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ORIGINAL ARTICLE

Long-term outcome of older patients with newly diagnosed *de novo* acute promyelocytic leukemia treated with ATRA plus anthracycline-based therapy

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Treatment outcome in older patients with acute promyelocytic leukemia (APL) is lower compared with younger patients, mainly because of a higher induction death rate and postremission non-relapse mortality (NRM). This prompted us to design a risk- and age-adapted protocol (Programa Español de Tratamientos en Hematología (PETHEMA)/HOVON LPA2005), with dose reduction of consolidation chemotherapy. Patients aged ⩾60 years reported to the PETHEMA registry and were treated with all-*trans* retinoic acid (ATRA) plus anthracycline-based regimens according to three consecutive PETHEMA trials that were included. We compared the long-term outcomes of the LPA2005 trial with the preceding PETHEMA trials using non-age-adapted schedules (LPA96&LPA99). From 1996 to 2012, 389 older patients were registered, of whom 268 patients (69%) were eligible. Causes of ineligibility were secondary APL (19%), and unfit for chemotherapy (11%). Median age was 67 years, without relevant differences between LPA2005 and LPA96&LPA99 cohorts. Overall, 216 patients (81%) achieved complete remission with no differences between trials. The 5-year NRM, cumulative incidence of relapse, disease-free survival and overall survival in the LPA2005 vs the LPA96&99 were 5 vs 18% ($P=0.15$), 7 vs 12% ($P=0.23$), 87 vs 69% ($P=0.04$) and 74 vs 60% ($P=0.06$). A less intensive front-line regimen with ATRA and anthracycline monochemotherapy resulted in improved outcomes in older APL patients.

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INTRODUCTION

Unlike other acute myeloid leukemia subtypes, acute promyelocytic leukemia (APL) is relatively uncommon in older patients.[1,2] Treatment of APL is characterized by a high sensitivity to anthracyclines and differentiating agents, such as all-*trans* retinoic acid (ATRA) and arsenic trioxide (ATO), leading to a high cure rate (up to 80%).[3] However, outcomes with state-of-the-art treatment are still poorer in older patients with APL compared with younger patients.[4–10]

A previous report of two consecutive Programa Español de Tratamientos en Hematología (PETHEMA) trials showed that older patients with APL can be successfully treated using ATRA plus anthracycline for induction and consolidation. However, relative high mortality rates were noted during induction and postremission therapy, mainly because of hematological toxicity, compared with younger patients.[4] This observation led us to design subsequent protocols based on age- and risk-adapted therapy, with reduced chemotherapy intensity for patients aged 60 years or more (LPA2005 trial).[11] Reduced intensity chemotherapy strategies have also been implemented by other groups, which have resulted in less treatment-related deaths.[5,7,8,12,13] However, most of these studies have been performed in relatively small series.[7,8,12,13] Solid data regarding outcomes with modern APL treatment in older patients are still lacking.

The objective of the present study was to evaluate long-term outcomes in a large series of older patients with APL treated with ATRA plus anthracycline-based regimens in three consecutive multicenter PETHEMA trials to demonstrate improvements and benefits provided by an age- and relapse risk-adapted approach.

SUBJECTS AND METHODS

Eligibility

Patients with age 60 years or above (older) reported to the multicenter and multinational PETHEMA APL registry are required to be diagnosed with APL with a demonstration of the t(15;17) or *PML/RARA* rearrangement. Patients were not eligible if they met at least one of the following exclusion criteria: (1) Eastern Cooperative Oncology Group performance status at presentation >3; (2) hepatic, renal, cardiac or other severe

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comorbidities that limit the administration of chemotherapy in the opinion of the treating physician; and (3) antecedents of primary malignancy or exposure to leukemogenic agents (those patients were classified as secondary APL). Informed consent was obtained from all patients. According to the Declaration of Helsinki, the protocols were approved by the Research Ethics Board of each participating hospital.

Therapy of APL

Details on therapy have been previously reported elsewhere and are detailed in Figure 1.[14–16] In the LPA96 trial, all patients received the same schedule, regardless of age and relapse-risk score: induction therapy consisted of oral ATRA and idarubicin given on days 2, 4, 6 and 8 (AIDA regimen), consolidation with three courses of anthracycline monochemotherapy and maintenance with alternant ATRA and low-dose methotrexate and mercaptopurine for 2 years. In the risk-adapted LPA99 trial, apart from the omission of the day 8 dose of idarubicin during induction for patients older than 70 years, the AIDA schedule was consistent for all ages. Consolidation comprised three courses of anthracycline monochemotherapy for low-risk patients, and reinforced consolidation with ATRA and a higher idarubicin dose for intermediate- and high-risk patients. In the age- and risk-adapted LPA2005 trial (from May 2005), the consolidation schedule was modified in older patients as follows: ATRA was added to the three consolidation courses for low-risk patients, and mitoxantrone was given for 3 days instead of 5 days during the second consolidation course in all patients, regardless of their relapse-risk score.

Management of coagulopathy and differentiation syndrome (DS) was made according to the recommendations for each subsequent PETHEMA trial, as previously described elsewhere.[11,14,15,17–19]

Study definitions and end points

Remission induction response was assessed according to the revised criteria by Cheson *et al*.[20] Criteria for molecular remission, molecular persistence, molecular relapse and extramedullary relapse in central nervous system (CNS) or other localization have been published elsewhere.[17,21] Molecular persistence or molecular relapse were considered as therapeutic failure.

