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Management of Jehovah's Witnesses with acute lymphoblastic leukemia. Twenty years of experience in a reference hospital in Mexico City.

Manejo de Testigos de Jehová con leucemia linfoblástica aguda. Veinte años de experiencia en un hospital de referencia de la Ciudad de México

Christian Ramos-Peñafiel,[1] Carlos Martínez-Murillo,[1] Irma Olarte-Carrillo,[2] Etta Rozen-Fuller,[1] Victoria Ferrer-Argote,[1] Daniela Pérez-Sámano,[1] Adán Germán Gallardo-Rodríguez,[3] Adolfo Martínez-Tovar

Abstract

OBJECTIVE: To describe the treatments used to extend recommendations for the care of Jehovah's Witnesses patients.

MATERIALS AND METHODS: A retrospective study including patients treated from 1999 to 2019 at the General Hospital of Mexico in Mexico City, Jehovah's Witnesses who received a treatment scheme for acute lymphoblastic leukemia without transfusion support.

RESULTS: A total of 11 Jehovah's Witnesses patients, 7 adults (mean age, 41 years) and 4 pediatric patients (mean age, 8 years) were treated. When classifying according to the hemoglobin level, 5/11 patients had hemoglobin levels less than 6 g/dL at diagnosis, 3/11 between 6 to 9 g/L, and 3/11 with levels higher than 10 g/dL. Of the four pediatric patients, all achieved a complete remission; in adults 4/7 achieved a complete remission, and 3/7 had a failure in induction. At the end of the follow up, 6/7 relapsed to bone marrow compared to 2/4 pediatric patients. The different hemoglobin values at diagnosis did not significantly impact survival or the percentage of relapse.

CONCLUSIONS: The treatment of Jehovah's Witnesses patients is possible without transfusion support but with the combination of high doses of sanguineous stimulants to average the prognosis of patients with acute lymphoblastic leukemia.

KEYWORDS: Acute lymphoblastic leukemia; Human erythropoietin.

Resumen

OBJETIVO: Describir los tratamientos prescritos para ampliar las recomendaciones para el cuidado de los pacientes Testigos de Jehová.

MATERIALES Y MÉTODOS: Estudio retrospectivo realizado con pacientes atendidos de 1999 a 2019 en el Hospital General de México en la Ciudad de México, se incluyeron Testigos de Jehová que recibieron un esquema de tratamiento contra leucemia linfoblástica aguda sin soporte transfusional.

RESULTADOS: Se trataron 11 pacientes Testigos de Jehová, 7 adultos (edad media, 41 años) y 4 pacientes pediátricos (edad media, 8 años). Al clasificar según la concentración de hemoglobina, 5/11 pacientes tenían concentraciones de hemoglobina menores a 6 g/dL al diagnóstico, 3/11 entre 6 y 9 g/L y 3/11 concentraciones mayores a 10 g/dL. De los cuatro pacientes pediátricos, todos lograron la remisión completa;

[1] Hematology service.
[2] Molecular Biology Laboratory.
[3] Hematology research department.
Hospital General de México Dr. Eduardo Liceaga, Mexico City.

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Correspondence
Christian Omar Ramos Peñafiel
leukemiachop@hotmail.com

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en adultos 4/7 lograron una respuesta completa y 3/7 fallaron en la inducción. Al final del seguimiento, 6/7 recayeron en la médula ósea en comparación con 2/4 pacientes pediátricos. Los diferentes valores de hemoglobina al momento del diagnóstico no afectaron significativamente la supervivencia ni el porcentaje de recaída.

CONCLUSIONES: El tratamiento de los pacientes Testigos de Jehová es posible sin soporte transfusional, pero con la combinación de altas dosis de estimulantes sanguíneos para obtener el pronóstico de los pacientes con leucemia linfoblástica aguda.

PALABRAS CLAVE: Leucemia linfoblástica aguda; eritropoyetina humana.

