Inotuzumab ozogamicin as chemotherapy-sparing salvage in a 67-year-old man with primary refractory B-cell acute lymphoblastic leukemia with high-risk genomic features

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\section*{ABSTRACT}

Older adults with acute lymphoblastic leukemia (ALL) continue to have a poor prognosis, in part due to greater chemotherapy-related toxicities. We herein report a 67-year-old man with Philadelphia chromosome (Ph)-negative B-cell ALL, who exhibited refractoriness to 3 different regimens of induction chemotherapy and experienced multiple complications including intracranial bleeding and respiratory failure, who achieved minimal residual disease (MRD)-negative complete response (CR) after a single cycle of inotuzumab ozogamicin (IO). His ALL was characterized by several high-risk mutations, which may have contributed to chemotherapy-refractory disease. Our case supports incorporating IO into front-line induction regimens for older adults with high-risk B-cell ALL.

\section*{1. Introduction}

Acute lymphoblastic leukemia (ALL) is an aggressive hematologic malignancy arising from precursor lymphoid cells. While > 85% of adult ALL patients achieve morphologic complete response to induction chemotherapy, subsequent relapse is common [1]. True primary refractory ALL is less common. Herein we report an older adult with incidentally-diagnosed ALL who demonstrated no cytoreduction following three different chemotherapy regimens and experienced severe deconditioning from multiple complications, but achieved minimal residual disease-negative (MRD-) complete response (CR) following inotuzumab ozogamicin (IO) monotherapy. Pre-IO molecular studies revealed several high-risk somatic mutations, including NRAS and CDKN2A. This case joins a growing body of literature supporting incorporation of IO into frontline therapy for older ALL patients with high-risk cytogenetic or molecular findings.

\section*{2. Case report}

A 67-year-old man with remote history of seizure, immune thrombocytopenia and localized prostate adenocarcinoma (Gleason 3 + 4) was found to have B-cell ALL (B-ALL) during pre-prostatectomy workup at an outside hospital. Complete blood count (CBC) upon diagnosis showed white blood cells (WBC) $11.86 \times 10^3/\mu L$ with 6% blasts, hemoglobin 8.5 g/dL, and platelets $24 \times 10^3/\mu L$. Bone marrow (BM) aspirate (\textbullet\textsuperscript{1}, Fig. 1) differential showed > 80% blasts and core biopsy revealed hypercellular marrow (100%) with blasts diffusely infiltrating the marrow space (Table S1). Multiparameter flow cytometry (FACS) demonstrated a blast population with very low CD45 expression, uniformly positive for CD34, CD10, CD19, HLA-DR, and CD38, and negative for CD20, T-cell, and myeloid markers. Cytogenetic studies showed normal karyotype; FISH revealed trisomy 17 at low level and was negative for t(9;22), the Philadelphia (Ph) chromosome (Fig. 1B).

