Leukemia Research 85 (2019) 106217

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Research paper

High-dose etoposide and cyclophosphamide in adults and children with primary refractory and multiply relapsed acute leukaemias: The Royal Marsden experience

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ARTICLE INFO

Keywords:
High dose
Etoposide
Cyclophosphamide
Refractory
Relapsed
Leukemia

ABSTRACT

Introduction: For patients with primary refractory and relapsed acute leukaemias allogeneic stem cell transplantation is the only hope for cure, but morphological remission is not always achieved after standard salvage regimens. Here we review the experience with high-dose etoposide and cyclophosphamide (HD-Et/Cy) in relapsed/refractory acute leukaemias at the Royal Marsden Hospital.

Patients and Methods: Twenty-three patients (15 adults, 8 children) with refractory/relapsed acute myeloblastic (n = 18; 78%), lymphoblastic (n = 4; 17%) or biphenotypic (n = 1; 4%) leukaemia who had failed to respond to at least one previous line of chemotherapy received HD-Et/Cy at our institution between 2006 and 2015.

Results: Overall response rate was 21.7% (95%CI 4.0–40.0). Median overall survival was 14.8 months (95%CI 9.1–49.1). Eight (35%) patients (7 AML, 1 biphenotypic leukaemia) proceeded to allogeneic transplant after one cycle of HD-Et/Cy: four of them (50%; 3 adults, 1 child) in complete remission and another four children (50%) with aplastic bone marrow with scattered blasts. Among the transplant recipients, three with AML (38%), ie. one adult (responder) and two children with aplastic bone marrow with scattered blasts, became long-term survivors 9.8, 4.4 and 2.5 years post-HD-Et/Cy, respectively. Toxicity profile was comparable to similar regimens with no

Abbreviations: 95%CI, 95% confidence interval; ALL, acute lymphoblastic leukaemia; AML, acute myeloblastic leukaemia; ASCT, allogenic stem cell transplant; BM, bone marrow; CTCAE, common toxicity criteria for adverse events; CR, complete remission; CRp, remission with insufficient platelet recovery; C1D1, Cycle 1 Day 1; EFS, event free survival; HD-Et/Cy, high-dose etoposide / cyclophosphamide; ORR, overall response rate; OS, overall survival; PR, partial remission; SCT, stem cell transplant

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https://doi.org/10.1016/j.leukres.2019.106217
Received 12 June 2019; Received in revised form 11 August 2019; Accepted 12 August 2019
Available online 13 August 2019

treatment-related deaths. The most common grade 3–4 toxicity was febrile neutropenia (96%).
Conclusions: HD-Et/Cy can salvage patients with refractory/relapsed AML who remain candidates for allogeneic stem cell transplantation after failure of standard salvage regimens and do not have access to clinical trials.

1. Introduction

The prognosis of patients with acute myeloblastic leukaemia (AML) has improved substantially over recent decades, with current survival rates of approximately 35–50% in adults [1,2] and 68–76% in children [3–5]. For patients with acute lymphoblastic leukaemia (ALL), survival rates are up to 30–40% in adults [6,7] and approach 90% in children [8,9]. However, a significant proportion of patients still fail to achieve complete remission (CR) following standard therapy or subsequently at relapse. Clinical outcomes for these patients remain dismal. For patients with relapsed AML, the estimated 5-year overall survival (OS) is 10–12% in adults [10] and 29–34% in children [11–13]; whereas for patients with relapsed ALL, the 5-year OS in adults is 7–10% [14,15] and the 3-year and 10-year OS in children are 57% and 36%, respectively [16,17]. Hence, there is an unmet need for more effective therapies for patients with relapsed or refractory acute leukaemias.

Multiple chemotherapeutic regimens have been used for salvage therapy in primary refractory or multiply relapsed acute leukaemias with the aim of achieving CR in order to proceed to an allogeneic stem cell transplant (ASCT). Brown and colleagues first used the combination of high-dose etoposide and cyclophosphamide (HD-Et/Cy) in the 1980s as a salvage regimen for relapsed and refractory acute leukaemias and lymphomas, achieving CR in 35% of cases [18]. Subsequently, HD-Et/Cy has been used in small case series or single-arm studies as salvage therapy for primary refractory or multiply relapsed acute leukaemia with CR rates of 28–57% [19–21].

