Acute renal failue in the transretinoic acid syndrome

A. Sastre, E. Gago, M. Baños and E. Gómez
Nephrology Department. Hospital Central de Asturias. Oviedo.

SUMMARY

The all-trans retinoic acid (ATRA) is the treatment of first line of acute promyelocytic leukemia (APL). ATRA is usually well tolerated, but a few major side effects can be observed, ATRA syndrome (RAS) being the most important of them, potentially fatal. The manifestations of this Syndrome are fever, weight gain, pulmonary infiltrates, pleural or pericardial effusions, hypotension, liver dysfunction and renal failure. **Material and methods:** We studied to the 29 patients diagnosed in (january of 2002-december of 2004) of acute promyelocytic leukemia (APL), which were treated with ATRA, all received the 45 dose of mg/m^2/d. The diagnosis of the leukemia was made by citomorphologist analysis. The criterion of renal insufficiency, it was an increase of the creatinina superior to 20% of the basal level. The definition of the transretinoico acid Syndrome was based on the clinical criteria of Frankel. **Results:** Fourteen patients presented the Transretinoico Syndrome (48.3%), 11 of which (37.9%) died. The fundamental differences between the patients with or without ATRA were: fever (14 vs 9, p=0,017), gain of weight (14 vs 0, p = 0,000), pleural effusion (14 vs 2, p = 0.000), pulmonary infiltrates (13 vs 1, p = 0,000), cardiac failure (12 vs 2, p = 0,000), respiratory distress (12 vs 4, p = 0,003), presence of renal failure (10 vs 4, p = 0,02), necessity of substitute renal treatment (6 vs 0, p = 0,006) and arterial hypotension (12 vs 3, p = 0,001). The acute renal failure appeared in 10 of the 14 patients with SAR (71.4%), to 12 ± 5 (1-25) days of the beginning of the treatment and their duration it was of 14 ± 5 (1-46) days. Six (60%) needed substitute renal treatment and 5 (50%) died. Of the patients who survived, only a patient continues in dialysis. In both patient in that renal biopsy was made, the study showed signs of cortical necrosis. **Conclusions:** The appearance of acute renal failure in the course of the SAR is frequent, being observed deterioration of the renal function that needs substitute renal treatment in more than half the cases. The association of RAS with renal failure entails the high mortality (50%). The diagnosis and the precocious restoration of suitable the preventive measures and therapeutic are very important to avoid in possible the this serious complication of the treatment with ATRA.

Key words: **All-trans retinoic acid. All-trans retinoic acid syndrome. Retinoic acid syndrome. Acute promyelocytic leukemia. Acute renal failure.**

Correspondence: Aránzazu Sastre López
Hospital Huca
Avda. Fernández Ladreda, 30
24005 León
E-mail: aranchasastre@hotmail.com

