Clofarabine, cyclophosphamide and etoposide as single-course re-induction therapy for children with refractory/multiple relapsed acute lymphoblastic leukaemia

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Summary

The safety and efficacy of the combination clofarabine/cyclophosphamide/etoposide were evaluated in children with advanced acute lymphoblastic leukaemia (ALL). The study enrolled 25 paediatric patients (median age 12.5 years) with either refractory (n = 17; 68%) or multiple relapsed (n = 8; 32%) ALL to receive clofarabine 40 mg/m², cyclophosphamide 400 mg/m² and etoposide 150 mg/m², daily for 5 consecutive days. No patient died from treatment-related complications. The most common adverse events were febrile neutropenia, mucositis and reversible liver toxicity; no case of liver veno-occlusive disease was reported. The overall remission rate was 56%: 13 patients (52%) achieved complete remission (CR) and one (4%) CR without platelet recovery (CRp). In seven of the 13 (54%) patients achieving CR, remissions were of sufficient duration to allow patients to receive allogeneic haematopoietic stem cell transplantation. The probability of CR/CRp was greater in the 17 patients with B cell precursor ALL than in the eight with T-ALL (76% vs. 12%, respectively, P < 0.01). The 18-month overall survival probability was 39% and 0% in patients who did or did not respond to the treatment, respectively (P < 0.01). These data suggest that the clofarabine/cyclophosphamide/etoposide regimen is well tolerated and can induce clinical response in a relevant proportion of children with refractory/multiple relapsed ALL.

Keywords: acute lymphoblastic leukaemia, childhood haematological malignancies, refractory/relapsed disease, clofarabine, combination therapy, allogeneic haematopoietic stem cell transplantation.
Antimetabolites are some of the most effective drugs against haematological malignancies. In particular, fludarabine and cladribine are active in the treatment of relapsed acute leukaemias, although their use is associated with important non-haematological toxicity (Estey et al., 1994; Krance et al., 2001; Gandhi et al., 2001; Plunkett & Gandhi, 2001), especially dose-limiting neurotoxicity (Spriggs et al., 1986; Warrell & Berman, 1986). Clofarabine (2-chloro-2'-fluoro-2'-deoxy-9-β-D-ara-binofuranosyladenine) is a second-generation purine nucleoside analogue synthesized with the aim of overcoming the limitations, in terms of both efficacy and non-haematological toxicity, of fludarabine and cladribine, while maintaining their best qualities (Kantarjian et al., 2007).

Phase I and II studies aimed at addressing the safety and efficacy of single-agent clofarabine have been conducted in both adults and paediatric patients (Kantarjian et al., 2003; Jeha et al., 2004, 2006). These studies have demonstrated that clofarabine is active in different subtypes of resistant/multiple relapsed leukaemia, leading to overall remission (OR) in about 20% of paediatric patients, without inducing the typical neurotoxicity of first-generation nucleoside analogues. In view of the results obtained in these studies, clofarabine has been approved as single agent for the treatment of paediatric patients aged 1–21 years with ALL failing at least two prior regimens by both the Federal Drug Agency in the United States and the European Medicinal Evaluation Agency in Europe.

As clofarabine inhibits DNA polymerases, ribonucleotide reductase and DNA repair, there is a rationale for considering the combination of this drug with agents able to damage DNA, such as cyclophosphamide and etoposide (Yamauchi et al., 2001). Recently, Hijiya et al. (2007) reported encouraging, although preliminary data, on a phase I dose-escalating trial investigating the safety of different doses of clofarabine combined with cyclophosphamide and etoposide for treatment of refractory or relapsed ALL.

This report describes the results of a multicentre study carried out in paediatric patients with either multiple relapsed or refractory ALL who received a single course of clofarabine therapy combined with cyclophosphamide and etoposide with the aim of re-inducing remission.

