ACTA ONCOLOGICA
2021, VOL. 60, NO. 11, 1520–1526
https://doi.org/10.1080/0284186X.2021.1971291

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Acute promyelocytic leukemia (APL) in very old patients: real-life behind protocols

Serena Rosati[a], Carmelo Gurnari[b,c], Massimo Breccia[a], Ida Carmosino[a], Emilia Scalzulli[a], Enrico Montefusco[d], Salvatore Perrone[e], Ombretta Annibali[f], Vincenza Martini[g], Giulio Trapè[h], Gioia Colafigli[a], Malgorzata Trawinska[i], Clara Minotti[a], Giuseppe Cimino[e], Agostino Tafuri[j], Giuseppe Avvisati[f], Maurizio Martelli[a], Maria Teresa Voso[k,l] and Roberto Latagliata[a,h]

[a]Department of Translational and Precision Medicine, Sapienza University, Rome, Italy; [b]Department of Biomedicine and Prevention, PhD in Immunology, Molecular Medicine and Applied Biotechnology, University of Rome Tor Vergata, Rome, Italy; [c]Translational Hematology and Oncology Research Department, Taussig Cancer Center, Cleveland Clinic, Cleveland, USA; [d]Hematology, Ospedale Sant'Andrea, Rome, Italy; [e]Hematology, Polo Universitario Pontino, "Sapienza", Via A. Canova S.M. Goretti Hospital, Latina, Italy; [f]Unit of Hematology and Stem Cell Transplantation, Campus Bio-Medico University, Rome, Italy; [g]UOC Ematologia, Ospedale "Fabrizio Spaziani", Frosinone, Italy; [h]Hematology, Belcolle Hospital, Viterbo, Italy; [i]Hematology, Ospedale S. Eugenio, Roma, Italy; [j]Hematology Institute, La Sapienza University of Rome, S. Andrea Hospital, Rome, Italy; [k]Laboratorio di Neuro-Oncoematologia, Fondazione Santa Lucia, Rome, Italy; [l]Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy

ABSTRACT

Background: Acute promyelocytic leukemia (APL) is uncommon among subjects aged ≥ 70 years and the better therapeutic strategy represents an unmet clinical need.

Materials and methods: This prompted us to explore our real-life data on a retrospective cohort of 45 older APL patients (≥ 70 years) consecutively diagnosed at eight different hematologic institutions in Latium, Italy, from July 1991 to May 2019.

Results: Two patients (4.4%) died from early hemorrhagic complications before treatment could begin. Twenty-two patients (51.1%) (Group A) were enrolled or treated according to standard clinical protocols, while 21 (48.8%) (Group B) received an ATRA-based personalized approach due to poor performance status. Morphologic complete remission (CR) after induction therapy was achieved in 33 patients (76.7%) with 100% of patients in Group A and 52.3% in Group B ($p < 0.001$). Molecular CR was documented in 30 patients (69.7%) [20/22 (90.9%) in Group A and 10/21 (47.6%) in Group B ($p = 0.002$)]. Ten patients (23.2%) died during induction therapy, all in Group B. Five-year overall survival (OS) of the entire cohort was 46.1% (95% CI 28.2–64.0), with 72.6% (95% CI 42.9–100) in Group A vs. 27.2% (95% CI 7.5–46.9) in the Group B ($p = 0.001$).

Conclusions: The present analysis highlights that almost half of the patients received sub-optimal induction treatments and registered dismal outcomes demonstrating the importance of adopting standard therapies instead of modified or reduced personalized approaches also in the setting of frail older patients.

ARTICLE HISTORY
Received 18 March 2021
Accepted 17 August 2021

KEYWORDS
Acute promyelocytic leukemia; all-trans retinoic acid; arsenic trioxide; elderly patients; real-life data

Background

Acute promyelocytic leukemia (APL) is a rare disease in older subjects and only 1–6% of all patients with APL are older than 70 years at diagnosis [1,2]. The introduction of a tailored approach with the combination of all-trans retinoic acid (ATRA) and more recently of arsenic trioxide (ATO) has markedly changed the treatment strategy of this previously fatal disease, leading to impressive rates of cure [3–7]. However, data on ATRA and/or ATO combinations are based on international clinical trials enrolling younger subjects (aged <70 years), while few reports exist on very old patients concerning the feasibility of different ATRA regimens in this challenging population [8–14].

