Panobinostat as part of induction and maintenance for elderly patients with newly diagnosed acute myeloid leukemia: phase Ib/II panobidara study

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ABSTRACT

This phase Ib/II trial combined the pan-deacetylase inhibitor panobinostat with chemotherapy followed by panobinostat maintenance in elderly patients with newly diagnosed acute myeloid leukemia. Patients with prior history of myelodysplastic syndrome were excluded and 38 evaluable patients were included in the study (median age: 71 years; range: 65-83). Study patients received an induction with idarubicin (8 mg/m^2 iv days 1-3) plus cytarabine (100 mg/m^2 iv days 1-7) plus panobinostat po at escalating doses (days 8, 10, 12, 15, 17 and 19) that could be repeated in non-responding patients. Patients achieving complete remission received a consolidation cycle with the same schema, followed by panobinostat maintenance (40 mg po 3 days/week) every other week until progression. Thirty-one patients were treated at the maximum tolerated dose of panobinostat in the combination (10 mg) with good tolerability. Complete remission rate was 64% with a time to relapse of 17.0 months (12.8-21.1). Median overall survival for the whole series was 17 months (5.5-28.4). Moreover, in 4 of 5 patients with persistent minimal residual disease before maintenance, panobinostat monotherapy reduced its levels, with complete negativization in two of them. Maintenance phase was well tolerated. The most frequent adverse events were thrombocytopenia (25% grades 3/4), and gastrointestinal toxicity, asthenia and anorexia (mainly grades 1/2). Five patients required dose reduction during this phase, but only one discontinued therapy due to toxicity. These results suggest that panobinostat is one of the first novel agents with activity in elderly acute myeloid leukemia patients, and suggest further investigation is warranted, particularly in the context of maintenance therapy. This trial is registered at *clinicaltrials.gov identifier: 00840346.*

Introduction

Acute myeloblastic leukemia (AML) is known as a disease of the elderly, with a median age at diagnosis of between 69 and 72 years.[1,2] Age is a well-defined adverse prognostic factor and elderly AML patients have a dismal prognosis.[3,4] Those able to tolerate intensive chemotherapy have complete remission (CR) rates of 40%-65% with a 10%-30% rate of early deaths. However, responses are short-lived and median overall survival (OS) is 6-8 months.[2-6] Therefore, these patients represent an unmet medical need. New strategies are required to improve CR rates and, most importantly, to prolong time to relapse (TTR) and OS.

Several novel agents have been explored in recent years, such as FMS-like tyrosine kinase receptor-3 (FLT3) inhibitors, novel cytotoxic agents, cell cycle inhibitors, monoclonal antibodies, and also hypomethylating agents or histone deacetylase inhibitors.[7] However, over the last decade, only modest improvements in the survival of this patient population have been seen.[3]

Epigenetic deregulation is a key feature of the pathophysiology of AML, resulting in aberrant transcription of genes involved in cell growth, proliferation, differentiation, and apoptosis.[8-10] Attempts to restore this epigenetic deregulation by using hypomethylating agents have been successful, and have led to the approval of 5-azacytidine and decitabine based on the positive results obtained in the MDS/AZA-001[11] and DACO-016[12] trials, respectively.

Histone acetylation is another major epigenetic mechanism that is maintained by the correct balance of histone deacetylases (DACs) and histone acetyltransferases (HATs).[13-15] In leukemic cells, this balance is disrupted by different mechanisms,[16,17] and, therefore, the use of DAC inhibitors has been proposed as an attractive approach for AML patients, especially in the elderly population.[18,19]

Panobinostat (NVP-LBH-589) is a pan-deacetylase inhibitor, which demonstrated potent activity against AML cell lines and primary AML cells, and also potentiated the action of several standard-of-care anti-AML compounds, particularly anthracyclines, in experiments performed in our laboratory.[20]

Here we report the safety and efficacy of the first trial to evaluate the activity of a DACi, panobinostat, in combination with chemotherapy followed by a maintenance phase with DACi in monotherapy in newly diagnosed AML patients over 65 years of age.

