



Universiteit
Leiden
The Netherlands

Lenalidomide added to standard intensive treatment for older patients with AML and high-risk MDS

Ossenkoppelaar, G.J.; Breems, D.A.; Stuessi, G.; Norden, Y. van; Bargetzi, M.; Biemond, B.J.; ... ; Swiss Grp Clinical Canc Res SAKK

Citation

Ossenkoppelaar, G. J., Breems, D. A., Stuessi, G., Norden, Y. van, Bargetzi, M., Biemond, B. J., ... Kuball, J. (2020). Lenalidomide added to standard intensive treatment for older patients with AML and high-risk MDS. *Leukemia*, 34, 1751-1759.
doi:10.1038/s41375-020-0725-0

Version: Publisher's Version

License: [Creative Commons CC BY 4.0 license](#)

Downloaded from: <https://hdl.handle.net/1887/3181549>

Note: To cite this publication please use the final published version (if applicable).



Acute myeloid leukemia

Lenalidomide added to standard intensive treatment for older patients with AML and high-risk MDS

G. J. Ossenkoppele¹ · D. A. Breems² · G. Stuessi³ · Y. van Norden⁴ · M. Bargetzi⁵ · B. J. Biemond⁶ · P. A von dem Borne⁷ · Y. Chalandon⁸ · J. Cloos¹ · D. Deeren⁹ · M. Fehr¹⁰ · B. Gjertsen¹¹ · C. Graux¹² · G. Huls¹³ · J. J. J. W. Janssen¹ · A. Jaspers¹⁴ · M. Jongen-Lavrencic¹⁵ · E. de Jongh¹⁶ · S. K. Klein¹⁷ · M. van der Klift¹⁸ · M. van Marwijk Kooy¹⁹ · J. Maertens²⁰ · L. Michaux²¹ · M. W. M. van der Poel²² · A. van Rhenen²³ · L. Tick²⁴ · P. Valk¹⁴ · M. C. Vekemans²⁵ · W. J. F. M. van der Velden²⁶ · O. de Weerd²⁷ · T. Pabst²⁸ · M. Manz²⁹ · B. Löwenberg¹⁴ · for the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) and Swiss Group for Clinical Cancer Research (SAKK)

Received: 16 October 2019 / Revised: 24 December 2019 / Accepted: 22 January 2020 / Published online: 4 February 2020
© The Author(s), under exclusive licence to Springer Nature Limited 2020

Abstract

More effective treatment modalities are urgently needed in patients with acute myeloid leukemia (AML) of older age. We hypothesized that adding lenalidomide to intensive standard chemotherapy might improve their outcome. After establishing a safe lenalidomide, dose elderly patients with AML were randomly assigned in this randomized Phase 2 study ($n = 222$) to receive standard chemotherapy (“3 + 7”) with or without lenalidomide at a dose of 20 mg/day 1–21. In the second cycle, patients received cytarabine 1000 mg/m² twice daily on days 1–6 with or without lenalidomide (20 mg/day 1–21). The CR/CRi rates in the two arms were not different (69 vs. 66%). Event-free survival (EFS) at 36 months was 19% for the standard arm versus 21% for the lenalidomide arm and overall survival (OS) 35% vs. 30%, respectively. The frequencies and grade of adverse events were not significantly different between the treatment arms. Cardiovascular toxicities were rare and equally distributed between the arms. The results of the present study show that the addition of lenalidomide to standard remission induction chemotherapy does not improve the therapeutic outcome of older AML patients. This trial is registered as number NTR2294 in The Netherlands Trial Register (www.trialregister.nl).

Introduction

The incidence of acute myeloid leukemia (AML) is significantly rising as a function of age and overall the treatment outcome of therapy in advanced aged patients has remained dismal [1]. Performance status and comorbidities associated with higher age impact substantially on tolerance

of intensive antileukemic chemotherapy while prognostically unfavorable genetic abnormalities increase with age as do antecedent MDS, chronic myelomonocytic leukemia, and myeloproliferative neoplasm [2].

The standard of care for the fit older adult patient still consists of a number of cycles chemotherapy combining an anthracycline and cytosine-arabioside (ARA-C) (3 + 7) resulting in a significant proportion of about 50–60% patients that successfully attain a complete remission (CR) [2]. Unfortunately, such fairly high rates of good response only translate into a 2-year survival of around 15–20% [3]. Modest progress in outcome has been made recently. Dose intensification of daunorubicin results in a better outcome only for the subpopulation of AML patients between 60 and 65 years [4, 5]. Addition of mylotarg to standard induction treatment also offers an advantage for the AML patients between the age of 50 and 70 [6]. In a recent publication it was shown that postinduction OS, EFS, and cumulative incidence of relapse may be significantly better when

Members of the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) and Swiss Group for Clinical Cancer Research (SAKK) are listed below Acknowledgements

Supplementary information The online version of this article (<https://doi.org/10.1038/s41375-020-0725-0>) contains supplementary material, which is available to authorized users.

✉ G. J. Ossenkoppele
g.ossenkoppele@amsterdamumc.nl

Extended author information available on the last page of the article.

lomustine is added to 3 + 7 [7]. Also CPX-351, an encapsulation in nanoscale liposomes of cytarabine and daunorubicin at a synergistic 5:1 molar ratio, has been shown to be superior to 3 + 7 in secondary and therapy related AML of older age [8].

Moreover, reduced intensity allogeneic hematopoietic stem cell transplantation (HSCT) is reasonably well tolerated in terms of early toxicities and is currently broadly applied in patients at ages even over 70, mainly after attainment of CR [9].

