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Treatment strategies for diffusive large B-cell lymphoma

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Abstract

The treatment of diffusive large B-cell lymphoma (DLBCL) is generally based on multidrug chemotherapy, the association of cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) has become the standard therapy for DLBCL since the 1970s. The outcome of DLBCL has been substantially enhanced by the addition of the anti-CD20 monoclonal antibody rituximab. However, there is still some patients failed to the first-line treatment, those were considered as relapsed/refractory DLBCL, and thus we need to adjust the dose or change the therapeutics. In addition, different treatment strategies should be stratified according to age, the International Prognostic Index (IPI), performance status, stage, prognostic score and immunohistochemical biomarkers. Besides, many novel drugs are under investigation in DLBCL patients, especially CAR-T regimen will have great prospects for development.

Introduction

Diffusive large B-cell lymphoma (DLBCL) is the most common type of aggressive, non-Hodgkin lymphoma (NHL) [1,2]. Approximately 45% to 55% of patients with DLBCL can achieve complete remissions (CRs) after first-line therapy. A multi-drugs chemotherapy regimen containing cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) proved to be a very efficient treatment [3], especially in combination with the anti-CD-20 antibody rituximab [63]. Although, it can be curable in most patients, still there is a subgroup patient resistant to treatment. Those patients who failed to respond or relapse after first-line treatment were considered as the relapsed/refractory cases. Therefore, we need to assess the other regimens for salvage treatment. The duration of cycle therapy has varied from 14 to 21 days. In addition, many other regimens have been evaluated in various trials, such as: R-COMP, R-EPOCH, R- ACVBP, R-ICE, R-DHAP, autologous/allogeneic hematopoietic stem cell transplantation and so on. Novel drugs are also being developed. Thus, standard therapy should be administered as soon as possible after staging, especially in young and fit patients [7]. Regardless of which treatment we use, the ultimate goal should be to maximize initial cure rates to improve long-term survival while minimizing toxicity. We will review the current therapies, so that we can choose appropriate and personalized therapies for different patients.

The standard treatment

The treatment of DLBCL is generally based on multidrug chemotherapy, the CHOP regimen has become the standard therapy for DLBCL since the 1970s. In 2002, the chimeric anti-CD20 monoclonal antibody rituximab was added to CHOP (R-CHOP) appeared able to significantly ameliorate the outcomes of patients with DLBCL [8]. Otherwise, different treatment strategies should be stratified according to age, the International Prognostic Index (IPI; comprised of age, lactate dehydrogenase [LDH], stage, more than one extra nodal site, and performance status), performance status, stage and prognostic score, such as the standard treatment for elderly fit DLBCL patients is R-CHOP; in unfit and frail patients, chemotherapy at reduced intensity should be considered.

The goal should be to maximize initial cure rates to improve long-term survival while minimizing toxicity. There was a phase II trial has taken several approaches, including the addition of new agents onto an R-CHOP backbone. Such as: Addition of lenalidomide to R-CHOP in two phase II trials showed improved progression-free survival (PFS) compared with historical controls specifically for the ABC-DLBCL subtype [7].

The standard first-line treatment

R-CHOP-14 and R-CHOP-21

Different dose-dense regimens may influence the effect of treatment. In order to evaluate a possible superiority of the dose-dense regimen compared to standard chemo-immunotherapy, in the past few years several large randomized phase III studies comparing R-CHOP-21 (rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone over 21 days) with R-CHOP-14 (rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone over 14 days) were designed. One trial was run by the GELA group and restricted to elderly patients [9], the other two were conducted by British National Investigation (BNLI) [10] and Cunningham *et al.* [13], in all age and IPI risk patients. The results of these studies failed to demonstrate that dose-dense treatment with R-CHOP repeated every 2 weeks has a survival advantage than standard R-CHOP repeated every 3 weeks. In a multivariate analysis, no advantage was observed for dose-dense regimen, including young poor-risk patients

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and patients with higher risks. Therefore, in elderly patients, in order to limit toxicities, standard approach with 3-weekly R-CHOP is recommended [11]. But in another phase II trial, Gonzalez-Barca *et al.* [12] reported the results of a treatment with six courses of R-CHOP therapy given every 14 days, supported by pegfilgrastim prophylaxis, in patients affected by previously untreated DLBCL aged < 65 years or >65 years with low-risk IPI. They also found that the R-CHOP-14 regimen is more toxic in elderly patients, but it seems more flexible.