He was initially treated with an induction regimen adapted from the ECOG 1910 protocol (Table S2). Ommaya reservoir placement was complicated by subdural hematoma (SDH) requiring middle meningeal artery embolization. He also experienced multiple episodes of neutropenic fever (course timeline in Fig. 1A). He was transferred to a second institution, where he was found to have persistent B-ALL; BM FISH was also notable for trisomy 8 and del(20q) (\textbullet\textsuperscript{2}, Fig. 1). Notably, a concurrent myeloid neoplasm was suspected. He received a second induction with modified high-dose cytarabine/methotrexate per hyper-
Fig. 1. Major events of the case: (A) timeline with key stages highlighted in red color; (B) inductions and bone marrow disease status at different time points with relevant cytogenetic features. MSK = Memorial Sloan Kettering Cancer Center. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Fig. 2. Representative histologic sections, immunostains, flow cytometry plots, and genomic profiles prior to and following inotuzumab ozogamicin (IO). (A) Bone marrow core biopsy (●5) on arrival to this institution demonstrated markedly increased blasts with fine chromatin and distinct nucleoli (H&E, 400x), (B) patchy fibrosis and large aggregates of atypical megakaryocytes (H&E, 400x), and (C) increased background fibrosis as noted by reticulin stain. The blasts expressed (D) CD34 and (E) TDT by immunohistochemistry (400x); (F) aspirate smears showed blasts of variable size. Following one cycle of inotuzumab ozogamicin, core biopsy (●6) demonstrated (G) osteosclerotic changes in the bony trabeculae and essentially acellular marrow (H&E, 400x), with (H&I) patchy regeneration of hematopoiesis and mildly increased megakaryocytes (H&E, 400x) without an increased blast population expressing (J) CD34 or (K) TDT. Multiparameter flow cytometry from (L) prior to treatment (●5) revealed the blasts expressed CD45 (dim), CD19, CD22, CD20 (partial), CD10 (partial), and CD34, consistent with B-lymphoblastic leukemia, and (M) following treatment disclosed only rare events (●6) that represent plasma cells and rare B cells, without any immunophenotypic evidence of B-lymphoblastic leukemia. (N) Results of matched tumor/normal comprehensive genomic profiling for somatic mutations, of bone marrow biopsies A) prior to IO treatment (●5, Fig. 1A) and B) after blinatumomab consolidation (●8, Fig. 1A); persistence of BRCA1 and U2AF1 mutations is highlighted in yellow. * The NRAS exon 2 mutations were noted to occur on different alleles. † Mutations in CDKN2A reflect the same mutation affecting p14 and p16 through alternative splicing. ‡ The IKZF1 copy number losses fell slightly below our criteria for deletion. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
CVAD (Table S2), and again demonstrated no cytoresponse. In preparation for possible blinatumomab, he then began cyclophosphamide and vincristine (Table S2), with day 15 BM studies revealing persistent B-ALL (100% cellular marrow, diffusely infiltrated by B-lymphoblasts, Fig. 1), with course complicated by Klebsiella pneumoniae bacteremia. He was transferred to Memorial Sloan Kettering (MSK) for further management and consideration of new salvage therapy for his refractory B-ALL.

Upon admission to MSK, CBC revealed WBC 200/μL, hemoglobin 7.6 g/dL, platelets 1.2 × 10^4/μL. Restaging BM studies (Figs. 2A–F) noted 90% blasts on aspirate with variably cellular marrow (0%–90%) with patchy sheets of blasts. BM FACS again identified B-lymphoblasts expressing CD19, CD22 and CD34, CD45 (dim), and partial expression of CD10 and CD20 (Fig. 2L). No trisomy 8 or del(20q) was detected. Next-generation sequencing studies using the IMPACT-Heme platform (Supplementary Methods), with matched normal control (nail clippings), revealed 3 distinct, somatic NRAS mutations on different alleles, CDKN2A mutation, and IKZF1 loss (Fig. 2N). Targeted RNA sequencing (FusionPlex, Archer, Boulder, CO) and FISH showed no evidence of fusions characteristic of “Philadelphia chromosome (Ph)-like” ALL.

The patient’s early MSK course was complicated by acute-on-chronic SDH with slight mass effect at the time of transfer, coagulase negative Staphylococcus bacteremia (in the setting of infected MedPort), Clostridium difficile colitis, respiratory failure from invasive pulmonary aspergillosis (IPA), and severe deconditioning. IO was initiated as chemotherapy-sparing salvage for refractory B-ALL (cycle #1 [C1]): first dose 0.8 mg/m², subsequent doses 0.5 mg/m²; the second dose was briefly delayed in the setting of progressive delirium and respiratory failure attributed to his pre-existing SDH and IPA, and prolonged QTc attributed to multiple medications, including voriconazole (then changed to isavuconazole). However, his respiratory and mental status slowly improved during the interval between first and second dose of IO, and returned to near-baseline after completion of all 3 doses in C1. With his strength improved, and neutrophils slowly recovering, he was discharged home after a 33-day hospitalization. Of note, no neutropenic fever or new infection occurred during or after C1. Restaging BM biopsy performed day 27 post-IO demonstrated variable cellularity (<5%–50%) with foci of regenerative changes (Figs. 1B and 2G–K); FACS detected no abnormal immature B-cell population (Fig. 2M). Thus, MRD-negative CR with incomplete hematologic recovery (CRi) was achieved for the first time in 5 months since initial diagnosis.

