View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by VBN

Aalborg Universitet

AALBORG UNIVERSITY
DENMARK

Addressing the room for improvement in management of acute promyelocytic leukemia

Nørgaard, Jan M.; Friis, Lone S.; Kristensen, Jørgen S.; Severinsen, Marianne T.; Mølle, Ingolf; Marcher, Claus W.; Møller, Peter; Schoellkopf, Claudia; Nielsen, Ove J.; Preiss, Birgitte S.; Andersen, Mette K.; Kjeldsen, Eigil; Medeiros, Bruno C.; Østgård, Lene S.G.; for the Danish Acute Leukemia Group

Published in:
European Journal of Haematology

DOI (link to publication from Publisher):
10.1111/ejh.13229

Publication date:
2019

Document Version
Accepted author manuscript, peer reviewed version

Link to publication from Aalborg University

Citation for published version (APA):
Nørgaard, J. M., Friis, L. S., Kristensen, J. S., Severinsen, M. T., Mølle, I., Marcher, C. W., Møller, P., Schoellkopf, C., Nielsen, O. J., Preiss, B. S., Andersen, M. K., Kjeldsen, E., Medeiros, B. C., Østgård, L. S. G., & for the Danish Acute Leukemia Group (2019). Addressing the room for improvement in management of acute promyelocytic leukemia. *European Journal of Haematology*, *102*(6), 479-485. https://doi.org/10.1111/ejh.13229

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

? Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
? You may not further distribute the material or use it for any profit-making activity or commercial gain
? You may freely distribute the URL identifying the publication in the public portal ?

DR. JAN MAXWELL NORGAARD (Orcid ID : 0000-0002-3592-118X)

Article type : Original Article

Addressing the Room for Improvement in Management of Acute Promyelocytic Leukemia

By

Jan M. Nørgaard[1], Lone S. Friis[2], Jørgen S. Kristensen[1,3], Marianne T. Severinsen[4], Ingolf Mølle[1], Claus W. Marcher[5], Peter Møller[6], Claudia Schoellkopf[7], Ove J. Nielsen[2], Birgitte S. Preiss[8], Mette K. Andersen[9], Eigil Kjeldsen[1], Bruno C. Medeiros[10], and Lene S.G. Østgård[1] for the Danish Acute Leukemia Group

Affiliations:

1) **Department of Hematology, Aarhus University Hospital, Aarhus, Denmark.** J.M. Nørgaard, MD, Dr.med.sci, PhD, I. Mølle, MD, PhD, Eigil Kjeldsen, MD, Dr.med.sci, L.S.G. Østgård, MD, PhD.
2) **Department of Hematology, Rigshospitalet, Copenhagen, Denmark.** O.J. Nielsen, MD, Dr.med.sci., L.S. Friis, MD, PhD.
3) **Horsens Regional Hospital, Horsens, Denmark.** J.S. Kristensen, MD, Dr.med.sci.
4) **Aalborg University Hospital, Aalborg, Denmark.** M.T. Severinsen, MD, PhD.
5) **Department of Hematology, Odense University Hospital, Odense, Denmark.** C.W. Marcher, MD, PhD.
6) **Department of Hematology, Roskilde Hospital, Roskilde, Denmark.** P. Møller, MD.
7) **Department of Hematology, Herlev Hospital, Herlev, Denmark.** C. Schoellkopf, MD, PhD.
8) **Department of Pathology, Odense University Hospital, Odense, Denmark.** B.S. Preiss, MD.
9) **Department of Clinical Genetics, Rigshospitalet, Copenhagen, Denmark.** M.K. Andersen, MD, Dr.med.sci.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ejh.13229
This article is protected by copyright. All rights reserved.

Accepted Article

10) **Stanford University School of Medicine, Stanford, CA, United States.** B.C. Medeiros, MD.

Address of corresponding author, Jan Maxwell Nørgaard, MD, PhD, dr.med.sci.:
Department of Hematology
Aarhus University Hospital
Palle Juul-Jensens Boulevard 99
8200 Aarhus N
Denmark
E-mail: jannorga@rm.dk

Running head: Improving the management of APL

Abstract

Acute promyelocytic leukemia (APL) is highly curable. To achieve high cure rates, targeted therapy with retinoic acid (ATRA) must be started promptly at time of suspected diagnosis. Early death rates (EDRs, ≤30 days from diagnosis) differ markedly in patients treated on clinical trials compared to the general population.

Objectives and methods: We used the comprehensive Danish National Acute Leukemia Registry (DNLR) to investigate the incidence, treatment, EDR, and long-term clinical outcome in APL between 2000 and 2014.