As a consequence, on the basis of these data, the current standard of treatment for fit patients with DLBCL at diagnosis is chemotherapy CHOP in combination with rituximab every 21 days for six courses. In addition, the attenuated chemotherapy combined with rituximab, such as R-miniCHOP, can induce complete remission (CR) and long survival in fit patients older than 80 years [20].

Treatments for selected (young, frail, aggressive, high-risk (IPI ≥ 2), very elderly (> 80 years old), Ki-67+, CD5+ and so on) patients

R-COMP

The R-CHOP therapy as the first-line standard treatment for DLBCL is also associated with cardiotoxicity, so we need new treatment strategies to reduce toxicity. R- COMP (rituximab, cyclophosphamide, non-pegylated liposomal doxorubicin, vincristine and prednisolone) is an effective treatment alternative for DLBCL patients. Mian *et al.* [21] retrospectively compared the R-COMP and R-CHOP regimens as first-line therapy in 364 DLBCL patients and compared outcome and survival. They proved that both regimens are able to cure patients with DLBCL, but R-COMP therapy seems to have a greater association with treatment-related toxicity. Michael A. Fridrik *et al.* [22] also run a randomized controlled trial on patients with untreated CD20+ DLBCL who treated with conventional R-CHOP chemotherapy or R-COMP to compare which is more cardiotoxic. They measured left ventricular ejection fraction (LVEF) and N-terminal pro B-type natriuretic peptide (NT-proBNP) levels before each treatment cycle and after the end of treatment. They observed that infections and serious adverse events are more common in the R-CHOP arm while the overall remission rate and the complete remission rate were higher in the R-COMP arm, but the difference did not achieve statistical difference. So, there is no conclusive evidence prove that the R-COMP regimen is superior to R-CHOP regimen.

Radiotherapy

Radiotherapy(RT) is an important method of treatment, it is also valid for patients with early stage localized DLBCL. For patients mentioned above or who are particularly unresponsive to chemotherapy may be more suitable for mixed modality treatment with R-CHOP and consolidated radiotherapy. RT is effective in achieving high complete response (CR) rates and long-term freedom from relapse in 40 to 45% of patients [14-17]. Thomas P. Miller *et al.* [18] performed randomized trial to compare eight cycles of CHOP alone with three cycles of CHOP followed by involved-field RT that treated in patients with localized intermediate- and high-grade histologic subtypes of lymphoma. The conclusion is that a short cycle of CHOP followed by consolidation RT is superior to eight cycles of CHOP alone and can achieve higher PFS and OS. These results highlight the advantages of consolidation RT followed by chemotherapy. As a result, for patients with limited stage DLBCL, the three cycles of CHOP plus RT were widely adopted [19].

R-DA-EPOCH

Long-awaited results of the Cancer and Leukemia Group B(CALGB)/Alliance 50303 trial failed to show that dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin combined with rituximab (R-DA-EPOCH) was superior to the by-now old standard R-CHOP in patients with de novel DLBCL. Both regimens achieved similar efficacy in event-free and overall survival, but R-DA-EPOCH was more toxic. But in some special DLBCL patients, this therapy may be more advantage. To assess the benefit of R-DA-EPOCH regimen as a first-line treatment for patients with DLBCL presenting with unfavorable or aggressive features and autologous stem cell transplantation (ASCT) as a part of the first-line treatment for selected DLBCL patients with additional aggressive features. Vlatko Pejsa *et al.* [23] retrospectively analyzed 75 newly diagnosed DLBCL patients with Ki-67+ ≥ 80% or International Prognostic Index ≥ 2 who were treated with R-DA-EPOCH between 2005 and 2015.Of 24 DLBCL patients with additional aggressive features (Ki-67+ ≥ 90% or age-adjusted IPI ≥ 2) who were planned to receive consolidation with ASCT,17 patients underwent the procedure. The result showed that R-DA-EPOCH is a very effective therapeutic option as a first-line treatment of DLBC patients with unfavorable prognostic features irrespective of their age. ASCT provided additional benefit for DLBCL patients with additional aggressive features.

