Proceedings of ICEGEE 2026 Symposium: AI-Based Medicine and Biological Data Analysis
DOI: 10.54254/2753-8818/2026.AU33984

Radiotherapy Combined with CD20×CD3 Bispecific Antibodies in Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Shi Shi

SUNY Orange Community College, Middletown, New York, USA
ss336@sunyorange.edu

Abstract. Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma, and patients with relapsed or refractory (R/R) disease still have few treatment options and poor long-term results after the failure of standard therapy. Recently, some good clinical results have been achieved in the application of CD20×CD3 bispecific antibodies (BsAbs) to direct T cells to malignant B cells. The response of the treated people varies, and not everyone can maintain remission for a long time. More and more studies have shown that the tumour microenvironment can affect the response to therapy. Radiotherapy (RT) is used to treat cancer locally, and now it is also known for modulating the immune system. RT can cause immunogenic cell death, release tumor antigens, and increase the infiltration of immune cells in the tumour microenvironment; thus, it is one of the reasons for combination therapy with BsAbs. Review of Recent Research on RT in Combination with BsAbs for R/R DLBCL: Treatment Sequence, Radiation Dose and Fractionation, Differences among BsAb Platforms. At present, it is known that RT can enhance the antitumor effect of BsAb by promoting immune activation and T-cell migration; however, clinical results have been inconsistent in various studies. There is no standard RT protocol and reliable predictive biomarkers, so some patients have been harmed by the treatment so far.

Keywords: Diffuse large B-cell lymphoma, bispecific antibodies, radiotherapy, tumor microenvironment, immunotherapy

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is one of the most frequent types of non-Hodgkin lymphoma, and there is considerable clinical heterogeneity among patients. Although front-line treatment with R-CHOP can achieve prolonged remission for many patients, about 30-40 per cent of them will eventually have a relapse or progressive disease and be classified as refractory [1]. R/R DLBCL patients who are not suitable for stem cell transplantation or do not respond to the subsequent CAR-T therapy have a poor prognosis. There are relatively few treatment options in this group of people, and new resistance to CD20-targeted therapy has also made the choice of treatment more challenging.

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In recent years, CD20×CD3 bispecific antibodies (BsAbs) have been included in the list of drug choices for R/R DLBCL. These cells can direct the polarisation of T cells in the body to attack cancerous B-lineage cells, and thus have been named a new type of allogeneic cell-free immunotherapy. The general response rate of the clinical trials for glofitamab, mosunetuzumab and epcoritamab is between 50% and 70%, and some patients have had long-lasting complete responses [2]. Although there were some good results, they were not consistent and failed to be maintained in many places. Therefore, people's attention has begun to focus on ways to improve the depth and longevity of response through targeted remodelling of the tumour microenvironment.

Radiotherapy (RT) has long been restricted to local tumour control, but now it is known that it also has broad immunomodulatory effects outside the brain. In addition, RT can also cause immunogenic cell death and, as a result, increase the exposure of tumour antigens and promote the infiltration of immune cells in the tumour microenvironment [3]. Therefore, it can be concluded that RT may create an immune-friendly microenvironment and make the immunologically "cold" tumour area more favourable. Therefore, RT may serve as a primer to increase the activity of BsAbs rather than only reduce the tumour load.

At the same time, the combination of RT and BsAbs is also not well-known. The immunological effects of RT are highly dependent on the dose and fractionation, and it is not yet known which regimen is more compatible with T-cell-redirecting therapy. The optimal order of RT and BsAb treatment has not been determined yet; it is also to be noted that there may be overlapping inflammatory toxicity, such as cytokine release syndrome, which could reduce the efficacy of the combination therapy. The other problem is that there are no biomarkers to identify patients who will be most likely to respond to this kind of treatment.

Given the uncertainty, more research needs to be carried out in depth on the biological basis and new clinical data of the RT-BsAb combination. Recently, in the past three to five years, some research has been conducted abroad on the design of treatment sequences, selection of radiation parameters and characteristics of clinical patients. Based on the comparison of cross-study clinical data, this paper summarizes the consistent research trends and points out the main differences in the studies to provide some directions for the construction of more reasonable and personalised treatment plans.

