Treatments for non-Hodgkin lymphoma in HIV-positive patients: Quantifying incremental benefit from 1993 to 2004 by metaregression

In HIV-positive patients who develop non-Hodgkin lymphoma (NHL), it is widely accepted that outcomes can be improved by combining antiretroviral therapy with treatments directed at NHL. The clinician's armamentarium now includes highly active antiretroviral therapy (HAART), standard chemotherapy protocols for NHL (e.g., CHOP, EPOCH), and rituximab, but in the past decade, other less-effective treatments were available.

The paper by Castillo and Echenique [1] offered a comprehensive overview of all prospective studies conducted in this area and, in particular, provided a detailed dataset that can be useful for further analysis. Although therapeutic innovation has likely led to progressive improvements over the past years, this temporal trend has generally been explored only through narrative reviews; some "traditional" meta-analyses focused on hazard ratios or odds ratios have been carried out, but no attempt has been reported to quantitatively evaluate temporal trends and/or to apply metaregression [2] for studying this issue.

We describe the results of a metaregression focused on prospective studies conducted in this area from 1993 to 2004. Our objective was to determine the temporal trend for overall survival at 2 years in these patients. Relevant studies were identified through a literature search similar to that described by Castillo and Echenique [1]. Each clinical study was assigned to a specific calendar year that represented the midpoint of the respective enrolment interval. Temporal trends (focused on the end-point of 2-year survival) were determined using the same metaregression methods as those described previously [2]. Individual studies were weighted according to inverse variance (defined as $\sqrt{n}$ where n is the number of enrolled patients). The metaregression yielded a regression line along with its statistical significance.

A total of 18 treatment arms obtained from 14 papers were included in our study (overall sample size = 1,018 patients). This clinical material was similar to that examined by Castillo and Echenique [1], but a few treatment arms were left out because they did not provide the survival data needed for our analysis. In general, CHOP with or without rituximab was the regimen most frequently used.

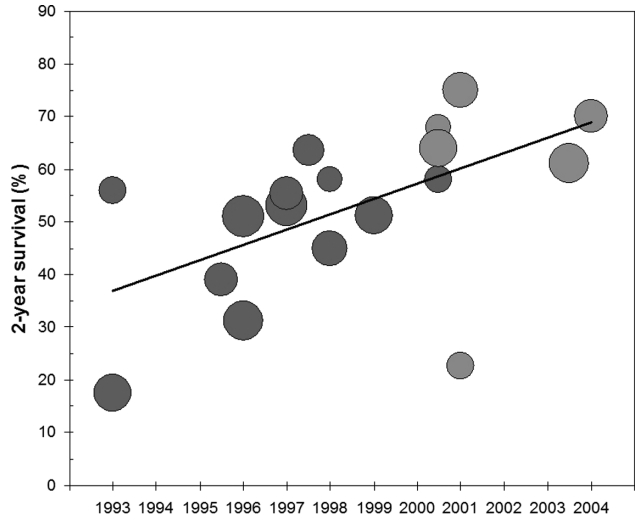

Figure 1. Metaregression plot: temporal trend of 2-year survival in prospective clinical studies evaluating HIV-positive patients with NHL. The graph refers to 18 treatment arms. The regression line (percent survival at 2 years = 2.892 × YEAR − 5726.775; $p = 0.012$) indicates an improvement of 2.89% per year over this period. Symbols: each study is represented by a circle the area of which is proportional to its statistical weight. Arms treated with rituximab are depicted in gray while all the others are in blue. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The results of our metaregression (Figure 1) found a significant improvement with time in 2-year survival. The regression line showed an increase in 2-year survival from 37.0% in 1993 to 68.8% in 2004. This improvement was largely driven by the introduction of rituximab; in fact, the arms employing rituximab ($N = 6$) had a significantly higher 2-year survival than those not employing rituximab ($N = 12$); mean values of 2-year survival (calculated on the basis of inverse variance statistical weighting) were 61.2% for rituximab versus 47.4% without rituximab ($p = 0.01$). Further details on our analysis are reported in the Supporting Information.

The main strength of our study is that a formal analytic tool has been employed to determine the temporal trend of outcomes in HIV-patients with NHL; quantifying these trends through metaregression in fact improves the statistical quality of the results. As in the analysis by Castillo and Echenique [1], the main limitation of our study is represented by the lack of patient-level data.

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Additional Supporting Information may be found in the online version of this article.

Conflict of interest: Nothing to report.

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Reply to A. Messori et al.

We thank Messori and collaborators for their comment on our previously published study [1] and appreciate the opportunity to expand on the discussion of therapies in patients with HIV-associated non-Hodgkin lymphoma (NHL).

In their correspondence, Messori and colleagues have performed a meta-regression analysis to evaluate the trend in the 2-year overall survival (OS) rate reported in prospective studies on patients with HIV-associated NHL between the years 1995 and 2004 [2]. They report an improvement in the 2-year OS, from 42.8% in 1995 to 68.8% in 2004, which represents a 26% absolute and a 60% relative improvement in 2-year OS in patients with HIV-associated NHL. They also report a median 2-year OS of 61% in patients treated with rituximab-containing regimens versus 48% in patients treated with chemotherapy alone.

