High-Dose Cyclophosphamide for the Treatment of Refractory T-Cell Acute Lymphoblastic Leukemia in Children

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Summary: Despite an almost 80% overall survival rate in pediatric T-cell acute lymphoblastic leukemia (T-ALL), there is a subset of patients who are refractory to standard chemotherapy regimens and could benefit from novel treatment approaches. Over a 2-year period, we treated 5 pediatric patients with refractory T-ALL, aged 3 to 15 years, with high-dose cyclophosphamide (CY) at a dose of 2100 mg/m^2 for 2 consecutive days either alone (n = 1) or in combination with other chemotherapy agents (n = 4). Four of these 5 patients had a 1.5 log decrease in disease burden. Three of the 5 patients had no evidence of minimal residual disease (MRD) after high-dose CY. One patient developed transient grade 4 transaminitis and 1 patient developed grade 3 typhlitis. All 5 patients ultimately proceeded to hematopoietic stem cell transplant when MRD levels were $<0.01\%$. Pediatric T-ALL patients with persistent MRD after treatment with conventional chemotherapy may respond to CY at escalated dosing.

Key Words: pediatric T-ALL, high-dose cyclophosphamide, oncology

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T-cell acute lymphoblastic leukemia (T-ALL) comprises 10% to 15% of newly diagnosed pediatric ALL patients.[1] The overall survival for these patients is approaching 80%.[1,2] A major predictor of adverse event-free survival and overall survival is the response to induction therapy. Patients with persistent evidence of disease, as measured by either flow cytometry or molecular markers, have a higher relapse rate compared with those patients who have a rapid response to initial therapy.[3,4] Hematopoietic stem cell transplant (HSCT) has demonstrated a survival advantage in patients with high-risk T-ALL in first complete remission (CR).[3,5,6] HSCT is most successful after achieving minimal residual disease (MRD) levels $<0.01\%$. Lymphoblastic leukemia patients with detectable residual disease before HSCT have significantly poorer outcomes.[7,8]

Achieving levels of disease $<0.01\%$ to optimize HSCT results can be difficult with conventional therapies in a subset of T-ALL patients and there are very few novel agents available for these patients who do not respond to standard drugs. In the past 15 years, nelarabine has emerged as an active agent in relapsed T-ALL patients[9] and is currently being studied in frontline therapies. Although nelarabine can successfully lead to remission states in many T-ALL patients, there remains a cohort of patients who do not respond.[9,10] Furthermore, nelarabine is associated with significant risks; most notably severe neurotoxicity.[11–14]

Over a 2-year period, we treated 5 patients with T-ALL (identified as refractory given persistence of disease at levels $>0.01\%$ despite multiple rounds of chemotherapy) using cyclophosphamide (CY) at much higher doses than utilized in conventional ALL protocols (2100 mg/m^2/d on 2 consecutive days). Our decision to explore high-dose CY (HD-CY) as a therapeutic modality in these patients was based on several factors. Current upfront therapies for pediatric patients with ALL either do not use CY[1] or utilize doses of this drug no higher than 1200 mg/m^2.[15,16] In contrast, CY is given routinely at higher doses[17–19] to patients with solid tumors, such as sarcomas and neuroblastoma. In addition, HD-CY is used as part of cytoreduction for HSCT in relapsed ALL patients with favorable results.[20] Furthermore, CY has been proven to be effective as a single agent in lymphoblastic leukemia. The first descriptions of CY responses in pediatric ALL patients are from the early 1960s when patients were given daily CY at doses of 2 to 7.5 mg/kg/d.[21,22] Studies involving solid tumor patients started utilizing higher doses of CY at 10 mg/kg/d.[23] In 1974, Steuber et al[24] treated 14 relapsed pediatric ALL patients with single-dose CY at 40 mg/kg for 4 days, and noted bone marrow remissions in 5 of these lasting 4 to 6 weeks. Most of these patients failed CY at lower doses. Early studies evaluating the effects of CY demonstrated more resistance of T cells compared with B cells,[25] possibly indicating that higher doses of CY are needed in T-ALL, as is the case with methotrexate.[26]

Risks of HD-CY include nausea, pancytopenia, cardiac toxicity, hemorrhagic cystitis, renal insufficiency, inappropriate antidiuretic hormone secretion (SIADH), and secondary malignancies. These make HD-CY an unattractive candidate drug for patients who have excellent survival rates without its use. However, in patients who have high relapse rates with current treatment regimens, HD-CY, despite the potential side effects, might be an acceptable alternative. We report here our experience treating 5 refractory T-ALL patients with HD-CY.

