Clinics of Oncology

Literature Review

ISSN: 2640-1037 |Volume 6

Relevant Features and Treatment Options of DLBCL Patients with Late Relapse After A 5-Year Remission

Yi Zhao*

Zhejiang University School of Medicine, Qingchun Road 79, Hangzhou, 310009, People's Republic of China

***Corresponding author:**

Yi Zhao,
Zhejiang University School of Medicine,
Qingchun Road 79, Hangzhou, 310009,
People's Republic of China,
E-mail: zhaoyi999@zju.edu.cn

Received: 07 Apr 2022
Accepted: 21 Apr 2022
Published: 27 Apr 2022
J Short Name: COO

Keywords:

Late relapse; Diffuse large B-cell lymphoma; Clinical features; Latent mechanism of relapse; Treatment

Citation:

Yi Zhao, Relevant Features and Treatment Options of DLBCL Patients with Late Relapse After A 5-Year Remission. Clin Onco. 2022; 6(5): 1-6

1. Abstract

Diffuse large B cell lymphoma (DLBCL) represents the most common type of non-Hodgkin lymphoma (NHL) and it is a potentially curable disease with the current standard of care of immunochemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) especially the addition of rituximab. However, a relevant number of patients who acquire complete remission for 24 consecutive months have the potential for recurrence. Particularly, late recurrence (LR) defined as 5 years after the complete remission occurs with a much lower incidence. In this review, we present the recent data regarding the special clinical behaviors, histologic findings, proposed mechanisms, patterns of late relapse, and appropriate treatment options for patients with late relapse of DLBCL. Meanwhile, some useful suggestions that could be used in clinical treatments and clinical trial design are provided. Altogether, our study expands the knowledge of the special group related to late relapse.

2. Introduction

Diffuse large B-cell lymphoma (DLBCL) is a common type and highly aggressive form of non-Hodgkin's lymphoma. Most patients have a good outcome after receiving treatment of CHOP or R-CHOP. These DLBCLs who are able to obtain and maintain a complete response for 24 consecutive months are treated as a cured population with a low probability of relapse. However, approximately one-third of patients experience disease recurrence after first-line treatment. The majority of these patients will relapse within the first 1-2 years 1. Little is known about the population-based clinical characteristics and potential mechanisms of late-onset recurrences. There is no accepted standard definition of late relapse in DLBCL, with the cut-off for relapse ranging from 2 to 5 years after the beginning of treatment or achievement of first complete remission (CR1). Considering the fact that many studies use late relapse after 5 years or more after achieving CR1, we put the spotlight on these people temporarily defined as late relapse (LR). The aim of the present study is to conclude clinically exploitable differences and latent mechanisms of DLBCL patients who present with late relapse, explore the role of rituximab before and after recurrence, and give some advice to cure patients of DLBCL with late relapse. Some limitations and implications relevant studies provided are also concluded.

3. Patient Characteristics and Initial Interventions

Despite the paucity of available data, the clinical difference between late relapses and early relapses (ER) as well as the general DLBCL deserves attention. The relapsing rate varied from different retrospective studies. Nearly 1-8% 1-4 of all DLBCL relapsed after 5 years or later from the diagnosis or the remission. These discrepancies may result from the different data sources for the population-based registry and divergent definitions of late relapse.

3.1. Patient Characteristics at Initial Diagnosis

To the best of the knowledge, late relapses after 5 years or more mark a small but distinct type of DLBCL with clearly different behaviors. Elderly patients tend to relapse whether early or late recurrence and there is no difference in gender between the two groups. It was widely accepted that these patients usually had a better performance status, a more favorable IPI (the International Prognostic Index) score and a lower level of elevated LDH (lactate

