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ORIGINAL ARTICLE

All-*trans* retinoic acid with daunorubicin or idarubicin for risk-adapted treatment of acute promyelocytic leukaemia: a matched-pair analysis of the PETHEMA LPA-2005 and IC-APL studies

Miguel A. Sanz[1,2] · Pau Montesinos[1,2] · Haesook T. Kim[3] · Guillermo J. Ruiz-Argüelles[4] · María S. Undurraga[5] · María R. Uriarte[6] · Lem Martínez[6] · Rafael H. Jacomo[7] · Homero Gutiérrez-Aguirre[8] · Raul A. M. Melo[9] · Rosane Bittencourt[10] · Ricardo Pasquini[11] · Katia Pagnano[12] · Evandro M. Fagundes[13] · Edo Vellenga[14] · Alexandra Holowiecka[15] · Ana J. González-Huerta[16] · Pascual Fernández[17] · Javier De la Serna[18] · Salut Brunet[19] · Elena De Lisa[20] · José González-Campos[21] · José M. Ribera[22] · Isabel Krsnik[23] · Arnold Ganser[24] · Nancy Berliner[25] · Raul C. Ribeiro[26] · Francesco Lo-Coco[27,28] · Bob Löwenberg[29] · Eduardo M. Rego[7] · on behalf of the IC-APL and PETHEMA and HOVON Groups

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Abstract Front-line treatment of acute promyelocytic leukaemia (APL) consists of all-*trans* retinoic acid (ATRA) and anthracycline-based chemotherapy. In this setting, a comparison of idarubicin and daunorubicin has never been carried out. Two similar clinical trials using ATRA and chemotherapy for newly diagnosed APL were compared using matched-pair analysis. One was conducted by the PETHEMA/HOVON group with idarubicin and the other by the International Consortium on APL (IC-APL) using daunorubicin. Three hundred and fifty patients from the PETHEMA/HOVON cohort were matched with 175 patients in the IC-APL cohort, adjusting for the significantly unbalanced presenting features of the two

✉ Miguel A. Sanz
msanz@uv.es

1 Hematology Department, University Hospital La Fe, Avinguda Fernando Abril Martorell, 106, 46026 Valencia, Spain

2 Department of Medicine, University of Valencia, Valencia, Spain

3 Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, USA

4 Clinica Ruiz de Puebla, Puebla, Mexico

5 Department of Hematology, Hospital del Salvador, Santiago, Chile

6 Asociación Española Primera de Socorros Mutuos, Montevideo, Uruguay

7 Hematology/Oncology Division, Department of Internal Medicine, Medical School of Ribeirão Preto and Center for Cell Based Therapy, University of São Paulo, Ribeirão Preto, Brazil

8 Hematology Division, Hospital Universitario Dr José E. González, Monterrey, Mexico

9 Fundação HEMOPE, Recife, Brazil

10 Hematology Division, Federal University of Rio Grande do Sul, Porto Alegre, Brazil

11 Hematology Division, Federal University of Paraná, Curitiba, Brazil

12 Hematology and Hemotherapy Center, University of Campinas UNICAMP, Campinas, Brazil

13 Hematology Division, Federal University of Minas Gerais, Belo Horizonte, Brazil

14 Department of Hematology, University Medical Center Groningen, Groningen, The Netherlands

15 Department of Hematology, Silesian Medical University, Katowice, Poland

16 Hospital Central de Asturias, Oviedo, Spain

17 Department of Hematology, Hospital General Universitario de Alicante, Alicante, Spain

18 Department of Hematology, Hospital 12 de Octubre, Madrid, Spain

19 Hospital Sant Pau, Barcelona, Spain

20 Department of Hematology, Hospital Maciel, Montevideo, Uruguay

entire cohorts. Complete remission (CR) rate was significantly higher in the PETHEMA/HOVON (94 %) than in the IC-APL cohort (85 %) (P=0.002). The distribution of causes of induction failure and the time to achieve CR were similar in both cohorts. Patients who achieved CR had comparable cumulative incidence of relapse and disease-free survival rates, but lower overall and event-free survivals were observed in the IC-APL cohort, which was mainly due to a higher death rate during induction therapy. A higher death rate during consolidation therapy was also observed in the IC-APL. These results show that daunorubicin and idarubicin have similar antileukaemic efficacy in terms of primary resistance, molecular persistence, as well as molecular and haematological relapse rates when combined with ATRA in treatment of APL. However, a higher toxic death rate during induction and consolidation therapy was observed in the IC-APL cohort. This trial was registered at www.clinicaltrials.gov as #NCT00408278 [ClinicalTrials.gov].

Keywords Acute promyelocytic leukaemia · Risk-adapted therapy · All-*trans* retinoic acid · Anthracyclines · Cytarabine · Prognostic factors · Matched-pair analysis

Introduction

The International Consortium on Acute Promyelocytic Leukemia (IC-APL), an initiative of the International Members Committee of the American Society of Hematology, recently reported [1] a significant improvement in the quality of care and treatment outcome in APL in the participating developing countries (Brazil, Chile, Mexico and Uruguay) as compared to historical controls [2]. These improvements showed that the IC-APL had achieved not only an efficient international network but also a significant reduction in the APL survival gap between the developed and developing countries.