He subsequently received a second cycle of IO [C2]. He then received a cycle of blinatumomab as bridging therapy prior to allogeneic hematopoietic cell transplantation (alloHCT) to limit exposure to IO, increase the interval between IO and alloHCT, and accordingly to reduce the likelihood of sinusoidal obstruction syndrome (SOS) post-HCT. BM studies confirmed continued MRD-negative CR of B-ALL (Figs. 1B, but morphologic/immunophenotypic findings of myelodysplastic syndrome (MDS) became evident. Dramatic radiographic improvement in his IPA was noted after C2 as well, contemporaneous with clinical improvement (Supplementary Figs. S1 and S2). On day 248 from the initial diagnosis of B-ALL, he successfully underwent alloHCT from a matched unrelated donor without significant complication (Fig. 1A). At the time of submission, he remains without evidence of B-ALL or MDS at 3 months post-alloHCT and fully functional in daily activities.

3. Discussion

ALL has a bimodal age distribution, with incidence first peaking in childhood and again around age 50 [1]. While pediatric ALL is associated with cure rates >80% in the modern era, adults with B-ALL exhibit long-term survival rates of around 40%; older adults (age > 60) exhibit particularly poor outcomes, with only 10%–15% achieving sustained CR [2]. Despite the overall poor prognosis, most adults with ALL (>85%) respond to initial induction or subsequent salvage and primary refractory B-ALL is relatively uncommon. Our patient had particularly refractory B-ALL, without meaningful cytoresponse following 3 different induction regimens.

Genomic profiling complements conventional cytogentic studies in risk-stratifying patients with ALL. Three NRAS mutations in different alleles, CDKN2A mutation, and IKZF1 loss might all have contributed to this patient’s refractoriness to conventional chemotherapy, though the patient’s B-ALL remained highly sensitive to IO. Of note, BM studies raised concern for MDS concurrent with B-ALL, with cytogenetic abnormalities (trisomy 8, del(20q)) characteristic of myeloid neoplasia accompanying dysplasia and abnormal myeloid blasts. Persistence of BRCA1 and U2AF1 mutations at high variant allele frequency and acquisition of new myeloid neoplasia-associated mutations (TET2, MPL), after clearance of B-ALL associated mutations (e.g. NRAS, CDKN2A) and during continued MRD-negative CRi of B-ALL, may reflect clonal evolution of MDS (Fig. 2N).

Ras pathway mutations have been identified at relapse in 25%–40% pediatric patients with ALL, though often are evident at low-level at diagnosis [3,4]. NRAS/KRAS mutations have been associated with resistance to salvage chemotherapy among pediatric patients with relapsed B-ALL [4]. Our patient had 3 NRAS mutations on different alleles prior to IO treatment. Although his mutational profile at diagnosis is unclear, NRAS mutations (either at diagnosis or arising during therapy) may have contributed to chemotherapy-refractory disease. His B-ALL was additionally associated with a CDKN2A mutation (affecting p14 and p16 through alternative splicing). CDKN2A and CDKN2B are located within 9p21 locus, encoding p14/ARF, p16/INK4A (by CDKN2A) and p15/INK4B (by CDKN2B), all of which function as tumor suppressors. Some reports suggest homozygous CDKN2A deletions are associated with poor response to chemotherapy and increased relapse rate in pediatric patients with B-ALL [5]. Loss of CDKN2A/2B was also an independent risk factor for short remission duration, high relapse rate and low overall survival in a German study of adults with Ph+ ALL, despite alloHCT in CR1 [6]. Finally, our patient exhibited copy number loss of IKZF1. IKZF1 encodes the lymphoid transcription factor IKAROS; its deletion is associated with poor prognosis in pediatric and adult B-ALL [7]. Concomitant loss of CDKN2A and IKZF1 is associated with poor prognosis in pediatric patients with high-level MRD following induction therapy [8] and has been described in Ph + + ALL. Prognostic significance of IKZF1 of lower deletion-load (~1.4 fold), as observed in this case, is less clear [7]. The prognostic implications of these findings are less established in patients treated with IO. After this case, we reviewed all MSK cases of IO-treated patients, including 6 patients with chemotherapy-refractory B-ALL harboring activating mutations in NRAS, mutation/loss of TP53, and/or mutation/loss of CDKN2A/2B (Table 1). All achieved CR/Cri and 3 of 6 patients were successfully bridged to alloHCT. Patients at our institution with relapsed/refractory B-ALL bearing other high-risk molecular features have similarly exhibited excellent response to IO, and a larger retrospective study is ongoing.