While in other subtypes of acute myeloid leukemia (AML) advanced age still represents the major adverse prognostic factor due to the more aggressive disease biology, in APL the recent improvement is also shared by older patients, with complete remission (CR) and disease-free survival (DFS) rates only slightly lower compared to the younger counterparts [8,10,15,16]. This difference is mainly due to a higher rate of early deaths (ED), occurring within 30 days from diagnosis, and deaths in remission [17]. Therefore, this survival disadvantage is strictly dependent on the patient's characteristics rather than more aggressive disease biology as in other AML subtypes [9,18]. In particular, severe coagulopathy at onset, the prevalence of cardiac diseases and other severe organ dysfunctions are the main reasons for the increased

CONTACT Roberto Latagliata latagliata@bce.uniroma1.it Hematology, Belcolle Hospital Strada Sammartinese - Viterbo, Italy
Supplemental data for this article can be accessed here.

mortality of older patients with APL [9,19]. As a consequence, ED rates for patients aged > 70 years are higher than 40% compared to 15% or lower in younger subjects (<50 years) [20–22].

Notwithstanding the impressive results achievable also in older APL patients treated with the same induction schemes employed in younger subjects [23], many older patients with poor performance status and/or high comorbidity burden at diagnosis are considered not eligible for intensive induction treatments by responsible physicians and managed with low-intensity or personalized approaches [24].

Up to now, few studies have reported treatment results in the group of very old APL subjects, with different outcomes and treatment schedules [9,10,18,25]. Thus, the efficacy and safety of a standard induction treatment as well as the possible role of a patient-adapted and less-intensive approach in this subset are still unclear, especially in real-life scenarios.

To evaluate these issues, we report on a retrospective analysis of all consecutive APL patients aged ≥ 70 years diagnosed and followed in the hematologic Centers of the Latium area.

Patients and methods

Patient selection

A retrospective cohort of 45 consecutive APL patients (M/F 27/18), aged ≥ 70 years and diagnosed at eight different hematologic institutions in Latium, Italy, from July 1991 to May 2019 was analyzed. The study was approved by the IRB of the involved Institutions.

Diagnosis of APL was initially established according to the French-American-British (FAB) [26] and later by WHO criteria [27], and confirmed in all patients by molecular identification of the *PML/RARα* hybrid gene by RT-PCR and/or karyotype detection of the *t*(15;17) in leukemic cells [6].

To avoid possible selection bias, particular attention was given to consider also patients managed outside of clinical trials because of comorbidities at diagnosis and patients dying immediately after APL diagnosis before starting any treatment.

Data regarding patient- and treatment-related characteristics were extracted from the institutional databases and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines when appliable [28].

Treatment schedules

Two different regimens employed in clinical controlled trials were considered as standard induction treatment as previously described:

- AIDA regimen [29], consisting of oral ATRA (45 mg/m^2/d) until hematologic CR and intravenous Idarubicin (IDA) (12 mg/m^2/d) given on days 2,4,6,8;
- ATRA + ATO regimen according to APL 0406 trial [3], consisting of oral ATRA (45 mg/m^2/d) and ATO (0.15 mg/Kg/d given as a two hours intravenous infusion) until hematologic CR or for a maximum of 60 days.

Definitions

Definition of ED was the following: (1) any death occurred from any cause after APL diagnosis and before treatment initiation and (2) any death occurred from any cause in the first 30 days after treatment initiation.

The relapse risk score was used to stratify patients in low, intermediate, and high-risk [30].

Performance status was defined according to Eastern Cooperative Oncology Group criteria [31].

Response criteria

Morphologic CR was defined as the presence of normal bone marrow cellularity with the absence of leukemic promyelocytes, with peripheral blood polymorphonuclear (PMN) and platelet counts > 1×10^9/l and > 100×10^9/l, respectively. Molecular CR was defined as the negativity at RT-PCR analysis for *PML/RARα* hybrid gene.

Statistical analysis

Data were expressed as mean ± standard deviation (SD) (normally distributed data), median and range (non-normally distributed data), or as percentage frequencies, and within-patient comparisons were made by unpaired *t*-test and χ^2 test, as appropriate, at significance levels of $p < 0.05$.

Overall Survival (OS) was calculated from the date of APL diagnosis to death due to any cause. Event-Free Survival (EFS) was calculated from the date of APL diagnosis to disease relapse or death due to any cause. For survival analysis, univariate Kaplan–Meier was performed.

All calculations were made using a standard statistical package (SPSS for Windows Version 15.0; Chicago, IL).

Results

Patient features at diagnosis

Overall, the median age at diagnosis was 75.5 years (range 70.0–87.1) with a male/female ratio of 1.5. The majority of patients (75.6%) were low/intermediate risk according to the relapse risk score, with an overt coagulopathy at diagnosis in 55.5% of cases. *PML/RARα* isoforms were equally distributed and 17.8% of patients showed a microgranular variant (M3v) at bone marrow morphologic evaluation (Table 1). As to major comorbidities, 28 patients (62.2%) had concomitant cardiologic diseases with hypertension as the most frequent, 13 (28.8%) had a clinical history of cancer, configuring the possibility of a secondary APL, and 11 (24.4%) were affected by diabetes.

