# Lower-intensity chemo-immunotherapy with cladribine, low-dose cytarabine, venetoclax and blinatumomab produces high response rates in patients with *BCR::ABL1*-negative B-cell/myeloid mixed phenotype acute leukemia

Mixed phenotype acute leukemia (MPAL) is a rare form of leukemia, accounting for <4% of all acute leukemias,[1] with an annual incidence of 0.35 cases per million person-years in the United States.[2] The 5th edition of the World Health Organization (WHO) Classification defines MPAL as the presence of blasts expressing more than one lineage-specific antigen; antigens may be expressed on a single population of blasts, or on two distinct blast populations of different lineages.[3] MPAL is further stratified based on the presence or absence of defining genetic abnormalities, such as *BCR::ABL1*, and *KMT2A*, *ZNF384* and *BCL11B* rearrangements.[3] In cases without defining genetic abnormalities, classification is based on immunophenotype, with B/myeloid MPAL being the most common subtype.[4] A recent study suggests that mixed phenotype can rarely be seen in acute myeloid leukemia (AML), particularly in the setting of *TP53* mutations and myelodysplasia-related changes, and is associated with a poor response to therapy.[5]

There is currently no standard of care for MPAL. Treatment options are based on small studies, with retrospective analyses favoring the use of acute lymphoblastic leukemia (ALL)-directed therapy and consolidation with allogeneic stem cell transplantation for all eligible patients.[6–8] Hybrid therapy, which incorporates agents that have activity in AML and lymphoid malignancies, achieves response rates similar to those produced by ALL-directed therapy but is generally associated with increased toxicity, limiting tolerability.[7] The treatment approach is particularly challenging for older or unfit patients who have high rates of toxicity and non-relapse mortality after intensive chemotherapy.[9] Newer available targeted therapies and highly effective monoclonal antibodies in this setting may be leveraged to reduce the toxicity of intensive chemotherapy and maintain efficacy. Case series have demonstrated the potential benefit of blinatumomab and venetoclax in this setting. In a case series of three patients treated with a FLAG (fludarabine, cytarabine, and filgrastim) backbone plus venetoclax, all achieved complete molecular remission and were alive at a median follow-up of 7 months.[10] In another case series of six patients treated with blinatumomab in combination with venetoclax and/or azacitidine, all achieved complete remission after the first cycle of therapy.[11] However, aside from clinical reports and case series, strong data to support the efficacy of venetoclax in MPAL are currently lacking. Cladribine, a purine nucleoside analog, has demonstrated potent activity in AML as well as lymphoid malignancies.[12] Herein, we present a series of four adult patients with *BCR::ABL1*-negative B/myeloid MPAL who were ineligible for intensive therapy and were treated with a hybrid regimen combining low-intensity chemotherapy with targeted B-ALL therapy. The patients' data were retrospectively collected in accordance with the Institutional Review Board of The University of Texas MD Anderson, and the research was conducted according to the Declaration of Helsinki.

The treatment backbone followed the published cladribine, low-dose cytarabine (LDAC), and venetoclax protocol in AML.[13] Briefly, the regimen consisted of a 28-day cycle of intravenous cladribine (5 mg/m² daily starting on day 1) for 4 to 5 days during induction and for 3 days during consolidation, combined with subcutaneous LDAC (20 mg twice daily starting on day 1) for 7 to 10 days during induction and for 5 to 7 days during consolidation. Venetoclax (400 mg daily or an equivalent dose with concomitant CYP3A inhibitors) was administered for 5 to 14 days and dexamethasone was administered for 4 days in each cycle. Intravenous blinatumomab was introduced 1 to 6 days after completion of the cladribine in each cycle and given as a continuous infusion for 14 to 18 days (Figure 1). All patients received antimicrobial prophylaxis per institutional policies. The patients' characteristics and outcomes are described in Table 1. The patients had a median age of 71 years at diagnosis (range, 55-77); three (75%) were female, and two had a prior history of malignancy (ovarian cancer in one patient and mantle cell lymphoma, prostate, and bladder cancer in another). The median white blood cell count, hemoglobin concentration, and platelet count at diagnosis were 3.45 $10^9$/L (range, 0.8-5.2), 7.9 g/dL (range, 7.1-11), and 101×$10^9$/L (range, 32-135), respectively. The median bone marrow blast percentage was 26% (range, 15-90), and no patient had central nervous system or extramedullary involvement at diagnosis. All patients had bilineage B/myeloid MPAL. The median proportion of myeloid blasts was 70% (range, 50-70), while the median proportion of B-cell lymphoid blasts was 30% (range, 30-50). All were negative for *BCR::ABL1* and *KMT2A*-rearrangement. Two patients harbored a *TP53* mutation at diagnosis, with one also having a *RUNX1* co-mutation. Both patients were categorized as having multi-hit *TP53*: one had a 17p deletion on cytogenetics,