INSUFICIENCIA RENAL AGUDA EN EL SÍNDROME DE ÁCIDO-TRANSRETINOICO

RESUMEN

*El ácido transretinoico es el tratamiento de primera línea de la Leucemia Promielocítica Aguda. Habitualmente es bien tolerado, pero puede tener efectos secundarios, de los cuales el más grave es el Síndrome de Ácido Transretinoico, potencialmente fatal. Las manifestaciones de este Síndrome son fiebre, ganancia de peso, infiltrados pulmonares, derrame pleural o pericárdico, hipotensión, insuficiencia hepática e insuficiencia renal. **Material y métodos:** Se estudiaron 29 pacientes diagnosticados en los últimos 3 años (enero de 2002-diciembre de 2004) de Leucemia Promielocítica Aguda que fueron tratados con ácido transretinoico a dosis de 45 mg/m²/día. El diagnóstico de la leucemia se realizó por análisis citomorfológico. La insuficiencia renal aguda (IRA) se definió como un incremento de la creatinina superior al 20% del nivel basal y el Síndrome de Ácido Transretinoico (SAR) por los criterios de Frankel. **Resultados:** Catorce pacientes presentaron el Síndrome Transretinoico (48,3%), 11 de los cuales fallecieron (37,9%). Las diferencias fundamentales entre los pacientes con o sin ATRA fueron: fiebre (14 vs 9, p = 0,017), ganancia de peso (14 vs 0, p = 0,000), derrame pleural (14 vs 2, p = 0,000), presencia de infiltrados pulmonares (13 vs 1, p = 0,000), insuficiencia cardiaca (12 vs 2, p = 0,000), distress respiratorio (12 vs 4, p = 0,003), presencia de IRA (10 vs. 4, p=0,02), necesidad de tratamiento renal sustitutivo (6 vs 0, p = 0,006) e hipotensión arterial (12 vs 3, p = 0,001). La insuficiencia renal se produjo en 10 de los 14 pacientes con SAR (71,4%), a los 12 ± 5 (1-25) días del comienzo del tratamiento y su duración media fue de 14 ± 5 (1-46) días. Seis (60%) necesitaron tratamiento renal sustitutivo y 5 (50%) fallecieron. De los pacientes que sobrevivieron, sólo un paciente continúa en diálisis. En los dos pacientes en los que se realizó biopsia renal, el estudio histológico mostró signos de necrosis cortical. **Conclusiones:** La aparición de insuficiencia renal en el transcurso del SAR es frecuente, precisando tratamiento renal sustitutivo en más de la mitad de los casos. La asociación de SAR con IRA conlleva una alta mortalidad. El diagnóstico y la instauración precoz de las medidas preventivas y terapéuticas adecuadas son muy importantes para evitar en lo posible esta grave complicación del tratamiento con ATRA.*

Palabras clave: ***Síndrome de ácido transretinoico. Síndrome ATRA. Leucemia promielocítica aguda. Insuficiencia renal aguda.***

INTRODUCTION

Promyelocytic acute leukemia (PAL) accounts for 8%-10% of acute myeloid leukemias. It has specific clinical and biological features: it is more prevalent in young people, leukopenia is present at the onset, and tends to progress with disseminated intravascular coagulation. Morphologically it features with atypical, hypergranular promyelocytes with plenty of Auer's bodies at both the bone marrow and peripheral blood. Cytogenetically there is a t (15; 17) translocation that leads to the hybrid gene PML/RAR due to the fusion of the PML genes at the chromosome 15 and the gene codifying for the retinoic acid receptor at the chromosome 17.[1]

The first line therapy for PAL comprises the administration of transretinoic acid (ATRA, Tretinoin®, 10 mg capsules), an anti-cancer agent that directly induces cellular differentiation at the bone marrow, cellular growth inhibition, and apoptosis. Although it is also cleared via the liver, its main clearance route is the kidney (60%), similarly to its metabolites.

In 1988, Huang *et al.*[1] were the first to demonstrate that ATRA achieved complete remission in 63%-96 % of PAL, together with control of coagulation

impairments, which was later on confirmed by others.[1-7] However, ATRA administration withholds important side effects. One of the most severe ones is the so-called Retinoic Acid Syndrome or ATRA Syndrome (RAS). It is characterized by sustained fever, dyspnea, respiratory distress, volume overload, hypotension and/or acute renal failure (ARF). It tends to progress with leukocytosis and parenchymal infiltration with mature myeloid cells. In more severe cases, it gives rise to decreased myocardial contraction and multiorgan failure. Respiratory distress arises within the syndrome clinical picture, and it is the most severe manifestation among all. RAS occurs in 6%-26% of the patients treated with ATRA,[8,1,9] and it onsets within 2-20 days from the start of the therapy with

retinoic acid (mean of 7 days). Its progression varies from torpid to hyperacute forms, and it may be fatal. Early diagnosis and treatment are essential for favorable progression of this syndrome.[1] Differential diagnosis is mainly with severe sepsis.

