**Treatment-related Acute Myeloid Leukemia Following Capecitabine Chemotherapy: A case report**

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**Abstract**

**Background:** Chemotherapy of cancers can have serious and dangerous side effects, of which the occurrence of secondary acute myeloid leukemia (AML) is one of them. Treatment-related AML (t-AML) is an example of secondary AML, that usually occurs in patients who have been previously treated with chemotherapeutic regimens that contain Alkylating agents, Topoisomerase inhibitors, Anthracyclines and maybe other drugs like fluorouracil derivatives. Several causes have been proposed for the occurrence of t-AML. Among them, most articles focused on chromosomal damage due to the treatment of primary disease with alkylating agents or topoisomerase II inhibitors. Despite the lower prevalence compared to Anthracyclines and Topoisomerase II inhibitors, t-AML following the administration of 5-FU is suspected.

**Case Present:** We reported a 60-year-old man diagnosed with primary colon cancer who developed t-AML 42 months after the treatment with 8 cycles of Capecitabine (1500 mg BD for 14 days every 3 weeks) monotherapy without radiation.

**Conclusion:** Our observations were in line with the results of other articles about 5-FU. So, according to the case reports about the occurrence of t-AML possibly caused by anti-metabolite drugs, especially in higher cumulative doses, we conclude that the lowest effective dose should be chosen, and the risks of treating primary cancer with anti-metabolites such as 5-FU and Capecitabine should be weighed along with its benefits.

**Background:** Acute myeloid leukemia (AML) is a class of hematologic malignancies which defines as the clonal proliferation of immature myeloid cells in the bone marrow(1). Various risk factors have been proposed for the occurrence of the disease, however, none of them are found in some patients. Some known risk factors for the development of AML are older age, smoking, male sex, and repeated exposure to chemicals such as formaldehyde and benzene (2).

The term “secondary AML” refers to patients who develop AML secondary to a previous disease such as myelodysplastic syndrome (MDS). Treatment-related AML (t-AML) is an example of secondary AML, that usually occurs in patients who have been previously treated with chemotherapeutic regimens or radiation therapy (RT). The most important chemotherapy medications that can cause AML include alkylating agents, topoisomerase inhibitors, and anthracyclines. About 10-20% of all AML patients are cases of secondary malignancies (3).

Several causes have been proposed for the occurrence of t-AML. Among
them, most articles focused on chromosomal damage due to the treatment of primary disease with alkylating agents or topoisomerase II inhibitors(4). To date, there are limited cases of t-AML following the use of Fluorouracil have been reported. In this paper, we report a case of t-AML following the administration of 5-FU for the treatment of colorectal cancer.

Case Present:

A.V., a 60-year-old man, presented progressive general weakness. His past medical history includes Sigmoid cancer from 4 years ago without peritoneal seeding or hepatic metastasis. Cancer staging according to the American Joint Committee on Cancer (AJCC) staging system was (T3N1MX). The primary carcinoembryonic antigen (CEA) was 5.37. The patient underwent a total colectomy with preservation of the rectum in March 2019. Pathological macroscopic and microscopic evaluation showed moderately differentiated adenocarcinoma and an adenomatous polyp with low-grade dysplasia.

A month after surgery, adjuvant chemotherapy began for the patient, including 8 cycles of Capecitabine (1500 mg BD for 14 days every 3 weeks) monotherapy without radiation. At the end of the treatment, the patient’s laboratory data were in the normal range, and the CEA was 1.1. Remission occurred after the treatment finished and remained for 42 months.

On admission, the patient’s chief complaint was general weakness. There were no special findings in the initial Physical examination such as fever or lymphadenopathy. No hepatosplenomegaly or skin lesions were observed. The patient's baseline laboratory data showed a leukocytosis (WBC 165.4* 10^3 /mcL) with 93% blast and 3% lymphocytes, thrombocytopenia (Plt: 15* 10^3 /mcL) and increase in inflammatory markers (CRP: 150.5 mg/L and LDH: 4397 U/L).

The serum tumor marker, carcinoembryonic antigen (CEA) level was 1.6. No evidence of colon cancer relapse was found by gastroscopy, colonoscopy, or whole-body positron emission tomography-computed tomography (PET-CT).

A bone marrow aspiration and biopsy (BMA/BMB) took from the patient, and the result was positive for Acute myeloblastic leukemia, type M4. The bone marrow cytogenetic analysis disclosed 48-50, XY [cp 18] (Fig 1). Immunohistochemical (IHC) studies of A.V.'s peripheral blood smear(PBS) sample showed that cells are including 93% blasts and 3% lymphocytes. The phenotype of blast cells was: CD34 Negative; CD 13,33,117 Positive; CD19,3,7,10 Negative; HLA-DR Negative Genotype analysis was negative for PML-RARα translocation [t (15;17) (p22;q21)].