We investigated the value of the addition of lenalidomide to standard chemotherapy in a randomized Phase 2 study. Lenalidomide belongs to the class of immunomodulatory drugs, which are orally available compounds, that modulate the immune system and other biologically important targets through antineoplastic, immunomodulatory, and anti-angiogenic properties. Effects both on the malignant clone and the microenvironment have been suggested [10]. In a published small single arm phase 2 study older adults with AML received lenalidomide as monotherapy at 50 mg daily for up to two 28-day cycles followed by maintenance therapy. Overall CR/CRi rate was 30, and 53% in patients completing high-dose lenalidomide with a median duration of 10 months (range, 1 to >17 months) [11]. Main toxicity was myelosuppression. Dosages as low as 10–15 mg given as monotherapy in R/R myeloid malignancies proved not to be effective [12]. Also in combination with ARA-C lenalidomide at a dosage of 10 mg did not appear to result in improved CR over single agent cytarabine [13]. Recently the safety and tolerability of lenalidomide with mitoxantrone, etoposide, and cytarabine (MEC) in relapsed/refractory AML were tested in a Phase I dose-escalation study. The MTD of lenalidomide combined with MEC was 50 mg/day 1–10. Results were promising in 17 patients treated at the MTD of which seven attained CR (41%) [14]. The aforementioned studies were all conducted in patients with relapsed/refractory (R/R) AML. No randomized controlled trials have been performed with lenalidomide in newly diagnosed older adults with AML.

Here we report the results of a Phase 2 randomized study concerning the addition of lenalidomide to standard chemotherapy in 222 patients with newly diagnosed AML or high-risk MDS.

Methods

Patients

Previously untreated patients, 66 years of age or older, with a cytologically confirmed diagnosis of de novo AML (excluding acute promyelocytic leukemia) or with refractory

anemia with excess of blasts and an International Prognostic Scoring System score of 1.5 or higher and a WHO performance score of 2 or less were eligible for inclusion. Patients with secondary AML progressing from antecedent myelodysplasia were also eligible. No previous treatment was allowed except for a short period of hydroxyurea. Exclusion criteria included clinically significant cardiovascular disease, including cerebrovascular accidents (<6 months before randomization), myocardial infarction (<6 months before randomization), unstable angina, New York Heart Association grade 2 or greater congestive heart failure, and serious cardiac arrhythmia requiring medication. Other standard general medical exclusions were also applied (detailed inclusion and exclusion criteria are presented in the Supplementary File 1). The trial was approved by the institutional review boards of all participating institutions. The study was performed in accordance with the Declaration of Helsinki, and all patients provided written informed consent.

Risk classification

Based on the karyotype and molecular genotype of the leukemic cells, patients were classified into prognostic categories according slight modifications of the ELN 2010 as described previously [15].

Study design and chemotherapy

Lenalidomide was provided free of charge by Celgene. The study was divided into two parts. The study started with a randomized dose selection run-in phase with 10 mg/day 1–21, 15 mg/day 1–21, and 20 mg/day 1–21 dose levels of lenalidomide and after evaluation of the toxicity profiles after each dose level the study was continued with lenalidomide at 20 mg/day as an open label randomized Phase 2 trial. A dose limiting toxicity (DLT) was defined as death within 31 days of start of cycle I and before initiation of start of cycle II, irrespective of the cause of death. In the HOVON/SAKK AML 43 the incidence of DLT defined in this way had been 13% [4, 5]. A patient was considered evaluable for DLT if the patients have had started cycle I after registration. A patient was considered to have no DLT if the patient was still alive at day 31 after start of cycle I or at start of cycle II (whichever comes first) The decision rules for dose selection are depicted in the Supplementary File 2.

In the second part of the study the safety, tolerability, and efficacy were assessed at the highest feasible dose lenalidomide. One interim analysis was performed on the primary endpoint according to protocol. Patients were randomly assigned to remission induction regimens with or without

lenalidomide. Cycle I included daunorubicin at 45 mg/m² (3-h infusion on days 1, 2, and 3) and cytarabine at a dose of 200 mg/m² (per continuous infusion on days 1–7) with or without lenalidomide at the assigned dose level. Cycle II contained cytarabine 1000 mg/m² q 12 h via 6 h infusion from day 1 to 6 (12 doses) with or without lenalidomide at 20 mg/day 1–21. Patients could be allografted off protocol according to local policy. MRD analysis and detection was performed as previously described [16].

Statistical analysis

The primary endpoint of the second part of the study is response rate. A patient is considered to have a response if the best response to remission induction therapy (cycle I and/or II) is a CR/CRi. Secondary endpoints are considered as exploratory and included: overall survival (OS), event-free survival (EFS), relapse free survival (RFS), early death (ED), and hematopoietic recovery. The definitions which are standard are according the ELN recommendations [17]. A planned futility interim analysis was incorporated after 100 patients were randomized

At this analysis, the study was to be stopped because of inefficacy if no difference in CR/CRi rate in favor of lenalidomide is to be expected i.e., upper limit of the 80% confidence interval (CI) of the difference in CR rate <15%, which is the case if the observed difference in response rate is <6% in favor of the lenalidomide treatment arm. Otherwise we would consider not to continue as Phase III. Kaplan–Meier survival curves and Cox tests were used to compare the survival distributions between the treatment arms.

Results

The study was activated in 2010 and closed after completion of accrual in 2014. Median FU of patients still alive is 51 months. The number of patients randomized to 10 and 15 mg lenalidomide were 58 and 51, respectively. According to the decision rules of the protocol no excess of DLTs was observed in comparison with the control arm. The same accounted for the 20 mg dosage. A summary of the run-in-phase study with Lenalidomide 10 and 15 mg is provided in the Supplementary Files 3 and 4.