RAS was described for the first time by Frankel in 1992.[1] Further on, it was corroborated by De Botton,[10] Fenauk,[11] Tallman,[12] and others. The largest series is the one by De Botton, with 413 cases of PA . In that series, the incidence of acute renal failure was 39%. Cases of isolated acute renal failure have also been described with RAS.[9]

Renal involvement in RAS has poorly been studied. We described below the prevalence and characteristics of RAS in a series of patients with LPM treated with ATRA at our Hospital, with special emphasis on renal aspects of this syndrome.

MATERIAL AND METHODS

Patients

Between January of 2002 and December of 2004, 29 patients have been diagnosed with PAL at the Hematology Department of the Hospital Central de Asturias. All of them were treated with ATRA. PAL diagnosis was by means of the cytomorphological study and was verified in all patients by the presence of the chromosomal translocation 15;17 and PML-RAR gene rearrangement.

RAS diagnosis was based on Frankel's criteria,[1] which require 3 of the following signs in the absence of other causes: fever, weight gain, pulmonary infiltrates, pericardial or pleural effusions, hypotension, liver failure and/or acute renal failure.

RAS-attributable acute renal failure was defined as an increase in serum creatinine of at least 20% from the one the patient had before ATRA therapy and with

absence of other nephrotoxic drugs or other causes for renal failure.

ATRA therapy was started within 24-72 hours before making the diagnosis, and it was administered p.o. at a 45 mg/m^2/day dose, divided into 2 doses. In some cases, this amount was modified according to the manifestation of drug-related side effects.

Complications from ATRA therapy were analyzed, specially focusing on RAS and renal involvement, and assessing all associated factors that would have contributed to renal function impairment as well as its progression. The following parameters were studied: gender, age, ATRA dose, hematocrit, hemoglobin, leucocytes and platelets counts, serum creatinine before ATRA therapy, fever, pleural and pericardial effusions, heart failure, weight gain, treatments, tumoral complications and progression, renal failure and its features.

Statistical analysis

Continuous variables were analyzed by the two-tailed Student's t test with Welch's correction when the populations had different standard deviations, and the chi-squared test or Fishers' exact test for categorical binary variables. The data are expressed as mean ± SD, except when otherwise indicated. Differences were considered to be significant when the probability was < 0.05. Survival curves were calculated by the Kaplan-Meyer method and their differences by the long rank test. Data analysis was performed with the software statistical package SPSS 10.0.

RESULTS

Clinical Manifestations of RAS

Of the 29 patients with PAL, 14 were males and 15 females, with a mean age of 48 ± 17 years. The most common clinical signs at PAL diagnosis were skin and mucosal pallor, and internal, skin, and mucosal hemorrhages, present in 100% of the patients and that were related with thrombocytopenia level and the presence of intravascular disseminated coagulation. Global mortality of ATRA- treated PAL patients was high: 11 out of 29 patients died (37.9%).

Fourteen out of 29 ATRA-treated patients had RAS (48.3%) and 15 did not (51.7%). The most frequent symptoms of RAS were: fever (100%), weight gain (100%), pleural effusion (100%), pulmonary infiltrates (92.8%), respiratory distress (85.7%), hypotension

(85.7%), heart failure (85.7%), renal failure (71.4%), liver failure (78.5%), and pleural effusion (21.4%).

Comparison of patients with and without RAS

Table 1 shows the characteristics of patients with and without RAS. The main differences between both groups were the following: fever (14 *vs*. 9; p = 0.017), weight gain (14 *vs*. 0; p = 0.000), pleural effusion (14 *vs*. 2; p = 0.000), presence of pulmonary infiltrates (13 *vs*. 1; p = 0.000), heart failure (12 *vs*. 2; p = 0.000), respiratory distress (12 *vs*. 4; p = 0.003), presence of ARF (10 *vs*. 4; p = 0.02), need for renal replacement therapy (6 *vs*. 0; p = 0.006), and arterial hypotension (12 *vs*. 3; p = 0.001). There were no differences by age, gender, ATRA dose, or the remaining parameters analyzed.