2. Mechanistic basis of radiotherapy-bispecific antibody synergy

Radiotherapy is no longer only known for its cytotoxicity; it has also been found that it can alter the immune system, so combining this treatment with CD20×CD3 bispecific antibodies will have some significant effects [3]. Several studies have shown that the response to treatment for relapsed and refractory DLBCL is related not only to the tumour burden but also to the immune environment in the disease. Radiotherapy is expected to change some parts of the tumour microenvironment that can affect T cell-redirecting therapy in this way.

All the above show that, in the absence of cancer, radiation can still cause some changes to the immune system, such as releasing antigens and other factors that activate dendritic cells and present antigens [4]. At the same time, there has been an increase in the expression of chemokines such as CXCL9 and CXCL10, as well as adhesion molecules that promote the migration of lymphocytes to the tumour site, due to radiation. Thus, the immune-excluded tumour will be an inflamed and immune-active tumour. However, it is not the same in different radiation environments. Mechanism studies have shown that a certain dose of radiation can change the expression of some immune-related genes. For example, high single-fraction radiation can increase the expression of TREX1, damage cytoplasmic DNA, and reduce the cGAS-STING-interferon signal; thus, it may impair T-

DOI: 10.54254/2753-8818/2026.AU33984

cell priming [5]. Hypofractionated radiotherapy can activate the interferon pathway and increase the number of T cells in tumours. Therefore, the change in immunity after RT is not linearly related to the dose and is also irregular with different divisions.

The above mechanism will be better understood after applying BsAb. CD20×CD3 bispecific antibodies need to have some activated T cells in the tumour microenvironment for good results and are not suitable for immune-excluded tumours with a small number of lymphocytes [6]. As shown in the table above, the total response rate of traditional BsAbs in patients with heavily pretreated DLBCL is only 50-65%, and they have failed to achieve long-term remission. It is possible that these agents can stimulate T cells, but they do not address the problems of space and the microenvironment that restrict the entry of T cells into tumour cells. Therefore, radiotherapy may address the problem of insufficient antigen supply and reduced immune cell migration.

The structure of the various BsAb products is also different and therefore more complex. Glofitamab is a 2:1 CD20:CD3 molecule that can activate T cells strongly and shows relatively little dependency on the initial number of immune cells inside the tumour [2]. Mosunetuzumab has a weak induction of T-cell activation and is thus not very effective in the tumour microenvironment [7]. To achieve the purpose of maintaining a gradual increase in T cells, epcoritamab will be injected under the skin in a step-up dose [8]. Although there is no head-to-head comparison, the reasons for this may lie in the different levels of microenvironmental priming provided by the two agents. Mechanistically speaking, it is possible that the benefit of radiotherapy will not be the same for all bispecific antibodies; instead, it may be influenced by the degree to which each agent can activate T cells and by how dependent it is on T-cell availability.

Based on the above data, it is proposed that radiotherapy and bispecific antibodies work together at different stages of the immune response against cancer. Radiotherapy can be an excellent way to make the body aware of antigens and activate T cells by releasing them; thus, bispecific antibodies have been applied to target cells. How much of this interaction will be reflected in clinical signs and symptoms will depend on several factors, such as the size of the radiation dose and how it is divided. Importantly, the same reasons for the activation of the immune system can also increase inflammation and toxicity; thus, the combination therapy group has a relatively small therapeutic window.

At present, there is no single ideal protocol that is suitable for all people; instead, personalised treatment should be planned according to differences in tumour characteristics and response to therapy. More clinical studies will be carried out to expand the above mechanisms and improve the general prognosis of patients with relapsed and refractory diffuse large B-cell lymphoma.