Conventional salvage for children and young adults with relapsed/refractory (R/R) B-ALL has historically consisted of intensive chemotherapy, which is tolerated poorly by older adults. Newly approved antibody-based therapies, including IO (targeting CD22) and blinatumomab (bispecific T-cell engager targeting CD3/CD19), have shown promising results in pediatric and adult patients with R/R B-ALL [9] and are better tolerated than standard chemotherapy in older adults. An ongoing study led by the Alliance for Clinical Trials in Oncology (A041703) is investigating the combination of IO and blinatumomab in adults with newly-diagnosed Ph-negative CD22+ B-ALL (NCT03739814). As patients with high-burden B-ALL exhibit suboptimal responses to blinatumomab, cytoresponse with cyclophosphamide/vincristine was attempted in our case, but was unsuccessful. While reported experience using IO to treat primary refractory B-ALL is limited, given high rates of observed response to IO in patients with high-burden B-ALL, we initiated IO while the patient was being...
Karyotype Selected Genomic Alterations Hx of CNS or EM Disease IO doses

| Pre-IO alloHCT? | Post-IO alloHCT? | Best response Post-IO |
|----------------|------------------|-----------------------|
| No             | Yes              | CR with negative MRD  |
| Yes            | No               | CR with positive MRD  |

Table 1.

Pre-IO alloHCT?

Profi les of MSK patients with refractory/relapsed B-ALL associated with NRAS mutations, TP53 loss/mutation, or CDKN2A loss treated with inotuzumab ozogamicin.

| #  | Sex | Age at Dx | Relapsed/Primary | Pre-IO | Profi le at Dx | Karyotype | Pre-IO | No 4 CR with positive MRD | Yes 3 CR with negative MRD |
|----|-----|-----------|------------------|--------|----------------|-----------|--------|--------------------------|--------------------------|
| 1  | M   | 48        | Relapsed/Primary  | Yes    | Complex (5 abnormal karyotypes) | Profiling immediately prior to IO | No      | Hypodiploidy (37 chr) at diagnosis | Loss of TP53; homozygous deletion of CREBBP; hemizygous deletion of IKZF2; profi ling immediately prior to IO |
| 2  | M   | 52        | Refractory       | No     | 47 chromo at diagnosis | Hypodiploidy | Yes    | CR with positive MRD | Yes (adenopathy at Dx) |
| 3  | F   | 13        | Relapsed/Primary  | Yes    | Complex immediately prior to IO | Profiling immediately prior to IO | Yes | TP53 R175H; loss of IKZF1 gene (7p12); loss of IGFI gene (9p12); TP53 R175H; profi ling immediately prior to IO | Yes (positive MRD) |
| 4  | M   | 45        | Relapsed/Primary  | Yes    | Complex immediately prior to IO | Profiling immediately prior to IO | Yes | TP53 R175H; profi ling immediately prior to IO | Yes (positive MRD) |
| 5  | M   | 64        | Relapsed/Primary  | Yes    | Complex immediately prior to IO | Profiling immediately prior to IO | Yes | TP53 R175H; profi ling immediately prior to IO | Yes (negative MRD) |
| 6  | F   | 12        | Relapsed/Primary  | Yes    | Complex immediately prior to IO | Profiling immediately prior to IO | Yes | TP53 R175H; profi ling immediately prior to IO | Yes (negative MRD) |

Incorporating IO into frontline therapy for elderly patients with B-cell ALL harboring high-risk cytogenetic/molecular features warrants investigation and ongoing studies will provide further data regarding safety and efficacy of IO in the frontline setting.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2019.100186.

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