Diagnosis of DS and the grading of severity were made according to the previously defined criteria.[19,22] Coagulopathy was diagnosed in case of prolonged prothrombin time and/or activated partial thromboplastin time with hypofibrinogenemia and/or increased levels of fibrin degradation products or D-dimers. Risk of relapse was established according to leukocyte and platelet counts at diagnosis, as reported previously.[21]

The primary end point was to compare the disease-free survival (DFS) between patients treated with non-age-adapted protocols (LPA96&LPA99) and those treated with an age-adapted protocol (LPA2005). Other study end points were overall survival (OS), cumulative incidence of relapse (CIR), non-relapse mortality (NRM), complete remission (CR) rate, hematological toxicity and hospitalizations during induction and consolidation.

Statistical analysis

X^2 with Yates' correction, Mann–Whitney *U*-test and Student's *t*-tests were used to analyze differences in the distribution of variables among patient subsets. Unadjusted time-to-event analyses were performed using the Kaplan–Meier estimate[23] and, for comparisons, log-rank test.[24] The probability of CIR and NRM were estimated by the cumulative incidence method.[25–27] OS was calculated from the date of starting induction therapy, whereas CIR, NRM and DFS were calculated from the date of CR. In the analysis of DFS, relapse, development of therapy-related myeloid neoplasms (t-MNs) and death in CR were considered uncensored events, whichever occurred first. For CIR analysis, death in CR and development of t-MNs were considered as a competing cause of failure. For the estimation of NRM, relapse and molecular persistence were considered as competing events. Characteristics selected for inclusion in the multivariate analysis for induction death and OS (using a logistic regression and a Cox proportional hazards model, respectively) were those for which there was some indication of a significant association in univariate analysis ($P < 0.1$), and, if available, those for which prior studies had suggested a possible relationship. Patient follow-up was updated on 30 March 2016. All *P*-values reported are two sided. Computations were performed using the R 2.15.1 software package.

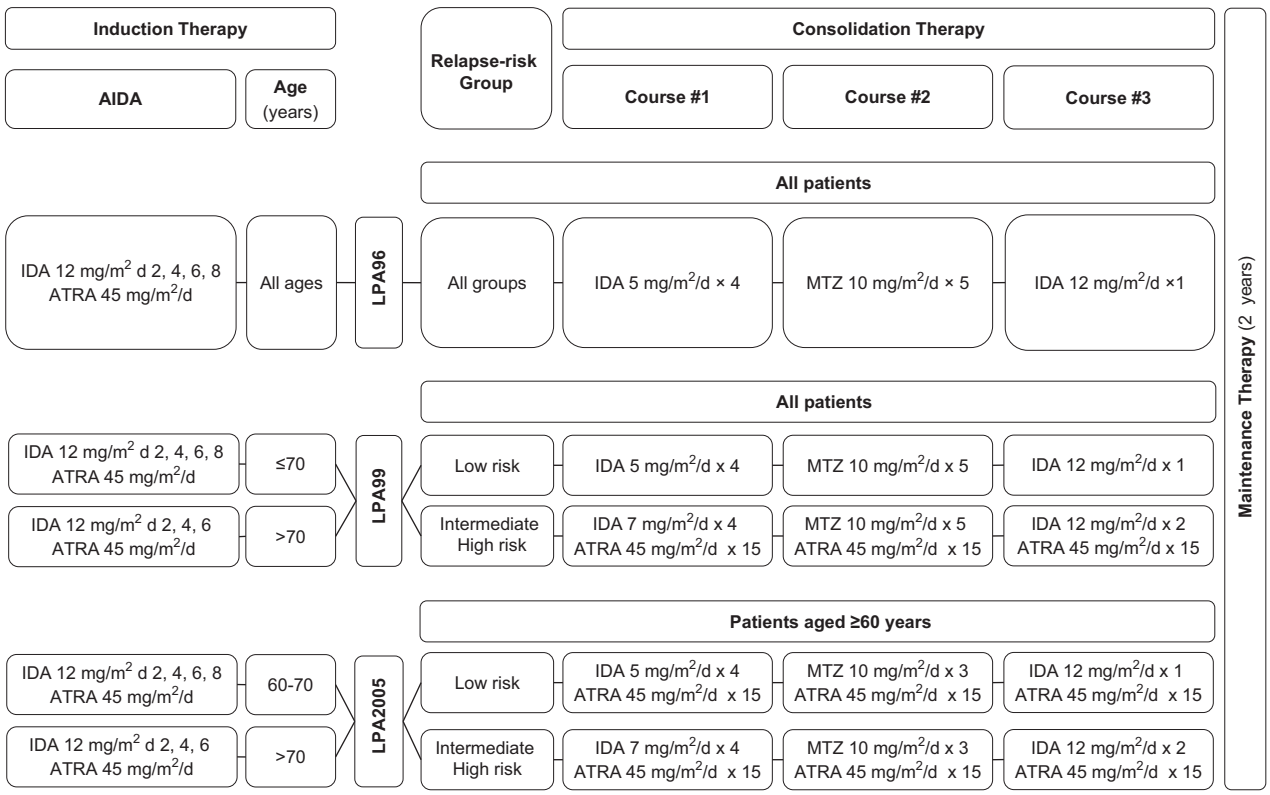

Figure 1. Treatment schedule of the LPA96, LPA99 and LPA2005 PETHEMA trials. Ara-C, cytarabine; ATRA, all-*trans* retinoic acid; IDA, idarubicin; MTZ, mitoxantrone.