The induction chemotherapeutic regimen started with Daunorubicin (120mg D1-D3) plus Cytarabine (300mg D1-D7). Unfortunately, the patient developed febrile neutropenia after the induction of remission and developed sepsis, and finally expired due to cardiac arrest on day 15 of admission.

Discussion:

t-AML refers to the condition that a patient develops AML after the treatment of primary cancer of all types (3). The prevalence of t-AML is reported at 10% of all cases diagnosed with AML (5, 6).

Two main subtypes of t-AML exist regarding Cytogenetic studies and received chemo/Radio therapeutic regimens. Type 1 usually occurred after treatment of primary cancer with Alkylating agents with or without radiation therapy. The time period between initial treatment and development AML is reported between 4 to 10 years. The probable cause for the long duration between receiving alkylating agents and developing t-AML is that recipients usually develop MDS first, and then it turns into AML(7).

Type 2 is less common and develops after the treatment with Topoisomerase II inhibitors. It has a shorter latency period of one to five years, which may be because this drug class directly affects myeloid cell lines and presents overt AML (7-13). However, due to the widespread use of these two drug classes together with or without radiotherapy, this classification is no longer used in the clinic.

t-AML development is rare following the administration of antimetabolites such as fluorouracil. Some studies reported the development of t-AML after treatment with a Platin-based, 5FU-containing regimen (14, 15). To date, there are only a few case reports available for the development of t-AML after initial treatment with 5-FU alone and/or with...
radiotherapy (16, 17). In such cases, 5-FU was administered with a cumulative dose of 5850 to more than 10000 mg/m2. the latency period between the administration of 5-FU and the development of t-AML in these studies was reported 12 to 39 months (16-19). Case reports are reviewed in Table 1.

Our Case had a history of exposure to Capecitabine (cumulative dose of 336000 mg) and developed AML 42 months after the exposure. Capecitabine is a prodrug and metabolized to its active metabolite, 5-fluoroxyuridine monophosphate (5-FUMP) inside the body, so despite there being no report of developing t-AML with that, it would not be out of mind. The latency period of developing t-AML was nearly similar between our case and other case reports. It seems that a higher cumulative dose of 5-FU is associated with the more rapid development of t-AML. However, more studies are needed to confirm this result.

**Genetic basis of t-AML:**

It seems that mutation is the main mechanism of developing AML following the administration of cytotoxic agents. Cytogenetic abnormalities such as -5 and -7/del(5q and 7q), translocation of (11q23), complex karyotypes, or +8 trisomy have been frequently seen in t-AML patients (17). Other cytogenetic abnormalities such as trisomy in one or more pairs of other chromosomes are also reported in t-AML patients (20). Baeu et al reported abnormalities in chromosomes 5 and 7 as the most common cytogenetic abnormalities in alkylating agents and/or radiotherapy recipients (9). The result of del. (5q and 7q) is haploinsufficiency in genes that are responsible for cell growth and proliferation (21).

An interruption in the expression of cell cycle control genes is also seen in t-AML patients, which can justify the occurrence of MDS/AML (22). Furthermore, some studies mentioned that CYP polymorphisms can play a role in the development of t-AML (23-26). Studies also mentioned that Germ-line mutations in the NF-1 and p53 tumor-suppressor genes are repeatedly seen in patients who develop t-AML following MDS (27, 28). Other probable causes of developing t-AML include induction of genome instability or a fusion oncogene, hyper-proliferation of mutant cells, and inflammation (24, 29, 30).

The cytogenetic analysis showed no abnormal translocations, but hyperploidy (trisomy in pairs 7,8, and 21) was seen in our patient.

**Clinical presentation and prognosis of t-AML:**

Alkylating agents, topoisomerase II inhibitors, and some other drugs like Bimolane are well-known for the development of t-AML (7). Anti-metabolites are less often suspected for the development of t-AML. However, the rate of developing t-AML in anti-metabolite recipients is higher compared to the general population (7, 13).

The time period between receiving chemo/radiotherapy for the primary disease and developing AML

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**Table 1: Case reports of developing t-AML following the treatment with 5-FU**