Twenty four point one percent of the sample showed other tumors besides PAL throughout their progression. RAS patients had 2 tumors (1 squamous carcinoma of the skin and 1 pancreatic cancer) and patients without RAS had 4 tumors (1 lymphoma, 1 cancer of the urethra, 1 basal cell carcinoma of the skin, and 1 squamous cell carcinoma of the skin). There were more deaths among patients with RAS (7 vs. 4; 50% *vs*. 26,7%, respectively), although the differences were not significant (p = 0.2).

The 5-year actuarial survival was slightly less than 50% in the RAS group and more than 70% in the group without RAS (Fig. 1A).

ARF Characteristics in RAS

Ten out of 14 RAS patients had ARF (71.4%). The main features are summarized in Table 2. The most important ones are commented below. All patients had normal renal function at the beginning of ATRA therapy (mean serum creatinine 0.89 ± 0.19 mg/dL). The average time from the beginning of ATRA therapy to diagnosis of ARF was 12 ± 7 (1-25) days. Duration of renal failure was 14 ± 5 (1-46) days. Renal failure progressed with oliguria and hypotension in 90% of the patients. Serum creatinine was 4.3 ± 2.5 mg/dL (range: 1.70-9.83). Six patients (60%) required renal replacement therapy. Fifty percent of the patients with RAS and ARF died, most of them due to multiorgan failure. Among patients surviving, only one still requires dialysis; in the remaining patients renal function was completely recovered.

A renal biopsy was performed in two cases. The histological study showed signs of cortical necrosis with acellular glomerular shapes, arteriolar thrombi, fibrinoid necrosis, necrotic tubules without cellularity, and rupture of the basal membranes.

Patients developing RAS and ARF were characterized by presenting almost all signs and symptoms of the syndrome, that is to say, they were related with a more aggressive condition, as it may be seen in Table 2. Apart from that, no differences were observed with the remaining parameters analyzed between patients with RAS and ARF and the remaining ATRA-treated patients (data not shown), so that no conclusions can

Table I. Characteristics of the patients with or without RAS

Variable	Patients with RAS (n = 14)	Patients without RAS (n = 15)	p
Age (years)	48 ± 16 (24-75)	47 ± 19 (8-88)	0.8
Gender male/female	9/5	5/10	0.1
ATRA dose (mg/m^2/day)	82 ± 6 (70-90)	79 ± 12 (50-90)	0.3
Pre-treatment creatinine (mg/dL)	0.91 ± 0.15 0.6-1.1)	0.86 ± 0.23 (0.5-1.33)	0.1
Pre-treatment leucocytes/micro L	13,711 ± 24,004 (1,100-90,600)	4,007 ± 6,629 (570-24,770)	0.1
Pre-treatment platelets/microL	4,648 ± 52,731 (7,000-183,000)	47,800 ± 46,817 (8,000-183,000)	0.9
Pre-treatment hemoglobin (g/dL)	9.8 ± 1.9 (6.2-12.9)	9.3 ± 2.4 (3.2-13)	0.5
Pre-treatment hematocrit (%)	29 ± 4.2 (20.4-35)	27.4 ± 7.1 (11-37)	0.4
Fever	14 (100)	9 (60)	0.017
Weight gain	14 (100)	0 (0)	0.000
Pleural effusion	14 (100)	2 (13)	0.000
Pulmonary infiltrates	13 (92.8)	1 (6)	0.000
Hearth failure	12 (85.7)	2 (13)	0.02
Respiratory distress	12 (87.5)	4 (26.6)	0.003
Acute renal failure	10 (71.4)	4 (26.6)	0.02
Renal replacement therapy	6 (42.8)	0 (0)	0.000
Hypotension	12 (87.5)	3 (20)	0.001
Associated tumors	2 (14%)	4 (26%)	0.6
Exitus	7 (50%)	4 (26.7%)	0.2

RAS = Transretinoic acid syndrome or ATRA syndrome; ATRA = Transretinoic acid.

