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SHORT REPORT

Relapsed Philadelphia chromosome-positive B-cell acute lymphoblastic leukaemia responds well to a combination of modified hyper-CVAD, blinatumomab and tyrosine kinase inhibitor

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Abstract

Introduction: Adults with relapsed or refractory Philadelphia chromosome-positive B-cell precursor acute lymphoblastic leukaemia (R/R Ph+ BCP-ALL) have a dismal outcome. Blinatumomab as a single agent has shown activity in R/R Ph- BCP-ALL, and second or third-generation tyrosine kinase inhibitors (TKIs) can produce high remission rates in Ph+ leukaemias. We aimed to assess the activity of blinatumomab and TKI in combination with intensive chemotherapy in the relapsed or refractory setting.

Methods: Ten patients with R/R Ph+ BCP-ALL were treated with the combination of a modified hyper-CVAD (mHCVAD) regimen (cyclophosphamide, vincristine, adriamycin, dexamethasone), blinatumomab and TKI (mainly ponatinib).

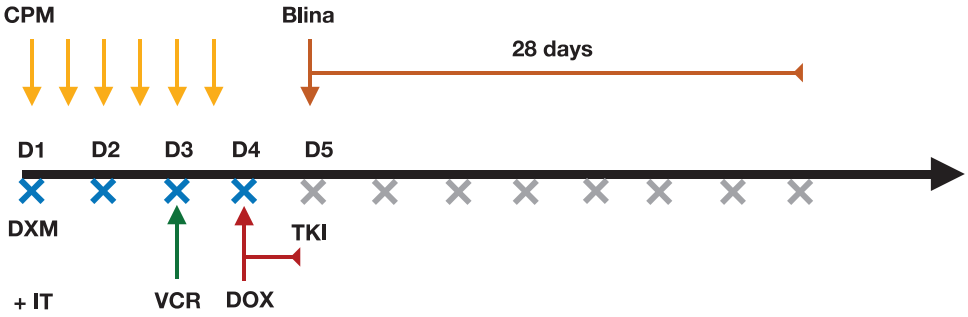
Results: Complete remission (CR) was achieved in 10/10 patients, with deep molecular responses, and 6/10 were alive in remission after a median follow-up of 19.4 months. Three major cardiovascular events were noted.

Conclusion: These preliminary data, suggest that the mHCVAD-blinatumomab-TKI (mainly ponatinib) regimen may achieve a high rate of CR with undetectable measurable residual disease in adults with R/R Ph+ BCP-ALL and could be proposed to such patients, but cardiovascular or infectious complications should be warning, especially in older or frail patients.

KEYWORDS
acute leukaemia, ALL, immunotherapy, tyrosine kinases

1 | INTRODUCTION

The dismal outcome of patients with refractory or relapsed (R/R) Philadelphia chromosome-positive B-cell precursor acute lymphoblastic leukaemia (Ph+BCP-ALL) deserves innovative therapies. There is no real standard of care for the treatment of R/R patients with Ph+BCP-ALL, which relies on chemotherapy (CT), CT with tyrosine kinase inhibitor (TKI) [1, 2] or TKI alone. More recently, blinatumomab



CPM : Cyclophosphamide 300mg/m²/12h D1 to D3
VCR : Vincristine 2mg/m² D3
DOX : Doxorubicin 25mg/m² in continuous infusion D4
DXM : Dexamethasone 40mg orally D1 to D4
Blina : Blinatumomab continuous intravenous perfusion, 9 µg/day for 7 days then 28 µg/day for 21 days
TKI : Tyrosine kinase inhibitor orally every day (Ponatinib 30mg/d, Dasatinib 140mg/d, Asciminib 200mg x2/d)
+ One intratechal injection (IT) before Blinatumomab start : Methotrexate 15mg, Cytarabine 40mg, Depomedrol 40mg

FIGURE 1 Treatment schedule.

[3, 4] or the combination of TKI+blinatumomab [5, 6], with or without CT, have shown promising results in first-line, but their use for R/R patients remains poorly reported. The hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) CT, broadly used in the treatment of BCP-ALL [7], has been modified several times to limit toxicities. Here, the goal of a shorter modified hyper-CVAD (mHCVAD) schedule, omitting D11–D14, was to limit toxicities while still maintaining an effective reduction in tumour burden.

2 | METHODS

Ten consecutive adult patients with R/R Ph+BCP-ALL were treated in a pilot study at Bordeaux University Hospital (France) between August 2020 and January 2023. All patients provided informed consent. They were considered fit for intensive CT, according to their age, comorbidities, and general condition. Of note, three patients with very high cardiovascular risk according to 2021 European Society of Cardiology guidelines [8] were nonetheless included.