Table 1. Clinical characteristics at diagnosis.

	All patients*	Group A	Group B	*p*-value
Male/Female, *n*° (%)	27/18 (60/40)	10/12 (46/54)	15/6 (71/29)	0.084
Median age, years (range)	75.5 (70.0–87.1)	73.4 (70.0–80.4)	78.2 (73.3–86.8)	<0.001
Relapse Spanish risk, *n*° (%): Low	18 (40.0)	13 (59.0)	5 (23.8)	0.063
Intermediate	16 (35.6)	6 (27.2)	10 (47.6)	
High	11 (24.4)	3 (13.8)	6 (28.6)	
APL subtype *n*° (%): M3	37 (82.2)	19 (86.3)	18 (85.7)	0.951
M3 variant	8 (17.8)	3 (13.7)	3 (14.3)	
PML-RARα isoform, *n*° (%): PML-RARα 1	19 (51.3)	9 (47.3)	10 (55.5)	0.882
PML-RARα 3	18 (48.7)	10 (52.7)	8 (44.5)	
Unknown	8	3	3	
Median WBC, × 10^9/l (range)	2.00 (0.54–286)	1.68 (0.54–46.8)	3.07 (0.74–94.0)	0.095
Median PLTs, × 10^9/l (range)	27 (4–302)	42 (4–185)	17 (7–302)	0.354
Coagulopathy at diagnosis, *n*° (%): Yes	25 (55.5)	10 (45.5)	13 (61.9)	0.280
No	20 (44.4)	12 (54.5)	8 (38.1)	
Performance status, *n*° (%): 0	7 (15.6)	5 (22.7)	2 (9.5)	0.013
1	18 (40.0)	13 (59.0)	5 (23.8)	
2	17 (37.8)	4 (18.3)	12 (57.2)	
3	1 (2.2)	/	/	
4	2 (4.4) 22 (4.4)	/	2 (9.5)	

*Comprising 2 patients died before treatment start.
APL: acute promyelocytic leukemia; WBC: White blood cells; PLT: platelets.

Induction treatments

Forty-three patients (95.5%) started therapy after diagnosis while two (4.4%) died because of early hemorrhagic complications before any form of treatment. Twenty-two patients (51.1%) (Group A) were enrolled in clinical controlled trials or were treated according to standard protocols [13 (59.0%) according to AIDA-like regimen, 9 (40.9%) according to the APL0406 study as previously specified], while 21 patients (48.8%) (Group B) received an ATRA-based personalized approach (ATRA alone in 11 cases, adapted AIDA with reduced IDA dosage to 5 mg/m^2 in four cases, adapted AIDA with a reduced number of IDA doses in three cases, ATRA + mitoxantrone/aracytin in two cases, ATRA + gentuzumab-ozogamicin in one case). Patients treated in Group A were younger (median 73.4 vs. 78.2 in Group B, $p \leq 0.0001$) and were characterized by better performance status, with 81.7% having ECOG <2 vs. only 33.3% in Group B ($p = 0.0019$, see also Table 1). No differences were found for other features at diagnosis, such as relapse risk score, presence of overt coagulopathy or *PML/RARα* isoforms as well as the incidence of M3v.

Induction results and toxicity

Overall, morphologic CR after induction therapy was achieved in 33 patients (76.7%, Table 2) at a median time of 41 days (range 30–50). All patients in Group A achieved morphologic CR compared to only 11 patients (52.3%) in Group B ($p < 0.001$). Molecular CR was documented in 30 patients (69.7%) at a median time of 102 days (range 63–174). Similarly, molecular CR was detected in the majority (20 out of 22, 90.9%) of patients in Group A and in only 10 out of 21 (47.6%) in Group B ($p = 0.002$).

Infectious complications during induction therapy (Table 3) were observed in 31/43 patients (72.0%) (four episodes of febrile neutropenia, eight sepsis, three cystitis, twelve pneumonitis, one oral abscess, one spondylodiscitis, one abdominal infection, one hepatitis C reactivation). ATRA syndrome occurred in 14/43 patients (32.5%). In addition, there were four episodes of respiratory failure, five episodes of arrhythmia, and four episodes of cardiac ischemia. During induction therapy, ten patients (23.2%) died from infections and hemorrhagic complications as the main cause, all in Group B (7 treated with ATRA alone and 3 treated with adapted AIDA): the median age of these patients was higher compared to patients of Group B who survived induction therapy but not statistically different [80.9 years (range 75.1–86.8) vs. 77.2 years (range 73.5–80.8), $p = 0.395$], with a trend of significance for higher median WBC count [9.1 × 10^9/l (range 0.7–94.0) vs. 2.0 × 10^9/l (range 1.0–11.3), $p = 0.086$]. On the whole, the overall ED rate for the 45 patients was 26.7% (12/45), when considering also the two patients who died before treatment start.

