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Infections in lymphoma patients treated with bispecific antibodies: A systematic review and meta-analysis.

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Abstract:

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Key Points

A high proportion of fatal and severe infections post bispecific antibody treatment were viral in etiology, highlighting the importance of prophylaxis, vaccination and investigation for viral reactivation.

Improved elucidation of risk factors for infections in bispecific-treated patients will help define periods of infection risk and guide prophylactic approaches.

ABSTRACT

Bispecific antibodies (BsAb) have rapidly entered the treatment paradigms of both indolent and aggressive lymphomas. Infection is a commonly reported toxicity of BsAb therapy, however characterization of infection patients among patients treated with BsAbs is poorly understood. A systematic review and meta-analysis of published studies of CD20-directed BsAb-treated lymphoma patients was performed. Twenty-seven studies, including 2100 patients, were included. Median follow-up was 12 months; 17% of patients had received prior cellular therapies. The pooled prevalence of infections of any-grade was 44% (95%CI:37-50%), with a prevalence of grade ≥3 infections of 20% (95CI:15-21%) and 3% of patients experiencing fatal infections (95%CI:2-5%). Infection rates did not differ between patients with aggressive or indolent lymphomas, or between BsAb monotherapy and combination therapy. Viral infections constituted a significant proportion (41%) of fatal infections. Future studies should closely examine the incidence of, and risk factors for, severe infections classically associated with T-cell depletion. As BsAbs are progressively incorporated into lymphoma treatment paradigms, the risk of infection needs to be comprehensively profiled, monitored and proactively managed with multidisciplinary approaches.

Bispecific antibodies (BsAb) have demonstrated efficacy in newly diagnosed and relapsed/refractory (R/R) lymphomas. BsAbs form immune synapses between effector cells (T-cells) and target cell surface markers; typically, CD19 and CD20 in B-cell lymphoma. BsAb use in myeloma has raised concerns about increased infection risk;[1] less is known about infection rates following BsAb-treatment for lymphoma. While some CD20-directed BsAb are now available for lymphoma as standard-of-care, approvals across jurisdictions such as the US, Canada and Europe are evolving rapidly. .[2] FDA approvals were largely based on small phase Ib/II studies, in heterogenous populations, with different dosing schedules, treatment durations and supportive care protocols. Despite regulatory approvals, there are no guidelines for anti-infective prophylaxis and an incomplete understanding of the rates, timing and types of infections experienced. Therefore, a systematic review and meta-analysis were undertaken to better characterize infection risks associated with BsAb therapy.

We conducted a PRISMA systematic review and meta-analysis (PROSPERO: CRD42023433207).[3] The search strategy is detailed in the supplement. Studies reporting infection outcomes following CD20-directed BsAb therapy for the treatment of B-cell lymphoma, in adult patients, were included. Study identification, data-extraction and bias-assessment,[4] were performed independently by two authors (GR/MM).

The primary outcome was the proportion of BsAb-treated lymphoma patients treated on clinical trial who experienced ≥1 infection of any grade. Secondary outcomes included the rate of severe (grade ≥3) and fatal (grade 5) infections. Sub-group analyses of severe infections were performed according to aggressive versus indolent lymphoma (defined by WHO diagnostic criteria),[5] monotherapy versus combination therapy, newly-diagnosed versus relapsed/refractory (R/R) disease, and bispecific agent. Observational studies were described separately.

Meta-analysis of proportions estimated the pooled infection incidence. Cochran's Q test examined heterogeneity. Secondary outcomes and subgroup analyses were performed using random effects models (Mantel-Haenszel). Institutional Review Board approval was not sought as this study did not constitute human participant research.

Of 1133 studies screened, 27 studies (2228 patients, 58% male) were included (Figure S1). Twenty-three clinical trials (2100 patients) and four observational studies (128 patients) reported infection outcomes following receipt of one of four CD20-targeting BsAbs (Table 1).

The median cohort age was 65 years (IQR:61.2–67). Patients received a median of 3 prior therapies (IQR:1–3) and had infrequently undergone autologous SCT (16%) or prior chimeric-antigen receptor T-cell (CAR-T) therapy (17%). The pooled prevalence of grade ≥3 cytokine release syndrome (CRS), immune-effector cell associated neurotoxicity (ICANS), and grade ≥3 neutropenia was: 3.3% (95%CI:0 – 2%), 1% (95%CI: – 2%), and 22% (95%:6–27%), respectively. Grade ≥3 leukopenia was 17% (6 studies, 490 patients). Treatment-emergent hypogammaglobulinemia was not routinely reported. Median follow-up was 12 months (IQR:6–15). Additional extracted variables are presented in Table S1.

