

# Capecitabine Induced Therapy Related Acute Myeloblastic Leukemia with t(10;11) (q22;q23) in a Patient with Breast Cancer

Meme Kanserli bir Hastada Capecitabin İlişkili ve t(10;11) (q22;q23) Pozitif Akut Myeloblastik Lösemi

Zübeyde Nur Özkurt, Ramazan Öcal, Mehmet Sezgin Pepeler, Burcu Ülküden

Gazi University Faculty of Medicine, Department of Hematology, Ankara, Turkey

## ABSTRACT

Capecitabine is an oral agent that is used either as single agent or in combination therapy. Therapy related acute myeloblastic leukemia after capecitabine use is rarely reported. We presented a 39-year-old woman with metastatic breast cancer. She admitted with acute myelomonocytic leukemia after treating with oral Capecitabine. t(10;11)(q22;q23) was determined in conventional cytogenetic analysis. She achieved complete remission with intensive chemotherapy but relapse developed. She died although the salvage chemotherapy. To our knowledge our patients is the first report with t-AML with t(10;11)(q22;q23) secondary to Capecitabine use for breast cancer treatment. Capecitabine should be carefully used especially in patients with high risk for t-AML.

**Key Words:** Capecitabine, therapy related acute myeloblastic leukemia, breast cancer, t(10;11)(q22;q23)

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## ÖZET

Capesitabin tek başına veya kombinasyon tedavileri ile kullanılabilen ve oral yolla kullanılan bir tedavi ajanıdır. Capesitabin kullanımı ile ilişkilendirilen tedavi ilişkili lösemi olguları oldukça nadirdir. Biz 39 yaşında metastatic meme kanserli bir olguyu sunduk. Hasta Capesitabin ile tedavi edildikten sonra akut myelomonositik lösemi ile başvurdu. t(10;11)(q22;q23) konvansiyonel sitogenetik çalışmada saptandı. İndüksiyon kemoterapi ile remisyon sağlanmasına karşın daha sonra relaps gelişti. Kurtarma kemoterapi verildi, ancak hasta kaybedildi. Bu vaka Capesitabin kullanımı sonrası t(10;11)(q22;q23) ile birlikte t-AML geliştiğini gösteren ilk rapordur. T-AML gelişimi yüksek hastalar Capesitabin kullanımı sırasında yakından izlenmelidir.

**Anahtar Sözcükler:** Capesitabin, tedavi ilişkili akut myeloblastik lösemi, meme kanseri, t(10;11)(q22;q23)

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## INTRODUCTION

Breast cancer is among the most frequent malignancy in females. The treatment of breast cancer rapidly developed, but the frequent cause of therapy related acute leukemia (t-AML) is still breast cancers (1). Cytotoxic chemotherapy is the main treatment of metastatic breast cancer. Capecitabine is a prodrug of Fluorouracil (FU), which is an antimetabolite with activity against certain cancers including colorectal, metastatic breast, prostate, renal cell, ovarian, and pancreatic cancers (2). Capecitabine is converted to FU via thymidine phosphorylase that is found higher levels in tumor than healthy tissue. Cytotoxicity of FU results from both the incorporation into RNA or DNA and blockade of thymidine synthesis. The drug has FDA approval more than 10 years. The toxicities of capecitabine are well known. Generally, the most frequent adverse effects of capecitabine are hyperbilirubinemia, diarrhea, nausea, hand-foot syndrome, and dermatitis. Hematological side effects of capecitabine including anemia, lymphopenia, neutropenia, and thrombocytopenia is well-known (2), however the leukemogenic effect of capecitabine was rarely reported (3-7). Here we present a patient with metastatic breast cancer and therapy related acute myeloblastic leukemia after capecitabine treatment.

## CASE REPORT

A 39-year-old woman was diagnosed as breast cancer with bone metastasis (stage IV) at February 2010. Estrogen receptor and HER2/neu were positive, and progesterone receptor was negative. She was treated with trastuzumab, tamoxifen, leuprolid acetate and ibandronic acid. 21 months later, treatment was changed to lapatinib (1250 mg/day) and capecitabine (2000 mg/m<sup>2</sup> orally on day 1 through 14 of a 21-day cycle) and ibandronic acid due to progression of bone lesion. Capecitabine was stopped at June 2013 due to thrombocytopenia. She was admitted to hospital due to fatigue at September 2013. Complete blood count revealed that hemoglobin was 7.4g/dl, white blood cell was 10500/mm<sup>3</sup>, and platelet was 15000/mm<sup>3</sup>. Blast cells were seen in peripheral smear. Bone marrow aspiration and flow cytometry revealed acute myelomonocytic leukemia. CD13, CD33, CD34, CD117, MPO, CD64, and CD11b were positive. In bone marrow biopsy, reticulin fibrosis (grade 2/3) and tree-lineage dysplasia were identified. Clonal 46XX, (10;11)(q22;q23) rearrangement was found in conventional cytogenetic analysis. JAK2 mutation and the rearrangements of BCR-ABL, PML-RARA, AML1, CBFβ-MYH11 were negative. She achieved complete remission with intensive chemotherapy (idarubicin and cytarabine), four courses of consolidation chemotherapy with high dose cytarabine was given.

