



Case report

A clinical challenge: Treatment of acute myeloid leukemia in a Jehovah's Witness



Daniela Cárdenas-Araujo*, Elías Eugenio González-López, Xitlaly Judith González-Leal, José Carlos Jaime-Pérez, David Gómez-Almaguer

Universidad Autónoma de Nuevo León, Hospital Universitario, Monterrey, Mexico

ARTICLE INFO

Article history:

Received 4 February 2016

Accepted 12 May 2016

Available online 4 June 2016

Introduction

The Jehovah's Witness religious movement is a Christian sect with over 2.6 million followers worldwide that forbids the transfusion of blood and blood components to its members.¹ There is limited experience in the treatment of Jehovah's Witnesses with acute myeloid leukemia (AML). Treatment of patients, who do not accept required blood support on religious grounds, is always a difficult problem. This dilemma is of particular concern in cases such as acute leukemia in which the physician himself, by choosing and applying appropriate treatment, may increase the need for transfusion support.²

The standard treatment for AML is seven days of an anthracycline and three days of cytarabine (7+3); with this regimen 70–80% of young adults and 40–60% of older adults, will achieve complete remission.³ The combination of cytarabine plus an anthracycline results in severe pancytopenia and therefore requires transfusion support.⁴ During induction chemotherapy, patients are given an average of 10.8 units of red blood cell concentrates and 8.5 platelet transfusions over a period of about 30 days.⁵

Corsetti et al. described a chemotherapy regimen designed for elderly AML patients that had low hematological toxicity, and response rates of 36%.⁶ In this setting, another drug, azacytidine is used to treat AML in elderly or fragile patients who are not candidates for an intensive chemotherapy regimen.⁷ However, since azacytidine was not available at our institution due to financial restrictions, we administered a combination of low-dose cytarabine plus valproic acid to our patient after she rejected standard AML therapy.

Case report

In June 2014, a 35-year-old female Jehovah's Witness presented weakness, fatigue, malaise and skin lesions of one month's duration. Peripheral blood was tested and her complete blood count (CBC) gave a hemoglobin (Hb) level of 8.6 g/dL, an elevated white blood cell count (WBC) of $30 \times 10^9/L$ and a platelet count of $71 \times 10^9/L$.

Upon physical examination of the skin, painless, nodular and violaceous lesions disseminated on the face, neck, trunk and extremities were identified as myeloid sarcomas. She also

* Corresponding autor at: Hospital Universitario, Universidad Autónoma de Nuevo León, Av. Madero y Gonzalitos, Col. Mitras Centro, Monterrey, CP. 64460, Mexico. Tel.: +52 18183 338111.

E-mail address: dra.danielacardenas@hotmail.com (D. Cárdenas-Araujo).

<http://dx.doi.org/10.1016/j.bjhh.2016.05.003>

1516-8484/© 2016 Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

presented with swollen and spongy gums and a soft painful and tender tissue tumor on the right side of the neck with a mean diameter of 6 cm.

A bone marrow aspiration revealed a hypercellular marrow with 70% monoblasts. Flow cytometry was performed revealing an aberrant immunophenotype consisting of two populations of blasts: the first was HLA-DR⁺, CD13⁺, CD33⁺ weak, CD34⁺, CD45⁺ weak, CD64⁺, CD117⁺, MPO⁺ in 50%, and the second population included 13% of the blasts with a HLA-DR⁺, CD33⁺, CD34⁺ weak, CD45⁺, CD56⁺, CD64⁺, CD123⁺, MPOc⁺ phenotype. Cytogenetic and molecular studies were not performed. She was diagnosed with AML not otherwise specified using the World Health Organization Classification. Biopsies of the skin and the soft tissue tumor were performed showing an infiltrate of monocytoid cells (MPO⁺, CD68⁺, CD34⁺, CD117⁺), which was consistent with leukemia cutis.

The patient and family were informed that the appropriate treatment (7 + 3) implied marked and prolonged myelosuppression requiring transfusion support, and the patient refused to grant consent for transfusions. A minimally myelosuppressive treatment plan consisting only of vinblastine for cytorreduction was then proposed and accepted. The patient was fully aware of the reduced probability of achieving a durable complete remission.

She was hospitalized at diagnosis and 10 mg of vinblastine was administered for cytorreduction. The next day the WBC count was $17.4 \times 10^9/L$. Four days later, the WBC was $4.5 \times 10^9/L$, Hb was 7.7 g/dL and the platelet count was $39 \times 10^9/L$.