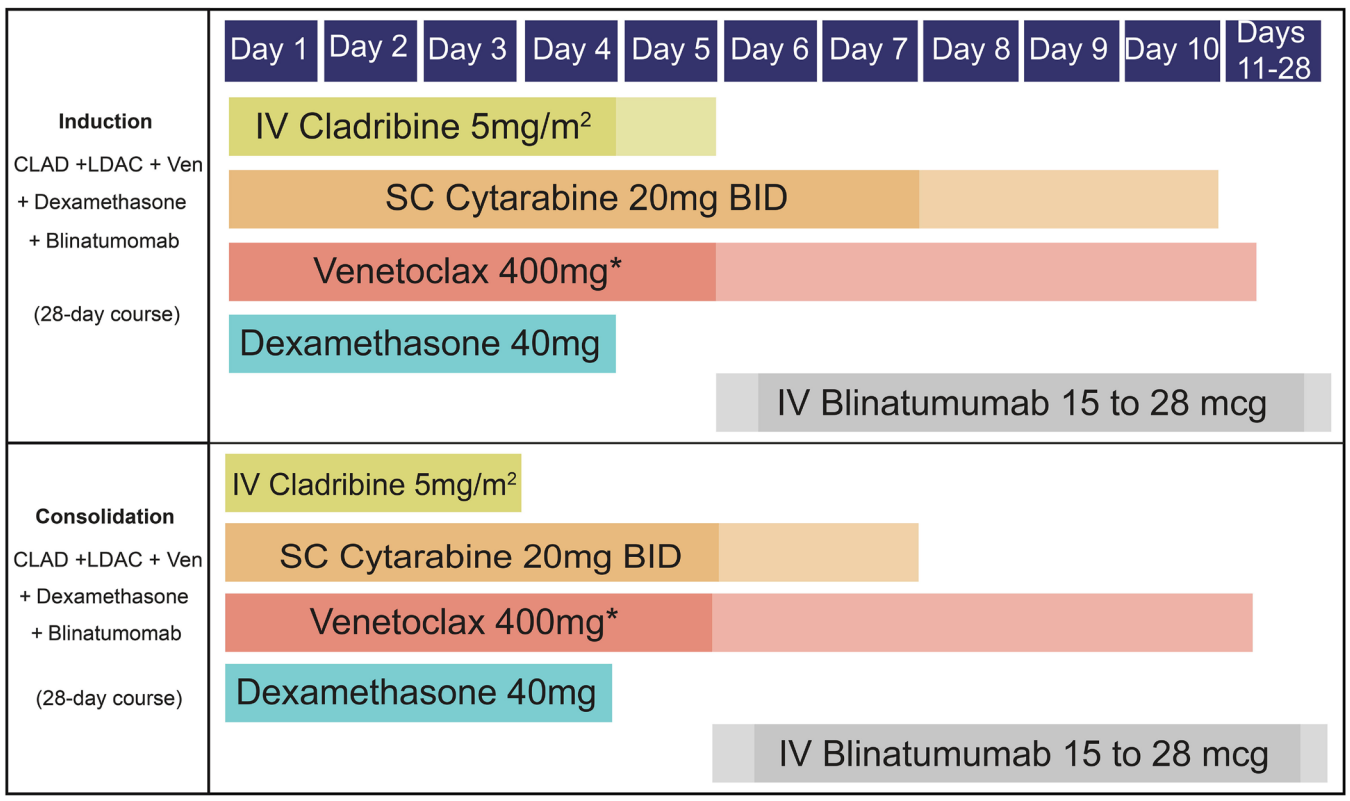


**Figure 1. Treatment schema.** Treatment schedule for cladribine + low-dose cytarabine + venetoclax + dexamethasone + blinatumumab. Note that the duration of cladribine and low-dose cytarabine administration varies between the induction and consolidation cycles. Venetoclax requires dose adjustment if cytochrome P450 3A inhibitors are administered concomitantly. CLAD: cladribine; LDAC: low-dose cytarabine; ven: venetoclax; IV: intravenous; SC: subcutaneous; BID: twice daily.