There are mounting data in the literature showing an improvement in response rates and survival in patients with HIV-associated NHL who are treated with rituximab in combination with chemotherapy. The correspondence by Messori and colleagues certainly adds to that body of evidence by means of a meta-regression analysis. Meta-regression indeed provides a more "granular" feeling to an otherwise categorical meta-analysis. Such "granularity" is clearly exemplified by the figure provided in their article. However, meta-regression analyses have inherent problems and caveats.

In this specific example, Messori and colleagues used the middle point of the enrollment interval as a representative point in time for the whole group. By using this approach, it is easy to fall into ecological fallacy, in which any inference about the individual is estimated based on the result of the group but might not represent the actual individual. As an example, a study enrolling patients between the years 1990 and 1999 will be assigned as year 1995 without having into account the potential differences in therapy that took place during that interval as it is likely that practices changed between 1990 and 1999.

Additionally, meta-regression analyses do not address other weaknesses of categorical meta-analyses such as missing data and lack of adjustment for other potential important factors. These two aspects, not surprisingly, go hand in hand. For example, it is likely that the addition of appropriate antibiotic prophylaxis, growth factor support and use of intrathecal chemotherapy to decrease central nervous system involvement, in addition to rituximab, have partially improved the outcome; however, this will be unlikely to be evaluated without patient-level data. A recent study presented in abstract format at the 2012 American Society of Hematology Annual Meeting attempts to address this issue by analyzing patient-level data on 1,546 patients with HIV-associated NHL from 19 studies [3]. Preliminary results show an improvement on response and survival rates in patients treated with rituximab and chemotherapy. A final peer-reviewed publication is eagerly expected.

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Reassessing an old claim: Natural selection of hemizygotes and heterozygotes for G6PD deficiency in Africa by resistance to severe malaria

In 1995, from work carried out in Kenya and in The Gambia, Ruwende et al. concluded that hemizygous G6PD-deficient male and heterozygous G6PD-deficient female children in Africa were similarly protected from severe malaria and were selectively advantaged in a malarial environment [1]. The recent publication of a detailed map of G6PD deficiency [2], again citing the Ruwende et al. paper in the context of studies of this genetic disorder, has prompted the question whether the data reported by Ruwende et al. can be considered accurate or not.

They are not, for the following cogent reasons:

1. Ruwende et al. typed only one G6PD deficiency (G6PD A−) mutation, namely *G6PD* 202 G → A (always found with *G6PD* A variant 376 A → G), on the wrong assumption that this was the major mutation underlying G6PD A− deficiency in The Gambia [1]. However, a key study from Senegal was published in *Haematologica* in 2006 reporting that a different mutation, *G6PD* 968 T → C, had a frequency of 10% in Senegalese Serer males, and a G6PD deficiency prevalence of 12% in that ethnic group [3]; remarkably, the *G6PD* 968 T → C mutation had been described in the literature since 1989 [4]. The Senegalese data reported by De Araujo et al. prompted a replication study and eventually *G6PD* 968 T → C was proven to be the most frequent A− mutation in The Gambia, present in 7% of males [5]. Therefore, since *G6PD* 968 T → C was overlooked by Ruwende et al., a large proportion of G6PD A−-deficient subjects were certainly misclassified as normal in their study, as pointed out by L. Luzzatto [6].
2. The *G6PD* 202 G → A mutation in The Gambia had already been reported at surprisingly low frequency level (less than 2%) in 2004 [7]. The real frequency of this mutation in Gambian males was subsequently confirmed to be 2–3% [5,8], not 5.9% as reported by Ruwende et al. The reason why they found such an inflated frequency is unknown.
3. The frequency of G6PD A− deficiency in Gambian males is approximately 10%, not 5.9% as reported by Ruwende et al.; the overall frequency of about 10% is accounted for by the sum of 968 T → C (7%) plus 202 G → A (3%). A third, non A− deleterious mutation, 542 A−>T (G6PD Santamaria) has a frequency of over 2% in males (5), bringing the total frequency of G6PD deficiency up to 12%. Interestingly, an 8.3% deficiency frequency, found by enzymatic activity colorimetric assay, was reported from The Gambia as early as 1965 [9].

The analysis carried out by Ruwende et al. was not statistically significant from Kenyan data alone, but was based on pooled data from Kenya and The Gambia: however, as detailed above, the latter data were invalid. Regrettably, the incongruences in the Ruwende et al. paper have never been thoroughly and systematically questioned, consequently the paper keeps being widely quoted, having reached a total of over 340 entries in Google Scholar (including the one by Guindo et al. [10]) with a potential misleading effect on studies of G6PD and malaria. It is at this point important to recognize that the Ruwende et al. work was based on largely incorrect data, which mandates a complete re-assessment of the conclusions reached at the time of its publication.

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