Table 2. Induction treatment outcomes.

	All treated patients		Group A		Group B		*p* value
	N	%	*N*	%	*N*	%	
Overall Response	43/45	95.5	22	51	21	49	
Morphologic CR	33	76.7	22	100	11	52.3	<0.001
Molecular CR	30	69.7	20	90.9	10	47.6	0.002
Death	10	23.2	0	0	10	47.6	<0.001

CR: complete remission.

Table 3. Complications during induction phase.

Complications	All treated patients	Group A	Group B	*p* value
Early death*	10 (23.2)	0	10 (47.6)	<0.001
ATRA syndrome*	14 (32.5)	8 (36.3)	6 (28.5)	0.586
Infections*	31 (72.0)	17 (77.2)	14 (66.6)	0.438
Respiratory failure*	4 (9.3)	1 (4.5)	3 (14.2)	0.272
Cardiac arrhythmia*	5 (11.6)	3 (13.6)	2 (9.5)	0.674
Cardiac ischemia*	4 (9.3)	1 (4.5)	3 (14.2)	0.272

*Expressed as *N* (%).

Post-induction treatments

Twenty-seven patients in CR proceeded to consolidation therapy (18 in Group A, nine in Group B); 18/27 patients received also maintenance therapy (11 in Group A, seven in

Group B). In addition, four patients (two in each Group) underwent maintenance therapy without a previous consolidation phase. The different consolidation and maintenance courses are reported in the Supplemental Table 1.

Follow-up

Nine out of 33 (27.2%) patients achieving CR (three in Group A and six in Group B) relapsed, after a median time of 13.9 months (IQR 9.4–27.5).

At the last follow-up, 15 patients (33.3%) were alive while 24 (53.3%) died (20 patients from ED or progressive disease and four patients from senectus or other unrelated causes while in CR), and six patients (13.3%) were lost to follow-up while in molecular CR.

Five-year EFS of the entire cohort was 39.8% (95% CI 22.1–57.5). When looking at differences according to treatment strategies, patients in Group A had a better five-year EFS when compared to Group B [57.1% (95% CI 23.1–91.1) in Group A vs. 18.2% (95% CI 2.1–34.3) in Group B; $p = 0.001$] (Figure 1(a)).

Five-year OS of the entire cohort was 46.1% (95% CI 28.2–64.0) with better outcomes for patients in Group A [72.6% (95% CI 42.9–100) in Group A vs. 27.2% (95% CI 7.5–46.9) in Group B, $p = 0.001$] (Figure 1(b)).

Of note, all the nine patients in Group A treated with the ATRA/ATO combination, all belonging to the low/intermediate relapse risk group, are alive and in molecular CR at a median time of 22 months from diagnosis (Figure 2(a,b)).

Discussion

The present analysis of our unselected cohort of APL patients aged $\geq$ 70 years was done considering a long interval of time, due to the rarity of APL in very old people: this represents a relative weakness of our data, as many diagnostic tools and different supportive measures were employed in this interval. However, our data highlight a real-life scenario where almost half of the patients were not considered eligible for a standard approach. This led to sub-optimal induction treatments, with a very high rate of ED and dismal outcomes compared to patients treated with standard therapy. As shown by our data, patients treated according to protocol guidelines (Group A) had a better outcome with an acceptable five-year EFS and OS of 57.1% and 72.6%, respectively, demonstrating that a standard "younger-like" approach is feasible and highly effective also in older patients. These results are in line with previous reports on case series of elderly APL patients treated with ATRA-chemotherapy approaches [8,10,11,14]. In a subgroup analysis of the MRC trial, 49 older patients (aged between 60 and 77 years) treated with ATRA-based approaches had a 4-year OS of 80% [15]. Moreover, in the same analysis, no differences were seen between patients treated with ATRA-chemotherapy and ATRA/ATO combination, as also shown in our data despite the shorter median follow-up time [15]. In a recent retrospective analysis on 120 very old patients with APL (aged $\geq$ 75 years) the "Programa para el Tratamiento de Hemopatias Malignas" (PETHEMA) group reported good survival outcomes in terms of OS (53% at three years for low/intermediate-risk patients treated with AIDA regimen), finding that age $\geq$ 85 years, relapse high-risk score and ECOG 4 were all independent risk factors for ED and shorter OS [10].