Our primary outcome of any-grade infections occurred in 44% patients treated with a CD20-BsAb (21 studies, 1961 patients, 95%CI:37-50%, I^2=88%). Twenty percent of patients experienced a grade ≥3 infection (19 studies, 1791 patients, 95%CI:15 – 21%). The causes of severe infections were incompletely reported (12/19 studies, Table S2); four studies reported the cause of all Grade 3 or 4 infections,[6-9] two studies reported only the proportion of severe infections attributable to COVID-19,[10,11] and six studies reported the aetiology of at least one severe infection in addition to COVID-19.[12-16] Aggregated across studies, just 133 of 319 (42%) grade ≥3 infections had an aetiology reported. Among these 133, the commonly reported causes of severe infection were COVID-19 (32%), clinically-diagnosed pneumonia (26%) and sepsis (12%), Severe opportunistic infections were reported specifically in six studies (included in Table S2), including HSV/VZV reactivations (9 patients), CMV, EBV and severe influenza (2 patients each), toxoplasmosis (1 patient),*Pneumocystis pneumonia* (1 patients), and fungal pneumonia (fungus not specified, 1 patient)

Fatal infections occurred in 79/1774 patients (3%, 95%CI:2-5%). The cause of fatal infection was reported in 67% (54/79, Table 2). Of reported infections, microbiologically-confirmed fatal infections (53%) were more common than clinically-defined fatal infections (15%). Viral infections were the most common microbiological cause of fatal infections (41%, 32/79), largely reflecting COVID-19 mortality (91% of viral infections), followed by fungal infections (6% of total fatal infections, predominately *Pneumocystis,* and one case of systemic mycosis) and bacterial infections (5% of total fatal infections). One case of fatal toxoplasmosis was reported.[16] In the included observational studies, viral infections were also the most common cause of fatal (73%) and severe infections (100%), which detailed 75 infections (11 fatal) (Table S3).

Several planned sub-analyses were then performed. The rate of all-grade (47 vs. 48%), grade ≥3 (20 vs. 21%) and fatal infections (4% vs. 3%) did not differ significantly between patients with DLBCL versus follicular lymphoma (Table S4).

Additionally, in DLBCL, the rates of all-grade (41 vs. 49%, p = 0.17) and severe infections (19 vs. 20%, p=0.91) did not differ between patients with DLBCL who received BsAb for first-line therapy (4 studies, 164 patients), or for relapsed-refractory disease (8 studies, 715 patients, p=0.17). In follicular lymphoma, the pooled rates of all-grade infections (59% vs. 26%) and grade ≥3 infections (25% vs. 5%, p<0.01, Figure S1) were significantly higher in patients receiving BsAb for R/R follicular lymphoma (4 studies, 372 patients) compared to the single published study examining first-line FL treatment with epcoritimab (39 patients).

When considering monotherapy with BsAb, there were no differences in all-grade (49% vs. 50%) or grade ≥3 infections (18 vs. 27%) in R/R DLBCL patients receiving a BsAb as monotherapy compared to combination therapy (FigureS2). The impact of combination therapy could not be analysed in patients receiving upfront treatment because all BsAb were administered in combination with chemotherapy.

In agent-specific analyses, in DLBCL patients receiving BsAb as first-line therapy, there were no significant differences in severe infection rates between BsAb products (Figure S3a). In R/R DLBCL, the significant differences observed between products was driven by single studies of mosunetuzumab (9%, 95%CI:4–17%) and odronextamab (37%, 95%CI:29–45%, Figure S3b), In follicular lymphoma, rates of grade ≥3 infection did not differ significantly between patients treated with mosunetuzumab (2 studies, 133 patients, 25%, 95%CI:7-42%) and epcoritimab (1 study, 111 patients, 13%, 95%CI:7-20%, p>0.05).

Our systematic review of infections in lymphoma patients receiving bispecific antibodies reveals a notable rate of all-grade (44%) and grade ≥3 (20%) infections, with highly variable reporting of infection type. The etiologies of severe (grade ≥3) and fatal infections were underreported. Yet, infection remains a prominent cause of treatment interruption, non-disease-related treatment discontinuation, and non-relapse mortality.[7,17] Preventative strategies including antimicrobials, infection screening and vaccination require a detailed understanding of the types of infections they aim to prevent; likewise for diagnostic investigation. Infection reporting is crucial to the safe implementation of these approaches.

A significant proportion of serious and fatal infections were viral, in contrast to other R/R lymphoma treatments for R/R lymphoma like CAR T-cell therapy, where fatal bacterial infections predominate.[18] Fatal viral infections were frequently due to COVID-19, which highlights the importance of understanding both antibody and T-cell specific responses to COVID-19 vaccine in the context of B-cell depletion, as well as optimal vaccine timing in this

cohort.[19] Additionally, reporting of centre-specific prophylaxis regimens could help elucidate whether the severe viral reactivations observed (e.g. CMV, VZV and HSV) – less commonly seen in lymphoma patients - would benefit from more intensive preventative approaches. For clinicians, our results highlight the importance of investigating reactivated or disseminated viral infection in the context of clinically compatible syndromes in a patient who has or is receiving BsAb.