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Methods

Study population

Patients over 65 years of age with *de novo* AML were included in the trial. Patients were excluded if they had previously received any antileukemic treatment including a histone deacetylase inhibitor (HDACi) or if they had had a previous diagnosis of promyelocytic AML (M3), secondary AML after MDS, or known brain or leptomeningeal involvement. Patients with a previous history of cardiomyopathy or significant diarrhea were also excluded from the trial.

Study design

This was a multicenter, national, open-label, single-arm, non-controlled study consisting of an initial phase Ib, following the classic 3+3 schedule, aimed at establishing the maximum tolerated dose (MTD) of the combination in this patient population. Four increasing doses of panobinostat (20, 30 and 40 mg with a -1 dose level at 10 mg) were planned. Once the MTD was defined, recruitment continued at the MTD during phase II to evaluate the safety and efficacy of the schema.

The initial schema included an induction cycle with idarubicin (8 mg/m^2 days 1-3) + cytarabine (100 mg/m^2 days 1-7) in combination with three weeks of oral panobinostat at escalating doses (days 8, 10, 12, 15, 17, 19, 22, 24 and 26). A second induction cycle could be administered in non-responding patients. Patients achieving CR/CRi received a consolidation cycle with the same schema followed by maintenance with 40 mg oral panobinostat (3 days/week) for three weeks on and one week off, initially for six months (this was subsequently amended to be continued until progression). Following the inclusion of 6 patients, excessive toxicity was observed (see Results) and the protocol was amended to reduce the schedule of panobinostat to two weeks in the induction cycles (days 8, 10, 12, 15, 17 and 19) and to every other week in the maintenance phase (Figure 1A).

The study was approved by the Institutional Review Board/Independent Ethics Committee of each participating center. All patients provided written informed consent before screening. Data were analyzed by the first author; all authors had access to primary clinical trial data. The trial was registered at *clinicaltrials.gov identifier 00840346*.

Safety assessment and dose-limiting toxicity criteria

Safety was assessed by monitoring all physical, cardiological and biological adverse events (AEs). They were graded according to the NCI CTCAE v.3.0.

Dose-limiting toxicity (DLT) was defined as any severe non-hematologic toxicity considered clinically relevant and related to the study treatment, occurring during the first 28 days following the first dose of panobinostat. Specific criteria for DLT are listed in *Online Supplementary Table S1*.

Efficacy assessment

The response to treatment was assessed according to the standard Cheson criteria.[21] The primary efficacy criterion was response rate [complete response (CR), complete response with incomplete hematologic recovery (Cri), partial response (PR), residual disease (RD)], but several other outcomes were also evaluated: time to relapse (TTR), duration of response (DOR), relapse-free survival (RFS), and overall survival (OS). The Kaplan-Meier method and the log rank test were used to evaluate the statistical significance of the comparisons. All statistical analyses were performed using SPSS (v.20.0; IBM Corp., Armonk, NY, USA).

Flow cytometry evaluation of minimal residual disease (MRD) was performed according to previously described methods.[22,23] The LYSIS II and Cell Quest programs (Becton/Dickinson) were used for data acquisition in FACScalibur and FACS Canto II, cytometers (Becton/Dickinson, Biosciences San Jose, CA, USA), and the Infinicyt (Cytognos, Salamanca, Spain) software was used for further data analysis.

For molecular biological analysis, mutation screening of the *FLT3* and *CEBPA* genes was performed following published protocols.[24-26] *NPM1* mutant transcripts and *WT1* mRNA levels were quantified using the MutaQuant and ProfileQuant kits (Ipsogen).

