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Case report

INOTUZUMAB OZOGAMICIN FOR RELAPSED/REFRACTORY ACUTE LYMPHOBLASTIC LEUKEMIA – A BRIDGE TO HAPLOIDENTICAL STEM CELL TRANSPLANTATION

Pivkova Veljanovska Aleksandra[1], Trajkova Sanja[1], Chadievski Lazar[1], Kochoski Bozidar[1], Cvetanoski Milche[1], Krstevska Balkanov Svetlana[1], Oranska Gordana[2], Ristevska Tara[1], Ridova Nevenka[1], Stojanoska Simona[1], Panovska Stavridis Irina[1]

[1]University Clinic for Hematology, Bone Marrow Transplantation Unit, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia
[2]University Clinic for Surgical Diseases "St. Naum Ohridski", Skopje, Republic of North Macedonia
e-mail: aleksandrapivkova@yahoo.com

Abstract

Introduction: At present, allogeneic hematopoietic stem cell transplantation (allo-HCT) is considered the only curative option for patients with R/R B-ALL with best outcomes achieved after effective salvage re-induction therapy and transplantation in complete remission (CR) without measurable residual disease (MRD). Inotuzumab ozogamicin (INO) is a CD22-directed humanized monoclonal antibody conjugated to the potent cytotoxin, calicheamicin, via an acid labile linker, which was developed as a targeted therapy for B-cell malignancies. In this paper, we present our center first experience with INO bridging treatment in R/R ALL before haploidentical stem cell transplantation.

Case presentation: We present a case of a 24-year-old female patient diagnosed as B-ALL during July 2021 at the University Clinic of Wurzburg, Germany where she initiated treatment according to German multicenter study group protocol for adult ALL (GMALL) regimen. She had disease relapse early during maintenance treatment. INO was administered in two cycles as monotherapy bridge to haploidentical transplant. The patient achieved MRD negativity and continued conditioning with thiotepa, busulfan and fludarabine. Immunosuppression was provided with posttransplant cyclophosphamide (PTCy), mycophenolate mofetil (MMF) and cyclosporine. Chimerism analysis on +1, +3, +6, +9 and +12 months post-transplant showed full chimerism with negative MRD.

Conclusion: Bridging patients safely to HSCT is the primary goal of post-relapse ALL treatment, but allo-HCT is associated with considerable treatment-related morbidity and mortality. Salvage with inotuzumab ozagamicin can provide a bridge to transplant in relapsed/refractory ALL.

Keywords: Inotuzumab ozogamicin, haploidentical stem cell transplantation, bridge to transplant

Introduction

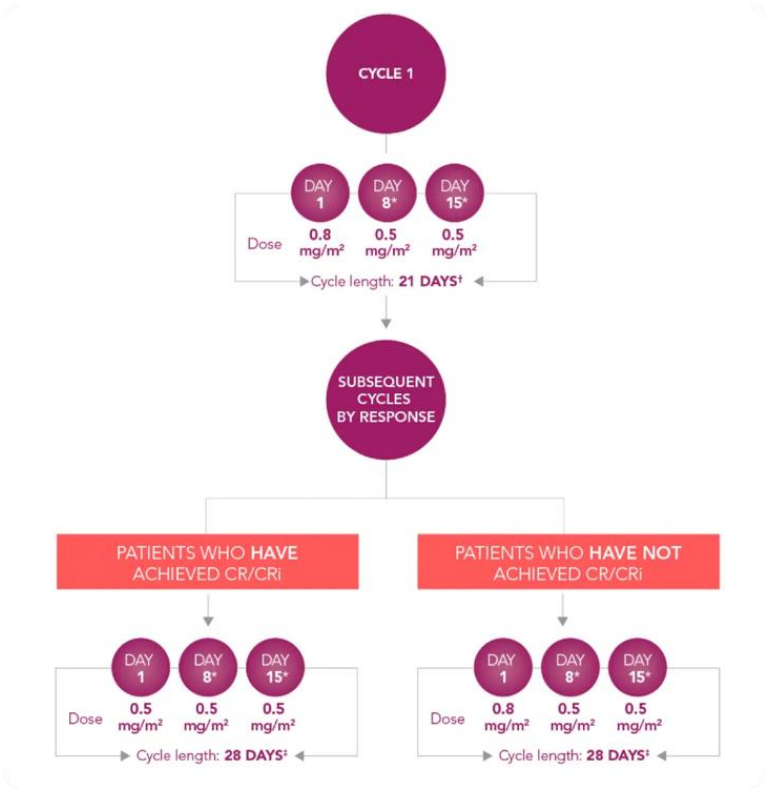
Inotuzumab ozogamicin (INO) is a CD22-directed humanized monoclonal antibody conjugated to the potent cytotoxin, calicheamicin, via an acid labile linker, which was developed as a targeted therapy for B-cell malignancies. Upon binding to CD22 and internalization, calicheamicin is off-set and binds to DNA, thereby leading to double-strand

