Inotuzumab Ozogamicin Monotherapy as an Outpatient Salvage Treatment in Relapsed Refractory B-Cell Acute Lymphoblastic Leukemia: Compassionate Access

Vivek S. Radhakrishnan[1] Ketan Modak[1] Saurabh J. Bhave[1] Jeevan Kumar[1] Mita Roychowdhury[1] Manik Ghosh[1] Mayur Parihar[2] Neeraj Arora[2] Deepak K. Mishra[2] Reena Nair[1] Mammen Chandy[1]

[1]Clinical Hematology Oncology and Hematopoietic Cell Transplantation, Tata Medical Center, Kolkata, West Bengal, India
[2]Laboratory Hematology, Cytogenetics, and Molecular Pathology, Tata Medical Center, Kolkata, West Bengal, India

Address for correspondence Vivek S. Radhakrishnan, MD, DM, MSc, PDF Clinical Hematology Oncology and Hematopoietic Cell Transplantation, Tata Medical Center, 14, MAR(EW), Newtown, Rajarhat, Kolkata, West Bengal 700160, India (e-mail: drvivekradhakrishnan@yahoo.com).

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Abstract

Relapsed and refractory (RR) acute lymphoblastic leukemia (ALL) poses unique and difficult challenges to a practicing clinician in India where access to novel immunotherapies is limited. Between 2017 and 2020, eight patients with B-cell ALL at our center received inotuzumab ozogamicin (IO) monotherapy on compassionate access, as salvage therapy after at least two lines of conventional therapy failure, and most often as outpatient infusion. Eight patients (21–60 years, three females) received IO. Three patients had morphologic relapse and five patients reported persistent measurable residual disease (MRD). The best response on IO therapy achieved was negative MRD in six of seven patients and complete response (CR) with persistent MRD in one. One patient died (intracranial hemorrhage) before completion of first cycle. All responding patients were transplant eligible and four patients (57%) underwent allogeneic hematopoietic cell transplantation (Allo-HCT). Median follow-up of this cohort is 9 months (4–29.6 months), four patients (57%) are alive as stable with negative MRD. No significant infusion reactions occurred during therapy. Three patients developed grades III and IV neutropenia, two patients showed grade III transaminitis, and two patients developed post-HCT severe sinusoidal obstruction syndrome (SOS). IO is a feasible outpatient based salvage therapy to improve the remission status in RR B-cell ALL.

Keywords
- inotuzumab ozogamicin
- minimal residual disease
- relapsed refractory B-cell ALL
- immunotherapy
- targeted therapy
- hematopoietic cell transplantation

Introduction

Adult acute lymphoblastic leukemia (ALL) comprise around 20% of all cases of ALL with an incidence of approximately 1.6 per 1,00,000.[1] Initial response rates are around 60 to 90%; however, only 30 to 50% maintained long-term disease-free survival.[2,3] Salvage regimens with conventional chemotherapy for relapsed-refractory (R/R) B-cell ALL yield a complete remission (CR) rate of 40% in first salvage and 10 to 20% in second salvage and beyond.[3,4] With low CR rates, only a few patients (5–20%) undergo allogeneic hematopoietic cell transplantation (Allo-HCT).[4-6] In the

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developed world, novel therapies are changing outcomes in R/R B-cell ALL and include antibody-drug conjugates (inotuzumab ozogamicin [IO]), bispecific antibodies (blinatumomab), and chimeric antigen receptor T-cell therapy (tisagenlecleucel).[7] At the time of manuscript preparation, these drugs are not licensed in India.

IO is a humanized monoclonal antibody conjugated to calicheamicin directed against CD22 receptor and approved for use in R/R B-cell ALL based on results of INO-VATE study.[8] CD22 is expressed in more than 90% of B-cell ALL.[9] Published data have shown better outcomes with IO as salvage regimen pre-HCT, compared with standard chemotherapy (CR: 80.7 vs. 33.3%, respectively, $p < 0.0001$).[10] Around 43 to 47% patients on IO proceeded to HCT.[8,10] IO is relatively safe and well tolerated, with a manageable toxicity profile.[11] Reports of sinusoidal obstruction syndrome (SOS) associated with IO is a concern in those undergoing HCT and with experience, recommendations exist for appropriate use today.[12] We present an audit of IO monotherapy (obtained through a compassionate access program) and its outcomes in R/R B-cell ALL, an initial experience from a tertiary care cancer center.

