Inotuzumab ozogamicin and blinatumomab sequential therapy for relapsed/refractory Philadelphia chromosome-positive acute lymphoblastic leukemia

Tomoaki Ueda, Kentaro Fukushima, Shinsuke Kusakabe, Koki Yoshida, Makiko Suga, Ritsuko Nakai, Midori Koike, Akihisa Hino, Keigo Akuta, Jun Toda, Yasuhiro Nagate, Yukiko Doi, Jiro Fujita, Takafumi Yokota, Naoki Hosen

A R T I C L E   I N F O

Keywords:
Philadelphia chromosome-positive acute lymphoblastic leukemia
Allogeneic stem cell transplantation
Inotuzumab ozogamicin
Blinatumomab

A B S T R A C T

To overcome the unfavorable outcome of refractory/refractory (R/R) Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-ALL) and conduct allogeneic stem cell transplantation (allo-SCT) safely, we designed a sequential therapy involving a single cycle of Inotuzumab ozogamicin (InO) and Blinatumomab (Blina). Two heavily treated and aged patients with R/R Ph-ALL were treated with the therapy. Both of them achieved complete molecular remission without cytokine release syndrome and underwent allo-SCT without veno-occlusive disease/sinusoidal obstruction syndrome. Although appropriate central nervous system prophylaxis should be added, the InO-Blina sequential therapy is a promising strategy for treating R/R Ph-ALL as a bridging regimen before allo-SCT.

1. Introduction

Although Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-ALL) is a disease with an unfavorable prognosis, its outcomes have dramatically improved with the introduction of tyrosine kinase inhibitors (TKIs) [1]. Using TKI-containing regimens, most patients can achieve complete remission (CR) and undergo allogeneic stem cell transplantation (allo-SCT) in a controlled disease status, which should improve the outcome of Ph-ALL. Additionally, promising data from previous research on ponatinib plus hyper-CVAD indicate the possibility of curing patients without allo-SCT [2]. However, once patients lose and/or cannot achieve CR, the outcome is poor, mainly due to the salvage regimen’s insufficient efficacy.

Recently, several new drugs have been introduced as salvage regimens for refractory/refractory (R/R) ALL. Inotuzumab ozogamicin (InO) is a humanized CD22 monoclonal antibody conjugated to calicheamicin [3], which has been shown to achieve a higher frequency of CR than conventional chemotherapy for R/R ALL [4]. However, as continuous InO treatment increases the risk of veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) [5], the number of InO treatments should be minimized, especially for patients who are planning to undergo allo-SCT afterward. Blinatumomab (Blina) is a bispecific T cell-engager antibody construct that directs T cells to CD19+ cells [6]. Although the efficacy of Blina is partial and cytokine release syndrome (CRS) is problematic for untreated R/R ALL patients [7], Blina is optimal for treating R/R ALL patients after CR achievement because it can achieve or keep MRD negativity with a low frequency of CRS and other side effects common in single-agent immunotherapy [8]. To use the advantages of these two drugs and bridge to allo-SCT safely, we designed a sequential regimen with a single cycle of InO and Blina (InO-Blina) for R/R Ph-ALL. In this paper, we report two cases of R/R Ph-ALL that were successfully treated with InO-Blina as a bridging regimen before allo-SCT. Written informed consent has been obtained from the patients to administer this therapy and publish their information.
Fig. 1.

A

Case 1

| uBMT (FLU/MEL/TBI) | DLI | uPBSCT (FLU/BU/TBI) |
|--------------------|-----|---------------------|
| Ponatinib (mg)     |     |                     |
| 15                 | 30  |                     |

Blina: blinatumomab; BM: bone marrow; DLI: donor lymphocyte infusion; FISH: fluorescence in situ hybridization for evaluating BCR/ABL mutation; FLU: fludarabine; IT: intrathecal (methotrexate [MTX], cytarabine, dexamethasone); MEL: melphalan; PB: peripheral blood; qPCR: quantitative polymerase chain reaction for detecting major BCR/ABL mRNA; TBI: total body irradiation; uPBSCT: unrelated peripheral blood stem cell transplantation.

Clinical course of case 1.

