Comment on Le Gouill et al, page 2307

DLBCL outcomes: much ventured, much GAINED

Andrew Davies | Southampton General Hospital

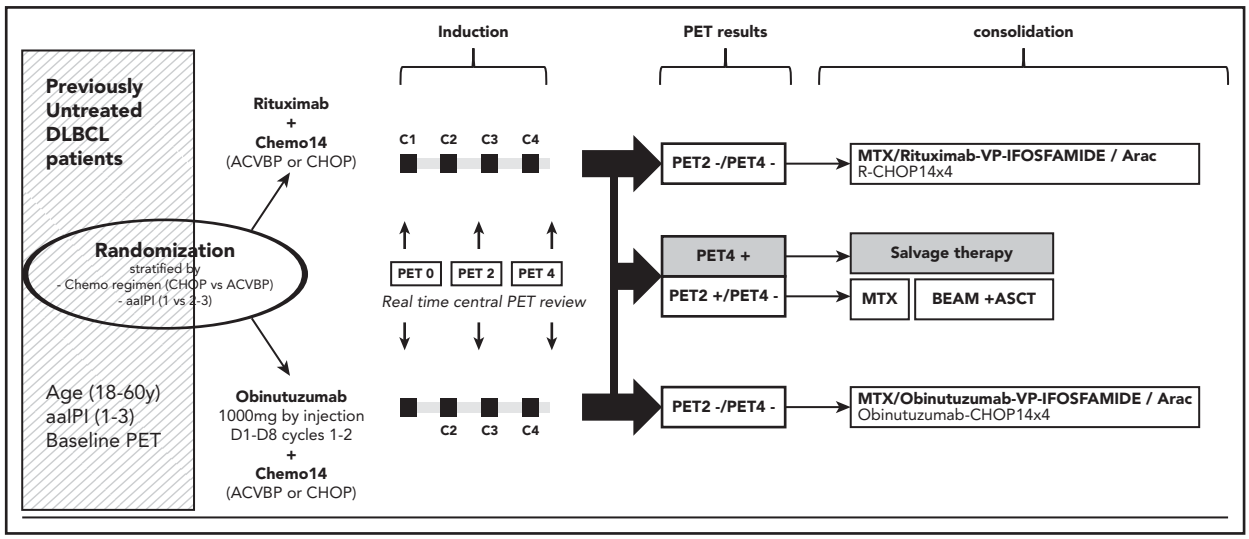
There have been many attempts to improve the outcomes of patients with diffuse large B-cell lymphoma (DLBCL). In this issue of *Blood*, the results of the GAINED study by Le Gouill et al take us on a further twist in this journey.[1] GAINED asks first whether employing the glycoengineered type 2 anti-CD20 antibody obinutuzumab rather than rituximab has efficacy benefits and, second, whether a positron emission tomography (PET)-driven approach can be used to identify patients at high risk of failure and to adapt consolidation strategies accordingly.

The patients were young and potentially fit for high-dose chemotherapy intensification. They carried an adverse risk factor defined by an age-adjusted International Prognostic Index ≥1. The design was simple. The patients received either CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone) on a 14-day schedule and were randomized to obinutuzumab or rituximab (see figure). Obinutuzumab did not provide any efficacy advantage over rituximab and was associated with more toxicity. This result firmly cements the observation of the GOYA study, which asked a similar question, albeit in a somewhat different population.[2]

The impact from GAINED comes from an evaluation of the positron emission tomography (PET)-directed consolidation approach. Interim PET scans were performed and prospectively reviewed centrally after both cycles 2 and 4 of CHOP or ACVBP. This approach is a triumph of delivery logistics. The interpretation was based upon the quantitative maximum standard update value reduction criteria (ΔSUV_{max}) where the SUV of the most fluorodeoxyglucose-avid lesion at baseline is compared with that observed on the interim imagining. This quantitative approach has been shown to perform better than a visual analysis methodology.[3] The difference is important, as the success of a PET response-adapted approach in DLBCL has been limited by high false-positive rates. Moskowitz et al performed biopsies on visually assessed PET-positive lesions, after 4 cycles of rituximab-CHOP (R-CHOP). Active lymphoma was identified in only 13% of the specimens. Those patients who were PET positive but biopsy negative achieved outcomes identical with those who were PET negative.[4] Similarly, semiquantitative analysis of the interim PET by the Deauville score has been shown to lack predictive accuracy.[5,6]