Materials and Methods

Between 2017 and 2020, adult patients with R/R B-cell ALL who failed at least two prior lines of therapy (including the persistence of measurable residual disease [MRD]) received IO monotherapy under a compassionate use program for India, from Pfizer. Compassionate access program is available from established and reputed pharmaceutical companies on selected innovator drugs which are licensed by regulatory agencies abroad, and not yet licensed for sale in India by the Indian Government's drug regulatory agencies. Qualified oncology and hematology physicians from established centers can apply to the pharmaceutical company after confirming the availability of a compassionate use program. Once a patient and physician eligibility check is determined, the physician issues an authorized prescription and the patient applies for a government license to import the drug on a named-patient-access program from the Central Drugs Standard Control Organization (CDSCO). On the grant of the license, the company facilitates the delivery of a predetermined and permitted quantity of the drug to the patient. The applying physician of the patient undertakes to follow established protocols and safety standards for the administration of the drug, to provide utilization statements, and to report serious adverse events.

Patients of ≥18 years, with CD22 positive leukemic blasts with no prior history of SOS and having either morphological or molecular persistence of disease, received IO. Patients who received a minimum of one full cycle of IO were included for evaluation. All patients received IO as per a recommended fractionated dose schedule of 0.8 mg/m^2 on day 1, 0.5 mg/m^2 on days 8 and 15 in a 21- to 28-day cycle.[11] From the second cycle onward, if patient was in Complete Remission/Complete Remission with incomplete count recovery, IO was given at a dose of 0.5 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. Disease response assessment was done after every two cycles of therapy. Morphologic complete remission was defined as (M1) with <5% blasts on bone marrow aspirate, M2 with 5 to 20% blasts and M3 as more than 20% blasts. Flow cytometry-based MRD measurement was determined.[13] The Common Terminology Criteria for Adverse Events (CTCAE v5.0) was used to grade toxicities during and for 30 days post-IO therapy.[14] Those patients who underwent HCT, adverse events during and post-HCT were noted. Descriptive statistics were employed and the primary endpoint of analysis was complete response. The data collection and analysis has followed the recommendations of the Helsinki declaration of 1964 and amendments thereafter, and our institutional review board provided a waiver for this study.

Results

Eight patients were eligible for compassionate access and seven patients were evaluable, as one patient with prolonged severe thrombocytopenia and prior bleeding died due to an intracranial hemorrhage in the first week of cycle 1. Patient characteristics are detailed in ►**Table 1**. Two patients had morphological disease persistence while five had MRD persistence. Barring the first dose, all patients received this therapy in the outpatient service. Details of individual patient, IO therapy received, and outcomes are documented in ►**Table 1**.

Of the seven evaluable, all patients achieved deeper remissions and six (85.7%) were in MRD-negative status. All patients post-IO were eligible for transplant at best response, only four patients (57%) proceeded to Allo-HCT due to financial constraints and logistics. In the post-HCT setting, two patients are alive and in remission after 2 years and 4 months, respectively, one patient developed grade-IV SOS and died, the fourth patient (Ph + ALL T315I mutated) developed relapse by D + 43 and died thereafter. Among the three non-HCT patients, one patient (persistent MRD, post-IO) developed progressive disease and died. The remaining two received post-IO maintenance ALL therapy (vincristine, dexamethasone, methotrexate, and 6-mercaptopurine). They are alive and in remission at last follow-up. One of the two patients required modification in maintenance therapy due to chronic liver disease (Child–Pugh B, hepatitis-B related). At a median follow-up duration of 9 months (4–27.6 months), four (57%) patients are alive and maintaining remission.

IO monotherapy was relatively safe and well-tolerated. No infusional toxicities were observed. Neutropenia of grades III and IV was seen in three patients (first cycle) and hepatic dysfunction (transaminitis) of grades III and IV in two patients. Two patients developed SOS post-HCT. A disproportionate rise in hemoglobin level was seen in three patients who received a minimum of two cycles of IO (►**Fig. 1**), this is an observation not evaluated in detail which warrants further exploration.