BACKGROUND

Jehovah's Witnesses (JW) is a Christian movement founded in 1870 in the United States; due to their rejection of the use of blood components, various authors around the world have issued different recommendations for the care of these patients, especially for surgical or obstetric events.[1] Because of this, there have been multiple legal battles for the lack of acceptance of transfusion of whole blood, platelet concentrates, fresh frozen plasma, or some other blood component, arguing individual autonomy for the acceptance of their treatment. This legal situation has been especially increased in pediatric patients and/or in the different vulnerable groups.[2,3] Despite this autonomy, in cases where life is at risk, the different legal codes require medical personnel to use the blood components.[4] With the use of different blood stimulants (erythropoietin, granulocyte colony stimulating factors) JW care has been improved, especially with < 7 g/dL hemoglobin levels, where the combination of intravenous iron, erythropoietin, or the administration of oxygen carriers may be an acceptable option.[5,6]

Transfusion support is an important part in the treatment of cancer patients for they improve oxygen transport capacity and the speed of chemotherapy distribution.[7] In turn, 10% of cancer patients show a high risk of bleeding, requiring the administration of frozen fresh plasma or platelet concentrates, especially in those with hepatic failure or associated disseminated intravascular coagulation.[8] Tenenbaum et al. in Germany described their experience of the care of 14 JW children over a 16-year period, concluding that cancer treatment may be possible with the combination of different strategies such as iron, granulocyte colony stimulating factors, interleukin 11, or erythropoietin.[9] Recently, Shallis et al. described their experience of caring for JW patients with myeloid neoplasms (myelodysplasia, acute myeloid leukemia); although the patient with myelodysplasia, showed adequate tolerance to treatment with Azacytidine. The cases with secondary myeloid leukemia, such as acute myeloid leukemia, showed a fatal outcome due to complications associated with treatment as well as transfusion needs.[10] The experience of caring for JW with leukemia is mainly based on the experience of very small cases or series. For example, in acute myeloid leukemia, the treatment is individualized combining agents such as asparaginase, vincristine, mitoxantrone, azacytidine or modifications of the 7+3 scheme.[11-14] Cullis et al. reported their experience in the care of 5 cases with acute leukemia, two of them with ALL remission induction was based on the combination of vincristine, prednisone, and in

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the first case asparaginase was added. The two cases integrated remission (case No. 2 requiring 2 induction cycles) reaching the maintenance stage.[15]

In developing countries, the experience of JW treatment is still limited, especially due to the different legal controversies. Mexico is a country with a majority of Catholic beliefs, but it is estimated that there are a total of 13,245 congregations of JW (1 JW per 151 inhabitants).[16]

In our country, in the penal code, article 15, fraction V reflects the need to safeguard one's own or another's legal welfare from a real, current, or imminent danger, which forces health personnel to apply the transfusion to preserve life if there is no other therapeutic option.[17]

Recently in Northern Mexico, a judge withdrew custody of the parents of a minor with ALL to authorize the transfusion and continue his treatment.[18] Due to the great controversy for their care, there is little experience on how to treat JW patients and most of the recommendations suggest combining drugs commonly used in ALL in order to integrate a complete remission. In our center, we only have the previous experience of the care of three JW cases with an induction scheme based on vincristine, prednisone, bleomycin achieving complete remission in the three.[19]

This paper presents the experience of 20 years of treatment of JW patients treated in the Hematology department of the General Hospital of Mexico without transfusion support and under legal advice.

MATERIALS AND METHODS

A retrospective study including patients treated at the Department of Hematology of the General Hospital of Mexico from 1999 to 2019. All patients had informed consent for treatment and informed consent was provided in the case of pediatric patients. For the treatment of pediatric patients, advice was provided by the legal area of the institution. The diagnosis of Acute Lymphoblastic Leukemia was based on the criteria of the World Health Organization.[20]

Treatment strategy

The patients were basically treated in two periods, the first from 1999 to 2005, when the treatment was individualized according to the experience of the attending physician, and the second period after 2005, in which the patients were treated according to the institutional protocol.[21] Remission induction was based on vincristine (1.5 mg/m^2 SC), steroids (prednisone 60 mg/m^2 SC, continuously for 28 days) and daunorubicin (60 mg/m^2 SC) was added to the scheme induction according to the hemoglobin level.

After the induction scheme, a 2-year consolidation and maintenance stage were continued based on 6-mercaptopurine (50 mg/m^2 SC) and weekly intramuscular 50mg Methotrexate. In patients treated between 1999-2005, the consolidation scheme was based on weekly combinations of L-Asparaginase (5000 IU/m^2 intramuscular SC) with Bleomycin 10 IU/m^2 SC, weekly, especially in those cases with splenomegaly or persistence of lymphadenopathy.