Treatment in the IC-APL trial was identical to that of the LPA2005 trial reported by the Programa Español de Tratamiento en Hematologia/Dutch-Belgian Hemato-Oncology Cooperative Group (PETHEMA/HOVON) [3], except for the replacement of idarubicin by daunorubicin due to its better availability and lower cost in the participating countries. The similar design of the two protocols offers a unique opportunity to compare the outcomes of a study conducted in developed countries (PETHEMA/HOVON) with the other in developing countries (IC-APL), as well as the relative efficacy of idarubicin and daunorubicin. Except for the study reported by the French-Belgian-Swiss and PETHEMA groups [4] that compared ATRA plus daunorubicin with cytarabine versus ATRA combined with idarubicin alone, a suitable comparison of these two anthracyclines has never been carried out in APL. In spite of the increasing use of arsenic trioxide (ATO), the interest of this comparison at the present time is indisputable, since for several reasons anthracyclines are still a mainstay of treatment of APL in a substantial part of the world.

The aforementioned similarity of IC-APL and PETHEMA-HOVON trials led us to design the present study to compare the use of two different anthracyclines in APL. Due to potential differences in pretreatment characteristics between the idarubicin-based trial of PETHEMA/HOVON and the daunorubicin-based trial used in developing countries, i.e. Brazil, Chile, Mexico and Uruguay (IC-APL trial) (Appendix), we performed a matched-pair analysis.

Methods

Eligibility

The eligibility criteria in both trials were a diagnosis of de novo APL with demonstration of the t(15;17) and/or of the *PML/RARA* rearrangement in leukaemic blasts, normal hepatic and renal function, no cardiac contraindication to anthracyclines and an Eastern Cooperative Oncology Group (ECOG) performance status [5] less than 4. In the IC-APL 2006 trial, eligibility was limited to adult patients between 15 and 75 years of age. Informed consent was obtained from all patients. This study was conducted according to the Declaration of Helsinki; the research ethics board of each participating hospital approved the protocols.

Therapy

A complete description of the therapeutic protocols is given elsewhere [1, 3]. Figure 1 summarizes the ATRA and chemotherapy dose and schedule for induction, consolidation and maintenance therapy in both PETHEMA/HOVON LPA2005

[21] Department of Hematology, Hospital Virgen del Rocio, Sevilla, Spain

[22] Department of Hematology, Hospital Germans Trias i Pujol, Badalona, Spain

[23] Department of Hematology, Hospital Puerta de Hierro, Madrid, Spain

[24] Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany

[25] Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[26] Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA

[27] Department of Biopathology, University Tor Vergata, Rome, Italy

[28] Santa Lucia Foundation, Rome, Italy

[29] Department of Hematology, Erasmus University Medical Center, Rotterdam, Netherlands

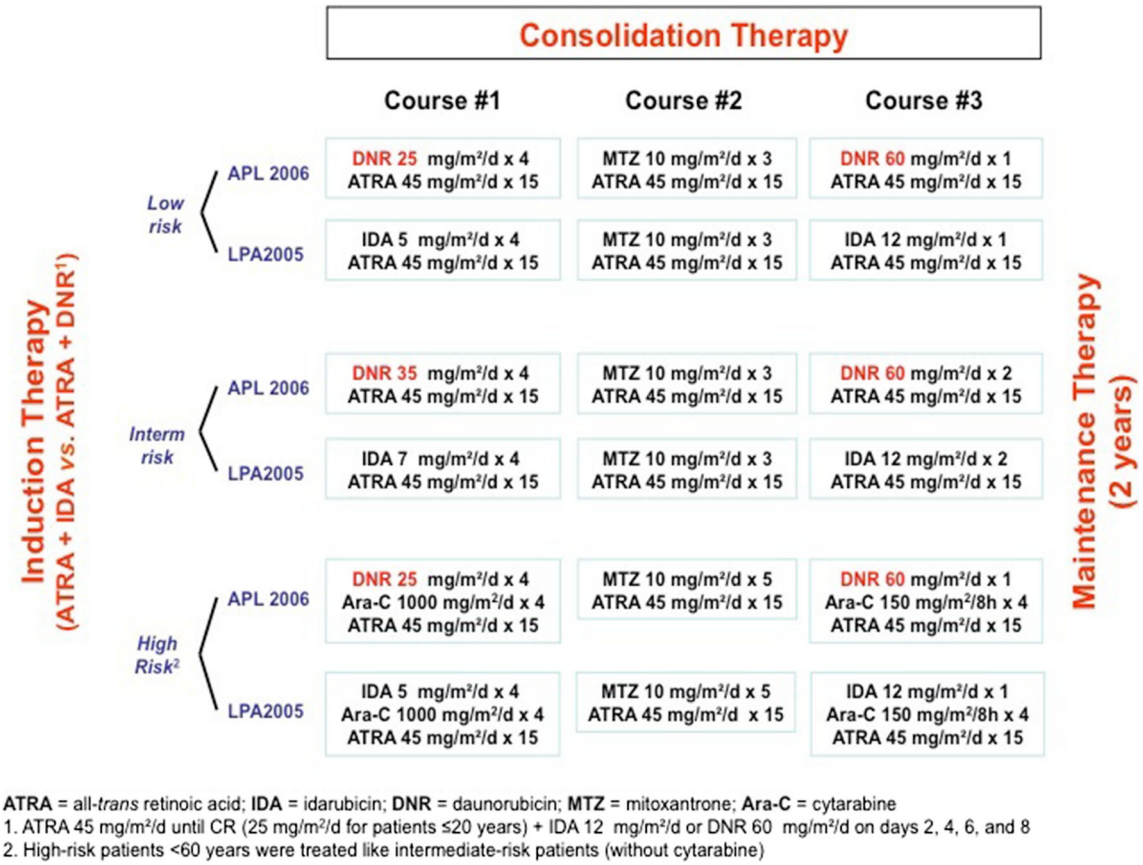

Fig. 1 Treatment schedule of the IC-APL 2006 and PETHEMA/HOVON LPA2005 trials. High-risk patients older than 60 years did not receive cytarabine and were treated as intermediate-risk patients