Results: Twenty-two of 41 deaths occurring in 122 APL patients were EDs which were primarily caused by intracranial hemorrhage, disseminated intravascular coagulation (DIC), sepsis, and multiorgan failure. The overall EDR was 18.0%, whereas clinical trial participants had an EDR of 6.7%. Fifteen patients recruited to the NCRI AML17 APL trial from 2010 to 2013 were younger and had decreased mortality (HR 0.18, CI 0.04 – 0.86, p=0.02) compared

This article is protected by copyright. All rights reserved.

Accepted Article

to contemporarily treated patients (n = 15) not recruited to a clinical trial. Performance status, leukemia origin, and Sanz-score were independent prognostic variables.

Conclusions: The very low EDR for on-trial patients is not observed in the general cohort of APL patients. Diagnostic awareness emerges as the greatest clinical challenge in management of APL.

Key words: Acute Promyelocytic Leukemia, Early Death, Diagnostic Awareness, Prognosis

Introduction

Since the introduction of all-trans retinoic acid (ATRA) in the treatment of APL nearly 30 years ago, outcomes have improved significantly. When used as a single agent, ATRA induces complete remissions in more than 90% of treated patients but remissions are short lived.[1] Over the last decades improved long-term outcomes have been obtained by combining ATRA with chemotherapeutic agents – in particular anthracyclines - as in the ATRA and idarubicin regimen (AIDA).[2,3] More recently, we showed that in *de novo* APL patients, mainly treated with ATRA in combination with anthracyclines, survival reverts to normal after only three months of treatment, whereas survival of non-*de novo* APL patients remains inferior.[4] Pivotal studies have demonstrated the superiority of arsenic trioxide (ATO) in combination with ATRA for all APL patients in all risk groups.[5-9] ATO in combination with ATRA is now approved by both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) for use as first line therapy in adult patients with low- and intermediate risk APL and as second line therapy in relapsed APL patients.[10,11] Although the ATO and ATRA-regimen in some studies appears to be efficient and well-tolerated in pediatric APL patients, it is still not recommended in children.[12,13] The ability to generalize the results

This article is protected by copyright. All rights reserved.

Accepted Article

of recent clinical trials has been debated. In a single institution retrospective analysis, significant EDR differences were reported between patients recruited to clinical trials and patients treated off trial (3% and 21%, respectively).[14]

In addition, while early death rates in clinical trials are reported to range between 2 and 9%, broader population-based studies report significantly higher early death rates. Ranging between 17% and 35%.

The most common cause of EDR in APL is the hemorrhagic diathesis, primarily due to an increased fibrinolysis caused by the secretion of plasminogen activators and lysosymal enzymes of the leukemic cells.[15] The resolution of this specific coagulopathy occurs in parallel with the induction of a leukemic remission which in most cases occurs within 30 days from the start of therapy.[16]

Given the availability of our comprehensive national acute leukemia registry (DNLR),[17,18] we sought to study of the epidemiology, EDR, and long-term outcome in adult patients with APL treated in Denmark from 2000 through 2014. The aim of the study was to describe the clinical characteristics, treatments, short- and long-term clinical outcomes of APL patient in Denmark in search of areas of possible improvements and to determine the clinical impact of clinical trial enrollment on the outcomes of patients with APL.

Methods

Study population

We used the Danish National Acute Leukemia Registry (DNLR) to identify patients diagnosed and treated for APL during the 15-year time period 01 January 2000 through 31 December 2014. We identified acute leukemia patients fulfilling at least 1 specific diagnostic criterion consistent with APL, i.e. patients registered with FAB M3-morphology and/or WHO ICD-O-code 9866/3. Patients

This article is protected by copyright. All rights reserved.

Accepted Article

fulfilling ≥1 specific diagnostic criterion for APL were included in the study cohort. The diagnostic criteria were: presence of the chromosomal translocation t(15;17)(q24;q21), a FISH analysis confirming the presence of the PML-RARA fusion gene, and/or a PCR analysis confirming the presence of the PML-RARA fusion gene product. Rare variants of APL, i.e. cases of acute leukemia with complex rearrangements involving PML-RARA, and cases with t(11;17)(q13;q21), t(11;17)(q23;q21), or t(5;17)(q35;q21) were excluded.[16,19]

Throughout the study period, the standard of care for treating APL was an ATRA-containing regimen. The Danish population (5.6 million in 2014) has free access to tax-supported health-care. Treatment of APL is centralized, and patients are treated at only five (increased to six since 2012) university hospitals. No treatment of acute leukemia takes place in private hospitals. This registry study was approved by the Danish Data Protection Agency (Datatilsynet, Sundhedsdatastyrelsen, approval no. 2014-41-3204).

