Acquired aplastic anemia: a demographic, clinical, and therapeutic survey of a single institution in Mexico City.

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Abstract

BACKGROUND: Acquired aplastic anemia (AA) pathophysiology involves immune mechanisms. Risk classifications to stratify AA severity are employed to define treatment.

OBJECTIVE: To analyze therapeutic response and survival in patients with AA.

PATIENTS AND METHOD: A retrospective study was done in which diagnosis and therapy response were establish following 2009 AA British guidelines. Data collected from patients admitted between January 1998 and December 2007 were analyzed.

RESULTS: In the study period 51 patients were identified. At diagnosis 2 of 19 cases had paroxysmal nocturnal hemoglobinuria clones. Median age in the remainder patients (22 females and 27 males) was 35 years (range 17 to 78 years). Eleven, 28 and 10 patients had non-severe, severe, and very severe AA, respectively. Seven patients with severe AA received bone marrow transplantation (BMT). All of them remain in complete response (CR) with a median follow-up of 1,675 days. Median survival in non-BMT patients (n=42) with non-severe, severe, and very severe AA was 1,253, 895, and 447 days, respectively (p<0.001). Forty patients received immunosuppressive therapy and androgens. Overall response (CR+PR; partial response) with immunosuppressive therapy and androgens was 51% and 38.5%, respectively. Overall response was significantly higher in BMT patients than in those treated with immunosuppressive therapy and androgens (p=0.002). No statistically significant difference in overall response was recorded between patients who received immunosuppression and androgens. Median survival in non-BMT patients with CR (1,577 days), PR (1,213 days) and no response (408 days) was statistically significant different (p<0.02).

CONCLUSIONS: Long standing classifications are still useful to stratify survival and therapy response in AA. BMT remains the best therapeutic option, and seemingly immunosuppression and androgens render similar response rates in AA.

KEYWORDS: aplastic anemia; demography; epidemiology; survival; bone marrow transplantation; immunosuppression; androgens

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Anemia aplástica: estudio demográfico, clínico y terapéutico de una institución en la Ciudad de México

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Resumen

ANTECEDENTES: la fisiopatología de la anemia aplástica involucra mecanismos inmunitarios. Para elegir el tratamiento de la anemia aplástica se usan las clasificaciones para estratificar la gravedad de la enfermedad.

OBJETIVO: analizar la respuesta terapéutica y la supervivencia de enfermos con anemia aplástica.

PACIENTES Y MÉTODO: estudio retrospectivo en el que el diagnóstico y respuesta terapéutica se establecieron de acuerdo con las guías británicas de anemia aplástica de 2009. Se analizó la información recabada de pacientes ingresados entre enero de 1998 y diciembre de 2007.

RESULTADOS: en el periodo de estudio se identificaron 51 enfermos. Al diagnóstico 2 de 19 pacientes tuvieron clonas de hemoglobina paroxística nocturna. La mediana de edad en el resto de los enfermos (22 mujeres y 27 mujeres) fue de 35 años (límites: 17-78 años). Once, 28 y 10 pacientes tuvieron anemia aplástica moderada, grave y muy grave, respectivamente. Siete enfermos con anemia aplástica grave recibieron trasplante de médula ósea (TMO) y todos permanecen en respuesta completa (RC) con mediana de seguimiento de 1,675 días. La mediana de supervivencia en los 42 pacientes no trasplantados con anemia aplástica moderada, grave y muy grave fue de 1,253, 895 y 447 días, respectivamente (p<0.001). Cuarenta enfermos recibieron inmunosupresión y andrógenos. La respuesta total (RC + respuesta parcial; RP) con inmunosupresión y andrógenos fue de 51 y 38.5%, respectivamente, sin diferencia estadísticamente significativa. La respuesta en los pacientes trasplantados fue significativamente mejor que en los tratados con inmunosupresión o andrógenos (p<0.002). La mediana de supervivencia en los enfermos no trasplantados con respuesta total (1,577 días), respuesta parcial (1,213 días) y sin respuesta (408 días) fue estadísticamente diferente (p<0.02).