METHODS

A waiver of authorization to conduct this retrospective review was approved by the Memorial Sloan-Kettering Cancer Center (MSKCC) institutional review board. All patients received CY 2100 mg/m^2/d over 2 consecutive days

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for a total course dose of 4200 mg/m^2. They received aggressive intravenous hydration and 48-hour continuous infusions of Mesna (4200 mg/m^2) to reduce the risk of hemorrhagic cystitis. Four patients received therapy in the pediatric day hospital as outpatients, whereas 1 was electively admitted to the hospital for the drug administration. All patients received ondansetron for antiemetic prophylaxis. MRD evaluation of bone marrow responses was measured by flow cytometry at University of Washington, Seattle, WA. Patients were defined as MRD negative if leukemic blasts were either undetectable or at levels of $<0.01\%$ of total mononuclear cells by flow cytometry. Classification of early T-cell precursor phenotype (ETP) was based on the criteria as previously published by Coustan-Smith et al[27]: absence of CD1a and CD8 expression, weak CD5 expression, and presence of a stem cell or myeloid marker on T-ALL blasts. Data analyses for patients are current as of July 2013.

RESULTS

Patients

Five male patients with refractory T-ALL, were treated at our institution from January 2011 to November 2012. Ages at diagnosis ranged from 3 to 15 years (median, 9 y). Four patients were transferred to our institution for care after having received induction therapy at a different hospital; the fifth patient was treated from diagnosis at MSKCC.

The detailed characteristics of these patients at presentation are provided in Table 1. Two patients had a phenotype consistent with precursor T-cell ALL; 1 patient was identified as having ETP and 2 patients had incomplete diagnostic flow cytometry (either myeloid or stem cell markers were missing) but remainder of phenotype consistent with ETP. One patient had CNS disease; the remaining 4 had no CNS involvement at diagnosis.

Three patients received a 4-drug induction (daunorubicin, vincristine, pegaspargase, and a glucocorticoid); 1 patient received the same 4-drug induction followed on day 14 with high-dose cytarabine therapy (Capizzi II) due to poor response and ETP; and 1 patient received a 5-drug induction according to NY II induction (Fig. 1)

Treatment

The time from diagnosis to receiving HD-CY was 1.7 to 5.2 months (median, 3 mo). The first patient received HD-CY with alemtuzumab as blasts expressed CD52 on flow cytometry. The patient only received 3 doses of alemtuzumab at therapeutic dosing (10 mg/m^2). The second patient was treated with HD-CY alone; the other 3 consecutive patients received HD-CY in combination with a multidrug regimen as the first 2 patients tolerated HD-CY either alone or with alemtuzumab with minimal toxicity. They received HD-CY on days 1 and 2 and then received vincristine (1.5 mg/m^2) on days 8 and 15, and started a 7-day course of dexamethasone (26 mg/m^2/d) on day 8. All patients received filgrastim.

Responses

All 5 patients had responses to HD-CY (Fig. 2). Three patients achieved MRD < 0.01% after HD-CY. The other 2 patients had a decrease in disease burden by 1.59 and

TABLE 1. Patient Characteristics

Patient	Age at Diagnosis (y)	CNS Status	WBC at Diagnosis ($\times 10^3$)	Cytogenetics	Phenotype	Disease Burden After Induction Therapy* (%)	Time (mo) From Dx to Receiving HD-CY	Concurrent Drugs With HD-CY	Disease Burden Pre-1st HD-CY (%)	Disease Burden Post-1st HD-CY (%)	# Cycles of Therapy to Achieve MRD < 0.01%	Status Post-BMT Time (mo)
1	3.4	1	169	46 XY	Pre T†	9.5	3.2	Alemtuzumab	0.35	< 0.01	5	A-NED 27 +
2	8.9	2	67	46 XY, Del 7q	Pre T	6.8	5.2	None	0.03	< 0.01	5	A-NED 20 +
3	6.5	1	7.6	46 XY	ETP	0.36‡	1.7	Vcr and Dex	0.36	< 0.01	2‡	A-NED 12 +
4	13.9	1	Not available	Not available	Pre T	13.3	3	Vcr and Dex	2.7	0.07	5	D-relapse 5
5	15	1	3	47XY, + 13	Pre T†	26.3	2	Vcr and Dex	4.9	0.08	6	A-relapse 12

