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Stuck in traffic: a bispecific antibody-mediated immune re-engagement after allogeneic stem cell transplantation

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S.B. conceived the report, collected and analyzed the clinical data, performed the literature review, and drafted the manuscript.
M.W. and S.K. contributed to revision of the manuscript.
D.G. contributed to the conceptual framework of the report, and reviewed and edited the manuscript.
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For original data, please contact sboisclair1@northwell.edu

Relapse following allogeneic hematopoietic stem cell transplantation (alloHSCT) remains a major cause of treatment failure in patients with B-cell lymphoma. Mechanisms of disease relapse include inadequate pre-transplant disease control, graft failure, or more commonly, impaired immune surveillance despite donor engraftment[1] Accordingly, patient frailty, delayed immune reconstitution, and relapse biology warrant consideration when selecting therapy. In patients with sustained full donor chimerism and adequate systemic immune reconstitution, therapeutic strategies capable of re-engaging donor-derived immune effector cells and augmenting the graft-versus-lymphoma (GvL) effect represent a biologically rational approach.

We describe a 40-year-old man with del(17p) non-germinal center diffuse large B-cell lymphoma (DLBCL) transformed from marginal zone lymphoma treated with epcoritamab for post-transplant relapse. He had received multiple prior lines of therapy including rituximab monotherapy, lenalidomide plus rituximab, umbralisib, and bendamustine plus obinutuzumab for marginal zone lymphoma followed by G-CHOP (obinutuzumab, cyclophosphamide, doxorubicin, vincristine, prednisone) and R-DHAP (rituximab, dexamethasone, high-dose cytarabine, cisplatin) as bridging to chimeric antigen receptor T-cell (CAR-T) therapy for transformation to DLBCL. He was evaluated for alloHSCT after detection of minimal residual disease (MRD) by ClonoSEQ assay (tracked from the DLBCL clone) five months following CAR-T therapy with no measurable disease on PET/CT. The rationale for consolidative alloHSCT despite CAR-T failure was supported by the patient's high-risk biology and emerging evidence of durable remissions in selected patients achieving disease control with CAR-T prior to transplantation[2,3].

The patient received reduced-intensity conditioning with Fludarabine (30 mg/m^2 daily on day -7 to -2), Busulfan (130 mg/m^2 daily, on days -3 and -2), and rabbit anti-thymocyte globulin (rATG; 5mg/kg total, escalated over day -4 to -2), followed by a peripheral blood matched-unrelated donor graft with post-transplant cyclophosphamide, abatacept and bortezomib for graft-versus-host disease (GVHD) prophylaxis. Full donor chimerism was achieved by day +30.

Disease assessment at day +60 demonstrated no evidence of lymphoma, with negative MRD by ClonoSEQ assay. At day +180, MRD surveillance became positive and imaging revealed a new right external iliac lymph node measuring 4.8×2.8cm. Subsequent PET/CT confirmed a single FDG-avid lymph node, with no additional nodal, splenic, marrow, or extranodal disease identified. At the time of biopsy confirming DLBCL relapse, the patient remained with complete donor chimerism.

Given these features, the patient was treated with single-agent epcoritamab, a CD20×CD3 bispecific antibody. Donor lymphocyte infusion (DLI) was not feasible due to lack of available donor product. Furthermore, local radiation therapy was not pursued, as it is most effective for consolidation after achieving response with systemic therapy or for palliation, but would not be recommended as monotherapy for relapsed aggressive lymphoma in patients who are candidates for systemic treatment. After three cycles of therapy, imaging demonstrated complete resolution of the involved lymph node without new lesions, and MRD testing reverted to negative.

Treatment was well tolerated with no cytokine release syndrome, immune effector cell-associated neurotoxicity, loss of donor chimerism or GVHD. The patient did develop intermittent thrombocytopenia without need for transfusion, and neutropenia requiring growth factor support, but experienced no infectious complications. Anti-infective prophylaxis included antiviral, antifungal and pneumocystis jirovecii pneumonia prophylaxis; intravenous immunoglobulin was

not administered. Given favorable response after 3 cycles, he received an additional 6 cycles with continued MRD negativity (total of 9 cycles of therapy), prior to treatment discontinuation. Given the sustained complete remission with MRD negativity, a second allogeneic HCT is not currently planned, and the patient will continue surveillance, including MRD testing every 2 months.