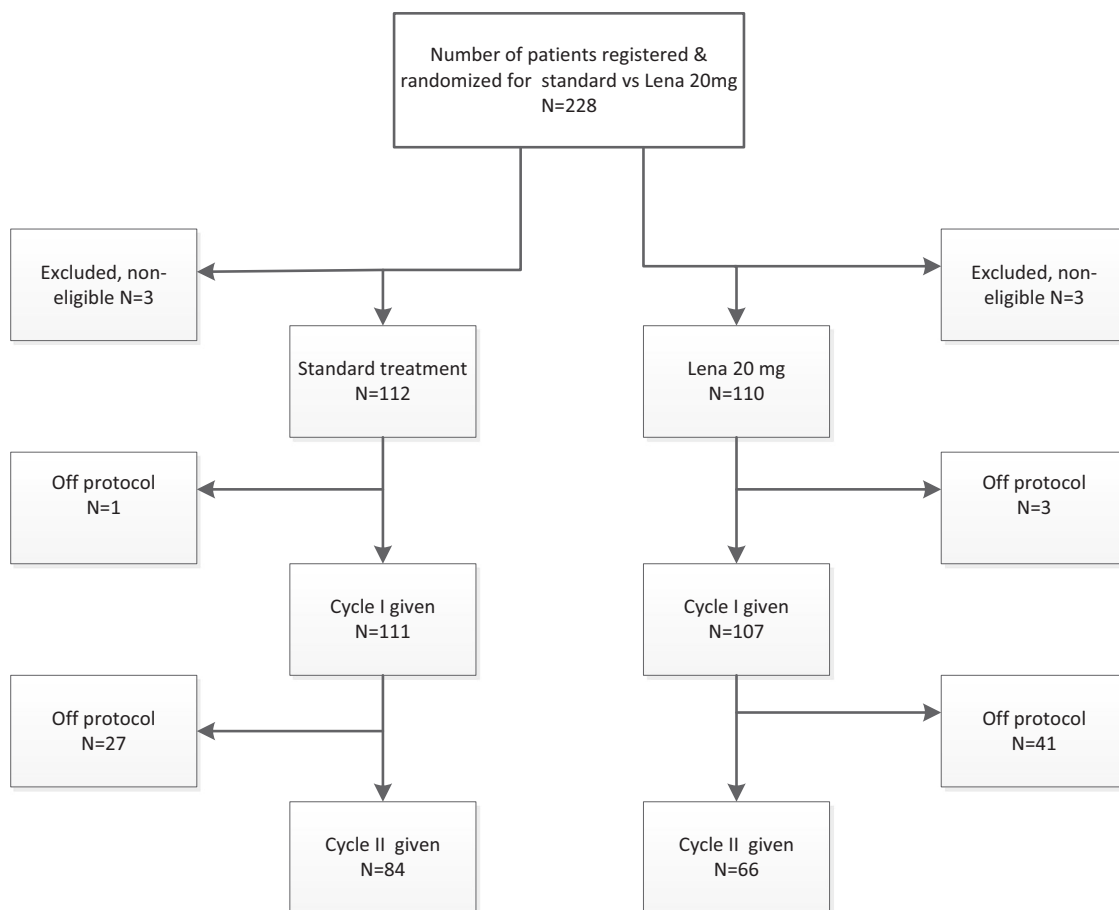


Fig. 1 Consort diagram.

We continued according protocol with lenalidomide 20 mg in the second part of the study. Although the DLT in this population was not reached we decided not to escalate because of toxicity results noted in a parallel HOVON study in young patients (HOVON132, Eudract number: 2013-002843-26) at a dosage of Lenalidomide 20 mg in combination with intensive treatment. The analysis presented here is restricted to the 228 patients randomized for treatment with the 20 mg dose of lenalidomide (CONSORT diagram shown in Fig. 1), from which 222 eligible patients are included in the analyses.

Patients

Patient characteristics at diagnosis by treatment arm are shown in Table 1. Median age of the patients in both arms is 69 years (range 65–84). The arms are well balanced for major prognostic factors, slightly more patients were above 70 years in the investigational arm (39 vs. 29%), but with no difference in mean age. A prior hematological disease was present in 8% of the population.

Treatment, response, and outcome

Of 222 eligible patients, 218 patients received the first treatment cycle and 216 (99%) received full doses of daunorubicin according to the protocol and 214 (98%) received full doses of cytarabine in cycle 1. However only 69 patients out of 107 (64%) completed the full series of doses of lenalidomide according to schedule. The majority of the patients without dosage according to protocol stopped early due to toxicity. This may have been due to the fact that this was not a blinded study and toxicities could be attributed to the experimental drug which is a known phenomenon in non-blinded studies associated already with a relatively substantial level of toxicity. In case a patient prematurely discontinued lenalidomide administration the median numbers of days between first and last dose was 12.

In cycle 2 cytarabine could be administered full dose in 77 of 84 patients (92%) in the standard arm and in 62 of 66 patients (94%) of the experimental arm while lenalidomide was administered according to schedule in 37 of 66 patients (56%). Median number of days given in those patients that stopped early was 12.

Patients assigned to the standard treatment arm and lenalidomide treatment arm respectively showed similar CR/CRi rates on induction 69%; (95% CI: 60–77%) versus 66%; (95% CI: 58–75%). Twenty-one patients in the standard arm versus 12 in the experimental arm received an alloHSCT. There were no significant differences with respect to OS, EFS, RFS, ED between both arms (see Table 2 and Fig. 2). A subanalysis of Lenalidomide

Table 1 Baseline characteristics of patients assigned to intensive induction chemotherapy with or without lenalidomide 20 mg.

