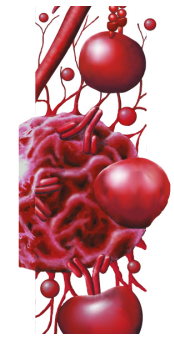
Case Report

Immunotherapy



Concomitant use of blinatumomab and donor lymphocyte infusion for mixed-phenotype acute leukemia: a case report with literature review

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Blinatumomab and donor lymphocyte infusion (DLI) combination is a promising cancer therapy, whereby blinatumomab might achieve an initial reduction in leukemic-cell burden using T cells, and after tumor clearance, DLI can potentially stimulate the donor immune system to achieve longer lasting remission. Here, we present a 51-year-old female with mixed phenotype acute leukemia who had a hematologic relapse 3 months after she received total body irradiation-based myeloablative allogeneic hematopoietic stem cell transplantation from an unrelated human leukocyte antigen matched (10/10) donor and achieved complete remission with minimal residual disease negativity by multi-parameter flow cytometry using the combination of blinatumomab and DLI. To the best of our knowledge, this is the first report to describe the use of blinatumomab and DLI combination therapy in the treatment of B/myeloid mixed phenotype acute leukemia.

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Mixed phenotype acute leukemia (MPAL) is a rare subtype of leukemia that expresses antigens of more than one lineage, and it represents about 5% of all acute leukemia [1,2].

Based on the World Health Organization (WHO) classification of Tumor of Hematopoietic and Lymphoid Tissues, it is classified under acute leukemia of ambiguous lineage. Immunophenotypic features of MPAL include B/myeloid, T/myeloid, B- and T-cell lineage or tri-lineage leukemia. The B-cell/myeloid phenotype comprises 59% of all MPAL [3–5]. Outcomes for MPAL are poor when compared with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) [2,6,7].

According to the WHO criteria, B-cell lineage is defined by the expression of CD19 together with other B-cell-associated markers. MPO is the single most specific marker to assign the myeloid component of an MPAL [8]. In cases with negative MPO, evidence of monoblastic markers such as CD11c, CD14, CD36, CD64 or lysozyme would be helpful to establish the diagnosis [9,10].

Optimal treatment has not been established. However, ALL-type chemotherapy for MPAL patients was found superior to AML-type regimens [6,11]. Matutes *et al.* reported a better complete remission rate (85%) with ALL-type therapy when compared with AML-type therapy (41%) [3]. Recent retrospective analyses showed favorable outcomes in MPAL patients consolidated with allogeneic hematopoietic stem cell transplantation (allo-HSCT) [12–15].

Future Medicine

Table 1. Selected adult cases treated with blinatumomab with or without donor lymphocyte infusion.

Study (year)	N	Disease	Disease status before the initiation of blinatumomab	Treatment	Outcome
Ronchetti *et al.* (2014)	1	B-ALL	Post-transplant marrow relapse	Five cycles of blinatumomab	Achieved MRD-negative CR after cycle 1; skin aGVHD occurred on day 7 of cycle 1
Ueda *et al.* (2016)	4	B-ALL	Patient 1: post-transplant marrow relapse	Cycles 1 & 2: Blinatumomab Cycles 3 & 4: Blinatumomab + DLI	CR after cycle 2; skin aGVHD before cycle 3; extramedullary relapse (sacral, lung mass) 6 mo after cycle 1; marrow relapse 11 mo after cycle 1; death due to relapse
			Patients 2 and 3: post-transplant MRD-positive CR	Cycles 1 & 2: Blinatumomab Cycle 3: Blinatumomab + DLI	Patients 2 and 3: Remained in CR for 13 and 7 mo, respectively; grade III late onset skin and gut aGVHD in patient 2 after cycle 3
			Patient 4: post-transplant extramedullary relapse (CNS, lung, thorax)	Cycles 1 & 2: Blinatumomab Cycle 3: Blinatumomab + DLI	Tremor and orthostatic hypotension at cycle 1; extramedullary disease (liver, bone, pericardium, popliteal fossa) after cycles 2 and 3
Linder *et al.* (2016)	1	B-ALL	Marrow relapse after multi-chemotherapy	One cycle of blinatumomab	Achieved MRD-negative CR after cycle 1; remained in CR for 6 mo after initiation of therapy; CRS occurred on day 3
Alcharakh *et al.* (2016)	1	B/myeloid MPAL	Post-transplant marrow relapse	Five cycles of blinatumomab	Remained in CR 11 mo after diagnosis; skin aGVHD; no CNS toxicity or CRS
Khan *et al.* (2016)	1	B-ALL	Post-transplant marrow relapse	Two cycles of blinatumomab	Remained in CR with 100% donor chimerism for 8 mo after HSCT; nausea, diarrhea, increased LFTs after 2 cycles of blinatumomab suggesting GVHD
El Chaer *et al.* (2018)	2	B/myeloid MPAL with t(9;22)	Patient 1: MRD-positive CR after multi-chemotherapy including dasatinib	One cycle of blinatumomab followed by allo-SCT	Remained in CR 6 months after diagnosis; no CRS or neurological toxicity; undetectable MRD after cycle 1
		B/myeloid MPAL	Patient 2: MRD-negative CR	Induction chemotherapy was held due to AEs. Three cycles of blinatumomab followed by allo-SCT	Remained in MRD-negative CR 14 months after diagnosis
Present case	1	B/myeloid MPAL	Post-transplant marrow relapse	Cycle 1: Blinatumomab Cycles 2, 3 & 4: Blinatumomab + DLI	Achieved MRD-negative CR after one cycle of blinatumomab; remained in CR 15 months after marrow relapse; extramedullary disease after fourth cycle

