

Treatment of acute promyelocytic leukemia: A single institution experience

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ABSTRACT

The results of the treatment of 14 patients with promyelocytic leukemia (PML) treated with all trans-retinoic acid (ATRA), combined chemotherapy (CT) and prophylactic prednisone are reported; the median age was 30 years (range 7 - 49). A complete remission (CR) was obtained in 13 / 14 patients (93%). All patients were given ATRA fully as outpatients; the CR was achieved after the administration of ATRA in five patients, whereas in the remaining eight, CT was required to achieve it. There were no instances of the ATRA syndrome. One patient relapsed with a PML/RAR- α negative PML 575 days after achieving the CR, failed to respond again to ATRA and died. The median overall (OS) and disease free survival (DFS) has not been reached, being above 4,000 days, whereas the 12-month DFS was 93%, the three and five years DFS being 85%. The treatment employed differs from others in: Oral prednisone is used prophylactically, ATRA is given on an outpatient basis and adriamycin is used instead of other anthracyclines. The results are similar to those obtained in other centers worldwide and it is possible that the prophylactic administration of prednisone precluded the development of the full-blown ATRA syndrome in this group of patients.

Tratamiento de la leucemia promielocítica aguda. Experiencia de una sola institución

RESUMEN

Se informan los resultados del tratamiento en una sola institución de 14 pacientes con leucemia aguda promielocítica (LAPM) en quienes se empleó la combinación de ácido holotrans-retinoico (ATRA) quimioterapia combinada y prednisona profiláctica. La mediana de edad fue de 30 años (rango 7-49). Se obtuvo remisión completa (hematológica y molecular) (RC) en 13 pacientes (93%); a todos los pacientes se les administró el ATRA de manera ambulatoria. La RC se obtuvo con el ATRA en cinco pacientes; en los demás la RC se obtuvo después de habérseles administrado la quimioterapia con citarabina/adriamicina. No hubo ningún caso de síndrome de ATRA. Un paciente recayó con una LAPM PML/RAR- α negativa, 575 días después de haber logrado la RC y falleció. Otro paciente recayó 20 meses después de haber logrado la RC y fue rescatado con el mismo esquema de tratamiento: permanece en segunda remisión molecular por más de seis años. La mediana de supervivencia (SV), tanto global como libre de recaídas de todo el grupo, no se ha alcanzado y es mayor de 4,000 días, en tanto que la SV a 12 meses fue de 93% y a tres y cinco años de 85%. El esquema de tratamiento usado difiere de otros en que se usa prednisona oral, se administra el ATRA de manera ambulatoria y se usa adriamicina y no otras antraciclinas; los resultados son similares a los obtenidos con otros esquemas parecidos en otros sitios del mundo; es posible que el uso profiláctico de prednisona haya eliminado la ocurrencia del síndrome de ATRA.

Key words. Promyelocytic leukemia. Treatment. All trans-retinoic acid (ATRA). Mexico.

Palabras clave. Leucemia promielocítica. Tratamiento. Ácido holotransretinoico (ATRA). México.

INTRODUCTION

Acute promyelocytic leukemia (APL), the M-3 variant of the FAB classification, is characterized by a reciprocal and balanced t (15;17) translocation with a gene rearrangement that fuses the retinoic acid receptor alpha (RAR- α) gene with a putative transcription factor PML gene;¹ this chimerical PML/RAR- α gene encodes a functionally altered retinoic acid receptor.²⁻⁵ Reverse transcriptase polymerase chain reaction (RT-PCR) techniques are useful in the detection of PML/RAR- α messenger RNA (mRNA) for diagnosis, follow-up and the study of residual disease after treatment.⁴⁻⁸ PML is exquisitely sensitive to the administration of supraphysiological amounts of all-trans retinoic acid (ATRA): Most patients with APL achieve complete remission when given ATRA solely.^{7,8} Only APL patients displaying the PML/RAR- α mRNA are responsive to ATRA.⁵⁻⁸ ATRA-induced complete remissions (CR) in APL are short and frequently PML/RAR- α (+),^{4,6,8} and myelosuppressive chemotherapy (CT) supported or not by either bone marrow (BM) or peripheral blood stem cell grafts may render molecular remissions, which are associated with longer disease-free survivals.^{4,6-9}

It is clear now that the prevalence of APL is higher in Mexican mestizos than in Caucasians,^{10,11} on the other hand, multicenter prospective studies in our country to assess the results of treatment of PML patients with ATRA have been conducted and reported,^{12,13} these studies have introduced some changes in the therapeutic approach which have resulted in cost-lowering.¹³ We analyze here the results obtained in the treatment of a group of fourteen patients with APL treated and followed-up in a single institution.