and IC-APL 2006 trials (referred to from now on as the PETHEMA and IC-APL trials, respectively). Briefly, induction therapy in the PETHEMA trial consisted of oral ATRA 45 mg/m^2/day until morphologic complete remission (CR) and intravenous idarubicin 12 mg/m^2 on days 2, 4, 6 and 8. The fourth idarubicin dose given on day 8 was omitted for patients older than 70 years. For patients younger than 20 years, the ATRA dose was adjusted to 25 mg/m^2. Patients in CR received three monthly risk-adapted consolidation cycles with ATRA (45 mg/m^2/day for 15 days) and chemotherapy according to previously defined risk categories [5]. For low-risk patients, the first cycle consisted of idarubicin (5 mg/m^2/day for 4 days), the second of mitoxantrone (10 mg/m^2/day for 3 days) and the third of idarubicin (12 mg/m^2/day for 1 day). Intermediate-risk patients received a reinforced dose of idarubicin in the first cycle (7 mg/m^2/day) and third cycle (12 mg/m^2/day for 2 days). High-risk patients received the same doses of idarubicin as low-risk patients, but combined with cytarabine in the first (1000 mg/m^2/day for 4 days) and third cycle (150 mg/m^2/8 h for 4 doses), as well as 5 days of mitoxantrone instead of 3 in the second cycle. High-risk patients older than 60 years did not receive cytarabine and were treated as intermediate-risk patients. Patients who tested negative for *PML/RARA* at the end of consolidation received maintenance therapy with oral mercaptopurine (50 mg/m^2/day), intramuscular or oral methotrexate (15 mg/m^2/week) and oral ATRA (45 mg/m^2/day for 15 days every 3 months) over 2 years. Central nervous system prophylaxis was not given.

In the IC-APL trial, idarubicin was replaced by daunorubicin at a ratio 1:5, i.e. each 1 mg of idarubicin was substituted by 5 mg of daunorubicin [1].

Laboratory studies and supportive measures

Details of laboratory studies for diagnosis, assessment of response and molecular monitoring of minimal residual disease, as well as a complete description of recommended supportive measures, were reported elsewhere [1, 3]. Only patients with a WBC count greater than 5×10^9/L at presentation or during the first 2 weeks of ATRA therapy received differentiation syndrome (DS) prophylaxis with dexamethasone (2.5 mg/m^2/12 h intravenously for 15 days).

Definitions and study endpoints

Remission induction response was assessed according to the recently revised criteria by Cheson et al. [6]. For morphological assessment of leukaemia resistance, it was required that

sufficient time had passed to allow for full terminal differentiation of the malignant promyelocytes (up to 40–50 days). Molecular remission was defined as the disappearance of the *PML/RARA*-specific band visualized at diagnosis on an ethidium bromide gel, using RT-PCR assays with a sensitivity level of one cell in 10^{-4}. Molecular persistence was defined as PCR positivity in two consecutive bone marrow samples collected at the end of consolidation therapy. Molecular relapse was defined as previously reported [7]. Non-relapse mortality (NRM) was defined as death from any cause without prior relapse. DS was diagnosed and graded for severity according to previously defined criteria [8]. Relapse-risk groups were defined as reported elsewhere [3] as follows: low-risk patients had a WBC count less than 10×10^9/L and a platelet count greater than 40×10^9/L; intermediate-risk patients had a WBC count less than 10×10^9/L and a platelet count less than 40×10^9/L; and high-risk patients had a WBC count equal to or greater than 10×10^9/L.

Matching procedure

Matching was made with the Diamond and Sekhon method [9] using the package *Matching* in R version 3.0.2 (The CRAN project). The variables used for matching were selected among those significantly unbalanced between the two cohorts and also considered potential prognostic factors for treatment outcomes. For each patient from the IC-APL cohort, two matched patients from the PETHEMA cohort were selected. Out of an overall number of 747 cases, we obtained 350 patients from the PETHEMA cohort matched to 175 control individuals from the IC-APL cohort. Five out of the 180 cases from the IC-APL cohort were not included for matching because of missing fibrinogen data.

Statistical analysis

Patient- and disease-related variables for the two cohorts were compared using the chi-square tests for categorical variables and Mann-Whitney *U* test for continuous variables. Overall survival (OS), disease-free survival (DFS) and event-free survival (EFS) were calculated using the Kaplan-Meier method. The log-rank test was used for comparison of survival curves. Cumulative incidence of relapse and non-relapse mortalities (CIR and CI-NRM, respectively) were calculated in the competing risks framework, treating each other as a competing risk [10, 11]. OS and EFS were calculated from the date of the initiation of induction therapy. CIR and CI-NRM, as well as DFS, were calculated from the date of CR. For OS, death from any cause was the uncensored event; those alive or lost to follow-up were censored at the date they were last known to be alive. Relapse, development of therapy-related myeloid neoplasms (t-MNs) and death from any cause were considered uncensored events in the analysis of DFS and EFS, whichever occurred first. For all estimates in which the event "relapse" was considered as an end point, haematologic and molecular relapses, as well as molecular persistence at the end of consolidation, were each considered uncensored events. All *P* values are two sided at the significance level of 0.05. All calculations were performed using R 3.0.2 (the Comprehensive R Archive Network [CRAN] project [http://cran.r-project.org/]).

