Real-world experience with decitabine as a first-line treatment in 306 elderly acute myeloid leukaemia patients unfit for intensive chemotherapy

CANDONI ANNA (ORCID ID: 0000-0003-4436-1310)

BORLENGHI ERIKA (ORCID ID: 0000-0002-4666-3817)

LATAGLIATA ROBERTO (ORCID ID: 0000-0002-7741-862X)

REAL-WORD EXPERIENCE WITH DECITABINE AS A FIRST-LINE TREATMENT IN 306 ELDERLY ACUTE MYELOID LEUKAEMIA PATIENTS UNFIT FOR INTENSIVE CHEMOTHERAPY.

Running Title: First-line decitabine in elderly patients with AML

Monica Bocchia [1], Anna Candoni [2], Erika Borlenghi [3], Marzia Defina [1], Carla Filì [2], Chiara Cattaneo [3], Vincenzo Sammartano [1], Renato Fanin [2], Margherita Sciumè [3], Anna Sicuranza [1], Silvia Imbergamo [4], Marta Riva [5], Nicola Fracchiolla [6], Roberto Latagliata [7], Emanuela Caizzi [8], Francesco Mazziotta [9], Giulia Alunni [10], Eros Di Bona [11], Monica Crugnola [12], Marianna Rossi [13], Ugo Consoli [14], Giulia Fontanelli [15], Giuseppina Greco [16], Gianpaolo Nadali [17], Francesco Rotondo [18], Elisabetta Todisco [19], Catia Bigazzi [20], Enrico Capochiani [21], Alfredo Molteni [22], Massimo Bernardi [23], Monica Fumagalli [24], Michela Rondoni [25], Barbara Scappini [26], Anna Ermacora [27], Federico Simonetti [28], Michele Gottardi [29], Daniela Lambertenghi Deliliers [30], Maria Grazia Michieli [31], Claudia Basilico [32], Carlotta Galeone [33], Claudio Pelucchi [33], Giuseppe Rossi [3]

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[1] Unità di Ematologia, Azienda Ospedaliera Universitaria Senese e Università di Siena, Siena, Italy
[2] Clinica Ematologica, Centro Trapianti e Terapie Cellulari, Azienda Sanitaria Universitaria Integrata, Udine, Italy
[3] UO Ematologia, ASST Spedali Civili di Brescia, Brescia, Italy
[4] Ematologia ed Immunologia Clinica, Azienda Ospedaliero-Universitaria, Padova, Italy
[5] S.C. Ematologia, Dipartimento di Ematologia e Oncologia, Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy
[6] Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Italy
[7] Ematologia - Dipartimento di Biotecnologie Cellulari ed Ematologia, Università Sapienza, Roma, Italy.
[8] S.C Ematologia Clinica, Ospedale Maggiore, Azienda Sanitaria Universitaria Integrata, Trieste, Italy
[9] Dipartimento di Oncologia, dei Trapianti e delle Nuove Tecnologie, Sezione di Ematologia, Università di Pisa, Pisa, Italy
[10] S.C. Oncoematologia con Autotrapianto, Dipartimento di Medicina e Specialità Mediche, University of Perugia, Perugia, Italy
[11] Unità Operativa Ematologia, Ospedale S.Bortolo, Vicenza, Italy
[12] Divisione di Ematologia, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy
[13] Cancer Center - IRCCS Humanitas Research Hospital, Rozzano, Milano, Italy
[14] UOC Ematologia, ARNAS Garibaldi, Catania, Italy
[15] UOC Oncologia, UOS Ematologia, Ospedale San Giuseppe, Empoli, Italy
[16] Ospedale Cardinale G.Panico, Tricase, Italy
[17] UOC Ematologia, Azienda Ospedaliera Universitaria Integrata, Policlinico GB Rossi, Verona, Italy
[18] Unità di Ematologia, Ospedale Infermi, Rimini, Italy
[19] Divisione di Onco-Ematologia, IEO Istituto Europeo di Oncologia IRCCS, Milano, Italy
[20] UOC Ematologia e Terapia Cellulare, Ospedale C. e G. Mazzoni, Ascoli Piceno, Italy
[21] UOC Ematologia Aziendale, Azienda Toscana Nord-Ovest, Livorno, Italy
[22] UOC Ematologia, ASST Cremona, Italy
[23] UO Ematologia e Trapianto Midollo Osseo, IRCCS Istituto Scientifico Universitario San Raffaele, Milano, Italy
[24] UO Ematologia e CTA, ASST Monza, Ospedale San Gerardo, Monza, Italy
[25] UOC Ematologia, Azienda Unità Sanitaria Locale della Romagna, Ravenna, Italy
[26] Dipartimento di Ematologia, Ospedale Careggi, Firenze, Italy
[27] UOC Medicina Interna, Azienda Ospedaliera S. Maria Angeli, Pordenone, Italy
[28] UOC Ematologia Aziendale, Ospedale Versilia, Azienda Toscana Nord-Ovest, Lido Di Camaiore, Lucca, Italy
[29] UOC Ematologia, Azienda ULSS9, Ospedale Ca' Foncello, Treviso, Italy
[30] ASST Santi Paolo e Carlo, Presidio Ospedale San Paolo, Milano, Italy