Patients and methods

Study group

Patients aged 15 years or less at time of diagnosis and 21 years or less at the time of treatment were eligible. Patients must have had a performance status ≤2 according to Eastern Cooperative Oncology Group criteria and no active infections. Other eligibility criteria included: patients serum bilirubin ≤2× upper limit of normal (ULN) for age; aspartate transaminase and alanine transaminase ≤5× ULN; and serum creatinine <2× ULN. Disease status was assessed by history, clinical evaluation, morphological, cytogenetic and immunophenotyping analysis. Patients’ parents gave written informed consent before treatment. This study was conducted according to guidelines active in each institution participating in the trial and in accordance with the principles of the Helsinki Declaration.

Treatment plan

Clofarabine was administered intravenously at a dosage of 40 mg/m² over 2 h daily, while cyclophosphamide was given at a dose of 400 mg/m² in 1 h and etoposide was infused at a dosage of 150 mg/m² in 2 h. Clofarabine was administered before each dose of cyclophosphamide and etoposide. All drugs were administered for 5 consecutive days. Dose calculation was based on body-surface area obtained from height and actual weight. Prophylactic steroids were given to prevent cytokine release syndrome in patients with more than 30 × 10⁹ blast cells/l in peripheral blood at time of treatment. No patient had active central nervous system (CNS) disease at time of treatment as shown by diagnostic lumbar puncture. In view of this finding and of the possible, unknown interaction of the triple combination with intrathecal chemotherapy, none of the patients received CNS prophylaxis. Responding patients were given allogeneic HSCT if a suitable donor was immediately available or were given consolidation courses of chemotherapy including multiple agents active against ALL cells, chosen according to the treating physician’s preference. Two out of the 25 patients were given a second course of clofarabine, cyclophosphamide and etoposide as consolidation therapy.

Response criteria

Response to treatment was assessed using morphological, cytogenetic and immunophenotyping analysis. Complete remission (CR) was defined as the following: absence of physical signs of leukaemia or detectable leukaemia cells on peripheral blood smears; BM with active haematopoesis and <5% leukaemia cells; an absolute granulocyte count >1 × 10⁹/l, and a platelet count >100 × 10⁹/l; and normal cerebrospinal fluid. A CRp was defined as the presence of all the criteria required for CR with the exception of a platelet count >100 × 10⁹/l. The OR rate was defined as the number of patients who achieved CR or CRp divided by the number of treated patients. Partial response (PR) was defined as 5% to 25% marrow blasts, an absolute granulocyte count >0.5 × 10⁹/l, and a platelet count >25 × 10⁹/l. The National Cancer Institute (NCI) Common Toxicity Criteria (version 3.0) (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf) was the basis upon which all adverse events were described and graded, based on the treating physician’s assessment.

Patient monitoring

History and physical examination, complete blood count, serum chemistry and BM aspirate were performed before
starting chemotherapy. Echocardiogram was performed before treatment and at time of haematopoietic recovery. Serum levels of C-reactive protein, procalcitonin and galactomannan were obtained at least once a week during the aplasia period.

Supportive therapy
All patients were hospitalized for treatment. In the days following chemotherapy and until haematopoietic recovery, 23 patients remained in the in-patient ward, receiving daily physical examination, complete blood count and serum chemistry, while two patients were managed in the outpatient unit.

Supportive therapy was administered according to protocols active in each institution that enrolled patients into the study. All children were given acyclovir for prevention of herpes-viruses infection. Prophylactic antibiotics (ciprofloxacin or amoxicillin conjugated with clavulanic acid) were administered to all children. Broad spectrum antibiotics were given if a patient became febrile. Voriconazole was administered for preventing fungal infections in 15 patients, starting 2 d after completion of chemotherapy until neutrophil recovery, while the others were given fluconazole. Antifungal therapy against both yeasts and moulds was modified if there was clinical evidence of proven/probable fungal infection (diagnosed according to criteria previously published) (Ascioglu et al, 2002).

Recombinant human granulocyte-colony stimulating factor (G-CSF) was not used to accelerate neutrophil recovery, except in one patient.

Cyclophosphamide-induced haemorrhagic cystitis was prevented through the use of uromitexan, which was infused at the dose of 120% of the cyclophosphamide dose.