Results

Accrual and patient characteristics

Information on enrolment, eligible patients, those lost to follow-up, as well as those excluded from analysis in both trials

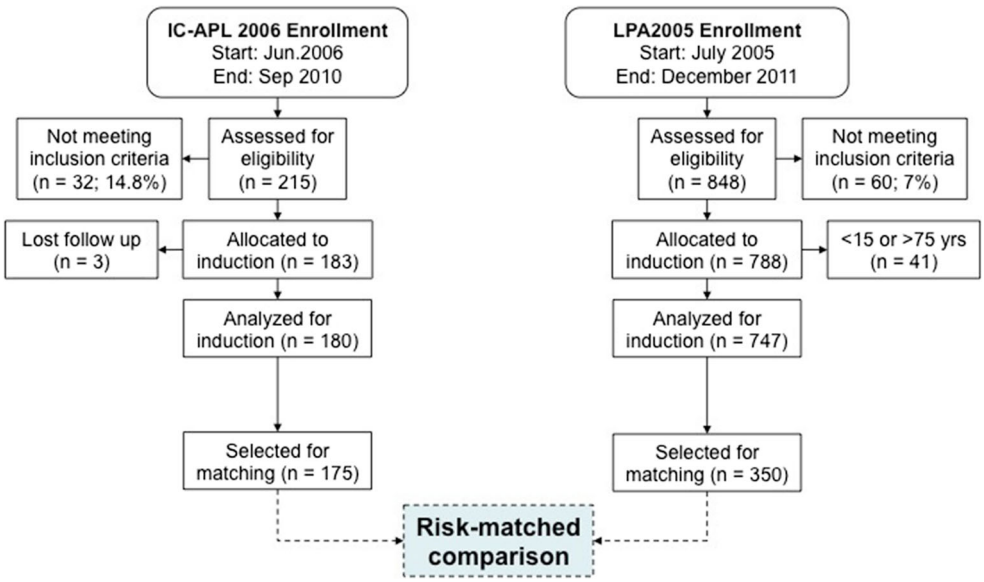

Fig. 2 Consolidated Standards of Reporting Trials (CONSORT) diagram for the PETHEMA/HOVON LPA2005 and IC-APL 2006 trials

Table 1 Demographic and baseline characteristics of the study population

Characteristic	PETHEMA/HOVON Before matching		IC-APL All patients		*P* value	PETHEMA/HOVON Matched patients		*P* value
	Median (range)	No. (%)	Median (range)	No. (%)		Median (range)	No. (%)	
Overall		747 (100)		180 (100)			350	
Age, years	43.0 (15.0–74.0)		34.0 (15.7–73.5)			37.0 (15.0–74.0)		
<18		14 (2)		7 (4)	<0.0001		8 (2)	0.3
18–40		318 (43)		113 (63)			202 (58)	
41–60		303 (41)		51 (28)			123 (35)	
61–70		86 (12)		8 (4)			11 (3)	
>70		26 (3)		1 (1)			6 (2)	
Gender								
Male		375 (50)		87 (48)	0.7		168 (48)	1
Female		372 (50)		93 (52)			182 (52)	
ECOG (n=643)								
0–2		606 (94)		163 (90)	0.05		302 (94)	0.1
3		37 (6)		17 (9)			17 (5)	
Fever								
No		474 (68)		83 (46)	<0.0001		184 (53)	0.2
Yes		223 (32)		97 (54)			166 (47)	
WBC count, $\times 10^9$/L	2.7 (0.2–176)		3.6 (0.1–132)			3.4 (0.1–132)		
≤5		471 (67)		101 (56)	0.03		205 (59)	0.6
5–10		66 (9)		21 (12)			33 (9)	
10–50		163 (22)		42 (23)			90 (23)	
>50		47 (6)		16 (9)			22 (6)	
Platelet count, $\times 10^9$/L	24 (1–235)		23 (2–128)			22 (1–197)		
≤40		545 (73)		139 (77)	0.3		284 (81)	0.3
40 or higher		202 (27)		41 (23)			66 (19)	
Relapse-risk group								
Low		169 (23)		24 (13)	0.02		51 (15)	0.9
Intermediate		368 (49)		98 (54)			187 (53)	
High		210 (28)		58 (32)			112 (32)	
Haemoglobin, g/dL	9.4 (3.6–17.7)		8.6 (3.4–15.6)			8.7 (4.0–14.4)		
≤10		450 (60)		143 (79)	<0.0001		254 (73)	0.1
>10		297 (40)		37 (21)			96 (27)	
Creatinine, mg/dL	0.8 (0.3–8.0)		0.8 (0.2–2.2)			0.8 (0.3–1.8)		
≤1.4		673 (97)		176 (98)	0.9		343 (99)	0.5
>1.4		19 (3)		4 (2)			4 (1)	
Fibrinogen, mg/dL	179 (20–1277)		157 (0–605)			162 (37–825)		
≤100		123 (18)		49 (28)	0.004		94 (27)	0.9
>100		566 (82)		126 (72)			256 (73)	
Albumin, g/dL	4.1 (2.1–6.0)		4.0 (2.2–5.3)			4.0 (2.1–5.7)		
≤3.5		115 (19)		41 (25)	0.1		62 (21)	0.4
>3.5		495 (81)		124 (75)			240 (79)	
PML/RARα isoform								
BCR1/BCR2		294 (58)		111 (67)	0.04		147 (60)	0.2
BCR3		213 (42)		55 (33)			97 (40)	

