A phase 1/2 trial of lenalidomide and dexamethasone in adult patients with refractory/relapsed acute lymphoblastic leukemia

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ABSTRACT

Objectives: Adult patients with refractory/relapsed ALL have poor survival outcomes with current chemotherapies. We aimed to determine safety and efficacy of lenalidomide, an oral immunomodulator, in these patients.

Methods: This phase 1/2 trial (EUDRACT # 2009-009372-13) included 10 patients who received 28-day cycles of oral lenalidomide 25 mg/day, days 1 through 21, in combination with oral dexamethasone 40 mg/day on days 1, 8, 15, 22. Primary endpoints were tolerance and the overall response rate (ORR). Secondary endpoints included overall survival (OS) and quality of life.

Results: The most common grade 3 or 4 adverse events were myelosuppression. The ORR among the participants who could be evaluated was 28.6% (95% confidence interval [CI], 0–62.2%). The median OS was 92 days (range, 43–133 days). All patients have died because of progressive disease. Quality of life remains stable during treatment cycles.

Discussion and conclusion: The safety of combination therapy consisting of lenalidomide plus dexamethasone is consistent with ambulatory administration. Efficacy should be reevaluated in a larger series including patients less intensively previously treated.

KEYWORDS

Acute lymphoblastic leukemia; relapse; refractory; prognosis; lenalidomide

Introduction

Most therapeutic advances in adult acute lymphoblastic leukemia (ALL) have arisen from adaptation of ALL treatment in children. Applications of pediatric schedules to adults have thus been used, providing increased drug intensity at several stages of treatment with mainly larger cumulative doses of corticosteroids, vincristine, and l-asparaginase. With current regimens, the complete remission (CR) rate reaches 80–90% and survival rates at 5 years range from 67 to 78% which compare favorably to rates between 34 and 41% observed with the former protocols [1]. Despite improvements in upfront treatment, the outcome in patients with refractory/relapsed (R/R) ALL remains dismal. Salvage chemotherapy results are modest in this setting [2–4]. Only 30–40% of adults achieve a second CR and 10–20% in further salvages. The median overall survival (OS) ranges from 4.5 to 8.4 months and 5-year survival rates are just 7–10%. At this stage, only allogeneic stem cell transplantation (SCT) offers a chance of long-term survival. However, only few patients can be bridged to allogeneic SCT [2,3]. There is therefore an unmet need for novel agents in the treatment of patients with R/R ALL to improve outcome [5].

Lenalidomide is a second-generation immunomodulatory compound which, either as single agent or in combination with other drugs, has shown interesting results as a therapeutic option for patients with R/R multiple myeloma or other hematological malignancies. Lenalidomide has been approved in combination with dexamethasone for the treatment of multiple myeloma [6,7] and in combination with rituximab for the treatment of mantle-cell lymphoma [8]. Numerous clinical trials, as a single agent or in combination therapy, are currently ongoing in B-cell non-Hodgkin lymphoma, and it has clearly demonstrated anti-leukemic activity in chronic lymphocytic leukemia patients [9,10]. Lenalidomide displays pleiotropic anti-tumor effects, including stimulation of T-cell and natural killer-cell expansion, inhibition of tumor-associated angiogenesis and lymphangiogenesis, and induction of apoptosis through the downregulation of cyclin D1 [11–16].

Based on these clinical and biological data in B-cell malignancies, we hypothesized that management of B-cell lineage ALL with this biologic agent might offer patients a potential disease control with a favorable side effect profile relative to chemotherapy approaches. We therefore conducted an “open-label” multicenter, phase 1/2 study to evaluate the safety and efficacy of the combination of lenalidomide and...
dexamethasone, as used in multiple myeloma, in the treatment of adult patients with R/R B-cell lineage ALL.

Patients and methods

Patient eligibility

The study (EUDRACT # 2009-009372-13) was conducted at four French centers of the Rhône-Alpes Auvergne region. The study enrolled adult patients (≥18 years old) with documented B-cell lineage ALL, who were refractory or had failed to at least two treatment regimens (bone marrow transplantation could be considered as one line of treatment). Inclusion of patients with Philadelphia chromosome-positive (Ph+) ALL was authorized in the presence of a T315I mutation and absence of investigational trial targeting this abnormality. Other requirements for enrollment included an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, a life expectancy of at least 3 months, an adequate liver function (AST and/or ALT not > 3 times the upper limits of the normal range), an adequate renal function (calculated creatinine clearance >50 ml/minute), the absence of uncontrolled infection, the absence of central nervous system involvement, the absence of known neoplastic malignancy during the past 5 years, no grade ≥ 2 peripheral neuropathy, or a contraindication for dexamethasone. To avoid potential embryo-fetal toxicity, patients had to agree with the Risk Evaluation and Mitigation Strategy program (REMS) and to use an effective method of contraception during the study.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice and applicable regulations. Written informed consent was obtained from each patient before any study procedure was undertaken. The Institutional Review Board at Saint-Etienne University Hospital approved the study and the contents of the informed consent document.