dehydrogenase) at diagnosis in contrast to patients with early relapse but part of these had diverged slightly [1,3-6]. Additionally, this population was more likely to have a lower stage, a lower incidence of B-symptoms, a lower level of beta [2]-microglobulin (B2M), and a higher frequency of GCB (germinal center B-cell) subtype in contrast to early relapses [5,7]. However, extra-nodal presentation at diagnosis (89.5% vs. 65.8%; p = 0.04) and extra-nodal-only disease over time (73.7% vs. 48.2%; p =0.04) were more common in LR cases 8. Compared with the usual population of DLBCL, patients with LR showed the same tendency 2. Koh et al 9 illustrated that germinal center or activated B cell subtypes of DLBCL did not predict ER or LR. Altogether, patients with late recurrence have several distinct features at the start of diagnosis compared with the early relapsing ones or the general ones of DLBCL (Table 1). Although some of their conclusions are obvious, this is an apparent paradox of the event of late recurrence associated with superior clinical outcomes at diagnosis, probably showing that a previous presentation is an external appearance of a lymphoma skilled in hiding.

Table 1: Patient characteristics at initial diagnosis among the population of late relapsing DLBCL.

Clinical characteristics at diagnosis that differed from those with early relapse of DLBCL										
Investigators	LR (years)	PS	Stage	LDH	IPI	B-symptoms	GCB	Extra-nodal presentation	B2M	CNS relapse
Vose et al [4]	>5	better	lower	Lower	NR	×	NR	NR	NR	NR
Kang et al [5]	>2	×	lower	Lower	lower	Lower	higher	NR	Lower	lower
Modvig et al [1]	>5	better	×	×	lower	×	NR	×	NR	×
Xian et al [8]	>5	NR	NR	NR	NR	NR	NR	higher	NR	NR
Vannata et al [3]	>5	×	better	lower	lower	×	NR	×	NR	NR
Jong et al [7]	>4	NR	NR	NR	NR	NR	higher	NR	NR	NR
Koh et al [9]	>2	NR	lower	lower	NR	NR	×	lower	NR	NR
Raheja et al [6]	>2	×	×	lower	lower	×	NR	×	NR	NR
Clinical characteristics at diagnosis that differed from those of the usual population of DLBCL										
Larouche et al [2]	>5	NR	lower	NR	lower	NR	NR	higher	NR	NR
Suzuki et al [13]	>5	NR	NR	NR	NR	NR	lower	NR	NR	NR
Wang et al [10]	>2	NR	NR	NR	NR	NR	higher	NR	NR	NR

LR indicates late relapse; PS, Karnofsky Performance Status (KPS) or Eastern Cooperative Oncology Group Performance Status (ECOG PS); LDH, Lactate dehydrogenase; IPI, the International Prognostic Index; GCB, germinal center B-cell; B2M, beta (2)-microglobulin; CNS, central nervous system; NR, not reported; and ×, no significant difference statistically.

3.2. Patient Characteristics and Outcomes at Relapse

Relapsing data of initial clinical characteristics from two centers were collected and analyzed, and there was no difference between patients who had DLBCL or indolent histology at the time of initial diagnosis [2]. Meanwhile, they concluded that DLBCL usually relapsed with DLBCL histology, with a few patients having indolent histologies, like follicular lymphoma (FL). Another document in 2010 4 showed the same tendency. The process from the first DLBCL to relapsed lymphoma was depicted in Figure 1. This phenomenon raised the question of whether patients underwent transformation from indolent to aggressive histology or patients occurred a de novo malignancy. Larouche et al 2 included primary DLBCL with an indolent component and found that having an indolent component at diagnosis was associated with indolent histology at relapse (P= .028). Wang et al 10 focused on the cell of origin (COO) of lymphoma and found that in patients with DLBCL alone at diagnosis, the GCB subtype had a higher incidence of relapse with indolent lymphoma, predominantly FL. Based on the knowledge that a concurrent FL component at the time of diagnosis was predominantly seen in the GCB subtype of DLBCL, it was possible that a small fraction of patients with GCB-subtype DLBCL had an undiagnosed FL component at first, which may lead to a late relapse. A study 2 enrolled 1,492 patients demonstrated that five-year Overall survival (OS) for patients with DLBCL relapse was 27% worse than that of patients with indolent lymphoma (75%). Another prospective study 10 proved that patients who relapsed with DLBCL along with a concurrent indolent lymphoma had a worse prognosis than those who relapsed with DLBCL alone. However, this conclusion depended on the data that defined late relapse as 2 years later. OS was significantly longer in the late relapse group compared with the early relapse group (median, 2.4 years vs. 1.0 years) 5. These were in keeping with cohorts from other studies 1,3 while some scientists 2,8 disagree with this viewpoint. Interestingly, Vose et al 4 found that late relapsing patients' OS was better in the first 3 years after follow-up. Things changed as time goes by. The survival rate at 5 years (32% vs. 20%) and 10 years (13% vs. 14%) after relapse were not different statistically. The possible reasons behind the discrepancy need us to explore