Patient 1 received HD-CY with alemtuzumab. Patient 2 received HD-CY as a single agent. Patients 3, 4, and 5 received HD-CY with vincristine and corticosteroids.
*Disease burden measured by multicolor flow cytometry at University of Washington.
†Diagnostic flow cytometry lacked either myeloid or stem cell marker panel to exclude ETP.
‡Patient 3 received a 4-drug induction followed by high-dose cytarabine (Capizzi II) on day 14 of induction due to blasts % > 25%.
A indicates alive; A-relapse, alive with disease; BMT, bone marrow transplant; CNS, central nervous system status at time of diagnosis; Dex, dexamethasone; D-relapse, died of relapse; ETP, early T-cell precursor; HD-CY, high-dose cyclophosphamide; MRD, minimal residual disease; NED, no evidence of disease; Vcr, vincristine; WBC, white blood cell count.

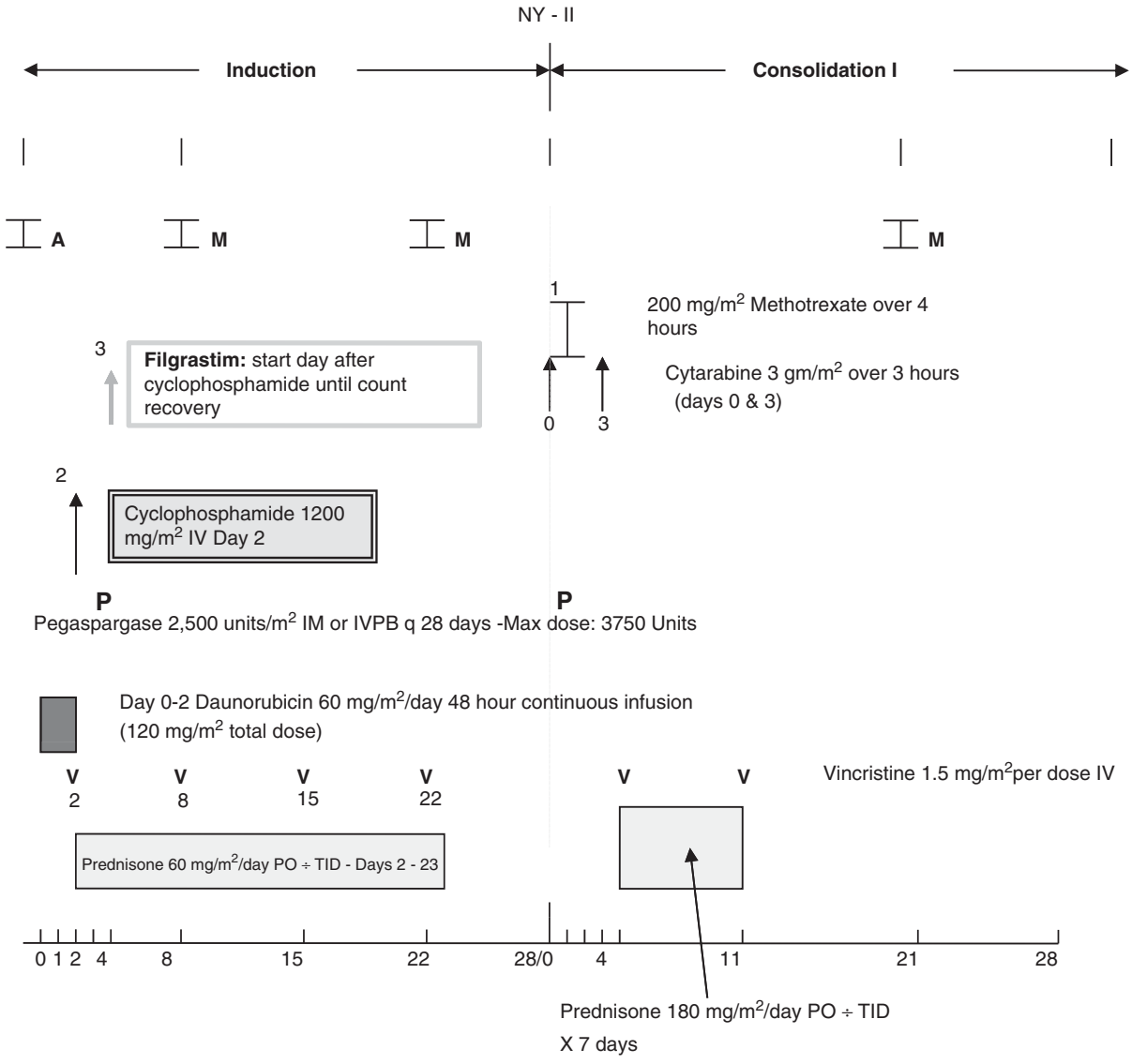

FIGURE 1. Protocol schema for New York II induction and consolidation 1. A indicates intrathecal cytarabine; M, intrathecal methotrexate.

1.79 log; one of these patients became MRD negative after receiving an additional cycle of HD-CY at 50% dosing and 1 achieved negative MRD after nelarabine. As no patients had morphologic evidence of disease before HD-CY, we could not use blast percentage a response criterion.

Figure 2 summarizes the treatment regimens the 5 patients received. They consisted of standard chemotherapy for T-ALL, including anthracyclines, vincristine, cytarabine, methotrexate, glucocorticoids, and asparaginase, and the