EXCEPTIONAL CASE REPORT

blood advances

Activity of blinatumomab in lymphoblastic leukemia with impaired T-cell immunity due to congenital immunodeficiency

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Key Points

- Blinatumomab is effective in patients with congenital partial T-cell immunodeficiency.
- T-lymphopenia, whether congenital or acquired, does not compromise the efficacy of blinatumomab.

Blinatumomab, a single-chain, bispecific, T-cell–engaging antibody targeting CD19, is effective in B-precursor acute lymphoblastic leukemia (BCP-ALL), even in the context of chemotherapy-related partial T-cell immunodeficiency. We report 2 patients with BCP-ALL and congenital T-cell immunodeficiency, who obtained an excellent response to blinatumomab. The first, a 6-year-old girl with Schimke immuno-osseous dysplasia (SIOD) and combined immunodeficiency disorder (CID) obtained a minimum residual disease–negative (MRD^-) remission of high hyperdiploid BCP-ALL with blinatumomab. At last follow-up, the remission had been sustained for 14 months from diagnosis. The second was a 9-year-old boy with Omenn syndrome and CID who received a mismatched bone marrow transplant from his mother at the age of 4 months and was diagnosed with $t(3;11)^+$ (KMT2A-LARS2) BCP-ALL 9 years after his transplant. He received a 4-drug induction followed by blinatumomab for persistent MRD as a chemotherapy-sparing bridge to transplant and achieved an MRD^- remission. T-lymphopenia, whether congenital or acquired, does not compromise the efficacy of blinatumomab.

Introduction

Blinatumomab is a single-chain recombinant antibody construct of an anti-CD3 single-chain variable fragment (scFV) fused with an anti-CD19 single-chain variable fragment via a short peptide linker.[1] The cytotoxicity of the antibody is mediated by cytokines released from activated T cells after engagement of the antibody with $CD19^+$ and $CD3^+$ cells.[2] Several studies have demonstrated its activity in the relapse/refractory and minimum residual disease (MRD) settings in children and adults.[3,4]

We describe 2 patients with $CD19^+$ B-precursor acute lymphoblastic leukemia (BCP-ALL) against a background of primary T-cell immunodeficiency in whom blinatumomab as a chemotherapy toxicity-sparing agent was successful in inducing an MRD^- remission.

Signed consent to publish anonymized information was obtained from legal guardians.

Case descriptions and methods

Case 1

A 6-year-old Croatian girl with a background of Schimke immuno-osseous dysplasia (SIOD) was diagnosed with BCP-ALL with a presenting white cell count of 1.62×10^9/L. She had no central nervous system (CNS) disease, and her leukemia was cytogenetic good-risk with high hyperdiploidy. Six months earlier, she had developed nephrotic syndrome for which she had a suboptimal response to steroid therapy. A renal biopsy demonstrated focal segmental glomerulosclerosis of perihilar type

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Table 1. Immune status of patients before initiation of chemotherapy

	Case 1 results	Case 2 results
White blood cell count	1.62	4.83
Lymphocyte count	1.10	0.79
$CD3^+$ cells		
%	28.8	70
Absolute count	0.32	0.52
$CD19^+$ cells		
%	25.8	3
Absolute count	0.28	0.02
$CD16^+CD56^+$ cells		
%	44.0	27
Absolute count	0.48	0.20
$CD3^+CD4^+$ cells		
%	10.8	36
Absolute count	0.12	0.27
$CD3^+CD8^+$ cells		
%	17.1	29
Absolute count	0.19	0.21
CD4s; $CD4^+CD45RA^+CD27^+$ (naive) cells		
%	27.9	9
Absolute count	0.03	0.04
CD4s; $CD4^+CD45RA^+$ $CD31^+$ (recent thymic emigrants), %	20.3	NA
TRECs*	Negligible	442 /10^6 T cells
Spectratyping	4 of 24 V-β families with a Gaussian distribution	16 of 24 V-β families with a Gaussian distribution

Cell counts are expressed as $\times 10^9$/L.
*The tenth percentile for TRECs in an age range of 6 to 12 years is 8534 TRECs/10^6 T cells.

leading to stage 4 chronic kidney disease, hypertension, and anemia. SIOD is a rare autosomal-recessive disorder[5] caused by a mutation in *SMARCAL1* (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin, subfamily-a–like-1), a gene involved in maintaining the integrity of the genome.[6] Affected patients, as in the present case, have progressive renal disease caused by focal segmental glomerulosclerosis, vasculopathy, combined immunodeficiency, and risk of lymphoproliferative disease and bone marrow failure.

Immunophenotyping demonstrated absolute lymphopenia that was disproportionate in $CD3^+CD4^+$ cells (120×10^6/L). Her proportion of naive $CD4^+$ T cells ($CD4^+CD45RA^+CD27^+$) was markedly reduced for age (29%), and her T-cell receptor excision circles (TRECs) were negligible, demonstrating a significant reduction in recent thymic emigrants. Baseline immunological testing before chemotherapy was initiated is outlined in Tables 1 and 2.