and it is necessary to extend the follow-up time appropriately. It is obvious that patients with late recurrence have good clinical presentations, but whether the survival outcomes are better among late relapsing patients in comparison with early relapsing ones or not is still a matter of debate.

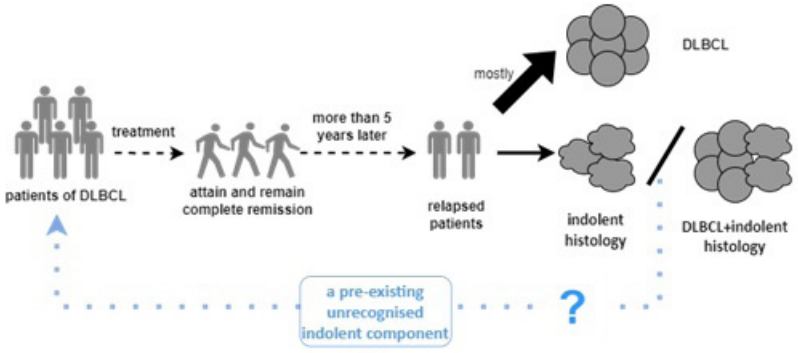

Figure 1: The histological change from the primary DLBCL to relapsed lymphoma.

3.3. Initial Interventions

Because patients included in this analysis were treated over many years, initial treatments were heterogeneous. However, most retrospective studies enrolled patients treated in the pre-rituximab era, and data including the use of rituximab on the treatment of late relapse are scanty. A recent clinical trial 3 discussing the effect of rituximab on 264 patients in 2019, showed that the addition of front-line rituximab lessened the overall risk of relapse, especially late relapses. 40% of 264 patients without rituximab-containing relapsed while only 21% of 435 patients treated in the rituximab era relapsed ($P < 0.001$). Among the population after the registration of rituximab, 82 of 156 (53%) patients got an early relapse and 10 of 35 (29%) patients relapsed after more than 5 years ($P = 0.014$). The finding by Modvig et al 1 was in accordance with the results. However, other studies 2,11 draw a completely different conclusion. In Bertrand Coiffier's study 12, the incidence of late relapse was slightly higher in the R-CHOP arm (10% compared with 5% in the CHOP arm). However, this observation was counterbalanced obviously by the greater risk of early relapses which occurred in the CHOP arm. In other words, although there is a higher risk of late relapse in the R CHOP arm, those in the CHOP arm tend to relapse within 5 years so this is still debated. Radiotherapy was used at initial diagnosis sometimes and recommended to improve the rate of remission by eradicating minimal residual disease (MRD) after induction chemotherapy. Some studies [1,3] observed that radiotherapy significantly diminish the rate of early recurrence, while it did not reduce the incidence of events related to late relapses. It was possible that the presence of MRD at the end of therapy gave rise to an early lymphoma relapse whereas a late relapse might reflect a late reappearance of 'de novo disease' due to clonal instability from radiotherapy.