Central nervous system (CNS) prophylaxis consisted of the application of intrathecal chemotherapy, methotrexate, hydrocortisone, and cytarabine, on days 1, 14, and 28 of the remission induction cycle. Complete remission (CR) was considered when patients presented less than 5% of lymphoid blasts in the bone marrow scan on the day +28 of treatment and absence of peripheral blood blasts. The presence of more than 5% blasts was considered as relapse at any time during treatment.

Support treatment

Supportive treatment included the administration of recombinant human erythropoietin (rHuEPO) at doses of 50 to 75 IU/kg/day, granulocyte colony stimulating factor (FECG) 150-300µg subcutaneously every 24hrs. In conjunction with the erythropoietin scheme, intravenous iron was calculated according to the Ganzoni formula (total iron dose = [current weight x (current 15-Hb) x 2.4 + iron stores]).[22] In cases of persistent anemia with disappearance of the blasts and erythroblastic response in the bone marrow (BM), calcium folinate was added at a dose of 30 mg/day. No transfusions of erythrocyte or platelet concentrates were performed during induction or during consolidation.

Statistical analysis

The statistical SPSS software, version 20.0 was used. For the survival analysis, the Kaplan Meier method was used; the comparison of disease-free survival was performed with the historical record of treatment of ALL using the log rank test. The risk of different levels of hemoglobin on the possibility of death or relapse was estimated using the Odds ratio and Fisher's exact test (p value ≤ 0.05, 95% CI).

Ethical considerations

In all cases, informed consent was documented for the start of treatment; in the case of pediatric patients there was also an informed consent for the child. In turn, in adult patients, legal advice was requested by the institution in order to abide the current regulations of JW care.

RESULTS

In 20 years, a total of 11 JW patients have been tended at the Hematology service of the General Hospital of Mexico (**Table 1**). Most were adult patients (n = 7). The average age for adult patients was 41 years (range 19 to 68 years); for pediatric patients the median was 8 years (range 2 to 14 years). The average time of onset symptoms were 3 weeks (average 1 to 6 weeks). Clinically, 5/11 showed hepatomegaly at diagnosis, 4/11 splenomegaly and 2/11 lymphadenopathies. None of the cases presented CNS infiltration at the time of diagnosis. The average hemoglobin levels were 7.4 g/dL for adult patients (3.5-10.5 g/dL) and 5.4 g/dL for pediatric patients (4.6-2.2 g/dL). When classifying cases according to the hemoglobin level, 5/11 had hemoglobin levels less than 6 g/dL at diagnosis, 3/11 showed levels between 6 to 9 g/dL, and 3/11 had levels above 10 g/dL. The average leukocyte count at diagnosis was 56.8 x 10^3/µL (range 1.0 to 200 x 10^3/µL) and for platelets it was 45.2 x 10^3/µL (range 18 to 94 x 10^3/µL).

When classifying the cases according to the leukocyte count, 45.5% (n=5) had figures higher than 30 x 103/mcl. No case showed infiltration to the central nervous system. Only one case showed positivity for the BCRABL1 transcript. According to risk, 8/11 were classified as high risk.

Treatment result

Of the four pediatric patients, all achieved a complete remission, in adults 4/7 achieved a CR and 3/7 had a failure in induction. The average time to integrate this CR was 31 days (time 21-36 days). The main cause of treatment failure was due to both, complications related to febrile neutropenia (n = 2) and hemorrhagic complications (n = 1). During their follow-up, patients were maintained with supportive treatment using erythropoietin to maintain hemoglobin levels higher than 10 g/dL and administration of colony stimulating factor in case of neutrophil values were less than 0.8 x 10^3/µL at any time during treatment. The treatment of patients treated before 2005 was based on the considerations

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Table 1. Main recommendations for the care of Jehovah's Witnesses patients with acute lymphoblastic leukemia

Induction strategy
Stratify the clinical and molecular risk (BCRABL1, AF4MLL, ETV6RUNX1)
In the case of hyperleukocytosis, start a 7-day steroid
Pretreatment scheme and assess the favorable response to steroids (< 1000 blasts on day 0).
Add erythropoietin 50 to 250 UI/kg daily or 40,000 units weekly
Combine with filgastrim 150-300 µg BS daily to maintain neutrophil levels above 0.8 x 103/µL
Use folic acid daily, cobalamin and intravenous iron according to the Ganzoni formula
Consider induction therapy using vincristine (1.5 mg/m^2 IV, days 1, 8, 15) in conjunction with prednisone (60 mg/m^2 PO for 28 days), in case the hemoglobin level is higher than 6 g/dL add daunorubicin 45 mg/m^2 BS induction weekly for three doses.
Consolidation and maintenance
In the case of integrating a complete response, continue with any consolidation scheme, central nervous system prophylaxis, and maintenance adding erythropoietin BS twice a week (50 UI/kg) to maintain hemoglobin levels above 10 g/dL.