Given the lack of effective therapies for patients with refractory or multiply relapsed leukaemias, our institution adopted in 2006 the regimen proposed by Johny et al as salvage therapy [20]. This study describes our institutional experience with HD-Et/Cy in adults and children with primary refractory or multiply relapsed acute leukaemias.

2. Patients and methods

Our main objective was to review the safety and efficacy of HD-Et/Cy in adults and children with primary refractory or multiply-relapsed acute leukaemias treated at the Royal Marsden NHS Foundation Trust between the 1st January 2006 and the 31st December 2015.

2.1. Patients

Adults and children aged ≥1 year diagnosed with primary refractory or relapsed AML, ALL or biphenotypic leukaemia who had been treated with HD-Et/Cy were eligible for the study. Decision to treat with HD-Et/Cy was done at physician's discretion based on the patient's clinical condition, patient/parents' preferences, availability of novel therapies/early phase trials and donor availability for allogeneic stem cell transplant. Eligible patients had received at least one previous line of chemotherapy prior to HD-Et/Cy. Those cases who had received high-dose etoposide and/or cyclophosphamide exclusively as part of conditioning regimens for ASCT were excluded. Patients' records were reviewed for extraction of clinically relevant data following approval by our institutional review board.

2.2. Treatment

Patients were treated according to the regimen reported by Johny et al [20]: etoposide 2.4 g/m^2 as a continuous intravenous infusion over 34 h commencing on day 1; and cyclophosphamide 2 g/m^2 intravenous infusion over 2 h daily on days 3–5.

Response was assessed in bone marrow (BM) aspirate or trephine before each course of HD-Et/Cy and after that at day 28 (± 3 days) post-HD-Et/Cy, if absolute neutrophil count $\geq 0.5 \times 10^9$ cells/L, or earlier if strong clinical suspicion of refractory disease; alternatively BM aspirate/trephine was done at day 35 (± 3 days) post-HD-Et/Cy, regardless of the absolute neutrophil count. Patients who were not fit for the procedure, especially in the context of clinical suspicion of refractory disease, evidence of blasts on morphology/immunophenotyping in peripheral blood was considered sufficient evidence of treatment failure. All objective responses to treatment were confirmed with bone marrow aspirates/trephines. Cytogenetic analysis, where available, was also used to determine remission status. Treatment with HD-Et/Cy was discontinued once disease progression was documented. Supportive care was provided according to local institutional guidelines, including antifungal and P. jirovecii prophylaxis.

2.3. Definitions

Patients were considered *adults* if aged ≥18 years at the time of administration of HD-Et/Cy; and *children* if they were aged between 1 and 17 years at the time of administration of HD-Et/Cy. Primary refractory acute leukaemias included those which had not responded to at least one previous line of chemotherapy considered standard of care at the time of initial diagnosis. Relapsed acute leukaemias included those which had recurred after having achieved morphologic CR with first line treatment and had not responded to at least one previous line of chemotherapy considered standard of care at the time of disease recurrence.

Response was defined as per the recommendations of the International Working Group for Therapeutic Trials in AML [22]. Treatment failure included those patients who did not achieve CR, complete remission with insufficient platelet recovery (CRp) or partial remission (PR) following one cycle of HD-Et/Cy. Patients who died as a result of complications of HD-Et/Cy were classified as treatment-related deaths.

Event free survival (EFS) was defined from Cycle 1 Day 1 (C1D1) of HD-Et/Cy to date of relapse, death or last follow-up, whichever occurred earlier. For patients with treatment failure, EFS was censored at C1D1 of HD-Et/Cy. OS was defined from C1D1 of HD-Et/Cy to date of death or last follow-up.

2.4. Statistical analysis

Safety was assessed by the incidence and severity of adverse events, which were graded according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. Efficacy was assessed using the overall response rate (ORR) after one cycle of HD-Et/Cy, the EFS and the OS. The ORR was presented as the overall proportion of patients with CR, CRp or PR with the 95% confidence interval (95% CI). EFS and OS were calculated using Kaplan-Meier methods. Median survival rates were presented with the 95% CI.