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Primary malignancy</th>
<th>Chemotherapy regimen</th>
<th>Cumulative 5FU dose (mg/m²)</th>
<th>Time to develop t-AML (months)</th>
<th>7-3 induction regimen</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>E-SCC</td>
<td>Nedaplatin plus 5-FU along with daily RT</td>
<td>3500</td>
<td>After complete remission</td>
<td>Not mentioned</td>
<td>All four expired</td>
</tr>
<tr>
<td>2</td>
<td>E-SCC</td>
<td>Cisplatin plus 5-FU</td>
<td>8000</td>
<td>55</td>
<td>Not mentioned</td>
<td>All two expired</td>
</tr>
<tr>
<td>1</td>
<td>Sigmoid colon cancer - Stage IIIB</td>
<td>Leukoverin plus 5-FU</td>
<td>8500</td>
<td>39</td>
<td>Idarubicin plus Ara-C</td>
<td>Complete remission</td>
</tr>
<tr>
<td>1</td>
<td>Gastric cancer</td>
<td>5-FU plus Leukoverin</td>
<td>&gt;10000</td>
<td>12</td>
<td>Mitoxantrone plus Ara-C</td>
<td>Complete remission</td>
</tr>
<tr>
<td>1</td>
<td>Rectal adenocarcinoma</td>
<td>RT with concomitant Capecitabine and three post-radiation cycles of Capecitabine</td>
<td>&gt;10000</td>
<td>16</td>
<td>ATRA Plus Idarubicin</td>
<td>Complete remission</td>
</tr>
<tr>
<td>1</td>
<td>Colorectal adenocarcinoma stage III</td>
<td>5-FU and the subsequent RT</td>
<td>5850</td>
<td>30</td>
<td>Daunorubicin plus Ara-C</td>
<td>Expired</td>
</tr>
<tr>
<td>1</td>
<td>Colorectal adenocarcinoma with peritoneal and liver metastases</td>
<td>Capecitabine</td>
<td>&gt;10000</td>
<td>24</td>
<td>Refused treatment</td>
<td>Expired</td>
</tr>
</tbody>
</table>

1: 5-Fluorouracil. 2: esophageal squamous cell carcinoma. 3: Radiation therapy. 4: Cytarabine. 5: All-trans retinoic acid
varies from months to years and depends on many factors such as chemotherapeutic agent class, cumulative dose of chemotherapeutic drugs or radiation, and dose intensity in each chemotherapy cycle (8, 31, 32).

The clinical presentation is the same in all types of AML (24). In patients who received alkylating agents, t-AML occurs following the presentation of MDS with symptoms of fatigue, fever and cytopenia (9). In topoisomerase II inhibitors recipients, MDS phase does not exists and patients present with overt AML (11). In all case reports of developing t-AML following the administration of 5-FU, patients presented with common symptoms of overt AML including general weakness, fatigue, fever and weight loss in addition to cytopenia and presenting blasts in peripheral blood smear and bone marrow sample (16-19, 33). Our patient’s primary symptom was general weakness and anorexia. Physical examination was negative for fever, lymphadenopathy, organomegaly or skin lesions. The patient's baseline laboratory data showed a leukocytosis with 93% blast and 3% lymphocytes, thrombocytopenia and increase in inflammatory markers.

Patients who develop t-AML have a poor prognosis compared to other patients with AML (20, 34, 35). Samra et al mentioned that overall survival and relapse-free survival is significantly worse in t-AML patients compared to other AML patients. Furthermore, the mortality rate in remission was higher in t-AML patients compared to AML patients (51% vs 16%) (36). It seems like the reason for poor outcomes in this population is the higher incidence of unfavorable karyotypes and cytogenetic abnormalities, respecting that patients with favorable karyotype and good performance status have treatment outcomes same as patients with de novo AML (37-40). However, a recent retrospective study on 742 AML patients showed that t-AML patients had older age but similar mutation profile compared to other AML patients (36).

A brief review of genetic and clinical features of t-AML subtypes and comparison to our case is reviewed in Table 2.

**Treatment of t-AML:**

The treatment of t-AML is the same as the de novo form, including the standard dose of an Anthracycline (D1-D3) plus Cytarabine (Ara-C) (D1-D7) for induction of remission, following a consolidation regimen with a high dose of Cytarabine (HiDAC). In reported cases, 3 studies used Idarubicin plus Ara-C, one study used Mitoxantrone and one study used Danorubicin plus Ara-C for the induction of remission. Except for the Danorubicin recipient, other patients reached complete remission (CR) and also received consolidation treatment with HiDAC (16-19). Although it seems like the achievement of CR is expected

