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A Case of Daratumumab-Induced Significant Decrease in Donor-Specific HLA Antibodies and Remission Induction Before Haploidentical Stem Cell Transplantation in a Refractory B-ALL Patient

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Abstract

Objective: To explore the method of eliminating donor-specific anti-HLA antibodies (DSA) in haploidentical stem cell transplantation (haplo-SCT). **Methods:** We present a refractory B-cell acute lymphoblastic leukemia (ALL) patient who had strongly positive DSA, but had no human leukocyte antigen–matched donor. Although CD38 expression on leukemia cells was negative, daratumumab combined with etoposide and venetoclax therapy was chosen for her. **Results:** She achieved a significant decrease in DSA levels and complete remission on the combination therapy with daratumumab. She then received a haplo-SCT from a daughter as a donor and had a successful engraftment of donor stem cell. In haplo-SCT, strongly positive DSA levels, directed against donor HLA antigens, could be significantly reduced by daratumumab therapy before transplantation and successfully bridge subsequent haplo-SCT. **Conclusion:** Although CD38 expression is negative in leukemia cells, refractory B-ALL patients may still benefit from combination therapy with daratumumab. We need further clinical observation.

Keywords

acute lymphoblastic leukemia, haploidentical stem cell transplantation, donor-specific anti-HLA antibodies, daratumumab

Introduction

Acute lymphoblastic leukemia (ALL) is a highly heterogeneous disease with a high risk of relapse, mainly due to high-risk cytogenetic abnormalities[1–3]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT), especially the human leukocyte antigen (HLA)-matched sibling donors (MSDs) and matched unrelated donors (MUDs), is an important option for the prevention of ALL recurrence[4]. The limited availability of MSDs and MUDs limits the acceptance of allo-HSCT for ALL patients[5]. Haploidentical stem cell transplantation (haplo-SCT) has become an important alternative approach for such patients[6,7]. However, the donor-specific anti-HLA antibodies (DSA) are considered an important barrier for the successful engraftment of donor stem cell. Identification of DSA is one of the important causes of primary graft failure (PGF) in haplo-SCT and other types of HLA-mismatched donor transplantation[8–10]. These antibodies are considered to have a weak to low level of mean fluorescence intensity (MFI) if the values range from 1,000 to 3,000; moderate-level MFI, values from 3,000 to 5,000; and strong-level MFI, values >5,000[11].

Several desensitization strategies have been used to decrease the total antibody load of DSA to reduce the risk of

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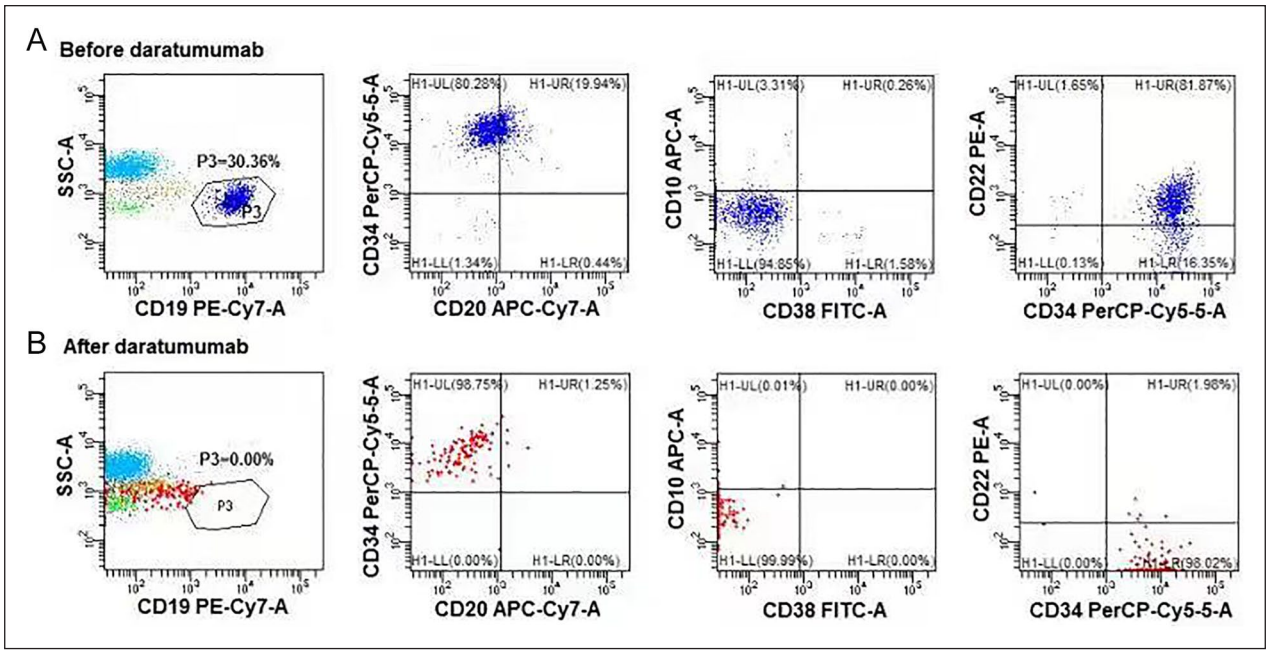