RESULTS

Accrual and patient characteristics

Between November 1996 and November 2014, 389 consecutive older patients were registered from several institutions from Spain, The Netherlands, Poland, Argentina, Uruguay, The Czech republic and Colombia (see group above the References). Of these patients, 268 (69%) were eligible and 121 (31%) were excluded because of secondary APL (19%), Eastern Cooperative Oncology Group 4/unfit for intensive chemotherapy (11%) or protocol violation (1%) (Table 1). Compared with patients included in the LPA96&99 trials, those included in the LPA2005 trial had a higher albumin and uric acid serum levels, and less fever at diagnosis (Table 2). A Consolidated Standards of Reporting Trials (CONSORT) diagram for the subsequent LPA96&99 and LPA2005 PETHEMA trials is shown in Figure 2.

Induction therapy

Response and induction mortality. Two hundred and sixteen out of 268 eligible patients (81%) achieved CR, and 52 (19%) died during induction. Leukemic resistance was not observed. Among patients treated with LPA96&99 trials, 105 out of 135 (78%) achieved CR, and 30 (22%) died during induction. In the LPA2005 trial, 111 of 133 patients (84%) achieved CR and 22 (16%) died during induction. No significant differences in CR rate and causes of induction death were observed between protocols (Table 3). The multivariate analysis showed that creatinine level >1.3 mg/dl ($P=0.001$) and white blood cell count higher than 10×10^9/l ($P<0.001$) were independent risk factors for induction death.

Differentiation syndrome. A complete data set about DS was available in 255 patients (95%), 135 from the LPA96&99 trials and 120 from the LPA2005 trial. Severe DS was reported in 36 patients (14%), and moderate DS in 46 patients (18%), without differences between protocols (Table 3).

Consolidation therapy

First course. Among 216 patients who achieved CR, 212 (98%) received the first course. One patient died of cardiogenic shock during this course, and three patients discontinued the schedule and followed with maintenance therapy after this course.

Second course. Two hundred and eight (96%) patients received the second course as planned. Two patients died, and five patients discontinued the schedule and followed with maintenance therapy after this course.

Third course. Two hundred and one (93%) patients received the third course as planned. Two patients died owing to infections during this course.

Hematologic toxicity and hospitalization

Table 4 shows grade 4 neutropenia, grade 3–4 thrombocytopenia and hospitalization duration in induction and consolidation according to each trial. No significant differences were observed between the trials during induction and the third consolidation course. During the first consolidation course, severe neutropenia and thrombocytopenia were significantly prolonged in the LPA2005 trial compared with the LPA96&99 trials. During the second consolidation course, severe neutropenia and thrombocytopenia, as well as hospitalization, were significantly prolonged in the LPA96&99 trials compared with the LPA2005 trial.

Maintenance treatment

Maintenance therapy was started in 199 (92%) out of 216 patients who achieved CR. A complete data set assessing maintenance therapy was available for 150 of those patients. Overall, 819 maintenance cycles were reported (mean of 5.5 cycles per patient). Any grade $\geqslant1$ hematologic toxicity occurred in 124 cycles (15%) (among 45 patients). Thrombocytopenia was developed in 76 patients (9%), and neutropenia in 59 patients (7%). Any grade $\geqslant1$ non-hematologic toxicity occurred in 261 cycles (32%) (among 77 patients). Hepatotoxicity was developed in 166 (20%), oral disorders in 50 (6%) and diarrhea in 38 patients (5%). Four patients died because of infectious complications during maintenance (three in the LPA96&99 trials and one in the LPA2005 trial). Excluding patients who relapsed during maintenance treatment, 93% patients treated according to the LPA2005 protocol finished the planned schedule vs 88% who were included in the LPA96&LPA99 trials.

Long-term outcomes and prognostic factors

Long-term outcomes of APL patients in the PETHEMA LPA96&99 and LPA2005 trials are shown in Table 5.

Table 1. Causes of non-eligibility for PETHEMA trials in older patients diagnosed with APL

PETHEMA trial	*All protocols,* N *(%)*	*LPA96,* N *(%)*	*LPA99,* N *(%)*	*LPA96&99,* N *(%)*	*LPA2005,* N *(%)*
Total non-eligible	121 (100)	14 (100)	39 (100)	53 (100)	68 (100)
Secondary APL	73 (60)	9 (64)	24 (62)	33 (62)	40 (59)
Extreme age	10 (8)	2 (14)	1 (3)	3 (6)	7 (11)
Previous comorbidities	12 (10)	1 ((7)	4 (10)	5 (9)	7 (11)
Cardiac dysfunction	3 (2)	0 (0)	2 (5)	2 (4)	1 (1)
Pulmonary disease	2 (2)	0 (0)	0 (0)	0 (0)	2 (3)
Chronic renal impairment	1 (1)	0 (0)	1 (3)	1 (2)	0 (0)
Several concomitant diseases	6 (5)	1 (7)	1 (3)	2 (4)	4 (6)
APL-related complications	21 (17)	1 (7)	9 (23)	10 (19)	11 (16)
CNS hemorrhage	10 (8)	0 (0)	7 (18)	7 (13)	3 (4)
Pulmonary hemorrhage	2 (2)	0 (0)	0 (0)	0 (0)	2 (3)
Serious thrombotic events	4 (3)	0 (0)	1 (3)	1 (2)	3 (4)
Acute renal impairment	2 (2)	1 (7)	0 (0)	0 (0)	1 (1)
Infection	2 (2)	0 (0)	1 (3)	1 (2)	1 (1)
Hepatic disorder	1 (1)	0 (0)	0 (0)	0 (0)	1 (81)
Protocol violation	5 (4)	1 (7)	1 (3)	2 (4)	3 (4)

Abbreviations: APL, acute promyelocytic leukemia; CNS, central nervous system; PETHEMA, Programa Español de Tratamientos en Hematología.