R-EPOCH

DLBCL patients with high Ki-67 expression who receive R-CHOP therapy seemed to have poor efficacy. Jia-Jia Huang *et al.* [24] treated 44 untreated patients by R-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) and 132 untreated patients by R-CHOP to investigate whether R-EPOCH is superior to R-CHOP therapy. In the R-EPOCH group, 42 patients (95.5%) were eligible for response evaluation. 35 patients (83.3%) was achieved CR, and partial remission was achieved in 6 patients (14.3%). At 3-years, the progression-free survival(PFS) was 86.6% in the R-EPOCH arm and 59.7% in the R-CHOP arm. The overall survival(OS) was 89.9% and 70.2%. They did hole research based on the International Prognostic Index, gender, and Ki-67 expression, and they found in patients with a low-to-intermediate-risk IPI (IPI score of 0-3), the R-EPOCH group resulted in better survival outcomes than did the R-CHOP regimen. Their data suggest that in untreated DLBCL patients with high Ki-67 expression, especially in those of low-to-intermediate IPI risk, R-EPOCH as a first-line treatment could be superior to R-CHOP.

R-ACVBP

The GELA group [25] did an open-label randomized trial compared dose-dense rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone(R-ACVBP) with sequential consolidation 3-weekly R-CHOP for 8 courses in a randomized trial in 183 patients age 18-59 with low-risk IPI. At 3-years, the PFS and OS respectively of 7% and 92% in the R-ACVBP arm, 73% and 84% in the R-CHOP21 arm. Febrile neutropenia occurred in R-ACVBP arm were more than in patients those who treated with R-CHOP21. R-ACVBP has been reported to improve OS in younger patients with aggressive disease, although hematologic toxicity limits its use to younger patients.

There are more methods of treatment, such as: R-mini-CHOP, R-miniCEOP, pre-phase treatment and so on. We should choose the most appropriate treatment for different patients.

Treatment for relapsed/refractory patients

R-ICE and R-DHAP

For the patients who failed to respond or relapse after first-line treatment considered as the relapsed/refractory cases, they were supposed to the salvage regimen of high-dose therapy followed by autologous hematopoietic stem cell transplantation (auto-HSCT), which remains the standard of care with curative potential for patients with refractory or relapsed DLBCL. The two widely used regimens worldwide consist of either R-ICE (rituximab, ifosphamide, carboplatin, and etoposide), or R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and cisplatin) followed by consolidative autologous stem cell transplant(ASCT). The CORAL trial conducted by Gisselbrecht [26] and colleagues compared R-ICE with R-DHAP, in these two induction regimens in young patients with relapsed/refractory DLBCL, they found no difference in the 3-year event free survival (EFS) and 3-year overall survival (OS).

Autologous and allogeneic hematopoietic stem cell transplantation (SCT)

The National Comprehensive Cancer Network (NCCN) guidelines advised patients with refractory or relapsed DLBCL who partially or completely respond to the second-line chemo- therapy could have auto-HSCT or all-HSCT in selected cases as the consolidation therapy, those who were failed to mobilise and with persistent bone marrow involvement were included [49]. As the second line therapy, auto-HSCT has been established as a standard treatment for transplant eligible patients who have relapsed or refractory DLBCL, and it showed increased EFS and OS compared with conventional chemotherapy [26,27]. Lazarus *et al.* [50] reported that compared to auto-HSCT patients, allo-HSCT patients had significantly worse 1-year probabilities of OS, PFS, and treatment-related mortality (TRM), but the differences were not significant at 3 or 5 years. But this does not mean that allo-HSCT has no effect. The European Group for Blood and Marrow Transplantation (EBMT) database was scanned for a first allo-HSCT in relapsed DLBCL after a previous auto-HSCT. Three-year non-relapse mortality (NRM) was 28.2%, PFS was 41.7%, and OS was 53.8% [51], which indicated that as the third line therapy, allo-HSCT was also effective for relapsed or refractory patients.