During the study period, ATRA was initiated shortly after clinical suspicion of an APL diagnosis at all centers. However, the standard treatment regimen varied between institutions until 2009. Various anthracyclines (or anthracenedione) in combination with Ara-C were used in combination with ATRA. Since 2009, all centers used AIDA as the standard regimen[4]. Furthermore, during the period January 2010 to October 2013, the Danish centers participated in the UK Medical Research Council (MRC)-led randomized phase III study of AIDA versus ATRA and arsenic, the NCRI AML17 APL trial.[6]

Definitions and clinical variables endpoints

The date of diagnosis was the date of the bone marrow aspiration confirming the APL diagnosis. Performance status was measured according to the Eastern Cooperative Oncology Group (ECOG)/World Health Organization (WHO) scale and grouped as (0, 1, ≥2).[20] The Sanz/PETHEMA and GIMEMA-risk score was used to separate patients into low- (WBC ≤10 x 10^9/L and platelet count >40 x 10^9/L), intermediate- (WBC ≤10 x 10^9/L and platelet count ≤40 x 10^9/L), and high-risk (WBC count >10 x 10^9/L) patients.[3]

This article is protected by copyright. All rights reserved.

Accepted Article

Patients were followed until death, emigration or the date of last follow up (18 February 2016). Overall survival was calculated as the time from the day of diagnosis until day of death, emigration or last follow up. ED was defined as death within the first 30 days from diagnosis. Very early death (VED) was defined as death occurring day 1 through day 7 from date of diagnosis.

Statistical analysis

Descriptive statistical methods were used to describe the baseline characteristics of the final study cohort. We obtained information about the Danish population size per calendar year from Statistics Denmark (http://www.dst.dk/en/Statistik) and calculated the annual incidence of APL. We compared the prevalence of APL and the distribution of APL/non-APL for calendar years 2000 – 2004, 2005 – 2009, and 2010 – 2014 using One-way Anova. We compared EDRs by these time periods using Kruskal-Wallis test.

The primary measures of short- and long-term outcome were day 30-mortality and overall survival. The Kaplan-Meier method was used to construct estimates of survival curves and survival was compared using log-rank test. We used binary regression (relative risk [RR]) to estimate the association between patient-associated and leukemia-associated parameters to risk of death within 30 days (ED). Cox proportional hazards regression (hazard ratios [HRs]) was used to evaluate associations between clinical and biological parameters and overall survival. The proportional hazard assumption was evaluated and accepted (log minus log plots). Two-sided 95% confidence intervals (95% CI) were used throughout.

All statistical analyses were done using the IBM-SPSS (ver. 20, IBM, Armok, New York, USA) statistical package or STATA (ver. 14, Stata Corporation, College Station, Texas, USA).

Accepted Article

This article is protected by copyright. All rights reserved.

Results

Overall, 3,836 patients, 15 years of age or older, were registered with an acute leukemia in the DNLR. We excluded patients having either a non-APL-acute myeloid leukemia (non-APL AML, n=3,401) or acute lymphoblastic leukemia (ALL, n=295). Of the 3,836 acute leukemia patients, 2,134 (55.6%) were males. The median age at time of diagnosis was 68 years (range 15 – 99 years). Overall, 3,090 (80.6%) had a cytogenetic analysis performed at time of diagnosis.

The final study cohort consisted of 122 patients with confirmed APL. The annual incidences of APL and non-APL AML were 0.15 and 4.17 per 100,000 per years, respectively. Incidences did not change over time (p=0.69 and p=0.20, one-way ANOVA, respectively). Thus, APL comprised 3.5% of all AML cases.

The median age of the APL patients was 51 (range 15 – 83 years). Sixty-seven (54.9%) were male patients. The median presenting leukocyte count was 2.5 x 10^9/L and thirty-seven patients (30.3%) had high risk APL (WBC> 10 x 10^9/L) at diagnosis.

One-hundred-seven patients had APL arising *de novo*, and 15 patients had secondary- or therapy-related APL according to described criteria.[21] These 15 patients had APL secondary to treatment for breast cancer (6 cases), non-Hodgkin lymphoma (one case), treatment for multiple myeloma (one case), myelodysplastic syndrome (one case), and chemotherapy and/or radiotherapy for a variety of other cancers (5 cases). Finally, one patient developed APL after mitoxantrone treatment for multiple sclerosis. Baseline characteristics are listed in Table 1.

The methods of diagnostic confirmation are given in Supplementary Table S1. One hundred and two (83.6%) cases were confirmed by cytogenetic analysis. Treatment information is also shown in Table S1. The most frequently used remission-induction- and consolidation regimen was AIDA, initiated in 56 (45.9%) of cases. Eight patients (6.6%) enrolled in the NCRI AML17 APL-trial were treated with

This article is protected by copyright. All rights reserved.