Table 2. Demographic and baseline characteristics of the study population according to the PETHEMA trial

Characteristic	*LPA96*		*LPA99*		*LPA96&99*		*LPA2005*		P-*value*[a]
	Median (range)	n *(%)*	*Median (range)*	n *(%)*	*Median (range)*	n *(%)*	*Median (range)*	n *(%)*	
Overall		30 (100)		105 (100)		135 (100)		133 (100)	
Age (years)	68 (60–78)		67 (60–83)		68 (60–83)		67 (60–84)		0.92[b]
60–69		16 (53)		68 (65)		84 (62)		85 (64)	0.68
70–79		14 (47)		34 (32)		48 (36)		43 (32)	
⩾80		0 (0)		3 (3)		3 (2)		5 (4)	
Gender									
Male		18 (60)		45 (43)		63 (47)		63 (47)	0.99
Female		12 (40)		60 (57)		72 (53)		70 (53)	
ECOG	1 (0–3)		1 (0–3)		1 (0–3)		1 (0–3)		0.79[b]
0–1		19 (68)		66 (65)		85 (65)		77 (69)	0.68
2–3		9 (32)		36 (35)		45 (35)		35 (31)	
Fever									
No		18 (60)		67 (64)		85 (63)		93 (77)	0.03
Yes		12 (40)		37 (36)		49 (37)		28 (23)	
Coagulopathy									
No		4 (13)		32 (30)		36 (27)		25 (40)	0.09
Yes		26 (87)		73 (70)		99 (73)		37 (60)	
Hemoglobin (g/dl)	7.9 (4.3–15.2)		9.5 (4–14.1)		9.3 (4–15.2)		9.7 (4.3–17.7)		0.29[b]
⩽10		21 (70)		61 (58)		82 (61)		74 (56)	0.47
>10		9 (30)		44 (42)		53 (39)		59 (44)	
WBC ($\times 10^9$/l)	1.5 (0.3–84.1)		2 (0.2–122.3)		1.9 (0.2–122.3)		1.5 (0.3–112.4)		0.29[b]
⩽10		23 (77)		81 (77)		104 (77)		109 (82)	0.44
10–50		4 (13)		19 (18)		23 (17)		20 (15)	
>50		3 (10)		5 (5)		8 (6)		4 (3)	
Platelet count ($\times 10^9$/l)	25 (2–156)		19 (3–207)		25 (2–207)		25 (2.4–235)		0.96[b]
⩽40		21 (70)		67 (64)		88 (65)		92 (69)	0.57
>40		9 (30)		38 (36)		47 (35)		41 (31)	
Relapse-risk group									
Low		8 (27)		34 (32)		42 (31)		37 (28)	0.38
Intermediate		15 (50)		47 (45)		62 (46)		72 (54)	
High		7 (23)		24 (23)		31 (23)		24 (18)	
Creatinine (mg/dl)	0.95 (0.6–1.7)		0.99 (0.3–2.4)		1 (0.3–2.4)		0.9 (0.5–9)		0.21[b]
⩽1.3		28 (93)		90 (91)		118 (91)		112 (93)	0.93
>1.3		2 (7)		9 (9)		11 (9)		9 (7)	
Uric acid (mg/dl)	3.6 (1.2–7.4)		4.2 (1.4–10.1)		4.2 (1.2–10.1)		4.9 (1.1–10.5)		0.005[b]
⩽7		28 (97)		80 (93)		108 (94)		98 (88)	0.21
>7		1 (3)		6 (7)		7 (6)		13 (12)	
Albumin (g/dl)	4 (2.2–4.9)		3.7 (2.3–6.0)		3.7 (2.2–6)		4 (2–6)		0.01[b]
⩽3.5		9 (36)		33 (39)		42 (39)		30 (27)	0.11
>3.5		16 (64)		51 (61)		67 (61)		80 (73)	
Fibrinogen (mg/dl)	166 (35–627)		178 (0–720)		175 (0–720)		210 (20–890)		0.31[b]
⩽170		15 (50)		45 (45)		60 (46)		43 (64)	0.13
>170		15 (50)		55 (55)		70 (54)		77 (36)	
Morphologic subtype									
Hypergranular		22 (73)		86 (82)		108 (80)		102 (84)	0.46
Microgranular		8 (27)		19 (18)		27 (20)		19 (16)	
PML/RARα									
BCR1/BCR2		17 (59)		54 (57)		71 (58)		48 (56)	0.89
BCR3		12 (41)		40 (43)		52 (42)		38 (44)	
CD34									
Positive		4 (22)		8 (11)		12 (13)		16 (20)	0.32
Negative		14 (78)		66 (89)		80 (87)		65 (80)	
CD56									
Positive		0 (0)		13 (20)		13 (17)		5 (8)	0.18
Negative		10 (100)		53 (80)		63 (83)		58 (92)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PETHEMA, Programa Español de Tratamientos en Hematología; WBC, white blood cell. [a]*P*-value compares variables between LPA96&99 and LPA2005 groups. [b]*P*-value compares continuous variables.