MATERIAL AND METHODS

Patients

All consecutive patients with APL studied and treated for more than 30 consecutive days in the Centro de Hematología y Medicina Interna de Puebla (Puebla, México) were prospectively entered in the study from August 1993 to January 2005.

Diagnosis

Peripheral blood and BM smears stained with May Grunwald Giemsa were studied and the classification was done according to the FAB classification.¹⁴ The immunophenotype of the malignant cells

was analyzed through flow cytometry.^{15,16} By means of reverse transcriptase polymerase chain-reaction (RT-PCR), the PML/RAR- α fusion gene was investigated^{6,17} at diagnosis and along the treatment.

Treatment

All patients were started in ATRA (Hoffman-La Roche AG) 45 mg/m² po, daily together with prednisone (50 mg/m² po, daily during 21 days), prior to any treatment, at the time of diagnosis. ATRA and prednisone were given on an outpatient basis in patients fully active, able to stay in their houses, with relatives or friends or in nearby-hotels, a fair educational level, and able to visit the clinic every day.¹³ If the white blood cell count (WBC) raised above 30 x 10⁹/L, ATRA was reduced to 20 mg/m² po, and intravenous myelosuppressive chemotherapy (CT) in one or two doses (cytarabine) was delivered until achieving 10 x 10⁹/L WBC. ATRA was given until reaching a complete hematological remission, as defined by usual criteria.¹⁴ Two weeks after achieving CR, a combined 7 + 3 CT course using cytarabine and adriamycin (cytarabine 100 mg/m² in infusion for seven days and adriamycin 45 mg/m² in bolus for three days)¹⁸ was delivered, on an outpatient basis. Once the blood cell counts had recovered an additional course of 5 + 2 CT was given. At this point, patients were allocated to receive follow-up therapy with oral daily mercaptopurine (50 mg/m²), oral weekly methotrexate (25 mg/m²) and oral daily ATRA (6 mg/m²) until completing 12 months from the start of treatment.

RESULTS

Twenty six patients with APL presented at the Centro de Hematología y Medicina Interna de Puebla from August 1993 to January 2005. Of these, 12 were either early exits (four) or lost to follow-up in the 30 days after the diagnosis. Fourteen patients were followed for more than 30 days and therefore, prospectively accrued in this study; they were observed for periods ranging from 67 to 4,177 days (median 1,370). The median age was 30 years, (range 7-49); there were seven females. The chimerical PML/RAR- α gene was shown in all patients at diagnosis. A complete, molecular remission was obtained in 13/14 patients (93%); one patient died at day 67 after showing refractoriness to the treatment. All patients were given ATRA fully as outpatients; seven patients developed a white blood cell count above 30 x 10⁹/L, but there were no instances of the full-blown

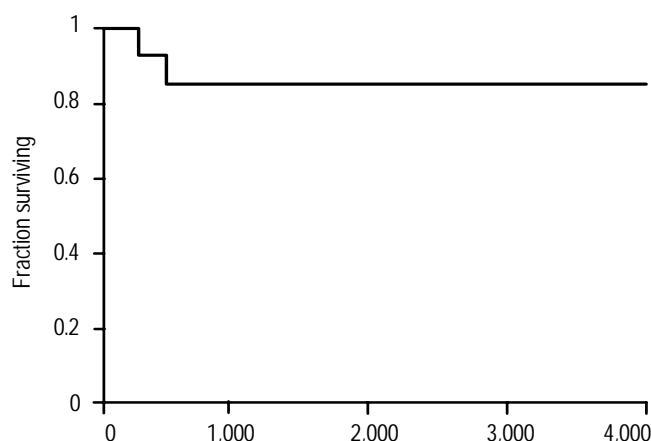


Figure 1. Overall and disease-free survival according to Kaplan and Meier method of the 14 individuals with acute promyelocytic leukemia.