**Table 1.** Patients' characteristics.

| Characteristics | Patient #1 | Patient #2 | Patient #3 | Patient #4 |
|---|---|---|---|---|
| Age at diagnosis, years | 55 | 77 | 71 | 71 |
| Sex | F | M | F | F |
| Hemoglobin, g/dL | 7.8 | 8.1 | 7.1 | 11 |
| WBC count, x10$^9$/L | 0.8 | 5.2 | 3.2 | 3.7 |
| Platelets, x10$^9$/L | 73 | 32 | 130 | 135 |
| Blasts, % | 24 | 27 | 90 | 15 |
| Cytogenetics | Complex* | No metaphases | Diploid | Diploid |
| Somatic mutations | *TP53, RUNX1* | *TP53* | No | *ASXL1, IKZF1* |
| N of cycles | 2 | 2 | 3 | 2 |
| Best response to therapy | CR | CR | CR | CR |
| Best MRD response# | Negative | Negative | Negative | Negative |
| Status | Dead | Alive | Alive | Alive |

*Complex karyotype defined as three or more chromosomal abnormalities; #Measurable residual disease determined by flow cytometry. F: female; M: male; WBC: white blood cell; CR: complete response; MRD: measurable residual disease.

while the other had two *TP53* mutations with variant allele frequencies greater than 10%. One patient had *ASXL1* and *IZKF1* mutations. One of the three patients with available cytogenetics had a complex karyotype.

Three patients were treated with cladribine, LDAC, venetoclax, and blinatumomab as front-line therapy. One patient (patient #3) was initially diagnosed in an outside institution with 'acute undifferentiated leukemia' and was treated with one cycle of intravenous decitabine and venetoclax with residual disease. Upon confirming MPAL, the patient received cladribine, LDAC, venetoclax, and blinatumomab as first salvage therapy, achieving complete remission. Each patient received two to five doses of intrathecal chemotherapy with cytarabine or methotrexate. Three patients received two cycles of therapy, and the remaining patient received three cycles. One patient is currently receiving ongoing treatment with azacitidine, venetoclax and blinatumomab, while another patient opted to transition to palliative care.

Overall, the treatment was well tolerated, with no unexpected adverse events. Two patients experienced grade 3 neutropenic fever during induction, and two developed

neurological events related to blinatumomab, including grade 2 headache and grade 1 encephalopathy. One patient had a grade 1 elevation of alanine aminotransferase levels. The median time to absolute neutrophil count recovery above $1\times10^9$/L in each cycle was 30 days (range, 28-33), while the median time to platelet recovery above $100\times10^9$/L was 21 days (range, 19-29). One responder patient did not recover a platelet count above $100\times10^9$/L during follow-up. No therapy-related mortality was noted.

All patients treated with first-line cladribine, LDAC, venetoclax, and blinatumomab were assessed for response after the first cycle of induction and after each subsequent cycle. All three (100%) patients treated frontline achieved composite complete remission and undetectable minimal residual disease (MRD) by flow cytometry (sensitivity $10^{-4}$). The patient who was initially treated with decitabine and venetoclax achieved complete remission after cycle 1 and undetectable MRD after two cycles of therapy and was bridged to allogeneic stem cell transplantation. At the last follow-up, three patients were alive with a median follow-up of 4.2 months (range, 4.2–9.8) after diagnosis. One patient experienced disease progression with AML subtype 5 months after achieving complete remission and also had progressive metastatic ovarian cancer, dying 6 months after the initial diagnosis.

Older and unfit patients with *BCR::ABL1*-negative B/myeloid MPAL have a poor prognosis, with age being one of the most important predictors of overall survival and therapy-related mortality in MPAL.[14] The optimal treatment approach for this population remains challenging and should balance efficacy with the risk of toxicity and mortality. In these older, unfit patients with adverse risk prognostic factors, including *TP53* mutations, we observed that a hybrid treatment combining drugs active against both AML and ALL, along with targeted therapy for B-ALL, is a viable approach with very manageable side effects and no early therapy-related mortality. We acknowledge the short follow-up in our cohort; however, early responses are encouraging, with four of four (100%) patients achieving complete remission with undetectable MRD. This response rate appears higher than that reported with hypomethylating agents, with or without venetoclax, in patients categorized as having AML with mixed phenotype.[5] The patient who experienced relapsed disease had only a myeloid-lineage clone, which may reflect a resistant clone and could also represent a mechanism of escape from targeted therapy such as blinatumomab.[15] Although longer follow-up is needed, these data highlight the viability of treating older or unfit patients with B/myeloid MPAL with cladribine, LDAC, venetoclax and blinatumomab. This observation requires confirmation in a prospective clinical trial.

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**Contributions**

TMK designed the study. RSA and W-YJ collected and analyzed the data and drafted the manuscript. W-YJ, DH, FGH, ACG, GCI, KJ, JS, EJ, FRK, HK and TMK treated patients and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

**Data-sharing statement**

To protect patients' confidentiality, the data underlying the study are not publicly available. Reasonable requests by researchers for de-identified data should be directed to the author for correspondence.

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