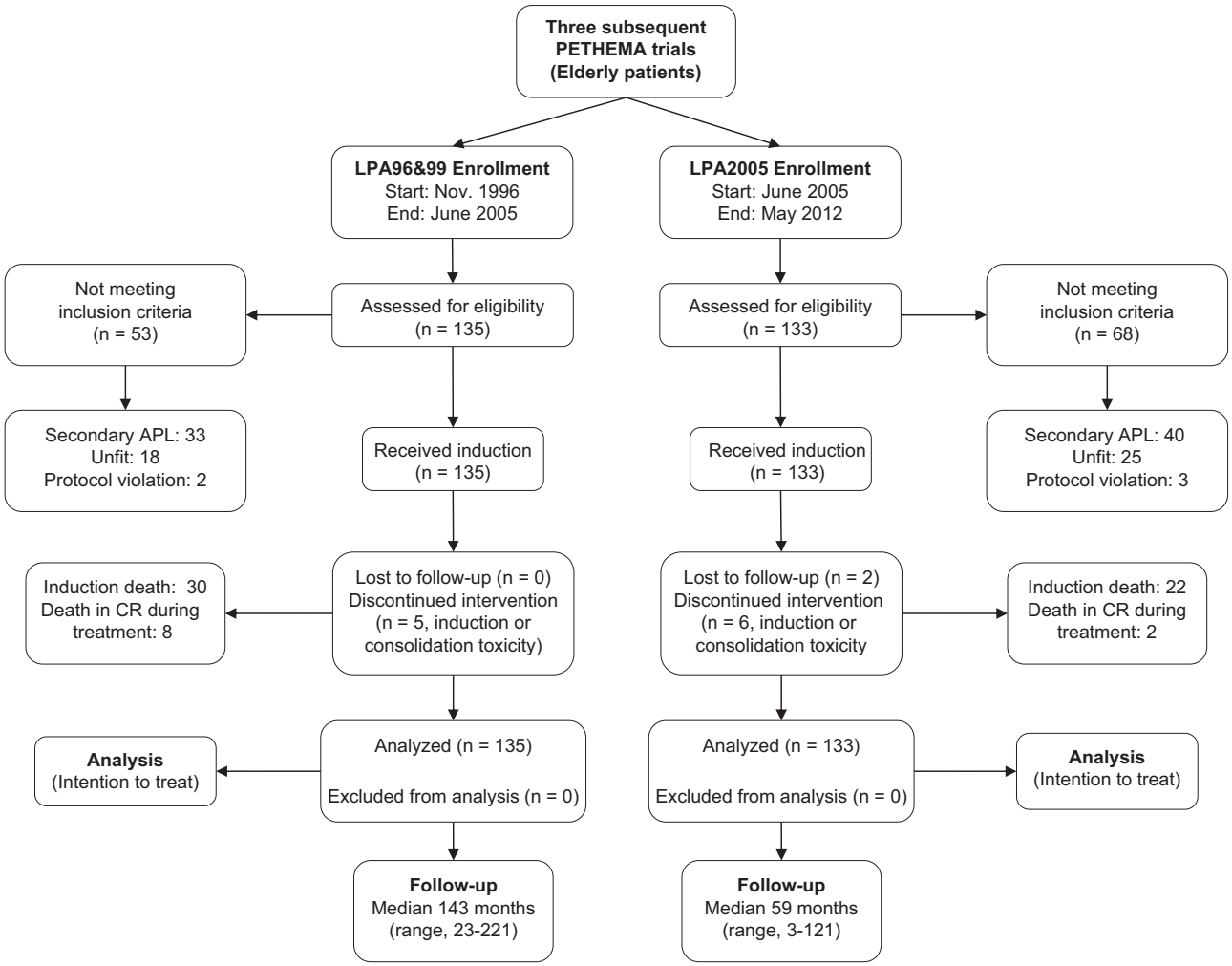

Figure 2. Consolidated Standards of Reporting Trials (CONSORT) diagram for the subsequent LPA96&99 and LPA2005 PETHEMA trials.

Overall survival. The median follow-up of patients of the LPA96&99 trials was 143 months (range, 23–221 months) vs 59 months (range, 3–121 months) of those in the LPA2005 trial. The 5-year OS was 60 in the LPA96&99 trial vs 74% in the LPA2005 trial ($P = 0.06$) (66% vs 77% in patients aged 60–69 years old, and 49 vs 68% in patients $\geqslant 70$ years old) (Figure 3a). The multivariate analysis showed that age > 70 years old ($P = 0.04$), high risk-group ($P < 0.001$), LPA96&99 trials ($P = 0.02$), CD34 positivity ($P = 0.02$) and creatinine > 1.3 mg/dl ($P < 0.001$) were independent adverse risk factors for OS.

Non-relapse mortality. Forty-two patients died in first CR (median age 69 years, range, 60–84 years). Of them, 10 died during consolidation or maintenance treatment: 8 in the LPA96&99 trials, and 2 in the LPA2005. In addition, 21 patients died due to secondary neoplasm (see below). Eleven patients died off therapy owing to causes unrelated to APL therapy, six in the LPA96&99 trials (one cardiac failure, one traumatic brain injury, one infection, one complications after surgical intervention and one unknown) and five in the LPA2005 trial (one myocardial infarction, one traumatic brain injury, two infections and one acute ischemia in the right lower limb).