Results

The initial schema resulted in unacceptable toxicity

Six patients were included in the initial intensive schedule, which was too toxic for these elderly patients. Three related deaths were observed: one was due to a renal failure in induction, a second was due to a fungal sepsis during reinduction, and the third involved a septic shock during consolidation in a patient in CR. In addition, 2 patients experienced a significant delay in recovery from the aplasia of the induction, which was longer than three months in one case. Accordingly, the protocol was amended to reduce the dose of panobinostat in the induction cycles and in the maintenance phase; the final treatment schedule is shown in Figure 1A.

Characteristics of the patients included after amendment

Forty patients were included in the final schedule, 2 of whom could not be evaluated due to exclusion criteria (one had a concurrent diagnosis of multiple myeloma and the other had base-line QTcF prolongation). Of the 38 evaluable patients in the study cohort, 20 were enrolled in phase Ib and 18 in phase II. A flow chart of the patients enrolled in the trial is presented in Figure 1B. Median age was 71 years (range: 65-83 years) with one-third of patients being 75 years old or over. Base-line characteristics of the 38 patients are shown in Table 1.

Determination of the maximum tolerated dose of panobinostat in combination with cytarabine and idarubicin

Twenty patients were included in the phase Ib dose escalation part of the trial. Seven patients were initially assigned to dose level one (20 mg of panobinostat). One of them died on day +7 due to a tumor lysis syndrome, before initiating panobinostat and therefore was not considered evaluable for MTD. Two of the 6 MTD-evaluable patients at this dose fulfilled the DLT criteria: both presented with a G3 hyperbilirubinemia, and one of them also had a G3 generalized edema. According to the protocol, subsequent patients were treated at the lower -1 dose level (10 mg). No DLT was observed in the first 3 evaluable patients, and 10 mg was defined as the MTD of panobinostat in this combination. According to the protocol, the cohort was expanded with 10 more patients in phase I, confirming the safety of this combination. Subsequently, 18 more patients were treated at this same dose in phase II, with a total of 31 patients treated at the MTD. Interestingly, age and other base-line characteristics of patients included in the 10 mg *versus* the 20 mg cohorts were similar. Patients initially treated at 20 mg in phase Ib continued treatment at this dose if it was tolerated; they will be reported separately, as they received a dose over the MTD.

Panobinostat in combination with idarubicin and cytarabine at the maximum tolerated dose and followed by maintenance produces a favorable outcome

Twenty (64%) of the 31 patients treated at the MTD achieved CR: 17 with the first induction, 2 with reinduction, and one achieved CRi with reinduction that converted into CR during maintenance. Three patients (10%) achieved PR, 5 (16%) presented with refractory disease, while the remaining 3 (10%) patients were not evaluable for response due to death in induction.

The response rate of patients treated at 20 mg was no better than that obtained with 10 mg panobinostat, with 2 patients each achieving CR, CRi and refractory disease (29% each), and one death during induction (13%).

From the 20 patients who achieved CR/CRi at the MTD dose, one was removed from the study during induction due to toxicity, and 3 patients died from infectious complications during consolidation. Therefore, 16 patients started the maintenance phase with panobinostat monotherapy. TTR of the 20 patients who achieved CR was 17.0 months (12.8-21.1 months) with a DOR of 16 months (10.4-21.5 months) and a RFS of 14 months (2.1-25.9 months) (Figure 2A). Figure 2B shows the individual outcome (time on treatment) of patients who achieved CR during the treatment. It is interesting to note that 4 patients were still on maintenance therapy at the time of publication of this report, 15 (2 cases), 22 and 30 months after inclusion in the trial.

Finally, with a median follow up of 24 months (13-37 months), the median OS was 17 months (5.5-28.4 months) (Figure 3A), increasing to 21 months (ND-ND) in those patients achieving CR (Figure 3B).

Table 1. Demographic characteristics of the 38 patients included in the trial after amendment.

