

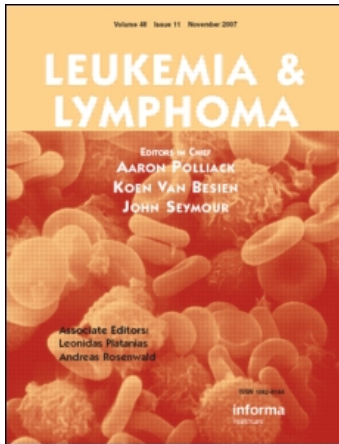
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### Limited prognostic value of the International Prognostic Score in advanced stage human immunodeficiency virus infection-related Hodgkin lymphoma treated with the doxorubicin, bleomycin, vinblastine, and dacarbazine regimen

Blanca Xicoy <sup>ab</sup>; Josep-María Ribera <sup>ab</sup>; Pilar Miralles <sup>c</sup>; Juan Berenguer <sup>c</sup>; Rafael Rubio <sup>c</sup>; Beatriz Mahillo <sup>c</sup>; María-Eulalia Valencia <sup>c</sup>; Eugenia Abella <sup>b</sup>; Armando López-Guillermo <sup>b</sup>; Ana Sureda <sup>b</sup>; Mireia Morgades <sup>a</sup>; José-Tomás Navarro <sup>ab</sup>; Herminia Esteban <sup>c</sup>; On Behalf of Gesida and Gelcab Groups, Spain

<sup>a</sup> Institut Català d'Oncologia-Hospital Universitari Germans Trias i Pujol, Badalona, Spain <sup>b</sup> GELCAB group, Spain <sup>c</sup> GESIDA group, Spain

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LETTER TO THE EDITOR

**Limited prognostic value of the International Prognostic Score in advanced stage human immunodeficiency virus infection-related Hodgkin lymphoma treated with the doxorubicin, bleomycin, vinblastine, and dacarbazine regimen**

BLANCA XICOY<sup>1,3</sup>, JOSEP-MARÍA RIBERA<sup>1,3</sup>, PILAR MIRALLES<sup>2</sup>, JUAN BERENGUER<sup>2</sup>, RAFAEL RUBIO<sup>2</sup>, BEATRIZ MAHILLO<sup>2</sup>, MARÍA-EULALIA VALENCIA<sup>2</sup>, EUGENIA ABELLA<sup>3</sup>, ARMANDO LÓPEZ-GUILLERMO<sup>3</sup>, ANA SUREDA<sup>3</sup>, MIREIA MORGADES<sup>1</sup>, JOSÉ-TOMÁS NAVARRO<sup>1,3</sup>, & HERMINIA ESTEBAN<sup>2</sup>;  
ON BEHALF OF GESIDA AND GELCAB GROUPS, SPAIN

<sup>1</sup>Institut Català d'Oncologia-Hospital Universitari Germans Trias i Pujol, Badalona, Spain, <sup>2</sup>GESIDA group, Spain, and <sup>3</sup>GELCAB group, Spain

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In patients infected with human immunodeficiency virus (HIV), Hodgkin lymphoma (HL) displays a more aggressive behavior than in non-immunocompromised patients. However, in the highly active antiretroviral therapy (HAART) era, several studies have shown that the response rate and survival of these patients are similar to that of immunocompetent patients [1–4]. In our series of patients with advanced stage HIV-related HL, treated with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) and HAART, the immunological response to HAART had a positive impact on overall survival (OS) and event-free survival (EFS) [4].

The International Prognostic Score (IPS) is a useful seven-factor prognostic score for prediction of outcome in newly diagnosed patients with HL in advanced stages. However, patients with HIV-related HL were excluded from this prognostic model [5]. The accuracy of IPS for outcome prediction in these patients has not been extensively studied. Spina *et al.* [6] reported the results of the Stanford V regimen and HAART in patients with bulky limited stage or advanced stages (III and IV) HIV-related HL, with a significantly different 3-year freedom from progression (FFP) and shorter survival in patients with IPS higher than 2 (83% *vs.* 52%,  $p=0.02$ ). The results

were comparable with those observed in HIV-negative patients with HL treated with the same schedule [7].