ATRA and ATO as *per* protocol. A third of all patients (mainly from the early part of the study period) were treated with combinations of ATRA and chemotherapy as *per* local institutional preference.

Because the APL diagnosis was not suspected at initial presentation, 10 patients (8.2%) did not receive ATRA treatment. Median survival in these 10 patients was median 3.5 days (range: 1 to 1,729 days) and only one patient survived beyond day 30. In this single surviving patient, the initial treatment regimen (daunorubicin and cytarabine 3 + 10) did not contain ATRA, but ATRA was added to the subsequent treatment (AIDA-regimen). In the remaining 9 patients, APL was confirmed when the patient was dying or had passed away. Not receiving ATRA in the primary treatment was associated with higher risk of ED ($p<0.0001$, Fisher's exact test).

Autologous stem cell transplantation (SCT) was used in second complete remission in 4 patients with APL relapsing after first line treatment. Treatment with allogeneic SCT did not take place in the present cohort.

During 740 person-years observation period, 41 deaths occurred. In Supplementary Table S2 survival estimates at day 30, day 90, 1-, 5-, and 10 years are given for patients according to prognostic factors. Kaplan-Meier survival plots are shown in Figure 1. Twenty-two of these 41 deaths (53.6%), occurred within 30 days from diagnosis, resulting on an EDR of 18.0%. The EDRs in *de novo*- and in non-*de-novo* APL patients were 16.8% and 26.7%, respectively. Comparing the 5-year time periods (2000 – 2004, 2005 – 2009, and 2010 – 2014), no differences in the EDR and overall survival were noted (Kruskal-Wallis test and log rank test, respectively).

Very early deaths were primarily caused by intracranial hemorrhage, while deaths occurring day 8 to day 30 were primarily caused by multiorgan failure, sepsis, or DIC (Table 2).

This article is protected by copyright. All rights reserved.

Late deaths were primarily caused by other cancers (n=4) or other causes (n=4)(Table 2). Notably, two patients with *de novo* APL, initially treated with ATRA and chemotherapy (ATRA, daunorubicin, and cytarabine, one case, and ATRA and idarubicin, one case), died from therapy-related acute myeloid leukemia (non-APL AML). Only a single patient died from treatment refractory APL (Table 2).

Supplementary Table S3 shows the association between patient- and leukemia-related factors and death within 30 days. WHO/ECOG PS score ≥2 and high Sanz risk score were independently associated with increased risk of ED in the adjusted analysis.

The association between risk factors and overall survival are shown in Table 3 and in Figure 1. Performance status ≥2, non-*de novo* APL, and Sanz high risk score were all associated with an overall increased risk of death.

A total of 15 Danish patients were recruited to the MRC/NCRI AML 17 trial. During the same time period, 15 Danish patients were treated off-protocol. Supplementary Table S4 describes the characteristics of APL patients by trial status. None of the off-trial patients received ATO in their treatment. Patients treated on-trial were on average 9.1 years younger and had significantly lower risk of death (HR=0.18, CI 0.04-0.86). Other clinical parameters were evenly distributed between the two groups.

Discussion

Prompt recognition of suspected APL and timely initiation of ATRA reduce EDR in APL. However, they remain the greatest clinical challenge in managing patients with APL. Early death rates in APL treated with the ATRA-ATO combination in clinical trials has been reported to range between 2 and 9% .[5,6,22,23] In contrast, EDRs of 17 to 35% have been reported in non-clinical trial subjects with APL

This article is protected by copyright. All rights reserved.

Accepted Article

treated with ATRA and chemotherapy.[24-28] We found that the overall EDR in our population-based national APL cohort was 18% without significant variation throughout the study period. Lack of or delay in ATRA treatment (due to missed/delayed diagnosis) in initial therapy was highly significantly associated with dismal outcomes. Additionally, in a subgroup analysis, we show that participation in an APL clinical trial was associated with lower EDR and long-term clinical outcome comparable to results from published clinical phase III trials.

The baseline characteristics of APL patients in Scandinavian and north European countries are strikingly similar. Notably, however, median age at time diagnosis and incidences differ between European and American cohorts. In Sweden, the median age of 56 years, and the annual incidence rate of 0.15 per 100,000 are strikingly similar to our results and those reported in the Netherlands.[29] In contrast, a US SEER-based cohort had a median age of 44 years and an annual incidence of 0.23 per 100,000,[26] while the mean age at diagnosis was 47.9 years and the age-adjusted incidence rate was 0.083 per 100,000 in a Canadian population-based cohort.[27] As expected, the annual incidence rate of APL in our Danish national AML cohort, which includes only 2% patients of non-western origin[30], is in line with incidences found in the North European populations and with a lower incidence rate than seen in ethnically mixed populations. A higher annual incidence rate in populations of southern European, Hispanic, and non-western origin has previously been noted.[27,31,32] Apart from being of more mixed ethnic composition, the two North-American studies included children. However, since APL is extremely rare in children, the inclusion of children is an unlikely explanation for these differences.[33]

The most frequent cause of ED in our cohort was multiorgan failure, sepsis, and DIC, while intracranial bleeding was the dominant cause of death during the first week after diagnosis. Considering the population-based setting, the observed EDR of 18% is relatively low compared to previous reports. Throughout the study period, a liberal use of platelet transfusions was

This article is protected by copyright. All rights reserved.