Percentages may not sum to 100 because of rounding

is shown in Fig. 2. Prior to matching, patients in the IC-APL (n=180) and PETHEMA cohorts (n=747) were comparable for most baseline characteristics except for age, fever, haemoglobin level, relapse-risk group and fibrinogen level. Table 1 shows the characteristics of the whole PETHEMA series before matching (n=747); the PETHEMA cohort after matching according to age, fever, haemoglobin, fibrinogen levels and relapse-risk score (n=350); and the patients of the IC-APL cohort for whom these data were available (n=175).

Induction therapy

The response to induction therapy and causes of induction death in the IC-APL and PETHEMA cohorts are shown in Table 2. A statistically significant difference in CR rate between the IC-APL cohort (85 %; 95 % CI, 79.8–90.2 %) and the matched PETHEMA cohort (94 %; 95 % CI, 91.5–96.5 %) was observed (P=0.003). The median time to achieve CR was 38 days (range, 14 to 151) in the IC-APL cohort and also 38 days (range, 13 to 91) in the PETHEMA cohort (P=NS). The median time to reach neutrophil counts greater than 1×10^9/L and platelet counts greater than 50×10^9/L in the IC-APL cohort was 25 days (range, 5 to 50 days) and 22 days (range, 0 to 51 days), respectively, whereas in the PETHEMA cohort, it was 25 days (range, 5 to 63 days) and 20 days (range, 3 to 81 days), respectively. These differences were not statistically significant.

All the induction failures in both cohorts were due to death during induction. No primary resistance to therapy was observed. Haemorrhage, infection and DS accounted for most of the deaths during induction therapy in both the IC-APL and PETHEMA cohorts (Table 2). Differences in the proportion of lethal haemorrhages, infections and DS did not achieve statistical significance (P=0.08; P=0.13; P=0.08, respectively).

Treatment outcome

Median follow-up from diagnosis among survivors in the IC-APL and PETHEMA trials was 28 months (range, 7–62 months) and 38 months (range, 1–90 months), respectively. At the time of analysis, 75 % of all patients enrolled and 90 % of those achieving CR were alive in the IC-APL cohort, whereas in the PETHEMA cohort, these percentages were 88 and 96 %, respectively. Seven and four patients in the IC-APL and PETHEMA cohorts died in first CR due to infection (5 and 1.2 %, respectively; P=0.04). Deaths in the first CR from other causes were not observed in the IC-APL cohort. Five additional patients from the PETHEMA cohort died in the first CR, three during maintenance therapy (one infection; one chronic renal failure; one gastric adenocarcinoma) and two off therapy (one t-MN; one cerebral haemorrhage without thrombocytopenia).

Molecular persistence of the *PML/RARA* rearrangement at the end of consolidation therapy was detected in one case for each cohort. In the IC-APL cohort, four of nine relapses were detected molecularly and three were extramedullary relapses. In the matched PETHEMA cohort, eight of 26 relapses were detected molecularly and seven patients had extramedullary relapse.

Table 3 shows treatment outcome in terms of CIR, CI-NRM, DFS, OS and EFS at 2 years in the IC-APL and matched PETHEMA cohorts. Differences in these outcomes were not statistically significant, except for OS and EFS. The 2-year CIR for the IC-APL and matched PETHEMA cohorts were very similar, 5.6 % (95 % CI, 1.1–10.0 %) and 6.6 % (95 % CI, 3.7–9.5 %; P=0.8), respectively. Regarding CI-NRM, it was 4.6 % (95 % CI, 1.3–7.9 %) in the IC-APL cohort and 2.3 % (95 % CI, 0.6–4.0 %) in the matched PETHEMA cohort, but this difference did not reach statistical significance (P=0.1). The 2-year OS and EFS for the IC-APL

Table 2 Induction outcome of APL patients in the IC-APL and PETHEMA trials

Characteristic	IC-APL All patients (N=180)		PETHEMA/HOVON Matched patients (N=350)		P value
	Median (range)	No. (%)	Median (range)	No. (%)	
Morphologic CR		153 (85)		329 (94)	0.003
Days to CR	38 (14–151)		38 (13–91)		NS
Days to PMN >1×10^9/L	25 (5–50)		25 (5–63)		NS
Days to Platelets >50×10^9/L	22 (0–51)		20 (3–81)		NS
Causes of induction death		27 (100)		21 (100)	NS
Haemorrhage		13 (48)		12 (55)	0.08
Infection		7 (26)		5 (22)	0.13
Differentiation syndrome		5 (18)		2 (12)	0.08
Other		2 (8)			

NS not significant at the two-sided 0.05 level

Table 3 Treatment outcome of APL patients in the IC-APL and PETHEMA trials

Outcome, at 2 years	IC-APL All patients		PETHEMA/HOVON Matched patients		*P* value
	%	95 % CI	%	95 % CI	
CI-NRM	4.6	1.3–7.9	2.3	0.6–4.0	.1
CIR	5.6	1.1–10.0	6.6	3.7–9.5	.8
Disease-free survival	89.8	84.6–95.4	90.7	87.4–94.1	.3
Overall survival	79.4	73.6–85.7	91.5	88.6–94.5	.0008
Event-free survival	76.2	69.9–83.1	85.6	81.9–89.5	.004

CI-NRM cumulative incidence of non-relapse mortality, *CIR* cumulative incidence of relapse

cohort were 79.4 % (95 % CI, 73.6–85.7 %) and 76.2 % (95 % CI, 69.9–83.1 %), respectively, whereas they were 91.5 % (95 % CI, 88.6–94.5 %) and 85.6 % (95 % CI, 81.9–89.5 %) for the matched PETHEMA cohort (P=0.0008 and P=0.004) (Figs. 3 and 4).