3. Potential Mechanism of Late Relapse

4.1. Oncogenic Events

There are some oncogenic events about late recurrence (Table 2). Recently, Suzuki et al. 13 suggested that oncogenic events related to late relapses (relapse at >5 years), such as acquired overexpression of MYC or BCL2, had the possibility to drive relapse, although it is not considered specific for late relapse. Meanwhile, they revealed that patients with limited-stage DLBCL and late relapse tended to have CD79B and/or MYD88 tumor mutations and the non-GCB type of DLBCL at the initial presentation. Similarly, the observation from 13 cases of patients with relapse after a disease-free interval of more than 4 years by Jong et al 7 proved that GC (germinal center) features, defined by combined expression of CD10, BCL-6, and BCL-2 protein, encompassed a distinct group of DLBCL with better overall survival but possibly a characteristic risk for late relapse. By identifying copy number variations (CNVs) on 39 tumor samples from a homogeneous series of patients, Broséus et al 14 found that CNVs among those who relapsed more than one year were associated with immune response, with deletions of B2M (20%) and CD58 (10%), cell proliferation regulation, with duplications of HES1 (25%) and DVL3 (20%), and transcription regulation, with MTERF4 deletions (20%).

Table 2: oncogenic events of late recurrence.

Investigators	Relapsing time	Oncogenic events
Suzuki et al	>5 years	overexpression of MYC or BCL2
Jong et al	>4 years	germinal center features (CD10, BCL-6, and BCL-2 protein)
Broséus et al	>1 years	deletions of B2M and CD58; duplications of HES1 (25%) and DVL3; MTERF4 deletions

These oncogenic events talked above give an implication for targeted therapy and we hope there will be more and more relevant genetic analysis about late relapsing patients of DLBCL.

4.2. Minor Subclonal Evolution During Relapses

It is important to note that the majority of relapsing DLBCL belong to clonally related relapse. In some cases, minor subclones, not susceptible to chemotherapy, hide and survive in DLBCL. These subclones persist subclinically acquiring additional stimulation, determined by when and how resistance to treatment had occurred, eventually generating clinically-evident relapse. On basis of this knowledge, researchers put forward the classification that there were two distinct genetic evolution patterns (Figure 2) in clonally related DLBCL recurrences, namely early-divergent/branching and late-divergent/linear evolution [15,16]. The diverged subclone in early-divergent evolution appears to arise earlier, substitutes the major diagnosis subclone and becomes dominant at the time of recurrence. The preexisting, chemoresistant and divergent diagnosis subclones are capable of eventually regenerating entire relapse tumors. The second relapse pattern, late-divergent/linear evolution, most closely reflecting the current concept of DLBCL recurrence, has a limited degree of divergence between primary and relapse tumors. The relapse tumors arose linearly from the major diagnosis clone (often more abundant) and redeveloped due to the changes of the epigenetic landscape and genetic mechanisms. The underlying mechanism of this long latency need to add more details but we can see a trend that an increasing number of investigators pay more attention to this special group recently. In both modes, the initial lymphomas arise from the putative common progenitors (depicted by blue circles). During the process of the evolution of lymphomas, heterogeneous subclones (depicted by green, yellow and deep blue circles) come into being after acquiring some mutations (depicted by lightning). However, only the minor subclone obtaining constant mutations (depicted by yellow or deep blue lightning) survive while the remaining part (green circles) disappears due to the temporary mutations. After the treatment, the minor clones amplify (showed by "X") and become dominant subclones over time. In early-divergent/branching evolution, diagnosis-relapse pairs had significantly more mutations at different sites in the relapse samples, yielding a maximal genetic distance from the primary and relapse tumor to a common progenitor. In the late-divergent mode, the dominant diagnosis and relapse clones cluster together very closely, showing a minimal genetic distance in comparison with the first scenario.