Statistical analysis
The study was an open-label, multicentre, nonrandomized phase II trial. The study objective was to estimate the OR rate. The data cut-off for this study was December 31, 2008. Patients were censored at time of last follow-up, while death was counted as an event in the calculation of overall survival (OS). Quantitative variables were reported as median and range. Patient- and disease-related variables were analysed for their prognostic value on probability of obtaining CR or CRp. The following variables were tested for their potential influence on the probability of obtaining response to treatment with clofarabine, cyclophosphamide and etoposide: patient gender (male versus female), immunophenotype (BCP ALL versus T ALL), WBC at diagnosis (values above versus those below the median), previous HSCT (yes versus no), patient age at treatment (patients younger versus those older than the median age) and disease phase at time of treatment (patients with ALL in second or third BM relapse versus those with resistant/ refractory leukaemia). The probability of OS was estimated by the Kaplan–Meier method, and expressed as 18-month probability, with the corresponding 95% confidence interval (CI). P values < 0.05 were considered significant.

Results
Patients and treatment
Between October 2006 and August 2008, 25 patients (18 males and seven females) were enrolled and treated in six Italian paediatric centres. Their characteristics are presented in Table I. Eight children were treated for a second (n = 6) or third (n = 2) BM relapse, while 17 patients were resistant to the last course of chemotherapy. Among these latter 17 patients, six proved to be resistant to two courses of chemotherapy used to treat a first BM relapse, four were resistant to one course of chemotherapy used to treat a first BM relapse and the remaining seven were resistant to one course of chemotherapy used to treat a second BM relapse. In the majority of these patients, the last treatment before clofarabine, cyclophosphamide and etoposide was administered according to the Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP) REC 2003 protocol, which is based on a Berlin–Frankfurt–Münster backbone (Paganin et al,

Table I. Patient characteristics (N = 25).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients enrolled</td>
<td>25 (100%)</td>
</tr>
<tr>
<td>Gender: male/female</td>
<td>18/7 (72%/28%)</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>8 (1–15)</td>
</tr>
<tr>
<td>WBC at diagnosis (x10⁹/l)</td>
<td>30 (1–360)</td>
</tr>
<tr>
<td>First-line protocol</td>
<td></td>
</tr>
<tr>
<td>AIEOP ALL 2000</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>AIEOP ALL 95</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>DFCI ALL</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td></td>
</tr>
<tr>
<td>B lineage</td>
<td>17 (68%)</td>
</tr>
<tr>
<td>T lineage</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>National Cancer Institute classification at diagnosis</td>
<td></td>
</tr>
<tr>
<td>Standard risk</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>High risk</td>
<td>17 (32%)</td>
</tr>
<tr>
<td>Cytogenetic abnormalities at diagnosis</td>
<td></td>
</tr>
<tr>
<td>t(9;22)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>t(12;21)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Hyperdiploid karyotype</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Hypodiploid karyotype</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Age at treatment (years)</td>
<td>12.5 (range, 4–21)</td>
</tr>
<tr>
<td>Disease status at treatment</td>
<td></td>
</tr>
<tr>
<td>Second relapse</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>Third relapse</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Refractory disease</td>
<td>17 (68%)</td>
</tr>
<tr>
<td>Previous allogeneic HSCT</td>
<td>7 (29%)</td>
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</tbody>
</table>

AIEOP, Associazione Italiana di Ematologia e Oncologia Pediatrica; DFCI, Dana Farber Cancer Institute; HSCT, Haematopoietic Stem Cell Transplantation.

*Patients with B cell precursor ALL were classified in standard and high risk according to the criteria reported by Smith et al (1996), while those with T-ALL were considered at high risk.
2008). The median BM blast percentage in the overall population at time of treatment was 75% (range, 40–100%). Seventeen patients were diagnosed with BCP ALL and eight with T-cell ALL. Two patients had Ph+ BCP ALL; both had been previously treated with imatinib mesylate. Seven patients had previously received an allograft; the median time elapsing from HSCT to treatment with clofarabine, cyclophosphamide and etoposide was 10 months (range, 3–42). In four out of these seven patients, total body irradiation was part of the preparative regimen, while the remaining three patients had been prepared for HSCT with a busulfan-based conditioning.