12 20 23 27 40 (Months)

B

Case 2

| uBMT (FLU/MEL/TBI) |
|--------------------|
| Blina             |

Dasatinib (mg)

100

Blina: blinatumomab; BM: bone marrow; CNS: central nervous system; CSI: craniospinal irradiation; FLU: fludarabine; IT: intrathecal; MEL: melphalan; JALSG 202-O: JALSG ALL 202-O protocol; PB: peripheral blood; qPCR: quantitative polymerase chain reaction for detecting minor BCR/ABL mRNA; TBI: total body irradiation; uBMT: unrelated bone marrow transplantation.

Clinical course of case 2.

9 10 13 17 19 30 (Months)
2. Case 1

A 51-year-old Japanese man was diagnosed with Ph+ALL in 2018. He started induction therapy with imatinib and prednisone and then achieved hematological CR. However, he refused to continue treatment and dropped out. Three months later, he experienced hematologic relapse with a T315I point mutation; consequently, he received salvage therapy with hyper-CVAD/MA plus ponatinib and achieved cytogenetic CR with MRD positivity. Then, he received allogeneic bone marrow transplantation (allo-BMT) from an human leukocyte antigen (HLA) 8/8 allele-matched unrelated donor, conditioned by 150 mg/m² fludarabine (FLU), 140 mg/m² melphalan (MEL), and 3 Gy total body irradiation (TBI), followed by maintenance therapy with ponatinib. Unfortunately, he experienced hematological relapse eight months later and received two cycles of donor lymphocyte infusion (CD3⁴ cells: 1 × 10⁶ cells/kg and 1 × 10⁷ cells/kg). Although the tumor burden was not reduced in the bone marrow (BM) (blast 53.2%), the number of blasts in the peripheral blood (PB) was controlled. He then received a single cycle of InO (0.8 mg/m² on day 1 and 0.5 mg/m² on days 8 and 15) and achieved cytogenetic CR. He received two cycles of Blina (cycle 1: 9 μg on days 1–7 and 28 μg on days 8–28, cycle 2: 28 μg on days 1–28) without CRS. After two cycles of Blina, BM examination revealed MRD negativity, although he did not experience severe side effects and maintained good performance status (PS=0) . Two weeks after the second cycle of Blina, he started conditioning chemotherapy with 150 mg/m² fludarabine (FLU), 9.6 mg/kg busulfan, and 3 Gy TBI and received allogeneic peripheral blood stem cell transplantation from a HLA 8/8 allele-matched unrelated donor. He did not experience VOD/SOS and maintained complete molecular remission (CMR) for more than one year (Figure 1A).

3. Case 2

A 67-year-old Japanese man was diagnosed with Ph+ALL in 2018. He started induction chemotherapy according to the regimen described by the JALSG ALL202-O protocol [1], followed by hyper-CVAD/MA plus ponatinib [2], and achieved CR. After three cycles of hyper-CVAD/MA plus ponatinib, the copy number of minor BCR/ABL mRNA was elevated. The regimen was switched to miniMEC; however, the disease progressed. We then started the JALSG ALL202-O induction regimen [1] plus dasatinib because the patient did not have a T315I point mutation. Although he did not achieve CR, the tumor burden was reduced (BM blast 87.0%→29.3%, PB blast 5967/μL→0/μL). Next, we started InO as a salvage regimen. After a single cycle of InO (0.8 mg/m² on day 1 and 0.5 mg/m² on days 8 and 15), the number of leukemia cells was dramatically reduced, and CR was achieved with small MRD (8.7 copies/μg RNA) and no severe side effects. We then switched to Blina, conducted one cycle (9 μg on days 1–7 and 28 μg on days 8–28), and the patient achieved CR. No severe side effects, including CRS, were observed, and his PS was maintained (PS=0). Immediately after the last dose of Blina, he started conditioning chemotherapy with 150 mg/m² FLU, 100 mg/m² MEL, and 3 Gy TBI, and then received allo-BMT from a HLA 7/8 allele-matched unrelated donor. He did not experience VOD/SOS.