Figure 1. Immunophenotype of leukemia cells by FCM before and after combination therapy with daratumumab. (A) Before daratumumab: Malignant B lymphocytes characterized as CD19+CD22+CD34+CD10dim and CD20−CD38− by FCM. (B) After daratumumab: She achieved CR with CD19−CD22−CD34+CD10−CD20−CD38− by FCM. FCM: flow cytometry; CR: complete remission.

PGF: plasmapheresis or immunoabsorption, monoclonal antibody to CD20+ B lymphocytes (rituximab), inhibitors against antibody-producing plasma cells (bortezomib), intravenous immunoglobulins, donor HLA antigen (platelet or white blood cell) infusions, and inhibition of complement cascade[12]. These desensitization strategies have been used in solid organ transplantation and allo-HSCT[13–15]. They improved the risk of PGF and the survival rate of patients in transplantation of partially mismatched hematopoietic stem cell donors.

Here we present a patient with refractory B-cell ALL, with strongly positive DSA levels, directed against donor HLA antigens. Before her haplo-SCT, we chose daratumumab combined with chemotherapy for this patient, and she achieved a significant decrease in DSA levels and complete remission (CR).

Medical History Presentation

A 36-year-old female patient was diagnosed with common B-cell ALL. After one course of VDCLP (vincristine, daunorubicin, cyclophosphamide, L-asparaginase, and prednisolone), two cycles of CAM (cyclophosphamide, cytarabine, and 6-mercaptopurine), and two courses of high-dose methotrexate combined with venetoclax chemotherapy, her disease did not achieve CR with 30.36% leukemia cells in the bone marrow (BM) by flow cytometry (FCM) (Fig. 1A). Except for a daughter haploid donor, she had no sibling donor and HLA-matched or HLA-mismatched unrelated donor for her allo-HSCT. Unfortunately, strong MFI level values were found in her DSA test (immunomagnetic beads liquid chip technology) (Table 1). In addition, her ABO blood group could not be detected because of the loss of erythrocyte antigen expression.

Although CD38 expression on leukemia cells was negative, daratumumab (16 mg/kg) combined with etoposide and venetoclax therapy was chosen for her. After one cycle of combination therapy, she achieved CR with a significant decrease in DSA levels (Fig. 1B, Table 1). At the same time, her erythrocyte antigen expression recovered, and her ABO blood group could be detected. After a second course of the same combination therapy, the DSA levels remained low and stable (Table 1); consequently, she was prepared to receive haplo-SCT from her daughter as a donor.

To further reduce DSA levels, she received corticosteroids (40 mg/day, from day -7 to day 0) and high-dose immunoglobulin (0.5 g/kg, on day −2, −1) before allo-HSCT. She did not receive plasmapheresis prior to haplo-SCT because of insufficient plasma; in addition, she did not receive rituximab because she had contracted pneumonia during the previous combination chemotherapy. The myeloablative conditioning regimen included total body irradiation (3 Gy/day, for 3 days), cyclophosphamide, fludarabine, and cytarabine. Graft-versus-host disease prophylaxis consisted of antithymocyte globulin, cyclosporin A, and mycophenolate mofetil. The dose of CD34+ cells from the donor was 4.81×10^6 cells/kg and the dose of CD3+ T cells from the donor was 7.12×10^8 cells/kg. On the day of the donor stem cell

Table 1. Change in DSA Levels After Daratumumab Therapy.