Discussion

In the subset of nonresponding B-cell ALL, use of novel therapies holds the promise of cure by achieving CR with negative

Table 1 Inotuzumab Ozagamycin (IO) treatment and outcomes

Characteristic	UPN1	UPN2	UPN3	UPN4	UPN5	UPN6	UPN 7
Age/sex	21/F	22/M	51/M	27/F	33/M	29/F	23/M
Prior regimens*	1. BFM-95 2. HyperCVAD 3. BVD	1. ICICLE 2. HyperCVAD 3. BMAD	1. BFM-90 2. HyperCVAD ± bortezomib	1. BFM-95 2. HyperCVAD 3. BED	1. BFM-90 + dasatinib 2. CLOVE	1. BFM-2002 2. HyperCVAD 3. BED	1. ICICLE IR 2. ICICLE HR 3. BED + IV Methotrexate 3 g/m^2
Significant comorbidities	None	None	Hepatitis B core antibody +	None	None	None	Obesity, hypertension
Disease status pre-IO	MRD positive (2.05%)	MRD positive (0.07%)	MRD positive (0.09%)	Not in CR	Not in CR	MRD positive (0.17%)	MRD positive (0.05%)
Line of therapy with IO	4th	4th	3rd	4th	3rd	4th	4th
CD22 expression (%)	91.10	94.60	46.50	68	88.90	96	90
Karyotype	Normal karyotype	Normal karyotype	Normal karyotype	Normal karyotype	47XY, +X, t(9,22) (q34;q11.2)	Normal karyotype	Normal karyotype
High-risk cytogenetic/molecular markers[a]	Negative	Negative	Negative	None	BCR-ABL1 with T315I mutation	Negative	Negative
Number of IO cycles	4	2	6	3	1	6	1
Post-IO best response	CR, MRD negative	CR, MRD negative	CR, MRD negative	CR, MRD positive	CR, MRD negative	CR, MRD negative	CR, MRD negative
Infusion reactions	No	No	No	No	No	No	No
Proceeded to allogeneic HCT	Yes	Yes	No	No	Yes	No	Yes
Conditioning regimen	Flu-TBI myeloablative	Cy-TBI myeloablative	NA	NA	Flu-TBI myeloablative	NA	Flu-TBI myeloablative
Donor type	Haploidentical	MSD	–	–	MSD	–	MSD
Neutrophil engraftment (d)	Did not engraft	D + 15	NA	NA	D + 13	NA	D + 15
Platelet engraftment	Did not engraft	D + 13	NA	NA	D + 17	NA	D + 14
SOS	Yes, severe	No	NA	NA	No	NA	Yes, severe
Other transplant morbidities	Mucositis grade-IV, sepsis	Mucositis grade III	NA	NA	Mucositis grade IV	NA	Mucositis grade III
Disease status post-HCT	NA	CR MRD negative, D + 28, D + 365	NA	NA	CR MRD negative, D + 28	NA	CR MRD negative, D + 28
Subsequent therapy, post-IO/post-HCT	–	On follow-up	Maintenance therapy	Progression after 3-month alternative medicine	Relapse (day + 47) Ponatinib + BED	Maintenance therapy	On follow-up
Status at last follow-up (cut-off November 30, 2020)	Dead	Alive, in remission	Alive, in remission, chronic liver disease	Dead	Dead	Alive, in remission	Alive, in remission
Cause of death	Transplant related mortality (SOS)	–	–	Disease progression	Disease relapse	–	–
Follow-up period (mo)	6.5	27.4	27.6	6.3	5.9	13.5	4

Abbreviations: GMALL-German Modified ALL Treatment Protocol; BFM- Berlin-Frankfurt-Munster; ICICLE- Indian Childhood Collaborative Leukaemia Group (IR: Intermediate risk, HR: High risk); BED- Bortezomib-etoposide-dexamethasone; BVD- bortezomib-vincrisitine- dexamethasone; BMAD- bortezomib, mitoxantrone, Peg Asparaginase, dexamethasone; B-HyperCVAD – Bortezomib with HyperCVAD. CR: complete morphological remission; MRD: minimal residual disease

Toxicity: As per CTCAE grading v5.0

Note: Molecular/Cytogenetic panel done in the institute: ETV6/RUNX1, BCR/ABL1, KMT2A(MLL), TCF3(E2A).