BR

Bendamustine is an alkylating agent with properties of a purine analogue. It has been confirmed to be active in indolent B cell lymphomas and chronic lymphocytic leukemia, this lead to the study of the combination of bendamustine and rituximab in aggressive NHL. Ogura *et al.* [28] run a phase I study of BR in patients with relapsed or refractory aggressive B-cell NHL showed the combination to be well tolerated with promising efficacy. In addition, Michinori Ogura *et al.* [4] run a phase II study about BR in patients with relapsed/refractory DLBCL, they evaluated overall response rate (ORR), CR, PFS, and safety. Francesca Merchionne *et al.* [5] also analyzed 29 patients with relapsed/refractory DLBCL treated with combination BR, their data showed that in these 29 patients, ORR was 50%, the median PFS and duration of response (DOR) were 8 months and 24.7 months. Both analysis showed that BR is a promising salvage regimen of patients with relapsed/refractory DLBCL with limited therapeutic options. Besides, Ohmachi *et al.* [29] and Vacirca *et al.* [30] also found that BR therapy play a role in the treatment of patients with relapsed or refractory DLBCL who were not eligible for autologous stem cell transplant.

GDP/R-GDP

Alden A.Moccia *et al.* [31] conducted a retrospective analysis. From September 2002 to June 2010, 235 patients with relapsed/refractory DLBCL or Hodgkin's Lymphoma(HL) who received Gemcitabine, Cisplatin, and Dexamethasone (GDP) as salvage therapy are were enrolled in this study. They concluded that GDP chemotherapy in patients with relapsed/refractory DLBCL or HL was an effective and well-tolerated out-patient salvage therapy. Hou Y *et al.* [6] conducted a research including 50 patients with recurrent or refractory aggressive B-cell NHL, including DLBCL (n=30) and follicular lymphoma grade 3b (n=20) who received Rituximab, Gemcitabine, Cisplatin, and Dexamethasone (R-GDP) therapy between January 2005 and December 2010. They concluded that R-GDP chemotherapy is an effective salvage regimen for patients with refractory or relapsed aggressive B-Cell NHL and helpful for high-dose chemotherapy (HDC) /autologous stem cell transplantation (ASCT).

Some relative researches

Danielle M. Greenawalt *et al.* [34] performed whole exome sequencing (WES) on 47 patients with DLBCL that persisted after R-CHOP treatment, 8 matched to primary biopsies. They compared genomic alterations from the relapsed/refractory (RR) cohort against two treatment-naive DLBCL cohorts. They observed an increase in BCL2 mutations (21% to 38% of samples), BCL2 amplifications (3% to 6% of samples) and CREBBP mutations (31% to 42% of samples) in the RR cohort, supported by acquisition of mutations in these genes in relapsed compared to diagnostic biopsies from the same patient. These findings hold significance for a number of emerging targeted therapies aligned to genetic targets and biomarkers in DLBCL, reinforcing the importance of time-of-treatment biomarker screening during DLBCL therapy selection. Overall, their findings highlight shifts in mutational composition across DLBCL patient populations with respect to R-CHOP treatment. Continued molecular characterization of cohorts in the treatment naïve and post treatment settings is necessary to improve therapeutic strategies for RR patients.

Novel drugs

Patients ineligible for transplant or who relapse after ASCT, and those who fail to respond to second line or salvage chemotherapy, represent an unmet medical need for which new therapeutic strategies are required. With the development of science, several new drugs have been found, such as: immonomudulating agents (IMiDs); mTOR (mammalian target of rapamycin) inhibitors; histone deacetylase (HDAC) inhibitors; Bruton Tyrosine Kinase (BTK); Coltuximab ravtansine and so on. Further studies and more trials should be done for these novel drugs so that we can increase the long-term survival of patient with DLBCL.

Lenalidomide

Patients with relapsed DLBCL not suitable for autologous stem cell transplantation(ASCT) or relapsed after ASCT have a low likelihood of cure. Single-drug maintenance after salvage therapy might be an attractive strategy to prolong survival in these patients. Lenalidomide is an oral agent with multiple mechanisms of action including immunomodulatory, anti-angiogenesis, modulator of the microenvironment, and direct anti-tumor activity. Andres J M Ferrari *et al.* [32] run a phase2 trial, in this open-label, they recruited HIV-negative adults with untreated or transformed DLBCL and relapsed disease responsive to conventional rituximab-containing salvage therapy from 12 oncology-hematology centers in Italy. All patients were

given oral lenalidomide 25mg per day for 21 of 28 days until lymphoma progression or unacceptable toxicity (severely compromises organ function, quality of life, or both). It's result confirmed the efficacy of lenalidomide in relapsed/refractory DLBCL.