newer agent, nelarabine. All regimens achieved some decrease in disease burden except the fourth (methotrexate, daunorubicin, and cytarabine) that patient 5 received (Fig. 2), which resulted in an increase in MRD level from 0.08% to 0.3%. Figure 3 demonstrates the response of MRD to 4 different cycles: HD-CY, high-dose methotrexate (8000 mg/m^2 weekly $\times 2$ consecutive weeks), nelarabine (650 mg/m$^2 \times 5$ consecutive days), and consolidation 1 of New York II[15] (Fig. 1) HD-CY decreased disease burden by >1.5 log for 4 patients. The other 3 regimens failed to impact MRD levels to that degree. Nelarabine had a >1 log response in 1 patient. High-dose methotrexate and consolidation 1 of New York II did not decrease MRD levels >1 log in any patient.

All patients proceeded to an allogeneic HSCT with negative marrow MRD and no evidence of CNS disease. The median time to transplant from diagnosis was 6 months with a range of 4 to 7 months. Four patients are alive at the time of publication with a median of 16 months (range, 12 to 27 mo) posttransplant. Two patients relapsed at 3 and 7 months posttransplant; 1 is alive at 12 months from transplant and 1 patient died of relapsed disease.

Toxicities

The period of neutropenia after HD-CY ranged from 14 to 16 days. The first patient was admitted with uncomplicated fever and neutropenia with no documented infection. The second patient received chemotherapy in the hospital because of significant morbidity after a previous chemotherapy

