Maintenance therapy with alternating azacitidine and lenalidomide in elderly fit patients with poor prognosis acute myeloid leukemia: a phase II multicentre FILO trial

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LETTER TO THE EDITOR

Maintenance therapy with alternating azacitidine and lenalidomide in elderly fit patients with poor prognosis acute myeloid leukemia: a phase II multicentre FILO trial

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For patients with acute myeloid leukemia (AML), aged over 60 years old presenting with poor prognosis factors such as, adverse cytogenetics, previous myelodysplastic syndrome (MDS) or therapy-related AML (t-AML), the outcome remains particularly dismal. It is generally accepted that these patients are candidates for palliative care or investigational therapy only. In such poor prognosis patients, although complete remission (CR) rates around 60% have been reported after induction chemotherapy,[1,2] no standard post-remission schedule has consistently improved survival. The relapse rate is still over 60%, leading to an overall median disease-free survival (DFS) of <1 year (range: 4–11 months). Both azacitidine and lenalidomide have single-agent activity in patients older than 60 years with untreated AML through non-overlapping mechanisms that could even be synergistic.[3] Sequential or concomitant administration of these two drugs in high-risk MDS or AML unfit patients led in most reports to higher and earlier hematological response rates[4–10] than after treatment with either of those drugs as single-agent. However, these cohorts were small, CR rates usually $<20\%$ and the duration of responses short. Maintenance with hypomethylating agents[11–13] or in combination with lenalidomide[14] following chemotherapy-induced CR has been reported in a few patients.

We hypothesized that the above-described drugs, used alternately as maintenance therapy, could be more effective on the residual disease of patients in CR, especially in patients at high risk of relapse, with limited toxicity. The FILO (French Innovative Leukemia Organization, previously Goelams), tested this hypothesis in a phase II trial.

Fit patients (performance status (PS) 0–2), 60 years of age or older, with poor-risk AML, were included. Poor-risk AML was defined by centrally reviewed poor-risk cytogenetics defined according to the European LeukemiaNet, previous MDS or therapy-related AML (t-AML). Patients with prior myeloproliferative neoplasm or MDS treated with azacitidine, decitabine or lenalidomide were excluded. The study was approved by an ethical committee (ID 2010/23 CPP Ouest II, Angers) and registered by clinicaltrials.gov as NCT01301820. All patients provided written informed consent. All patients received a classical FILO induction protocol[10] ICL including lomustine 200 mg/m^2 day 1, idarubicin 8 mg/m^2 days 1–5, cytarabine 100 mg/m^2 days 1–7 continuous infusion and granulocyte colony-stimulating factor from day 15 until hematological recovery. Only patients who reached CR after one induction cycle received maintenance therapy. Patients in CR without platelets reconstitution ($<5\%$ bone marrow blasts on day 35 but platelet count $<100\times10^9$/l), or failure were subsequently treated according to their physician's choice. Maintenance included 12 cycles of alternating azacitidine (sc 75 mg/m^2/day, days 1–7) and lenalidomide (10 mg/day, days 1–21) every 28 days. Maintenance began after centralized randomization with either azacitidine (arm A) or lenalidomide (arm B). Maintenance cycles could be initiated at day 28 of the previous course if neutrophils and platelets were above 1×10^{-9} and 100×10^{-9}/l, respectively. If these levels were not reached at day 42, the next cycle was initiated at a reduced dose of 50 mg/m^2/day or 5 mg/day for azacitidine and lenalidomide, respectively. Granulocyte colony-stimulating factor was allowed in case of severe neutropenia ($<0.5\times10^{-9}$/l) over 7 days or if febrile neutropenia occurred. Red blood cells or platelets transfusions thresholds were 8 g/dl hemoglobin and 20×10^{-9}/l platelets respectively. The NCICTCAEv4 was used to report toxicities. The primary endpoint was a 2-year DFS improvement of at least 20% compared to historical data (increment from 15[ref. 2] to 35%). Assuming a CR rate of 55% in this population following ICL induction,[2] a type 1 error of 5% and a power of 80%, 117 patients had to be included.