Biological inhibitors

mTOR inhibitors

mTOR (mammalian target of rapamycin) inhibitors, among which the most important are temsirolimus and everolimus [43,44]. mTOR is a protein kinase, which has an important role in regulating growth factors and stimulating angiogenesis. Witzig *et al.* [44] conducted a phase II trial in 77 relapsed/refractory aggressive NHL patients with a median age of 70 years, with ORR of 30% (range 20-41%) and a median duration of response of 5.7 months.

HDAC inhibitors

Other molecules under investigation are histone deacetylase (HDAC) inhibitors, such as vorinostat, analyzed in a phase II trial in 18 elderly DLBCL patients with relapsed-refractory disease, with a median age of 66 years [45]. Vorinostat showed well tolerability, with common adverse events including diarrhea, fatigue, nausea, anemia and vomiting. Preliminary efficacy data on 18 patients demonstrated ORR of only 5.6%, but it must be noted that patients included in this study were highly pretreated.

BTK inhibitors

Inhibitors of Bruton Tyrosine Kinase (BTK), such as Ibrutinib, are researched in many B cell malignancy, included in DLBCL [46]. BTK plays an important role in intracellular signaling pathway of B-cell receptor (BCR), very important in lymphoma genesis. Advani *et al.* [47] conducted a trial with Ibrutinib in 56 patients who affected by relapsed/refractory B-cell malignancies, among which 7 DLBCL patients, with promising results. Wilson et al [48] introduced the results of a phase II trial with ibrutinib in 80 cases of relapsed/refractory DLBCL. Ibrutininb produced complete or partial response of DLBCL patients to a certain extent.

CC-122

The thalidomide analogue CC-122, a new immunomodulatory drug that acts as a pleiotropic pathway modifier, has demonstrated anti-lymphoma activity through its binding to cereblon (CRBN), leading to the subsequent ubiquitination of Aiolos and Ikaros. As tumor immunosurveillance in patients with refractory DLBCL has shown diminished natural killer (NK) cell populations and cytotoxic activity, Cubillos-Zapata C *et al.* [35] studied the modulatory and tumor-surveillance effects of CC-122 on the immune system of three DLBCL patients. Their data suggest that CC-122 treatment in DLBCL patients restores the innate immune response after discontinuing therapy. However, T-cell activation analyzed by CD28 expression in the patients treated for DLBCL showed a significant increase at day 30 after initiation of treatment in the CD8 and δγ+ cells, suggesting a delayed effect of CC-122. In conclusion, clinical and immune response analyses demonstrate a promising outcome in DLBCL patients. Based on their results, CC-122 anti-lymphoma activity in patients with refractory DLBCL might be explained by tumor flare at 7 days followed by immunomodulation, cytotoxic activity, T-cell activation and a change in adaptive immune response with a subsequent positive clinical outcome.

Ublituximab

It has improved clinical outcomes for patients with B-cell non-Hodgkin lymphoma (B-NHL) since the rituximab was added to the treatment of B-cell malignancies [41,42]. However, just as patients who become resistant to conventional chemotherapy, the emergence of acquired resistance to rituximab has gradually become the significant clinical issue. We require effective biologicals with activity that can overcome previously acquired rituximab resistance. Ublituximab is a novel Monoclonal antibodies (MAb) targeting a unique epitope on the CD20 antigen which produced in the rat cell line YB2/0. Sawas A *et al.* [40] organized a phase 1/2 trial of ublituximab, in patients with relapsed/refractory B-NHL or CLL previously exposed to rituximab. 35 Patients with B-NHL (n = 27) and CLL (n = 8) had a median of 3 prior therapies are enrolled and received treatment of ublituximab. According to their research data ublituximab showed well-tolerated and effective responses in patients with heavily pre-treated.