Study design

The dose and schedule of lenalidomide and dexamethasone selected for this current study was based on the one used in multiple myeloma. Lenalidomide was given orally at a dose of 25 mg/day on days 1 through 21 of 28-day cycles, in combination with dexamethasone given weekly at 40 mg per os once daily on days 1, 8, 15, 22 of each 28-day cycle. Cycles were continued until disease progression, development of unacceptable adverse effects, or withdrawal from the study.

Patients with a prior history of deep-vein thrombosis or pulmonary embolism received prophylactic antithrombotic treatment at the discretion of the investigator. Tumor lysis syndrome prophylaxis consisted of hyperhydration and hypouricemic treatment. Prophylactic growth factors, such as granulocyte colony-stimulating factor, were empirically administered because of the hematological toxicity of lenalidomide. Biphosphonates and other supportive therapies, such as prophylaxis against herpes zoster, were allowed at the investigator’s discretion.

Efficacy and safety assessments

Primary endpoints were overall response rate (ORR) (defined as CR, complete remission without complete platelet count recovery [CRp] or partial response [PR]) and safety (type, frequency, and severity of adverse events, and their relationship to study drug). The initial response assessment was performed at the end of cycle 1. Patients were eligible to receive additional cycles of treatment if a response to treatment (CR, CRp, or PR) or sufficient clinical activity (a ≥50% decrease in leukemic cell counts in the peripheral blood and/or bone marrow or evidence of clinical response in the lymph nodes or mediastinal mass) were observed. Patients achieving CR and having an identified HLA compatible donor could undergo allogeneic SCT. CR was defined as no evidence of circulating blasts or extramedullary disease, a bone marrow with ≤5% blasts, and recovery of peripheral counts (platelets ≥100 G/l and absolute neutrophil count ≥1 G/l). CRp was defined as meeting all criteria for CR except for recovery of platelet counts to ≥100 G/l. PR was defined as complete disappearance of circulating blasts, a bone marrow with >5 to ≤25% blasts, and appearance of normal progenitor cells or a bone marrow with ≤5% blasts that did not qualify for CR or CRp. The severity of adverse events was graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE version 3.0 Toxicity Scale). The intent-to-treat (ITT) population comprised all enrolled patients regardless of whether they received the study drug. The safety population included all patients who met the protocol requirements and received at least one dose of the study drug. The efficacy evaluable (EE) population included patients who met the protocol requirements and were evaluated after receiving at least one cycle of the study drug.

Secondary endpoints included: time to response, duration of response, and overall survival (OS) (calculated from the beginning of salvage therapy to the time of death).

Quality of life analysis

Health-related quality of life was measured with the use of the EORTC-QLQ-C30 questionnaire, which
includes a general questionnaire that assesses physical well-being, emotional well-being, social well-being, and functional well-being – with higher scores on each component indicating higher quality of life. The assessment was performed at baseline, and after each cycle.

Statistical analysis

A Simon’s two-stage design was initially planned [17] with accrual of 13 patients in the first stage and 14 additional patients in the second stage if at least one response was initially observed. Treatment could be considered efficient if at least four responses were observed (α = 0.05, power = 0.8). Actually, because of a smaller number of patients leading to premature arrest of inclusions, statistics were mainly descriptive. Exact binomial 95% confidence intervals (CIs) were reported for proportions. Kaplan–Meier methodology was used to estimate distribution of OS (time of treatment initiation to death).

Results

Patient characteristics

Between February 2010 and August 2013, 10 patients were enrolled in the study. Table 1 shows patients’ baseline characteristics and prior therapies. One patient with a relapsed T-cell lineage ALL and one patient with a tyrosine kinase inhibitor (TKI) refractory Ph+ ALL, but without T315I mutation, were inappropriately included and were not considered for the EE and the safety population analyses. However, they were considered for the ITT analysis. Only eight patients were therefore included in the safety population analysis and only seven in the EE population analysis since one patient did not complete the first cycle because he died from hemorrhagic complication on day 12 (Figure 1).

The median age of the population analyzed for safety was 63 years (range, 46–74 years). There were two females and six males. Two patients were treated for relapsed Ph+ ALL (with T315I mutation) and six patients for relapsed B-cell lineage ALL. At the time of inclusion, all patients had already received one or two prior lines of therapy; none underwent SCT either during first line or in rescue after the first relapse. After first-line therapy, only two patients obtained a long first CR: >2 years and >5 years, respectively. After second-line therapy, only one patient achieved CR and kept this status for a very short period of time (14 days). The mean white blood cell (WBC) count at inclusion was 8.7 G/l with a mean peripheral blast cell count of 4.3 G/l.