Table II. Characteristics of renal failure in patients with RAS and ARF

Age (years)	47 ± 16 (24-67)
Gender (male/female)	6/4
Acute renal failure	10/14 (71.4%)
ATRA dose (mg/m²/day)	83 ± 5 (80-90)
Onset of ATRA to ARF (days)	12 ± 7.8 (1-25)
Durantion of ARF (days)	14 ± (1-46)
Creatinine before ATRA (mg/dL)	0.89 ± 0.19 (0.5-1.33)
Creatinine (mg/dL)	4.2 ± 2-5 (1.7-9.83)
Oliguria	9/10 (90%)
Renal replacement therapy	6/10 (60%)
Exitus	5/10 (50%)
Progression to chronic dialysis	1/6 (16.6%)
Fever	10/10 (100%)
Weight gain	10/10 (100%)
Hypotension	9/10 (90%)
Pleural effusions	10/10 (100%)
Hearth failure	9/10 (90%)
Pulmonary infiltrates	9/10 (90%)
Liver failure	7/10 (70%)

RAS = Transretinoic acid syndrome or ATRA syndrome; ARF = Acute renal failure; ATRA = Transretinoic acid.
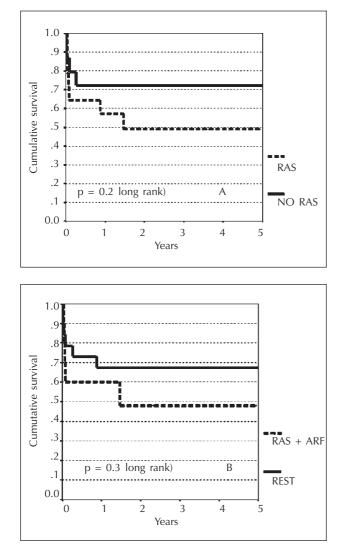
Figure 1. A) Actuarial survival (Kaplan-Meier) of patients with and without RAS; B) Actuarial survival (Kaplan-Meier) of patients with RAS and ARF, as compared with the remaining series.

be drawn that would indicate what ATRA-treated patients would develop RAS and ARF.

Four patients treated with ATRA also had renal failure but did not meet RAS criteria. The cause was attributed to drug toxicity (including ATRA) and hipovolemia.

The five-year actuarial survival was also slightly less than 50% in the RAS group, and more than 70% in the group without RAS (Fig. 1B).

DISCUSSION

RAS was described for the first time by Frankel in 1992,[1] who established the clinical criteria of this syndrome. It is a complication of ATRA therapy for PAL, and it is characterized by increased capillary permeability that leads to fever, hypotension, and fluid leakage, which seems to be related with increased secretion of vasoactive interleukins including IL-1, IL-2, IL-6, IL-8, and tumoral necrosis factor. The three basic pathophysiologic mechanisms described are: systemic inflammatory response, endothelial damage with capillary leakage syndrome, and microcirculation obstruction that leads to tissular infiltration.[13-16] These mechanisms are triggered by the effect of ATRA on promyelocytes differentiation during which there is synthesis and release of interleukins, serine proteases, and expression of endothelial adhesion molecules, and that histopathologically manifest with promyelocytes infiltration in several organs, especially the kidney, liver, and lung, where pulmonary edema, hemorrhage, and intra-alveolar fibrinous exudates occur. Although ATRA is also used for treating other conditions, such as myelodysplastic syndromes, metastases of small cell lung cancer, neural tumors, and prostatic cancer,[3,4,8] RAS has only been described with PAL treatment due to the selective action of ATRA at the promyelocyte level and not on other cellular strains.

The diagnosis of this condition is essentially clinical,[1,2,15-20] and is some cases it may be difficult to differentiate it from the underlying disease or its septic complications.[21,22] RAS prevalence ranges 6%-26 % of all PAL treated with ATRA, although regional variations have been described.[1,10] In our series, it was higher, almost 50%. We also had a higher percentage of

patients needing renal replacement therapy (20.7 % *vs*. 3-5%) and higher mortality (37.9% *vs*. 5-30%). These high percentages observed in our patients may be due to higher severity of the condition or to later diagnosis and treatment, since in the published series RAS started on average 7 days after the onset of ATRA therapy (2-35 days)[10,12] and in our series it was 14 days (range: 1-25).