4. Discussion

We conducted sequential therapy with InO-Blina for two R/R Ph+ALL patients and successfully achieved CR before allo-SCT. Case 1 was with T315I point mutation and post-allo-SCT relapse and case 2 involved an aged patient with chemo-TKI refractory disease. Despite being a single agent, InO has a significant anti-leukemic effect, with an 80.7% CR rate even for R/R ALL, and is more effective if the tumor burden is lower in BM and PB [4]. In our cases, partly because we reduced the number of blasts in peripheral blood before InO through prior therapies, both patients could successfully achieve CR with just one cycle of InO administration. Furthermore, both patients achieved and/or kept MRD negativity using Blina as a consolidation therapy and underwent allo-SCT while in the MRD-negative disease status, which is the most critical factor against relapse. From the perspective of safety, our InO-Blina sequential therapy also provides several benefits to the patients. First, because continuous treatment by InO is known to increase the occurrence of VOD/SOS after allo-SCT [5], our regimen could minimize the risk of VOD/SOS by administering only one cycle of InO. Second, we could avoid the event of CRS by using Blina during CR because the tumor burden is highly correlated with CRS [9]. Third, as InO and Blina are non-chemotherapeutic regimens, we could prevent the deterioration of the patients’ conditions and implement allo-SCT with a good PS, even though the patients were heavily treated and aged. However, because both InO and Blina may not pass through the blood-brain barrier, this regimen might be insufficient from the perspective of CNS prophylaxis. Moreover, the patient in case 2 experienced CNS relapse after unrelated BMT. Combination with sufficient cycles of IT and/or high-dose methotrexate/ cytarabine could overcome this problem. Moreover, if the patients are scheduled to receive CD19 chimeric antigen receptor T cell therapy, CD19 expression should be carefully examined because reduced CD19 expression sometimes occurs after Blina administration [10].

This is a case report; a larger-scale clinical trial is required to confirm the efficacy and safety of InO-Blina sequential therapy. The ongoing US Alliance for Clinical Trials in Oncology study A041703 for R/R Ph negative ALL patients (clinicaltrials.gov ID #NCT03739814) would be helpful in this respect.

In conclusion, the single-cycle InO and Blina sequential regimen would be effective and safe for R/R Ph+ALL as a bridging regimen before allo-SCT. Appropriate CNS prophylaxis should be added to prevent CNS relapse and maximize the advantages of the regimen.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None.

Acknowledgments

We would like to thank all clinicians and medical staff who contributed to the patients’ care.

References

[1] Y. Hatta, S. Mizuta, K. Matou, S. Ohtake, M. Iwana, S. Sugii, N. Doki, H. Kanamori, Y. Ueda, C. Yoshida, N. Dobashi, T. Maeda, T. Yujiri, F. Momma, Y. Ito, F. Hayakawa, J. Takeuchi, H. Kiyoi, Y. Miyazaki, T. Naoe, Final analysis of the JALSG Ph+ALL202 study: tyrosine kinase inhibitor-combined chemotherapy for Ph+ALL, Ann. Hematol. 97 (2018) 1535–1545, https://doi.org/10.1007/s00277-018-3323-8.
[2] E. Jabbour, N.J. Short, F. Ravandi, X. Huang, N. Daver, C.D. Niardro, M. Konopleva, N. Pemmaraju, W. Wierda, G. Garcia-Manero, K. Sasaki, J. Cortes, R. Garies, J.D. Khoury, J. Jorgensen, N. Jain, J. Alvarez, S. O’Brien, H. Kantarjian, Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: long-term follow-up of a single-centre, phase 2 study, Lancet Haematol 5 (2018) e618–e627, https://doi.org/10.1016/S2352-3026(18)30176-5.
[3] J.F. DiJoseph, D.C. Armellino, E.R. Boghaert, K. Khandke, M.M. Dougher, L. Sridharan, A. Kunz, P.R. Hamann, B. Gorovits, C. Udata, J.K. Moran, A. Poggeplewell, S. Stephens, P. Frost, N.K. Damle, Antibody-targeted chemotherapy with CMC-544: a CD22-targeted immunonoconjugate of calicheamicin for the

3
treatment of B-lymphoid malignancies, Blood 103 (2004) 1807–1814, https://doi.org/10.1182/blood-2003-07-2466.

