Sponsor: Sanofi **Drug substance(s):** clofarabine	**Study code:** CLOFAL07263 (OBS15639)

Title of the study:

Specified Drug Use Surveillance for effectiveness evaluation of Evoltra monotherapy in Japanese Patients with Refractory/Relapsed Acute Lymphoblastic Leukemia

Study period:

Registry initiation date [first patient in (FPI)]: 26th June 2014

Registry completion date [last patient out (LPO)]: 08th April 2016

Study Status: Completed

Phase of development: NA

Objectives:

To collect information on the effectiveness of Evoltra® monotherapy in the actual clinical setting in Japanese patients with acute lymphoblastic leukaemia (ALL).

Methodology:

Among patients enrolled in the all patient surveillance (CLOFAL06952: Drug Use Investigation of Evoltra for Acute Lymphoblastic Leukemia patients.), the patients started Evoltra monotherapy after 1st May 2014 were registered for this post-marketing surveillance (multicenter, non-controlled, noncomparative, observational study). Data were collected using the paper CRF.
No. of patients: 16 patients with relapsed/refractory ALL treated with Evoltra monotherapy were planned to be registered (14 patients as the effectiveness analysis population).
Inclusion Criteria: Patients with relapsed/refractory ALL treated with Evoltra monotherapy
Exclusion Criteria: Patients treated with Evoltra in combination with other curative agents (anticancer drugs)
No. of Centers: All Evoltra administered centers where will be contracted.
Observation period: "Evoltra is administered daily for 5 consecutive days, then discontinued at least for 9 days" is defined as a cycle. Observation period is from initial administration of the drug to the end of final cycle, until 6 cycles as maximum.
Effectiveness: To evaluate the effectiveness, a modified version of the COG (Children's Oncology Group) standard was used, and the investigator judged it according to the following standard at the end of the final cycle. The effectiveness was evaluated by the best over-all response (CR, CRp or PR), and the remission rate and the responder rate (effectiveness rate) were evaluated by "CR+CRp" and "CR+CRp+PR", respectively.
Complete remission (CR): Meet all of the following conditions:
- No leukemic cells are found in the peripheral blood, and no extramedullary infiltration
- Less than 5% of leukemia cells in bone marrow
- Platelet count and neutrophil count in peripheral blood have recovered to ≧100,000/mm3 and ≧1,000/mm3, respectively

Complete remission without recovery of platelet count (CRp):
- Meet all CR criteria except platelet count recovery (≧100,000/mm3)

Partial remission (PR):
- No leukemic cells are found in peripheral blood
- Leukemic cells in bone marrow are 5% or more and 25% or less, and normal blood cell precursors are observed. Or if less than 5% of leukemic cells in bone marrow, but do not meet the criteria for CR and CRp

Ineffective: do not meet the criteria for CR, CRp and PR

Safety: The information on the adverse events (AEs), the serious AE (SAEs), relationship to Evoltra, grade of toxicity, outcomes and abnormal changes in clinical laboratory parameters (hematology and clinical chemistry) were collected.
Statistical analysis: The following items were aggregated or analyzed.
1. Patient disposition
1) No. of cases enrolled and CRF collected
2) No. of cases for effectiveness and safety analysis
3) No. of cases excluded from analysis, and reasons
2. Effectiveness
1) The best over-all response (CR, CRp or PR)
2) The remission rate: rate of "CR+CRp"
3) The responder rate (effectiveness rate): rate of "CR+CRp+PR"
3. Safety
1) Incidence of ADRs

Treatment:

Marketed Evoltra was used as treatment product.

Follow the "Dosage and administration" of package insert in Japan:

Usually the dose of 52 mg/m2 (body surface area) of clofarabine is administered as an intravenous infusion over 2 hours daily for 5 consecutive days, then discontinued at least for 9 days as a cycle.

And repeat cycles. The dose of clofarabine can be decreased according to the patient condition.