In the PETAL trial, patients with a positive interim PET after 2 cycles (PET2) of R-CHOP, assessed by local evaluation of ΔSUV_{max}, were randomized to continue with R-CHOP or receive an intensified Burkitt chemotherapy protocol.[6] Those who were interim PET negative were randomly assigned to continue R-CHOP or to receive the same treatment with 2 additional doses of rituximab. Neither experimental arms improved efficacy, but the study clearly defined the ΔSUV_{max} as a robust tool to distinguish those patients with chemotherapy-sensitive tumors from those with resistant tumors.

The postinterim PET strategy was different in GAINED. Those patients who were



Study design. aaIPI, age-adjusted International Prognostic Index; ACVBP: doxorubicin (75 mg/m^2 at day 1), prednisone (60 mg/m^2, days 1-5), cyclophosphamide (1200 mg/m^2 at day 1), vindesine (2 mg/m^2 at days 1 and 5), and bleomycin (10 mg at days 1 and 5); ASCT, autologous stem cell transplantation; BEAM, carmustine (300 mg/m^2 at day 6); etoposide (200 mg/m^2 from days −6 to −3); cytarabine (200 mg/m^2 every 12 hours from days −6 to −3); melphalan (140 mg/m^2 at day −2); C, cycle; CHOP, cyclophosphamide (750 mg/m^2 at day 1), doxorubicin (50 mg/m^2 at day 1), vincristine (1.4 mg/m^2; maximum, 2 mg at day 1), and prednisone (40 mg/m^2, days 1-5); MTX, methotrexate. (See Figure 1 in the article by Le Gouill et al that begins on page 2307.)

PET2 and PET4 negative were consolidated, with either obinutuzumab/R-CHOP ×4 or the conventional ACVBP consolidation strategy, which incorporates high-dose methotrexate, ifosfamide, and etoposide, followed by cytarabine with assigned anti-CD20 antibody.[7] Those who had not achieved PET2 negativity but had responded by PET4 went on to high-dose chemotherapy with peripheral blood progenitor cell rescue. Those who were still positive after 4 induction cycles received further therapy at the investigator's discretion. Over two-thirds of the patients were negative after the first interim PET2 scan. An additional 15% of patients had achieved PET negativity by PET4 and, after high-dose chemotherapy, their outcomes were the same as those of patients who were PET2 negative. Unlike PETAL, the adverse prognostic value of the positive interim PET in GAINED could be overcome with intensification of therapy. This is, of course, a nonrandomized observation and is potentially subject to selection, yet 85% of patients in $PET2^{+}$/$PET4^{-}$ group received the planned therapy. Such an intensive approach, in the absence of proven residual disease, may be a hard sell in the wider community, yet trying to deliver a powered randomization in such a small population would present a significant challenge. There is no doubt that the results for the whole population were excellent. In a group of young patients with at least 1 adverse clinical risk factor, the 2-year progression-free survival (PFS) was 83%. Would this approach be applicable in patients aged >60 years who are physiologically fit enough for high-dose chemotherapy? These excellent outcomes furthermore rely on the provision of high-quality PET quality control with central reporting, which may not be so readily deliverable when employed across a population. Innovative approaches for the 16% that remained PET positive after cycle 4 are needed, given that their 2-year PFS was only 62%.

