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FOR THE COMPARISON OF THESE CHARACTERISTICS BETWEEN THE RUMMEL STUDY AND THE PRIMA TRIAL
LETTER TO THE EDITOR

Comparative effectiveness of treatments for newly diagnosed follicular non-Hodgkin lymphoma

Andrea Messori, Valeria Fadda, Dario Maratea & Sabrina Trippoli

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In newly diagnosed follicular non-Hodgkin lymphoma (NHL), treatment is indicated in patients who show certain clinical characteristics (such as B symptoms, hematopoietic impairment, bulky disease, vital organ compression, ascites or pleural effusion, rapid lymphoma progression). This point has recently been emphasized by the 2014 European Society for Medical Oncology (ESMO) guideline for follicular NHL [1].

As regards the different treatment options, several combination regimens have been tested in recent decades, but only a few are recognized to be the current standard of care. According to the ESMO guidelines, current standards of care include R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) without R maintenance, R-CHOP with R maintenance and bendamustine + R [1].

To comparatively assess the effectiveness of the above three treatments, we conducted a Bayesian meta-analysis. The clinical material was represented by randomized controlled trials (RCTs) that evaluated one of these three regimens in treatment-naïve patients with follicular NHL.

Our end-point was progression-free survival (PFS) at 2 years. Our results found the best effectiveness profile for R-CHOP with R maintenance.

The literature search required for our analysis was conducted in PubMed (last query on 30 December 2014) and covered the period from January 2000. A single search term ("non-Hodgkin lymphoma") was employed in combination with the filter "randomized controlled trials." Since the number of citations was small (fewer than 800), we analyzed all of these articles by examining the abstract or, when necessary, their full text, and we identified the RCTs that met our inclusion criteria. These criteria comprised: (a) randomized design; (b) previously untreated patients with indolent NHL; (c) evaluation of one of the three combination treatments mentioned above; (d) determination of PFS at 2 years for each treatment group; and (e) separate information on PFS available for patients with follicular NHL. For each trial, the probability of PFS at 2 years (including the effect of censoring) was obtained in numerical form from the published report, or was determined through a graphical analysis of Kaplan–Meier curves [2].

For our statistical analysis, we employed a Bayesian model of network meta-analysis [3,4]. This approach (available as fixed effects or random effects model) is advantageous because all treatments under comparison are incorporated into a single model; another advantage is that the Bayesian technique enables rank ordering of each treatment. This Bayesian model has been developed by the National Institute for Health and Care Excellence (NICE) Support Unit (UK) [4]. The output of the analysis consisted of the meta-analytic odds-ratio (OR) with credible interval (CI) along with ranking statistics.

Our literature search selected 575 citations; among these, three randomized studies [5–7] met our inclusion criteria (1773 patients, six treatment arms). The raw data of PFS for the three included trials have been reported elsewhere [8].

The 'BRIGHT' study [9] (aimed at the comparison of bendamustine + R vs. R-CHOP/R-cyclophosphamide, vincristine, prednisone [CVP]) was excluded because no information on PFS at 2 years was available, while the study by van Oers et al. [10] (comparing CHOP with no R maintenance vs. CHOP with R maintenance and R-CHOP with no R maintenance vs. R-CHOP with R maintenance) was excluded because the patients were not treatment-naive. In the PRIMA trial [7], after a total of 1202 treatment-naïve patients were enrolled and registered, randomization to either R maintenance or no maintenance was applied to the subgroup of 1019 patients who completed the induction treatment. To make the PFS data of this trial (that refer to randomized patients) comparable to those of the other included trials (that refer to treatment-naïve patients), the data of PFS in the PRIMA trial underwent an empirical adjustment (+4.7% relative increase in progression for registered patients in comparison with randomized patients) that was based on further information on the same patients reported in a more recent analysis [11]. This approximation, which is described in detail elsewhere [8], was thought to be acceptable for the purposes of our analysis. Besides the three treatments selected according to our study protocol, one further treatment (i.e. CHOP) was evaluated in our analysis because this treatment acted as a comparator in some studies.

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The results of our Bayesian meta-analysis are presented in Figure 1 according to the fixed effects model; this model determined a better goodness of fit in comparison with the random effects model (the data of which are not shown). In the pairwise comparisons [Figure 1(A)], all differences were statistically significant except that between bendamustine + R and R-CHOP. R-CHOP + R maintenance proved to be more effective than each of the other three treatments. Figure 1(B) illustrates the ranking histograms. The ranks for individual treatments (with 95% CrI) were as follows: CHOP 4 (4–4); R-CHOP 2 (3–2); bendamustine + R, 3 (2–3); R-CHOP + R maintenance, 1 (1–1).

While our results were successful in synthesizing the evidence available for these treatments, some limitations of our analysis were unavoidable. Besides the approximation mentioned above whereby we handled the survival data of the PRIMA trial, another limitation is that we used the criteria for the various studies (e.g., the Rummel study vs. the PRIMA trial) differed in number of respects histologic sub-typing (i.e. grade 3a disease); such differences could have impacted to some extent on the 2-year PFS rates.

In conclusion, our study generated an updated synthesis of comparative effectiveness regarding current treatments for previously untreated follicular NHL. Both the ranking analysis and the values of OR for pairwise comparisons confirmed that R-CHOP + R maintenance is particularly effective in this disease condition, and in fact this regimen ranked first in effectiveness. Bendamustine + R did not differ from R-CHOP. On the other hand, CHOP clearly had the worst rank in effectiveness.

**References**