Renal involvement in RAS may be caused by several mechanisms, although many times the cause is multifactorial: endothelial damage-induced hypotension, with capillary leakage syndrome and microcirculation obstruction, tissular infiltration by mature lymphocytes that escape the bone marrow, and capilaritis due to overexpression of integrins (cellular adhesion molecules). The most frequent renal lesion is tubular necrosis[9] and renal infiltration by lymphocytes. There have been cases reported with granulomatous interstitial nephritis.[23] Cortical necrosis is very rare, but in the two biopsies performed in our series we observed sings of cortical necrosis with no cellularity and rupture of basal membranes, likely related to the severity of the condition and profound coagulation impairments.

The incidence of ARF in our patients with RAS was very high and severe. This may also be due to the disease severity and the delay in RAS diagnosis and treatment. These facts may explain the high mortality rate in this group.

Te fact that in patients with RAS + ARF almost all symptoms and signs of RAS are present suggests that ARF prevention measures should be stressed since RAS prognosis is worse when it is accompanied by ARF.

The efficacy of the specific therapy is controversial. It has been suggested that corticosteroid therapy (high dose dexamethasone) may be beneficial together with withdrawal of ATRA administration. Corticosteroids would exert their action through their known immunomodualtory mechanism.[25,26] In pour series, steroids were administered in only 42.8% of the patients, which might be contributed to the high mortality and severity observed. Besides, supportive measures at an intensive care unit and hemodialysis are only required. Appropriate hydration and avoidance of other nephrotoxic drugs use may help preventing renal damage.

To conclude, RAS is very common in PAL patients treated with ATRA; it usually sis sever and may have a high mortality rate. A high proportion of patients present acute renal failure usually requiring renal replacement therapy. The histological substrate of renal failure may be irreversible cortical necrosis. For all these reasons, correct diagnosis and treatment allow overdoing preventive measures and early implementing

appropriate therapeutic measures, which will likely contribute to improve the prognosis of this important complication of leukemia patients treated with transretinoic acid.