	Age	HLA-A	HLA-B	HLA-C	HLA-DR	HLA-DQ
Patient (mother)	36	01:01,02:01	08:01,35:01	07:02,03:03	15:02,15:01	05:01,06:02
Donor (daughter)	13	01:01,**32:01**	08:01,**52:01**	07:02,12:02	15:02,**04:05**	05:01,04:01
Molecular specificity	Specificity	Before therapy	After first therapy	After second therapy	Day 0 (immunoglobulin)	Day 7
HLA-I (MFI)						
A*32:01	A32	19,138.89	10,256.38	10,640.21	12,144.49	Negative
B*52:01	B52	16,160.91	8,482.32	7,455.16	8,721.4	Negative
HLA-II (MFI)						
DRB 1*04:04	DR4	19,606.25	12,341.13	9,289.78	8,258.89	Negative
DRB 1*04:01	DR4	19,131.51	11,638.18	9,386.64	8,682.2	Negative
DRB 1*04:03	DR4	16,333.14	9,105.7	7,601.77	7,239.81	Negative
DRB 1*04:05	DR4	15,719.31	8,961.4	6,366.44	6,141.03	Negative
DRB 1*04:02	DR4	14,776.56	7,920.72	7,103.39	6,332.34	Negative

DSA: donor-specific anti-HLA antibodies; HLA: human leukocyte antigen; Immunoglobulin: intravenous immunoglobulin, 1g/kg; MFI: mean fluorescence intensity of microbead reaction. The bold-faced indicates a different match between the patient and the donor.

infusion, her DSA levels continued to decline to negative (Table 1). She achieved minimal residual disease (MRD)-negative Cri by FCM at 14 days after haplo-SCT, while the donor chimerism according to short-tandem repeat was 98.12% at 14 days and 100.00% at 28 days after haplo-SCT. Her BM was myelodysplastic at 14 days and hyperplastic 28 days after haplo-SCT. Moreover, her neutrophils and platelets were engrafted 17 and 21 days after haplo-SCT, respectively. The DNA copies of Epstein–Barr virus (EBV) and cytomegalovirus (CMV) in the blood measured by quantitative polymerase chain reaction were monitored weekly after haplo-SCT. She received intrathecal chemotherapy to prevent central nervous system leukemia monthly after haplo-SCT. Thereafter, the MRD-negative status in the BM, full donor chimerism in the BM, negativity of EBV, and CMV DNA copies in the peripheral blood were maintained for 90 days.

Discussion

In our study, the patient with refractory B-ALL achieved a significant decrease in DSA levels and CR with the combination therapy of daratumumab, etoposide, and venetoclax. She then received a haplo-SCT from a daughter as a donor and had a successful engraftment of donor stem cells. This patient benefited from daratumumab in two ways. (1) Her strongly positive DSA levels directed against donor HLA antigens achieved a significant decrease. (2) Although the leukemia cells had CD38-negative expression, this refractory B-ALL patient achieved CR.

It was an important cause of PGF in the following haplo-SCT because of an association between DSA-positivity and PGF in the haplo-SCT noted in the previous studies[15–18]. In a study of 122 haplo-SCT recipients[15], the incidence of DSA-positivity was 18%, and PGF occurred in 32% of the DSA-positive recipients and in only 4% of DSA-negative recipients. Compared with DSA-negative recipients, the time of haploid stem cell engraftment was significantly delayed in DSA-positive recipients (18 vs 19 days). Desensitization strategies to decrease the antibody load of DSA, including plasmapheresis, rituximab, bortezomib, intravenous immunoglobulin, and donor HLA antigen infusion, have been suggested in DSA-positive recipients[11]. However, the results of these desensitization strategies have only been published in some case reports or small studies[13–15].

