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COMMENTARY

GOALs in relapsed DLBCL

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Commentary on: Georg Hess and colleagues: A phase II trial to evaluate the combination of Pixantrone and Obinutuzumab for patients with relapsed aggressive lymphoma – final results of the prospective, multicenter GOAL-trial. Br J Haematol 2022;198:482-491

The number of treatment options for patients with diffuse large B-cell lymphoma (DLBCL) have increased in recent years and include antibody based treatments, chemotherapy, small molecule inhibit and immunotherapy including cellular therapy (CAR-T).[1] Nevertheless, there remains an unmet clinical need and patients fail multiple treatments. In addition, our understanding of how to choose individual treatments for relapse (e.g. sequencing) is very limited. Salvage therapy followed by autologous stem-cell transplantation (ASCT) can lead to cure but only a fraction of patients with relapsed and refractory (R/R) DLBCL qualify for this treatment.[2,3] CAR-T cells provide a major advance for patients with DLBCL, but a considerable fraction of patients relapse after CAR-T cell treatment,[4] or are ineligible to receive CAR-T treatment.

The GOAL trial - presented in this issue of *BJH* - included R/R DLBCL patients who did not qualify for intensive treatment (including CAR-T cell therapy) and were treated with a combination of the CD20 antibody obinutuzumab and pixantrone.[5] A clear role for both drugs has yet to be found in the current treatment algorithms of DLBCL. Pixantrone is an aza-anthracenedione, initially developed to reduce cardiotoxicity. Monotherapy is approved and available in some parts of Europe for patients with relapsed/refractory aggressive NHL. A phase 3 trial (PIX301) demonstrated its effectiveness in relapsed/refractory aggressive NHL.[5,6] More recent data from Italy or the UK showed an overall response around 25%.[7,8] Obinutuzumab has not been shown to be superior to rituximab in aggressive lymphoma.[9]

The GOAL Trial[10] tested this combination in 68 patients. Overall response rate (ORR) (the primary endpoint) was 35% and the study failed to meet the predefined endpoint of response. Both PFS and OS were short at 2.8 and 8 months, respectively. Fewer prior treatment lines and normal LDH showed more favourable outcomes as is usually the case.

The study by Hess and colleagues (2022) is in line with a relevant, albeit small, proportion of patients with relapse of DLBCL who responded to chemoimmunotherapy. It is currently unclear if preselection based on clinical (and molecular) data may increase the response rate by "picking the right patient" for this regimen. Similarly, the effect of treatment lines to the immune system (and thus response to immunotherapy) is a topic of growing importance.

Much of the current momentum in DLBCL research and treatment is generated by CAR T-cell therapy, numerous bispecific antibodies or small molecule Inhibitors. Indeed, many of these treatments have already made their way into clinical practice since the completion of the study. While these are good news for patients, it is becoming increasingly challenging to select the appropriate therapeutic strategy – at the right time – based on a rational basis rather than practical aspects such as availability or insurance coverage. This may constitute a key future research agenda which we should tackle by leveraging technological advances and the availability of novel drugs.

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