CONCLUSIONES: las clasificaciones longevas son útiles aun para estratificar la supervivencia y respuesta terapéutica en anemia aplástica. El trasplante de médula ósea sigue siendo la mejor opción de tratamiento: al parecer la inmunosupresión y los andrógenos ofrecen tasas de respuesta parecidas en anemia aplástica.

PALABRAS CLAVE: anemia aplástica, demografía, epidemiología, supervivencia, trasplante de médula ósea, inmunosupresión, andrógenos.

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BACKGROUND

Aplastic anemia (AA) is defined as pancytopenia with a hypocellular bone marrow in the absence of an abnormal infiltrate and with no increase in reticulin. AA may be inherited or acquired and in nearly 80% of acquired cases the etiologic factor is not identified. Paroxysmal nocturnal hemoglobinuria (PNH) must be ruled out since a proportion of patients with AA at diagnosis or during their follow-up may present glycosylphosphatidylinositol (GPI)-deficient clones.

Epidemiologic data has revealed that the incidence of AA in Europe, Israel, United States of America, and Brazil is approximately 2 new cases per 1 million population per year, whereas in China, Malaysia, Mexico, and Thailand the incidence is higher ranging from 3.9 to 7.4 new cases per 1 million population per year. The incidence of AA varies bimodally with age, with one peak between ages 15 to 25 years and another peak at older than 60 years of age. AA occurs with equal frequency in both genders.

In most cases of acquired AA, pathophysiology is characterized by a T-cell mediated organ-specific destruction of the hematopoietic stem cell compartment. Hence, AA can be successfully treated with immunosuppressive therapy or hematopoietic stem cell transplantation. Although a controlled study revealed that androgen administration did not improve the survival in AA patients, some series have shown that androgens may ameliorate the cytopenias seen in children and adults suffering AA.

Herein we report the results of a 10-year retrospective analysis in patients with acquired AA who were treated with bone marrow transplantation (BMT), immunosuppressive therapy, and androgens at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán located in Mexico City.

PATIENTS AND METHODS

A retrospective analysis was done at Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City. Our Institute is a third-level public hospital which gives attention to patients older than 16 years of age requiring assistance in internal medicine and surgical areas. The data collected from the records of patients admitted between January 1998 and December 2007 with the diagnosis of acquired AA included: age, gender, pre-treatment full blood count values, type of therapy, response to therapy, status at latest follow-up, and causes of death. Follow-up was completed on December 31, 2008.

For confirmation of AA diagnosis the following conditions were obligatory: peripheral blood (at least two of the following three criteria): a) hemoglobin ≤10 g/dL, or hematocrit ≤30%; b) platelets ≤50x10^9/L; and c) leukocytes ≤3.5x10^9/L, or granulocytes ≤1.5x10^9/L. For bone marrow there had to be an adequate bone marrow biopsy specimen showing the following: a) decreased cellularity with the absence or depletion of all hematopoietic cells and b) the absence of fibrosis or neoplastic infiltration. AA cases were classified according to international criteria as non-severe, severe, and very severe.

Identification of GPI-anchored surface proteins to establish PNH diagnosis was performed by flow cytometry in 19 patients at diagnosis and in 21 cases during follow-up. At diagnosis, serology for A, B, and C hepatitis were done in 37 patients and cytogenetic analysis was performed in 20 cases.