It is worthy of note that, due to the peculiar incidence of the disease, older APL patients represent a very unique population, configuring a very difficult-to-treat setting [32]. Data from European-based registries demonstrate that patients diagnosed with APL aged >75 years represent ~5% of all APL cases, while in the Latin-American countries no patients over 75 years have been registered [10]. This more pronounced difference in developing countries is probably due to an underreported diagnosis of APL among frail older

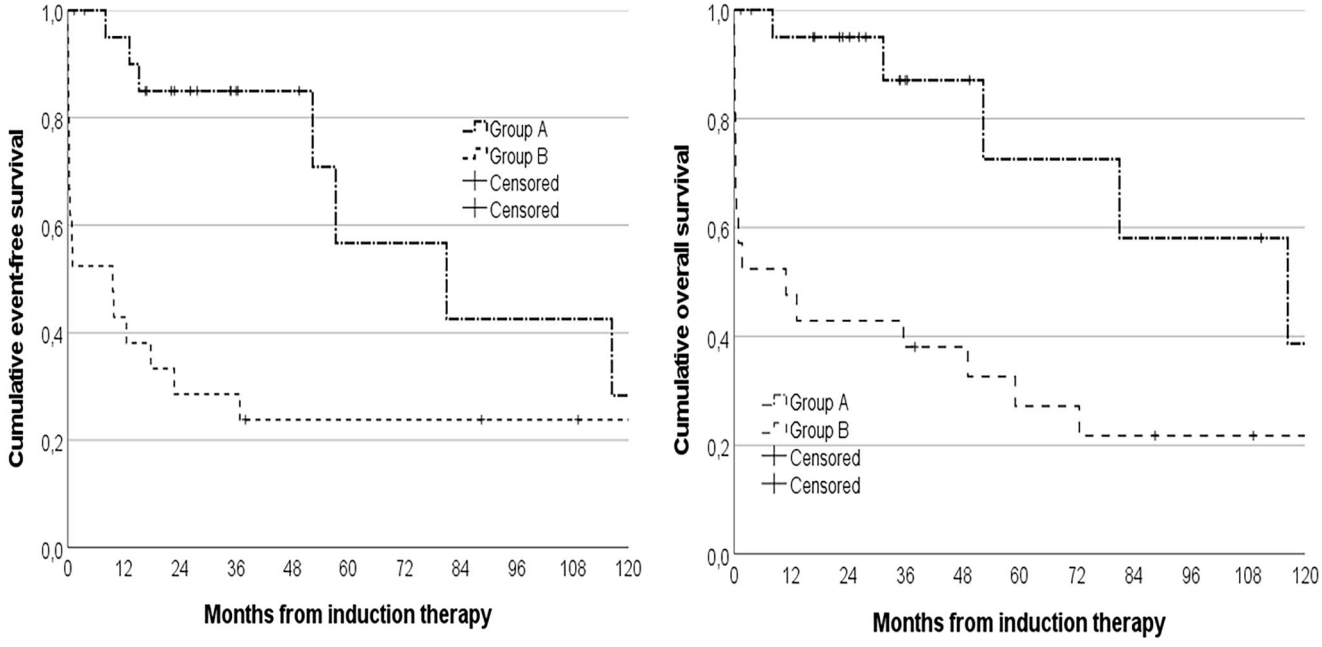

Figure 1. Cumulative event-free survival (1a) and cumulative overall survival (1 b) according to protocol enrollment.