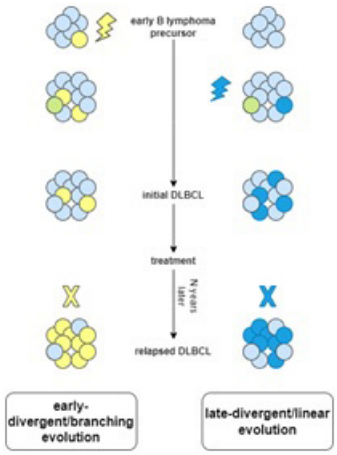

Figure 2: A model of early- and late-divergent modes of DLBCL relapse.

5. Management of Relapsed/Refractory DLBCL

Notably, the majority of patients with relapse are older than we expected. The overall prognosis for patients with late relapse is relatively poor, with 5-years overall survival rates of 55.4%, 42%, and 32% from different trials after the use of multidisciplinary approach [1,4,5]. The treatment strategies should be improved for the elderly group.

5.1. Salvage Regimens

There are dozens of salvage therapy regimens available, mostly involving rituximab in combination with standard antineoplastic agents. No randomized or prospective comparison of any salvage regimens was designed previously, so it was vague which salvage therapy regimen was preferable for the population of relapsed DLBCL. Based on the promising activity (objective response rate (ORR) was 83%) among relapsed patients with acceptable toxicity provided by eight cycles of R-GemOx 17 (rituximab 375 mg/m2 on day 1, gemcitabine 1000 mg/m2 and oxaliplatin 100 mg/m2 on day 2), Shen et al 18 hold a single-arm, open-label, phase 2 trial concentrating on elderly patients with DLBCL, demonstrating that the six cycles of R-GemOx (the same dose) regimen had similar efficacy (ORR was 75%) with acceptable toxicity. Given the comorbidities and age in the older, late relapsing people usually give up transplants and choose multi-agent salvage regimens. R-GemOx was the first choice among non-candidates for the transplant with older age. Djebbari et al 19 firstly demonstrated outcomes of R-GCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone) in late DLBCL relapse patients considered unfit for anthracycline-containing immunochemotherapy because of cardiac comorbidity, showing an effective function (ORR was 82.5% and 2-year PFS was 46.4%) in the elderly patient cohort with late DLBCL relapse. Meanwhile, gemcitabine relative dose intensity (RDI) was well retained with relatively controlled toxicity in most patients. No differential responses or survival was found according to the length of the first remission (≤5 years vs >5 years) so this trial gave late relapsing patients a therapeutic option. For patients of DLBCL who had late relapse, R-GemOx and R-GCVP regimen

were recommended and there is no difference in dosage and cycles compared with that in the general relapsed DLBCL. We can see a trend that future studies will make more effort to decrease the relapse rate without increasing toxicity in these patients with late relapse.

5.2. Using Rituximab Especially for Patients who Received Rituximab-Naive Treatment

A prospective randomized HOVON trial 20 demonstrated that patients who received rituximab-naive treatment had improved outcomes after the supplement of rituximab to second-line chemotherapy followed by ASCT. With a median follow-up of 2 years, there was a significant difference in failure-free survival (FFS24; 50% vs 24% $P < .001$), and progression-free survival (PFS24; 52% vs 31% $P < .002$). In keeping with this argument, long-term results of elderly patients with relapsed DLBCL 21 showed that patients treated with R-CHOP seemed to have more effective outcomes than those treated with CHOP only, and patients treated with a rituximab-containing regimen had a 2-year survival of 58% compared with 24% for those treated without rituximab (log-rank test, $P <.00067$). It seems that rituximab has the power to improve the survival time in the relapsing population who did not expose to rituximab previously, and rituximab still plays a role in the treatment among patients with late relapse.

