JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of Cancer Science and Research

Case Report

A Long Survival of a Secondary Acute Myeloid Leukemia Patient under Low-dose Cytosine Arabinoside and Valproic Acid

Mihaila RG[1*]

[1]University of Sibiu, Romania

*Corresponding author: Mihaila RG, MD, PhD, Professor, Lucian Blaga, University of Sibiu, Romania,

E-mail: romeomihaila@yahoo.com

Received: 04-22-2016

Accepted: 06-14-2016

Published: 06-22-2016

Abstract

The prognosis of elderly patients with acute myeloid leukemia is poor, especially when they have associated diseases that affect their performance status. Azacitidine, decitabine, and low-dose cytosine arabinoside are drugs of choice for the treatment of unfit patients with acute myeloid leukemia. Their combination with other adjuvant drugs worth to be studied, in order to increase the therapeutic effectiveness. We present a female patient who was treated with low-dose cytosine arabinoside and valproic acid. She is alive at 30 months since the diagnosis of acute myeloid leukemia.

Keywords: Acute Myeloid Leukemia; Cytosine Arabinoside, Valproic Acid

Background

Elderly patients with acute leukemia, especially those in which the disease appeared in the evolution of a myelodysplastic syndrome or a myelodysplastic/myeloproliferative neoplasm raise special problems of treatment due to their performance status. The use of low-dose cytosine arabinoside, azacitidine or decitabine in combination with various adjuvant drugs could be a solution for them.

Case Report

A 76 years old female patient came to the hospital for fatigue, asthenia, anorexia, and weight loss. An ambulatory blood count revealed a leukocytosis with 13% blasts. She was known with diabetes treated with oral antidiabetic agents, ischemic heart disease, essential hypertension, and deteriorative organic psychosyndrome. The physical examination showed: severe pallor, overweight status, liver anterior edge at 1.5 cm below the costal arch and impalpable spleen. She had no fever. Laboratory analysis confirmed the presence of leukocytosis (37,560/mm^3); in addition, she had severe anemia (the serum hemoglobin level was 5.3 g/dL), thrombocytopenia (40,000/mm^3), hyperuricemia (13.4mg/dL), and hypertriglyceridemia (229 mg/dL); the erythrocyte sedimentation rate was 152 mm/1 hour, in the absence of any detectable infections; a Coombs test was positive. The two bone marrow aspirations (made in the sternum and iliac crest) were white. The immunophenotypic examination performed from peripheral blood showed a population of atypical cells with the phenotype: CD10-, CD61-, CD41-, CD34-, CD33++, HLA-DR-, CD64-, CD14-, CD22s-, CD20-, CD5- CD4 -, CD8-, MPOic +. The histopathological examination of bone marrow biopsy diagnosed an acute myeloid leukemia (AML) occurred in the evolution of a myelodysplastic / myeloproliferative neoplasia.

She was treated with hydroxycarbamidum, then - mini doses of cytosine arabinoside (25 mg/day, 7 days), methylprednisolone and transfusions of red blood cells, followed by the negativation of Coombs test. One month later she returned with 23,080 white blood cells/mm^3, hemoglobin of 10 g/dL and 79,000 platelets/mm^3; she had 23% blasts in the peripheral blood. After two more courses of mini doses of cytosine arabinoside the complete remission was achieved and corticosteroids were

stoped.

Further, the patient was treated with valproic acid (500 mg daily) and monthly courses of mini doses of cytosine arabinoside (2x25 mg/day, 7 days). AML relapsed eleven months since the diagnosis. The patient had 50,630 cells/mm^3, hemoglobin blood level of 12.3 g/dL and 161,000 platelets/mm^3. She was treated with cytosine arabinoside 200 mg/day, 7 days, and idarubicine 15 mg/day, 3 days. At the exit from aplasia she had no blasts in the peripheral blood, and at her return, a month later, she had 4% blasts in bone marrow. She continued the daily treatment with valproic acid and the monthly administration of mini doses of cytosine arabinoside (2x25 mg/day, 7 days). The AML relapsed for a second time 24 months after the diagnosis (4,350 white blood cells/mm^3, but with 5% blasts in peripheral blood and 36-67% blasts in bone marrow). She was treated with the same course of chemotherapy used at the first disease relapse, followed by a new complete hematological remission. The maintenance was made with valproic acid and the monthly administration of mini doses of cytosine arabinoside, too.