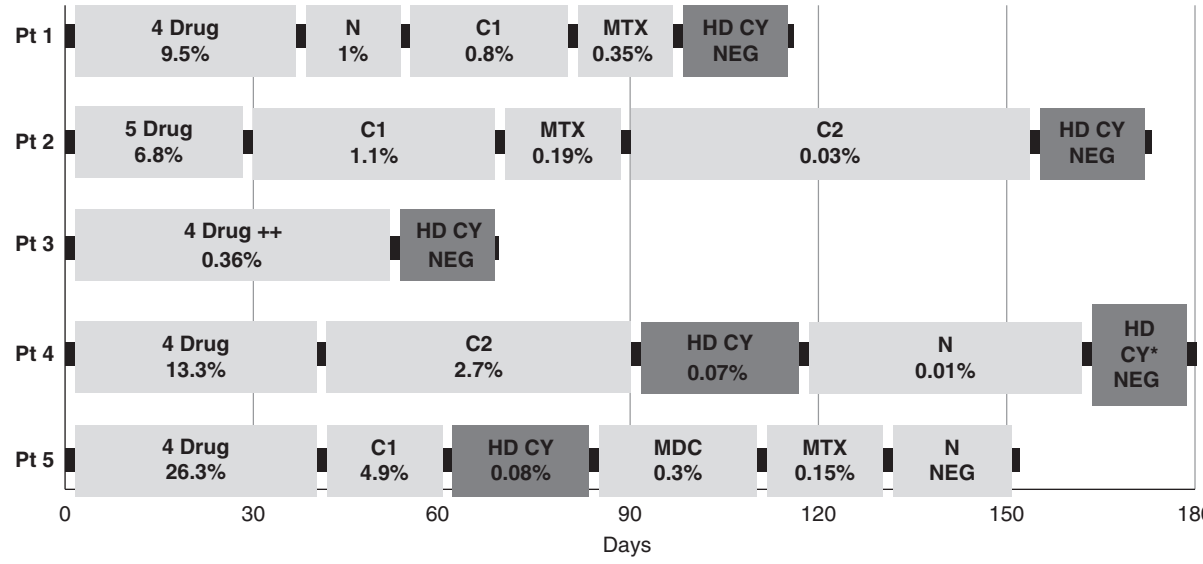

FIGURE 2. Each box represents a therapy cycle; the number in each box represents amount of disease detected by multicolor flow upon recovery from that cycle and NEG indicates that MRD was undetectable or <0.01%. HD-CY was given after 4 cycles of chemotherapy in the first 2 patients. The last 3 patients received HD-CY after only 1 or 2 cycles. The first cycle refers to induction therapy; 4 drug signifies daunorubicin, vincristine, pegaspargase, and glucocorticoid, 5 drug signifies cyclophosphamide added to the before-mentioned 4 drugs, 4 drug + + represents a 4-drug induction followed by high-dose cytarabine regimen (Capizzi II) on day 14 when patient was noted to have >25% blasts in the bone marrow. N, nelarabine (650 mg/m^2 × 5 d); C1, consolidation 1 cycle of New York II regimen consisting of cytarabine, methotrexate, vincristine, pegaspargase, glucocorticoid; C2, consolidation 2 cycle of New York II regimen[15] consisting of cyclophosphamide, thioguanine, vincristine, glucocorticoids, methotrexate (200 mg/m^2), daunorubicin, and cytarabine; MTX, high-dose methotrexate (8000 mg/m^2 × 2 wk); MDC, methotrexate (200 mg/m^2), daunorubicin, and cytarabine; HD-CY, high-dose cyclophosphamide (2100 mg/m^2 × 2 d); and HD-CY*, high-dose cyclophosphamide (2100 mg/m^2 × 1 d).

regimen including a fistula-in-ano that required a diverting colostomy. His past treatments had also been complicated by recurrent *Clostridium difficile* infections. After HD-CY, he developed a transient increase in ostomy output and an uncomplicated *C. difficile* colitis; both resolved without significant morbidity. The third patient developed transient grade 4 elevation of transaminases 2 weeks after HD-CY. Hepatic biopsy revealed mild iron overload which was likely unrelated to HD-CY. The fourth patient developed neutropenic enterocolitis on day 10 of this regimen; he received broad-spectrum antibiotics and fully recovered. The fifth patient had no complications.