[4] H.M. Kantarjian, D.J. DeAngelo, M. Stelljes, G. Martinelli, M. Liedtke, W. Stock, N. Gökbuget, S. O’Brien, K. Wang, T. Wang, M.L. Paccagnella, B. Sleight, E. Vandendries, A.S. Advani, Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia, N. Engl. J. Med. 375 (2016) 740–753, https://doi.org/10.1056/NEJMoa1509277, https://www.nejm.org/doi/10.1056/NEJMoa1509277.

[5] H.M. Kantarjian, D.J. DeAngelo, A.S. Advani, M. Stelljes, P. Kebriaei, R. D. Cassaday, A.A. Merchant, N. Fujishima, T. Uchida, M. Calbacho, A.A. Ejduk, S. M. O’Brien, E.J. Jabborov, H. Zhang, B.J. Sleight, E.R. Vandendries, D.I. Marks, Hepatic adverse event profile of inotuzumab ozogamicin in adult patients with relapsed or refractory acute lymphoblastic leukemia: results from the open-label, randomized, phase 3 INO-VATE study, Lancet Haematol 4 (2017) e387–e398, https://doi.org/10.1016/S2352-3026(17)30103-5.

[6] R. Bargou, E. Leo, G. Zugmaier, M. Klinger, M. Goebeler, S. Knop, R. Noppeney, A. Viardot, G. Hess, M. Schuler, H. Einsele, C. Brandl, A. Wolf, P. Kirchinger, P. Klappers, M. Schmidt, G. Riethmüller, C. Reinhardt, P.A. Baeuerle, P. Klappers, M. Schmidt, G. Riethmüller, C. Reinhardt, P.A. Baeuerle, P. Kufer, Tumor regression in cancer patients by very low doses of a T cell-engaging antibody, Science 321 (2008) 974–977, https://doi.org/10.1126/science.1158545.

[7] H. Kantarjian, A. Strin, N. Gökbuget, A.K. Fielding, A.C. Schuh, J.M. Ribera, A. Wei, H. Dombret, R. Foix, R. Basana, O. Arslan, M.A. Sanz, J. Bergeron, F. Demirkan, E. Lech-Maranda, A. Rambaldi, X. Thomas, H.A. Horst, M. Brüggemann, W. Klapper, B.L. Wood, A. Fleishman, D. Nagorsen, C. Holland, Z. Zimmerman, M.S. Topp, Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia, N. Engl. J. Med. 376 (2017) 836–847, https://doi.org/10.1056/NEJMoa1609978.

[8] N. Gökbuget, H. Dombret, M. Bonifacio, A. Reichle, C. Graux, C. Paul, H. Dieidrich, M.S. Topp, M. Brüggemann, H.A. Horst, V. Havelange, J. Stegmaier, H. Westela, V. Haddad, J.E. Benjamin, G. Zugmaier, D. Nagorsen, R.C. Bargou, Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia, Blood 131 (2018) 1522–1531, https://doi.org/10.1182/blood-2017-08-798222.

[9] N.V. Frey, D.L. Porter, Cytokine release syndrome with novel therapeutics for acute lymphoblastic leukemia, Hematology Am. Soc. Hematol. Educ. Program. 2016 (2016) 567–572, https://doi.org/10.1182/asheducation-2016.1.567.

[10] V. Pillai, K. Muralidharan, W. Meng, A. Bagashev, D.A. Oldridge, J. Rosenthal, J. Van Arnam, J.J. Melenhorst, D. Mohan, A.M. DiNofia, M. Luo, S. Cherian, J. R. Fromm, G. Wertheim, A. Thomas-Tikhonenko, M. Paessler, C.H. June, E. T. Luning Prak, V.G. Bhoj, S.A. Grupp, S.L. Maude, S.R. Rheingold, CAR T-cell therapy is effective for CD19-dim B-lymphoblastic leukemia but is impacted by prior Blinatumomab therapy, Blood Adv 3 (2019) 3539–3549, https://doi.org/10.1182/bloodadvances.2019000692.