Toxicity

Treatment-related toxicities are presented in Table II. No patient died due to treatment-related complications; moreover, no discontinuation of treatment due to adverse events was reported. In addition, no patient experienced tumour lysis, cytokine-release syndrome, skin rash, palmar-plantar erythrodysesthesia, or hepatic veno-occlusive disease (VOD). Hepatic dysfunction, as evidenced by grade 3 or lower transaminitis or hyperbilirubinemia or both, occurred in 16 patients. Elevation of transaminases occurred around day 5–6 (range, day 3–10) from the beginning of treatment. Hepatic function returned to baseline values within 10 d from the occurrence of liver toxicity in all patients. No significant cardiac dysfunction and/or abnormalities developed during the study period.

Haematological toxicity as evidenced by profound myelosuppression usually lasting longer than 20 d was observed. The median time to neutrophil (defined as an absolute granulocyte count $>0.5 \times 10^9/l$) and platelet recovery (defined as an absolute platelet count $>25 \times 10^9/l$) was 26 d (range, 18–42) and 28 d (range, 18–57), respectively.

Almost 85% of the patients developed at least one episode of fever of unknown origin (FUO). Among documented infections, six patients developed pneumonia and two had septicaemia. Probable fungal pneumonia was diagnosed in three out of the six patients who developed pneumonia. Of the 25 children enrolled in the study, 16 (64%) died. All deaths were due to disease progression.

Response and outcome

Thirteen patients (52%) achieved CR and one (4%) CRp, giving an OR rate of 56%. Two patients (8%) had PR and nine patients (36%) had completely resistant disease, resulting in a failure rate of 44%. Thirteen out of the 17 patients (76%) with BCP ALL achieved CR/CRp, while one of the eight patients with T-ALL (12%) responded to treatment ($P < 0.01$). Of the 17 patients who were refractory to their most recent prior regimen, eight (47%) achieved either CR or CRp. By contrast, six out of the eight patients (75%) with multiple relapsed ALL obtained CR (not statistically different from patients with refractory/resistant ALL). Both patients with Ph+ ALL obtained CR. Neither patient gender, WBC count at diagnosis, nor age at treatment influenced the probability to respond to the treatment (data not shown). Notably, four out of the seven patients (57%) who had previously received allogeneic HSCT responded to the treatment, as compared to 10 out of the 18 patients (56%) who had not been previously transplanted.

Seven out of the 13 patients (54%) who achieved CR subsequently proceeded to allogeneic HSCT from either a human leucocyte antigen (HLA)-matched sibling ($n = 2$), an unrelated donor ($n = 3$), or an HLA-partially matched family, donor ($n = 2$). In the other six patients, transplantation was not performed either because patients relapsed while searching for an unrelated donor (five children) or because of parents’ refusal. The median time interval between beginning of treatment on study and HSCT was 18 months (range 1.2–4). No case of hepatic VOD was recorded after transplantation. By contrast, none of the patients who had CRp, PR or who did not respond to the treatment with clofarabine, cyclophosphamide and etoposide received an allograft due to disease progression. Four out of the seven patients who were transplanted after having achieved CR are currently alive (three of them disease-free) with a median follow-up of 8 months (range, 4–17).

The probability of survival 18 months from the beginning of treatment for the entire cohort of patients was 20% (95%CI, 0–39%) as illustrated in Fig 1. Patients with BCP ALL had a significantly better probability of survival in comparison to those with T-ALL (33%, 95%CI, 4–62, vs. 0%, respectively, $P < 0.001$) (Fig 2). The 18-month Kaplan–Meier estimate of