CAR-T cell anti-cancer therapy

The adoptive transfer of T cells gene-targeted with chimeric antigen receptors (CARs) has emerged as an exciting cancer immunotherapy due to the induction of complete remissions (CRs) in patients with chemotherapy-refractory hematologic malignancies. The CAR is an antigen-receptor created by fusion of the antigen-receptor domain of an antibody to the activation and co-stimulatory proteins associated with the T cell receptor(TCR) complex [36-38]. Kochenderfer JN *et al.* [39] treated 22 patients with advanced-stage lymphoma in a clinical trial of CAR-19 T cells preceded by low-dose chemotherapy. Nineteen patients had diffuse large B-cell lymphoma, two patients had follicular lymphoma, and one patient had mantle cell lymphoma. Patients received a single dose of CAR-19 T cells 2 days after a low-dose chemotherapy conditioning regimen of cyclophosphamide plus fludarabine. Their results showed that CAR-19 T cells preceded by low-dose chemotherapy induced remission of advanced-stage lymphoma, and high serum IL-15 levels were associated with the effectiveness of this treatment regimen. CAR-19 T cells will likely become an important treatment for patients with relapsed lymphoma. CAR T cells could be the first-gene modified viable cellular immunotherapy approved for the treatment of cancer. But recently, according to US media reported, just a week after FDA approved the company using the new cancer treatment technique CAR-T cell, the agent suspended the trial because of the first case of death in patients treated with CAR-T cell anti-cancer therapy. We still have a lot to do with these researches.

In my site, each treatment regimen has advantages and disadvantages, CAR-T cell therapy has made a great progress in the treatment of DLBCL, and there is a great potential for development.

Conclusion

Currently, R-CHOP regimen is still the first-line treatment of DLBCL, but we also need to choose personality treatment therapies for different patients according to their age, the IPI, performance status, stage, prognostic score and so on. Patients with early stage localized disease or who are particularly unresponsive to chemotherapy may be more suitable for mixed modality treatment with R-CHOP and consolidated radiotherapy. Besides, some trials have shown that R-COMP regimen can also be able to cure patients with DLBCL as the first-line treatment and even superior to R-CHOP therapy in patients with CD20+ DLBCL. Other therapies such as: R-ABVD, R-EPOCH, R-ICE and so on. For elderly patients and young patients, dose-adjust regimens should be considered. Though, about half of the DLBCL patients can achieve CR, still there is a partial patient resistant to treatment. Those patients were considered as the relapsed/refractory cases. So that is why new treatment strategies are needed. Many clinical trials have assessed some second-line treatment strategies, such as

bendamustine combined with rituximab, hematopoietic stem cell transplantation, R-ICE, R-DHAP, R-GDB and some new drugs, all of these can achieve a certain effect. In general, our goal is to provide the appropriate treatment approaches to improve the outcome for patients with DLBCL.

Future perspective

In my opinion, the first-line standard treatment regimen for patients with DLBCL will still be the R-CHOP therapy at least in the next 5–10 years. To improve the patient's cure rate or remission rate, we need to take more personalized treatment. At present, patients are expected to use chemotherapy to achieve complete remission followed by hematopoietic stem cell transplantation to achieve cure. But for those who are not candidates for transplant or who relapse after ASCT, and those who fail to respond to second line or salvage chemotherapy, we recommend trying novel drugs, and I think bio immunotherapy has great prospects for development, especially CAR-T cell anti-cancer therapy. Although the CAR-T therapy is not well developed, there are a number of organizations around the world doing clinical research for it. I believe that in the near future, DLBCL patients' cure rate and long-term survival rate will be greatly improved.

Executive summary

1. The standard first-line treatment of DLBCL is chemotherapy CHOP in combination with rituximab every 21 days for six courses.
2. For young or elderly patients with DLBCL, we can adjust the dose of medicines to reduce toxicity. We can try other treatments (R-COMP, R-EPOCH, R-ACBVP and so on) when R-CHOP therapy used in some special DLBCL patients such as: CD5 positive DLBCL, Ki-67 positive DLBCL showed limited benefits.
3. RT also play a role in treatment of patients with limited stage DLBCL.
4. Those who failed to first-line treatment was supposed to salvage chemotherapy (R-ICE, R-DHAP, GDP/R-GDP, BR) followed by stem cell transplantation.
5. Novel drugs (Lenalidomide, Biological inhibitors, CC-122, Ublituximab, CAR-T cell anti-cancer therapy) can be used in patients with relapsed/refractory DLBCL or who are ineligible for stem cell transplantation or fail to respond to previous chemotherapy.

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