Discussion

This study shows that two similar treatments for newly diagnosed APL consisting of ATRA and anthracycline-based chemotherapy, only differing for the replacement of idarubicin (PETHEMA/HOVON) by daunorubicin (IC-APL), had a comparable antileukaemic efficacy in terms of CIR and DFS rates. The lower OS and EFS rates in the trial carried out in developing countries are mainly due to a higher death rate during induction and consolidation. Interestingly, no cases with primary resistant leukaemia were observed in either series and the incidence of relapse was also very similar.

Although the results of several recent clinical trials portend an increasing role of ATO in APL [12–16], to the best of our knowledge, arsenic-based regimens have been so far adopted as the standard of care only in some single institutions from China [17], Iran [18] and India [19], i.e. in countries where a cheaper locally produced arsenic compound provides a more affordable treatment approach than ATRA plus chemotherapy. However, this is not the scenario in a substantial part of the rest of the world, where currently available ATO is considerably more expensive, making it unaffordable for many countries. In addition, in the USA and the European Union, ATO has not yet been approved for newly diagnosed APL by regulatory agencies. In this scenario, we consider that all efforts to refine and optimize the conventional approach with ATRA plus anthracycline-based chemotherapy are timely and warranted. In this regard, the identical design of the two trials compared here, which only differed by the type of anthracycline, provided us with the unique opportunity of i) assessing the relative efficacy of daunorubicin and idarubicin in the treatment of APL and ii) comparing treatment outcomes in two different socio-economic contexts. Since a randomized trial was not possible, we chose a matched-pair analysis to compare two independent studies as the most suitable way to minimize the effects of non-treatment-related variables on outcomes.

The crude comparison of both cohorts showed significant differences in some presenting features such as age, fever, relapse-risk group, as well as haemoglobin and fibrinogen levels. Interestingly, after accounting for the potential effect of these variables in the matched PETHEMA cohort, the differences in the CR rate were still statistically significant. How should we interpret the statistically significant difference in CR rate between the two cohorts? Is it due to differences in the antileukaemic efficacy and toxicity of daunorubicin compared with idarubicin or might differences in the supportive therapy in the two studies play a role? A detailed analysis of induction outcomes, including the causes of induction failure and the kinetics of haematological recovery, showed that, despite the fact that both cohorts had a similar time to CR and haematological recovery, the induction failure rate was higher in the IC-APL cohort. The most likely explanation would be related to the probable differences in supportive care. In fact, the increased induction failure rate in the IC-APL cohort was only due to an increased death rate during induction, with no

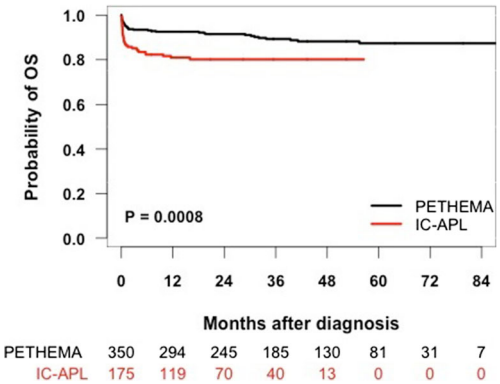

Fig. 3 OS for the IC-APL and matched PETHEMA cohorts

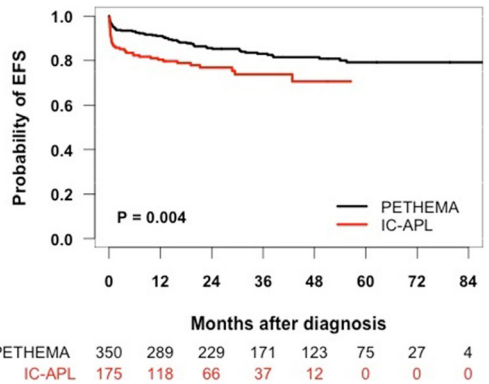

Fig. 4 EFS for the IC-APL and matched PETHEMA cohorts

case of primary resistant leukaemia observed in either cohort. Although differences in the distribution of deaths due to haemorrhage, infection and DS were not statistically significant between the two cohorts, DS-associated mortality among those patients developing moderate or severe DS was significantly higher in the IC-APL cohort compared with the PETH EMA cohort (12 vs. 3 %, respectively; P=0.01). Potential differences in the management of DS and supportive measures might be implicated in the different DS-associated mortality observed in the two cohorts.

Although the differences in CI-NRM between the IC-APL and PETHEMA cohorts did not reach statistical significance (4.6 vs. 2.3 %; P=0.1), these differences became statistically significant when the comparison was confined to NRM during consolidation (4.8 vs. 1.2 %; P=0.04). The most likely explanation for this higher death rate due to infectious complications in the IC-APL would be a probable suboptimal prevention and treatment of infections during consolidation cycles.