Analysis of infection rates by advanced disease, aggressive disease, and combination therapy, did not identify any specific BsAb cohorts at higher infection risk. These results contrast some observational studies highlighting advanced disease and extensive pre-treatment as risk factors for infection in lymphoma patients, which reflect the cohorts of patients who are typically treated on clinical trials.[20] Based on currently available information, some risk factors for infection cannot be separated by subgroup meta-analysis, which is a limitation of our study. For example, first-line BsAb-regimens were administered with CHOP chemotherapy, likely confounding the effect of disease stage and combination therapy on infection outcomes. Agent-specific effects were likely also confounded with follow-up duration; odronextamab demonstrated the highest any-grade infection rate in the context of the longest median follow-up.[21,22] Comprehensive registries and accelerated public access to individual patient data will help reduce inter-study heterogeneity, and rapidly identify cohorts at higher infection risk.[23,24]

Additionally, evaluation of host- and treatment-related risk factors for opportunistic infections, may be critical to understanding infection in BsAb-treated patients, given the small but notable occurrence these infections in a haematological population where these infections are relatively uncommon. The duration of neutropenia, lymphopenia and hypogammaglobulinemia were infrequently reported; insufficient data precluded regression analysis. Cumulative steroid exposure was also underreported, differed notably between treatment regimens and correlated with BsAb-therapy duration. Recent studies suggesting that continuous T-cell reduction with BsAbs may induce functional T-cell exhaustion may provide a further mechanistic explanation for the occurrence of opportunistic infections in BsAb-treated patients.[25] Future studies should report more detail around the timing of infections to help compare the relative contribution of early CRS (and its treatment), steroids and drug ramp-up with the effects of long-term exposure to BsAb. Prospectively collected minimum dataset of validated risks for opportunistic infection, such as depth of cytopenia, steroid burden, and infection prophylaxis may help better define these periods of infection risk.[23] It also provides impetus for consideration and investigation of time-limited and/or response-adapted BsAb therapy, especially in curative contexts such as DLBCL.[14]

The analysis presented is limited by incomplete reporting of infections across different grades and incomplete reporting of infection etiologies. Similarly, information specific to COVID-19 risk, such as vaccination status, predominant viral strain, and timing of COVID-19 infection was not available to provide further comment on the high proportion of COVID-19 deaths observed. Significant heterogeneity across product, lymphoma sub-type and combination therapy was observed, and while addressed by planned sub-group analyses, resulted in small groups available for pooled analysis.

As BsAbs are increasingly integrated into a broader range of treatment paradigms for lymphoma, the risk of infection needs to be fully characterized, monitored and managed. The fatal and severe viral and fungal infections in this cohort contrast to the higher rates of bacterial infections following other anti-lymphoma therapies and highlights the potential for rapid induction of B- and T-cell dysfunction as a CD20-BsAb class-effect. Comprehensive registries and enhanced reporting as part of clinical trials are required to design and implement careful strategies to minimize morbidity and mortality associated with increased utilization of BsAb.

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Table 1 – Summary of included clinical trials by malignant target and bispecific product.

Malignant Target	Bispecific antibody	Number of Trials	Lymphoma subtype (No. of trials)	Number of patients	All Grade Infection (%, *95%CI*)	Median length of follow-up (IQR)
CD20	Epcoritamab	7	Aggressive (5), Indolent (1), B-cell NHL NOS (1)	470	39 *(29 - 47)*	11.4 (6.1-17.1
	Glofitamab	7	Aggressive (6), B-cell NHL NOS (1)	618	42 *(30 – 53)*	10.6 (6 – 15)
	Mosunetuzumab	6	Aggressive (3), Indolent (2), B-cell NHL NOS (1)	599	43 *(47 - 50)*	12.5 (8 – 28.5)
	Odronextamab	3	Aggressive (1), Indolent (1), B-cell NHL NOS (1)	414	59 *(48 – 69)*	21 (N/A)

Table 2 – Aetiology of Fatal Infections

	N, %
Fatal Infections	79
Microbiologically Confirmed	**42 (53% of fatal infections)**
Viral	32 (41% of fatal infections)
SARS-COV-2	> 29*
Epstein-Barr Virus	1
CMV	1**
PML	1
Bacterial	4 (5% of fatal infections)
Gram negative bacteraemia	4
Fungal	5 (6% of fatal infections)
Candidemia	1
Pneumocystis jirovecii pneumonia	3
Systemic mycoses	1
Protozoan	
Toxoplasmosis	1
Clinically Diagnosed	**12 (15% of fatal infections)**
Sepsis	4
Pneumonia	8
Aetiology not reported	**25 (32% of total infections)**

* Some studies reported > the reported number of SARS-COV-2 infections

** Following first-line therapy