Efficacy

Evaluable patients received a median of two treatment cycles (range, one to four cycles). Patient numbers were small for the analyses, which should be interpreted in this context. The ORR was 28.6% (95% CI, 0–62.2%) with two patients achieving partial response after one or two courses. No CR was observed. Three other patients who had shown sufficient treatment activity (with a decrease in blast cell count ≥50% as compared to baseline in peripheral blood) pursued additional treatment cycles. Response duration was short (three cycles) and no patient could undergo allogeneic SCT procedure. Median OS was 92 days (range, 43–133 days). All evaluable patients have died because of progressive disease.

Regarding ITT population analysis, ORR was 20% (95% CI, 0–44.8%) with only two PR. Median OS was 81 days (range, 12–133 days).

Adverse events

Treatment was associated with toxic effects that have been reported previously with these agents. Treatment was mainly ambulatory. No patient experienced tumor lysis syndrome or thrombotic complications. In the safety population, there was no death due to treatment-related adverse events. One patient died early (day 12) from hemorrhage before completing cycle 1. This was related to severe refractory thrombocytopenia and not attributed to the studied drug combination. The most common grade 3 or 4 adverse events were hematological adverse events including neutropenia, thrombocytopenia and anemia, and were manageable with standard interventions. Median durations of neutropenia <0.5 G/l and platelets <20 G/l were of 15 days and 13 days, respectively. Grade 3 or 4 non-hematologic adverse events are listed in Table 2. Grade 3 infections requiring hospitalization – including two cases of pneumonia and three cases of bacteremia (one Bacillus gram-negative, one Listeria monocytogenes, one Pneumococcus) – were reported during cycles. All resolved with the administration of antibiotics and supportive care.

Quality-of-life assessment

The completion rate of the EORTC-QLQ-C30 questionnaires was 50% at any given time point. Quality-of-life scores remained stable throughout treatment cycles. Global health status scoring was comparable between the beginning and the end of each cycle.

Discussion

Treatment of refractory/relapsed adult ALL remains a considerable challenge. Despite promising data in B
Patients N°1 to 8 were analyzed for safety. Patients N°1 to 7 were analyzed for efficacy. Patient 8 was not evaluable since he died before completion of the first cycle. Patients 9 and 10 were inappropriately included.

A recent Japanese phase 1 dose-escalation study enrolled nine patients with relapsed T-cell aggressive leukemia/lymphoma [19]. The optimal dose was identified as 25 mg/day given continuously which is currently being tested in a phase 2 study. T-cell lineage ALL was not included in our trial, but the patient remained with a stable disease for two cycles.

The major limitation of this trial was the small number of included patients, which was much lower than the number initially planned leading to a premature ending of the trial before validation of our hypothesis regarding treatment efficacy in accordance to Simon’s two-stage design plan. This was mainly due to the concurrent development of trials based on monoclonal antibody therapy.

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| Patient | First-line treatment | Second-line treatment | Disease status at inclusion cytogenetics | WBC (G/l) | PB% of blasts | BM% of blasts | Best response and time to best response | No. of cycles | Status at last follow-up |
|---------|----------------------|-----------------------|----------------------------------------|-----------|---------------|---------------|----------------------------------------|--------------|-------------------------|
| #1 48 years/F | GRAALLOS | REFRACTORY. B-ALL 46,XX t(6;7)(p21,q11) | Decreased blast cell count in PB | 12 | 77 | 70 | End of cycle 1 | 4 | Dead 100 days |
| #2 62 years/M | GRAALLOS | SECOND RELAPSE. B-ALL 58-59,XY, +1,+2,+5,+6,+8,+10, +11,+14,+18,+19,+21,+21 | Decreased blast cell count in PB | 40 | 53 | 85 | End of cycle 1 | 2 | Dead 92 days |
| #3 74 years/F | EWALL-Ph+ | REFRACTORY. Ph+ ALL (T315I mutation) | PR | 2.6 | 2.7 | 45 | End of cycle 1 | 3 | Dead 92 days |
| #4 61 years/M | GRAALLOS | REFRACTORY. B-ALL | PR | 1.06 | 13.2 | 71 | End of cycle 2 | 3 | Dead 133 days |
| #5 67 years/M | EWALL-Ph+ | REFRACTORY. Ph+ ALL (T315I mutation) | PD | 3.2 | 3 | 80 | | 1 | Dead 69 days |
| #6 46 years/M | GRAALLOS | REFRACTORY. B-ALL | Decreased blast cell count in PB | 7.8 | 40 | 80 | End of cycle 1 | 2 | Dead 43 days |
| #7 65 years/M | EWALL-SA | FIRST RELAPSE. B-ALL. NORMAL | PD | 1.9 | 18 | 95 | | 1 | Dead 70 days |
| #8 67 years/M | GRAALLOS | REFRACTORY. B-ALL. NORMAL | NE | 1.1 | 24 | ND | | 12 | Dead 12 days |
| #9 62 years/M | GRAAPH05 | SECOND RELAPSE. Ph+ ALL t(9;22) with complex cytogenetics | Decreased blast cell count in PB | 74 | 76 | 86 | | 16 | Days 15 |
| #10 72 years/F | GRASSPALLA2 | FIRST RELAPSE. T-ALL | Decreased blast cell count in PB | 6.7 | 1 | 95 | | 2 | Dead 122 days |