A week later, she complained about progressive dysphagia and an increase in the myeloid sarcomas to about 10 cm. Her CBC revealed WBC $15 \times 10^9/L$, Hb 8 g/dL and platelet count $100 \times 10^9/L$. She received 17 mg mitoxantrone and intermediate dose of Ara-C (two doses of 1.5 g IV b.i.d.). The next day both the dysphagia and tumor mass disappeared. Treatment was uneventful, with neither infectious nor hemorrhagic complications, however on Day +12 she presented with severe pancytopenia [Hb: 6 g/dL, absolute neutrophil count (ANC): 0, platelet count: $30 \times 10^9/L$], therefore we decided to change the treatment regimen and low dose Ara-C and valproic acid were given in an outpatient setting.

A month later (Day +26) her CBC revealed Hb 9.1 g/dL, WBC $4.05 \times 10^9/L$, ANC 0, and platelet count $130 \times 10^9/L$. She received Ara-C (20 mg b.i.d.) as a subcutaneous injection for four days, subsequent courses of low dose Ara-C were planned after at least 21 days, with valproic acid starting at 5 mg/kg daily divided in two equal doses. Dose escalation of valproic acid was carried out according to patient tolerance until the plasma therapeutic range (50–100 mcg/mL) was reached. This patient also received prophylactic antibiotics if the ANC dropped below $0.5 \times 10^9/L$. She received levofloxacin (500 mg PO every day), acyclovir (400 mg b.i.d.) and itraconazole (100 mg daily). The patient refused erythropoietin due to religious beliefs. In every cycle one more day of Ara-C was added if the Hb was >7 g/dL and platelet count $>30 \times 10^9/L$. During the sixth course she received seven days of Ara-C, after which severe cytopenias developed; it was decided to reduce the Ara-C to six days in the next course. In the eighth cycle, she presented with hyperleukocytosis ($176 \times 10^9/L$) and the size of

the myeloid sarcomas increased. At that time, 10 mg of vinblastine were again administered, and cytorreduction (WBC $3.05 \times 10^9/L$) with ANC 0 was obtained, along with reduction in the size of the sarcomas.

She received eight courses of treatment without transfusions or infectious complications visiting the outpatient clinic for a checkup twice a week; during this time, she was able to perform her basic daily activities, social and religious.

After the last course of therapy, she presented a cough with expectoration but was afebrile. A chest X-ray revealed bilateral peripheral pulmonary infiltrates consistent with bilateral pneumonia of unknown etiology. She refused to be hospitalized and was managed with antibiotics at home. The patient died eight months after diagnosis.

Discussion

There is only one report of successful remission induction using standard chemotherapy (7 + 3) in a Jehovah's Witness with AML.⁸ In another report, a 20-year-old woman was diagnosed with AML by morphology in 1979, but without molecular, cytogenetics or flow cytometry confirmatory studies. She was treated with vincristine, prednisone and Ara-C and was cured at the time of the report.⁹ On the grounds of having only a morphology diagnosis and the patient responded to that specific treatment, we hypothesize that this case may have been a lymphoblastic leukemia. There are other case reports on patients surviving longer than our patient, however all were treated in an inpatient setting, and/or had infectious complications.¹⁰

We acknowledge that azacitidine is a therapeutic option for patients with myelodysplastic syndromes and older patients with AML.¹¹ Its use in a Jehovah's Witness has been reported, however because of its elevated costs it was not a valid option for this patient.

Herein we report our experience treating a Jehovah's Witness using vinblastine, low dose Ara-C and valproic acid but without blood transfusions, based on a treatment for elderly patients published by Corsetti et al.⁶ who reported an overall response rate of 35% and an overall median survival of eight months (range: 2–36). These authors included histone deacetylase inhibitors, such as valproic acid, which have a proven efficient to overcome differentiation arrest of AML blasts.¹² We decided to use this regimen because of its response rates. Low dose Ara-C has been used in several regimens of phase II trials for AML for several years giving responses that include complete response.¹³ This therapy is well tolerated and can be given in an outpatient or home care setting.

Vinblastine is a drug rarely used in the treatment of AML. Vinca alkaloids, such as vinblastine, target microtubule dynamics by binding to tubulin monomers and dimers.¹⁴ They have been used in relapse or refractory AML patients. There are some studies using vinblastine in combination therapy with Ara-C, VP 16-213 (etoposide) and vincristine for relapsed AML.¹⁵ The drug has been used as monotherapy in children with AML, with a reported remission rate of 53%.¹⁶

Gómez-Almaguer et al. reported reduction of blasts in peripheral blood of AML patients after the administration of

vinblastine, with a 77% response rate of patients within the first weeks of treatment. Thus, vinblastine is a less costly and less toxic option for palliative cytoreduction.¹⁷ Our patient initially received vinblastine alone, but a week later, the mass reappeared. So we concluded that vinblastine can be used at the start of the treatment to decrease tumor burden in LMA, but it should be followed by supplementary therapy. We did not know whether vinblastine would lead to additional transfusion requirements, but in the experience of our service, it is a safe drug to reduce or eliminate the necessity of blood transfusions in elderly people or in palliative care treatment.

