



Case Report

Severe Toxicity of Clofarabine combined to Cyclophosphamide and Etoposide in two Children with Relapsed Acute Lymphoblastic Leukaemia (ALL)

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Abstract

Clofarabine use has been reported to be safe in previous studies. We report 2 cases of relapsed ALL in children, one of them occurring after bone marrow transplantation. The patients were treated with clofarabine 40 mg/m², etoposide 100 mg/m² and cyclophosphamide 440 g/m². They developed severe toxicity leading to death, with multi-organ failure developing less than 10 days after chemotherapy. Details of the patients' evolution are given. Severe adverse events of clofarabine in children seem not to be as rare as reported.

Keywords: clofarabine, acute lymphoblastic leukaemia, relapse, toxicity

Introduction

Acute lymphoblastic leukaemia (ALL) is the most common paediatric cancer. Survival rate have been improved from 10% in the sixties to more than 80% nowadays. However, near 20% of children relapse with bad prognosis, particularly early relapses [1, 2]. Therapies for relapsed and refractory ALL remain unsatisfactory, that

is why new therapeutic strategies are needed, such as clofarabine

Clofarabine, a second-generation purine nucleoside analogue, has shown promising activity in relapsed and refractory paediatric ALL [3]. In previous phase I and II clinical trials using clofarabine as a single agent [4-7] or in combination [3,8-10], various adverse events have been

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described, related to clofarabine, minor (vomiting, skin rash, febrile neutropenia) but also more serious (veno-occlusive disease, capillary leak syndrome, renal failure). Despite the incidence of such serious adverse event was not negligible, the use of clofarabine has been stated to be safe, both as single agent and in combination with etoposide and cyclophosphamide.

In the aim of making physicians aware of the possible major toxicity of clofarabine, we report two cases of death occurring after clofarabine/cyclophosphamide/etoposide (CCE) courses. Moreover, as such adverse events were reported but not described; we will detail the clinical signs and evolution. The two cases have been registered by the French authorities of marketed drugs supervision (n° LY20120309 and LY20120310).

Case Report 1

A 6-year old girl was diagnosed with B-cell common ALL, with no bad prognosis criteria (CD10+ ALL, hyperdiploidy, good response to the prophase, low minimal residual disease (MRD) at the end of induction). She relapsed two months after completing chemotherapy according to the EORTC 58951 protocol [11]. She did not achieve complete remission after Coprall protocol [12] but after FLAG protocol [13]. An unrelated donor bone marrow transplantation (BMT) was performed after a conditioning regimen including total body irradiation, etoposide and anti-thymocyte globulins. No complications occurred and full engraftment and complete remission were still observed 3 months after BMT. Unfortunately, medullar relapse (diagnosed on increased minimal residual disease) occurred 5 months after BMT, which justified a CCE course including clofarabine (40 mg/m², D1-5) in combination with etoposide (100 mg/m², D1-5) and cyclophosphamide (440 mg/m², D1-5). Before starting CCE chemotherapy, blood cultures were negatives, blood analysis was: leukocytes 5.10⁹ /l, haemoglobin 119 g/l, platelets 53 10⁹ /l, kidney function was normal (creatinine 52 µmol/l, Na 140 mmol/l, K 3.8 mmol/l) and

liver function quite normal (ASAT 74 UI/l, ALAT 83 UI/l, ALP 308 UI/l, GGT 29 UI/l).

Immediately after the completion of the first day of chemotherapy course (day 1), various toxicity signs appeared:

- day 1: AST/ALT: 74/83 IU/l, plasma creatinine: 33 µmol/l
- day 1 : muscle and joint pain, vomiting, diarrhoea
- day 2 : lingering fever, tachycardia, vomiting, ionic disturbances (hypokaliemia 2.8 mmol/l),
- day 3 : capillary leak syndrome with hyponatremia (134 mmol/l) and hypokaliemia (3.4 mmol/l), trend to hyperphosphoremia (1.42 mmol/l) without hypocalcemia, hepatomegaly,: AST/ALT: 111/103 IU/l
- day 4 : acute renal failure,
- day 5 : respiratory distress, renal impairment and pulmonary oedema, AST/ALT: 304/169 IU/l, plasma creatinine: 83 µmol/l
- day 6 : renal failure (serum creatinine 133 µmol/l), polypnea with decreased SaO₂ (92-94%) , hypotension (6/2), AST/ALT: 532/223 IU/l
- day 7 : capillary leak syndrome, liver cytolysis (AST/ALT reached respectively 643 and 227 IU/l and gamma-glutamyl-transferase 247 IU/l, without hyperbilirubinemia), plasma creatinine: 133 µmol/l, non identified febrile neutropenia (treated by triple antibiotherapy and caspofungin), transfer to intensive care unit where she underwent on hemodialysis, OHF mechanical ventilation, management of cardiac disorders,
- day 8 and after : clotting disorders (fibrinogen 2 g/l, prothrombin rate 83%, antithrombin III 52 IU/l), acute pancreatitis (lipase up to 502 IU/l), multi-organ failure leading to death. Repeated ultrasound imaging showed

normal ventricular function and pericardial effusion which recovered before death.

Case Report 2

A 5 year-old girl developed ALL, common B-cell variant with no bad prognosis criteria (CD 10+, translocation t(12; 21), low MRD at the end of induction). She was treated according to the EORTC 58951 protocol [11], but relapsed only 10 months after the diagnosis. She did not achieve remission after Coprall protocol neither IDA-FLAG protocol [13]. She was further treated with clofarabine (40 mg/m², D1-5) in combination with etoposide (100 mg/m², D1-5) and cyclophosphamide (440 mg/m², D1-5). Before starting CCE chemotherapy, blood cultures were negatives, blood analysis was: leukocytes 0.1.10⁹ /l, haemoglobin 95 g/l, platelets 25 10⁹ /l, kidney function was normal despite a weak hyponatremia (creatinine 22 µmol/l, Na 132 mmol/l, K 4.3 mmol/l) and liver function was normal too (ASAT 44 UI/l, ALAT 43 UI/l, GGT 24 UI/l). Following the first day (day 1) of chemotherapy administration, several toxicity signs appeared.