AE: Adverse event; aGVHD: Acute graft-versus-host disease; ALL: Acute lymphoblastic leukemia; CNS: Central nervous system; CR: Complete remission; CRS: Cytokine release syndrome; CT: Chemotherapy; DLI: Donor lymphocyte infusion; mo: month; MPAL: Mixed phenotype acute leukemia; MRD: Minimal residual disease; N: Total number of patients.

Blinatumomab, a bispecific CD19-directed CD3 T-cell engager, is a US FDA-approved drug for relapse and/or refractory (R/R) CD19 expressing B-ALL [16,17]. Blinatumomab may augment the efficacy of donor T lymphocyte when given concomitantly with DLI and enhance anti-leukemic activity [18]. Currently, blinatumomab and its combination with different regimens (chemotherapy, monoclonal antibodies or other immunotherapies) have been evaluating in several clinical trials for patients with $CD19^+$ MPAL (NCT03643276, NCT02879695, NCT03541083). To build the body of knowledge about this combined therapy, we present a case of relapsed MPAL safely treated with blinatumomab and donor lymphocyte infusion following allo-HSCT.

Methods

Search strategy

A comprehensive literature search was performed using PubMed, EMBASE, Web of Science and Cochrane Central Register of Controlled Clinical Trials (CENTRAL) database up to 24 December 2018. MeSH terms and keywords of blinatumomab, donor lymphocyte infusion (DLI), mixed phenotype acute leukemia, B/myeloid subtype, acute leukemia were used. After removal of irrelevant and duplicated publications, eight articles (n = 21 patients) were selected for inclusion in this review. Cases were summarized in Table 1. Two abstracts (n = 11) were not included in the table as they had limited information. Those were mentioned in the discussion section.

Case presentation

A 51-year-old Caucasian female was diagnosed with B-cell/myeloid MPAL when she presented with the complaints of fatigue, muscle pain, cramping, headaches, decreased appetite and cough of 2-week duration in September 2015. Routine laboratory tests showed severe anemia, and peripheral blood revealed 27% circulating blast cells on a peripheral blood smear. The blasts were positive for CD4, CD14, TdT, MPO, CD10, CD19, sCD22, CD34,