Figure 1 summarizes the treatment schedule which included mHCVAD from day (D)1 to D4, consisting in cyclophosphamide 300 mg/m^2 BID D1–D3, vincristine 2 mg D3, doxorubicin 25 mg/m^2 BID in continuous infusion D4, dexamethasone 40 mg orally D1 to D4 and one intrathecal injection of methotrexate 15 mg, cytarabine 40 mg and depomedrol 40 mg. Blinatumomab was started at D5 as continuous intravenous perfusion, 9 µg/day for 7 days then 28 µg/day for 21 days. TKI were also initiated on D5, respectively, ponatinib at an initial dose of 30 mg/day (n = 8), then lowered to 15 mg if a complete response (CR) was achieved, dasatinib 140 mg/day (n = 1, patient #2), or, because of pre-exposure to ponatinib in first line, asciminib 200 mg ×2/day (n = 1, patient #9). Patients with central nervous system (CNS) involvement received additional bi-weekly intrathecal injections before initiating blinatumomab in order to reach CNS negativity. A granulocyte colony-stimulating factor was administered until neutrophil recovery. All patients received antifungal prophylaxis with micafungin during aplasia.

Bone marrow (BM) was evaluated between D35 and D42 after mHCVAD initiation, according to hematologic reconstitution. Upon reaching CR, 1–3 (median 2) consolidation cycles were initiated with high-dose methotrexate and cytarabine, alternating with mHCVAD, according to Kantarjan et al. [7], while blinatumomab was continued as 28-day cycles every 35 days (median 3, 1–4), together with TKI maintenance. Eligible patients with donors received allogeneic HSCT. Measurable residual disease (MRD) was assessed in BM and peripheral blood samples by molecular quantitation of *BCR::ABL1* rearrangement (10^{-5} sensitivity threshold), Ig/TCR (10^{-4} or 10^{-5} sensitivity threshold) and flow cytometry (10^{-5} sensitivity threshold).

3 | RESULTS

Patient characteristics are provided in Table 1. They were five men and five women with a median age of 64 years, with a median of 1 previous line of treatment, including autologous (n = 1) or allogeneic (n = 3) hematopoietic stem cell transplantation (HSCT). All were still *BCR::ABL* positive and *ABL1* TKI mutations were detected for eight of them.

All patients received the mHCVAD regimen and blinatumomab without dose concession. Nine of them went on with consolidations, the last one being considered unfit for further CT. All concomitantly received 28-day blinatumomab cycles. TKI treatment was continued as maintenance.

CR was ultimately achieved in the 10 patients, seven of them being *BCR::ABL1* MRD-negative at first assessment, and four of five evaluable patients Ig/TCR MRD-negative. Three patients were able to receive allo-HSCT after a median of two (range 2–3) additional cycles of blinatumomab and CT. Two of them had negative *BCR::ABL1* MRD before HSCT. HSCT was not considered for the seven others because of age

TABLE 1 Patient characteristics.

Characteristics	*N* = 10
Age, median years [range]	64 [19–71]
Male sex, *N* (%)	5 (50)
Treatment received as first line, *N* (%)	
Standard chemotherapy + consolidations	10 (100)
EWALL-PH	6 (10)
GRAAPH 2005	1 (10)
GRAAPH 2014	3 (10)
ESPHALL-02	1 (10)
1st generation TKI (imatinib)	6 (60)
2nd generation TKI (dasatinib or nilotinib)	4 (40)
Autologous SCT, *N* (%)	1 (10)
Allogeneic SCT, *N* (%)	3 (30)
Number of previous lines before mHCVAD-Blina-TKI, *N* (%):	
One line	8 (80)
Two lines	1 (10)
Three lines	1 (10)
Previous Inotuzumab ozogamicin	0 (0)
Previous CD19 CAR-T cells	0 (0)
Time to relapse, *N* (%)	
<1 year	1 (10)
Between 1 and 2 years	2 (20)
≥2 years	7 (70)
Central nervous involvement at relapse, *N* (%)	1/9 (11)
Leukocytosis (> 30 G/L blasts) at relapse, *N* (%)	2 (20)
Bone marrow blast cells, median	86,5
Splenomegaly *N* (%)	1 (10)
Hepatomegaly *N* (%)	0 (0)
Lymph node enlargement, *N* (%)	0 (0)
The best response during the first cycle, *N* (%)	
CR	10 (100)
BCR::ABL1 MRD1, *N* (%)	
<10−5	7 (70)
<10−4	0 (0)
<10−3	1 (10)
<10−2	1 (10)
≥10−2	1 (10)
Allogeneic HSCT after response, *N* (%)	3 (30)
DLI after response, *N* (%)	1 (10)
Cardiovascular risk (ESC 2021 guidelines), *N* (%)	
Low	4 (40)
Moderate	3 (30)
High	0 (0)
Very high	3 (30)
ABL1 TKI mutation at relapse, *N* (%)	
E255V	1 (10)
E459G	1 (10)
M351T	1 (10)
T315I	3 (30)
Y253H	2 (20)
No mutation found	2 (20)