The 5-year NRM was 18% in the LPA96&99 vs 5% in the LPA2005 trial ($P = 0.15$) (14% vs 7% in patients aged 60–69 years old, and 27% vs 13% in patients $\geqslant 70$ years old) (Figure 3b).

Secondary neoplasms. Among patients achieving CR, 24 patients (11%) developed a secondary neoplasm, 18 patients in the LPA96&99 trials (11 solid tumors and 7 t-MNs), and 6 in the LPA2005 (3 solid tumors and 3 t-MNs). The median time to develop a secondary neoplasm from the date of APL diagnosis was 51 months (range, 6–112 months). Twenty-one patients died because of the secondary neoplasm (median time from CR to death was 66 months, range, 10–174 months). Cumulative incidence of secondary neoplasms (solid tumor and t-MN) at 5 and 10 years was 8% and 16%, respectively. No predictive factors for this event were found.

Cumulative incidence of relapse. Overall, 20 patients relapsed: 1 molecular persistence (1 in the LPA96&99 trial), 16 hematological relapses (9 in the LPA96&99 and 7 in the LPA2005) and 3 molecular relapses (all in the LPA96&99 trials). The site of hematological relapse was bone marrow in 13 patients, and CNS in 3. The 5-year CIR was 12% in the LPA96&99 vs 7% in the LPA2005 trial ($P = 0.23$) (Figure 3c).

Disease-free survival. The 5-year DFS was 69% in the LPA96&99 vs 87% in the LPA2005 trial ($P = 0.04$) (71 vs 88% in patients aged 60–69 years old, and 65 vs 85% in patients $\geqslant 70$ years old) (Figure 3d).

Table 3. Induction outcome and DS of APL patients in the PETHEMA LPA96&99 and LPA2005 trials

	LPA96		*LPA99*		*LPA96&99*		*LPA2005*		P-*value*[a]
	n	%	n	%	n	%	n	%	
Overall	30	100	105	100	135	100	133	100	
Response									
CR	24	80	81	77	105	78	111	83	0.31
Death	6	20	24	23	30	22	22	17	
Hemorrhage	3	10	10	9.5	13	9.6	10	7.5	0.99
Infection	2	6.7	9	8.6	11	8.1	6	4.5	0.68
DS	1	3.3	3	2.9	4	3.0	3	2.3	0.99
Thrombosis	0	0	2	1.9	2	1.5	3	2.2	0.99
Differentiation syndrome (n = *255)*									
Severe	6	21	14	15	20	15	16	13	0.54
Moderate	4	14	5	5	21	16	25	21	
Absence	18	64	76	80	94	69	79	66	

Abbreviations: APL, acute promyelocytic leukemia; CR, complete remission; DS, differentiation syndrome; PETHEMA, Programa Español de Tratamientos en Hematología. [a]*P*-value compares LPA96&99 and LPA2005.

Table 4. Hematological toxicity and hospitalization during induction and consolidation therapy in the LPA96&99 and LPA2005 trials

Cycle of treatment	*LPA96*	*LPA99*	*LPA96&99*	*LPA2005*	P-*value*[a]
	Mean days (range)	*Mean days (range)*	*Mean days (range)*	*Mean days (range)*	
Induction (n = *197)*					
Grade 4 neutropenia duration	21 (12–33)	20 (5–43)	21 (5–43)	22 (0–43)	0.08
Grade 3–4 thrombocytopenia duration	19 (14–27)	19 (4–33)	19 (4–33)	20 (0–53)	0.41
Hospitalization duration	37 (24–53)	37 (19–65)	37 (19–65)	37 (23–87)	0.87
Consolidation 1 (n = *193)*					
Grade 4 neutropenia duration	9 (0–28)	13 (0–46)	12 (0–46)	16 (0–44)	0.01
Grade 3–4 thrombocytopenia duration	1 (0–23)	10 (0–43)	7 (0–43)	14 (0–56)	< 0.001
Hospitalization duration	4 (0–26)	9 (0–35)	8 (0–35)	9 (0–38)	0.29
Consolidation 2 (n = *190)*					
Grade 4 neutropenia duration	19 (0–42)	21 (0–45)	21 (0–45)	16 (0–56)	0.002
Grade 3–4 thrombocytopenia duration	20 (0–68)	19 (0–63)	19 (0–68)	10 (0–72)	< 0.001
Hospitalization duration	10 (0–25)	11 (0–36)	10 (0–36)	6 (0–36)	< 0.001
Consolidation 3 (n = *173)*					
Grade 4 neutropenia duration	8 (0–70)	14 (0–55)	12 (0–70)	16 (0–62)	0.08
Grade 3–4 thrombocytopenia duration	7 (0–60)	15 (0–62)	13 (0–62)	16 (0–79)	0.24
Hospitalization duration	1 (0–8)	3 (0–34)	3 (0–34)	4 (0–39)	0.11

[a]*P*-value compares continuous non-parametric variables between LPA96&99 and LPA2005 groups.