**Address for Correspondence / Yazışma Adresi:** Zübeyde Nur Özkurt, MD, Gazi University Faculty of Medicine, Department of Hematology Yenimahalle, Ankara, Turkey  
E-mail: zubenurozkurt@yahoo.com

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Letrozole was started due to metastatic bone lesion related to breast cancer. After 10 months of leukemia free survival, relapse was identified. FLAG-Ida salvage chemotherapy was administered, and partial remission was obtained. After, re-induction with FLAG-Ida regime percentage of blasts in the bone marrow increased markedly. She received best supportive care, but she died 18 months after the leukemia diagnosis.

## DISCUSSION

t-AML is a well-known late complication of cancer therapy including chemotherapy, radiotherapy and immunosuppressive treatment (1, 8). In the classic forms of t-AML, leukemia develops within 5-7 years following chemotherapy with alkylating agents such as melphalan and cyclophosphamide or radiotherapy. The other agents causing t-AML is topoisomerase-II inhibitors. Topoisomerase-II inhibitors related t-AML occurs within 2-3 years and it is rapidly progressive with higher blast count, and it has poor prognosis inspite of the high response rate of induction therapy (1). Topoisomerase inhibitors related t-AML with is characterized by translocations involving MLL, PML-RARA or core binding factor (CBF) genes.

We documented the relationship between t(10; 11)(q22;q23) and capecitabine induced t-AML. Clinical course and laboratory findings of our case were similar to t-AML related topoisomerase inhibitors. Leukemic manifestation occurred within 3 years after use of capecitabine, and blastic infiltration, tree-lineage dysplasia with MLL gene abnormality was found.

After the first remission induction therapy complete remission was achieved, but leukemia free survival was quite short. The MLL gene was identified in 11q23 translocation, and various 11q23 translocations have been observed until now (1, 8). There are limited information about AML with t(10; 11)(q22;q23) (9, 10), but the reports published recently showed that the t(10; 11)(q22;q23) is a poor prognostic feature despite intensive induction and allogeneic stem cell transplantation (11, 12).

Several studies reported that breast cancer therapy is a risk factor of t-AML (1, 13, 14). Addition of G-CSF to routine therapy regimens, use of antracyclines, cyclophosphamide, radiotherapy, and high dose therapy followed by autologous stem cell transplantation were described as significant risk factors for t-AML (1). Capecitabine induced t-AML in patients with breast cancer was not reported yet and classically capecitabine is not accepted as a leukemogenic agent. To our knowledge the presented patient is the first report with t-AML secondary to capecitabine use for breast cancer treatment. Literature review revealed only five patients were reported developed t-AML after therapy with capecitabine until now (3- 7). These patients' characteristics were shown in table 1. All of these patients had gastrointestinal cancer and they were older than our patient. Poor prognostic course of our patient was similar to other t-AML secondary capecitabine except who had acute promyelocytic phenotype. The leukemia free survival was very short despite the intensive chemotherapy regimens. In addition she was not accepted as a candidate for allogeneic stem cell transplantation since her breast cancer was not in remission.

In conclusion, capecitabin might have a leukemogenic effect via MLL gene in our patient. This group of AML has very poor prognosis, and capecitabine should be used carefully especially in patients with high risk for t-AML.

**Table 1.** The characteristics of patients with Capecitabine induced t-AML

Patient's age/sex (Reference)	Primary cancer	Cancer therapy	Interval between capecitabine therapy and t-AML	Leukemia subgroup	Cytogenetic disorder	Leukemia treatment	Response/ Survival
63/Female (3)	Colorectal cancer	Capecitabine	12 months	AML M4	t(6;11)	Palliation	-/2 months, died
58/Male (4)	Colorectal cancer	Capecitabine + radiotherapy	16 months	AML M3	t(15;17)	Idarubicine+ ATRA	CR/ 1 month, alive
66/Male (5)	Colorectal cancer	Capecitabine	11 months	AML	-	?	?/unknown
68/Male (6)	Gastric cancer	Oxaliplatin + Capecitabine	48 months	AML M3	t(15;17),	ATRA+ ATO	CR/ 32 months, alive
63/Male (7)	Esophageal cancer	Oxaliplatin + Capecitabine	29 months	AML M5	47,X,der(Y) t(Y;3)(q12;q21), +8	Daunorubicine+ cytarabine	CR/ 2 months, died
42/Famale current case	Breast cancer	Transtuzuma b+ Capecitabine	33months	AML M4	t(10;11)(q22;q23)	Idarubicine+ cytarabine 4HDAC consoludation FLAG-Ida salvage RI	CR/ 18 months, died

## Conflict of interest

No conflict of interest was declared by the authors.

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