When more is just more, not better: a recurring lesson

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TITLE	A phase III comparison of CHOP *vs*. m-BACOD *vs*. ProMACE-CytaBOM *vs*. MACOP-B in patients with intermediate- or high-grade non-Hodgkin's lymphoma: results of SWOG-8516 (Intergroup 0067), the National High-Priority Lymphoma Study.
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The advent of combination chemotherapy in the 1970s ushered in a new era of combating cancer, and the observation that CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) could lead to cures in advanced stage aggressive lymphomas was revolutionary at the time. The subsequent decade reflected a flurry of single arm, and sometimes single institution, trials adding the latest cytotoxic agents to this backbone with phase II trials of MACOP-B, m-BACOD, and ProMACE-CytaBOM, suggesting superior efficacy compared to CHOP. The historical background was that CHOP offered complete remission rates of roughly 50% and cure rates of around 30%, whereas the second-generation regimens were said to double the cure rate. Investigators argued heavily for intensification as a way to improve the cure rate even though these “second-generation” regimens were significantly more toxic, particularly in the era prior to routine anti-emetics, antimicrobial prophylaxis, and growth factor support.

SWOG-8516 (Intergroup 0067), also called the National High-Priority Lymphoma Study, was an ambitious four-armed trial that sought to resolve the issue by comparing these augmented regimens against CHOP.[1] Among 1,138 registered patients, 899 eligible patients were randomized. There were five stratification factors: bone marrow infiltration, bulky disease, age (65 years as cutoff), LDH elevation, and Working Group Formulation histologic group (D or E *vs*. F, G, H *vs*. J). It is notable that this was a young patient population, and included pediatric patients. Efficacy outcomes were strikingly similar; with a median follow up of 35 months, the 3-year progression-free survival was 41-46% and 3-year overall survival 50-54% with no statistically significant differences between any of the arms (Figure 1). There were, however, significant differences in terms of fatal toxicity/non-relapse mortality: 1% CHOP, 3% ProMACE-CytaBOM, 5% m-BACOD, and 6% MACOP-B. This trial established CHOP as a formidable therapeutic backbone that has proved difficult to supplant. With the exception of adding rituximab, and perhaps now polatuzumab vedotin (for B-cell histologies) and brentuximab vedotin (for CD30$^+$ T-cell histologies), CHOP is still considered the standard chemotherapy regimen for both B- and T-cell aggressive lymphomas.

Through a modern lens, there are many aspects of this paper that now seem outdated: this was a mixture of B- and T-cell histologies based on a now-obsolete classification system, over 20% of patients were ineligible after pathology review, no transformed lymphomas were included, and this was a pre-PET (and pre-gallium) era whereby responses were more difficult to determine. It is provocative to consider whether CHOP would have remained the “winner” if we had had modern histopathologic classification to assess genomic and biologic features, and institution of full supportive care.

Nevertheless, there are many important lessons to be learned from this iconic trial. The first is that “more” is not always “better”, and several subsequent trials evaluating dose density, increasing chemotherapy intensity or even high-dose chemotherapy with autologous stem cell rescue were all negative trials (reviewed by Sehn and Salles[2]). Furthermore, despite an excellent rationale and impressive single arm data, there are many trials of R-CHOP + X that are negative. This may be due to biologic heterogeneity and an unselected patient population, but also because prolonged time from diagnosis to treatment is an inadvertent selection factor. In S8516/0067, the control arm fared better than expected, perhaps due to these factors.

Despite all these caveats, the National High-Priority Lymphoma Study set a bar for future trials. It is noteworthy