Table 5. Long-term outcomes of older APL patients in the PETHEMA LPA96&99 and LPA2005 trials

Trial	*Total patients,* n	*OS (%)*				*CR,* n	*NRM (%)*				*CIR (%)*				*DFS (%)*			
		2 y	*5 y*	*10 y*	*P-value*[a]		*2 y*	*5 y*	*10 y*	*P-value*[a]	*2 y*	*5 y*	*10 y*	*P-value*[a]	*2 y*	*5 y*	*10 y*	*P-value*[a]
LPA96	30	73	63	50		24	4	17	34		12	12	12		83	71	54	
LPA99	105	68	59	50		81	10	19	24		6	12	12		84	69	63	
LPA96&99	135	69	60	50	0.06	105	9	18	27	0.15	8	12	12	0.23	84	69	61	0.04
LPA2005	133	78	74	58		111	3	5	25		4	7	7		93	87	68	

Abbreviations: APL, acute promyelocytic leukemia; CIR, cumulative incidence of relapse; complete remission; DFS, disease-free survival; NRM, non-relapse mortality; OS, overall survival; PETHEMA, Programa Español de Tratamientos en Hematología; y, years. [a]P compares LPA96&99 vs LPA2005 cohorts.

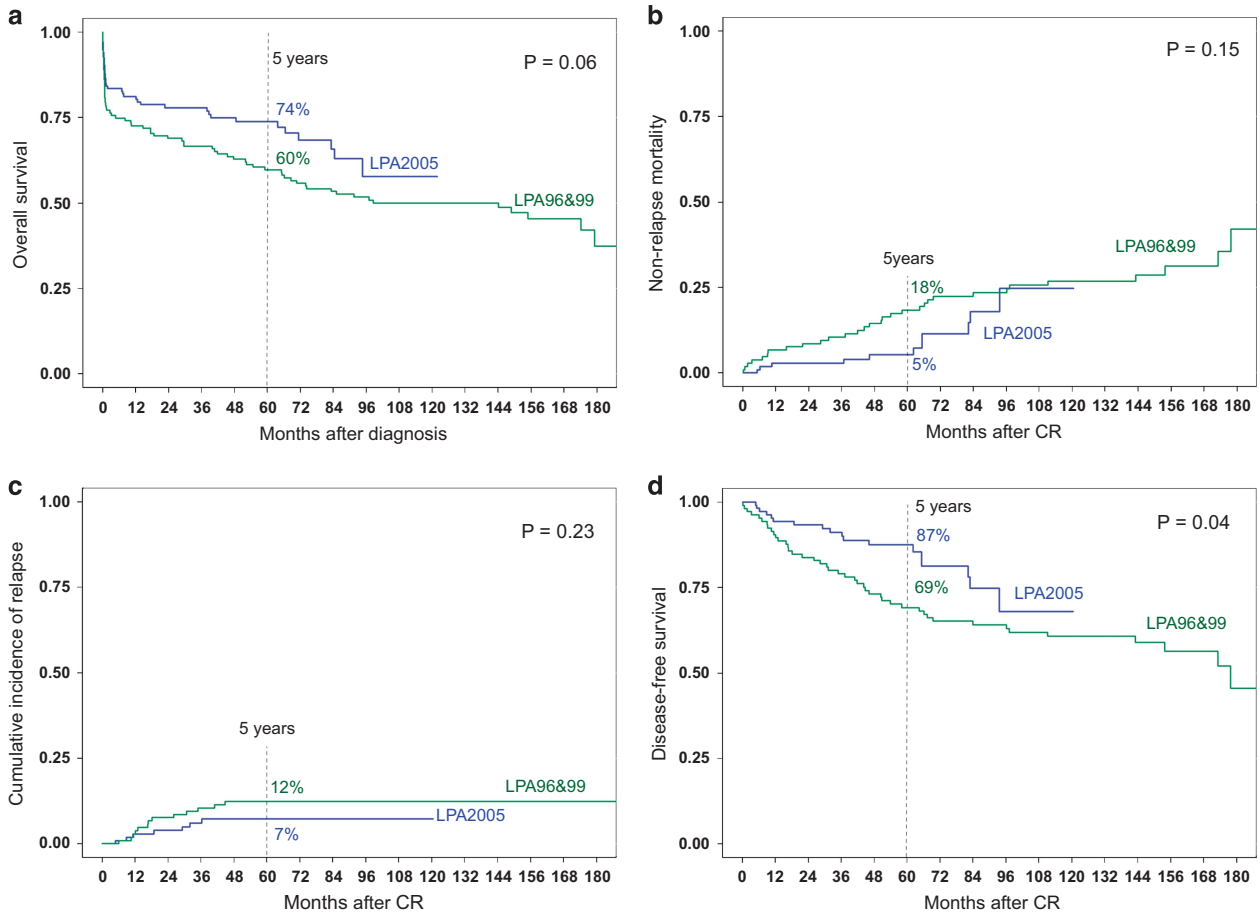

Figure 3. (**a**) OS in older patients according to the PETHEMA trial. (**b**) NRM in older patients according to the PETHEMA trial. (**c**) CIR in older patients according to the PETHEMA trial. (**d**) DFS in older patients according to the PETHEMA trial.

DISCUSSION

This large study in older APL patients with long-term follow-up shows that a less intensive age- and risk-adapted treatment (LPA2005 trial) resulted in a significant reduction of treatment toxicity, high antileukemic efficacy and improved 5-year DFS and OS compared with previous non-age-adapted approaches (LPA96 and LPA99 trials).

As APL is rare in older patients, there are only a few relatively small series addressing treatment outcomes in this setting.[4–6,8–10] Although our study was based on a historical, non-randomized comparison of three subsequent protocols, it was performed in an unprecedented large series of older patients with newly diagnosed APL with a prolonged follow-up. We acknowledge that the potential improvements in supportive management could have had an impact on therapeutic outcomes across the study periods. It should be noted that a homogeneous supportive management was recommended for patients according to the three subsequent protocols.[11,14,15,17–19] As expected, a sizable proportion of older patients (31%) were not eligible for intensive treatment owing to secondary APL, a poor clinical condition at presentation or comorbidities. However, the remaining eligible patients for treatment were analyzed on an intent-to-treat basis.