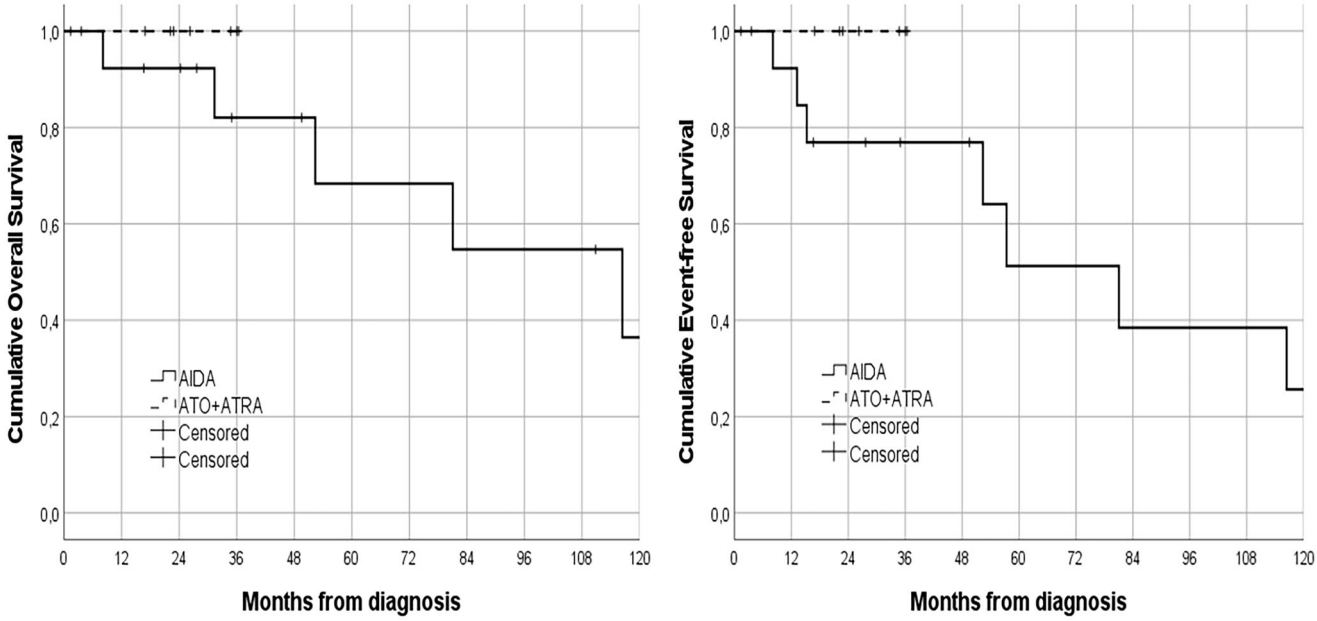

Figure 2. Cumulative overall survival (2a) and cumulative event-free survival (2 b) for Group A patients treated with ATRA-chemotherapy vs. ATRA + ATO approach ($p = 0.352$ and $p = 0.185$, respectively).

individuals, whose sudden death is often misdiagnosed as the result of a cerebrovascular accident, therefore masking a possible APL-related thrombo-hemorrhagic ED [1,33,34]. In the present study, to avoid selection bias as far as possible, we asked participating Centers for the referral of all patients $>$ 70 years with a diagnosis of APL performed, even those who died before starting any treatment. Unfortunately, a rate of patients was certainly lost due to primary referral to non-hematologic structures, like emergency departments, or death at home from cerebral hemorrhage misinterpreted as ischemic stroke. We are aware that this is another point of weakness of the present study.

In our recent analysis of 222 patients treated at two main Institutions in Rome, the ED rate was 7% (15/222), being cerebral hemorrhage the major cause of mortality (7/15, 3.1% of total), and older patients the more prone to experience such complication (median age 60 vs. 47 in non-hemorrhagic patients, $p = 0.039$) [19]. Similar results were reported in another study by Sun *et al*. on 288 adults with APL that showed an ED rate of 5.9% and older age ($\geq$60 years) as the only independent risk factor for this complication (Hazard ratio 15.057, $p = 0.004$) while the relapse-risk category did not have a significant prognostic role [17]. In the present study, the ED rate was 26.7%, a percentage more similar to those reported in previous studies conducted specifically on older patients: [11,20] it is worthy of note that ED occurred only in the group B, but no difference was observed as to median age compared to group B patients who survived to induction therapy, with only a trend for a higher WBC median value. It is conceivable that age-related cerebrovascular angiopathy, unveiled and exaggerated at APL onset by the typical thrombo-hemorrhagic imbalance, may play a role in this increased proclivity to ED. Moreover, the high frequency of cardiovascular diseases among older (62.2% in our cohort), and in particular hypertension, may increase the risk of fatal cerebral hemorrhage [9].

Our results demonstrate that, beyond older age, a high ECOG is one of the main reasons affecting physician choice on whether elderly patients are a candidate or not to standard treatment regimens, as previously shown in the aforementioned PETHEMA study [10]. Of note, all patients in our cohort not experiencing ED achieved morphologic CR, further emphasizing that APL treatment was very effective in eradicating leukemia, and patient's characteristics rather than disease biology played a role in determining outcomes. As mentioned, older patients share an intrinsic higher vulnerability not only to hemorrhage but also to infections and cardiac complications, all possible adverse events of the induction phase of APL, ultimately affecting OS [23]. Therefore, additional prudence and judiciously conducted choices with the application of specific geriatric comorbidity scores rather than the sole clinical judgment are warranted [35,36].