Patients received different treatments including: BMT from a human leukocyte antigen (HLA)-matched sibling donor; immunosuppressive therapy with cyclosporine A (CSA; 5 mg/kg daily),
horse anti-thymocyte globulin (ATG; 10 mg/kg for 5 consecutive days followed by CSA), and cyclophosphamide (45 mg/kg for 4 consecutive days); androgens such as danazol (200 mg to 600 mg daily), oxymetholone (1 mg/kg to 2 mg/kg daily), and mesterolone (25 mg to 75 mg daily). Supportive care include red blood cell transfusion when Hb level was ≤8 g/dL and platelet transfusion when platelet count was ≤10x10^9/L or ≤20x10^9/L in the presence of fever. Irradiated blood components were transfused to patients who underwent BMT. Six-month response was categorized as complete response (CR), partial response (PR), and non-response (NR) following the criteria of an expert committee on AA.21

Statistical analysis
Probability estimates were obtained with the Kaplan-Meier method and differences between survival patterns were calculated by log-rank statistics. Multivariate proportional-hazards regression analysis used the Cox method. Fisher’s exact test was used to establish differences between independent groups.

RESULTS
From January 1998 to December 2007, 57,721 new admissions were registered in our hospital and 51 cases were diagnosed as having AA. At diagnosis, PNH test was performed in 19 patients and two of them showed GPI-deficient circulating cells and were excluded from the analysis (Table 1). The median age in the remainder cases (22 females and 27 males) was 35 years (range 17 to 78 years). Idiopathic and secondary AA was recorded in 37 (75.5%) and 12 patients, respectively. Agricultural pesticides (12 cases) were the most frequent factor associated with bone marrow failure. From 21 patients in whom PNH test was performed during follow-up GPI-deficient circulating cells were detected in 2 cases (Table 1). Three out of 4 patients with PNH positive test were males, their median age was 35 years, and all had severe AA. First-line therapy in one case was BMT, immunosuppressive therapy was given in 2 cases, and one patient received androgens. Only the patient who received BMT achieved CR. Two out of 3 patients received second line-therapy, patient No. 2 accepted only supportive care. Patient No. 3, previously treated with mesterolone, responded to CSA and patient No. 4, previously treated with CSA, responded to danazol, both cases achieved PR. At last follow-up all patients were alive, even the one in supportive care, with a median survival time of 2805 days (Table 1). Nineteen out of 20 patients had normal cytogenetics and only case showed a complex karyotype (≥3 abnormalities). This woman had severe AA and did not respond to either CSA or androgens and died 185 days after diagnosis due to brain hemorrhage. HBV and HCV antibodies were detected in two and one cases, respectively, and HAV antibodies were identified in 5 patients.

Eleven patients (22%) had non-severe AA, 28 (57%) severe AA, and 10 cases (20%) were categorized as very severe AA. Seven patients (4 women) aged 17 to 43 years (median 33 years) with severe AA received BMT from HLA-matched sibling donors. Only one patient developed chronic graft versus host disease and no other case presented BMT-related complications. All BMT patients remain alive in CR with a follow-up time of 1,127 to 3,380 days (median 1,675 days) (data not shown).

Figure 1 shows the survival of 42 cases, two with PNH clones identified during follow-up after AA diagnosis. Patients who receive BMT (n=7) were not included in survival analysis. Median survival in patients with non-severe, severe, and very severe AA was 1,253 days (range 258 to 2,700 days), 895 days (12 to 3,872 days), and 447 days (13 to 2,849 days), respectively. Median survival in patients with severe and very severe AA was
statistically shorter as compared to that recorded in patients with non-severe AA (p<0.001). Also, median survival in patients with very severe AA was statistically reduced when compared with patients with severe AA (p<0.001). Median follow-up in these 42 patients was 874 days.