	N.	%
Sex		
Male	17	45%
Age (range)	71 (65-83)	
≥70 years	26	68%
≥75 years	12	32%
ECOG		
0-1	36	95%
2	2	5%
BM blasts		
Morphology	44 (20-93)	
Flow cytometry	45 (4-93)	
Hemoglobin	9.3 (7.5-13,7)	
Platelets	54 (10-504)	
Leukocytes	3.5 (0.9-194)	
> 10(x10⁹/L)	12	32%
>50(x10⁹/L)	7	18%
Type of AML		
t(8;21)	1	3%
inv 16	1	3%
11q23	3	8%
AML with trilineage dysplasia	9	24%
Minimally differentiated	1	3%
AML without maturation	6	16%
AML with maturation	8	21%
Acute monocytic AML	4	10%
Acute myelomonocytic AML	2	5%
Acute erythroid AML	3	8%
Cytogenetics		
Good / intermediate	26	69%
Unfavorable	7	18%
No metaphases	5	13%
Molecular biology		
FLT3-ITD	6	16%
NPM1 mutations	8	21%
WT1 overexpression	24	63%
CEBPA mutations	0	0%
ND / NE	8	21%

ND: not done; NE: not-evaluable; BM: bone marrow.

Safety of the combination of panobinostat with cytarabine and idarubicin at maximum tolerated dose

Despite the advanced age of this patient population, treatment at the MTD of panobinostat was safe and panobinostat did not substantially increase the toxicity beyond that typical of standard induction chemotherapy (Table 2). In line with this, no significant delay in recovery from the aplasia was observed, as the median time to CR confirmation with normal blood counts was 30 days (range: 24-56 days). Although patient numbers are small, those treated at 20 mg required more than 30 days to recover (32 and 45 days for the 2 patients achieving CR; 37 and 73 days for those achieving CRi), confirming the toxicity of the combination at higher doses of panobinostat.

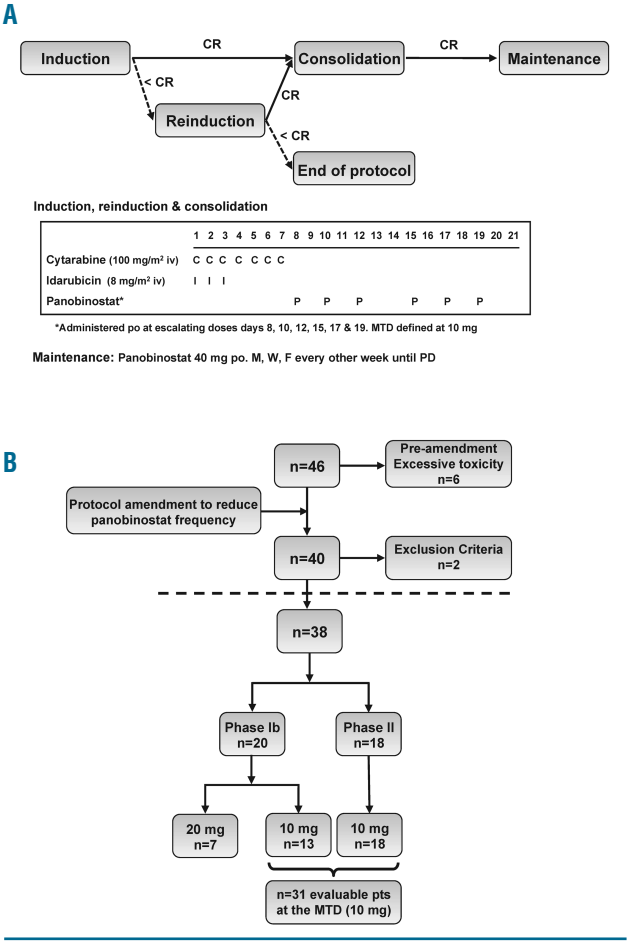

Figure 1. (A) Final schema of the panobidara trial. (B) Flow chart of patients included in the trial.

Table 2. Most frequent non-hematologic adverse events during the intensive cycles (induction/consolidation), irrespective of the relationship with the study drugs.