	Standard arm	Lenalidomide 20 mg	Total
Sex			
M	71 (63%)	63 (57%)	134 (60%)
F	41 (37%)	47 (43%)	88 (40%)
Age groups			
≤70 years	79 (71%)	67 (61%)	146 (66%)
>70 years	33 (29%)	43 (39%)	76 (34%)
Age			
Mean; SD	69.6; 3.16	70; 3.49	69.8; 3.33
Median; range	69; 66–84	69; 65–81	69; 65–84
WHO performance			
0	52 (46%)	43 (39%)	95 (43%)
1	43 (38%)	55 (50%)	98 (44%)
2	13 (12%)	8 (7%)	21 (9%)
3	0	1 (1%)	1 (0%)
?	4 (4%)	3 (3%)	7 (3%)
Diagnosis			
MDS	12 (11%)	10 (9%)	22 (10%)
AML	100 (89%)	100 (91%)	200 (90%)
Prior HM			
No	104 (93%)	96 (87%)	200 (90%)
Yes	7 (6%)	11 (10%)	18 (8%)
Risk AML (ELN 2010)			
Good	14 (13%)	18 (16%)	32 (14%)
Intermediate	16 (14%)	14 (13%)	30 (14%)
Poor	56 (50%)	56 (51%)	112 (50%)
Very poor	26 (23%)	22 (20%)	48 (22%)
NPM1 mutation			
Neg	67 (60%)	69 (63%)	136 (61%)
Pos	20 (18%)	23 (21%)	43 (19%)
FLT3ITD			
Neg	78 (70%)	82 (75%)	160 (72%)
Pos	10 (9%)	13 (12%)	23 (10%)
EVII overexpression			
Neg	72 (64%)	72 (65%)	144 (65%)
Pos	9 (8%)	12 (11%)	21 (9%)
CEBPA DM			
Neg	70 (63%)	79 (72%)	149 (67%)
Pos	4 (4%)	3 (3%)	7 (3%)
FLT3ITD × NPM1 mutation			
Pos × Pos	7 (6%)	9 (8%)	16 (7%)
Pos × neg	2 (2%)	4 (4%)	6 (3%)
Neg × Pos	11 (10%)	14 (13%)	25 (11%)
Neg × Neg	65 (58%)	65 (59%)	130 (59%)

Gene mutations.

For each parameter: if not 100% the remaining % is unknown.

NPM1 nucleophosmin-1, *FLT3* fms-like tyrosine kinase-3, *CEBPA* CCAAT/enhancer-binding protein alpha, *EVII* ecotropic virus integration 1 gene.

compliant patients showed neither significant differences in comparison to the standard arm in any of the clinical outcome parameters (not shown). Statistically significant

Table 2 Outcome of treatment of patients assigned to intensive induction chemotherapy with or without lenalidomide 20 mg.

Outcomes	Standard treatment	Lena 20 mg	Logistic/cox regression		
			OR/HR	95% CI	P value
Complete remission (CR/CRi) CI	77 (69%)	73 (66%)			
CR/CRi (after cycle I)	54 48%	58 (54%)			
Early death					
Early death (<30 days)	11 (10%)	10 (9%)			
Death within 60 days	20 (20%)	22 (20%)			
OS at 3 years	35% ± 5	30% ± 4	1.01	0.74–1.36	0.96
By age groups					
≤70	41% ± 6	21% ± 7			
>70	38% ± 6	17% ± 6			
EFS at 3 years	19% ± 4	21% ± 4	1.0	0.75–1.33	1.0
RFS at 3 years	24% ± 5	28% ± 5	0.97	0.68–1.39	0.89

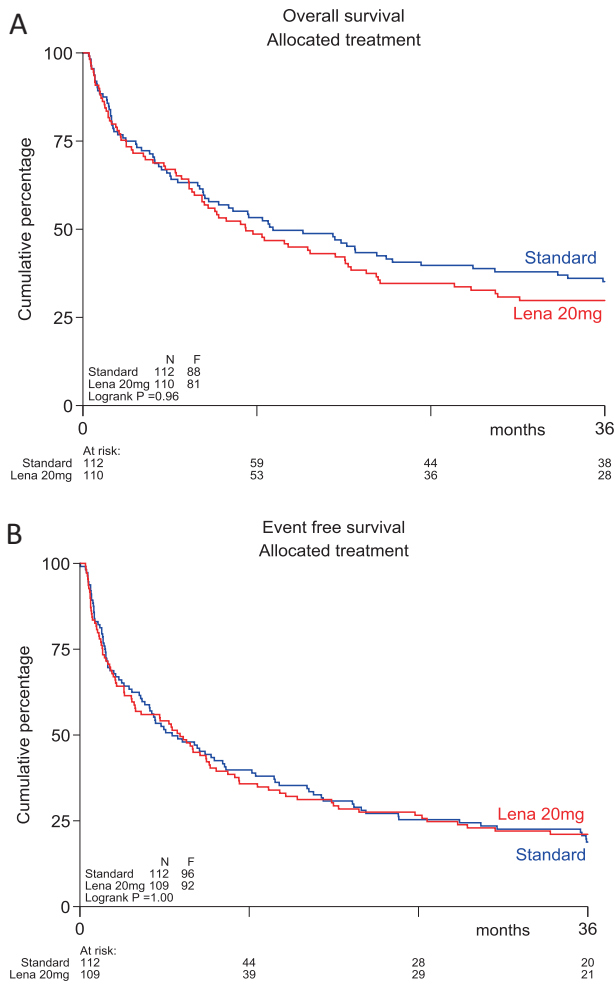


Fig. 2 Effect of addition of lenalidomide to a standard regimen of daunorubicin and cytosine-arabinoside. Shown are OS(2A) and EFS (2B).

differences for OS between patient above and below 70 years of age ($p < 0.001$) as well as between good/intermediate versus poor/very poor risk AML ($p < 0.001$) were apparent (Supplementary Figs. 1 and 2).