At diagnosis, 2/49 patients did not receive any treatment due to massive brain hemorrhage. As shown in Table 2 in the non-severe group 9 patients were treated with CSA. In 5 cases CSA was used as first-line therapy obtaining 4 CR and one PR and in 4 patients the drug was used as second-line treatment finding one CR and one PR. In this same group, 6 patients were treated with androgens as first-line therapy and 3 cases achieved a PR (Table 2). In the severe group

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**Table 1.** Demographic and clinical data in patients with paroxysmal nocturnal hemoglobinuria positive test

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNH diagnosis</td>
<td>Admission</td>
<td>Admission</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Age (years)/gender</td>
<td>33/male</td>
<td>40/male</td>
<td>36/male</td>
</tr>
<tr>
<td>Aplastic anemia severity</td>
<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>First line therapy</td>
<td>BMT</td>
<td>CSA</td>
<td>Mesterolone</td>
</tr>
<tr>
<td>Response 1st line therapy</td>
<td>CR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Second line therapy</td>
<td>None</td>
<td>SC</td>
<td>CSA</td>
</tr>
<tr>
<td>Response 2nd line therapy</td>
<td>NR</td>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td>Survival (days)</td>
<td>1,436</td>
<td>2,370</td>
<td>3,872</td>
</tr>
<tr>
<td>Status last follow-up</td>
<td>Alive/CR</td>
<td>Alive/NR</td>
<td>Alive/PR</td>
</tr>
</tbody>
</table>


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**Table 2.** Response to immunosuppressive therapy and androgens in non-bone marrow transplantation patients according to aplastic anemia severity

<table>
<thead>
<tr>
<th>Type of anemia</th>
<th>N</th>
<th>CR</th>
<th>PR</th>
<th>Overall response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-severe (n=11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine-A</td>
<td>9</td>
<td>5</td>
<td>2</td>
<td>78</td>
</tr>
<tr>
<td>Androgens</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>Severe (n=20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine-A</td>
<td>14</td>
<td>3</td>
<td>5</td>
<td>57</td>
</tr>
<tr>
<td>Anti-thymocyte globulin</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Androgens</td>
<td>16</td>
<td>1</td>
<td>6</td>
<td>44</td>
</tr>
<tr>
<td>Very severe (n=9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine-A</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Anti-thymocyte globulin</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Androgens</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

CR: complete response; PR: partial response.
14 pacientes fueron tratados con CSA. En 10 casos CSA fue utilizado como terapia de primera línea obteniendo 2 CR y 3 PR y en 4 casos el fármaco fue utilizado como terapia de segunda línea obteniendo 1 CR y 2 PR. En este mismo grupo, 4 pacientes fueron tratados con ATG, en 3 como terapia de primera línea y uno como terapia de segunda línea y sólo uno de estos logró PR. Un paciente en el grupo severo recibió ciclofosfamida como terapia de segunda línea sin respuesta. En este mismo grupo, 16 pacientes fueron tratados con andrógenos, en 8 como terapia de primera línea, encontrando 1 CR y 2 PR y en 8 casos como terapia de segunda línea obteniendo 1 CR y 4 PR (Tabla 2). En el grupo muy severo 8 pacientes fueron tratados con CSA. En 6 casos CSA fue utilizado como terapia de primera línea obteniendo 1 CR y 1 PR y en 2 pacientes el fármaco fue utilizado como terapia de segunda línea sin respuesta. Un paciente en el grupo muy severo recibió ATG como terapia de primera línea y alcanzó PR y 4 casos fueron tratados con andrógenos, 3 como terapia de primera línea y uno como terapia de segunda línea sin respuesta. Según el tratamiento, la respuesta global (CR+PR) empleando BMT, inmunosupresión (CSA, ciclofosfamida, y ATG), y andrógenos fue de 100%, 51% y 38.5%, respectivamente. La respuesta global fue significativamente mayor en los pacientes que realizaron BMT comparado con los tratados con inmunosupresión y andrógenos (p=0.002). No se registraron diferencias estadísticamente significativas en la respuesta global entre los pacientes que recibieron inmunosupresión y andrógenos (p=0.002). En ambos análisis univariado y multivariado, el Hb <10 g/dL, ANC <0.2x10⁹/L, ALC >1x10⁹/L, y PC <20x10⁹/L mostraron un impacto del tiempo de supervivencia significativa (Tabla 3). Solo Hb <10 g/dL y ANC <0.2x10⁹/L en ambos análisis univariado y multivariado fueron asociados con una respuesta significativamente menor (Tabla 3). Todas las otras variables, como la edad, el género, y el recuento de eritrocitos no mostraron un impacto significativo en la supervivencia y la respuesta al tratamiento (datos no mostrados).