breaks and apoptosis. The treatment has shown high rates of response in relapsed and refractory (R/R) acute lymphoblastic leukemia (ALL) in single-agent studies, with fewer adverse effects than traditional cytotoxic chemotherapy[1]. Patients with ALL who have measurable residual disease (MRD) positivity after treatment are at an increased risk of relapse and experience poorer outcomes. At present, allogeneic hematopoietic stem cell transplantation (allo-HCT) is considered the only curative option for patients with R/R B-ALL with best outcomes achieved after effective salvage re-induction therapy and transplantation in complete remission (CR) without MRD[2,3]. In this study, we present our center first experience with INO bridging treatment in R/R ALL before haploidentical stem cell transplantation.

Case presentation

We present a case of a 24-year-old female patient diagnosed as B-ALL during July 2021 at the University Clinic of Wurzburg, Germany, where she initiated treatment according to German multicenter study group protocol for adult ALL (GMALL) regimen[4]. She received induction, consolidation cycles after which due to MRD negativity she continued maintenance treatment since August 2021. The maintenance treatment consisted of mercaptopurine, methotrexate, intrathecal prophylaxis and pegylated asparaginases. In September 2022 she had a severe Covid 19 pulmonary infection when a decrease in the elements of the blood count was noticed, WBC $1.5x10^9$/L, Plt $28x10^9$/L, Hgb 70 g/dL. A bone marrow biopsy revealed complete remission with no evidence of disease relapse. In July 2023 she was admitted at the University Clinic for Hematology in Skopje, Republic of North Macedonia due to hemorrhagic purpura when her laboratory analysis confirmed thrombocytopenia Plt $8x10^9$/L. Bone marrow aspiration confirmed disease relapse with over 80% infiltration with blast cells. The analysis of clonality of B cell receptor showed monoclonal B cell population. HLA DNA typing revealed she has no family sibling donor 10/10, and World Marrow Donor Association (WMDA) registry search showed lack of potential 10/10 unrelated donors. The patient was referred to receive treatment with available immunotherapy as a bridge treatment to haploidentical allo-HSCT. INO was administered to the patient in a total of 2 cycles. Premedication with a corticosteroid, antipyretic, and antihistamine was used prior to each dose of INO. Due to circulating lymphoblasts, cytoreduction with a combination of steroids and vincristine to a peripheral blast count of $\leq 10.000/mm^3$ was administered prior to the first dose of cycle 1of INO.