Finally, an induction therapy based on a chemotherapy-free ATRA/ATO combination is particularly attractive for older and frail patients because of the well-established high anti-leukemic efficacy and the lower rate of toxicity [3–5,37]. A Chinese study showed that ATO is safe and efficacious as a single-agent in older patients with APL, reporting an OS of 69.3% at 10-year [37]. A more recent International Collaborative Study evaluating 433 patients with APL aged$\geq$ 70 years also demonstrated that ATO added to ATRA and/or chemotherapy is feasible and effective in frail older patients [8]. Moreover, the authors underline that the international recommendations regarding supportive care measures during induction helped lowering the mortality rate from 28% between 1990 and 1999 to 15% in the last two decades, possibly overcoming the complications related to

chemotherapy-containing regimens especially in older patients [6,8]. As a matter of fact, our results, despite the low number of patients and the shorter follow-up time, suggest that also the ATRA/ATO combination may represent a valid alternative for frail older patients with APL.

As a consequence, it is mandatory, whenever possible, to adopt standard therapies instead of modified or reduced personalized approaches to improve outcomes and provide durable remission and quality of life also to this challenging subset of patients. The application of specific selection criteria and a multispecialistic approach comprehensive of a geriatric evaluation may help to better select patients suitable for standard therapies.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Massimo Breccia http://orcid.org/0000-0003-1163-6162
Salvatore Perrone http://orcid.org/0000-0001-8196-0481

References

[1] de la Serna J, Montesinos P, Vellenga E, et al. Causes and prognostic factors of remission induction failure in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and idarubicin. Blood. 2008;111(7):3395–3402.
[2] Iland HJ, Collins M, Bradstock K, et al. Use of arsenic trioxide in remission induction and consolidation therapy for acute promyelocytic leukaemia in the Australasian leukaemia and lymphoma group (ALLG) APML4 study: a non-randomised phase 2 trial. Lancet Haematol. 2015;2(9):e357-366–e366.
[3] Lo-Coco F, Avvisati G, Vignetti M, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med. 2013; 369(2):111–121.
[4] Cicconi L, Platzbecker U, Avvisati G, et al. Long-term results of all-trans retinoic acid and arsenic trioxide in non-high-risk acute promyelocytic leukemia: update of the APL0406 Italian-German randomized trial. Leukemia. 2020;34(3):914–918.
[5] Platzbecker U, Avvisati G, Cicconi L, et al. Improved outcomes with retinoic acid and arsenic trioxide compared with retinoic acid and chemotherapy in Non-High-Risk acute promyelocytic leukemia: Final results of the randomized Italian-German APL0406 trial. J Clin Oncol. 2017;35(6):605–612.
[6] Sanz MA, Fenaux P, Tallman MS, et al. Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the european LeukemiaNet. Blood. 2019;133(15): 1630–1643.
[7] Gurnari C, De Bellis E, Divona M, et al. When poisons cure: the case of arsenic in acute promyelocytic leukemia. Chemotherapy. 2019;64(5-6):238–247.
[8] Kayser S, Rahmé R, Martínez-Cuadrón D, et al. Outcome of older (≥70 years) APL patients frontline treated with or without arsenic trioxide-an international collaborative study. Leukemia. 2020; 34(9):2333–2341.
[9] Ferrara F, Finizio O, D'Arco A, et al. Acute promyelocytic leukemia in patients aged over 60 years: multicenter experience of 34 consecutive unselected patients. Anticancer Res. 2010;30(3):967–971.
[10] Salamero O, Martínez-Cuadrón D, Sobas M, PETHEMA and PALG Groups, et al. Real life outcomes of patients aged ≥75 years old with acute promyelocytic leukemia: experience of the PETHEMA registry. Leuk Lymphoma. 2019;60(11):2720–2732.
[11] Ades L, Chevret S, De Botton S, et al. Outcome of acute promyelocytic leukemia treated with all trans retinoic acid and chemotherapy in elderly patients: the european group experience. Leukemia. 2005;19(2):230–233.
[12] Borlenghi E, Cattaneo C, Schieppati F, et al. Acute promyelocytic leukemia in patients aged >70 years is not rare and highly curable: a single center series of 21 unselected patients. Leuk Lymphoma. 2019;60(2):531–534.
[13] Martínez-Cuadrón D, Montesinos P, Vellenga E, et al. Long-term outcome of older patients with newly diagnosed de novo acute promyelocytic leukemia treated with ATRA plus anthracycline-based therapy. Leukemia. 2018;32(1):21–29.
[14] Latagliata R, Breccia M, Fazi P, et al. GIMEMA AIDA 0493 amended protocol for elderly patients with acute promyelocytic leukaemia. Long-term results and prognostic factors. Br J Haematol. 2011;154(5):564–568.
[15] Burnett AK, Russell NH, Hills RK, et al. Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial. Lancet Oncol. 2015;16(13):1295–1305.
[16] Walter RB, Othus M, Burnett AK, et al. Resistance prediction in AML: analysis of 4601 patients from MRC/NCRI, HOVON/SAKK, SWOG and MD anderson cancer center. Leukemia. 2015;29(2): 312–320.
[17] Sun J, Zhu J, Zhou D, et al. Factors affecting early death and survival of patients with acute promyelocytic leukemia treated with ATRA-Based therapy regimens. Clin Lymph Myel Leuk. 2019;19(1): e63–e70.
[18] Disperati P, Minden MD, Gupta V, et al. Acute promyelocytic leukemia in patients aged 70 years and over - a single center experience of unselected patients. Leuk Lymphoma. 2007;48(8): 1654–1658.
[19] Gurnari C, Breccia M, Di Giuliano F, et al. Early intracranial haemorrhages in acute promyelocytic leukaemia: analysis of neuroradiological and clinico-biological parameters. Br J Haematol. 2021; 193(1):129–1111. /bjh.17018.
[20] Lehmann S, Ravn A, Carlsson L, et al. Continuing high early death rate in acute promyelocytic leukemia: a population-based report from the swedish adult acute leukemia registry. Leukemia. 2011; 25(7):1128–1134.
[21] Martinez-Cuadron D, Sobas M, Vellenga E, et al. Incidence and risk factors for early death among 2421 APL patients: the PETHEMA registry experience. HemaSphere. 2019;3(S1):78–79.
[22] Naymagon L, Moshier E, Tremblay D, et al. Predictors of early hemorrhage in acute promyelocytic leukemia. Leuk Lymphoma. 2019;60(10):2394–2403.
[23] Sham RL, Tallman MS. Treatment of acute promyelocytic leukemia in the very elderly: case report and review of the literature. Leuk Res. 2004;28(12):1347–1350.
[24] Rahmé R, Ades L, Thomas X, et al. Reducing mortality in newly diagnosed standard-risk acute promyelocytic leukemia in elderly patients treated with arsenic trioxide requires major reduction of chemotherapy: a report by the french belgian swiss APL group (APL 2006 trial). Haematologica. 2018;103(11):e519–e521.
[25] Ono T, Takeshita A, Kishimoto Y, et al. Long-term outcome and prognostic factors of elderly patients with acute promyelocytic leukemia. Cancer Sci. 2012;103(11):1974–1978.
[26] Bennett JM, Catovsky D, Daniel MT, et al. Proposed revised criteria for the classification of acute myeloid leukemia. A report of the French-American-British cooperative group. Ann Intern Med. 1985;103(4):620–625.
[27] Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the world health organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–2405.
[28] von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147(8):573–577.
[29] Lo-Coco F, Avvisati G, Vignetti M, et al. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by