cCD79a and negative for CD2, CD3, CD5, CD7, CD13, CD20 and CD33. The bone marrow aspiration and biopsy showed a 90% marrow cellularity, a myeloid erythroid ratio (M:E) 14.04, megakaryocytes 0.9/high power field with abnormal cytogenetics 45,XX,del(9)(p21),-20(11)/ 46,XX,del(9),del(20)(q11.1). She was treated with the Southwestern Oncology Group (SWOG) Phase III trial protocol (E1910), randomized to chemotherapy-only arm, and achieved complete remission (CR1) by day 27 of remission induction therapy. During her CR1, in April 2016, she underwent 10/10 HLA-matched unrelated donor peripheral stem cell infusion (MUD-PBSCT) with myeloablative conditioning with cyclophosphamide (60 mg/kg on day-6, -5) and total body irradiation (200 cGY b.i.d. day-3, -2, -1). Graft-versus-host disease (GvHD) prophylaxis included rabbit anti-thymocyte globulin (thymoglobulin) (25 mg iv. on day -3; 2 mg/kg on days -2, -1 and +2), cyclosporine and low dose methotrexate. Bone marrow biopsy performed at day 31 post-transplantation was negative for any morphologic or immunophenotypic evidence of leukemia and the patient had 100% donor chimerism. For transplantation, CD34+ cell dose was 5.07×10^6/kg. 3 months following allogenic stem cell transplantation, the patient relapsed with mixed phenotype acute leukemia with 63.2% blasts and 90% cellularity on bone marrow biopsy. Therapy was started with a combination of blinatumomab and DLI. Blinatumomab was administered as described [19]. Intrathecal chemotherapy with methotrexate (12 mg) was given during the treatment. After one cycle of blinatumomab, the patient achieved complete hematologic remission (CR2) and 100% donor chimerism with no detectable minimal residual disease (MRD). No evidence of cytogenetic abnormality was detected. The first dose of DLI (1×10^7/kg CD3+ cells) was administered during cycle 2 of blinatumomab (28 mcg) without adverse events. The patient received two additional cycles of DLI (3×10^7/kg CD3+ cells) with cycles 3 and 4 of blinatumomab. Shortly after the completion of cycle 4, the patient started having neurologic symptoms with urinary retention and weakness in bilateral legs for 2 days. An MRI showed a large enhancing soft tissue lesion within the dorsal and left lateral epidural space (from T3 to T7), with extension into the left prevertebral space consistent with relapse and tumor infiltration. She underwent a laminectomy and a biopsy was consistent with extramedullary involvement of the patient's known B/myeloid mixed lineage acute leukemia. Blinatumomab and DLI therapy was stopped and the patient was treated with 15 fractions of radiation therapy, followed by five cycles of hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (hyper-CVAD) salvage regimen with intrathecal cytarabine and methotrexate. The patient continued morphologic, flow cytometric and molecular marrow CR for 14.6 months after hematologic relapse. Written and verbal informed consent was obtained from the patient for this study.

Discussion

We report a case of relapsed B-cell/myeloid mixed-phenotype acute leukemia treated successfully with blinatumomab and DLI combination therapy. To date, there have been no reports of B-cell/myeloid MPAL treated with this combination therapy. As a limitation of our study, data on chimerism at the time of relapse were not available before starting blinatumomab.

An optimal treatment for MPAL has not been well established because of the lack of randomized studies [20]. There is still ongoing controversy over whether ALL- or AML-type regimen should be used for MPAL patients [21]. Based on the limited published data, ALL type regimen followed by allogeneic stem-cell transplant may be recommended. However, research into the role of targeted therapies in MPAL is needed.

Blinatumomab, an FDA-approved drug, is one of the promising targeted therapies that demonstrated effectiveness in improving outcomes of the patients with relapsed and/or refractory B-ALL [19,22,23]. DLI has limited benefit in treating relapsed ALL [24,25]. There are lack of data regarding the use of blinatumomab and DLI combination therapy in patients with MPAL.

Recently, El Chaer *et al.* reported two patients with $CD19^+$ B/myeloid MPAL treated with blinatumomab [26]. Patient 1 who had t(9;22) received blinatumomab due to MRD positivity by flow cytometry at the end of induction therapy with cytarabine, daunorubicin and daily dasatinib. Mild hypercellularity and 2% regenerating blasts were observed in bone marrow after one cycle of blinatumomab, and MRD was not detected by flow cytometry or by PCR. The patient achieved MRD-negative status after receiving blinatumomab with dasatinib. After one cycle of blinatumomab, the patient received allo-HSCT and remained in CR 6 months after diagnosis. Patient 2 received induction therapy with hyper-CVAD after diagnosis of B/myeloid MPAL. Day 27 BMBx showed no blasts, and MRD was negative by flow cytometry. Due to the adverse events observed with induction therapy, treatment was switched to blinatumomab. The patient received three cycles of blinatumomab. During CR1, the patient underwent allo-HSCT and remained in CR with negative MRD for 14 months after diagnosis. No blinatumomab-related toxicities were observed in both patients.

Similarly, previous report on the use of blinatumomab as a salvage treatment in a 45-year-old patient with post-transplant relapsed MPAL showed that patient achieved CR after completion of fifth cycle of blinatumomab without significant complications and remained in CR for 11 months after the initiation therapy (Table 1) [27].