Longitudinal immune monitoring demonstrated early recovery of donor-derived lymphocyte populations following allo-HSCT (Figure 1). Absolute $CD3^+$ and $CD8^+$ T-cell counts, as well as natural killer ($CD16^+/56^+$) cell counts, started recovering by day +30 and remained stable through relapse. However, $CD4^+$ T-cell counts remained persistently low, with a CD4:CD8 ratio of less than 1 (0.21 to 0.33). Within 3 months of epcoritamab initiation, sustained increases in $CD4^+$, $CD3^+$, and $CD8^+$ T-cell counts were observed, consistent with pharmacologic immune re-engagement rather than spontaneous immune reconstitution.

This report demonstrates feasibility of CD20×CD3 bispecific therapy post-transplant and provides mechanistic insight into relapse biology with preserved donor chimerism and incomplete effector cell recovery. This relapse pattern supports a functional and spatial immune escape, wherein immune surveillance is preserved systemically but insufficient within a localized tissue microenvironment[6–8]. To interpret this discordance between circulating immune recovery and localized relapse, tissue-level immune trafficking and regulation must be considered.

Effective GvL activity requires not only the presence of donor-derived effector cells in the circulation, but also appropriate trafficking and functional engagement within disease-containing lymphoid tissues (Figure 2A). $CD4^+$ T cells play a central role in maintaining lymphoid architecture and chemokine gradients necessary for immune cell trafficking, homing and persistence[4]. ATG has been associated with prolonged $CD4^+$ and naïve T-cell lymphopenia[5] and with impaired thymic output of $CD4^+$ T-cells[6,7]. ATG can also directly upregulate PD-1 expression on T-cells, which within the tumor microenvironment, can further suppress effector T-cell activity and deactivate donor-derived tumor surveillance[8]. Additionally, trafficking chemokine receptor expression (i.e. CXCR3 and CCR5) and adhesion molecules are frequently dysregulated post-transplant[9] suggesting that peripheral immune counts may not reflect tissue immune function[5]. Our patient with persistent $CD4^+$ lymphopenia may have had impaired trafficking with functional lymphocyte dysregulation within nodal tissue (Figure 2B). The rapid clearance of disease exemplifies a CD3-engaging bispecific antibody's ability to overcome such reversible immune escape.

Published experience with epcoritamab post alloHSCT setting is extremely limited, and immunologic mechanisms underlying response remain poorly defined in this context. CD3-engaging bispecific antibodies function by simultaneously binding CD3 on T cells and tumor-associated antigens on malignant cells, triggering T-cell activation and cytotoxicity independent of major histocompatibility complex[10] (Figure 2C). While sustained $CD8^+$ T-cell cytotoxicity has traditionally been thought to depend on $CD4^+$ T-cell–derived helper signals, solid tumor studies have shown that $CD8^+$ T-cells activated by bispecific antibodies can mediate direct cytotoxicity even without $CD4^+$ help[11]. Additionally, $CD8^+$ T-cells activated by CD3 bispecific antibodies produce IFN- γ, which induces local chemokine production (i.e. CXCL9, CCL5) recruiting additional effector cells to tumor sites[11]. Specifically, epcoritamab's clinical activity is associated with significant expansion of CD4+ and CD8+ cells and sustained B-cell depletion[12]. In our patient, the pronounced $CD4^+$ and $CD8^+$ T-cell expansions observed following epcoritamab initiation (Figure 1) are consistent with direct CD3-mediated activation of donor-derived effector cells and restoration of helper signals critical for sustained immune surveillance.