As for the relative antileukaemic efficacy in both trials, all outcomes related to the incidence of primary and secondary resistance are indicative of a similar efficacy of the two anthracyclines. Apart from the already-mentioned absence of patients with refractory leukaemia (primary resistance) in either cohort, molecular persistence of the *PML/RARA* rearrangement at the end of consolidation therapy was only detected in one patient in each cohort. It should also be noted that CIR curves did perfectly overlap in both the crude and matched comparisons. A similar overlap was also observed between the different risk groups (data not shown). Differences in other treatment outcomes, such as OS and EFS, were mainly due to the impact on these outcomes of deaths during induction and consolidation therapy.

In conclusion, the comparison of two trials with the same design and strategy for the treatment of newly diagnosed APL showed a similar antileukaemic efficacy in terms of primary resistance, molecular persistence, as well as molecular and haematological relapse rates. Although a significant reduction in treatment-related mortality during induction and post-remission therapy was achieved in developing countries using the IC-APL as compared to their historical studies [2], important differences still persist when comparing these outcomes to those of developed countries. In countries in which ATO-based regimens still represent an unaffordable approach for newly diagnosed APL, efforts for improvement with conventional treatments based on ATRA and chemotherapy should mainly focus on reinforcing supportive care, rather than implementing radical changes in the antileukaemic strategy.

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Authors' contribution M.A.S. conceived the study and analysed and interpreted the data; M.A.S., F.L-C., A.G., N.B., R.C.R., B.L. and E.M.R. wrote the paper; P.M. and H. K. performed the statistical analyses; E.M.R., G.J.R.-A., M.S.U. and L.M. were the national coordinators in Brazil, Mexico, Chile and Uruguay, respectively; M.R.U., R.H.J., H. G-A., R.A.M.M., R.B., R.P., K.P., E.M.F., E.V., A.H., Ch.R., P.F., J.d.S., S.B., E.d.L, J.G-C., J.M.R. and I.K. included data of patients treated in their institutions, reviewed the manuscript and contributed to the final draft.

Conflict of interest The authors declare that they have no conflict of interest.

Appendix

The following institutions and clinicians participated in the study: Argentina (Grupo Argentino de Tratamiento de la Leucemia Aguda)—Complejo Médico Policia Federal, La Plata: L. Palmer; Fundaleu, Buenos Aires: S. Pavlovsky, G. Milone, I. Fernández; Hospital Clemente Álvarez, Rosario: S. Ciarlo, F. Bezares; Hospital de Clínicas, Buenos Aires: F. Rojas; H. Longoni; Hospital General San Martín, La Plata: M. Gelemur, P. Fazio; Hospital Rossi, La Plata: C. Canepa, S. Saba, G. Balladares; Hospital San Martín de Paraná, Entre Ríos: P. Negri; Instituto Privado de Hematología, Paraná: M. Giunta; Instituto de Trasplante de Médula Ósea, La Plata: J. Milone, MV. Prates; Hospital Tornú, Buenos Aires: D. Lafalse; Colombia—Fundación Valle del Lili, Cali: F.J. Jaramillo Echevarry; FOSCAL, Bucaramanga: C. Sossa Melo; Czech Republic—Faculty Hospital, Brno: J. Mayer, M. Protivankova; IHBT, Prague: J. Scwarz; Slovakia—UNLP, Kosice: Jana Jurkovicova; Spain (Programa Español de Tratamiento de las Hemopatías Malignas)—Basurtuko Ospitalea, Bilbao: J. M. Beltrán de Heredia; Complejo Hospitalario de Segovia: J.M. Hernández; Complexo Hospitalario Xeral-Calde, Lugo; J. Arias; Complejo Hospitalario, León: F. Ramos; Fundación Jiménez Díaz, Madrid: A. Román; Hospital 12 de Octubre, Madrid: J. de la Serna; Hospital Carlos Haya, Málaga: S. Negri; Hospital Central de Asturias, Oviedo: C. Rayón; Hospital Clinic, Barcelona: J. Esteve; Hospital Clínico de Valladolid: F.J. Fernández-Calvo; Hospital Clínico San Carlos, Madrid: J. Díaz-Mediavilla; Hospital Clínico San Carlos (H. Infantil), Madrid: C. Gil; Hospital Clínico Universitario, Santiago de Compostela: M. Pérez-encinas; Hospital Clínico Universitario, Valencia: M. Tormo; Hospital Clínico Universitario Lozano Blesa, Zaragoza: M. Olave; Hospital de Cruces, Barakaldo: E. Amutio; Hospital del Mar, Barcelona: C. Pedro; Hospital de Navarra, Pamplona: A. Gorosquieta; M. Viguria; M. Zudaire; Hospital Dr Negrín, Las Palmas: T.