Daratumumab is a human monoclonal antibody that binds to CD38-expressing cells; it has been used in the treatment of relapsed multiple myeloma[19,20]. Daratumumab targeting plasma cells that express the protein CD38, a type II transmembrane glycoprotein, may be an effective method of plasma cell depletion, which promotes desensitization. In one study, daratumumab significantly reduced anti-HLA antibodies and anti-HLA DSA in animal models, and in two transplant clinical patients before and after solid organ transplantation[21]. In the field of solid organ transplantation, daratumumab has also been used in solid organ transplant candidates to decrease allosensitization, to counteract antibody-mediated rejection (AMR), and to allow solid organ transplantation[21–24]. Nevertheless, in allo-HSCT, especially haplo-SCT, daratumumab was used to treat immune dysregulation induced by incomplete immune recovery following allo-HSCT. This includes warm autoimmune hemolytic anemia, refractory cold agglutinin disease, Evans syndrome, and pure red cell aplasia following allo-HSCT[25–28]. However, studies of allo-HSCT in hematologic malignancy, which are similar and show reduction in anti-HLA antibodies and anti-HLA DSA by daratumumab in solid organ transplant candidates, have not been reported.

Despite CD38-negative expression in her leukemia cells, this patient with refractory B-ALL achieved CR on the

combination therapy with daratumumab. In a preclinical study, the protein CD38 on leukemic cells was demonstrated to be expressed at varying degrees in 37 acute myeloid leukemia (AML) and 12 T-cell ALL patients, who were newly diagnosed[29]. It has also been indicated that daratumumab is significantly effective in a T-ALL patient-derived xenograft (PDX) model and in AML-PDX[29,30]. Some case reports have indicated that daratumumab is effective in relapsed/refractory T-ALL patients[31,32]. However, treatment with daratumumab in relapsed/refractory B-ALL was only reported in one case report[33]. In our refractory B-ALL patient, why is the combination therapy with daratumumab effective in the state of CD38-negative expression in leukemia cells, despite having received venetoclax therapy before?

Conclusion

In haplo-SCT recipients, daratumumab therapy before transplantation could significantly reduce strongly positive DSA levels directed against donor HLA antigens and successfully bridge subsequent haplo-SCT. Whether refractory B-ALL patients might still benefit from combination therapy with daratumumab despite negative CD38 expression in their leukemia cells still need further clinical observation and investigation.

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Authors Contributions

Concept and design: DQ and ZXL.
Drafted or revised the manuscript: LX.
Acquisition of data: ZHB and ST.
Writing, review, and/or revision of manuscript: DQ.

Ethical Approval and Consent to Participate

The patient agreed to the use of her specimens and data for our study in accordance with the Declaration of Helsinki.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

Declaration of Conflicting Interests

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References

1. Chiaretti S, Vitale A, Cazzaniga G, Orlando SM, Silvestri D, Fazi P, Valsecchi MG, Elia L, Testi AM, Mancini F, Conter V, et al. Clinico-biological features of 5202 patients with acute lymphoblastic leukemia enrolled in the Italian AIEOP and GIMEMA protocols and stratified in age cohorts. Haematologica. 2013;98(11):1702–10.
2. Lafage-Pochitaloff M, Baranger L, Hunault M, Cuccuini W, Lefebvre C, Bidet A, Tigaud I, Eclache V, Delabesse E, Bilhou-Nabéra C, Terré C, et al. Impact of cytogenetic abnormalities in adults with Ph-negative B-cell precursor acute lymphoblastic leukemia. Blood. 2017;130(16):1832–44.
3. Giebel S, Marks DI, Boissel N, Baron F, Chiaretti S, Ciceri F, Cornelissen JJ, Doubek M, Esteve J, Fielding A, Foa R, et al. Hematopoietic stem cell transplantation for adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission: a position statement of the European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant. 2019;54(6):798–809.
4. Cornelissen JJ, van der Holt B, Verhoef GE, van't Veer MB, van Oers MH, Schouten HC, Ossenkoppele G, Sonneveld P, Maertens J, van Marwijk Kooy M, et al. Myeloablative allogeneic versus autologous stem cell transplantation in adult patients with acute lymphoblastic leukemia in first remission: a prospective sibling donor versus no-donor comparison. Blood. 2009;113(6):1375–82.
5. Aljurf M, Weisdorf D, Alfraih F, Szer J, Müller C, Confer D, Hashmi S, Kröger N, Shaw BE, Greinix H, Kharfan-Dabaja MA, et al. Worldwide network for Blood & Marrow Transplantation (WBMT) special article, challenges facing emerging alternate donor registries. Bone Marrow Transplant. 2019;54(8):1179–88.
6. Metheny L, de Lima M. Hematopoietic stem cell transplant with HLA-mismatched grafts: impact of donor, source, conditioning, and graft versus host disease prophylaxis. Expert Rev Hematol. 2019;12(1):47–60.
7. Yang B, Yu R, Cai L, Bin Guo, Chen H, Zhang H, He P, Lu X. Haploidentical versus matched donor stem cell transplantation for patients with hematological malignancies: a systemic review and meta-analysis. Bone Marrow Transplant. 2019;54(1):99–122.
8. Luznik L, O'Donnell PV, Symons HJ, Chen AR, Leffell MS, Zahurak M, Gooley TA, Piantadosi S, Kaup M, Ambinder RF, Huff CA, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biol Blood Marrow Transplant. 2008;14(6):641–50.
9. Ciurea SO, Mulanovich V, Jiang Y, Bassett R, Rondon G, McMannis J, de Lima M, Shpall EJ, Champlin RE. Lymphocyte recovery predicts outcomes in cord blood and T cell-depleted haploidentical stem cell transplantation. Biol Blood Marrow Transplant. 2011;17(8):1169–75.
10. Ciurea SO, Saliba R, Rondon G, Pesoa S, Cano P, Fernandez-Vina M, Qureshi S, Worth LL, McMannis J, Kebriaei P,