Abbreviations: 6MP: 6-mercaptopurine; CR1: first complete remission; Endox: endoxan; F: female; M: male; MTX: methotrexate; ND: not done; NE: not evaluable; PB: peripheral blood; PD: progressive disease; PR: partial remission; Vcr: vincristine; WBC: white blood cell.

Clinical trials (induction chemotherapy): EWALL-Ph+ combining dexamethasone + dasatinib + vincristine [26]; EWALL-SA combining dexamethasone + vincristine + l-asparaginase [1]; GRASPALL-01 combining GRASPA (l-asparaginase loaded red blood cells) + dexamethasone + vincristine + methotrexate + cytarabine [28]; GRAALL05 combining prednisone + daunorubicin + vincristine + cyclophosphamide + l-asparaginase [19].

T-cell lineage ALL was not included in our trial, but the patient remained with a stable disease for two cycles. The major limitation of this trial was the small number of included patients, which was much lower than the number initially planned leading to a premature ending of the trial before validation of our hypothesis regarding treatment efficacy in accordance to Simon’s two-stage design plan. This was mainly due to the concurrent development of trials based on monoclonal antibody therapy.
Figure 1. CONSORT flow diagram. Abbreviations: EE: efficacy evaluable; ITT: intention-to-treat; PD: progressive disease; PR: partial remission; pt(s): patients; SD: stable disease.
Table 2. Hematological and non-hematological grade 3 or 4 adverse events in the safety population (16 cycles).

| Adverse events | Grade 3 | Grade 4 |
|----------------|---------|---------|
| Hematological events | | |
| Anemia | 2 (44%) | 1 (6%) |
| Neutropenia | 4 (25%) | 10 (62.5%) |
| Thrombocytopenia | 3 (19%) | 12 (75%) |
| Non-hematological events | | |
| Increased SGOT or SGPT | 3 (19%) | 0 |
| Increased bilirubin | 1 (6%) | 0 |
| Increased GGT | 4 (25%) | 0 |
| Hyperglycemia | 1 (6%) | 0 |
| Serious infections requiring hospitalization | 5 (31%) | 0 |
| Bleeding | 0 | 1 (6%) |

Abbreviations: SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; GGT: gamma-glutamyl transferase.

Despite high rate of grade 3/4 hematologic toxicity, the combination of lenalidomide with dexamethasone appeared feasible as an ambulatory treatment and toxicities observed were easily manageable as compared to those potentially observed with polychemotherapy regimens. These treatment-related side effects were expected as we used the maximum tolerated dose of lenalidomide (25 mg daily). There were no treatment-induced deaths and the stable trajectory of health-related quality of life reflected the overall absence of cumulative treatment-related toxic effects. Although only two PRs were observed in our short series of very high-risk ALL patients, further studies testing lenalidomide in combination with cytotoxic agents or immune-based therapies should certainly be explored. In mantle-cell lymphoma, combinations of lenalidomide with rituximab were shown to be highly promising with high response rates [20,21]. In relapsed or refractory aggressive lymphoma, addition of lenalidomide to polychemotherapy yielded encouraging results with high ORR [22,23] leading to ongoing large randomized trials to confirm these results and determine the optimal position of lenalidomide in the association.

In B-cell lineage ALL, new therapeutic strategies are becoming available with the development of immune therapies that recruit (bispecific T cell engager) or modify (chimeric antigen receptor T cells) patient's own T cells to fight leukemic cells [24,25]. These new approaches lead us to predict that, in a few years, ALL therapy might be based heavily on non-chemotherapeutic approaches. In this setting, given lenalidomide's unique immune stimulatory properties and its oral bioavailability, there is potential for further development of this compound in concomitant or sequential combination regimens with these new anti-tumor agents. However, the current challenge in R/R ALL patients is to propose an effective and safe salvage regimen that could serve as a bridge to allogeneic SCT. Because of recent encouraging data with combination therapies involving lenalidomide in other B-cell malignancies, further investigations should focus on better determining lenalidomide mechanism of action in ALL and testing various combinations, in order to optimize its efficacy.

Disclosure statement

No potential conflict of interest was reported by the authors.

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