University of Groningen

Late relapses in diffuse large B-cell lymphoma

Nijland, Marcel; Kluin-Nelemans, Hanneke C.

Published in:
Leukemia & Lymphoma

DOI:
[10.1080/10428194.2020.1716224](https://doi.org/10.1080/10428194.2020.1716224)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Nijland, M., & Kluin-Nelemans, H. C. (2020). Late relapses in diffuse large B-cell lymphoma: where to move next? *Leukemia & Lymphoma*, 61(5), 1005-1006. <https://doi.org/10.1080/10428194.2020.1716224>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

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

Marcel Nijland & Hanneke C. Kluin-Nelemans

To cite this article: Marcel Nijland & Hanneke C. Kluin-Nelemans (2020) Late relapses in diffuse large B-cell lymphoma: where to move next?, *Leukemia & Lymphoma*, 61:5, 1005-1006, DOI: [10.1080/10428194.2020.1716224](https://doi.org/10.1080/10428194.2020.1716224)

To link to this article: <https://doi.org/10.1080/10428194.2020.1716224>

Published online: 04 Feb 2020.

Submit your article to this journal [↗](#)

Article views: 101

View related articles [↗](#)

View Crossmark data [↗](#)

COMMENTARY

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

Marcel Nijland and Hanneke C. Kluin-Nelemans

Department of Hematology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands

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

CONTACT Marcel Nijland m.nijland@umcg.nl Department of Hematology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands

This commentary accompanies an article to be published in *Leukemia & Lymphoma*. Please refer to the table of contents of the print issue in which this commentary appears.

© 2020 Informa UK Limited, trading as Taylor & Francis Group

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.

ORCID

Marcel Nijland <http://orcid.org/0000-0002-2740-2873>
Hanneke C. Kluin-Nelemans <http://orcid.org/0000-0003-2617-9427>

References

- [1] Maurer MJ, Ghesquieres H, Jais JP, et al. Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy. *J Clin Oncol.* 2014;32(10):1066–1073.
- [2] Jakobsen LH, Bogsted M, Brown PN, et al. Minimal loss of lifetime for patients with diffuse large B-cell lymphoma in remission and event free 24 months after treatment: A danish population-based study. *J Clin Oncol.* 2017;35(7):778–784.
- [3] Kang J, Chae H, Hong JY, et al. Distinct clinical characteristics at diagnosis in patients with late relapses compared with early relapses of diffuse large B-cell lymphoma treated with R-CHOP. *Leuk Lymphoma.* 2020;1–7.
- [4] Chapuy B, Stewart C, Dunford AJ, et al. Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. *Nat Med.* 2018;24(5):679–690.
- [5] Schmitz R, Wright GW, Huang DW, et al. Genetics and pathogenesis of diffuse large B-cell lymphoma. *N Engl J Med.* 2018;378(15):1396–1407.
- [6] de Jong D, Glas AM, Boerrigter L, et al. Very late relapse in diffuse large B-cell lymphoma represents clonally related disease and is marked by germinal center cell features. *Blood.* 2003;102(1):324–327.
- [7] Sehn LH, Berry B, Chhanabhai M, et al. The revised international prognostic index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood.* 2007;109(5):1857–1861.
- [8] El-Galaly TC, Jakobsen LH, Hutchings M, et al. Routine imaging for diffuse large B-cell lymphoma in first complete remission does not improve post-treatment survival: A danish-swedish population-based study. *J Clin Oncol.* 2015;33(34):3993–3998.
- [9] Wang Y, Farooq U, Link BK, et al. Late relapses in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. *J Clin Oncol.* 2019;37(21):1819–1827.
- [10] Roschewski M, Dunleavy K, Pittaluga S, et al. Circulating tumour DNA and CT monitoring in patients with untreated diffuse large B-cell lymphoma: a correlative biomarker study. *Lancet Oncol.* 2015;16(5):541–549.
- [11] Scherer F, Kurtz DM, Newman AM, et al. Distinct biological subtypes and patterns of genome evolution in lymphoma revealed by circulating tumor DNA. *Sci Transl Med.* 2016;8(364):364ra155–364ra155.
- [12] Kurtz DM, Scherer F, Jin MC, et al. Circulating tumor DNA measurements as early outcome predictors in diffuse large B-cell lymphoma. *J Clin Oncol.* 2018; 36(28):2845–2853.
- [13] Maurer MJ, Jakobsen LH, Schmitz N, et al. Age and time to progression predict overall survival (OS) in patients with diffuse large B-cell lymphoma (DLBCL) who progress following frontline immunochemotherapy (IC). *Blood.* 2019;134:400.
- [14] Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: Results from the international SCHOLAR-1 study. *Blood.* 2017; 130(16):1800–1808.
- [15] Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med.* 2017;377(26):2531–2544.
- [16] Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol.* 2020;38:155–165.