Adverse events and hematological recovery

In Supplementary Table 1, the number of adverse events (AEs) in cycles 1 and 2 by diagnosis category, common toxicity criteria (CTC) grade, and arm of randomization are given. The frequencies of grade 3 and 4 CTCs appear generally similar in both. The two treatment arms were comparable with respect to the maximum grade of events and serious AEs (Table 3). A more detailed analysis of events known to be associated with lenalidomide showed no difference in thromboembolic complications (Table 3).

Time to neutrophil or platelet recovery between the two groups did not significantly differ after cycle I nor after cycle II but a trend to delayed recovery was observed in the lenalidomide arm for both neutrophil and platelet regeneration (Fig. 3 and Supplementary Fig 3) and also more nights were spent in the hospital by patients treated with lenalidomide.

Measurable residual disease (MRD)

In 60 patients (29 in the standard arm and 31 in the experimental arm) MRD was assessed. These limited numbers do not allow for a meaningful comparative survival analysis. In the control arm 72% became MRD negative as compared with 81% in the lenalidomide arm. OS at 2 years was 61% for the MRD negative patients and 50% for the MRD positive patients ($p = 0.31$) (Supplementary Fig. 4).

Discussion

Intensive treatment remains the standard of care in older “fit” patients with AML but outcome is much worse as compared with the younger patient. Various previous therapeutic developmental attempts to improve outcome for these patients have failed. The HOVON-SAKK consortium

Table 3 Toxicities in patients assigned to intensive induction chemotherapy with or without lenalidomide during and after Cycle 1 and 2.

	Cycle 1 (<i>n</i> = 111)		significance <i>P</i> = 0.374	Cycle 2 (<i>n</i> = 107)		Significance <i>P</i> = 0.667
	Standard	Lenalidomide 20 mg		Standard	Lenalidomide 20 mg	
Maximum grade events ^a , no. of patients						
0	6	2		3	0	
2	9	6		7	4	
3	74	69		53	46	
4	16	24		13	10	
5	6	6		8	6	
Toxicities of special interest, no. of patients						
Myocardial infarction	0	0		0	2	
CVA	1	0		0	1	
Pulmonary embolism	0	0		0	0	
Thrombosis	3	5		2	1	
Serious adverse events, no. per patient Cycle 1 and 2 combined						
0	71 (63%)	58 (53%)				
1	31 (28%)	40 (36%)				
2	6 (5%)	7 (6%)				
3	3 (3%)	4 (1%)				
4	1 (1%)	1 (1%)				
Outcome last SAE if no. of SAEs >1, no. of patients Cycle 1 and 2 combined						
Resolved	5 (50%)	6 (50%)				
Death	3 (30%)	6 (50%)				
Ongoing at death	2 (20%)	6 (50%)				
No of nights in hospital						
Mean; SD	29;10	32;9		31; 11	30; 11	
Median(range)	28 (13–92)	31 (12–64)		28 (0–70)	31 (2–59)	

^aDetails of toxicities in Supplementary Table 1.

has decided already quite some years ago instead of performing large randomized trials to embark on a new trial design adding promising drugs to a standard chemotherapy backbone in a Phase 2 randomized setting with the possibility to proceed to a phase III study depending on the results defined by strict criteria.

Here we report on the study approach dealing with the question of the added therapeutic value of lenalidomide to standard chemotherapy. Unfortunately, as many other studies conducted in the setting of AML in patients of older age, also the current study failed to demonstrate a clear benefit for the investigational treatment approach. The CR/CRi rates and survival values were similar in both arms.

It is interesting to see how well patients with intermediate and good risk performed. Around 60–70% are alive at 3 years and notably around 20–25% of patients with a poor and very poor risk profile were still alive after 3 years.

Most of these patients are probably cured, a phenomenon that has not been observed in the majority of patients that are treated with low intensity cytotoxic and hypomethylating therapy. These observations underline and confirm the value of intensive treatment in properly selected older adult patients.

Whether lenalidomide should be regarded as an inactive drug in the setting of AML cannot be entirely definitively concluded from the results of the current study. The schedule of only two short cycles of application of lenalidomide in the current study may have been inadequate. It is to be noted that lenalidomide in other treatment indications where it has shown therapeutic activity (e.g., in MDS, myeloma) is usually applied during prolonged intervals. Also the dosage could have been too low although 20 mg day 1–21 in combination with intensive chemotherapy seems quite high. Therefore we cannot exclude the possibility that lenalidomide may exert a beneficial anti-AML effect in case of a