5.3. Hematopoietic Stem-Cell Transplantation (HSCT)

Relapsed patients who achieved CR and those who do not achieve CR but are still responding to treatment are candidates for consolidation with high-dose therapy and autologous stem cell transplantation (ASCT). A retrospective analysis 22 was performed on the data from 35 consecutive patients who had undergone ASCT for relapsed DLBCL. The median OS and progression-free survival (PFS) were significantly better among the 8 patients developing relapse at > 1 year than others, with results of 5.9 years vs 0.4 years, and of 2.9 years vs 0.6 years. Ngu et al 23 only included transplant-eligible patients, finding that patients with late relapses (＞2 years) had a higher likelihood of response to initial salvage therapy (ORR was 82%) and that patients undergoing HSCT had better outcomes. In addition, several studies targeting the treatment of relapsed patients in DLBCL have reported a potential for curability after receiving allogeneic transplantation, with prolonged OS as high as 48% at 4 years 24. Sadly, allogeneic transplantation has a difficulty in finding a matched donor and a higher ratio of non-relapse mortality than relapse-related mortality. All together allogeneic transplantation is usually reserved for select patients who have failed in ASCT.

New targeted drugs used in relapsed or refractory DLBCL with favorable effects such as PD-1 and BCL-2 inhibitors possibly have a beneficial impact on patients with late relapse. To our knowledge, there is no trial regarding the effect of these drugs among patients who experience late recurrence. There is a call to use these novel approaches to treat the special group considering the existing limited treatment options.

6. Discussion

Investigators have gotten into trouble when studying the special group that occurs a recurrence after 5-year remission. First, only a small number of patients developed late relapse so the conclusion from those slender samples was not convincing. Second, the paucity of paired primary/relapse samples brought a big challenge. It was tough for investigators to find the initial tumor specimens at diagnosis and there was another possibility that they obtained the samples, but these were too old which might have affected the results of the pathological marking and genetic analyses. It is important to note that relapse in DLBCL likely occurred after more than 20 years. For example, Baral et al 25 wrote a letter to introduce a patient of large cell diffuse non-Hodgkin's lymphoma who relapsed with the regional disease after 22 years following radiation treatment in 1991. As for the group with very late relapse, usually more than 10 years, investigators want to figure out the question of whether these relapses are true clonally related DLBCL or represent the development of a second, unrelated DLBCL through analysis of immunoglobulin (IG) V(D)J gene rearrangements or genome-wide approaches such as next-generation sequencing (NGS). These results have some implications for clinical thoughts and clinical trial design. It is essential to counsel patients because achieving remission for 5 years does not mean a cure and the late-relapse risk remains. Prolonging follow-up of these patients is appropriate when researchers work on clinical trials. The DNA extracted from the paraffin-embedded sections in the tissue blocks rather than slides is suitable for clonal analysis by polymerase chain reaction (PCR)-based methods, highlighting the need for the paraffin-embedded samples. The occurrence of late relapse, at least in part, result from the genetic evolution of the primary tumor. It is, therefore, advisable that investigation of the exact changes that occur during the recurrence of DLBCL is beneficial for the identification of genetic drivers of the process and prognostic as well as predictive markers. Furthermore, a better knowledge of the genetic landscapes provides new perspectives for personalized targeted therapies.

7. Conclusion

In conclusion, the clinical features are talked about in this review, showing an apparent paradox that late recurrences are associated with superior clinical behaviors at diagnosis. We also find that DLBCL usually relapses with DLBCL histology, with a few patients having indolent histologies (maybe caused by a pre-existing unrecognized indolent component). Some oncogenic events about late recurrence are shown in this review and the model of early- and late-divergent modes of DLBCL relapse explains the minor subclonal evolution during relapses. However, the real story behind the late recurrence remains inconclusive and several existing

debates, as well as questions presented in this study, need further investigation. Finally, some useful suggestions that could be used in clinical treatments and clinical trial design are provided. Altogether, our study expands the knowledge of the special group of DLBCL related to late relapse.

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