BS: body surface; IV: intravenous; PO: per os (orally).

of the attending physician; all cases treated subsequently were based on the adaptation of the institutional scheme. The case summary is described in **Table 2**

Survival and relapses

The median follow-up was 210 days (2 to 820 days). At the end of the follow-up, 6/7 adult patients relapsed to bone marrow unlike pediatric patients, in which 2 of the patients relapsed. There were no cases of relapse to the central nervous system during the follow-up period. When analyzing survival, only 3/7 adult patients remained alive, unlike pediatric patients where the majority (2/4) remained alive. Compared to the historical record of our center, JW patients showed a higher number of relapses (log rank 0.008), which finally compromised survival. The results are summarized in **Figure 1**

Risk factors associated with failure

Different risk factors related to both relapse and survival were analyzed. Together with the value of leukocytes (30 x 10^3/µL), the type of patients (pediatric vs adults), or the different hemoglobin levels (7 g/dL or 5 g/dL) were analyzed. The risk of each study variable is described in **Table 3**

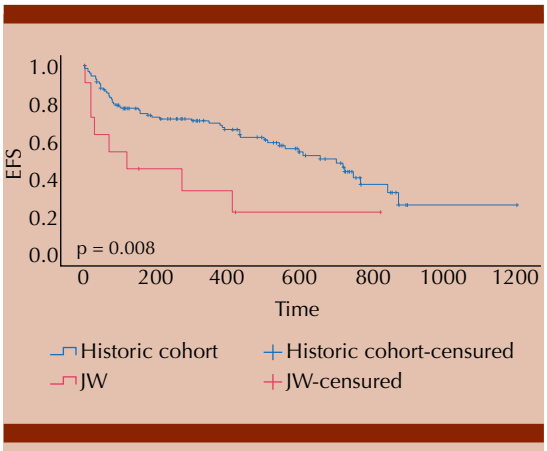

Figure 1.

DISCUSSION

Anemia associated with leukemia is directly related to spinal block that generates leukemic cells, but in turn, the use of different types of therapeutic strategies, especially with aggressive regimens, particularly increases hematological toxicity, requiring adequate transfusion support to improve treatment tolerance.[23,24,25] The prognosis of a patient with pediatric ALL or adult ALL is based on the combination of both biological factors (mutations such as BCRABL1, AF4MLL, leukocytosis, positivity of the minimum residual disease) and of different clinical variables, being

Table 2. Main characteristic of Jehovah's Witnesses cases

Case	Age	Sex	Hb (g/dL)	Characteristics	Induction strategy	Response
1 (1999)	10	Male	7.2	WBC 165.5 x 10^3/µL, 46 XY, B phenotype	Prednisone, vincristine, bleomicin, daunorrubicin	Complete response
2 (2001)	6	Male	4.9	WBC 23.2 x 10^3/µL, 46 XY, B phenotype	Prednisone, vincristine, bleomicin, asparaginase	Complete response
3 (2002)	14	Male	4.6	WBC 13.63 x 10^3/µL, No karyotype, B phenotype	Prednisone, vincristine, bleomicin	Complete response
4 (2002)	2	Female	4.7	WBC 36.27 x 10^3/µL, hyperdiploid karyotype, B phenotype	Prednisone, vincristine	Complete response
5 (2000)	19	Female	3.3	WBC 10.4 x 10^3/µL, 46 XX, B phenotype	Prednisone, vincristine, bleomicin, asparaginase	Failure
6 (2003)	19	Male	6.4	WBC 54.3 x 10^3/µL, 46 XY, B phenotype	Prednisone, vincristine, bleomicin	Complete response
7 (2005)	25	Male	5.7	WBC 200 x 10^3/µL, 46 XY, B phenotype	Prednisone, daunorrubicin, vincristine	Failure
8 (2007)	41	Female	9.2	WBC 1.3 x 10^3/µL, 46 XX, B phenotype	Prednisone, daunorrubicin, vincristine	Complete response
9 (2010)	68	Male	9.9	WBC 115.7 x 10^3/µL, No karyotype, B phenotype	Prednisone, daunorrubicin, vincristine	Failure
10 (2015)	56	Female	7.2	WBC 2.8 x 10^3/µL, 46 XX, B phenotype	Prednisone, daunorrubicin, vincristine	Complete response
11 (2018)	59	Male	10.5	WBC 1.7 x 10^3/µL, BCRABL1 positive, B phenotype	Prednisone, daunorrubicin, vincristine	Complete response