The treatment dose schedule of immunotherapy in ALL is presented in Figure 1. During INO administration, thrombocytopenia was observed with platelets count to $20x10^9$/L. After the second cycle, a bone marrow analysis was performed and showed complete remission and MRD negativity. The patient was referred to haploidentical allo-HCT from her haploidentical sister. Conditioning was provided with myeloablative regimen Thiotepa 5 mg/kg day -6 to day -5, Fludarabine 30 mg/m^2 from day -5 to day -2 Busulfan 3.2 mg/kg from day -4 to day -2 (Figure 2). Immunosuppression was made with cyclosporine, mycophenolate mofetil (MMF) and post-transplant cyclophosphamide (PTCy) 50 mg/kg on day +3 and day +4 after stem cell infusion. On day 0, $4.5x10^6$/kg CD34+ cells from HLA haploidentical sister were infused. The patient was engrafted on day +14 with Ne $1.2x10^9$/L and day +15 with platelets $47x10^9$/L. In the early post-transplant setting, the patient experienced two febrile episodes mainly caused by Gram-negative bacteria. She had CMV reactivation on day +42, and was treated with oral ganciclovir. On day +95, she showed signs of skin graft versus host disease (GVHD) gr I/II, treated with low doses of corticosteroids. Chimerism analysis on +1, +3, +6, +9 and +12-months post-transplant showed full chimerism with negative MRD. The patient is without immunosuppression and leukemia free +14 months



CR = complete remission; Cri = complete remission with incomplete hematologic recovery

Fig. 1. Treatment dose schedule of immunotherapy with inotuzumab ozogamicin in ALL[3]

Table 1. Patient, graft and donor characteristic during MRD transplant for ALL

Parameter	*Value*
Disease status before transplant	ALL-MRD negative
Patient body weight (kg)	64
HPC Apheresis (ml)	325
Number of apheresis procedures	1
CD34+cells/kg	$5.6x10^6$/kg
Engraftment (day)	
WBC>1.0×10^9/L	+14
Plt>20×10^9/L	+15
Transfusion policy	
Er transfusions - units (filtered and irradiated)	
Plt concentrates	6
Donor characteristics	120 doses
mismatched related	
CMV IgG	6/10
CMV IgM	positive
Blood Type	negative
Donor	
Patient	
Conditioning	0 Rh (+)
MAC conditioning	A Rh (+)
Immunosuppression	Thiotepa/Busulfan/Fludarabin/r ATG Cyclosporine/MMF

ALL- acute lymphoblastic leukemia, MRD - measurable residual disease, MMF - mycophenolate mofetil, CMV-cytomegalovirus, WBC - white blood cells, Plt - platelets, MNC - mononuclear cells, HPC - hematopoietic cells

after haploidentical stem cell transplantation. The patient and donor transplant characteristics are presented in Table 1.

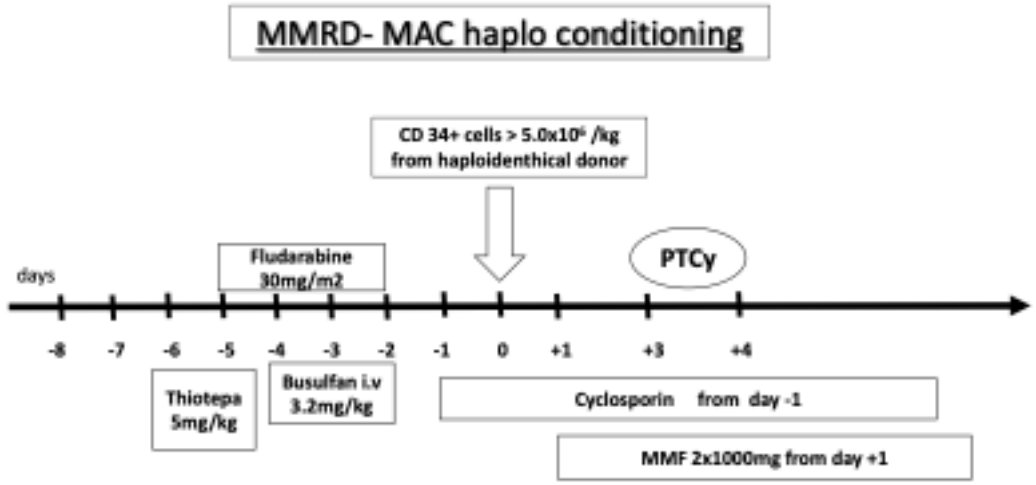


Fig. 2. Conditioning regimen for haploidentical HCT in patient with ALL

Discussion

Immunotherapy with monoclonal antibodies such as blinatumomab and inotuzumab ozogamicin is an innovative treatment for achieving MRD negativity before allo-HCT in patients with R/R ALL. The presented case, although MRD negative in CR1 before starting the maintenance treatment according to GMALL regimen, experienced early relapse. The treatment options in early relapse for ALL to achieve CR 2 and bridge to transplant are limited in terms of conventional chemotherapy. Recent recommendations prefer immunotherapy, CAR-T cell therapy or clinical trial treatment in this setting[2]. Ne gi naogjam 3 i 4 referenca