ATRA syndrome. The molecular remission was achieved after the administration of ATRA in five patients, whereas in the remaining eight, chemotherapy (CT) was required to finally achieve it. The median time of administration of ATRA in order to achieve the CR in the five individuals was 48 days (range 30-71). One patient relapsed with a PML/RAR- α negative PML 575 days after achieving the CR and failed to respond again to ATRA, dying eleven days after the relapse; the idea of a secondary leukemia *versus* a true leukemic relapse was considered in this patient.²² Another patient relapsed 20 months after achieving the CR and was retreated with the same schedule achieving a second CR, which has lasted for over six years; he was given an autologous stem cell transplant after achieving the second CR. Three patients received an autologous peripheral blood stem cell transplantation^{4,6,9,19} after achieving the molecular remission, in two instances during the first CR and in one, during the second CR (*vide supra*). The median overall (OS) and disease-free survival (DFS) has not been reached, being above 4,000 days, whereas the 12-month DFS was 93%, the three and five years DFS being 85%. Figure 1 shows the Kaplan-Meier²⁰ survival plot of these patients; the flat line after 500 days of follow-up is noteworthy.

DISCUSSION

An overrepresentation of APL has been reported among acute myelogenous leukemia patients of Latin-American origin either residents in Latin-American countries^{10,21-27} or living in the United States of America.^{21,25} In Mexican Mestizos living in Mexico, our single-institution experience in the city of Pue-

bla –where APL represents 20% of patients with AML–¹⁰ has been confirmed nationwide.^{11,24,26,27} Interestingly, the distribution of the subtypes of the breakpoint cluster regions (bcr's) of the PML/RAR- α fusion gene is different in Mexicans when compared with those found in Caucasians, since a significantly increased frequency of the bcr1 subtype of the PML/RAR α was found in Mexico.²⁸

Substantial progress has occurred in the treatment of APL because of improved understanding of the pathophysiology of the disease and identification of a molecular target. Novel agents such as ATRA (alone or combined with chemotherapy) and, more recently, arsenic trioxide have produced complete remission in most patients with newly diagnosed APL and/or relapsed or refractory disease, respectively. Use of these targeted therapies has resulted in evolution of the disease from one that was historically one of the most fatal subtypes of acute myeloid leukemia to one that appears curable in 70% to 80% of patients.²⁹ The targeted approach to treatment of this disease can be taken as a paradigm for the treatment of other leukemias. Results from several randomized studies have evaluated various regimens of ATRA alone or in combination with CT to determine optimal induction therapy in patients with newly diagnosed APL. These include studies conducted by the European APL group (APL 91 and APL 93 trials), the North American Intergroup, and the Medical Research Council (MRC);²⁹ we also conducted and published such a study some years ago.¹³ All these studies have shown that ATRA combined with CT renders better results than CT alone, the combination being currently the front-line therapy in patients afflicted by this disease. The roles of both consolidation therapy with CT including anthracyclines as well as the maintenance therapy with ATRA, mercaptopurine and methotrexate have been also well defined.²⁹

The method which we have previously published and employed to treat patients with PML,¹³ includes prednisone during the first three weeks of treatment; this addition has resulted in the eradication of the ATRA syndrome, which in our hands is no longer a problem; prospective studies to define the definite role of steroids in this setting are needed. Stemming from economic restraints, we have elected to use adriamycin –which is cheaper–, instead of other anthracyclines such as idarubicin which has been shown to be particularly useful in APL,²⁹⁻³¹ but is considerably more expensive. In addition, we elected to deliver ATRA fully on an outpatient basis, thus diminishing hospitalization costs. With this protocol,

in a single institution and during a period of 11 years, we have been able to obtain a complete remission rate of 93%, with a 5-year survival of 85%, figures similar to those obtained in larger multicenter studies, and better than those obtained in a previous Mexican multicenter study.¹³

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