Analysis of the following variables age, gender, Hb level, reticulocyte count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and platelet count (PC) as predictors of survival and therapy response was done. In both, univariate and multivariate analysis, Hb <10 g/dL, ANC <0.2x10⁹/L, ALC >1x10⁹/L, and PC <20x10⁹/L showed a statistically significant deleterious impact on survival (Table 3). Only Hb <10 g/dL and ANC <0.2x10⁹/L in both univariate and multivariate analysis were associated with a statistically significant lower response (Table 3). All other variables such as age, gender, and reticulocyte count did not significantly impact survival and treatment response (data no shown).

Overall mortality reached 41%; 12 patients died due to central nervous system hemorrhage, 7 cases died of pneumonia, and one patient developed acute myeloid leukemia.

DISCUSSION

The incidence of AA varies between geographic regions.3-11,13 In México one study estimated the annual incidence of AA in patients >15 years old in 3.8 cases per million individuals.12 In the current ten-year retrospective study it was found that from 57,721 new admissions 49 cases (0.08%) corresponded to AA. Also as reported by other authors in the present study sex ratio showed a slight, although not significant, male predominance.3,12 AA mainly affects young adults.3 This is in line with the median age recorded in our patients, 35 years.

In relation to etiology, herein 75.5% of cases were idiopathic and in 12 patients bone marrow failure was associated to agricultural pesticides exposure. Similar data have been reported in other series.1 HAV, HBV, and HCV antibodies were detected in some of our patients however none of them had clinical and laboratory evidence of viral hepatitis. This is in contrast...
with other reports showing a close association between AA and viral hepatitis.\textsuperscript{15} The number of GPI-deficient clones, employing a cut-off level $\geq 1\%$ in granulocytes, were similar at diagnosis (10.5\%) and during follow-up (9.5\%). These frequencies are lower than those reported by other authors in larger populations employing similar criteria.\textsuperscript{22,23}

The classifications of Camitta and Bacigalupo\textsuperscript{16,19} were used to stratify AA severity in our population. With these simple classifications we were able to depict three survival curves which were statistically different between them: longer survival in non-severe cases compared with severe and very severe patients, and shorter survival in very severe cases when compared with severe AA patients (p<0.05; Figure 1). These long standing classifications\textsuperscript{16,19} take into account reticulocyte, neutrophil and platelet counts along with bone marrow cellularity. Herein, employing a multivariate analysis, it was found that the following independent variables: Hb $< 10$ g/dL, ANC $< 0.2 \times 10^9$/L, ALC $> 1 \times 10^9$/L, and PC $< 20 \times 10^9$/L at diagnosis had statistically deleterious impact in survival (Table 3). It is not surprising that Hb level (a surrogate of reticulocyte count), ANC, and PC impacted survival negatively in our patients since these parameters are included in classical classifications for AA severity.\textsuperscript{16,19} Herein ALC $> 1 \times 10^9$/L also had a deleterious effect in survival. This finding supports the notion that lymphocytes play a central role in the pathophysiology of AA.\textsuperscript{15}