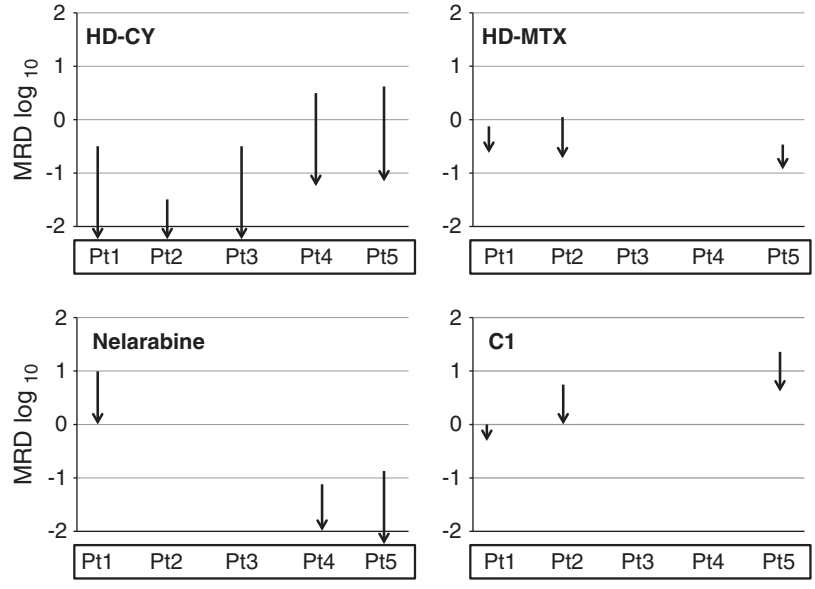

FIGURE 3. Minimal residual disease (MRD) responses to specific regimens. MRD was measured before and after each cycle for each patient; each line represents the decrease in MRD from the start of the cycle to recovery of counts. Arrows falling below −2 represent undetectable disease. Not all patients received all 4 regimens. C1 indicates consolidation 1 of NY II; HD-CY, high-dose cyclophosphamide; HD-MTX, high-dose methotrexate.

No patients developed SIADH, cardiac toxicity, renal insufficiency, or hemorrhagic cystitis.

DISCUSSION

Patients with T-ALL who have residual disease after induction therapy have a poor prognosis[3] and HSCT in CR1 is usually recommended as an alternative to continued chemotherapy.[5] HSCT results for T-ALL patients are significantly superior in those who have achieved MRD < 0.01%. Few options exist for patients with T-ALL who are newly diagnosed and refractory to conventional chemotherapy drugs.

Nelarabine is one of the most studied novel agents for relapsed T-ALL in recent years. From 2001 to 2005, 72 subjects were enrolled on a Children's Oncology Group pilot trial to evaluate the safety of incorporating nelarabine into frontline therapy for pediatric T-ALL patients. These patients had acceptable toxicity with only 1 developing a Guillan-Barre-like syndrome.[28] On the basis of these results, nelarabine is currently being studied in a phase III trial in newly diagnosed patients with high-risk T-ALL by the Children's Oncology Group.[29] Patients are identified as high risk based on MRD levels >1% after induction therapy as detected by flow cytometry. This trial is still ongoing, the results are blinded, and the impact of nelarabine in frontline therapy for T-ALL patients is unknown. Gamma-secretase inhibitors are promising targeted therapies; however, they are still being investigated in phase I studies in the relapse setting and their role in T-ALL patients is yet to be determined.[30]

In this report, we describe our experience in 5 consecutive patients with refractory T-ALL with HD-CY. All 5 had a decrease in disease burden and were ultimately able to proceed to HSCT. Furthermore, we observed minimal morbidity when HD-CY was given either as a single agent or combined with other therapies. One patient developed neutropenic enterocolitis after HD-CY when it was given in combination with dexamethasone and vincristine. Although combination of conventional dose CY with other agents is not novel, it is possible that including higher dosing of CY will achieve improved responses in this patient population.

It is possible that some of the responses to HD-CY that we report here are due to the other drugs administered. The patient that received alemtuzumab only received 3 doses at therapeutic level, hence it is unlikely that the response in disease was due to alemtuzumab. The 3 patients that received dexamethasone and vincristine had all previously received vincristine and another glucocorticoid, prednisone, during induction without achieving CR.

Our study provides real-time analysis of responses to individual drugs or regimens (Fig. 3). HD-CY lowered MRD by >1.5 log in 4 patients; the fifth patient had only 0.03% MRD before HD-CY and became MRD negative after receiving HD-CY. Surprisingly, single-agent nelarabine alone did not lower MRD levels >1.5 log for the 3 patients we treated; patient 5 did achieve MRD negativity after nelarabine. High-dose methotrexate also resulted in disappointing results and lowered MRD levels <1 log. Even multidrug regimens failed to decrease MRD burden by >1 log.

This study is limited by the small number of patients as it is a single institution experience. However, we present encouraging bone marrow response data in patients with refractory T-ALL for whom there are very few viable other options available. We tried multiple regimens and demonstrated reproducible responses to HD-CY in this refractory patient population. Although novel agents are needed and are being investigated for refractory T-ALL patients, escalating the dose of CY for these patients may lead to improved responses and successful transition to HSCT.

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