Jones RB, et al. Reduced-intensity conditioning using fludarabine, melphalan and thiotepa for adult patients undergoing haploidentical SCT. Bone Marrow Transplant. 2010;45(3): 429–36.
11. Gladstone DE, Bettinotti MP. HLA donor-specific antibodies in allogeneic hematopoietic stem cell transplantation: challenges and opportunities. Hematology. 2017;1:645–50.
12. Ciurea SO, Cao K, Fernandez-Vina M, Kongtim P, Malki MA, Fuchs E, Luznik L, Huang XJ, Ciceri F, Locatelli F, Aversa F, et al. The European Society for Blood and Marrow Transplantation (EBMT) consensus guidelines for the detection and treatment of donor specific anti-HLA antibodies (DSA) in haploidentical hematopoietic cell transplantation. Bone Marrow Transplant. 2018;53(5):521–34.
13. Baran DA, Lubitz S, Alvi S, Fallon JT, Kaplan S, Galin I, Correa R, Courtney MC, Chan M, Spielvogel D, Lansman SL, et al. Refractory humoral cardiac allograft rejection successfully treated with a single dose of rituximab. Transplant Proc. 2004;36(10):3164–66.
14. Everly JJ, Walsh RC, Alloway RR, Woodle ES. Proteasome inhibition for antibody-mediated rejection. Curr Opin Organ Transplant. 2009;14(6):662–66.
15. Ciurea SO, Thall PF, Milton DR, Barnes TH, Kongtim P, Carmazzi Y, López AA, Yap DY, Popat U, Rondon G, Lichtiger B, et al. Complement-binding donor-specific anti-HLA antibodies and risk of primary graft failure in hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2015;21(8):1392–98.
16. Yoshihara S, Maruya E, Taniguchi K, Kaida K, Kato R, Inoue T, Fujioka T, Tamaki H, Ikegame K, Okada M, Soma T, et al. Risk and prevention of graft failure in patients with preexisting donor-specific HLA antibodies undergoing unmanipulated haploidentical SCT. Bone Marrow Transplant. 2012;47(4):508–15.
17. Ciurea SO, de Lima M, Cano P, Korbling M, Giralt S, Shpall EJ, Wang X, Thall PF, Champlin RE, Fernandez-Vina M. High risk of graft failure in patients with anti-HLA antibodies undergoing haploidentical stem-cell transplantation. Transplantation. 2009;88(8):1019–24.
18. Chang YJ, Zhao XY, Xu LP, Zhang XH, Wang Y, Han W, Chen H, Wang FR, Mo XD, Zhang YY, Huo MR, et al. Donor-specific anti-human leukocyte antigen antibodies were associated with primary graft failure after unmanipulated haploidentical blood and marrow transplantation: a prospective study with randomly assigned training and validation sets. J Hematol Oncol. 2015;8:84.
19. Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, Minnema MC, Lassen U, Krejcik J, Palumbo A, van de Donk NW, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. N Engl J Med. 2015;373(13):1207–19.
20. Van de Donk NWCJ, Pawlyn C, Yong KL. Multiple myeloma. Lancet. 2021;397(10272):410–27.
21. Kwun J, Matignon M, Manook M, Guendouz S, Audard V, Kheav D, Poullot E, Gautreau C, Ezekian B, Bodez D, Damy T, et al. Daratumumab in sensitized kidney transplantation: potentials and limitations of experimental and clinical use. J Am Soc Nephrol. 2019;30(7):1206–19.