Accepted Article

recommended, and more recently, additional use of supplement with fresh frozen plasma/fibrinogen/cryoprecipitate has been recommended by European LeukemiaNet, which may explain our findings.[16] Also, travel time to a hematological center may affect and explain differences in reported EDR. Longer distance may prolong the time from initial presentation of symptoms to a correct diagnosis and start of ATRA treatment. In Denmark, the geography is confined with rarely more than 100 kilometers to the nearest hospital department with highly specialized hematological service. In Sweden, United States, and in Canada this is obviously not the case.

One main finding of our present study was the striking difference in EDR between trial patients and patients treated off-trial.

Clinical trials often exclude older patients (e.g. patients over 60 years of age) and patients with poorer performance status (e.g. patients with ECOG/WHO PS >2). Not surprisingly, patients included in the NCRI AML17 APL trial were younger (on average 9.1 years), although other baseline characteristics were similar between clinical trial participants and non-participants. It is particularly noted, though, that our on-trial patients had PS 0 to 1, whereas two of our off-trial patients had PS 4 (Table S4). This may have contributed to the worse outcome of the off-trial patients. The APL diagnosis was clinically confirmed before trial enrolment and patients too sick to be able to consent would not be included in the trial. Importantly, all patients dying before treatment initiation would count as off-trial patients thus introducing immortal time bias. Selection of less fit APL patients away from clinical trials was recently reported in a single institution experience.[14] Thus, apart from the treating physician's preferences, being old, frail, and very ill may obviously keep patients from trial participation.

Our observation that acute leukemia patients who participate in clinical trial do better than off-trial patients, corroborate well with our previous observations that non-APL AML patients with favorable characteristics are selected into clinical trials. However, even when adjusting for the baseline differences, trial-patients have better outcomes.[34] Notably, in our present cohort of 30 APL patients,

This article is protected by copyright. All rights reserved.

Accepted Article

none of the 15 patients treated off-trial received ATO in their treatment while 8 of the 15 patients treated on-trial received ATO and ATRA in combination. This difference in treatment may very well have contributed to the better outcome of on-trial patients. In our cohort, two cases of therapy related neoplasms (non-APL AML) were observed in patients after ATRA and anthracycline-containing chemotherapy for *de novo* APL, which may be another clinical benefit from eliminating anthracyclines from APL regimens.[6,8]

An evident strength of the present study is that we have data from a complete and truly population-based cohort of APL patients with complete and long-term follow-up, encompassing both trial participants and non-trial participants. This study has, however, a number of limitations. These include the small number of patients, the limited number of events due to the favorable prognosis, the various treatment regimens used during the first part of the study period (supplementary Table S1), and the limited number of details in DNLR concerning causes of death including ED (multi organ failure/sepsis/DIC being combined into one entity, Table 2), all limiting the analytic possibilities. Though the coverage and accuracy of AML diagnoses including APL diagnosis in the DNLR has been shown to be close to 100%, probably some APL patients remain undiagnosed. However, as for any population-based report, it is likely that some undiagnosed APL patients may die from intracranial hemorrhage or DIC prior to or during admission in non-hematological departments. Additionally, though only 20% of patients are diagnosed with acute leukemia without a cytogenetic analysis being performed, we cannot rule out misclassification of some APLs as non-APLs. These unaddressed issues will all tend to underestimate the true EDR in APL.

The current very efficacious targeted treatment regimens yield cure-rates of more than 90 % in patients treated within clinical trials. Consequently, the room for improvement of the prognosis in APL patients seems dependent on a high degree of clinical awareness, prompt initiation of ATRA treatment, and a rapid confirmation of the diagnosis. Undoubtedly, more APL patient lives can be saved by improving diagnostic awareness, while further survival benefits from new treatment

This article is protected by copyright. All rights reserved.

Accepted Article

regimens may be less obtainable. Initiatives to reduce EDR are greatly warranted. Raising awareness of the diagnosis in non-hematological specialties and keeping a stock of ATRA capsules, at all times, in emergency wards may be means to decrease early death rates in APL.