Between March 2011 and February 2013, 117 fit elderly patients (55% males, median age 69 years, range: 60–80) from 27 FILO centers received induction therapy. Eighty-three patients had poor cytogenetics, including complex karyotype ($N=65$), monosomal karyotype ($N=54$), chromosome 5 anomaly ($N=61$), chromosome 7 anomaly ($N=44$), chromosome 3q anomaly ($N=9$), del(17p) ($N=33$), tri(8) ($N=15$) or involvement of 11(q23) ($N=5$). Among them, 33 also had an antecedent of MDS and 27 therapy-related

Table 1. Patients characteristics, complete remission rates, disease-free survival and overall survival

	N *(%)*	*CR %*	*Median DFS months*	P	*2 years DFS %*	*median OS months*	P	*2 years OS %*
All patients	117	56	7.9		12.3	10.0		21.4
Age $\geqslant 70$	48 (41)	58.3	8.6	0.12	17.9	9.3	0.67	20.8
PS 0 vs 1 vs 2	36 vs 66 vs 12	72 vs 48 vs 50	15.7 vs 5.1 vs 6.3	0.012	19.2 vs 6.3 vs 0	18.7 vs 9.2 vs 4.6	0.002	41.7 vs 13.6 vs 8.3
WBC $>2.9\times10^9$/l	58 (49.5)	50	7	0.16	10.3	8.6	0.017	13.8
Poor cytogenetics	83 (70.9)	53	5.1	0.004	6.8	8.1	0.0001	10.8
MDS only	19 (16.2)	68.4	16.8	0.008	30.8	37.2	0.0001	52
Therapy-related AML only	10 (8.5)	80	12.4	0.58	12.5	17.2	0.11	50

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; DFS, disease-free survival; MDS, myelodysplastic syndrome; OS, overall survival; PS, performance status.

Table 2. Toxicity of azacytidine and lenalidomide courses

	Azacitidine courses	*Lenalidomide courses*	P
N	219	222	
Median time between courses	31 days	28 days	0.019
Courses with dose reduction	9.6%	21.6%	0.01
Grade 3/4 neutropenia	46.8/27.3%	39.7/17.6%	0.16/0.024
Antibiotics for fever at home	6.9%	7%	0.99
Hospitalization for febrile neutropenia	0.5%	2.7%	0.099
RBC transfusions	5%	5.4%	0.99
Grade 3 thrombocytopenia	20%	16%	0.31
Platelets transfusions	8.6%	4.9%	0.13

AML. Of the 34 patients without poor cytogenetics, 19 had an antecedent of MDS, 10 therapy-related AML and 5 both. At the end of induction, 56% ($n=65$) of the patients achieved CR, 9% ($n=11$) had died, whereas 35% ($n=41$ including 5 CR without platelets reconstitution) failed to achieve CR. PS was the only characteristic of significant prognostic value for reaching CR (PS 0 vs 1/2, $P=0.015$) (Table 1). Although not statistically significant, patients who were considered as poor-risk only due to previous MDS or other cancer had a trend toward a better CR rate (68.4% and 80%, respectively).

The safety of post-remission therapy was evaluated in the 65 CR patients, randomly assigned to start maintenance in arm A ($N=31$) or arm B ($N=34$). Patients received a median number of six courses. The 12 planned maintenance cycles were received by 21 patients (32%). The interval between courses was longer than the planned 28 days in 61 and 44% of patients after azacitidine and lenalidomide cycles, and was delayed for more than 7 days in 26 and 18% of patients, respectively. Mild toxicity was observed (Table 2). Hematopoietic toxicity, the most frequent adverse event, was acceptable in terms of grade 4 neutropenia, curative ambulatory antibiotics administration, rehospitalisation because of fever or transfusions. Maintenance courses were interrupted in 44 patients, primarily due to relapse ($n=34$, 77%), allogeneic stem cell transplantation ($n=4$, 9%), cycle count error ($n=1$ who did not receive the last cycle) or toxicities ($n=5$, 11%), including 4 after lenalidomide (depression, vascular purpura and gastroenteritis, hematopoietic toxicity and sudden death in a patient with previous cardiac ischemia). One atrial fibrillation led to azacitidine interruption. In addition, 20 grade 3–4 adverse events (5.6%/cycle) without treatment interruption occurred in a similar proportion of patients after lenalidomide (herpes zoster infection, vomiting, hepatic toxicity, peripheral neuropathy, deep vein thrombosis, rash, diarrhea (2 patients), bleeding (2 patients) and cutaneous squamous cell carcinoma) or azacitidine (herpes zoster infection, hepatic toxicity, cardiac toxicity (2 patients), creatinine alteration, cataract, diarrhea, bleeding and insomnia).