### Table II. Treatment-related toxicity (N = 25).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Kidney (%)</th>
<th>Heart (%)</th>
<th>Liver (%)</th>
<th>Lung (%)</th>
<th>CNS (%)</th>
<th>Infections (%)</th>
<th>Metabolic/laboratory (%)</th>
<th>Mucositis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20 (80)</td>
<td>24 (96)</td>
<td>9 (36)</td>
<td>23 (92)</td>
<td>24 (96)</td>
<td>12 (48)</td>
<td>13 (52)</td>
<td>10 (40)</td>
</tr>
<tr>
<td>1</td>
<td>3 (12)</td>
<td>1 (4)</td>
<td>4 (16)</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>5 (20)</td>
<td>4 (16)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>2</td>
<td>2 (8)</td>
<td>0 (0)</td>
<td>6 (24)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6 (24)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>3</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6 (24)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>8 (32)</td>
<td>2 (8)</td>
<td>3 (12)</td>
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<tr>
<td>4</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>Total</td>
<td>25 (100)</td>
<td>25 (100)</td>
<td>25 (100)</td>
<td>25 (100)</td>
<td>25 (100)</td>
<td>25 (100)</td>
<td>25 (100)</td>
<td>25 (100)</td>
</tr>
</tbody>
</table>

CNS, central nervous system.
survival for patients who did or did not achieve a CR or CRp was 39% (95% CI, 5–73%) and 0%, respectively (P < 0.001) (Fig 3). Among the 14 patients who responded to treatment, leukaemia recurrence was observed in six (43%) patients. The median duration of remission for the 14 patients who achieved either CR or CRp, censoring patients at time of transplantation, was 6 months (range, 3–8.5). The median survival duration of the 11 patients who did not respond to treatment or had PR was 3 months (range, 1–7).

Discussion

This multicentre study showed that, for children with multiple relapsed or resistant ALL, a single combination course of clofarabine, cyclophosphamide and etoposide was associated with acceptable organ toxicity and showed promising activity with an OR rate >50%. In addition, this regimen was particularly effective in BCP ALL and induced remission of sufficient duration to allow many patients with a suitable donor to proceed to HSCT, even from an HLA-disparate donor. This combination of agents might also be considered for patients who had previously received allogeneic HSCT.

The rationale for combining these three cytotoxic agents lay with the observation that cyclophosphamide induces DNA interstrand cross-links. These cross-links can be rapidly repaired by leukaemia cells, as demonstrated in chronic lymphocytic leukaemia (CLL) lymphocytes after in vitro exposure to activated cyclophosphamide (Yamauchi et al, 2001). Pre-treatment with clofarabine, leading to inhibition of both ribonucleotide reductase and DNA synthesis and repair, may significantly prevent or even impede completion of DNA strand break repair, resulting in an increase in apoptosis of leukaemia blasts. Support to this hypothesis is provided by a recent report on the combined use of clofarabine and cyclophosphamide in adults with acute leukaemia, showing that clofarabine followed by cyclophosphamide was associated with increased DNA damage and apoptosis in both myeloid and lymphoid blasts obtained both from peripheral blood and BM (Karp et al, 2007). Etoposide binds to topoisomerase II and inhibits its function in ligating cleaved DNA molecules resulting in the accumulation of single- or double-strand DNA breaks. This hampers DNA replication and transcription, and promotes apoptotic cell death.

The drug dosages chosen for this study were based on the preliminary data presented by Hijiya et al (2007) with some modifications, namely a decrease in cyclophosphamide dosage and an increase in etoposide dosage. This scheme proved to be safe and tolerable, as none of the 25 patients enrolled in our study died due to treatment-related complications. The only relevant toxicity that we observed was that related to liver dysfunction, although this was never fatal and always reversible. Hepatic toxicity has been frequently reported when clofarabine was used as single agent, as well as in combination with other drugs, including cyclophosphamide and cytarabine (Kantarjian et al, 2003; Jeha et al, 2004; Faderl et al, 2005; Jeha et al, 2006; Karp et al, 2007; Faderl et al, 2008). In a phase II extension of the initial escalating dose, phase I study reported
by Hijjya et al (2007), four out of the eight enrolled patients given the same combination of drugs, but at slightly different dosages (i.e. clofarabine 40 mg/m² per day, cyclophosphamide 440 mg/m² per day and etoposide 100 mg/m² per day, for 5 consecutive days), developed severe, life-threatening hepatotoxicity (three veno-occlusive disease, one hyperbilirubinemia) (Hijjya et al, 2008). In view of these findings, that study was amended to exclude patients with prior HSCT, viral hepatitis and/or cirrhosis, or elevated conjugated bilirubin levels (Hijjya et al, 2008). There is no obvious explanation for the significantly better tolerability of the treatment in our population. It is possible that the different dosages of drugs, the prolonged hospitalization of our patients and the aggressive policy of prophylaxis that we adopted against infections may have contributed to the absence of severe, life-threatening toxicity in our cohort. Nevertheless, we recommend careful and frequent monitoring of liver function, as well as avoidance of concomitant administration for prevention of infection of drugs known to have potential liver toxicity or pharmacological interactions, such as voriconazole.