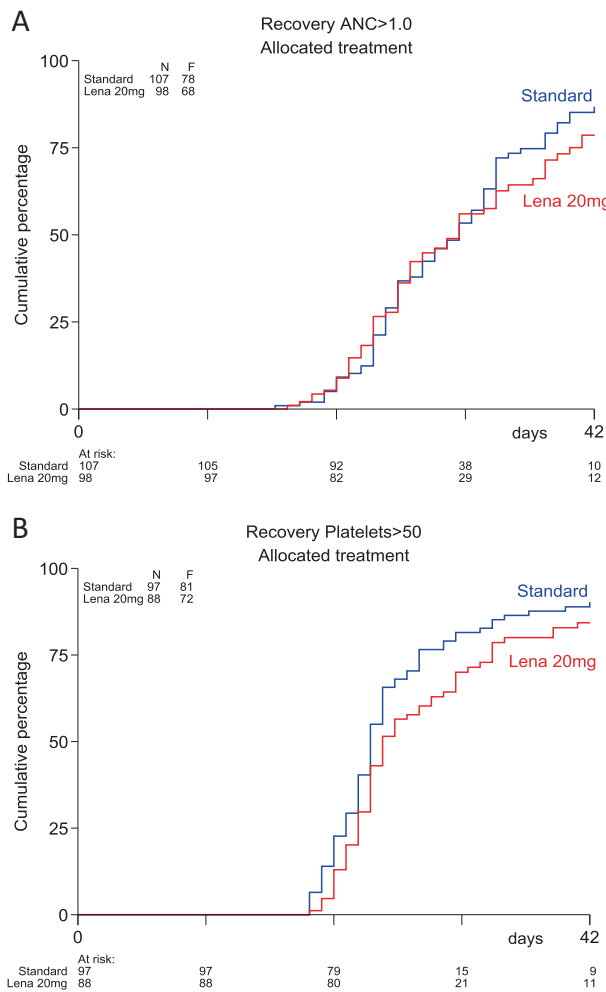


Fig. 3 Recovery time in days to achieve a neutrophil count of $>1 \times 10^9/l$ (3A) and platelet count of $>50 \times 10^9/l$ (3B) in Cycle 1.

regimen of administration that enables both induction and postinduction exposure to the drug. Furthermore we did not evaluate the possibility of a beneficial effect of lenalidomide in the maintenance setting.

Numerous new drugs are currently emerging and suggest new avenues of treatment. Especially the data in unfit patients or relapse/refractory AMLs for the IDH1,2 inhibitors (enasidenib and ivosidenib), FLT3 inhibitors and the bcl2-inhibitor Venetoclax in combination with LDAC or HMAs are very promising and most probably will be game changing for AML treatment [18–22]. Also new immunotherapeutic drugs will most likely enrich our therapeutic arsenal in the near future [23]. Hopefully intelligent designed combinations of these drugs either added to intensive treatment or administered as combo's or triplets will change the prospects for these AML patients who in terms of frequencies represent the highest medical need.

Study design, data analysis, preparation of publication

The study was designed by the Leukemia Working Group of the HOVON/SAKK Cooperative Groups, the HOVON Data Center was responsible for the central datamanagement and YvN performed the analysis of the data. The decision to publish was made by the cooperative group. GO and subsequently BL and YvN produced the first version of the manuscript, which was circulated for comments to the other authors.

Acknowledgements The authors thanks the local and central data managers as well as the HOVON Datacenter Trial team. Dutch Cancer Foundation for financial support. Celgene for free drug supply and financial support to conduct the study.

The Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) and Swiss Group for Clinical Cancer Research (SAKK) D. A. Breems³⁰, Havelange³¹, M-C Vekemans³¹, I. Moors³², F. van Obberg³³, J. A. Maertens³⁴, B. Hodossy³⁵, S. Vansteeweghen³⁵, L. Lammertijn³⁵, D. Deeren³⁶, C. Graux³⁷, A. Sonet³⁷, A. Triffet³⁸, B. T. Gijtsen¹¹, M. Bargetzi⁵, J. Passweg³⁹, D. Heim³⁹, San Giovanni⁴⁰, Georg Stuessi⁴⁰, T. Pabst²⁸, D. Betticher⁴¹, Y. Chalandon⁴², O. Spertini⁴³, M. Gregor⁴⁴, U. Hess⁴⁵, M. Fehr⁴⁵, M. G. Manz⁴⁶, S. K. Klein¹⁷, B. J. Biemond⁶, G. J. Ossenkoppele⁴⁷, A. van de Loosdrecht⁴⁷, J. J. W. M. Janssen⁴⁷, J. W. J. van Esser⁴⁸, M. Van der Klift⁴⁸, R. E. Brouwer⁴⁹, D. Van Lammeren-Venema⁵⁰, M. D. Levin⁵¹, L. W. Tick⁵², M. C. J. C. Legdeur⁵³, G. Huls⁵⁴, E. Vellenga⁵⁴, M. Hoogendoorn⁵⁵, J. H. Veelken⁵⁶, P. A. van dem Borne⁵⁶, H. C. Schouten⁵⁷, O. de Weerd⁵⁸, W. J. F. M. van der Velden⁵⁹, J. Cornelissen¹⁵, M. Jongen-Lavrencic¹⁵, B. Wouters¹⁵, H. G. M. Raaijmakers¹⁵, B. Löwenberg¹⁵, J. Kuball⁶⁰, A. Van Rhenen⁶⁰, M. Van Marwijk Kooy⁶¹

³⁰Ziekenhuis Netwerk Antwerpen, Antwerp, Belgium; ³¹Hôpital St. LucV, Brussels, Belgium; ³²UZ Gent, Gent, Belgium; ³³Hôpital. St Paul Jolimont, Haine, Belgium; ³⁴UZ Gasthuisberg, Leuven, Belgium; ³⁵Citadelle, Liege, Belgium; ³⁶AZ Delta, Roeselare, Belgium; ³⁷CHU UCLNamur (Godinne), Yvoir, Belgium; ³⁸Charleroi-CHU, Charleroi, Belgium; ³⁹University Hospital, Basel, Switzerland; ⁴⁰Ospedale San Giovanni, Bellinzona, Switzerland; ⁴¹Kantonsspital, Fribourg, Switzerland; ⁴²University Hospital (HUG), Geneva, Switzerland; ⁴³University Hospital, Lausanne, Switzerland; ⁴⁴Kantonsspital, Luzern, Switzerland; ⁴⁵Kantonsspital, St. Gallen, Switzerland; ⁴⁶University Hospital, Zurich, Switzerland; ⁴⁷University Medical Center, location VUMC, Amsterdam, Netherlands; ⁴⁸Amphia, Breda, Netherlands; ⁴⁹RDGG, Delft, Netherlands; ⁵⁰Hagaziekenhuis, The Hague, Netherlands; ⁵¹ASZ, Dordrecht, Netherlands; ⁵²Maxima MC, Eindhoven, Netherlands; ⁵³Medisch Spectrum Twente, Enschede, Netherlands; ⁵⁴UMCG, Groningen, Netherlands; ⁵⁵MCL, Heerlen, Leeuwarden, Netherlands; ⁵⁶LUMC, Leiden, Netherlands; ⁵⁷MUMC, Maastricht, Netherlands; ⁵⁸St. Antonius Hospital, Nieuwegein, Netherlands; ⁵⁹Radboudumc, Nijmegen, Netherlands; ⁶⁰University Hospital Utrecht, Utrecht, Netherlands; ⁶¹Isala, Zwolle, the Netherlands