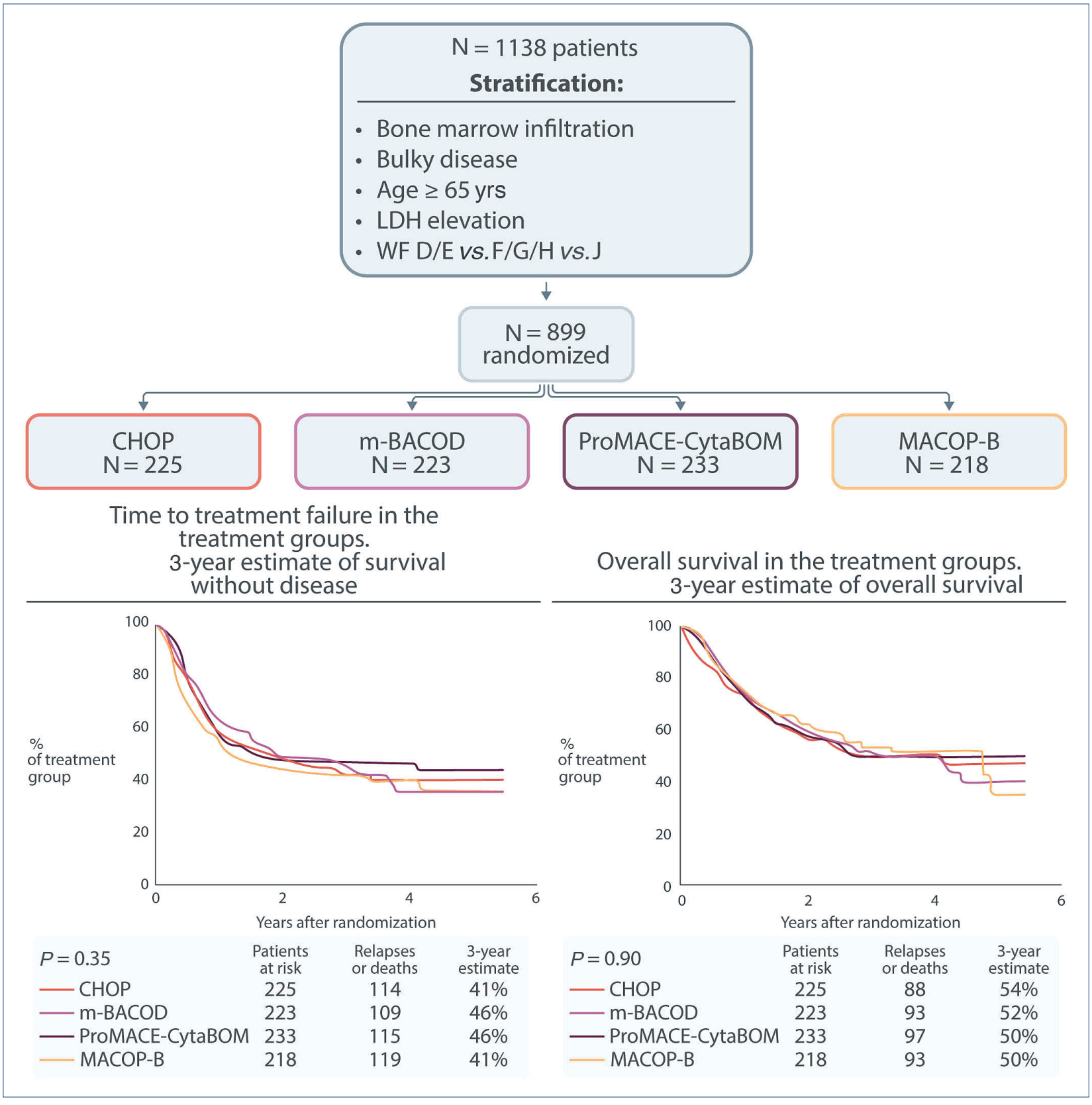

Figure 1. Schema and results of the National High-Priority Lymphoma Study. Figure adapted with permission from Fisher *et al.* Ann Oncol 1994.

that this trial was a product of the United States Intergroup mechanism, and it is far from likely that a four-arm trial comparing regimens would be feasible if only for-profit entities were involved. As we move to an increasingly targeted (and more expensive) era, this is a critical point to consider if CHOP is to be dethroned. Overall, S8516/0067 definitively showed that "more is not better", provided a backbone that remains firmly entrenched in the therapeutic armamentarium, and was one of the first combination regimens to show curability of advanced stage lymphomas.

Disclosure

No relevant conflicts of interest to disclose.

References

1. Fisher RI, Gaynor ER, Dahlberg S, et al. A phase III comparison of CHOP vs. m-BACOD vs. ProMACE-CytaBOM vs. MACOP-B in patients with intermediate- or high-grade non-Hodgkin's lymphoma: results of SWOG-8516 (Intergroup 0067), the National High-Priority Lymphoma Study. Ann Oncol. 1994;5(Suppl 2):91-95.
2. Sehn LH, Salles G. Diffuse large B-cell lymphoma. N Engl J Med. 2021;384(9):842-858.