risk-adapted consolidation for adults younger than 61 years: results of the AIDA-2000 trial of the GIMEMA group. Blood. 2010; 116(17):3171–3179.

[30] Sanz MA, Lo Coco F, Martín G, et al. Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups. Blood. 2000;96:1247–1253.

[31] Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern cooperative oncology group. Am J Clin Oncol. 1982;5(6):649–655.

[32] Lengfelder E, Hofmann WK, Nolte F. Management of elderly patients with acute promyelocytic leukemia: progress and problems. Ann Hematol. 2013;92(9):1181–1188.

[33] Jácomo RH, Melo RA, Souto FR, et al. Clinical features and outcomes of 134 brazilians with acute promyelocytic leukemia who received ATRA and anthracyclines. Haematologica. 2007;92(10): 1431–1432.

[34] Ghavamzadeh A, Alimoghaddam K, Rostami S, et al. Phase II study of single-agent arsenic trioxide for the front-line therapy of acute promyelocytic leukemia. J Clin Oncol. 2011;29(20): 2753–2757.

[35] Wedding U, Ködding D, Pientka L, et al. Physicians' judgement and comprehensive geriatric assessment (CGA) select different patients as fit for chemotherapy. Crit Rev Oncol Hematol. 2007; 64(1):1–9.

[36] Klepin HD, Neuendorff NR, Larson RA, et al. Treatment of acute promyelocytic leukemia in older patients: recommendations of an international society of geriatric oncology (SIOG) task force. J Geriatr Oncol. 2020;11(8):1199–1209.

[37] Zhang Y, Zhang Z, Li J, et al. Long-term efficacy and safety of arsenic trioxide for first-line treatment of elderly patients with newly diagnosed acute promyelocytic leukemia. Cancer. 2013; 119(1):115–125.