ABVD is presently considered the standard treatment for patients with advanced stage HL. The aim of this study was to evaluate the IPS as a predictor of outcome in patients with advanced stage (III or IV) HIV-related HL treated with ABVD and HAART.

From 1996 to 2005, 62 patients with newly diagnosed HIV-related HL in advanced stage were treated with 6–8 cycles of ABVD and HAART since diagnosis in 15 Spanish hospitals [4]. Six percent of the 53 evaluable patients received radiotherapy. The parameters included in the IPS (serum albumin level  $<4$  g/dL, hemoglobin  $<10.5$  g/dL, male sex, age  $\geq 45$  years, stage IV, WBC  $\geq 15 \times 10^9/L$ , lymphocyte count  $<0.6 \times 10^9/L$  or  $<8\%$  of the WBC, or both) were retrospectively recorded and complete data were available in 60 patients. The IPS score was defined as the number of adverse prognostic factors at diagnosis, and patients were classified into two groups: IPS score 0–3 *vs.* higher than 3. Patients were restaged according to the Cheson *et al.* criteria [8]. CR rate, OS, EFS and FFP were analyzed.

The median age of the series was 38 years (range 24–62) and 52 patients (87%) were males.

Forty-eight patients (77%) had been receiving HAART for a median of 12 months (range 1–109) at the time of HL diagnosis. However, the median of CD4 lymphocyte count at the time of HL diagnosis was 117/ $\mu$ L (range 5–1209) and only 21 out of 55 evaluable patients were in virologic response (viral load lower than 50 copies/mL) at diagnosis of HL. The most frequent HL subtype was mixed cellularity (23 patients, 38%). Twenty-two patients (40%) had an Eastern Cooperative Oncology Group (ECOG) score equal or higher than 2 and 41 (68%) were in stage IV, with bone marrow involvement in 33 out of 60 (55%) of patients. Six to eight cycles of standard ABVD therapy were completed in 48/58 (83%) of patients according to the policy of each center. Thirty-three patients (55%) had an IPS of 0–3 and 27 (45%) had an IPS higher than 3. The CR rate was 91% in the group with a prognostic score 0–3 compared to 81% in the group with IPS higher than 3 ( $p = 0.24$ ). The 5-year (95%CI) OS probabilities were 84% (71–97%) and 63% (43–83%) for groups with IPS 0–3 and IPS > 3, respectively ( $p = 0.06$ ) (Figure 1), whereas 5-year (95%CI) EFS probabilities were 79% (63–95%) and 63% (43–83%) for patients with IPS 0–3 and with IPS higher than 3, respectively ( $p = 0.09$ ). Differences in FFP at 5 years were not statistically significant (82% [67–97%] vs. 83% [68–98],  $p = 0.65$ ). When a comparison of IPS scores 0–2 ( $n = 15$ ) vs. > 2 ( $n = 45$ ) was performed, no differences in OS (85% vs. 70%,  $p = 0.26$ ) or in FFP (79% vs. 74%,  $p = 0.51$ ) were observed.

In the IPS prognostic model, each additional factor reduced the plateau of FFP by about 8%. Moreover, each factor conferred an approximate 7% reduction in cure rate at 5 years (rate of FFP of disease of 66% and rate of OS of 78% at five years).