	Grades 1/2	Grades 3/4	Grade 5	Total
Gastrointestinal				
Diarrhea	20 (65%)	2 (6%)		22 (71%)
Nausea /vomiting	16 (52%)			16 (52%)
Mucositis	12 (39%)			12 (39%)
Dyspepsia	14 (45%)			14 (45%)
Constipation	12 (39%)			12 (39%)
Hemorrhoids	8 (26%)			8 (26%)
Infectious				
Febrile neutropenia /sepsis*	18 (58%)	5 (16%)	3 (10%)	26 (84%)
Cellulitis	5 (16%)			5 (16%)
Cardiovascular				
Cardiac abnormalities	2 (6%)	2 (6%)	1 (3%)	5 (16%)**
Thrombosis	2 (6%)			2 (6%)
Other				
Edemas	17 (55%)	1 (3%)		18 (58%)
Skin rash	16 (52%)			16 (52%)
Liver abnormalities	7 (23%)	1 (3%)		8 (26%)
Asthenia	6 (19%)	2 (8%)		8 (26%)
Hypokalemia		7 (23%)		7 (23%)

*Irrespective of the infectious localization. **Two G1 ventricular premature complexes; two atrial fibrillations (one G3 and another one G4 as it caused an acute pulmonary edema); and a G5 acute pulmonary edema.

The main non-hematologic toxicity was gastrointestinal (GI), with 71% of patients suffering diarrhea, most of them G1-2 (65%), with only 2 patients (6%) reaching grade 3. Other common GI toxicities were nausea, mucositis, dyspepsia and constipation, which were present in 40%-50% of cases, again, mainly grades 1 and 2. Five patients experienced cardiac AEs. Two patients developed atrial fibrillation, and 2 developed episodes of cardiac insufficiency with pulmonary edema, one of which resulted in death. Serial ECGs were performed according to the protocol and no additional significant abnormalities were found.

Overall, 3 (10%) deaths were observed during induction, all of which were unlikely to have been related to the treatment under investigation: one patient died from a respiratory infection, another from an acute pulmonary edema before starting panobinostat, and the third from a fatal head trauma. Three more patients died in CR during consolidation from serious infectious AEs (only one of them considered to be treatment-related by the investigator).

No dose reductions of panobinostat were required during these intensive cycles. Apart from the aforementioned toxic deaths, only one patient discontinued the trial in the intensive cycles due to toxicity (a septic shock in induction that occurred before initiating panobinostat).

Panobinostat maintenance is well tolerated in this patient population

The most important AEs in the maintenance phase are summarized in Table 3. Overall, treatment was well tolerated, with only a minority of patients experiencing hematologic toxicity; thrombocytopenia was the most frequent, present in 25% of patients at grades 3/4. The most important non-hematologic toxicity was again GI toxicity, especially diarrhea (69% of patients), nausea (50%) and dyspepsia (31%), but mostly at grades 1 and 2 (Table 3). One-third of the patients experienced low-grade asthenia or anorexia. Highlighting the safety of this maintenance phase, only 5 of the 16 patients treated at the MTD who reached maintenance required dose reductions of panobinostat during this phase, with one of them reducing dosage twice (total 6 reduction events). Reasons for the 6 reductions were hematologic toxicity (2 cases), GI (2 cases), hematologic and GI AEs (1 case) and investigator decision (1 case). Panobinostat was discontinued during maintenance in one patient due to a septic shock in cycle 3.

Table 3. Hematologic and non-hematologic adverse events related to panobinostat during maintenance.