Infections were a common event observed in this study as would be expected in this heavily pre-treated population with profound and long-standing immune- and myelo-suppression. Indeed, in our patients, 26 d was the median time required to reach neutrophil recovery after treatment. This duration of neutropenia, together with the lypholytic effect displayed by the triple combination of cytotoxic drugs, may have facilitated the occurrence of infections, especially those of fungal origin. Despite the relevant incidence of infectious complications, no patient died, again possibly thanks to the hospitalization of the children, and the active monitoring for infections and intensive prophylaxis against bacterial and fungal infections.

The combination of clофarabine, cyclophosphamide and etoposide in this population of patients with advanced childhood ALL was associated with an OR rate of 56%. Of particular interest is the observation that almost half the patients who achieved either CR or CRp were refractory to their most recent prior regimens. Children with BCP ALL had a greater chance of benefiting from the treatment than those with T-ALL. There is no immediate explanation for the association of response to this regimen with the immune phenotype of blast cells. In particular, there was no difference in terms of patients resistant/refractory to the last course of chemotherapy between our children with either BCP- or T-ALL (data not shown). It is well known that patients with BM relapse of T-ALL have a dismal prognosis, irrespective of the time elapsing between diagnosis and leukaemia relapse (Einsiedel et al, 2005; Paganin et al, 2008). It is also possible to speculate that T-ALL blasts are less sensitive to clофarabine-based triple therapy than those belonging to B-lineage differentiation. In this regard, a recent in vitro study reported that clофarabine appeared to be marginally more effective in B-lineage ALL than in T-ALL (Beesley et al, 2007). It must be also mentioned that in the phase II study of single agent clофarabine by Jeha et al (2006), two out of five patients with T-ALL responded, one with a CR and one with a CRp, suggesting that further exploration of clофarabine in T-ALL is warranted. It remains to be tested whether relapsed T-ALL patients may derive better benefit from alternative experimental treatment strategies based on the use of other novel antileukaemia agents such as nelarabine or forodesine (Beesley et al, 2007; DeAngelo et al, 2007; Larson, 2007).

The response achieved with clофarabine was of sufficient duration to allow many patients with a suitable donor to proceed to allogeneic HSCT. It is noteworthy that we did not observe any apparent increase in transplantation-related organ toxicity in the seven patients who were transplanted after having reached CR with the triple combination, including two patients with a history of prior transplantation at study enrolment.

The current study represents a further step in the development of treatment based on clофarabine in childhood ALL, employing the drug in combination with other cytotoxic agents for which a strong pharmacological rationale of combined use exists. In view of its good safety profile and of the promising results obtained in this population, further investigation of this regimen is warranted in patients experiencing first leukaemia relapse and at very high risk of treatment failure (i.e. those belonging to S3/S4 groups of BFM classification, currently treated with combinations of multiple agents including high-dose methotrexate, high-dose cytarabine, daetametazole, vincristine, 1-asparaginase, fludarabine) (Einsiedel et al, 2005; Paganin et al, 2008) as well as for children with ALL in first CR and high level of minimal residual disease, with the aim of decreasing tumour burden before transplantation.

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Disclaimers

The authors do not have any potential conflict of interest to disclose.

References