Acknowledgements

This work was supported by The Danish Cancer Society (research grant DP08160)

Contributors

JMN was the corresponding author and takes primary responsibility for the paper including final submission of this. JMN, BCM, and LGØ designed the study. JMN, LSF, JSK, MTS, IM, CWM, PM, CS, and OJN recruited patients. BSP, MKA, and EK performed the cytogenetic analyses and reviewed these. JMN and LGØ performed the statistical analyses and wrote drafts of the paper. All authors approved the final version of the manuscript.

Declaration of conflicts of interest

The authors report that there are no relevant conflicts of interests to declare

Role of the funding source

The funder of the study had no influence on the study design, data collection, data interpretation, manuscript writing, and the final report. The corresponding author had full access to all the data of the study and had the responsibility for final submission of the report.

This article is protected by copyright. All rights reserved.

Accepted Article

Accepted Article

References

1. Huang ME, Ye YC, Chen SR, et al. Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. *Blood.* 1988;72(2):567-572.
2. Sanz MA, Martin G, Rayon C, et al. A modified AIDA protocol with anthracycline-based consolidation results in high antileukemic efficacy and reduced toxicity in newly diagnosed PML/RARalpha-positive acute promyelocytic leukemia. PETHEMA group. *Blood.* 1999;94(9):3015-3021.
3. Sanz MA, Lo Coco F, Martin 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(4):1247-1253.
4. Biccler JL, Ostgard LSG, Severinsen MT, et al. Evolution of relative survival for acute promyelocytic leukemia patients alive at landmark time-points: a population-based study. *Leukemia.* 2018.
5. 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.
6. 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.
7. Lo-Coco F, Di Donato L, Gimema, Schlenk RF, German-Austrian Acute Myeloid Leukemia Study G, Study Alliance L. Targeted Therapy Alone for Acute Promyelocytic Leukemia. *N Engl J Med.* 2016;374(12):1197-1198.
8. 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.
9. 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.
10. EMA Arsenic Trioxide. Accessed 24.01.2019.
11. FDA Arsenic Trioxide. Accessed 24.01.2019.
12. Kayser S, Schlenk RF, Platzbecker U. Management of patients with acute promyelocytic leukemia. *Leukemia.* 2018;32(6):1277-1294.
13. Creutzig U, Dworzak MN, Bochennek K, et al. First experience of the AML-Berlin-Frankfurt-Munster group in pediatric patients with standard-risk acute promyelocytic leukemia treated with arsenic trioxide and all-trans retinoid acid. *Pediatr Blood Cancer.* 2017;64(8).
14. Micol JB, Raffoux E, Boissel N, et al. Management and treatment results in patients with acute promyelocytic leukaemia (APL) not enrolled in clinical trials. *Eur J Cancer.* 2014;50(6):1159-1168.
15. Testa U, Lo-Coco F. Prognostic factors in acute promyelocytic leukemia: strategies to define high-risk patients. *Ann Hematol.* 2016;95(5):673-680.
16. Sanz MA, Grimwade D, Tallman MS, et al. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood.* 2009;113(9):1875-1891.
17. Ostgard LS, Norgaard JM, Severinsen MT, et al. Data quality in the Danish National Acute Leukemia Registry: a hematological data resource. *Clin Epidemiol.* 2013;5:335-344.
18. Ostgard LS, Norgaard JM, Raaschou-Jensen KK, et al. The Danish National Acute Leukemia Registry. *Clin Epidemiol.* 2016;8:553-560.

This article is protected by copyright. All rights reserved.