3. Results

3.1. Patients

Overall 23 cases with primary refractory or multiply relapsed acute leukaemias, including 15 adults (65%) and 8 children (35%), received at least one cycle of HD-Et/Cy at our institution in the study period. The median age was 30.2 years (range 2.2–63.6). Patient characteristics are

Table 1
Baseline patient characteristics.

Age groups[1]	
Adults (≥18 years)	15 (65.2%)
Children (< 18 years)	8 (34.8%)
Median age (range) in years[1]	
Whole cohort	30.2 (2.2 – 63.6)
Adults	53.4 (23.9 – 63.6)
Children	5.9 (2.2 – 16.7)
Gender	
Female	8 (34.8%)
Male	15 (65.2%)
Immunophenotyping	
AML	18 (78.3%)
B-ALL	2 (8.7%)
T-ALL	2 (8.7%)
Biphenotypic leukaemia	1 (4.4%)
Status	
Primary refractory	8 (34.8%)
Relapsed	15 (65.2%)
High-risk cytogenetics	
Yes[2]	12 (52.2%)
No	11 (47.8%)
Previous lines of chemotherapy	
Median (Range)	2 (1 – 4)
1 regimen	1 (4.4%)
2 regimens	13 (56.5%)
≥3 regimens	9 (39.1%)
WBC on Cycle 1 Day 1 (x10^9 cells/L)	
Median (Range)	4.1 (0.2 – 176.2)
0-19.9	19 (82.6%)
20-49.9	2 (8.7%)
≥50	2 (8.7%)
Blast count in BM pre-HD-Et/Cy (%)	
Median (Range)	38 (6 – 98)
5-24.9%	6 (26.1%)
≥25%	15 (65.2%)
N/A[3]	2 (8.7%)

ALL: acute lymphoblastic leukaemia; AML: acute myeloblastic leukaemia; BM: bone marrow; HD-Et/Cy: high-dose etoposide and cyclophosphamide; N/A: not available; WBC: white blood cells.

[1] At the time of administration of HD-Et/Cy.

[2] Complex karyotype [n = 6], FLT3-ITD mutation [n = 2], t(6;11) [n = 1], t(6;9) [n = 1], trisomy 13 [n = 1] and t(3;11) plus t(9;22) plus trisomy 8 [n = 1].

[3] One patient with primary refractory leukaemia and one patient with relapsed leukaemia were diagnosed according to clinical findings and the presence of circulating blasts in peripheral blood.

summarised in Table 1. Overall, 8 patients (35%) had primary refractory acute leukaemia (7 AML, 1 ALL) and 15 patients (65%) had multiply relapsed acute leukaemia (11 AML, 3 ALL, 1 biphenotypic leukaemia). All children treated with HD-Et/Cy had AML. One adult patient had been initially diagnosed at the age of 14 years with B-ALL and presented with a relapse 8 years later; he received HD-Et/Cy after a second relapse at the age of 24 years. Both adults and children had received at least two previous lines of treatment, including in all cases FLAG-based chemotherapy (with or without idarubicin) prior to HD-Et/Cy. As an exception, a 53 year-old woman with AML and a background of myelodisplasia had only received one line of treatment (FLAG-Ida) prior to HD-Et/Cy. Three patients (13%) had received prior SCT in first remission, one autologous SCT in an adult with biphenotypic leukaemia, one ASCT in an adult with T-ALL; and another ASCT in second remission in a child with B-ALL who experienced a late relapse in adult age.

All patients had documented BM involvement at the start of HD-Et/Cy, except in two cases for whom the diagnosis of refractory/relapsed disease was established by the presence of blasts on morphology and immunophenotyping in peripheral blood: one adult with primary refractory AML and a child with relapsed AML. Five patients (22%), one adult and four children, had a lumbar puncture done prior to HD-Et/Cy: no blasts were detected in the cerebrospinal fluid in any case.

Table 2
Toxicity of high-dose etoposide and cyclophosphamide in adults and children with refractory or relapsed acute leukaemias according to CTCAE v4.03.