Compliance with ethical standards

Conflict of interest The authors declare no relevant competing financial interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

- Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. *N Engl J Med*. 2015;373:1136–52.
- Ossenkoppele G, Löwenberg B. How I treat the older patient with acute myeloid leukemia. *Blood*. 2015;125:767–74.
- Krug U, Gale RP, Berdel WE, Müller-Tidow C, Stelljes M, Metzeler K, et al. Therapy of older persons with acute myeloid leukaemia. *Leuk Res*. 2017;60:1–10.
- Löwenberg B, Ossenkoppele GJ, van Putten W, Schouten HC, Graux C, Ferrant A. Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON) et al. Therapy of older persons with acute myeloid leukaemia. *Leuk Res*. 2017;60:1–10.
- Löwenberg B, Ossenkoppele GJ, van Putten W, Schouten HC, Graux C, Ferrant A. Swiss Group for Clinical Cancer Research (SAKK) Collaborative Group et al. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med*. 2009;361(Sep):1235–48.
- Castaigne S, Pautas C, Terré C, Raffoux E, Bordessoule D, Bastie JN, Acute Leukemia French Association, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. *Lancet*. 2012;379:1508–16.
- Pigneux A, Béné MC, Salmi LR, Dumas PY, Delaunay J, Bonmati C, French Innovative Leukemia Organization, et al; Improved survival by adding lomustine to conventional chemotherapy for elderly patients with aml without unfavorable cytogenetics: results of the LAM-SA 2007 FILO trial. *J Clin Oncol*. 2018; JCO2018787366. <https://doi.org/10.1200/JCO.2018.78.7366>.
- Lancet JE, Uy GL, Cortes JE, Newell LF, Lin TL, Ritchie EK, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. *J Clin Oncol*. 2018;36:2684–92.
- Levin-Epstein R, Oliai C, Schiller G. Allogeneic hematopoietic stem cell transplantation for older patients with acute myeloid leukemia. *Curr Treat Options Oncol*. 2018;19:63.
- Kotla V, Goel S, Nischal S, Heuck C, Vivek K, Das B, et al. Mechanism of action of lenalidomide in hematological malignancies. *J Hematol Oncol*. 2009;2:36 <https://doi.org/10.1186/1756-8722-2-36>
- Fehniger TA, Uy GL, Trinkaus K, Nelson AD, Demland J, Abboud CN, et al. A phase 2 study of high-dose lenalidomide as initial therapy for older patients with acute myeloid leukemia. *Blood*. 2011;117:1828–33.
- Zeidan AM, Smith BD, Carraway HE, Gojo I, DeZern A, Gore SD. A phase 2 trial of high dose lenalidomide in patients with relapsed/refractory higher-risk myelodysplastic syndromes and acute myeloid leukaemia with trilineage dysplasia. *Br J Haematol*. 2017;176:241–7.
- Griffiths EA, Brady WE, Tan W, Vigil CE, Thompson JE, Ford LA, et al. A phase I study of intermediate dose cytarabine in combination with lenalidomide in relapsed/refractory acute myeloid leukemia. *Leuk Res*. 2016;43:44–8.
- DeAngelo DJ, Brunner AM, Werner L, Avigan D, Fathi AT, Sperling AS, et al. A phase I study of lenalidomide plus chemotherapy with mitoxantrone, etoposide, and cytarabine for the reinduction of patients with acute myeloid leukemia. *Am J Hematol*. 2018;93:254–61.
- Löwenberg B, Pabst T, Maertens J, van Norden Y, Biemond BJ, Schouten HC, Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) and Swiss Group for Clinical Cancer Research (SAKK) et al. Therapeutic value of clofarabine in younger and middle-aged (18–65 years) adults with newly diagnosed AML. *Blood*. 2017;129:1636–45.
- Terwijn M, van Putten WL, Kelder A, van der Velden VH, Brooimans RA, Pabst T, et al. High prognostic impact of flow cytometric minimal residual disease detection in acute myeloid leukemia: data from the HOVON/SAKK AML 42A study. *J Clin Oncol*. 2013;31:3889–9.
- Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129:424–47.
- Stein EM, DiNardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood*. 2017;130:722–31.
- DiNardo CD, Stein EM, de Botton S, Roboz GJ, Altman JK, Mims AS, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med*. 2018;378:2386–98.
- Cortes J, Perl AE, Döhner H, Kantarjian H, Martinelli G, Kovacovics T, et al. Quizartinib, an FLT3 inhibitor, as monotherapy in patients with relapsed or refractory acute myeloid leukaemia: an open-label, multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2018;19:889–903.
- Wei AH, Strickland SA Jr, Hou JZ, Fiedler W, Lin TL, Walter RB, et al. Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: results from a Phase Ib/II Study. *J Clin Oncol*. 2019;JCO1801600. <https://doi.org/10.1200/JCO.18.01600>.
- DiNardo CD, Pratz K, Pullarkat V, Jonas BA, Arellano M, Becker PS, et al. Venetoclax combined with decitabine or azacitidine in treatment-naïve, elderly patients with acute myeloid leukemia. *Blood*. 2019;133:7–17.
- Beyar-Katz O, Gill S. Novel approaches to acute myeloid leukemia immunotherapy. *Clin Cancer Res*. 2018;24:5502–15.