Summary Results:

Participants (actual):

In total, 31 patients from 24 sites were registered, and 30 CRFs were collected. The safety analysis population was comprised of 27 patients, 3 patients (registered from sites without contracts for this study) were excluded from the safety analysis. The effectiveness population was consisted of 20 patients, 7 patients (2: off-label use, 5: treated concomitantly with any curative agents except Evoltra) were excluded from the effectiveness analysis. (Fig. 1)

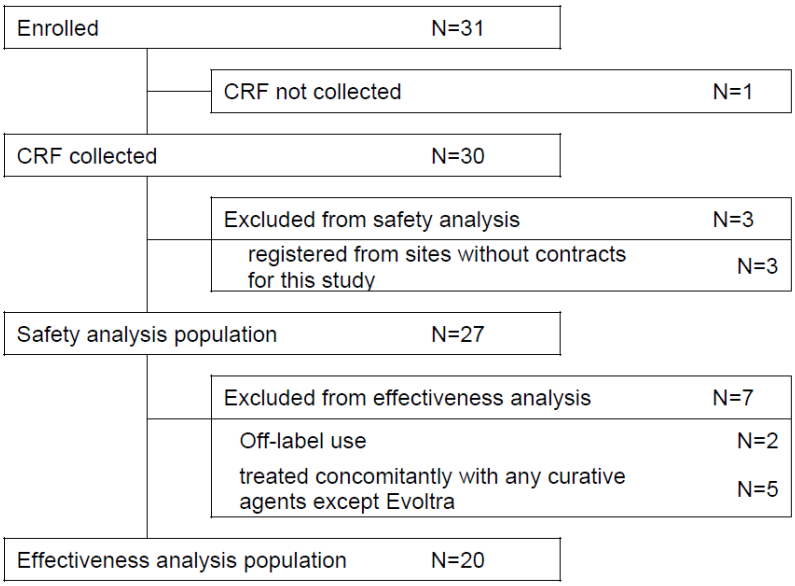

Fig. 1 Patient disposition

Participant characteristics and primary analyses:

Baseline characteristics

The baseline characteristics in the safety analysis population:

The numbers of male and female patients were 16 (59.26%) and 11 (40.74%), respectively. Age (mean±S.D.) was 33.7±20.3 years old (median: 25.0 years old, min. – max.: 5 – 66 years old). The number of patients diagnosed with relapsed/refractory acute lymphoblastic leukemia (ALL) was 25 (92.59%). Body surface area (mean±S.D.) was 1.50±0.37 m2 (median: 1.60 m2, min. – max.: 0.6 – 2.0 m^2). 15 patients (55.56%) had any complications. The numbers of patients with complications of liver dysfunction and renal dysfunction were 4 (14.81%) and 3 (11.11%), respectively. Most patients were treated with Evoltra for one cycle [16 patients (59.26%) for 1 cycle, 7 patients (25.93%) for 2 cycles, 2 patients (7.41%) for 3 cycles, 1 patients (3.70%) for 4 cycles, 0 patient (0.00%) for 5 cycles, 1 patients (3.70%) for 6 cycles].

The baseline characteristics in the effectiveness analysis population:

The numbers of male and female patients were 11 (55.00%) and 9 (45.00%), respectively. Age (mean±S.D.) was 36.0±20.7 years old (median: 29.0 years old, min. – max.: 5 – 66 years old). The number of patients diagnosed with relapsed/refractory acute lymphoblastic leukemia (ALL) was 20 (100.00%). Body surface area (mean±S.D.) was 1.54±0.38 m^2 (median: 1.62 m2, min. – max.: 0.6 – 2.0 m^2). 12 patients (60.00%) had any complications. The numbers of patients with complications of liver dysfunction and renal dysfunction were 3 (15.00%) and 3 (15.00%), respectively. Most patients were treated with Evoltra for one cycle [13 patients (65.00%) for 1 cycle, 5 patients (25.00%) for 2 cycles, 1 patient (5.00%) for 3 cycles, 1 patient (5.00%) for 4 cycles]. At onset of the disease, most patients were classified as L1 (8 patients, 32.00%) and L2 (14 patients, 56.00%) by the French-American-British (FAB) classification. Types of leukemic cells were B cells (13 patients, 65.00%) and T cells (7 patients, 35.00%). 18 patients (90.00%) were Philadelphia chromosome negative, 1 patient was positive, and 1 patient was not tested.

Effectiveness

To evaluate the effectiveness, a modified version of the COG (Children's Oncology Group) standard was used, and the investigator judged it according to the following standard at the end of the final cycle. The effectiveness was evaluated by the best over-all response (CR, CRp or PR), and the effectiveness rate was evaluated by CR+CRp+PR.