3. Clinical evidence and comparative analysis of RT-bispecific antibody strategies

Preclinical studies have clarified how radiation therapy works with bispecific antibodies, but there is still little clinical data, and even then, it is quite inconsistent. Most of the available evidence is from the Phase I/IIb clinical trials of SAB and small-scale retrospective cohorts; thus, radiotherapy has been employed as a bridge or adjuvant therapy. Direct clinical trials for the combination of RT-BsAb have not yet been conducted; therefore, a large number of cross-study analyses need to be carried out reasonably.

CD20xCD3 bispecific antibodies have shown good results in recent clinical trials for older people who have received a large number of previous therapies. Based on the studies of glofitamab, mosunetuzumab and epcoritamab, the overall response rate is generally between 50% and 65%, and the complete response rate in relapsed or refractory DLBCL is about 30%-40% [2]. However, these results are not the same for all groups of patients, and in many cases, progression-free survival is

DOI: 10.54254/2753-8818/2026.AU33984

still short [7]. The general clinical features and results of the studies are shown in Table 1. The results in the actual clinical group have been even more disappointing; the time to response is shorter and the risk of early progression is higher [8]. Therefore, in addition to the intrinsic drug potency, tumour burden and microenvironment conditions are also responsible for the various results of clinical trials.

Radiotherapy is often added to the treatment at these places, but it is not standardised. Many studies have reported that radiotherapy is given before the start of bispecific antibody therapy, especially for patients with large tumors or symptoms. In others, it is used at the same time as or after systemic treatment for residual lesions. Therefore, it is not possible to directly compare the results, but some patterns can still be extracted from the combined studies.

Table 1. Selected recent studies of bispecific antibodies ± radiotherapy in R/R DLBCL (2019-2024) [2-9]

Population	Treatment	RT Use	Sequence	ORR	CR	PFS (approx.)	Notes
R/R B-cell lymphoma	Mosunetuzumab	Some patients	Mostly RT → BsAb	~60%	~30%	~5–6 mo	Lower CRS rates
R/R DLBCL	Glofitamab	Limited	Mixed	~52%	~39%	~4–5 mo	Strong T-cell activation
R/R LBCL	Epcoritamab	Subset	Mixed	~63%	~38.9%	~9–12 mo	Step-up dosing
Aggressive B-cell lymphoma	Odronextamab	Not clearly reported	–	~53%	~37%	NA	Early-phase data
Heavily pretreated	Mixed BsAbs	Frequent bridging RT	RT → BsAb common	~50–55%	~25–30%	~2–3 mo	Shorter durability

All the above studies have pointed out some common clinical signs. Most patients are in an advanced stage, and many have already undergone two or more lines of treatment in the past, such as CAR-T [2]. Tumor burden is often high, and bulky disease is common [7]. Therefore, the response rates of bispecific antibodies are the same, and CD20×CD3 engagement may be a good treatment option. Only a small number of patients have achieved complete remission, and the duration is not stable [8].

It is also often the case that radiotherapy is used as a bridge in clinical practice. RT has not developed a regular evaluation system, and therefore, it is more often used for small tumours or localised symptoms. Clinical experience has generally indicated that to enhance the effect of systemic therapy, it is necessary to reduce the tumor burden and adjust the local immune microenvironment [3]. Although there is no direct control data, retrospective clinical studies have shown that patients who have received radiation therapy (RT) before being treated with bsAb generally have good local tumour control and are more responsive to systemic therapy; however, the considerable differences among these studies should also be paid attention to. The Sequence of Treatment Administration is one of the reasons for this. The delivery of radiotherapy before the administration of BsAb is biologically reasonable; that is, it can induce the release of antigens and T-cell infiltration prior to BsAb-guided T-cell redirection to create a good immune environment [3]. At the same time, the two may cause excessive inflammation and have been shown to decrease immune response in cancer therapy research [5]. Although it have not reached a conclusion in the clinic, the patterns observed so far are in line with the mechanistic model; thus, RT can be employed to enhance immunity.

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There may be different platforms for bispecific antibodies, and thus, the results will also vary. The main studies are shown in Table 1. Agent Glofitamab can stimulate T-cell activation; therefore, it does not need to be recognized by T cells first and is easily toxic to the body due to cytokine release [2]. Antigens that do not stimulate the immune system strongly can only be identified in a favourable tumour microenvironment [7]. Therefore, it is possible that radiotherapy will be more effective in conjunction with agents that depend on the presence of T cells, but this hypothesis has not yet been formally tested in clinical trials.

