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Case Report

Venetoclax-based low-intensity therapy in pediatric AML: A viable option for chemotherapy-intolerant patients

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Abstract: Childhood acute myeloid leukemia (AML) comprises 15-20% of pediatric leukemias and carries promising survival rates (60-70%) in high-income countries with use of intensive chemotherapy. This is associated with high treatment-related mortality in low- and middle-income countries, especially during induction, due to malnutrition, infections, and insufficient resources. Venetoclax, a BCL-2 inhibitor effective in older adults unfit for standard therapy, has shown potential in pediatric relapse AML. Here, we describe two children with newly diagnosed AML who developed life-threatening toxicities with intensive chemotherapy and were subsequently treated with venetoclax-based low-intensity regimens. Both patients achieved complete remission, attained measurable residual disease negativity, and maintained durable responses with minimal toxicity, allowing largely outpatient management. These cases suggest a promising, feasible alternative for chemotherapy-intolerant patients.

Keywords: Venetoclax, pediatric AML, low-intensity, chemotherapy, intolerance

Introduction

Acute myeloid leukemia (AML) accounts for 15-20% of childhood leukemias [1], with intensive chemotherapy remaining the mainstay of treatment with survival rates exceeding 60-70% in high-income countries (HICs) [2-4]. Over the past decades, HICs have achieved substantial gains through advances in supportive care, wider access to novel agents, and increased use of allogeneic hematopoietic stem cell transplantation (HSCT). However, these improvements have not translated equally to low- and middle-income countries (LMICs). In LMIC settings, maintaining chemotherapy intensity which is a critical determinant of cure in childhood AML is often not feasible due to poor tolerance and substantial treatment-related toxicity. A recent systematic review reported treatment-related mortality (TRM) rates as high as 23.2% in LMICs [5], with induction mortality alone accounting for over half of the deaths. Contributing factors include malnutrition, delayed diagnosis, high rates of multidrug-resistant infections, and a significant burden of invasive fungal infections. Such high TRM inevitably compromises survival outcomes.

Venetoclax, a selective BCL-2 (B-cell lymphoma 2) inhibitor, has transformed the treatment of older adults with AML who are unfit for intensive chemotherapy [6, 7]. The VIALE-A was a phase 3 randomized controlled trial involving treatment-naïve patients who were either elderly or otherwise ineligible to receive intensive chemotherapy and showed superior overall survival with a combination of azacytidine with venetoclax compared to azacytidine alone (14.7 months versus 9.6 months, hazard ratio for death, 0.66; P<0.001) with tolerable adverse events with no significant difference in quality of life [6]. Similarly, the VIALE-C trial assessed venetoclax in combination with low-dose cytarabine (LDAC) in a comparable patient population, showing clinical benefit in terms of remission rates and survival, although it did not meet its primary endpoint for statistical significance [8]. This lead to FDA approval of Venetoclax in this population and has also paved way for its use in younger, fit adults as well. In pediatric

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AML, venetoclax has been primarily explored in the relapsed/refractory setting [9-16]. Whether venetoclax, in combination with low-intensity chemotherapy, can be safely and effectively employed upfront in childhood AML, particularly in patients unable to tolerate intensive regimens, remains unknown. Here, we describe two cases of previously untreated childhood AML in whom a venetoclax-based low-intensity regimen was successfully used due to significant chemotherapy intolerance.

Case 1

A 13-year-old girl was diagnosed with AML harboring the *RUNX1::RUNX1T1* fusion and had severe pneumonia due to multidrug-resistant (MDR) *Klebsiella pneumonia* at presentation. She was deemed unfit for intensive induction and was started on low-dose metronomic chemotherapy with oral 6-thioguanine and etoposide as per SIOP-PODC guidelines [17]. Over the next two weeks, her pneumonia improved and her transfusion requirements markedly decreased. A day-30 bone marrow evaluation revealed morphological complete remission (CR) with a measurable residual disease (MRD) level of 0.69% by flow cytometry. She then received high-dose cytarabine (2 g/m^2 every 12 hours for 5 days), after which she had a complicated clinical course with NDM-1 *Klebsiella pneumoniae* bloodstream infection necessitating mechanical ventilation, vasopressor support, and prolonged ICU stay. Recovery was further complicated by septic encephalopathy, critical care neuropathy, and grade 4 pressure ulcers. Subsequent bone marrow evaluation showed ongoing complete remission with MRD 0.0012%. Given the life-threatening toxicities experienced with intensive therapy, further high-intensity regimens were abandoned. She was transitioned to a venetoclax-based, low-intensity protocol consisting of 28-day cycles of venetoclax (100 mg daily for 7 days, dose-adjusted for concomitant azole prophylaxis) and low-dose cytarabine (LDAC) (20 mg/m^2 for 7 days) delivered on an out-patient basis. This regimen was well tolerated, with no significant toxicities or hospital admissions. She has now completed 18 cycles, remains transfusion independent, and continues in MRD-negative remission for 24 months.