Molero; Hospital Dr Peset, Valencia: M. J. Sayas; Hospital Dr Trueta, Girona: R. Guardia; Hospital General de Albacete: F. Manso; Hospital General de Alicante: C. Rivas; Hospital General de Alicante (Oncología Pediátrica): C. Esquembre; Hospital General de Castellón: R. García; Hospital General de Especialidades Ciudad de Jaén: A. Alcalá; J.A. López; Hospital General de Jerez de la Frontera: V. Rubio; Hospital General de Murcia: M.L. Amigo; Hospital General de Valencia: M. Linares; Hospital Germans Trias i Pujol, Badalona: J. M. Ribera; Hospital Insular de Las Palmas: J. D. González San Miguel; Hospital Juan Canalejo, A Coruña: G. Debén; Hospital Joan XXIII, Tarragona: L. Escoda; Hospital La Princesa, Madrid: R. de la Cámara; Hospital Materno-Infantil de Las Palmas: A. Molines; Hospital do Meixoeiro, Vigo: C. Loureiro; Hospital Montecelo, Pontevedra: M.J. Allegue; L. Amador; Hospital Mutua de Terrasa: J.M. Martí; Hospital Niño Jesús, Madrid: L. Madero; A. Lassaletta; Hospital Ntra. Sra. de Sonsoles, Ávila: M. Cabezudo; Hospital Ramón y Cajal, Madrid: J. García-Laraña; Hospital Reina Sofía, Córdoba: R. Rojas; Hospital Río Carrión, Palencia: F. Ortega; Hospital Río Hortega, Valladolid: M. J. Peñarrubia; Hospital San Jorge, Huesca: F. Puente; Hospital San Rafael, Madrid: B. López-Ibor; Hospital Sant Pau, Barcelona: S. Brunet; Hospital San Pedro de Alcántara, Cáceres: J. M. Bergua; Hospital Santa María del Rosell, Cartagena: J. Ibáñez; Hospital Severo Ochoa, Leganés: P. Sánchez; Hospital Son Dureta, Palma de Mallorca: A. Novo; Hospital de Tortosa: LL. Font; Hospital Txagorritxu, Vitoria: J. M. Guinea; Hospital Universitario del Aire, Madrid: A. Montero; Hospital Universitario de Salamanca: M. González; Hospital Universitario La Fe, Valencia: M. A. Sanz, G. Martín, J. Martínez, P. Montesinos; Hospital Universitario La Fe (Hospital Infantil), Valencia: A. Verdeguer; Hospital Universitario La Paz (Hospital Infantil), Madrid: P. García; Hospital Universitario Marqués de Valdecilla, Santander: E. Conde; Hospital Universitario Príncipe de Asturias, Alcalá de Henares: J. García; Hospital Universitario Puerta del Mar, Cádiz: F.J. Capote; Hospital Universitario Puerta de Hierro, Madrid: I. Krsnik; Hospital Universitario Vall D'Hebron, Barcelona: J. Bueno; Hospital Universitario Materno-Infantil Vall D'Hebron, Barcelona: P. Bastida; Hospital Universitario Virgen de la Arrixaca, Murcia: A. Rubio; Hospital Universitario Virgen de la Arrixaca (Pediatría), Murcia: J.L. Fuster; Hospital Universitario Virgen del Rocío, Sevilla: J. González; Hospital Universitario Virgen de la Victoria, Málaga: I. Pérez; Hospital Virgen del Camino (Infantil), Pamplona: J. Molina; Hospital Virgen del Camino (Adultos), Pamplona: M.C. Mateos; M.A. Ardaiz; Clínica San Miguel, Pamplona: M. Rodríguez-calvillo; Hospital Xeral Cíes, Vigo; C. Poderós; Institut Català d'Oncologia, Hospitalet de Llobregat; M. Arnán, R. Duarte; Hospital de Fuenlabrada, Fuenlabrada: J.A. Hernández; Hospital General de Guadalajara, Guadalajara: M. Díaz-Morfa; Hospital Juan Ramón Jimenez, Huelva: E. Martín-Chacón; Hospital Doctor José Molina Orosa, Lanzarote: J.M. Calvo-Villas; Hospital Madrid Norte Sanchinarro, Madrid: D. García-Belmonte; Hospital U. La Paz, Madrid: D. Hernández-Maraver; Poland (Polish Adult Leukemia Group, PALG)—Silesian Medical University, Katowice: A. Holowiecka-Goral; Collegium Medicum Jagiellonian University, Krakow: B. Jakubas; City Hospital, Rzeszów: A. Skret-Norwicz; City Hospital, Poznan: P. Bizgalska-Skrzypek; Medical University, Lodz: A. Pluta; Universitary Hospital, Szczecin: R. Becht; Universitary Hospital, Wroclaw: M. Kielbinski; Center of Oncology, Kielce: M. Watek; Medical University, Warsaw: M. Paluszewska; City Hospital, Bydgoszcz: A. Gadomska; City Hospital, Krakow: E. Rzenno; Medical University, Bialystok: J. Piszcz; Institut of Hematology, Warsaw: A. Ejduk, J. Dobrzanska; City Hospital, Tornú: M. Calbecka, A. Kostyra; Medical University, Lublin: M. Malek; City Hospital, Chorzow: S. Grosicki; Medical University School, Gdansk: W. Knopinska; The Netherlands (The Dutch-Belgian Hemato-Oncology Cooperative Group, HOVON)—VU Medical Center Amsterdam: G. J. Ossenkoppele; Academic Medical Center, University of Amsterdam: J. van der Lelie; Erasmus University Medical Center, Rotterdam: B. Lowenberg, P. Sonneveld, M. Zijlmans; University Medical Center, Groningen: E. Vellenga; Gasthuisberg Hospital, Leuven: J. Maertens; OLVG Hospital, Amsterdam: B. de Valk; Den Haag Hospital, Leyenburg: P.W. Wijermans; Medical Spectrum Twente Hospital, Enschede: M.R. de Groot; Academic Hospital Maastricht: H.C. Schouten; St. Antonius Hospital, Nieuwegein: D.H. Biesma; Sophia Hospital, Zwolle: M. van Marwijk Kooy; Uruguay—Hospital Maciel, Montevideo: E. de Lisa

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