Abbreviations: CR, Complete remission/Complete remission with incomplete hematologic recovery; DLI, donor lymphocyte infusions; MRD, minimal residual disease; SCT, stem cell transplantation.

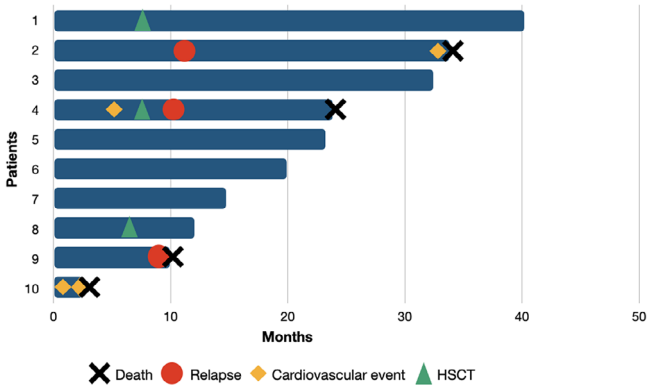


FIGURE 2 Swimmer plot of study patients.

(*n* = 3) or previous history of HSCT (*n* = 3), while the last patient had died.

With a median follow-up of 19.4 months, four patients have died (including two cases of non-relapse mortality, patients #2 and #10) and three relapses occurred, at a median time of of 9.6 months after treatment (Figure 2). All the patients who relapsed were CD19 positive. Patient #2 had a CNS relapse only (without BM involvement), without any ABL kinase domain mutation identified. Patients #4 and #9 had a BM relapse, without extramedullary involvement; one of them (#4) acquired an E255V mutation, and the other one died before any research on ABL kinase domain mutation. Two patients (#2 and #9) had an increase of *BCR::ABL1* MRD before cytologic relapse. Dasatinib dose escalation for patient #2 could not prevent CNS relapse. Adding ponatinib to asciminib for patient #9 however, allowed a *BCR::ABL1* MRD negativation before cytologic relapse 3 months later.

During induction, the median time from treatment initiation to neutrophil recovery was 12.5 days (range 3–21). Nine patients experienced febrile neutropenia (with documented bacteremia in one case), managed by broad-spectrum parenteral antibiotic therapy. Two invasive pulmonary fungal infections were documented, aspergillosis (*n* = 1) and co-infection with *Aspergillus* and *Scedosporium apiospermum*. These patients had neutropenia at enrollment due to leukemia and their overall aplasia period lasted more than 25 days. Patient #9 (with co-fungal

infection) was heavily immunocompromised due to treatment with methotrexate and tocilizumab for rheumatoid arthritis.

A grade 3 gastro-intestinal event was recorded in one patient with an oesophagal ulcer. In nine patients, at least one episode of fever was related to a cytokine release syndrome (CRS, grade 1 $n = 8$, grade 2 $n = 1$). One patient presented a grade 1 immune effector cell-associated neurotoxicity syndrome (ICANS). These events led to corticotherapy in only one case. Blinatumomab was continued during these incidents.

During consolidation, six patients experienced at least one bacteremia and another pulmonary-aspergillosis was recorded. Three patients receiving ponatinib had a grade ≥ 3 cardiac event leading to TKI discontinuation. The first (#10), a 74-year-old patient with a very high cardiovascular risk, experienced one grade 3 acute heart failure 24 h after ponatinib initiation and another fatal acute heart failure one month after ponatinib reintroduction. The second (#4), a 52-year-old patient with low cardiovascular risk, experienced grade 3 chronic dilated cardiomyopathy five months after ponatinib initiation (moderately reduced left ventricular function). The third patient (#2), a 66-year-old with a very high cardiovascular risk, treated with dasatinib, was switched to ponatinib after a relapse at 11 months. He experienced a grade 4 acute limb ischemia leading to death two years after ponatinib introduction. In both patients, ponatinib was given at the reduced dose of 15 mg per day at the time of the cardiovascular event.