### Table 3. Univariate and multivariate analysis of demographic and laboratory data on survival and treatment response

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>CI 95%</td>
</tr>
<tr>
<td>Hb $&lt; 10$ g/dL</td>
<td>5</td>
<td>2.5-12</td>
</tr>
<tr>
<td>ANC $&lt; 0.2 \times 10^9$/L</td>
<td>1</td>
<td>3-20</td>
</tr>
<tr>
<td>ALC $&gt; 1 \times 10^9$/L</td>
<td>0.36</td>
<td>0.12-0.88</td>
</tr>
<tr>
<td>PC $&lt; 20 \times 10^9$/L</td>
<td>1</td>
<td>0.15-0.97</td>
</tr>
<tr>
<td>Treatment response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb $&lt; 10$ g/dL</td>
<td>7</td>
<td>2-13</td>
</tr>
<tr>
<td>ANC $&lt; 0.2 \times 10^9$/L</td>
<td>4</td>
<td>2.1-10</td>
</tr>
<tr>
<td>ALC $&gt; 1 \times 10^9$/L</td>
<td>0.7</td>
<td>0.35-0.9</td>
</tr>
</tbody>
</table>

HR: hazard ratio; CI: confidence interval; p: p value; Hb: hemoglobin; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; PC: platelet count.
Seven of our patients with severe AA, one with PNH clones, received BMT from HLA-matched sibling donors. All remain alive in CR. This result is in line with most publications indicating that BMT with a HLA-matched sibling donor is the best curative treatment for severe and very severe AA cases, with 60 % to 80 % long-term survival.19

Immunosuppressive therapy for severe and very severe AA cases lacking compatible donor includes ATG and CSA alone or combined.23,24 In the present study, 4 patients with severe AA and one with very severe AA received ATG followed by CSA finding only PR in 2 cases (40%; Table 2). Regardless of AA severity, herein, 31 patients were treated with CSA: 9 with non-severe, 14 with severe and 8 with very severe AA. Overall response in severe and very severe AA cases was 45.5 % not significantly different to that found in patients exposed to ATG (Table 2). These results are in line with previous data showing that ATG and CSA produce comparable responses.25 We treated non-severe AA cases with CSA or androgens and although overall response was higher in CSA-treated patients (78%) than in androgen-treated cases (50%) the difference did not reach statistical significance. Twenty patients with severe and very severe AA also received androgens and while overall response was significantly higher in severe cases (75%) than in very severe cases (0%) the difference was not statistically different (Table 2). Several androgens have shown to improve cytopenias in AA patients.17,18 More recently, danazol has proven to induce hematologic response in 31.3 % of cases with AA refractory to immunosuppressive therapy26 and in 46 % of patients when used as first-line treatment.27 These data are similar to the overall response rate of 38.5 % recorded in our cases who received androgens as first-line or second-line therapy.

In the current study the multivariate analysis showed that only Hb < 10 g/dl and ANC <0.2x10^9/L at diagnosis were highly predictive of response regardless of the given treatment, i.e., immunosuppressive agents or androgens. Scheinberg et al28 showed in 316 patients with severe AA that those with absolute reticulocyte count (ARC) ≥25x10^9/L and ALC ≥1x10^9/L together had a much greater probability of response at 6 months following immunosuppressive therapy compared to patients with lower ARC and ALC. Our data failed to demonstrate this since ALC ≥1x10^9/L reached statistical significance in the univariate logistic regression model but not in the multivariate one. Of interest was the finding that in our study a baseline ANC <0.2x10^9/L, in both univariate and multivariate regression models, was highly predictive of response at 6 months whereas in the study of Scheinberg et al25 ANC <0.2x10^9/L did not predict response. Interestingly, in our study Hb <10 g/dL and ANC <0.2x10^9/L were similar in terms of predicting response in patients who received either immunosuppressive treatment or androgens.

The criteria used to qualify therapeutic response in our patients were originally design to evaluate immunosuppressive therapy in AA21 and these showed a strong association with survival (Figure 2), suggesting that these criteria can be employed also to qualify response to androgen treatment.

It has been shown, herein, that: a) long standing classifications are still useful to stratify survival and therapy response in AA, b) BMT in well selected cases remains the best therapeutic option, and c) seemingly immuno-suppression and androgens render similar response rates in AA.

REFERENCES