Adverse event[1]	G1	G2	G3	G4	Total
HAEMATOLOGICAL TOXICITIES: Responders only (n = 5; cycles = 6)[2]					
Neutropenia	0	0	0	6	6
Thrombocytopenia	0	0	0	6	6
NON-HAEMATOLOGICAL TOXICITIES: Whole cohort (n = 23; cycles = 24)					
Infection					
Febrile neutropenia	0	0	28	3	31
Lung infection	0	1	5	0	6
Hepatobiliary disorders Other: Hepatic lesions[3]	0	0	2	0	2
Herpes zoster reactivation[4]	0	0	1	0	1
Gastrointestinal					
Elevated bilirubin	9	12	0	0	21
Elevated ALT	9	3	3	0	15
Mucositis	0	4	9	0	13
Gastrointestinal haemorrage	0	0	2	0	2
Other					
Tumour lysis syndrome	0	0	7	0	7
Dermatological toxicity[5]	3	4	0	0	7
Epistaxis	0	0	2	0	2
Focal intracranial haemorrhage	0	1	0	0	1
Catheter-related thrombosis	0	1	0	0	1

ALT: alanine amino-transferase; CTCAE: common terminology criteria for adverse events.

[1] No grade 5 events related to high-dose etoposide and cyclophosphamide occurred.

[2] Haematological toxicities were evaluable in responders only.

[3] Liver lesions associated with suspected fungal infection (both cases presented concurrent changes in chest CT scan).

[4] Cutaneous involvement only.

[5] Rash: macular, maculo-papular, erythematous or purpuric (n = 4), exfoliative (n = 1), residual hyperpigmentation (n = 2).

3.2. Treatment

Twenty-two patients received one cycle of HD-Et/Cy and one adult with T-ALL received two cycles. Deviations from the HD-Et/Cy regimen reported by Johny et al [20] occurred on an individual basis, including: administration of cyclophosphamide in days 1 to 3 and etoposide in day 4, without variation of the doses, in one adult and two children; fractioning of the dose of etoposide (1600 mg/ m^2 over 24 h on day 1, and then 800 mg/m^2 over 12 h following completion of cyclophosphamide) due to issues with drug supply at the initiation of the cycle in one child; capping the doses of both etoposide and cyclophosphamide at 2 m^2 in 3 adults with body surface area > 2 m^2; gemtuzumab-ozogamicin was administered concurrently with HD-Et/Cy at the discretion of the treating physician in a 56 year-old man with primary refractory AML after two previous lines of chemotherapy and a 15 year-old boy with a relapsed AML treated with two previous lines of chemotherapy. No other anticancer therapies were administered concurrently with HD-Et/Cy in these two cases or the rest of the patients.

3.3. Safety

The toxicity data for HD-Et/Cy is shown in Table 2. All patients experienced severe bone marrow suppression as a result of their underlying disease and chemotherapy. The most common non-haematological grade 3–4 toxicity was febrile neutropenia, which occurred in 22 patients (96%) with 31 episodes of febrile neutropenia over a total 24 cycles of HD-Et/Cy. Three of these episodes (10%), one in an adult and two in children, required admission to an Intensive Care Unit. A 30 year-old woman with AML presented with altered sensation over the territory of the right 5th cranial nerve six days after C1D1 of HD-Et/Cy. An urgent head MRI scan was done with the suspicion of leptomeningeal dissemination. The MRI scan showed a cortical haemorrhage in

Table 3
Characteristics of responders and non-responders who proceeded to allogeneic stem cell transplant following high-dose etoposide and cyclophosphamide.