The difference between IPS 0–3 vs. > 3 was 23% in FFP of disease. Our series shows several differences compared with the IPS study. All patients were treated homogeneously with a regimens containing doxorubicin vs. 75% of the Hasenclever *et al.* series. The IPS study included 603 (13%) patients with stages I and II with poor prognostic factors whereas the present study was focused exclusively on patients with stages III–IV to ensure a homogenous therapeutic approach. We found a trend for better CR and OS rate for patients with lower IPS scores when a cut-off level of 3 was considered. These differences disappeared on considering 2 as a cut-off point. Five reasons might explain the differences in our results compared with the original study: First, the small sample size with a reduced number of events makes it difficult to establish powerful statistical comparisons; Second, the IPS score distribution in our series was different from that observed in the original IPS series (IPS 0–3, 54% vs. 81% and IPS higher than 3, 46% vs. 19%), a feature consistent with the more aggressive nature of HL in HIV-infected patients; Third, in our series early stages with bad prognostic factors were not included and all patients received the same schedule of chemotherapy together with HAART; Fourth, the possible favorable impact of response to HAART in the prognosis of HIV-related HL could have contributed to the homogeneous results in treatment in all IPS subgroups, hindering the search for difference; Fifth, some of the biologic items included in the IPS could have been influenced by the HIV infection itself, thus limiting the discriminative value of IPS score. Although our series only shows a trend for a better response to therapy and survival for patients when a cut-off level of 3 was considered (no differences were observed at

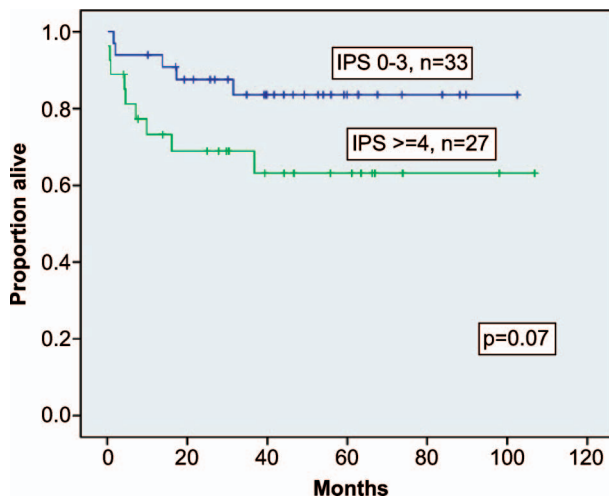


Figure 1. Overall survival according to International Prognostic Score. To view in colour online please go to: [www.informahealthcare.com/lal](http://www.informahealthcare.com/lal).

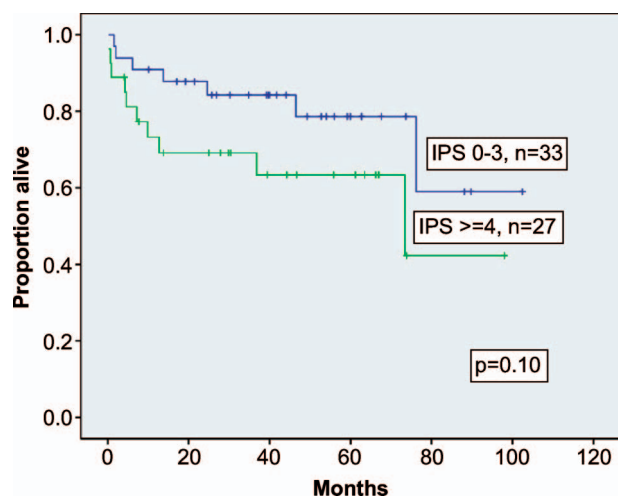


Figure 2. Event-free survival according to International Prognostic Score. To view in colour online please go to: [www.informahealthcare.com/lal](http://www.informahealthcare.com/lal).

a cut-off level of 2), other studies have shown the IPS score to be of great utility in patients with HIV-related HL. Again, some differences between these series could explain the slightly discordant results. In the series by Spina *et al.* including 59 patients with HIV-related HL treated with the Stanford V schedule, almost 30% of the patients included were in early stages with poor prognostic factors, and the survival was slightly inferior (3-year OS of 51% compared to 5-year OS of 76% of our series). This is the first study to analyze the impact of the IPS score in HIV-related HL in advanced stages treated with ABVD and HAART. Regardless a different distribution of patients in the subgroups with respect to the original series of Hasenclever *et al.* (with more patients with a high IPS score), only a trend for a poor response and survival was observed in patients with a high IPS score, thus limiting the prognostic value of IPS score in HIV-related HL in advanced stages.

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