In 2016, Ueda *et al.* published the first study on the use of blinatumomab and DLI in four patients with relapsed B-ALL after allogeneic HSCT [18]. DLI was co-administered with blinatumomab during the second or later cycles of blinatumomab. Methotrexate and low-dose tacrolimus (0.5 mg) were used as GvHD prophylaxis. Patient 1 with abnormal cytogenetics for del(*12p*) showed complete remission (CR) with MRD-negative status after two cycles of blinatumomab. After third and fourth cycles of dual therapy, cytogenetic remission was achieved. Grade I acute skin GvHD was reported before the first combination therapy. Extramedullary relapse ($CD19^+$ sacral mass and $CD19^-$ lung mass) and hematologic relapse with circulating blasts were reported 6 and 11 months after initiating blinatumomab, respectively. Patient 2 with hyperdiploidy achieved normal cytogenetics and nondetectable disease by flow cytometry after two cycles of blinatumomab (cycles 1 and 2) and continued CR for 13 months. Grade III late-onset acute skin and gut GvHD were reported after cycle 3 of dual therapy that resolved after a short course of low dose steroids and higher tacrolimus dose. Patient 3 remained in CR with MRD-negative status for 7 months after one cycle of dual therapy (cycle 3). It should be noted that patient 2 and 3 had marrow MRD-positive status when blinatumomab therapy was started. Patient 4 had isolated central nervous system (CNS) relapse in the cerebral spinal fluid and orbit following allo-HSCT treated with intrathecal chemotherapy and radiation. Blinatumomab was started after CNS treatment. Despite the combination therapy, the patient's extramedullary disease (lung, thorax, liver, bone and pericardium) progressed. CNS prophylaxis with intrathecal or systematic chemotherapy is warranted in ALL patients when considering the poor prognosis of CNS relapse with a median overall survival of 6 months [28]. In a study including ten post-transplant relapsed B-ALL patients receiving blinatumomab and DLI, higher response rates were reported with the combination therapy compared with blinatumomab monotherapy (70 vs 54%) [29]. One patient developed grade II acute GvHD after the dual therapy. Another one patient experienced grade I acute GvHD before DLI. No fatal toxicity was observed. Median two cycles of blinatumomab were administered, ranging from one to seven cycles. Total cycles of DLI and the doses were not provided.

Several reports have also supported the effectiveness of blinatumomab for the patients with B-ALL (Table 1) [30–32]. The case study using blinatumomab and DLI after the second allo-HSCT for a patient with precursor B-ALL demonstrated that the patient achieved MRD-negative CR 7 months after initiating blinatumomab without extramedullary relapse or blinatumomab-related toxicities [33]. DLI were administered using a dose-escalation protocol. After the second cycle of DLI, the patient developed overlap GvHD involving mouth and skin and systemic steroids were initiated due to progression of GvHD. The longest disease-free interval was reported with this combination therapy compared with the previous multi chemotherapies.

Conclusion

In this report, we describe the efficacy of blinatumomab and DLI in the treatment of B/Myeloid MPAL, a rare type of acute leukemia. Currently, there is no consensus on what is the optimal treatment strategy for MPAL. Dual blinatumomab and DLI therapy appears to be safe and promising in our patient who achieved MRD-negative clinical remission with this unique combination therapy. However, large prospective and multicenter studies are required to further investigate the safety and efficacy of this therapy and to compare this promising combination with the novel and existing agents in the appropriate setting.

Summary points

- There is no optimal treatment regimen for mixed phenotype acute leukemia. Acute lymphoblastic leukemia-based therapies may be used in this setting.
- Blinatumomab and donor lymphocyte infusion (DLI) combination therapy is a promising new concept in cancer therapy, whereby blinatumomab might achieve an initial reduction in leukemic cell burden using T cells, and after tumor clearance, DLI can potentially stimulate the donor immune system to achieve longer lasting remission.
- We present a case of relapsed mixed phenotype acute leukemia safely treated with combination therapy of blinatumomab and DLI which resulted in longer complete remission when compared with preceding allogeneic hematopoietic stem cell transplantation with chemotherapy.
- Large prospective studies are needed to determine the safety and efficacy of this promising combination therapy.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Informed consent

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

Authorship statement

All authors designed the study and wrote the paper.

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