#	Age[1] (yrs)	Gender	Immunoph.	Status	High-Risk Cytogenetics	Nº of prior regimens	Best response[2]	Blast count in BM pre-HD Et/Cy (%)	Blast count in BM post-HD Et/Cy (%)[2]	HSCT post-HD Et/Cy (conditioning)	EFS[3] (months)	OS[3] (months)	Status at last follow-up
RESPONDERS													
1	56.6	M	AML	Primary Refractory	No	2	CR[4]	38	4	Matched unrelated Source N/A (Fludarabine + Busulphan)	117.1	117.1	Alive/ Disease-free
2	63.6	F	AML	Primary Refractory	Complex karyotype	2	CR	6	2	Matched unrelated PB (Fludarabine + Melphalan + Alemtuzumab)	7.1	7.9	Dead
3	7.8	M	AML	Relapsed	t(11;19)	2	CR	28	< 5	Matched related PB (Fludarabine + Busulphan + Melphalan)	6.8	8.8	Dead
4	27.6	M	BL[5]	Relapsed	Complex karyotype	3	CRp	6	2	Mis-matched 9/10 Unrelated PB (Fludarabine + Melphalan)	11.6	13.8	Dead
5	23.9	M	T-ALL	Primary Refractory	14q11 rearrangement	3	PR[6]	21	1	No	3.6	11.8	Dead
NON-RESPONDERS WHO PROCEEDED TO ALLOGENEIC STEM CELL TRANSPLANT													
6	2.9	M	AML	Relapsed	Complex karyotype	3	TF	23	Aplasia with blasts	Mis-matched 9/10 unrelated PB (Cyclophosphamide + Busulphan + Melphalan)	N/A	52.8	Alive/ Disease-free
7	2.2	M	AML	Relapsed	Complex karyotype	2	TF	N/A[7]	Aplasia with blasts	Matched related PB (Cyclophosphamide + Busulphan + Melphalan)	N/A	30.1	Alive/ Relapsed[8]
8	4.0	M	AML	Relapsed	t(11;19)	3	TF	90	Aplasia with blasts	Matched unrelated UCB (Fludarabine + Thiotepa + Treosulfan)	N/A	17.2	Dead
9	8.0	F	AML	Primary Refractory	Complex karyotype	3	TF	52	Aplasia with blasts	Matched unrelated PB (Fludarabine + Melphalan + Alemtuzumab)	N/A	7.1	Dead

ALL: acute lymphoblastic leukaemia; AML: acute myeloblastic leukaemia; BL: biphenotypic leukaemia; BM: bone marrow; CR: morphologic complete remission; CRp: morphologic complete remission with incomplete platelet recovery; EFS: event-free survival; F: female; FU: follow-up; HD Et/Cy: high-dose etoposide and cyclophosphamide; HSCT: haematopoietic stem cell transplantation; Immunoph.: immunophenotyping; M: male; N/A: not available/applicable; OS: overall survival; PB: peripheral blood; TF: treatment failure; UCB: umbilical cord blood; #: patient number.

[1] Age at the start of HD-Et/Cy.

[2] After 1 cycle of HD Et/Cy (NB: blast count pre- and post-HD Et/Cy based on morphology).

[3] Assessed from Cycle1-Day 1 of HD Et/Cy.

[4] This patient also received concomitant gemtuzumab-ozogamicin.

[5] Myeloid and T lineages.

[6] CRp in the BM after one cycle of HD Et/Cy, but response classed as PR due to a persistent retrocrural nodal mass; after a 2nd cycle of HD Et/Cy, there was further progression of the nodal mass.

[7] Circulating blasts in peripheral blood after FLAG-Ida, BM aspirate not done pre-HD Et/Cy because patient clinically unwell for procedures.

[8] Isolated extramedullary relapse (lower limb) 11 months post-SCT, further salvage therapy with donor-lymphocyte infusion.

the left frontal lobe and a small haematoma in the right cerebellum, which was away from the right 5th nerve. There were no lesions in the cavernous sinuses and the meningeal enhancement was normal. At the time she had thrombocytopaenia grade 4 (platelets 6×10^9/L). No CSF was available pre- or post-HD-Et/Cy. She had refractory disease in the bone marrow after one cycle of HD-Et/Cy. Hence, this focal intracranial haemorrhage was most likely a result of the thrombocytopaenia in the context of refractory disease and the treatment with three lines of chemotherapy (including HD-Et/Cy). The intracranial haemorrhage was managed conservatively. The patient died 2.8 months later as a result of disease progression. Additionally, two children developed veno-occlusive disease (VOD) after allogeneic stem cell transplant (Table 3, patients #7 and #8).

There were no differences in the incidence of side effects between adult and paediatric patients (data not shown). There were no treatment-related deaths.