Case 2

An 11-year-old boy with AML harboring both FLT3 ITD mutation (allelic ratio 0.75) and NPM1 mutation was planned for standard 3+7 induction chemotherapy (Daunorubicin 60 mg/m^2 for 3 days with Cytarabine 100 mg/m^2 for 7 days) with midostaurin (25 mg BD from day 8-21). Treatment was truncated on day 5 (received Daunorubicin for 3 days, Cytarabine stopped after day 5, did not receive Midostaurin) due to febrile neutropenia and neutropenic enterocolitis, requiring prolonged ICU stay for septic shock. He recovered by day 45 of induction. End-of-induction marrow evaluation showed CR with a MRD level of 2.25%. Given his poor tolerance to intensive chemotherapy, a venetoclax-based low-intensity regimen was initiated. This consisted of 28-day cycles of venetoclax (100 mg daily for 7 days with concurrent azole prophylaxis), azacitidine (75 mg/m^2 daily for 7 days), and midostaurin (25 mg twice daily from day 8 to day 21). The regimen was well tolerated, and a bone marrow examination after two cycles confirmed CR with undetectable MRD. He subsequently received four additional cycles of venetoclax, azacitidine, and midostaurin, followed by single-agent midostaurin. The child remains in remission 14 months after diagnosis while continuing midostaurin monotherapy.

Discussion

The treatment of pediatric AML has advanced considerably over the years, with the dual goals of improving survival and reducing treatment-related morbidity and mortality. Standard intensive chemotherapy regimens, typically based on anthracycline-cytarabine combination, are effective but carry substantial TRM, particularly in LMICs. Administering intensive chemotherapy is especially difficult in patients who are unfit or unable to tolerate such regimens. These patients are often underrepresented in clinical trials and are more frequently encountered in LMICs than in HICs. Consequently, there is a pressing need for alternative, less toxic strategies tailored to the realities of LMIC healthcare systems.

Venetoclax, has emerged over the last decade as a promising agent for patients ineligible for intensive chemotherapy. While it is not effec-

tive as monotherapy due to rapid emergence of resistance, combining venetoclax with low-intensity therapy such as hypomethylating agents [6, 7] or LDAC [8] has shown synergistic activity and improved outcomes in adults. This approach is now widely adopted as the standard of care for elderly AML, but its role in younger, fit adults and children, however, remains largely unexplored. A recent phase III randomized trial [18] comparing venetoclax-HMA (hypomethylating agents) to standard 3+7 in younger adults with newly diagnosed AML reported higher complete remission rates and improved tolerability with venetoclax-HMA combination and comparable overall and progression-free survival. All patients who achieved complete remission in this trial went on to receive subsequent consolidation with high-dose cytarabine or allogeneic HSCT based on risk stratification. These findings support the efficacy of venetoclax-based low-intensity therapy as an induction strategy; however, whether such regimens can obviate or replace intensive consolidation approaches remains to be determined and warrants further prospective evaluation.

Given outcomes comparable to standard 3+7 induction in selected adult populations and its established use in unfit elderly patients with AML, venetoclax-based low-intensity regimens constitute a valuable therapeutic option for chemotherapy-intolerant children who might otherwise be limited to palliative care. Single-arm Phase II study from MD Anderson showed a 65% 2-year relapse-free survival with a combination of Venetoclax with low-dose azacytidine in adult AML who were in CR following intensive or low-intensity induction and unfit for HSCT [19]. In the two cases described here, venetoclax-based low-intensity therapy was delivered with minimal toxicity, without transfusion dependence or hospital admissions, and with sustained remission. In both cases, venetoclax-based regimens were employed not due to disease refractoriness, but because of life-threatening toxicity related to conventional chemotherapy. This positions venetoclax-based combinations as an effective “salvage induction” in children who cannot safely receive standard therapy. This approach is particularly relevant in LMICs, where resource constraints make the delivery of standard AML care challenging. Such regimens could improve not only survival but also quality of life, while being more feasible and potentially cost-effective.

Many unanswered questions remain regarding venetoclax use in childhood AML, including optimal dosing, duration, choice of partner agents, and the role and choice of consolidation including conventional chemotherapy and allogenic HSCT once the acute clinical crisis resolves. Furthermore, the long-term durability of remission with this approach is unknown.

To conclude, venetoclax-based low-intensity regimens may offer a feasible and less toxic therapeutic option for chemotherapy-intolerant children with AML, especially in LMIC settings. However, these observations are derived from a small case series and should therefore be interpreted with caution. Validation in larger, prospective pediatric cohorts is essential to define optimal patient selection, treatment strategies, and long-term outcomes before broader adoption of this approach.

Disclosure of conflict of interest

None.

Abbreviations

AML, Acute Myeloid Leukemia; HSCT, Hematopoietic stem cell transplant; HIC, High Income Countries; LMIC, Low-middle Income Countries; TRM, Treatment-related mortality; BCL-2, B-cell Lymphoma 2; MDR, Multi-drug resistant; CR, Complete remission; MRD, Minimal residual disease; LDAC, Low-dose Cytarabine; HMA, Hypomethylating agents.

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