DFS were similar in patients randomized to first receive azacitidine or lenalidomide indicating that the sequence of maintenance therapy had no impact on the outcome. Patients were thus pooled for subsequent analysis. The median follow-up for survivors was 38 months (range: 26.6–46.9). Median DFS for the whole group was 7.9 months (95% CI: 5.3–10.5) with a 2-year DFS of 12.3%. Median overall survival (OS) was 10 months, with a 2-year OS rate of 21.4%. Among the 65 patients who reached CR, relapse occurred in 55 patients at a median time of 7 months (range: 1–29.8 months), 65% of them occurred during the maintenance. The impact of prognostic factors on OS and DFS is shown Table 1. Patients with PS $\leqslant 1$ had a significantly better DFS and OS ($P=0.012$ and 0.002, respectively). Poor-risk cytogenetic was associated with the worse survival (median DFS 5.1 months, median OS 8.1 months). Isolated previous MDS or therapy-related AML were conversely associated with significantly better survival. Allogeneic stem cell transplantation was performed in 9 patients (7.7%) in CR ($n=4$), failure ($n=3$) or relapse ($n=2$). Despite 3 transplant-related deaths and 3 post-transplant relapses, allogeneic stem cell transplantation was associated with an improved median OS (24 vs 9 months, $P=0.019$) suggesting that allogeneic stem cell transplantation could be a valid option in the small group of poor-risk but fit elderly population.

Historical comparison with the previous FILO trial SA-2002[ref. 15] including the same ICL induction but 2 years chemotherapy maintenance included 78 poor-risk cytogenetics patients, 9 with previous cancer but none with previous MDS, with a CR rate of 59%. Characteristics of these patients were similar to our population except for less cancer antecedents (11.5 vs 27.3%, $P=0.02$). Median DFS and OS were not significantly different in poor-risk cytogenetics without previous MDS in the azacitidine–lenalidomide and SA-2002 groups (5.2 (95% CI: (4.1–7.9)) and 8.4 (95% CI: (4.4–10.7) and 6.7 (95% CI: (5.2–9.3)) and 6.6 (95% CI: (5.2–9.4)), respectively.

In this prospective multicentre phase II study, the tolerance and efficacy of post-CR monthly maintenance alternating azacitidine and lenalidomide or vice versa, for 12 courses, in poor-risk elderly AML patients was investigated. The tolerance of monthly alternate azacitidine and lenalidomide cycles was rather good, in line with previous small studies using sequential or concomitant azacitidine (75 mg/m^2 for 5 or 7 days) and lenalidomide (10–50 mg, for 14 to 28 days) in non-del(5q) high-risk MDS or AML patients.[4–10] In this trial, thrombocytopenia and neutropenia were the most common treatment-related adverse events. However very few antibiotics and hospital readmissions were required for febrile neutropenia. Extra hematologic adverse events were not remarkable and all previously reported.

Despite its good tolerance, this maintenance strategy did not show any trend for improvement in either DFS or OS, with DFS and OS similar to those observed in the previous FILO LAMSA02 trial.[15] Absence of benefit of decitabine maintenance in younger AML patients in CR over historical controls has also been recently reported.[13] An alternate schedule or association with other drugs might show a more favorable outcome (tested currently in NCT01041703 (decitabine after clofarabine) and NCT01757535 (oral azacytidine maintenance after daunorubicin-based induction)). Moreover, patients considered of poor-risk because of previous MDS or therapy-related AML without poor-risk cytogenetics seem to have a better outcome and may justify further investigation with these drugs.

CONFLICT OF INTEREST

MH, CR, AP received honoraria from Celgene for lectures. The remaining authors declare no conflict of interest.

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