During her next hospitalizations she presented two urinary infections that required antibiotics. These were, probably, the cause of a clostridium difficile colitis, that was treated with vancomycin (4x250 mg / day, 10 days) + metronidazole (3x500 mg / day, 10 days) + rifaximin (3x400 mg / day, 10 days). A relapse of her colitis appeared a month later and was treated with the same antibiotics schedule. Colitis has not recurred since then (in the last 3 months). The complete hematological remission persists at 30 months since the establishment of the diagnosis of AML.

Discussion

Studies that compare the efficacy of low-dose cytosine arabinoside and decytabine administred to elderly patients with AML can be found in the literature. One of them noted that both drugs have similar overall survival and toxicity [1]. We used low-dose cytosine arabinoside as decytabine was not available in Romania at the moment of diagnosis. The reason was that our patient was elderly, with associated diseases (dibetes, ischemic heart disease, arterial hypertension and deteriorative organic psychosyndrome), which gave them an ECOG status of 3. We used the classical schedule „3 + 7" only when the regimen with low-dose cytosine arabinoside + valproic acid was not effective (in relapses). But unlike the cited study, where the median overall survival was 5.5 months for each of the treatment groups [1], our patient is alive at 30 months since the moment of diagnosis, and her AML is in complete remission. Azacitidine associated with low-dose cytosine arabinoside was used in a study made on 27 patients with de novo AML and myelodysplastic syndrome-RAEB2. The patients received at least 4 cycles of treatment and the response to therapy ratios was not statistically significant different compared to the patients treated only with azacitidine. Instead, progression-free survival was longer in the group with the combined therapy compared to that treated with azacitidine in monotherapy and therapy-related toxicity was similar between the 2 groups [2]. So, this combination should be studied in larger groups of patients. Another combination was also studied: no difference in survival was found in a high propensity score group of patients aged ≥ 60 years treated with low-dose cytosine arabinoside, aclarubicin and granulocyte colony-stimulating factor priming versus daunorubicin and cytosine arabinoside [3].

The treatment with low-dose cytarabine associated with continuous valproic acid and intermittent ATRA adminstration conduced to complete hematological remission only in a small minority of those 36 AML patients reported by Fredly H and col., but side effects were unfrequently found. This combination can stabilize the disease in a subset of unfit AML patients [4]. A study that included 149 patients with myelodysplastic syndrome or AML treated with decitabine associated with valproic acid did not conduct to an improved outcome [5].

What is the benefit of valproic acid association? Valproic acid is a histone deacetylase inhibitor with anticancer activity, as it is a trigger of apoptosis through rassf1a expression induction [6]. A study made in vitro on primary AML cells also noted an increase of apoptosis, an induction of acetyl histone H3, and an antiproliferative effect after valproic acid +/- cytosine arabinoside [7]. It is accepted that valproic acid increases the survival in more than 20% of patients with advanced AML [8]. But some clinical studies that included a small number of AML elderly patients (ex 15) treated with valproic acid and low-dose cytosine arabinoside did not obtain hematologic remissions [7], even partial ones, but we can not draw reliable conclusions based only on them. Unfortunately, valproic acid has not been investigated in randomized clinical studies until recently [9]. It can be considered in unfit patients, as it is able to improve the blood values, according to the results of several studies; no important clinical toxicity was showed after its use [9].

The fact that our patient presented urinary infections during therapy with low-dose cytosine arabinoside is not accidental, especially as she has also diabetes. In a recent published study, it was found that infections appeared in 25% of cycles with low-intensity therapeutic regimens given to patients with AML. The presence of transfusion dependence and high serum levels of lactic dehydrogenase were predictors of infection occurence and the use of antibiotic prophylaxis was able to reduce the infectious complications [10]. But if the treatment of urinary infections favored the occurence of clostridium difficile colitis, it would be expected the same result after antibiotic prophylaxis. The usefulness of antibiotic prophylaxis is questionable in the current epidemiological context. An explanation for the occurrence of infections could be the decreased T cell viability and the diminishing of certain T cell cytokines release induced in vitro even by low levels of cytosine arabinoside, and especially by its combination with valproic acid and ATRA [11].