19. Grimwade D, Biondi A, Mozziconacci MJ, et al. Characterization of acute promyelocytic leukemia cases lacking the classic t(15;17): results of the European Working Party. Groupe Francais de Cytogenetique Hematologique, Groupe de Francais d'Hematologie Cellulaire, UK Cancer Cytogenetics Group and BIOMED 1 European Community-Concerted Action "Molecular Cytogenetic Diagnosis in Haematological Malignancies". *Blood.* 2000;96(4):1297-1308.
20. Miller SP, Brenner S, Horton J, Stolbach L, Shnider BI, Pocock S. Comparative evaluation of combined radiation-chlorambucil treatment of ovarian carcinomatosis. *Cancer.* 1975;36(5):1625-1630.
21. Granfeldt Ostgard LS, Medeiros BC, Sengelov H, et al. Epidemiology and Clinical Significance of Secondary and Therapy-Related Acute Myeloid Leukemia: A National Population-Based Cohort Study. *J Clin Oncol.* 2015;33(31):3641-3649.
22. Kelaidi C, Chevret S, De Botton S, et al. Improved outcome of acute promyelocytic leukemia with high WBC counts over the last 15 years: the European APL Group experience. *J Clin Oncol.* 2009;27(16):2668-2676.
23. Ravandi F, Estey E, Jones D, et al. Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin. *J Clin Oncol.* 2009;27(4):504-510.
24. 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.
25. Lehmann S, Deneberg S, Antunovic P, et al. Early death rates remain high in high-risk APL: update from the Swedish Acute Leukemia Registry 1997-2013. *Leukemia.* 2017.
26. Park JH, Qiao B, Panageas KS, et al. Early death rate in acute promyelocytic leukemia remains high despite all-trans retinoic acid. *Blood.* 2011;118(5):1248-1254.
27. Paulson K, Serebrin A, Lambert P, et al. Acute promyelocytic leukaemia is characterized by stable incidence and improved survival that is restricted to patients managed in leukaemia referral centres: a pan-Canadian epidemiological study. *Br J Haematol.* 2014;166(5):660-666.
28. McClellan JS, Kohrt HE, Coutre S, et al. Treatment advances have not improved the early death rate in acute promyelocytic leukemia. *Haematologica.* 2012;97(1):133-136.
29. Dinmohamed AG, Visser O, van Norden Y, et al. Treatment, trial participation and survival in adult acute myeloid leukemia: a population-based study in the Netherlands, 1989-2012. *Leukemia.* 2016;30(1):24-31.
30. Ostgard LSG, Norgaard M, Medeiros BC, et al. Effects of Education and Income on Treatment and Outcome in Patients With Acute Myeloid Leukemia in a Tax-Supported Health Care System: A National Population-Based Cohort Study. *J Clin Oncol.* 2017;35(32):3678-3687.
31. Ruiz-Arguelles GJ. Promyelocytic leukemia in Mexican Mestizos. *Blood.* 1997;89(1):348-349.
32. Douer D, Preston-Martin S, Chang E, Nichols PW, Watkins KJ, Levine AM. High frequency of acute promyelocytic leukemia among Latinos with acute myeloid leukemia. *Blood.* 1996;87(1):308-313.
33. Wennstrom L, Edslev PW, Abrahamsson J, et al. Acute Myeloid Leukemia in Adolescents and Young Adults Treated in Pediatric and Adult Departments in the Nordic Countries. *Pediatr Blood Cancer.* 2016;63(1):83-92.
34. Ostgard LS, Norgaard M, Sengelov H, et al. Improved outcome in acute myeloid leukemia patients enrolled in clinical trials: A national population-based cohort study of Danish intensive chemotherapy patients. *Oncotarget.* 2016;7(44):72044-72056.

Accepted Article

This article is protected by copyright. All rights reserved.

Accepted Article

Legends for figures

Legend for Figure 1.

Kaplan-Meier survival plots in 122 APL patients. **(A)** All 122 patients. **(B)** By age (p=0.002). **(C)** By APL-type (*de novo* n=107, non-*de novo* n=15, p=0.015). **(D)** By Sanz risk score (p=0.006). **(E)** By ECOG/WHO performance status (p<0.0001). **(F)** By trial participation status in 30 patients (years 2010 to 2013, p=0.02). Numbers at risk are indicated at 1-, 5-, and 10 years. Number of events between time-points are given in parenthesis.

This article is protected by copyright. All rights reserved.

Table 1.

Patient characteristics at time of diagnosis in 122 patients with confirmed acute promyelocytic leukemia

Age (years)	
Mean:	49.3 (range 15-83)
Median:	51 (range 15-83)
60 years or older:	40 patients
Sex (122 patients)	
Male:	67 (55%)
Female:	55 (45%)
White blood cell count (WBC; $x10^9$ per L)*	
Mean:	13 (range: 0.2-99.0)
Median:	2.5 (range: 0.2-99.0)
Unknown or missing:	3 patients
Peripheral blood platelet count ($x10^9$ per L)*	
Mean:	39(range: 5-168)
Median:	27 (range: 5-168)
Unknown or missing:	3 patients
Sanz risk score (Sanz *et al*., 2000), no. (%)*	
Low:	33 (27%)
Intermediate:	49 (40%)
High:	37 (30%)
Unknown or missing:	3 (3%)
Leukemia origin, no. (%)	
De novo APL	107 (88%)
Non-*de novo* APL	15(12%)
ECOG/WHO performance status no. (%)	
0:	53 (43%)
1:	49 (40%)
2:	9 (7%)
3:	5 (4%)
4:	6 (5%)

Percentages are rounded. *:3 missing.

Accepted Article

This article is protected by copyright. All rights reserved.

Table 2.