3.4. Efficacy

Efficacy outcomes are summarised in Table 3. All patients were evaluable for response. All patients had response assessments with BM aspirates/trephines, except for one adult with AML who had a baseline BM aspirate with 97% of blasts and was subsequently diagnosed with treatment failure due to the presence of blasts in peripheral blood at day 16 post-HD-Et/Cy. Additionally, two of the children who proceeded to allogeneic stem cell transplant in aplasia with blasts also developed blasts in peripheral blood post-BM for response assessment and pre-transplant

Overall, there were five responders (4 adults, 1 child), including 3 CR, 1 CRp and 1 PR (Table 3): the CR/CRp rate was 17.4% and the ORR (CR/CRp/PR) was 21.7% (95% CI 4.0–40%). Subsequently four of the responders proceeded to ASCT. An adult with T-ALL who achieved PR did not proceed to ASCT due to refractory disease after the second cycle of HD-Et/Cy (Table 3). Additionally, four non-responders also proceeded to an ASCT as a last-ditch attempt to treat their underlying disease. These were all children with AML who had aplastic BM with scattered blasts after one cycle of HD-Et/Cy. Thus, five out of eight children (63%) were able to proceed to ASCT. Overall, eight patients (4 responders, 4 non-responders) received ASCT after HD-Et/Cy. This was the first ASCT in all cases (one adult with AML had previously received an autologous SCT). The transplanted patients received their graft at a median of 50 days (range, 33–66) after C1D1.

The remaining 14 non-responders who did not proceed to ASCT, including the child who had received HD-Et/Cy plus gemtuzumab-ozogamicin, were subsequently treated with: palliative care only (n = 7); hydroxyurea as single agent or in combination with other holding chemotherapies (n = 4); mitoxantrone, sorafenib or methotrexate/asparaginase (n = 1 each).

The median follow-up (range) for the whole cohort was 2.8 months (1.0–117.1). One child who returned to his country of origin for palliative care was lost to follow-up 1.3 months after HD-Et/Cy; no other cases were lost to follow-up. The median OS (95% CI) for the whole cohort was 14.8 months (9.1–49.1). The 1-year OS (95% CI) for the whole cohort was 51% (29.1–69.3).

All five responders survived more than 6 months after HD-Et/Cy. One of the responders, an adult with primary refractory AML, who received HD-Et/Cy and gemtuzumab-ozogamicin, is currently a long-term survivor nearly ten years later (Table 3). The other four (3 adults, 1 child) died of further disease progression with a median duration of remission of 7.0 months (range, 3.6–11.6). Median OS of responders was 18.8 months (95% CI 10.9–n/a). The 1-year EFS and OS (95% CI) for the five responders were 60.0% (12.6–88.2) and 80.0% (20.4–96.9), respectively.

Among the four paediatric non-responders who proceeded to ASCT, two died due to disease progression after 7.1 and 17.2 months, respectively. The other two children are still alive: one who had entered stem cell transplant with blasts in peripheral blood and subsequently experienced an isolated extramedullary relapse 13 months post-HD-Et/Cy and is currently alive 2.5 years post-HD-Et/Cy; and another who remains disease-free 4.4 years post-HD-Et/Cy. The median OS was not reached. The non-responders who were not able to proceed to ASCT (n = 14) had a median OS of 9.1 months (95% CI 7.0–14.8).

4. Discussion

Patients with primary refractory or relapsed acute leukaemias have a dismal outcome. It is generally accepted that ASCT is necessary in any curative approach [23]. While 5-year OS is only 10–12% for adult patients with relapsed acute leukaemias, the 5-year OS for those patients who achieve second remission and subsequently undergo ASCT is 40–50% [10]. However, there is no standard of care to lead these patients into remission prior to ASCT and, whenever possible, participation in a clinical trial is recommended [24].

In recent years several new and promising drugs have been approved for the treatment of acute leukaemias. For AML these include midostaurin, a FLT3 inhibitor; enasidenib, an IDH2 inhibitor; CPX-351, a liposomal daunorubicin/cytarabine combination; gemtuzumab-ozogamicin, a CD33-directed antibody-drug conjugate; and venetoclax, a Bcl-2 inhibitor [25]. For ALL, these include tisagenlecleucel, the first-in-class CAR-T cell therapy; blinatumomab, a recombinant anti-CD19 antibody [26]; and inotuzumab-ozogamicin, a CD22-directed antibody-drug conjugate [27,28]. Many more are under clinical investigation. However, many patients with refractory/relapsed acute leukaemias do not have access to these novel therapies on the basis of a clinical trial or compassionate/expanded access programs. In this context, the costs of therapy and its accessibility should also be taken into consideration at the time of selecting a specific salvage regimen and, despite its shortcomings, HD-Et/Cy offers an affordable, *low-tech*, widely applicable method to reduce leukaemic burden.