WBC: white blood cell count.

the main one age of presentation followed by the time to achieve a first complete remission.[26]

Despite this, the main prognostic factor in JW patients continues to be hemoglobin levels at diagnosis, for depending on the figure, different drugs such as anthracyclines can be added to the induction scheme. Our series is one of the largest of JW patients who were treated on the basis of different chemotherapy regimens. A little less than half of the patients (45.5%) had figures less than 6g/dl at diagnosis, which forced the delay of subsequent doses of induction chemotherapy. Finally, when obtaining a CR, the consolidation and maintenance treatment scheme was continued without complications. Similar to anemia in cancer patients, supportive therapy was based on the addition of recombinant human erythropoietin (rHuEPO) in order to support erythropoiesis.

This strategy has been used in various critical situations in JW with favorable results.[27,28] The dose used in our study was 50 to 250 IU/kg in order to maintain hemoglobin levels close to 10g/dL that allowed the continuation of chemotherapy, but in some cases, doses of this strategy has been used in various critical situations in JW with favorable results. The dose used in our study was 50 to 250 IU/kg in order to maintain hemoglobin levels close to 10 g/dL that allowed the continuation of chemotherapy, but in some cases doses of erythropoietin alfa of 10,000 units can be used every second day, or 40,000 units per week, together with iron, folic acid, and cobalamin.[29,30] In addi-

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Table 3. Risk value of the different study variables

	Relapse			Death		
Variables	**OR**	**Range**	**p value**	**OR**	**Range**	**p value**
Hemoglobin < 5 g/dL	0.500	0.0313-7.9942	0.642	1.500	0.1360-16.5430	0.746
Hemoglobin < 7 g/dL	2.000	0.1251-31.9766	0.642	3.000	0.2547-35.3356	0.386
Leucocyte > 30 x 10^3/µL	0.300	0.0183-4.9081	0.398	3.000	0.2547-35.3356	0.386
Platelets < 50 x 10^3/µL	0.833	0.0509-13.6336	0.893	4.000	0.2652-60.3277	0.316
Adults *versus* children	6.000	0.3351-107.4259	0.223	4.000	0.2652-60.3277	0.316

OR: Odds ratio.
We used a χ^2 test for comparing categorical variables between groups; data was expressed in ranges. The risk of different levels of hemoglobin on the possibility of death or relapse was estimated using the Odds ratio and Fisher's exact test (p value ≤ 0.05.95% CI).

tion to erythropoietin, some cases of JW patients with leukemia have the combination of granulocyte colony stimulating factors (75 µg SC daily)[31] or, more recently, the addition of thrombopoietin receptor analogs (romiplostim) but always under the risk of thrombosis genesis, especially in cancer patients.[32] In our series, Interleukin 11 was used to improve platelet count in patients treated before 2005. In the past decade, this strategy was popular both for the treatment of spinal cord syndromes and for the prevention of chemotherapy-induced thrombocytopenia,[33] but with the arrival of new thrombopoietin receptor analogues this strategy has been displaced. Finally, and similar to the treatment regimens in both pediatric and adults, both the possibility of relapse and mortality is higher in the latter, but unlike expected it is not associated with different levels of hemoglobin at diagnosis. This suggests that with the use of an intensive support therapy (erythropoietin, granulocyte colony stimulating factor) together with iron, folic acid, and cobalamin it is feasible to maintain an induction scheme in patients with ALL. The recommendations for their attention are summarized in **Table 1**, without forgetting that in cases where life is at imminent risk and there is no therapeutic option, transfusion support must be used. In conclusion, the treatment of JW patients is possible with adequate support with stimulants.

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