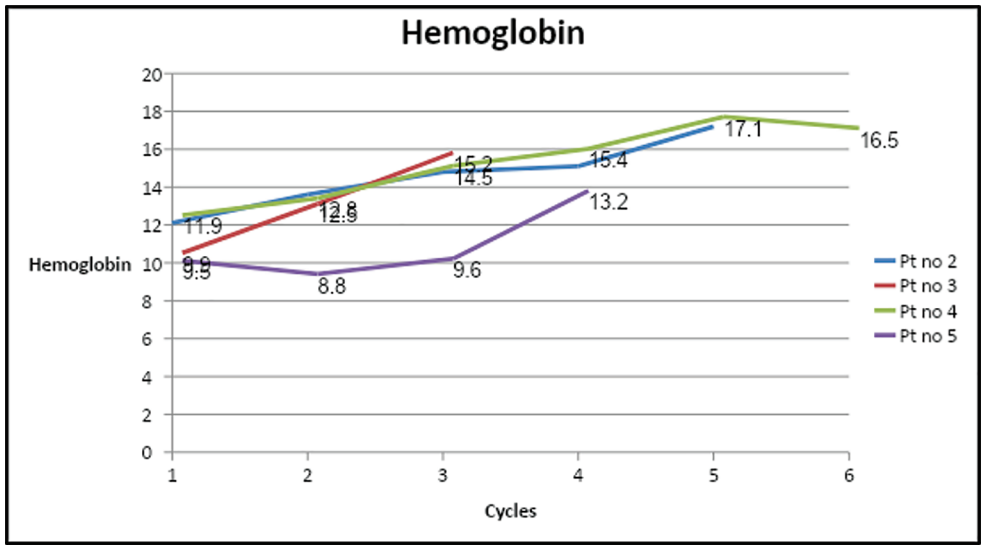

Fig. 1 Unique Patient-identification Number Hemoglobin levels (g/dL) in patients on IO therapy (three patients [UPN 2–3-4] had disproportionate increase after first dose of IO, UPN 5 given as a comparator). IO, inotuzumab ozogamicin; Pt., patient.

MRD followed by consolidation with Allo-HCT. In our setting, IO was well tolerated with manageable grades III and IV nonhematological toxicity and only one patient developed grade-IV neutropenia. All sessions of therapy, with the exception of the first, were administered as an outpatient. This must be seen in comparison to conventional cytotoxic therapies which are intensive and require hospitalization and supportive care.[5] IO was highly effective in achieving deeper CR rates in all seven evaluable patients. The response was not dependent on the number of prior regimens received, and possibly the disease burden. Out of seven transplant eligible patients, four proceeded to HCT. This is due to the predominant out-of-pocket nature of cancer treatment expenditure in India.[15] With a maximum follow-up period of 27 months, three patients are alive. Three patients died (one due to SOS and two due to relapse). IO was well tolerated in this patient group who were heavily pretreated. Liver dysfunction is noted in IO therapy, two patients developed grade-III transaminitis during treatment (self-remitting) and two patients developed grade-IV SOS post-HCT (one patient had received one cycle of IO and recovered, while the second patient who received four cycles of IO was heavily pretreated and underwent Total Body Irradiation conditioning and died). There were no major infectious episodes or other major organ toxicity while on IO. In the pivotal study, 79 of 164 patients (48.1%) from IO arm proceeded to HCT; among these patients, 18 of 79 patients (22.8%) developed SOS.[16]

Limitations and Conclusion

This series documents the initial experience with a novel targeted immunotherapy of B-cell ALL in a tertiary cancer center. Our study has some important limitations, it is a limited case series with only eight patients. Response rates were promising, possibly due to a lower disease burden among most patients. The disproportionate rise in hemoglobin has not been reported with IO elsewhere. It needs further evaluation and could be reactive. Compared with intensive conventional chemotherapies, IO monotherapy is a feasible outpatient-based alternative with excellent response rates and a bridge to a potentially curative HCT. The role of maintenance therapy post-IO-induced molecular remissions needs further evaluation in the transplant ineligible. IO monotherapy is established in salvage therapy of B-cell ALL and studies using IO in combination therapies and frontline therapy are progressing well.[17-19] Once available in India, it would benefit the Indian clinicians to conduct a prospective registry of patients receiving approved novel targeted therapies in ALL.

Ethics Approval

Tata Medical Center, Institutional Review Board (TMC-IRB) Ethics waiver number: EC/WV/TMC/47/20.

Authors' Contributions

Concept and design: V.S.R., R.N., and M.C.
Literature search: V.S.R. and K.M.
Clinical studies: V.S.R., S.J.B., J.K., R.N., M.C., K.M., and M.R.
Laboratory studies: D.K.M., N.A., and M.P.
Data acquisition, data analysis: K.M., M.G., and V.S.R.
Manuscript preparation: V.S.R. and K.M.
Manuscript editing: R.N. and M.C.
Manuscript review: V.S.R., K.M., S.J.B., J.K., D.K.M., N.A., M.P., R.N., and M.C.
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Conflict of Interest

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