The patients in our cohort had been extensively pre-treated and both adults and children had shown resistance to FLAG-based chemotherapy. The toxicity profile of HD-Et/Cy was comparable to that of other regimens used in this setting, such as the aforementioned FLAG-based chemotherapy. Additionally, the ORR of 22% in our cohort was comparable to that reported in previous studies using HD Et/Cy in patients who had received the standard first line plus at least one salvage regimen: ORR 28–32% [19,21]. Similarly, our CR/CRp rate of 17% was also comparable to that reported with other regimens, including cytarabine-based regimens, non-cytarabine combinations, hypomethylating agent-based regimens and single novel agents, used as second salvage therapy in adults with AML achieving a CR/CRp rate of 13% [29].

Interestingly, 17% (3/18) patients with refractory/relapsed AML treated with HD-Et/Cy have survived for more than 2 years, including one adult who remains alive and disease-free nearly ten years after HD-Et/Cy plus gemtuzumab-ozogamizin followed by ASCT.

Although only one child became a responder in our cohort, it is noteworthy that a further four children had a significant reduction in the burden of disease which was deemed acceptable to proceed to ASCT. This is relevant because children with refractory/relapsed AML can be salvaged with ASCT even if they have not achieved complete remission, especially if the blast count in the BM is < 10% [30]. Currently two of these four children with reduced burden of disease are long-term survivors and one of them remains disease-free more than 4 years from HD-Et/Cy.

This study has limitations, mainly the small and heterogeneous

population and the lack of a control group, as is also the case for other case series evaluating HD-Et/Cy [18–21]. Data on long-term EFS and OS may be influenced by the type of ASCT and other subsequent treatments that the patients received. The minimal residual disease (MRD) would have been useful to interpret individual outcomes, but this information was not consistently available. Additionally, patients with ALL may have also been under-represented in this study, since ALL tends to respond better to treatment than AML and due to the emergence of promising immunotherapies for ALL patients (e.g. blinatumomab, inotuzumab, CAR-T cell therapy). On this note, one adult with primary refractory T-ALL presented a CRp in the BM, but refractory disease in an isolated extramedullary mass. His response in the BM could have been anecdotal and therefore HD-Et/Cy cannot be recommended for patients with T-ALL on the basis of this single case. Conversely, the high prevalence of AML cases in this study may nevertheless reflect the limited amount of novel therapies available for this group of patients.

5. Conclusions

This is the first study of HD-Et/Cy reporting on both adults and children with refractory/relapsed acute leukaemias. The response rates achieved with HD-Et/Cy in our cohort were comparable to those reported with other established and experimental salvage regimens. This study shows that patients with refractory/relapsed AML may be salvaged following HD-Et/Cy and ASCT, including children with small volume disease after HD-Et/Cy. Hence HD-Et/Cy can be considered as a salvage therapy in both adults and children with refractory/relapsed AML with no access to relevant clinical trials, provided they have an acceptable performance status and a suitable donor available for further ASCT. Further validation of these findings in future studies may expand the limited treatment armamentarium which is currently available against refractory/relapsed AML.

Sources of funding

The authors acknowledge NHS funding to the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) to The Royal Marsden and The Institute of Cancer Research. Additionally, we acknowledge individual support by the Oak Foundation grantOCay-04-169 (LVM); and the Ira Sohn Foundation, Paediatric Drug Development Fellowship (FC).

Declaration of Competing Interest

LVM has had a Consulting role for Tesaro and has received travel/accommodation expenses from Bayer and Celgene. For the remaining authors no conflicts of interest were declared.

Acknowledgments

The authors would like to thank Julie Mycroft and Helen Underwood for their contributions.

The authors acknowledge NHS funding to the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) to The Royal Marsden and The Institute of Cancer Research. Additionally, we acknowledge individual support by the Sohn Foundation (FC) and the Oak Foundation grant OCay-04-169 (LVM).

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