Affiliations

G. J. Ossenkoppele¹ · D. A. Breems² · G. Stuessi³ · Y. van Norden⁴ · M. Bargetzi⁵ · B. J. Biemond⁶ · P. A von dem Borne⁷ · Y. Chalandon⁸ · J. Cloos¹ · D. Deeren⁹ · M. Fehr¹⁰ · B. Gjertsen¹¹ · C. Graux¹² · G. Huls¹³ · J. J. J. W. Janssen¹ · A. Jaspers¹⁴ · M. Jongen-Lavrencic¹⁵ · E. de Jongh¹⁶ · S. K. Klein¹⁷ · M. van der Klift¹⁸ · M. van Marwijk Kooy¹⁹ · J. Maertens²⁰ · L. Michaux²¹ · M. W. M. van der Poel²² · A. van Rhenen²³ · L. Tick²⁴ · P. Valk¹⁴ · M. C. Vekemans²⁵ · W. J. F. M. van der Velden²⁶ · O. de Weerdt²⁷ · T. Pabst²⁸ · M. Manz²⁹ · B. Löwenberg¹⁴ · for the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) and Swiss Group for Clinical Cancer Research (SAKK) · D. A. Breems³⁰ · Havelange³¹ · M-C Vekemans³¹ · I. Moors³² · F. van Obberg³³ · J. A. Maertens³⁴ · B. Hodossy³⁵ · S. Vansteenweghen³⁵ · L. Lammertijn³⁵ · D. Deeren³⁶ · C. Graux³⁷ · A. Sonet³⁷ ·

A. Triffet³⁸ · B. T. Gjertsen¹¹ · M. Bargetzi⁵ · J. Passweg³⁹ · D. Heim³⁹ · San Giovanni⁴⁰ · Georg Stuessi⁴⁰ · T. Pabst²⁸ · D. Betticher⁴¹ · Y. Chalandon⁴² · O. Spertini⁴³ · M. Gregor⁴⁴ · U. Hess⁴⁵ · M. Fehr⁴⁵ · M. G. Manz⁴⁶ · S. K. Klein¹⁷ · B. J. Biemond⁶ · G. J. Ossenkoppele⁴⁷ · A. van de Loosdrecht⁴⁷ · J. J. W. M. Janssen⁴⁷ · J. W. J. van Esser⁴⁸ · M. Van der Klift⁴⁸ · R. E. Brouwer⁴⁹ · D. Van Lammeren-Venema⁵⁰ · M. D. Levin⁵¹ · L. W. Tick⁵² · M. C. J. C. Legdeur⁵³ · G. Huls⁵⁴ · E. Vellenga⁵⁴ · M. Hoogendoorn⁵⁵ · J. H. Veelken⁵⁶ · P. A. von dem Borne⁵⁶ · H. C. Schouten⁵⁷ · O. de Weerd⁵⁸ · W. J. F. M. van der Velden⁵⁹ · J. Cornelissen¹⁵ · M. Jongen-Lavrencic¹⁵ · B. Wouters¹⁵ · H. G. M. Raaijmakers¹⁵ · B. Löwenberg¹⁵ · J. Kuball⁶⁰ · A. Van Rhenen⁶⁰ · M. Van Marwijk Kooy⁶¹

¹ Amsterdam University Medical Center, location VUMC, Amsterdam, Netherlands

² Netwerk Antwerpen, Antwerp, Belgium

³ Bellinzona-IOSI, Bellinzona, Switzerland

⁴ HOVON Data Center, Erasmus MC- Department of Hematology, Rotterdam, The Netherlands

⁵ Aarau- Kantonsspital, Aarau, Switzerland

⁶ Amsterdam University Medical Center, location AMC, Amsterdam, Netherlands

⁷ Leiden University Medical Center, Leiden, Netherlands

⁸ University Hospital and University of Geneva, Genève, Switzerland

⁹ Roeselare-AZ Delta, Roeselare, Belgium

¹⁰ St Gallen-Kantonsspital, St. Gallen, Switzerland

¹¹ Haukeland University Hospital, Bergen (N), Norway

¹² Yvoir-MontGodinne, Yvoir, Belgium

¹³ University Medical Center, Groningen, Netherlands

¹⁴ Hôpital Citadelle, Liège (B), Belgium

¹⁵ Erasmus University Medical Center, Rotterdam, Netherlands

¹⁶ Dordrecht ASZ, Dordrecht, Netherlands

¹⁷ Meander Medical Center, Amersfoort, Netherlands

¹⁸ Amphia-Breda, Breda, Netherlands

¹⁹ Isala Hospital, Zwolle, Netherlands

²⁰ Hospital Gasthuisberg, Leuven (B), Belgium

²¹ Center for Human Genetics, KU Leuven and University Hospitals Leuven, Leuven, Belgium

²² Maastricht University Medical Center, Maastricht, Netherlands

²³ UMC Utrecht, Utrecht, Netherlands

²⁴ MaximaMC Eindhoven, Eindhoven, Netherlands

²⁵ Hôpital St Luc, Bruxelles, Belgium

²⁶ Radboudumc Nijmegen, Nijmegen, Netherlands

²⁷ St Antonius Hospital, Nieuwegein, Netherlands

²⁸ Department of Oncology, University Hospital, Inselspital and University of Bern, Bern, Switzerland

²⁹ University Hospital, Zurich, Switzerland