Allo-HCT is the treatment of choice for most adult patients with ALL. Unfortunately, donor availability remains as one of the major challenges for transplant success in this patient population. Although HLA matched sibling donors are the preferred donors for allo-HCT, such donors are available for <30% of patients. For patients with no matched sibling donor, transplant from a matched unrelated donor (MUD) has similar transplant outcomes[5]. A meta-analysis of 13 trials comparing allo-HCT to chemotherapy with or without allo-HCT concluded that the benefit of allo-HCT for patients with ALL in first complete remission (CR1) was limited to patients younger than 35 years[6]. Recent studies have also shown that allo-HCT in CR1 yields outcomes similar to those in pediatric-inspired chemotherapy in patients who are minimal residual disease (MRD) negative, but improves outcomes in patients who are MRD positive[7]. The presented case has been referred to allo-SCT in CR2, from her mismatched family donor since the donor search revealed no potential 10/10 identical unrelated donors. Haploidentical HCT may shorten the time to transplant and promote the higher cure rates observed with traditional fully HLA-matched donor allo-HCT. The primary reason for decreased non-relapse mortality (NRM) with haploidentical HCT compared with MUD allo-HCT, 7/8 mismatched unrelated donor (MMUD) allo-HCT, seems to be significantly decreased rates of severe acute (aGVHD) and chronic (cGVHD) with haploidentical HCT using PTCy[8]. Our patient received myeloablative conditioning with TBF regimen; PTCy was administered as immunosuppressive therapy combined with calcineurin inhibitors and MMF. The patient experienced mild symptoms of aGVHD on skin due to corticosteroid treatment.

Standard chemotherapies for adult patients with ALL at first relapse provide CR rates of 31% to 46%, with 5-year overall survival (OS) rates of <20%. In the salvage setting, CR rates of 18% to 25% have been reported, with median OS of 3 to 4 months[8,9].

Salvage immunotherapies are approved to be the standard of care in R/R setting of ALL since achieving MRD negativity is hardly to be provided with standard chemotherapy approaches.

Several studies have identified age as a prognostic factor for survival in patients with R/R ALL[10]. To our knowledge, baseline bilirubin levels have not been associated with survival outcomes in ALL, but elevated bilirubin levels have been associated with use of INO, and pre-HCT bilirubin levels ULN were associated with an increased risk of VOD among patients receiving INO in the INO-VATE study[11]. Our patient had an increased risk of VOD due to a previous INO treatment; therefore, there were 50 days of gap between the last infusion of INO until initiation of the conditioning regimen. The transplant was performed with no VOD prophylaxis with defibrotide. The patient's liver enzymes were closely monitored on daily basis and no elevation of bilirubin and enzyme was observed.

Conclusion

Bridging patients safely to HSCT is the primary goal of post-relapse ALL treatment, but allo-HCT is associated with considerable treatment-related morbidity and mortality. Salvage with inotuzumab ozagamicin can provide a bridge to transplant in relapsed/refractory ALL. While the most common adverse events are cytopenias and infections, the drug is associated with an increased risk of VOD/SOS. Thus, minimizing the exposure to INO and using optimal number of cycles to achieve best response and MRD negativity will be the goal to balance risk of relapse against potential risk of toxicity. Haploidentical SCT using PTCy as the preferred alternative donor HCT for ALL given the superior OS seen relative to 7/8 HLA-MUD and UCB HCT. Data also suggests that OS is not different from haploidentical HCT using PTCy compared with traditional MSD and MUD HCT, but with a reduced risk of GVHD. Still more randomized confirmatory studies have to be initiated to confirm this treatment outcome.

Conflict of interest statement. None declared.

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