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 2</th>
<th>Other case reports</th>
<th>A. V.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible drugs</td>
<td>Alkylating agents</td>
<td>TPO II inhibitors</td>
<td>5FU</td>
</tr>
<tr>
<td>Prevalence</td>
<td>75% of t-AML cases</td>
<td>Up to 20% of t-AML cases</td>
<td>rare</td>
</tr>
<tr>
<td>Onset of development</td>
<td>4 to 10 years</td>
<td>1 to 5 years</td>
<td>12-39 mo.</td>
</tr>
<tr>
<td>Cytogenetic analysis of bone marrow</td>
<td>-5/del(5q)</td>
<td>Balanced translocations involving chromosome bands 11q23 or 21q22.</td>
<td>46,XY,t(3;21)(q26;q22)</td>
</tr>
<tr>
<td></td>
<td>-7/del(7q)</td>
<td>Clonal monosomy of chromosome 7</td>
<td>48-50, XY [cp 18]</td>
</tr>
<tr>
<td></td>
<td>Trisomy of chromosome 8</td>
<td>MLL gene translocations</td>
<td>46,XY, t(15;17)(q24;q21)</td>
</tr>
<tr>
<td></td>
<td>Loss of chromosomes 18 and 20</td>
<td></td>
<td>46-49,XX +8, +C</td>
</tr>
<tr>
<td></td>
<td>Germ-line mutations in the NF-1 and p53 tumor-suppressor genes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical feature</td>
<td>Approximately two-thirds of patients present with MDS and the remainder with AML with MDS features</td>
<td>Does not have a preceding MDS phase</td>
<td>Does not have a preceding MDS phase</td>
</tr>
<tr>
<td></td>
<td>Patients frequently present with cytopenias</td>
<td>Presents as overt acute leukemia, often with a prominent monocytic component</td>
<td>Presented as overt acute leukemia</td>
</tr>
<tr>
<td></td>
<td>Multi-lineage dysplasia is often present.</td>
<td></td>
<td></td>
</tr>
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</table>

**Table 2:** A comparison of characteristics between different types of t-AML

1: Topoisomerase. 2: 5-Fluorouracil. 3: Treatment-related AML. 4: Deletion. 5: Myelodysplastic syndrome

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in 5-FU recipients who developed t-AML, a review article has reported that remission was achieved in only a small number of t-the AML patients while using the conventional 7+3 regimen (24). Our patient also received a standard 7+3 regimen with Danorubicin plus Ara-C but developed febrile neutropenia during the recovery time, and finally expired because of sepsis and cardiac arrest.

Despite the conflicting treatment outcomes with standard treatments of AML in t-AML patients, there is no other proven choice for the treatment of this population. CPX351 is an investigational formulation that contains liposomal Daunorubicin plus Cytarabine which is under evaluation for the treatment of t-AML patients. Clinical studies have shown that CPX351 is effective and can have beneficial effects on patients’ performance status before allogeneic bone marrow transplantation (41-43).

Allogenic Hematopoietic Stem Cell Transplantation (HSCT) is another treatment for all-cause AML. Compare to de novo AML, patients with t-AML Samra et al also mentioned that both induction of remission with chemotherapy and HSCT had a higher rate of remission and survival in de novo AML patients compared to t-AML patients (36).

**Conclusion:**

Despite the lower prevalence compared to Anthracyclines and Topoisomerase II inhibitors, t-AML following the administration of 5-FU is suspected. We reported a case of a primary colon cancer patient who developed t-AML 42 months after the treatment with Capecitabine. Our observations were in line with the results of other articles about 5-FU. So, according to the case reports about the occurrence of t-AML possibly caused by anti-metabolite drugs, especially in higher cumulative doses, we conclude that lowest effective dose should be chosen, and the risks of treating the primary cancer with anti-metabolites such as 5-FU and Capecitabine should be weighed along with its benefits.
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Abbreviations:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full term</th>
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<tr>
<td>AML</td>
<td>Acute myeloid leukemia</td>
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<tr>
<td>t-AML</td>
<td>Treatment-related Acute myeloid leukemia</td>
</tr>
<tr>
<td>MDS</td>
<td>Myelodysplastic Syndrome</td>
</tr>
<tr>
<td>SFU</td>
<td>5-Fluoro uracil</td>
</tr>
<tr>
<td>RT</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>CEA</td>
<td>carcinoembryonic antigen</td>
</tr>
<tr>
<td>WBC</td>
<td>White Blood Cell</td>
</tr>
<tr>
<td>Plt</td>
<td>Platelet</td>
</tr>
<tr>
<td>IHC</td>
<td>Immunohistochemistry</td>
</tr>
<tr>
<td>HSCT</td>
<td>Hematopoietic Stem Cell Transplantation</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>BMA/BMB</td>
<td>Bone marrow Aspiration and Biopsy</td>
</tr>
<tr>
<td>5-Fluorouridine monophosphate</td>
<td>S-FUMP</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Ara-C</td>
</tr>
<tr>
<td>HIDAC</td>
<td>High dose Ara-C</td>
</tr>
<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
</tr>
<tr>
<td>PBS</td>
<td>Peripheral Blood Smear</td>
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</tbody>
</table>

Author’s contributions:

SA and AB collected and interpreted the patient data regarding the hematological disease.

NS and OA analyzed the patient’s data and were the major contributors to writing the manuscript.

All authors read and approved the final manuscript.

Ethics approval and consent to participate

Before writing the article, consent was obtained from the patient to use his medical information without mentioning his name or providing identifying information.

References