	Grades 1/2	Grades 3/4	Total
Hematologic			
Anemia		2 (12%)	2 (12%)
Neutropenia		2 (12%)	2 (12%)
Thrombocytopenia	1 (6%)	4 (25%)	5 (31%)
Gastrointestinal			
Diarrhea	10 (63%)	1 (6%)	11 (69%)
Nausea/vomiting	7 (44%)	1 (6%)	8 (50%)
Dyspepsia	5 (31%)		5 (31%)
Other			
Asthenia	4 (25%)	1 (6%)	5 (31%)
Anorexia	5 (31%)		5 (31%)
Fever/infections	2 (13%)	1 (6%)	3 (19%)
Skin rash	1 (6%)		1 (6%)
Hyperbilirubinemia	1 (6%)		1 (6%)

Efficacy of this treatment in patients with adverse prognostic features

We also evaluated the extent to which this treatment overcame adverse prognostic features (*Online Supplementary Figure S1*). There were no significant differences in outcome between patients over or patients below 75 years of age with respect to OS (14 *vs.* 17 months; P=0.9); however, a lower CR rate (50% *vs.* 71%) was observed in patients over 75 years old, although this was

not statistically significant (P=0.2). Patients with hyperleukocytosis (≥50x10^9/L leukocytes) had a lower CR rate (25% *vs.* 70%) and a worse OS (3 *vs.* 17 months) than those without, although neither of these differences were statistically significant (P=0.1 for both). Patients with adverse cytogenetic abnormalities or *FLT3*-ITD had a significantly lower CR rate (33% *vs.* 79%; P=0.04) and a non-significant trend towards a shorter OS (6 *vs.* 17 months; P=0.1).

Panobinostat maintenance can eradicate minimal residual disease after induction

To further assess the role of panobinostat monotherapy, we analyzed its ability to reduce the MRD in patients who began maintenance in CR but with persistence of residual disease. Two patients had persistent residual blasts by flow cytometry at that point. One of them progressed quickly during the first maintenance cycle. However, the other patient started the maintenance phase with 0.15% blasts, having been negative in the previous determinations, and panobinostat monotherapy was able to eradicate the MRD after 3 cycles. This patient remained in immunophenotypic remission until cycle 18 of maintenance, when he relapsed.

Regarding molecular biology, 3 patients had a positive marker at the time of starting maintenance. Panobinostat