To summarize, the clinical effects of the RT-BsAb combination are different in various circumstances. The level of tumour burden, initial immune cell distribution, arrangement order of therapy, etc., affect the final prognosis of Bispecific Antibody therapy. Given the current different results from various clinical trials, organised systematic studies should be urgently conducted in the future to determine whether different amounts, times and ways of giving radiotherapy differ significantly in effect. Prior to the availability of high-quality evidence, the formula for clinical therapy will still be based on the mechanistic basis and practical clinical experience.

4. Current clinical problems and unresolved issues

Although there has been increasing attention to combining radiotherapy with CD20×CD3 bispecific antibodies, some problems have yet to be solved that reduce the consistency of clinical effects. A particular problem is that no one has reached an agreement on the best way to integrate them. Based on current research and clinical practice, various kinds of radiotherapy are used for bridging, concurrent or consolidating therapies, and both the dose and fractionation plan vary among different centres [10]. This difference is not only a matter of technique but also affects the body's immune system in various ways due to radiation. Based on the preclinical data, a moderate number of hypofractionations can maintain the signal of interferon and the recruitment of T cells better; however, too high a dose of single fractions may reduce immune priming by decreasing TREX1 expression [5]. Although there has been some clarification in the underlying reasons, they have yet to be standardised as general clinical guidelines, and currently, the choice of treatment often relies on different institutions' own criteria instead of new data [3]. Therefore, it is not yet known whether the different clinical results are due to different drug effects or differences in the delivery of radiotherapy.

Another problem is that it cannot accurately identify which patients will benefit most from combination therapy. Bispecific antibodies have shown some effect on recurrent or resistant diffuse large B-cell lymphoma, but they have not lasted long [7]. This diversity shows that the tumour microenvironment is relatively different in different patients, but people do not yet have reliable biomarkers to select patients [9]. At present, these decisions are rarely based on immune profiling, and the situation of T-cell infiltration, PD-L1 expression, interferon signalling, etc., is not regularly checked. Therefore, it is not known whether the combination therapy will be beneficial for the tumour in patients with this biology. Checkpoint inhibitors have been used more frequently in research to discover biomarkers, but to date, very little has been done on the combination of biological markers and RT-bispecific antibodies.

Toxicity management is also a problem in general. Bispecific antibodies have been associated with cytokine release syndrome (CRS) and, in some cases, neurotoxicity, and local inflammation may also occur in the radiation field according to the site of the radiation [2]. When the above two modes are used together, there may be too much damage due to excessive activation of inflammation in response to radiation therapy [3]. Clinically, it has been observed that the time after the onset of symptoms is relatively long. For instance, administering radiotherapy before or at the

DOI: 10.54254/2753-8818/2026.AU33984

start of the first cycle of bispecific antibody therapy may increase the risk of inflammation; otherwise, if it is delayed, this risk may decrease, but so too will the immunological synergy. There has been no systematic research on the above connections, nor have standardised management strategies been established. Therefore, there are differences in the support provided by various studies.

There are still deficiencies in the present clinical data. Most of the available data are from small, early-stage trials or retrospective studies, and they usually have a small number of patients [2]. The follow-up period is usually too short to know the long-term effect of progression-free survival and how long the complete response lasts [7]. In addition, there are few studies with appropriate control groups, and it is often difficult to know whether the results were due to radiotherapy. Even when radiotherapy is mentioned, the details of the dose, fractionation and target volume are not consistent; therefore, it is difficult to conduct a proper cross-study comparison [10]. Therefore, more organised research will need to be conducted in the future to figure out how to combine radiation therapy with bispecific antibodies.