Time- and cause of death in 41 cases of APL*

	Day 1 – 7	Day 8 – 30	Day 31 – 90	Day 91 - ∞	Total
Multi organ failure/sepsis/DIC	3 (7%)	6 (15%)	2 (5%)	0	11 (27%)
Intracranial bleeding	4 (10%)	1 (2%)	1 (2%)	0	6 (15%)
Death during chemotherapy, NOS	3 (7%)	2 (5%)	1 (2%)	0	6 (15%)
Treatment-refractory or progressive disease	0	2 (5%)	2 (5%)	1 (2%)	5 (12%)
Other cancer (not leukemia)	0	0	0	4 (10%)	4 (10%)
Not leukemia related	0	0	0	4 (10%)	4 (10%)
Therapy related AML (t-AML, not APL)	0	0	0	2 (5%)	2 (5%)
Treatment-related in CR	0	0	1 (2%)	0	1 (2%)
APL relapse after autologous stem cell transplantation	0	0	0	1 (2%)	1 (2%)
Unknown or missing	0	1 (2%)	0	0	1 (2%)
Total	10 (24%)	12 (29%)	7 (17%)	12 (29%)	41 (100%)

*: Percentages are rounded.

Accepted Article

This article is protected by copyright. All rights reserved.

Table 3.

Cox proportional hazards regression analysis of factors of importance to overall survival (OS) in 122 APL patients*

	Crude Hazard Ratio (95%CI)	Adjusted Hazard Ratio (95%CI)
Age		
< 60 years	1 (reference)	1
≥ 60 years	2.54 (1.37– 4.69)	1.70 (0.87-3.32)
White blood cell count (x10^9 per L)		
≤10	1 (reference)	ND**
>10	2.46 (1.32-4.56)	
Platelet count (x10^9 per L)		
>40	1 (reference)	ND**
≤40	1,61 (0.78-3.30)	
Sanz risk score		
Low	1 (reference)	1
Intermediate	1.38 (0.56-3.42)	1.46 (0.57-3.72)
High	3.01 (1.26-7.18)	2.55 (1.04-6.28)
Leukemia origin		
De novo APL	1 (reference)	1
Non-*de novo* APL	2.45 (1.16-5.16)	2.91 (1.27-6.65)
WHO PS		
0	1	1
1	2.57 (1.11-5.96)	2.24 (0.96-5.23)
≥2	9.48 (4.03-22.34)	6.78 (2.81-16.37)
Sex		
Women	1 (reference)	1
Men	1.95 (1.01– 3.80)	1.94 (0.97-3.89)

*: Three cases with missing data were excluded.

**: The adjusted analysis included Sanz risk score which is based on WBC and platelet count.

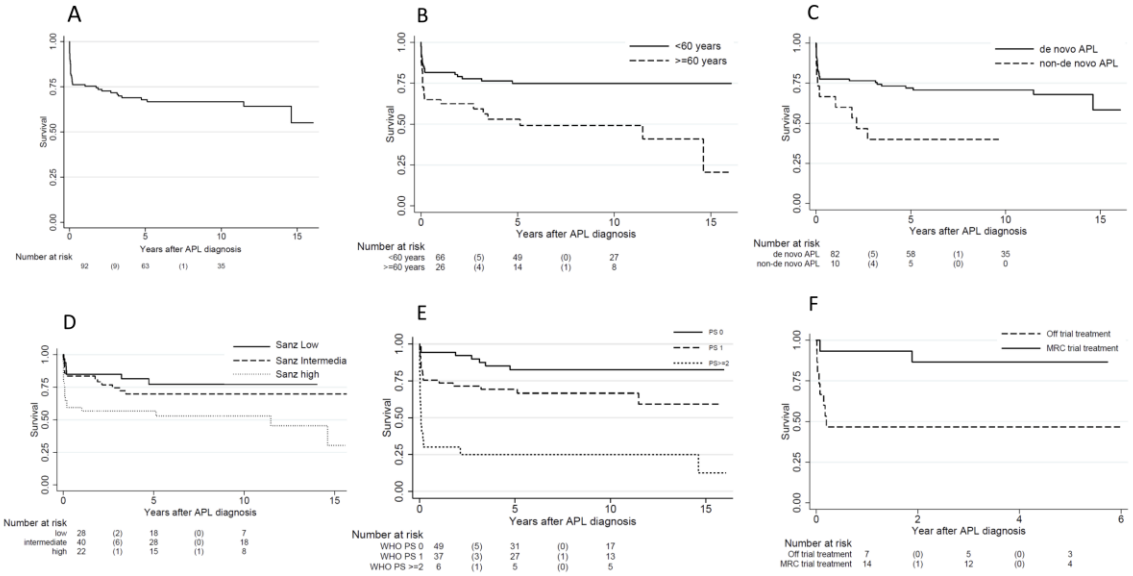
Number of events during the observation period in the analyzed 119 patients: n = 40.

Accepted Article

This article is protected by copyright. All rights reserved.

Accepted Article

Figure 1



This article is protected by copyright. All rights reserved.