REFERENCES

1. Frankel SR, Eardley A, Lauwer G y cols.: The «retinoid acid syndrome» in acute promyelocytic leukemia. *Ann Int Med* 117: 292-6, 1992.
2. Tallman M, Ardersen JW, Schiffer C y cols.: All trans retinoic acid in acute promyelocytic leukemia. *N Engl J Med* 337: 1021-9, 1997.
3. Gregnan F, Fagioll M, Alcalay M y cols.: Acute promyeloctic leukemia: from genetics to treatment. *Blood* 83: 10-25, 1994.
4. Fenax P, Chomienne C, Degos L: Treatment of acute promyelocytic leukemia. *Best Pract Res Clin Haematol* 14: 153-74, 2001.
5. Ohno R, Naoe T, Hirano M y cols.: Treatment of myelodysplastic syndromes with all-trans retinoic acid. *Blood* 81: 1152, 1993.
6. Huang M, Yu- Chen Y, Shu-Rong C y cols.: Use of all - trans retinoic acid in the treatment of acute promyelocytic. *Blood* 72 (2): 567-72, 1988.
7. De Granf N, Riesinger P, Reinhard H: Retinoids in the treatment of acute promyelocytic leukemia. *Klin Padiat* 207: 43-7, 1995.
8. Treat J, Friedland D, Luginbuhl W y cols.: Phase II trial of all-trans retinoic acid in metastatic non-small cell lung cancer. *Cancer Invest* 14: 415, 1996.
9. Flombaum CD, Isaacs M, Reich L y cols.: Acute renal failure associated with the retinoic acid syndrome in acute promyelocytic leukemia. *Am J Kidney Dis* 27: 134, 1996.
10. De Botton S, Dombret H, Sanz M y cols.: Incidence, clinical features, and outcome of all trans-retinoic acid syndrome in 413 cases of newly diagnosed acute promyelocytic leukemia. The European APL Group. *Blood* 92: 2712, 1998.
11. Fenauk P, Degos L: Treatment of acute promyelocytic leukemia. *Baill Clin Haematol* 9: 107-28, 1996.
12. Tallman M, Ardensen JW, Schiffer C y cols.: Clinical descripcion of 44 patient with caute promyelocytic leukemia who developed the retinoic acid symdrome. *Blood* 90: 90-5, 2000.
13. Larson RS, Tallman MS: Retinoic acid syndrome: manifestations, pathogenesis, and treatment. *Best Pract Res Clin Haematol* 16: 453-61, 2003.
14. Park CJ, Bae YD, Choi JY y cols.: Sweet's syndrome during the treatment of acute promyelocytic leukemia with all-trans retinoic acid. *Korean J Intern Med* 16: 218, 2001.
15. Martín M, Cisneros E, Slano F y cols.: The retinoic acid syndrome, a complication of promyelocytic leukemia therapy. *An Med Intern* 18 (4): 195-200, 2001.
16. Jung JI, Choi JE, Hahn ST y cols.: Radiologic Features of All-Trans-Retinoic Acid Syndrome. *AJR Am J Roentgenol* 178: 475, 2002.
17. Hickstein DD, Hickey MJ, Collins SJ: Transcriptional regulation of the leukocyte adherence protein beta subunit during human myeloid cell differentiation. *J Biol Chem* 263: 13863, 1988.
18. Sanz MA, Martín G, Díaz-Mediavilla J y cols.: All- trans- Retinoic Acid in Acute Promyelocytic Leukemia. *N Engl J Med* 338: 393-394, 1998.
19. Sanz MA, Martín G, Rayón C y cols.: A Modified AIDA Protocol With Anthracycline-Based Consolidation Results in High

Antileukemic Efficacy and Reduced Toxicity in Newly Diagnosed PML/RARalpha —Positive Acute Promyelocytic Leukemia. *Blood* 94: 3015-3021, 1999.

20. Letendre L, Levitt R, Pierre RV y cols.: Myelodysplastic syndrome treatment with danazol and cis-retinoic acid. *Am J Hematol* 48: 233, 1995.

21. Camacho LH, Soignet SL, Chanel S y cols.: Leukocytosis and the retinoic acid syndrome in patients with acute promyelocytic leukaemia treated with arsenic trioxide. *J Clin Oncol* 18: 2620, 2000.

22. Vahdat L, Maslak P, Miller WH Jr y cols.: Early mortality and the retinoic acid syndrome in acute promyelocytic leukaemia: Impact of leukocytosis, low-dose chemotherapy, PMN/RAR-alpha isoform, and CD13 expression in patients treated with all-trans retinoic acid. *Blood* 84: 3843, 1994.

23. Tomita N, Kanamori H, Fujita H y cols.: Granulomatous tubulointerstitial nephritis induced by all-trans retinoic acid. Anticancer Drugs 12: 677-80, 2001.

24. Cox NH, O'Brien HA: Sweet's syndrome associated with trans-retinoic acid treatment in acute promyelocytic leukemia. *Clin Exp Dermatol* 19: 51, 1994.

25. Gordon M, Jakubowski A, Frankel S y cols.: Neutrophil (PMN) function in patients with acute promyelocytic leukemia (APL) treated with all-trans retinoic acid (ATRA) (abstract). *Proc Annu Meet Am Soc Clin Oncol* 10: A761, 1991.

26. Margolin KA, Rayner AA, Hawkins MJ y cols.: Interleukin-2 and lymphokine-activated killer cell therapy of solid tumors: analysis of toxicity and management guidelines. *J Clin Oncol* 7: 486, 1989.