22. Doberer K, Kläger J, Gualdoni GA, Mayer KA, Eskandary F, Farkash EA, Agis H, Reiter T, Reindl-Schwaighofer R, Wahrmann M, Cohen G, et al. CD38 antibody daratumumab for the treatment of chronic active antibody-mediated kidney allograft rejection. Transplantation. 2021;105(2):451–57.
23. Matignon M, Joher N. Desensitization in kidney allograft recipients before transplantation using daratumumab. clinicaltrials.gov France: Créteil. 2020. https://clinicaltrials.gov/ct2/show/NCT04204980 [accessed 2022 Oct 6].
24. Witteles R. A phase 1 study of daratumumab for reduction of circulating antibodies in patients with high allosensitization awaiting heart transplantation. clinicaltrials.gov. 2020. https://clinicaltrials.gov/ct2/show/NCT04088903 [accessed 2022 Oct 6].
25. Schuetz C, Hoenig M, Moshous D, Weinstock C, Castelle M, Bendavid M, Shimano K, Tolbert V, Schulz AS, Dvorak CC. Daratumumab in life-threatening autoimmune hemolytic anemia following hematopoietic stem cell transplantation. Blood Adv. 2018;2(19):2550–53.
26. Tomkins O, Berentsen S, Arulogun S, Sekhar M, D'Sa S. Daratumumab for disabling cold agglutinin disease refractory to B-cell directed therapy. Am J Hematol. 2020;95(10):E293–95.
27. Blennerhassett R, Sudini L, Gottlieb D, Bhattacharyya A. Post-allogeneic transplant Evans syndrome successfully treated with daratumumab. Br J Haematol. 2019;187(2): e48–51.
28. Chapuy CI, Kaufman RM, Alyea EP, Connors JM. Daratumumab for delayed red-cell engraftment after allogeneic transplantation. N Engl J Med. 2018;379(19):1846–50.
29. Naik J, Themeli M, de Jong-Korlaar R, Ruiter RWJ, Poddighe PJ, Yuan H, de Bruijn JD, Ossenkoppele GJ, Zweegman S, Smit L, Mutis T, et al. CD38 as a therapeutic target for adult acute myeloid leukemia and T-cell acute lymphoblastic leukemia. Haematologica. 2019;104(3):e100–103.
30. Bride KL, Vincent TL, Im SY, Aplenc R, Barrett DM, Carroll WL, Carson R, Dai Y, Devidas M, Dunsmore KP, Fuller T, et al. Preclinical efficacy of daratumumab in T-cell acute lymphoblastic leukemia. Blood. 2018;131(9):995–99.
31. Ofran Y, Ringelstein-Harlev S, Slouzkey I, Zuckerman T, Yehudai-Ofir D, Henig I, Beyar-Katz O, Hayun M, Frisch A. Daratumumab for eradication of minimal residual disease in high-risk advanced relapse of T-cell/CD19/CD22-negative acute lymphoblastic leukemia. Leukemia. 2020;34(1):293–95.
32. Fulcher J, Berardi P, Christou G, Villeneuve PJA, Bredeson C, Sabloff M. Nelarabine-containing regimen followed by daratumumab as an effective salvage therapy and bridge to allogeneic hematopoietic stem cell transplantation for primary refractory early T-cell precursor lymphoblastic leukemia. Leuk Lymphoma. 2021;62(9):2295–97.
33. Voruz S, Blum S, de Leval L, Schoumans J, Solly F, Spertini O. Daratumumab and venetoclax in combination with chemotherapy provide sustained molecular remission in relapsed/refractory CD19, CD20, and CD22 negative acute B lymphoblastic leukemia with KMT2A-AFF1 transcript. Biomark Res. 2021;9(1):92.