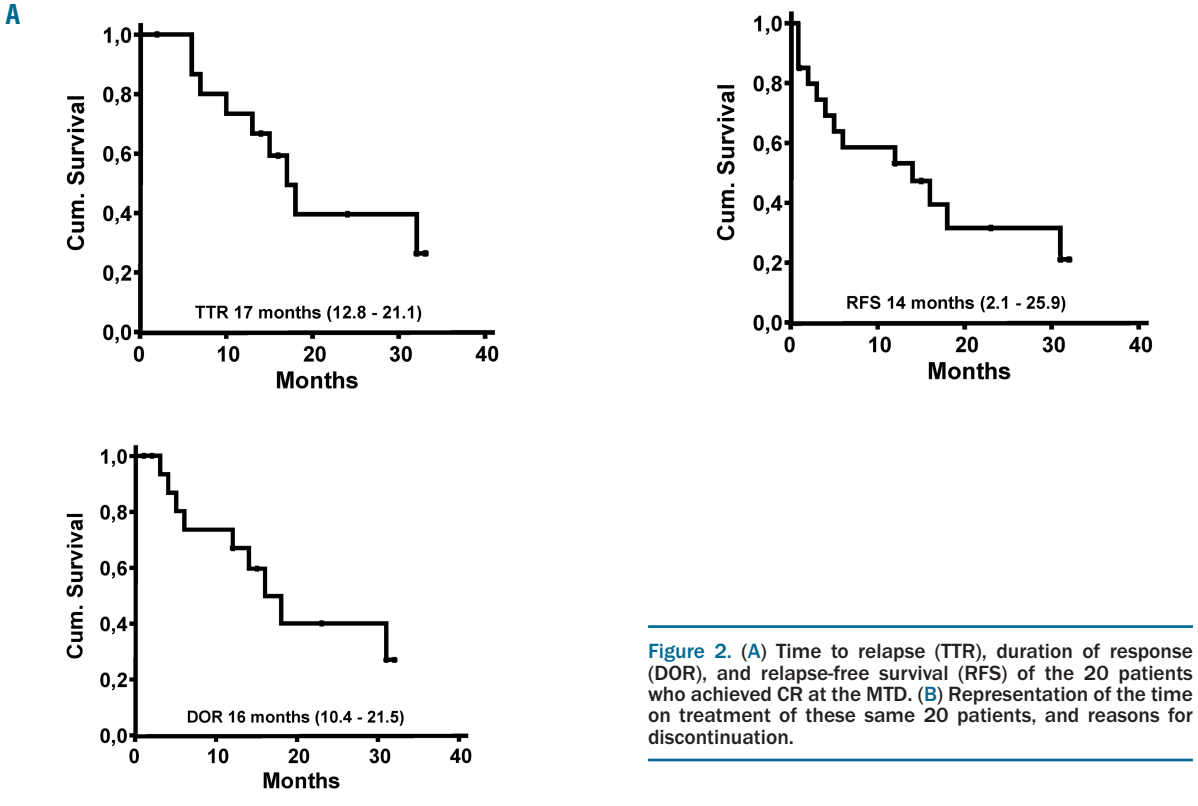

Figure 2. (A) Time to relapse (TTR), duration of response (DOR), and relapse-free survival (RFS) of the 20 patients who achieved CR at the MTD. (B) Representation of the time on treatment of these same 20 patients, and reasons for discontinuation.

maintenance was able to reduce the MRD levels in all 3 patients. In the first patient, *WT1* transcripts progressively decreased at three and six months after maintenance, but the patient progressed in cycle 10. In the second case, the *NPM-1* mutation was reduced to almost undetectable levels with panobinostat treatment and is now receiving cycle 30 as ongoing treatment. The third patient became *NPM-1* negative after the third cycle of maintenance and is currently on cycle 14 of treatment.

Discussion

The present trial was based on our previous pre-clinical experiments in which panobinostat showed a high pre-clinical antileukemic activity alone and in combination with anthracyclines.[20] We, therefore, decided to test this hypothesis focusing on fit AML patients aged 65 years or older, as novel therapeutic approaches are urgently needed for these patients. The design of the trial was based on the PETHEMA 99 study, which used exactly the same induction and consolidation but without panobinostat, and was followed by an intensification cycle with cytarabine plus daunorubicin.[27,28] As PETHEMA 99 did not include patients with a previous history of MDS, we decided to also exclude them from the trial reported here. Patients' characteristics of both studies were comparable in terms of adverse prognostic features, such as advanced age (>75years in 32% *vs.* 18% of patients, respectively) or adverse cytogenetics (present in 21% and 25% of evaluable patients, respectively). Given the similarities in design and patient population, we consider it to be a good comparator for evaluating the efficacy and safety of the addition of panobinostat during induction and in the maintenance phase.

The first finding of the trial was the toxicity in this frail population, that led to reduce the weeks of administration of panobinostat after chemotherapy, and made it impossible to escalate the dose of panobinostat in combination with cytarabine and idarubicin to over 10 mg. Consequently, this dose was defined as the MTD. Nevertheless, when using the MTD, the schema proved to be feasible, with the expected toxicity associated with intensive chemotherapy and relatively few early deaths: 3 patients (10%) in induction; and 3 others (10%) in CR during consolidation. This is similar, if not better, than the 19% of deaths during induction plus 7% in patients in CR in post-remission cycles achieved in the previous PETHEMA trial. It also compares favorably to the 13% 30-day mortality rate in the Swedish registry[2] and the 20%-30% 8-week mortality rate in the SEER study.[6] Moreover, despite the low dose of panobinostat used, and with the limitations of a small study, CR rate was 64%. This represents an improvement on the CR observed in the PETHEMA trial (55%) and that of other studies featuring intensive chemotherapy in similar populations (CR rates of 45%-55%).[2,6,29]

This study differs from others in the introduction of maintenance. This is still a controversial issue in AML, but in recent years, the discovery of novel targeted agents, some of which are orally administered and have an adequate safety profile, has encouraged research into this approach, especially in patients with poor prognostic features, such as the elderly.[30-34] In this trial, we have demonstrated that panobinostat is a feasible agent for maintenance in AML, since patients were able to remain on treatment for long periods without excessive toxicity. Despite the high dose of panobinostat administered during maintenance (40 mg), few patients required dose reduction, and, importantly, once this was done, patients could continue with the treatment.