This represents an additional mechanism amplifying anti-tumor response, previously shown to be central for CD3-engaging bispecific activity. [10] By enforcing immune synapse formation utilizing donor-derived, non-exhausted T-cells, epcoritamab likely can bypass deficiencies in endogenous trafficking or antigen presentation to restore local effector engagement. This pharmacologic redirection of donor immune cells may functionally recapitulate GvL activity without the need for DLI and without compromising graft integrity.

Rather than immune absence, post–alloHSCT relapse increasingly reflects lymphocyte dysregulation. The PD-1/PD-L1 axis is a major regulator of T-cell functional exhaustion within tumor microenvironments. Clinical experience with PD-1 blockade after alloHSCT, particularly in Hodgkin lymphoma, demonstrates that donor-derived T cells can be pharmacologically reactivated and graft-versus-tumor effects restored, but with significant increase in GVHD risk[13]. CD3-bispecific antibodies may offer a safer alternative by selectively redirecting T cells to tumor targets only. High-intensity CD3 signaling from the enforced immune synapse formation may partially bypass the PD-1 mediated inhibition and restore effector function, as PD-1 preferentially suppresses low-affinity T-cell responses while high-intensity TCR signaling is relatively resistant to checkpoint inhibition[14]. Due to this targeted redirection, the GVHD-protective effects of PD-1 signaling on alloreactive T cells in normal tissues can remain intact. Additional support of this class effect comes from blinatumomab. This CD3xCD19 bispecific antibody has demonstrated activity in MRD and relapse settings after alloHSCT, without increased risk of GVHD, supporting the feasibility of CD3-engaging immune redirection with fit donor T-cells in the post-transplant environment[15]. Together, checkpoint inhibition and CD3 redirection support a model in which relapse post alloHSCT driven by immune dysregulation may be reversible through targeted immune re-direction strategies.

Taken together, this case supports a model in which epcoritamab restored GvL activity by redirecting donor-derived immunologically fit effector T-cells. Post-alloHSCT bispecific therapy leverages a donor-derived, non-exhausted, T-cell repertoire, supporting these agents as a platform strategy rather than a drug-specific effect. In this context, bispecific engagement may overcome impaired trafficking and lymphocyte dysregulation while preserving donor chimerism and graft tolerance. Alternative explanations, including delayed GvL effects or spontaneous disease regression, cannot be excluded but appear less likely given the temporal association with therapy and the absence of immune reconstitution or graft change. This report is hypothesis-generating and not intended to establish efficacy. Prospective studies incorporating immune profiling are needed to define which patients with post alloHSCT relapse benefit most from bispecific therapy and to clarify optimal timing relative to MRD detection. These findings support prioritizing immune-redirecting therapies over cytotoxic treatment in post-transplant relapse, when donor immunity is present, but insufficiently engaged.

This case report was exempt from institutional review board approval per institutional policy. Informed consent was obtained from the patient for publication of this report.