Although we were unable to demonstrate a significant decrease in the induction death rate by the 1-day reduction of idarubicin, this rate fell into the range reported in other series of older patients receiving induction with AIDA (10–18%).[5,6,8–10] Apparently, the dose reduction of 1 day of idarubicin for LPA99 and LPA2005 induction did not impact on hematological toxicity and overall induction death rate. It should be noted that a nonsignificant decrease in the infectious-related death rate was observed for the LPA2005 trial, but this could be explained by the lower frequency of fever at presentation in this cohort,[18] rather than by the 1-day reduction of idarubicin. We can also speculate that the nonsignificant reduction in the induction death rate in the later trial (17 LPA2005 vs 22% LPA96&99) could rely on improvement of management in recent years, as well as in some favorable characteristics of patients (that is, higher albumin levels at presentation).[18] As previously reported by De la Serna *et al*.,[18] in the present study we confirm a higher induction death rate in older compared with younger patients when treated with an AIDA regimen. It should be noted that although bleeding remained as the most frequent cause of death, our target population showed a high rate of lethal infections, in line with the aforementioned study, in which age $\geqslant$60 years old was an independent adverse factor for this cause of induction death. In addition, as reported previously,[19] we confirm a higher incidence of DS in older patients (up to 30%). As previously reported by De la Serna *et al*.,[18] in the present study we confirm a higher induction death rate in older compared with younger patients when treated with an AIDA regimen. It should be noted that although bleeding remained as the most frequent cause of death, our target population showed a high rate of lethal infections, in line with the aforementioned study, in which age $\geqslant$60 years old was an independent adverse factor for this cause of induction death. In addition, as reported previously,[19] we confirm a higher incidence of DS in older patients (up to 30%).

The lower NRM observed in patients treated under the age-adapted LPA2005 trial could be explained by a lower hematological toxicity, especially during the second consolidation course,

leading to fewer toxic deaths in CR. Of note, grade 3–4 thrombocytopenia was prolonged during the first consolidation course of the LPA2005 trial compared with the LPA99 trial (14 vs 10 days). We can speculate that the addition of ATRA for low-risk patients could be related with this overall effect.

Probably, this reduced toxicity during consolidation has also had a favorable impact on toxicity during maintenance therapy. However, we cannot rule out that a shorter follow-up in the LPA2005 cohort accounts for fewer deaths due to second neoplasms.

The NRM rate (5% at 5 years) achieved with our age-adapted scheme compares favorably with another age-adapted approach reported by the GIMEMA group (10% deaths in CR),[8] and very favorably with other series using more intensive consolidation regimens (19–21% deaths in CR).[6,8–10] We must also emphasize that the reduced intensity of chemotherapy, leading to a higher degree of compliance and lower toxicity, did not result in an increased relapse rate (7% at 5 years), this being apparently better than reported in other trials using chemotherapy-based approaches (range, 16–28%).[6,8–10] Although the antileukemic benefit provided by the addition of ATRA to consolidation therapy has not yet been definitively demonstrated in randomized studies, it is reasonable to consider that there may be a role for this agent, as has been demonstrated for induction[28,29] and maintenance therapy.[29]

As a result of a reduction of the NRM while maintaining a high antileukemic efficacy, the age-adapted LPA2005 protocol also translated into a significant improvement in DFS that compares favorably with the non-age-adapted LPA96&99 protocols (87 and 69% at 5 years, respectively), and other reports (ranging from 48 to 65%).[6,8–10]

The question now is whether outcomes with an age-adapted ATRA plus anthracycline-based protocol are comparable to those with 'chemotherapy-free' schedules with ATRA plus ATO. Although this question should be addressed in well-designed trials, there is scarce information about ATO-based regimens in older patients. As far as we know, only two studies have reported results with ATO-based schemes in older patients.[13,30] A single-center non-randomized study carried out in China[30] in 33 patients reported a CR rate of 88%, toxic deaths in CR or secondary neoplasms were not observed and OS at 10 years was 69%. In a recent randomized, controlled, multicenter trial of the UK NCRI comparing treatment with ATO plus ATRA ($n = 25$) with an AIDA-based regimen ($n = 24$), OS at 4 years did not differ significantly between the treatment groups (80% and 74%, respectively).[13] Regardless, the era of chemo-free therapy with ATRA and ATO seems to be closer than years ago, but no study has shown better results than ATRA plus anthracycline-based protocol. We should highlight that the herein reported outcomes with chemotherapy-based protocols are not applicable to older patients with contraindication of chemotherapy or with secondary APL, being both subsets clear candidates for a chemo-free front-line approach.

Our study suggests that a less intense front-line regimen with ATRA and anthracycline monochemotherapy result in improved long-term outcomes in older patients with newly diagnosed APL. Future studies with even less intense chemotherapy regimens or with ATO plus ATRA schedules for older patients are warranted.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

DM-C, PM and MAS conceived the study, analyzed and interpreted the data; DM-C, PM and MAS wrote the paper; DM-C and PM performed the statistical analyses; EV, TB, OS, AH, SB, PF, CB, J-MR, MP-E, JS, JE, VR, JG-C, LE, MEA, MA, JA, SN and BL included data of patients treated in their institutions, reviewed the manuscript and contributed to the final draft.

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