- day 1: AST/ALT: 33/34 IU/l, plasma creatinine: 20 µmol/l, pre-existing hyponatremia supplemented by sodium infusions
- day 1 :sodium urinary leak
- day 5: tubulopathy with hypokaliemia (3.4 mmol/l), hypomagnesaemia (0.68 mmol/l), hypocalcemia (1.86 mmol/l) and hypophosphoremia (0.75 mmol/l),
- day 7 and after: extracellular dehydration with thirst, low blood pressure, tachycardia, acidosis and acute renal failure, persistent low natremia needing a daily supplementation until 15 meq/kg, plasma creatinine: 160 µmol/l
- ✓ abdominal compartmental syndrome and abdominal hypertension
 - ✓ increased AST and ALT (respectively 150 and 125 IU/l) and gamma-glutamyl-

transferase (91 IU/l), without hyperbilirubinemia

- ✓ clotting disorders: fibrinogen 6.8 g/l, prothrombin rate 79%,
- ✓ pulmonary, renal and mediastinal compression with hemodynamic disorders
- ✓ unidentified febrile neutropenia treated with piperacillin, ciprofloxacin, metronidazole and caspofungin
- ✓ transfer to intensive care unit on D10, where she underwent hemodialysis
- ✓ Progressive deterioration leading to death on day 13.

Discussion

Clofarabine has been demonstrated to be safe and active both as single agent and in combination with etoposide and cyclophosphamide [1,14,15]. The efficacy results reported in studies using clofarabine as single agent showed that the overall response rate (ORR) was around 20%, whereas in combination, ORR varied from 44 to 61%. In addition, the reported CR rates were 28 to 52% [3,8-10]. Consequently, clofarabine will probably be essential in refractory or relapsed ALL in the early future.

Nevertheless, adverse events (AE) are frequent with clofarabine or CCE combination. In a recent study in children, 65% of the patients experienced at least one episode of grade 3-4 toxicity [16]. In the study of Hijjiya et al [9], all the patients experienced at least one more than grade 3 AE, whereas Locatelli et al [10] reported only grade 3 or lower AE. Relatively few treatment-related deaths are reported in most studies. With the same regimen we used (clofarabine 40 mg/m², etoposide 100 mg/m² and cyclophosphamide 440 g/m²), Hijjiya et al [3] observed one death by multi-organ failure but late after clofarabine administration (at D100). No death neither occurred with regimens quite identical (clofarabine 40 mg/m², etoposide

150 mg/m² and cyclophosphamide 400 g/m²) (8,10), even with higher doses of clofarabine (up to 70 mg/m²/d) [17]. Conversely, in the phase II trial of Hijjiya et al [9], using the same drug regimen we used, 7 drug-related deaths among 25 patients were reported: one severe infection, two VOD, one septic shock, two acute renal failure and one pulmonary oedema. Three of them developed multi-organ failure, as in our two cases. Among the 15 pediatric patients reported by Inaba et al, the only death by multi-organ failure attributable to therapy occurred in a child who relapsed after hematopoietic stem cell transplantation [18].

There is no clinical description of the cases of multi-organ failure reported in previous studies. That is why it seemed interesting to us to give more details about the way the toxicity developed and how the patients evolved. For the two patients, the first signs of toxicity appeared rapidly after the completion of chemotherapy. They developed then various and different symptoms from each other, despite renal disorders were common.

Of note the two patients had refractory relapse: one patient received BMT 5 months before the second relapse and was heavily pre-treated. She suffered from a systemic candida infection after the first relapse and had many antifungal treatments including liposomal amphotericin B and azoles. Nevertheless, the infection was controlled and her renal function was normal at the time of CCE administration. Toxicity seems to be higher after BMT and in most of the study protocols with clofarabine, patients with prior hepatic dysfunction or BMT were excluded.

Our two patients had capillary leak syndrome, and renal insufficiency that evolved in a multi-organ failure, as already described with clofarabine [7] and were fatal despite symptomatic treatment. There was no concomitant tumor lysis syndrome which could have favoured renal impairment (isolated medullar relapse in the two cases). In the two cases the role of clofarabine could be scored as probable

[19]. Mechanisms of organ toxicity could not be defined precisely, as post-mortem examination could not be performed. Probable sepsis (at least for patient n°2) could have also participated to fatal evolution. Of note, these two patients were the first two consecutive ones treated with CCE in our center, suggesting that severe adverse event are not so rare. Such events occurring after clofarabine administration are mandatory to be reported, even if they should be considered as the consequence of complex chemotherapy. The cost of this drug and the very severe adverse events reported should be taken into account in the prescription of the drug. Should clofarabine be avoided for all relapses occurring early after BMT (less than 1 year) as well as for all patients who previously received heavy treatments with disturbances of hepatic or renal function? Should it be combined rather with other drugs? Even if it is difficult and not justified to draw conclusions upon a two-patient experience, the benefit/risk ratio in post-BMT patients remains questionable and should be more evaluated.

Further prospective evaluation is needed to better define the use of clofarabine in association, potentially with other drugs, in relapsed ALL patients.

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Conflict of Interest Statement

The authors have no conflicts of interest that are relevant to the content of this study.

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