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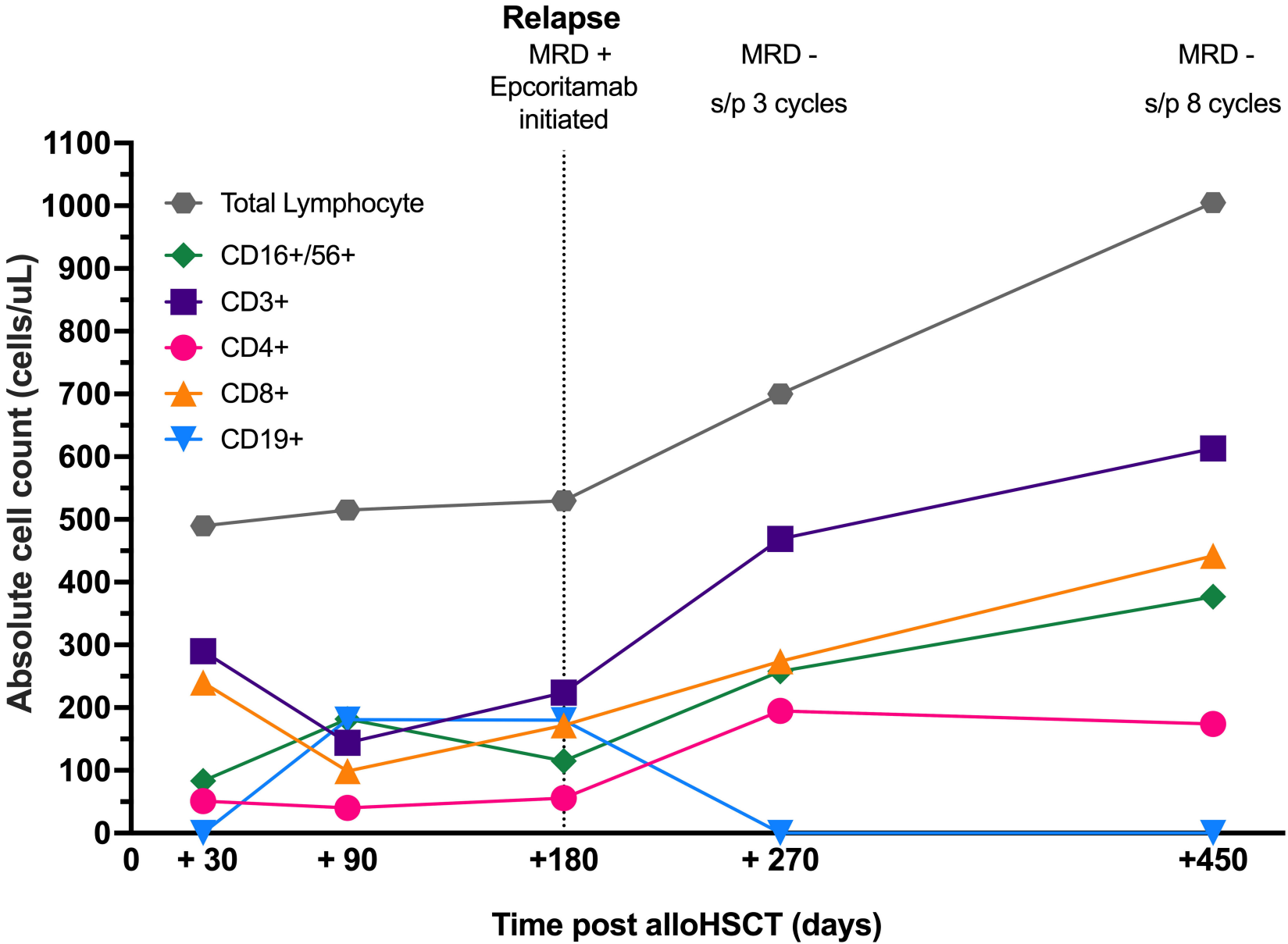
Figure Legend:
Figure 1: Post-transplant timeline with immune reconstitution

Figure 2: Immune trafficking in graft versus lymphoma, post-transplant spatial immune escape and bispecific antibody-mediated immune re-engagement. A) Effective graft-versus lymphoma (GvL) requires donor-derived effector cell trafficking, tissue infiltration and local immune amplification. B) After alloHSCT, persistent CD4+ lymphopenia, impaired trafficking and lymphocyte dysregulation may permit localized immune escape despite preserved systemic immune reconstitution. C) CD3-engaging bispecific antibody therapy enforces immune synapse formation and restores local effector engagement, functionally recapitulating GvL activity.