4 | DISCUSSION

This is indeed a small series, related to the rarity of R/R Ph+BCP-ALL. It nevertheless has the merit of having tested the proof-of-concept of the efficacy of the triple association of CT, blinatumomab and TKI. mHCVAD was chosen for its lesser toxicity and the administration of blinatumomab was delayed with the expectation that the tumour burden would have been reduced by the previous days of CT. With 100% of CR, currently sustained without additional therapy in 4 patients for more than 1 year, and long survival after allogeneic-HSCT in 3 (1 late death at 2 years), this schedule appears to be extremely promising and worth promoting. Of note, although all of the three patients who relapsed ultimately died, two of them could be rescued and died more than ten months after this relapse. A combination of ponatinib and blinatumomab was used after the patient treated with dasatinib relapsed. This patient reached an MRD-negative CR that lasted for 23 months before death from vascular complications. The other patient relapsed 3 months after allogenic-HSCT and was treated by vincristine-dexamethasone-ponatinib (then switched to dasatinib because of cardiac toxicity) and reached MRD-negative CR before relapsing 5 months later. These good results came at the price of infectious toxicity and cardiovascular events, indicating that such patients require close monitoring.

Data from the literature have already demonstrated the efficacy of TKI in these R/R patients, as well as blinatumomab alone. TKI efficacy is limited by emerging mutations, which appeared to be overcome here in the eight mutated patients. In a small subgroup of 13 relapsed patients, the association of blinatumomab and ponatinib has been reported to be associated with an 85% CR rate and 1-year event-free survival (EFS) of 57% [6]. A French retrospective study evaluated the efficacy of blinatumomab and ponatinib in 26 Ph+ R/R BCP-ALL and showed an impressive 96% CR rate. However, relapses were common and the 2-year EFS was only 31% [9]. Our team also previously showed that the combination of chemotherapy and blinatumomab was associated with a very high response rate in a small cohort of Ph- R/R BCP-ALL [10]. More abundant information is available about the safety and efficacy of associations in first-line therapy for Ph+ BCP-ALL. Similarly, the association of TKI and blinatumomab showed outstanding results in first-line therapy and may become a future standard of treatment for Ph+ BCP-ALL [5, 6]. However, the triple association applied in the present study does not seem to have been tested and reported.

Other immunotherapies are available for R/R Ph+ BCP ALL such as Inotuzumab-Ozogamicin which demonstrated an 80% CR rate and a median overall survival (OS) of 7.7 months [11]. ZUMA-3 showed that the chimeric antigen receptor T-cells KTE-X19 led to an overall CR/CRi rate of 71% and a median OS of 18.2 months on heavily pretreated patients [12]. These approaches could be valuable options for further relapse.

In conclusion, these preliminary data, in an acknowledged small series of patients, nevertheless suggest that the mHCVAD-blinatumomab-TKI (mainly ponatinib) regimen may achieve a high rate of CR with undetectable MRD in adults with R/R Ph+ BCP-ALL and could be proposed to such patients. Yet, cardiovascular and/or infectious events may mitigate the role of chemotherapy in older or frail patients and must be taken into consideration.

AUTHOR CONTRIBUTIONS

Gaétan Basile, Jean Galtier and Thibaut Leguay performed the research; Thibaut Leguay and Jean Galtierdesigned the research study; Gaétan Basile and Jean Galtier analyzed the data; Emilie Klein and Audrey Bidet performed biological investigations; Gaétan Basile, Jean Galtier, Titouan Cazaubiel, Edouard Forcade, Carmen Botella-Garcia, Clémence Mediavilla, Laurence Clément, Pierr-Yves Dumas, Arnaud Pigneux and Thibaut Leguay managed the patients; Gaétan Basile, Jean Galtier and Thibaut Leguay wrote the paper; all authors made substantial contributions to the research design and interpretation of data.

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CONFLICT OF INTEREST STATEMENT

Thibaut Leguay and Arnaud Pigneux received research funding from Incyte. All other authors report no conflict of interest related to the study treatment.

FUNDING INFORMATION

N/A

DATA AVAILABILITY STATEMENT

Data from this study is available upon reasonable request to the corresponding author.

ETHICS STATEMENT

No specific approval was required for these treatment schedules agreed upon in multidisciplinary concertation reviews.

PATIENT CONSENT STATEMENT

All patients provided informed consent

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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