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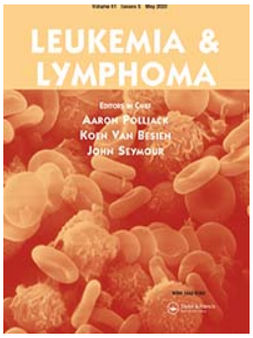

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COMMENTARY

Late relapses in diffuse large B-cell lymphoma: where to move next?

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For 20-years the combination of rituximab, cyclophosphamide, doxorubicine, vincristine, and prednisolone (R-CHOP) has been the standard treatment for diffuse large B-cell lymphoma (DLBCL). Up to 40% of DLBCL patients progress or relapse after R-CHOP treatment. Most DLBCL relapses occur within 2 years after diagnosis. Several registry studies have shown a low rate of relapse after 24 months, with a diminishing risk over time [1,2]. In line with these studies, Kang *et al.* describe in this Journal an incidence of late relapses of 6% of their patients [3]. In their large single-center study, they excluded, however, many high risk patients especially those with DLBCL at sanctuary sites.

Despite an increasing knowledge of the mutational landscape of DLBCL, there is limited data what underlies R-CHOP resistance and drives clonal evolution [4,5]. Although it is known that the late relapses are clonally related to the DLBCL at diagnosis, the mechanisms underlying this process remain elusive, thereby hampering any method to predict and, if at all possible, prevent the occurrence of such relapses [6].

Having been developed 25 years ago, the international prognostic index (IPI) score remains the most used prognostic model [7]. Attempts to improve the IPI score with molecular data are still limited and not routinely implemented [4,5]. The IPI score is prognostic in newly diagnosed patients, but can also estimate the risk of relapse after achieving a complete remission in first line [7,8]. Despite the inverse relation between risk factors for early and late relapse (LDH, stage and IPI score), described by Kang *et al* [3], it is unlikely that we will be able to identify patients based on these diagnostic parameters only. Identification of patients at increased risk of late relapses based on biological features (cell-of-origin) at diagnosis has so far been unsuccessful [9].

A development that might shed light on the pathophysiology of (late) relapses and help to identify patients at risk of treatment failure is the analysis of circulating tumor DNA (ctDNA) over time. ctDNA analysis based on next generation analysis of the immunoglobulin gene (CloneSeq) or gene panels (CappSeq) has shown promising results in genomic evaluation, staging and response evaluation of DLBCL [10–12]. However, for identification of late relapses this would require large biobanks and analysis of a significant number of (sequential) blood samples.

The risk of death for patients with a relapse follows a continuous risk model [13]. Generally, the outcome of patients refractory or relapsing within 1 year after R-CHOP treatment is dismal, with only 15% of patients achieving a long term remission. Most of these patients do not respond upon conventional salvage chemotherapy [14]. The outcome of patients relapsing after one year of R-CHOP fit for salvage chemotherapy is better but still unsatisfactory, with 50% of patients achieving a long term remission. Based on large registry studies, the impact on OS after 2 years for the population is limited [1,2,9]. In line with this, Kang *et al.* show a significantly better survival for patients with a late relapse as compared to a relapse within 2 years. Nevertheless, median OS for patients experiencing a late relapse was still unsatisfactory (2.4 years), with a 5-year OS of only 55.4% for those patients who received an autologous stem-cell transplantation [3]. There are several factors that might contribute to a poor outcome even in those patients with a late relapse. The most obvious reason is the lack of effective salvage strategies. Whereas salvage chemotherapy is a viable option for late relapse, not all patients are fit enough to undergo intensive chemotherapy. Only recently chimeric antigen receptor (CAR) T-cell therapy and the antibody drug conjugate (ADC) polatuzumab

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vedotin were approved for relapsed DLBCL and offer new treatment options [15,16]. Whereas there are promising data for novel ADCs and bispecific antibodies, as well as the combination of ibrutinib and lenalidomide, these drugs are not yet approved. Secondly, part of the relapses tends to occur at sanctuary sites, even in good risk patients. Patients with secondary central nervous system lymphoma have a poor outcome. And finally, there is a competing risk of death by unrelated disease, in a generally elderly patient population.

Taken together, the available data regarding late relapses in DLBCL indicate that the risk of relapse diminishes with passing of time and although it does not significantly contribute to the overall mortality for the population as a whole, outcome of relapsed DLBCL is still unsatisfactory. As long as prognostic factors at diagnosis are insufficient to predict the risk of late relapses, we will have to look for novel strategies, like ctDNA analysis, for identification of these patients. As in early relapse, there is a need for better salvage options in this population.

Disclosure statement

No potential conflict of interest was reported by the authors.

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