What else has GAINED shown us? Approximately half the centers elected to use ACVBP as the induction chemotherapy backbone. This is a regimen infrequently used outside France. Although the LNH03-2B study had demonstrated the superiority of this regimen to R-CHOP in a similar patient population,[7] both PFS and overall survival were identical in GAINED between the 2 chemotherapy backbones. ACVBP was more toxic and the logistics of administration more challenging. Although this outcome may serve to question its future use, more patients treated with ACVPB were PET2 negative, and thus, were spared high-dose therapy. A further important question regards the choice of 14-day CHOP delivery. Will this hold up to the more commonly used 21-day CHOP delivery? The study provided no additional biologically led insights. There were no differences in outcome according to cell of origin or in those that overexpressed MYC and BCL2.

Risk stratification in DLBCL is becoming more refined. In PETAL, combining total metabolic tumor volume with interim PET ΔSUV_{max} allowed a greater delineation of risk in DLBCL and added additional leverage in the early identification of patients at high risk of failure.[8] The evolution of dynamic response assessment methodologies that may incorporate information on baseline tumor biology, clinical prognostic scores, interim PET, and changes in circulating tumor DNA that will permit individualization of therapy.[9] However, we must learn how better to overcome tumor resistance. Be it with high-dose therapy, CAR Ts, or other novel agents, the results of GAINED have moved us a step further forward.

Conflict-of-interest disclosure: The author has received research funding, honoraria, and reimbursement of travel to scientific conferences from and served on the advisory boards of Celgene and Roche; received research support and honoraria from and served on the advisory boards of Gilead/Kite Pharma and Takeda; received honoraria and research support from Janssen; received research support from and served on the advisory board of Karyopharma; received research support and honoraria from Acerta Pharma, AstraZeneca, and ADC Therapeutics; received research support from BioInvent; and served on the advisory boards and received honoraria from Incyte and VelosBio. ■

REFERENCES

1. Le Gouill S, Ghesquières H, Oberic L, et al. Obinutuzumab vs rituximab for advanced DLBCL: a PET-guided and randomized phase 3 study by LYSA. *Blood*. 2021;137(17):2307-2320.

2. Vitolo U, Trněný M, Belada D, et al. Obinutuzumab or Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma. *J Clin Oncol*. 2017;35(31):3529-3537.

3. Casasnovas RO, Meignan M, Berriolo-Riedinger A, et al; Groupe d'étude des lymphomes de l'adulte (GELA). SUVmax reduction improves early prognosis value of interim positron emission tomography scans in diffuse large B-cell lymphoma. *Blood*. 2011;118(1):37-43.

4. Moskowitz CH, Schöder H, Teruya-Feldstein J, et al. Risk-adapted dose-dense immunochemotherapy determined by interim FDG-PET in Advanced-stage diffuse large B-Cell lymphoma. *J Clin Oncol*. 2010;28(11):1896-1903.

5. Schöder H, Polley MC, Knopp MV, et al. Prognostic value of interim FDG-PET in diffuse large cell lymphoma: results from the CALGB 50303 Clinical Trial. *Blood*. 2020;135(25):2224-2234.

6. Dührsen U, Müller S, Hertenstein B, et al; PETAL Trial Investigators. Positron Emission Tomography-Guided Therapy of Aggressive Non-Hodgkin Lymphomas (PETAL): A Multicenter, Randomized Phase III Trial. *J Clin Oncol*. 2018;36(20):2024-2034.

7. Récher C, Coiffier B, Haioun C, et al; Groupe d'Etude des Lymphomes de l'Adulte. Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial. *Lancet*. 2011;378(9806):1858-1867.

8. Schmitz C, Hüttmann A, Müller SP, et al. Dynamic risk assessment based on positron emission tomography scanning in diffuse large B-cell lymphoma: Post-hoc analysis from the PETAL trial [published correction appears in *Eur J Cancer*. 2020;136:207-208]. *Eur J Cancer*. 2020;124:25-36.

9. Kurtz DM, Esfahani MS, Scherer F, et al. Dynamic Risk Profiling Using Serial Tumor Biomarkers for Personalized Outcome Prediction. *Cell*. 2019;178(3):699-713.e19.

DOI 10.1182/blood.2020009964