Conclusion

We administered a combination of Ara-C and valproic acid in our AML patient, together with vinblastine when there was a high tumor burden. This regimen was well tolerated, with good response and regression of extramedullary infiltration. The patient survived for eight months without transfusions or infectious complications, and she was hospitalized only at diagnosis receiving the rest of the therapy as an outpatient. The alternative treatment described appears to be a valid option that offers an acceptable quality of life for AML patients refusing standard treatment that includes transfusions and hospitalization.

Conflict of interest

The authors declare no conflicts of interest.

REFERENCES

1. Brown NM, Keck G, Ford PA. Acute myeloid leukemia in Jehovah Witnesses. *Leuk Lymphoma*. 2008;49(4):817-20.
2. Boggs DR. Jehovah's witnesses with leukemia. *Hosp Pract (Off Ed)*. 1985;20(3):92, 94-5, 98 passim.
3. Döhner H, Estey EH, Amadori S, Appelbaum FR, Büchner T, Burnett AK, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood*. 2010;115(3):453-7.
4. Ohtake S, Miyawaki S, Fujita H, Kiyoi H, Shinagawa K, Usui N, et al. Randomized study of induction therapy comparing standard-dose idarubicin with high-dose daunorubicin in adult patients with previously untreated acute myeloid leukemia: the JALSG AML201 Study. *Blood*. 2011;117(8):2358-65.
5. Jansen AJ, Caljouw MA, Hop WC, van Rhenen DJSM. Feasibility of a restrictive red-cell transfusion policy for patients with intensive chemotherapy for acute myeloid leukaemia. *Transfus Med*. 2004;14(1):33-8.
6. Corsetti MT, Salvi F, Perticone S, Baraldi A, De Paoli L, Gatto S, et al. Hematologic improvement and response in elderly AML/RAEB patients treated with valproic acid and low-dose Ara-C. *Leuk Res*. 2011;35(8):991-7.
7. Cogle CR, Scott BL, Boyd T, Garcia-Manero G. Oral Azacitidine (CC-486) for the treatment of myelodysplastic syndromes and acute myeloid leukemia. *Oncologist*. 2015;20(12):1404-12.
8. Goldberg SL, Chan CS, Dawkins FW, Mehlman TW, Schechter GP. Should Jehova's witnesses be denied intensive chemotherapy for acute leukemia? *N Engl J Med*. 1990;322(11):777-8.
9. Broccia G. Long-term continuous complete remission of acute myeloid leukemia in a Jehovah's witness treated without blood support. *Haematologica*. 1994;79(2):180-1.
10. Garelus H, Grund S, Stockelberg D. Induction with azacytidine followed by allogeneic hematopoietic stem cell transplantation in a Jehovah's Witness with acute monocytic leukemia. *Clin Case Rep*. 2015;3(5):287-90.
11. Yamamoto Y, Kawashima A, Kashiwagi E, Ogata K. Case report a Jehovah's witness with acute myeloid leukemia successfully treated with an epigenetic drug, azacitidine: a clue for development of Anti-AML therapy requiring minimum blood transfusions. *Case Rep Hematol*. 2014;2014:141260.
12. Leyden M, Manoharan A, Boyd A, Cheng ZM, Sullivan J. Low dose cytosine arabinoside: partial remission of acute myeloid leukaemia without evidence of differentiation induction. *Br J Haematol*. 1984;57(2):301-7.
13. Baccarani M, Tura S. Differentiation of myeloid leukaemic cells: new possibilities for therapy. *Br J Haematol*. 1979;42(3):485-7.
14. Dhamodharan R, Jordan MA, Thrower D, Wilson L, Wadsworth P. Vinblastine suppresses dynamics of individual microtubules in living interphase cells. *Mol Biol Cell*. 1995;6(9):1215-29.
15. Sauter C, Fehr J, Frick P, Gmuer J, Honegger H, Martz G. Acute myelogenous leukemia: successful treatment of relapse with cytosine arabinoside, VP 16-213, vincristine and vinblastine (A-triple-V). *Eur J Cancer Clin Oncol*. 1982;18(8):733-7.
16. Geiser CF, Mitus JW. Acute monocytic leukemia in children and its response to vinblastine (NSC-49842). *Cancer Chemother Rep*. 1975;59:385-8.
17. Gómez-Almaguer D, Alejandro R, Hernández M, Alejandro A, et al. Artículo original. ¿Es la vinblastina útil en la leucemia aguda mieloblástica? *Rev Hematol Mex*. 2012;13(1):11-5.