Owing to the risks of excess chemotherapy toxicity reported in patients with SIOD,[7,8] she received weekly vincristine (50% of the normal dose) with prednisolone 40 mg/m^2 for 2 weeks instead of standard induction. Intrathecal cytarabine and hydrocortisone were administered instead of intrathecal methotrexate, to avoid the risk of delayed renal excretion and nephrotoxicity related to her preexisting poor renal function.[9] We were satisfied that the substitution would provide effective CNS prophylaxis, given her low-risk of CNS relapse. However, she developed anuric renal failure in week 2 of therapy for which she required hemofiltration followed by hemodialysis and peritoneal dialysis, with the latter continuing to date. In view of worsening renal function, induction chemotherapy was discontinued and switched to blinatumomab therapy, with a starting rate of 5 μg/m^2 per day. An assessment was not performed before blinatumomab treatment began, as she was unfit for general anesthetic because she was in intensive care with unstable blood pressure and undergoing hemofiltration. Within 48 hours of the initiation of blinatumomab, she developed grade 2 cytokine release syndrome (CRS), graded according to the American Society for Transplantation and Cellular Therapy criteria.[10] She required a bolus of fluid for hypotension and a brief interruption of the infusion. She had subsequent improvement in her fitness for anesthetic, and a second bone marrow aspirate (BMA) at day 12 of the infusion showed 8% blasts on flow cytometry. The blinatumomab infusion rate was increased to 15 μg/m^2 per day for the remaining 16 days of infusion, which she tolerated without a further episode of CRS. Her leukemia was in morphological remission with MRD of 0.009% on flow cytometry after the first cycle, which became flow- and PCR-negative after a second cycle. She subsequently received single-agent, low-dose oral mercaptopurine (15 mg/m^2 instead of 75 mg/m^2, because of myelosuppression at higher doses) with an intrathecal infusion of cytarabine in each of 3 consecutive months. She was unable to receive systemic or intrathecal methotrexate, as the drug is not dialyzed. At last follow-up, 14 months from diagnosis, her leukemia remained in molecular MRD^- remission.

Case 2

A 9-year-old White, British boy, diagnosed with RAG1-deficient SCID with Omenn syndrome[11] during infancy, underwent a $CD3^+$ /$CD19^+$–depleted maternal mismatched BMT at the age of 4 months. After the stem cell transplant (SCT), there was an early loss of myeloid donor chimerism and poor overall immune reconstitution. B-cell reconstitution did not occur, and long-term immunoglobulin replacement was necessary. The patient remained significantly $CD3^+CD4^+$ T-lymphopenic (270×10^6/L), but had evidence of some thymic output (9% naive $CD4^+$ T cells, 442 TRECs, Table 1). Despite the T-lymphopenia, he had a good quality of life with no significant or opportunistic infections; therefore, a second BMT was not performed because of the risk of toxicity and death. At the age of 9 years, he presented with tiredness and lethargy and was diagnosed with BCP-ALL. Cytogenetic analysis showed t(3;11) with a novel KMT2A-LARS2 fusion gene on RNA sequencing.

Owing to high-risk cytogenetics, he received a 4-drug induction as per the United Kingdom Acute Lymphoblastic Leukemia 2019 (UKALL2019) guidelines, after which he was in complete remission with a molecular MRD of 0.3% and flow MRD of 1.9%. Given concerns about resistant disease and prior unstable graft function, a second allogeneic stem cell transplant (allo-SCT) was considered during the first remission. Blinatumomab treatment was therefore commenced as a chemosparing consolidation therapy to minimize toxicity, with a view to proceeding to allo-SCT once an MRD level of $<1 \times 10^{-4}$ was achieved. MRD after 1 cycle of blinatumomab was negative by flow and molecular tests, which provided a bridge to a second T-cell receptor αβ/CD19–depleted paternal mismatched graft with add back of $CD45RO^+$ memory T cells. The neutrophils

Table 2. Treatment and blinatumomab responses

	Before blinatumomab		After blinatumomab	
	Treatment	MRD	Treatment	MRD
Case 1	VCR/pred × 2 wk	8% (predose escalation)	Low-dose oral mercaptopurine+IT Ara-C	Negative after cycle 2
Case 2	4 drug induction*	1.9%	Haploidentical BMT	Negative

Ara-C, cytosine arabinoside; BMT, bone marrow transplant; IT, intrathecal; pred, prednisone; VCR, vincristine.
*4-drug induction, regimen B of UKALL2019 protocol.[12]

and platelets were engrafted by days 17+ and 19+, respectively. He developed grade 2 acute graft-versus-host disease after discontinuing prophylaxis, but it resolved with a short course of systemic steroids. The leukemia remained in remission with 100% T-cell donor chimerism at 3 months after transplant. The outcome indicates that the patient had T-cell reconstitution after receiving a hemapoietic SCT.

Results and discussion

Despite severely impaired T-cell immunity before initiation of chemotherapy, these 2 patients obtained a molecular MRD response after 1 to 2 cycles of blinatumomab, as outlined in Tables 1 and 2. This observation is in keeping with the experience in patients with severe, acquired postchemotherapy T-lymphopenia, which does not compromise the response to blinatumomab. The reasons are not entirely clear, but suggest that blinatumomab can activate and secondarily expand a small, functionally normal T-cell pool across the reticuloendothelial system and exert a therapeutic effect. T-lymphopenia, whether congenital or acquired, should not deter from the use of blinatumomab as a toxicity-sparing agent in patients with multiple comorbidities and high risk of chemotherapy-related toxicity.

Authorship

Contribution: S.R. and A.C. wrote the paper and obtained consent from the parents; A.W. collected the data and contributed to clinical information; S.H.L. and M.S. contributed to clinical information and wrote the paper; and S.G. and A.V. designed the research and reviewed the paper.

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