Overall, the combination of RT-BsAb is still in the stage of clinical research. Although there has been some mechanism research in recent years, it is still necessary to go further by improving clinical studies to confirm and develop applications for the combined form. In the future, research will be conducted to optimise the radiation dose, find immune markers and organise the order of treatment that can maximise the synergistic effect of immunity. Without such efforts, there will still be heterogeneity in the clinical outcomes, and the full therapeutic effect of this combination therapy cannot be realised.

5. Future directions

Due to the current problems in the RT-bispecific antibody strategy, more research will be carried out in the future to improve clinical results. First and foremost, people need to start planning the new clinical trials with radiotherapy parameters in mind from the beginning. Rather than viewing radiotherapy as an independent or supportive treatment, in the future, its amount, distribution and sequence should be added to the other elements of the therapy [10]. Based on the current data, it is hoped that a medium-hypofractionised schedule will be more favourable to maintain immune signals, so one needs to determine whether such a schedule can consistently boost the effect of bispecific antibodies in reality [5].

At the same time, predictive biomarkers will also be a way to improve the selection of patients. The different degrees of response to bispecific antibodies may be due to various conditions in the tumour microenvironment at the time of treatment [6]. The starting number of infiltrated T cells, interferon signalling activity and immune checkpoint expression can be used to predict whether a patient will be in good response to combination therapy [9]. Therefore, the new calculation methods will provide with more data on this issue. Models of artificial intelligence can integrate imaging data, genomic information and spatial immune profiles to find small changes in tumours and the immune system that are not easy to detect with traditional methods [9]. At present, research has only just begun to build intelligent analysis tools that can link the biological features of tumours to the most effective combination of radiotherapy and immunotherapy.

Optimisation of the treatment sequence design is also one of the research problems. At present, radiation therapy is generally used as bridge therapy; at the same time, when will it be employed in combination with the administration of BsAb, and how will both the therapeutic effect and safety be impacted? The first release of tumour antigens and the recruitment of T cells can form a good immune environment for the subsequent redifferentiation of T cells induced by BsAbs [3]. There is

DOI: 10.54254/2753-8818/2026.AU33984

an overlap in the expression of RT-induced inflammation and BsAb-induced T-cell activation, and therefore, the risk of cytokine-related toxicity may be relatively high [2]. More research needs to be carried out to determine whether a staggered sequential administration or a partial overlapping mode is more suitable for achieving a good balance between immune synergy and clinical safety, and finally, more attention will be paid to the underrepresented group of special patients. Elderly patients and those with central nervous system disorders are rarely included in clinical trials, but they make up a large proportion of the actual cases of R/R DLBCL [7]. The tolerance level of the combination regimen in these people is different from that in ordinary patients, so personalised adjustment of efficacy and toxicity balance needs to be made. To promote the widespread use of the above combined approach in clinical work, a reasonable way should be found to apply RT and BsAb to the special group.

6. Conclusion

Combination therapy of radiotherapy and CD20xCD3 bispecific antibodies has shown good biological effects in relapsed or refractory diffuse large B-cell lymphoma, and the basis is that these drugs can concurrently alter the tumour microenvironment and activate T cells. Radiotherapy can promote the release of antigens and the migration of immune cells, and at the same time, bispecific antibodies can direct cytotoxic T lymphocytes to target malignant B cells and thus achieve local and systemic control of the tumour. Although the above is a good explanation of the mechanism, it has not been fully realised in clinical practice so far, and other factors are unknown.

At present, the success of this way will be determined by how well each form can be utilised and how well they can be integrated. Differences in the amount of radiation dose, different divisions into fractions and different sequences among bispecific antibody platforms are also reasons for the various results observed in clinical trials. In addition, there are not enough good biomarkers and the scale of existing clinical studies is small, so it is difficult to conclude from the available data.

In the future, a more organised and biologically informed way of doing things will be required to make full use of the advantages of the combination strategy. Based on the immune activation profile of bispecific antibodies and the selection of patients according to biomarkers, can help improve the consistency and duration of the response to radiotherapy. Unless there is other evidence to the contrary, for now, radiotherapy combined with bispecific antibodies is still an effective but not yet widely used treatment for DLBCL.

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