The present schema was also effective in delaying the occurrence of relapse, as the TTR of those patients achieving CR was 17.0 months, much longer than the 11.7 months achieved in our previous PETHEMA control. Moreover, in our study, the RFS was 14 months, which is also better than that reported in a joint analysis of several trials that used intensive induction (less than 9 months when focusing on elderly AML patients).[35] As further evidence of the efficacy of this agent, panobinostat maintenance was able to decrease the MRD levels in 4 out of 5 patients with eradication of MRD observed in 2 of them. One of these patients is of particular interest since the MRD had reappeared just before the maintenance phase, which may represent the first sign of potential relapse. However, the initiation of panobinostat maintenance reverted this situation, eradicating the disease for a second time and maintaining the patient relapse-free for a further 18 months.

Finally, the most important challenge in the treatment of elderly AML patients is to improve survival, as, even when receiving intensive treatment, they have a median OS of less than one year (usually 6-8 months).[2-6] This was also

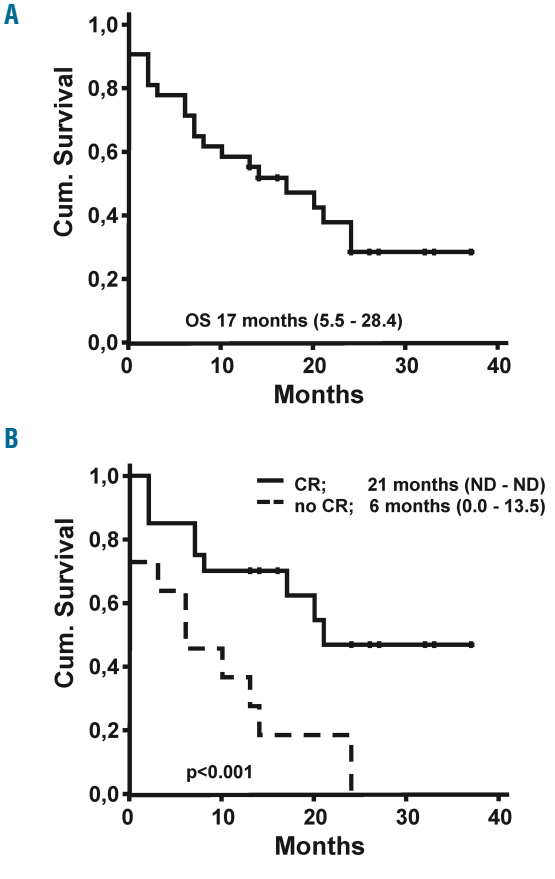

Figure 3. (A). Overall survival of patients treated at the maximum tolerated dose. (B). Overall survival in patients who achieved CR (n=20) *versus* those who did not (n=11).

the case in the previous PETHEMA 99 trial in which OS was 7.6 months. Interestingly, in our study, OS was 17 months, twice that reported for other trials (see above). Moreover, in those patients achieving CR, median OS was 21 months, which is also clearly superior to the 14.5 months of the PETHEMA trial.

In conclusion, our data demonstrate the safety and efficacy of panobinostat in combination with cytarabine and idarubicin, followed by a maintenance phase with panobinostat in monotherapy. The whole schema, including the maintenance phase, was able to improve the CR rate and the TTR of responding patients and, subsequently, the OS compared with previous controls, with a good tolerability. Moreover, although it was not implemented in our trial, the future evaluation of some biomarkers, such as histone or tubulin acetylation, could help to better define those patients that could benefit the most from deacetylase inhibitors such as panobinostat. These results identify panobinostat as one of the first novel agents with potential activity in elderly AML patients.

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Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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