It was showed that a histone demethylation encoding gene [UTX (KDM6A)] is able to increase the sensitivity to valproic acid in C. elegans, fact that highlights a functional relationship between the processes of protein acetylation and lysine-specific methylation and offers a promising novel therapeutic target [8]. In the future, a solution for AML patients who are resistant to treatment could be the use of valproic acid associated with a proteasome inhibitor (eg bortezomib), as this combination inhibits in vitro cell proliferation, arrests the cell cycle in G0-G1 phase and promotes apoptosis in some cell lines (HL60 and HL60A) [12].

References

1. Jacob LA, Aparna S, Lakshmaiah KC, Lokanatha D, Babu G et al. Decitabine Compared with Low-Dose Cytarabine for the Treatment of Older Patients with Newly Diagnosed Acute Myeloid Leukemia: A Pilot Study of Safety, Efficacy, and Cost-Effectiveness. Adv Hematol. 2015, 2015: 167029.

2. Atalay F, Ateşoğlu EB. Low Dose Cytosine Arabinoside and Azacitidine Combination in Elderly Patients with Acute Myeloid Leukemia and Refractory Anemia with Excess Blasts (MDS-RAEB2). Indian J Hematol Blood Transfus. 2016, 32(1): 46-53.

3. Minakata D, Fujiwara S, Ito S, Mashima K, Umino K et al. A low-dose cytarabine, aclarubicin and granulocyte colony-stimulating factor priming regimen versus a daunorubicin plus cytarabine regimen as induction therapy for older patients with acute myeloid leukemia: A propensity score analysis. Leuk Res. 2016, 42: 82-87.

4. Fredly H, Ersvær E, Kittang AO, Tsykunova G, Gjertsen BT, Bruserud O. The combination of valproic acid, all-trans retinoic acid and low-dose cytarabine as disease-stabilizing treatment in acute myeloid leukemia. Clin Epigenetics. 2013, 5(1): 13.

5. Issa JP, Garcia-Manero G, Huang X, Cortes J, Ravandi F et al. Results of phase 2 randomized study of low-dose decitabine with or without valproic acid in patients with myelodysplastic syndrome and acute myelogenous leukemia. Cancer. 2015, 121(4): 556-561.

6. Davood ZA, Shamsi S, Ghaedi H, Sahand RI, Mojtaba G et al. Valproic acid may exerts its cytotoxic effect through rassf1a expression induction in acute myeloid leukemia. Tumour Biol. 2016.

7. Lane S, Gill D, McMillan NA, Saunders N, Murphy R et al. Valproic acid combined with cytosine arabinoside in elderly patients with acute myeloid leukemia has in vitro but limited clinical activity. Leuk Lymphoma. 2012, 53(6): 1077-1083.

8. Forthun RB, Sengupta T, Skjeldam HK, Lindvall JM, McCormack E et al. Cross-species functional genomic analysis identifies resistance genes of the histone deacetylase inhibitor valproic acid. PLoS One 2012, 7(11): e48992.

9. Fredly H, Gjertsen BT, Bruserud O. Histone deacetylase inhibition in the treatment of acute myeloid leukemia: the effects of valproic acid on leukemic cells, and the clinical and experimental evidence for combining valproic acid with other antileukemic agents. Clin Epigenetics. 2013, 5(1): 12.

10. Bainschab A, Quehenberger F, Greinix HT, Krause R, Wölfler A et al. Infections in patients with acute myeloid leukemia treated with low-intensity therapeutic regimens: Risk factors and efficacy of antibiotic prophylaxis. Leuk Res. 2016, 42: 47-51.

11. Ersvaer E, Brenner AK, Vetås K, Reikvam H, Bruserud Ø. Effects of cytarabine on activation of human T cells - cytarabine has concentration-dependent effects that are modulated both by valproic acid and all-trans retinoic acid. BMC Pharmacol Toxicol. 2015, 16: 12.

12. Nie D, Huang K, Yin S, Li Y, Xie S et al. Synergistic/additive interaction of valproic acid with bortezomib on proliferation and apoptosis of acute myeloid leukemia cells. Leuk Lymphoma. 2012, 53(12): 2487-2495.