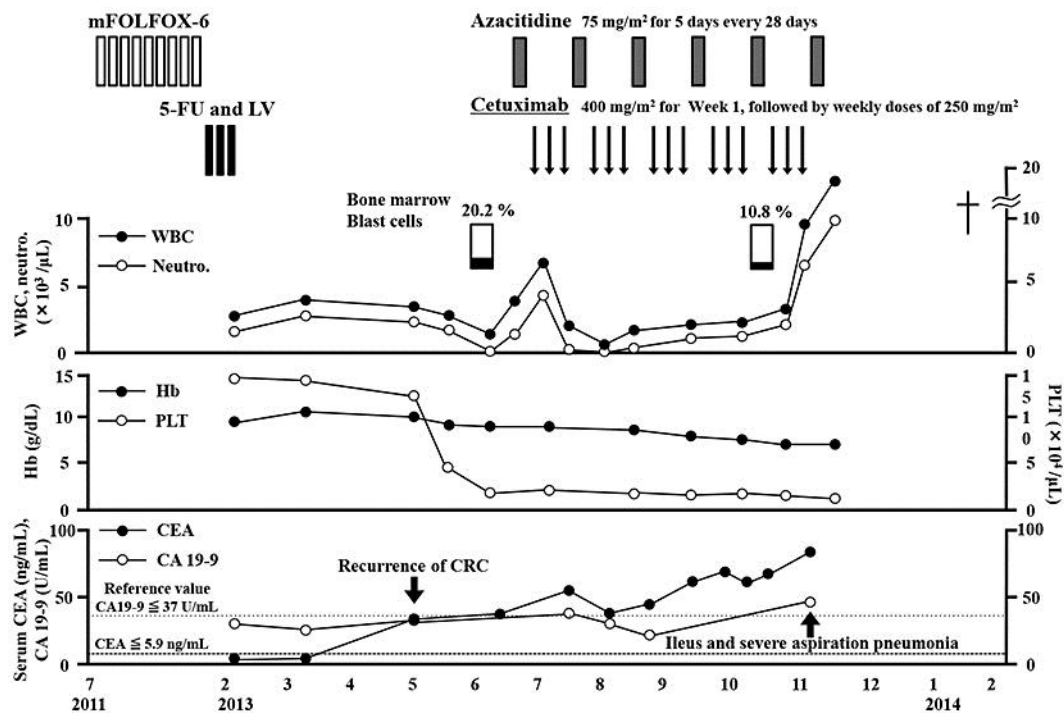
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**Table 1.** Reported cases of OXP-related leukemia

First author, year	Age, years/sex	Type of leukemia	Primary site	Chemotherapy regimen	Onset from OXP start, months	Karyotype	Treatment	Outcome
Carneiro, 2006 [7]	56/F	AML	Cecum	FOLFOX, FOLFOX and bevacizumab, LVFU2, and bevacizumab	28	Complex +8(21)	Cytarabine and mitoxantrone	Died from cecal cancer 2 months later; AML
Damodaran, 2012 [8]	63/M	AML	Esophagus	Capecitabine, OXP, and radiation	29	Complex add(5)(q13), add(7)(q32), +8	Daunorubicin and cytarabine	Died from sepsis; acute oliguric renal failure on day 20 of the treatment course
Merrouche, 2006 [9]	65/F	APL	Colon	LVFU2, irinotecan, LVFU2, and OXP	12	Complex	–	Died from APL rapidly before any specific treatment was started
Merlin, 2008 [10]	65/F	ALL	Colon	FOLFOX	12	Not done	–	Died from bleeding in the brain rapidly before any specific treatment was started
Vakili-Sadeghi, 2013 [11]	25/M	Chronic-phase CML	Rectum	LVFU2, FOLFOX, and FOLFIRI	20	Philadelphia chromosome positive	Imatinib, palliative chemotherapy	Achieved a hematologic response to imatinib but died from CRC nine months later; CML
Buxhofer-Ausch, 2006 [12]	56/M	Biphenotypic blast crisis of CML	Colon	Capecitabine and OXP; cetuximab and irinotecan	18	Philadelphia chromosome positive	Imatinib	Achieved a hematologic response after 3 weeks
Kadikoylu, 2013 [13]	66/M	Chronic-phase CML	Rectum	Capecitabine, 5-FU irinotecan, OXP	12	Philadelphia chromosome positive	Imatinib	Achieved a hematologic response after 1 month
Present case	74/M	AML	Colon	FOLFOX, 5-FU, and LV	21	Complex inv(3)(q21q26.2), del(5)(q13q33), add(7)(q11.2), add(11)(q23), del(16)(q11.1)	AZA and Cmap	Died from CRC 7 months later; AML

ALL = Acute lymphoblastic leukemia; APL = acute promyelocytic leukemia; CML = chronic myeloid leukemia; FOLFOX = infusional 5-FU, LV, and OXP; LVFU2 = LV plus 5-FU; FOLFIRI = LV, 5-FU, and irinotecan.



**Fig. 1.** Clinical course. The patient was diagnosed with peritoneal metastasis from CRC in July 2011. He received nine cycles of the mFOLFOX-6 regimen and three cycles of the 5-FU and LV only regimen, resulting in a clinical complete response. However, he relapsed within 3 months of the end of chemotherapy. In April 2013, laboratory tests showed pancytopenia, and bone marrow aspiration revealed normocellularity with multilineage dysplasia and 20.4% myeloblasts. He was diagnosed with t-AML. Moreover, his CRC had progressed, and he was treated with a combination therapy of AZA and Cmb. He died 7 months later from TRL.