Relapse
MRD +
Epcoritamab
initiated
MRD -
s/p 3 cycles
MRD -
s/p 8 cycles
Total Lymphocyte
CD16+/56+
CD3+
CD4+
CD8+
CD19+
Absolute cell count (cells/uL)
1100
1000
900
800
700
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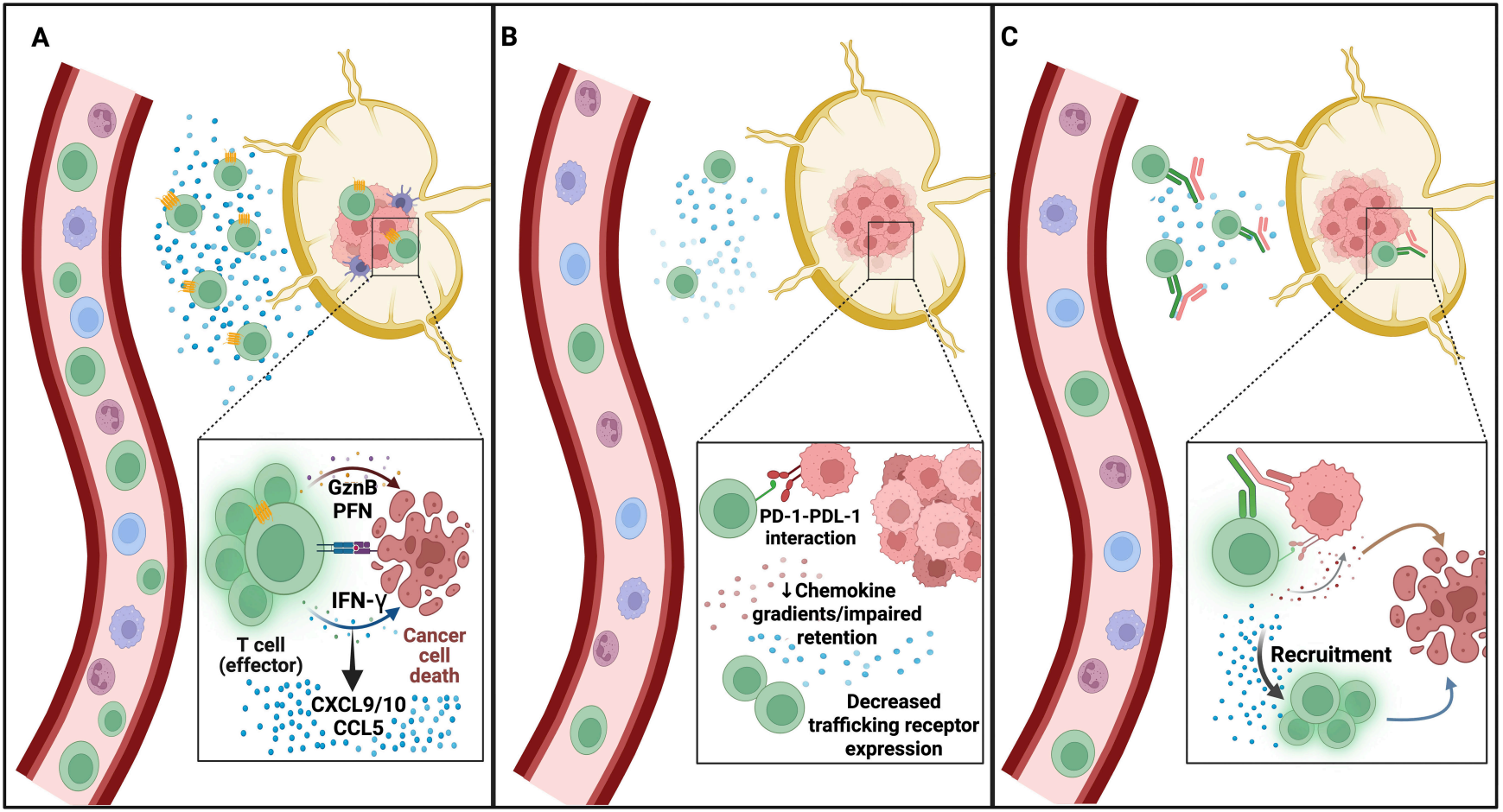
200
100
0
0
+ 30
+ 90
+180
+ 270
+450
Time post alloHSCT (days)


A
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Cancer
cell
death
CXCL9/10
CCL5
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PD-1-PDL-1
interaction
↓Chemokine
gradients/impaired
retention
Decreased
trafficking receptor
expression
C
Recruitment