Complete remission (CR): Meet all of the following conditions:

- No leukemic cells are found in the peripheral blood, and no extramedullary infiltration
- Less than 5% of leukemia cells in bone marrow
- Platelet count and neutrophil count in peripheral blood have recovered to ≧100,000/mm^3 and ≧1,000/mm^3, respectively

Complete remission without recovery of platelet count (CRp):

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Partial remission (PR):

- No leukemic cells are found in peripheral blood
- Leukemic cells in bone marrow are 5% or more and 25% or less, and normal blood cell precursors are observed. Or if less than 5% of leukemic cells in bone marrow, but do not meet the criteria for CR and CRp

Ineffective: do not meet the criteria for CR, CRp and PR

Of the 20 patients subject to efficacy analysis, the patients were evaluated as "CR" 5.00% (1/20 cases), “CRp” 0.00% (0/20 cases), “PR” 5.00% (1/20 cases), and “Ineffective” 90.00% (18/20 cases). The “CR+CRp” rate (remission rate) and “CR+CRp+PR” rate (effective rate) were 5.00% (1/20 cases) and 10.00% (2/20 cases), respectively (Table 1).

Table 1 Effectiveness in patients with relapsed/refractory ALL (Effectiveness analysis population, N=20)

	CR	CRp	PR	CR+CRp+PR	Ineffective
N	1	0	1	2	18
(%)	5.00%	0%	5.00 %	10.00%	90.00%

Safety

In the safety analysis set, ADRs were observed in 19 of the 27 patients (70.37%) shown in Table 2. The most common ADRs observed were neutrophil count decreased and platelet count decreased 22.22% (n=6) each, febrile neutropenia and white blood cell count decreased 18.52% (n=5) each, and Hepatic function abnormal 14.81% (n=4). Serious ADRs were observed in 16 of the 27 patients (59.26%). The most common serious ADRs observed were neutrophil count decreased 22.22% (n=6), febrile neutropenia, platelet count decreased, and white blood cell count decreased 18.52% (n=5) each, and anaemia 11.11% (n=3).

Table 2 Incidence of ADRs in patients of safety analysis population

Total patient number	27	
Number of patients with ADRs	19	
Incidence of ADRs (%)	70.37%	
ADRs (**SOC**/PT)	N	(%)
Infections and infestations	2	(7.41)
Septic shock	1	(3.70)
Cystitis Viral	1	(3.70)
Blood and lymphatic system disorders	11	(40.74)
Anaemia	3	(11.11)
Disseminated intravascular coagulation	1	(3.70)
Febrile neutropenia	5	(18.52)
Leukopenia	2	(7.41)
Neutropenia	3	(11.11)
Pancytopenia	1	(3.70)
Haematotoxicity	1	(3.70)
Metabolism and nutrition disorders	2	(7.41)
Hypercalcaemia	1	(3.70)
Hypocalcaemia	1	(3.70)
Hypokalaemia	1	(3.70)
Hypomagnesaemia	1	(3.70)
Cardiac disorders	1	(3.70)
Pericardial effusion	1	(3.70)
Vascular disorders	1	(3.70)
Capillary leak syndrome	1	(3.70)
Gastrointestinal disorders	4	(14.81)
Abdominal pain	1	(3.70)
Pancreatitis	1	(3.70)
Proctalgia	1	(3.70)
Stomatitis	1	(3.70)
Vomiting	1	(3.70)
Hepatobiliary disorders	6	(22.22)
Hepatic function abnormal	4	(14.81)
Liver disorder	2	(7.41)
Renal and urinary disorders	1	(3.70)
Renal impairment	1	(3.70)
General disorders and administration site conditions	6	(22.22)

	Chest pain	1	(3.70)
	Generalised oedema	1	(3.70)
	Malaise	1	(3.70)
	Mucous membrane disorder	2	(7.41)
	Pain	1	(3.70)
	Pyrexia	1	(3.70)
	Systemic inflammatory response syndrome	1	(3.70)
	Investigations	12	(44.44)
	Alanine aminotransferase increased	1	(3.70)
	Aspartate aminotransferase increased	1	(3.70)
	Blood bilirubin increased	1	(3.70)
	Blood creatinine increased	1	(3.70)
	Haemoglobin decreased	1	(3.70)
	Lymphocyte count decreased	2	(7.41)
	Neutrophil count decreased	6	(22.22)
	Platelet count decreased	6	(22.22)
	White blood cell count decreased	5	(18.52)

N: number of patients
ADRs were categorized by the ICH Medical Dictionary for Regulatory Activities (MedDRA) Ver. 22.1.

Issue date: 15/Jun/2023