[31] S.O.S. Terapia Cellulare e Chemioterapia Alte Dosi, Centro Riferimento Oncologico, Aviano, Italy
[32] ASST dei Sette Laghi Ospedale di Circolo, Varese, Italy
[33] Dipartimento di Scienze Cliniche e di Comunità, Università di Milano, Milano, Italy

Corresponding authors: Dr Anna Candoni and Prof. Monica Bocchia

Clinica Ematologica, Azienda Sanitaria Universitaria Integrata di Udine e Università di Udine

Ple Santa Maria Misericordia, 33100 Udine

E-mail: anna.candoni@asuiud.sanita.fvg.it

Unità di Ematologia, Azienda Ospedaliera Universitaria Senese e Università di Siena

Viale Bracci, 53100 Siena, Italy

Tel: +39-0577-586740

E-mail: bocchia@unisi.it

Abstract

Despite widespread use of decitabine to treat acute myeloid leukemia (AML), data on its effectiveness and safety in the real-world setting are scanty. Thus, to analyze the performance of Decitabine in clinical practice, we pooled together patient-level data of three multicentric observational studies conducted since 2013 throughout Italy, including 306 elderly AML patients (median age 75 years), unfit for intensive chemotherapy, treated with first-line decitabine therapy at the registered schedule of 20 mg/m^2/iv daily for 5 days every 4 weeks. Overall response rate (ORR), overall survival (OS) curves and multivariate hazard ratios (HR) of all-cause mortality were computed. Overall, 1940 cycles of therapy were administered (median, 5 cycles/patient). A total of 148 subjects were responders and, therefore, ORR was 48.4%. Seventy-one patients (23.2%) had Complete remission, 32 (10.5%) had Partial Remission and 45 (14.7%) had Hematologic improvement (HI). Median OS was 10 months for patients with favourable-intermediate cytogenetic risk and 6-months for those with adverse cytogenetic risk. Median RFS after CR was 10.9 months (95% CI: 8.7-16.0). In multivariate analysis, mortality was higher in patients with adverse cytogenetic risk (HR=1.58; 95% CI: 1.13-2.21) and increased continuously with WBC count (HR=1.12; 95% CI: 1.06-1.18). A total of 183 infectious adverse events occurred in 136 patients mainly (>90%) within the first 5 cycles of therapy. This pooled-analysis of clinical care studies confirmed, outside of clinical trials, the effectiveness of decitabine as first-line therapy for AML in elderly patients unfit for intensive chemotherapy. An adverse cytogenetic profile and a higher WBC count at diagnosis were , in this real life setting, unfavourable predictors of survival.

Key words: acute myeloid leukemia; decitabine; first line therapy; unfit patients.

Introduction

About 18,000 new AML cases are diagnosed every year in Europe.[1] The incidence rises steeply with age, with a median age at onset around 65 years in Europe and a peak in incidence occurring after age 75.[1,2] Therefore, AML is primarily a disease of ageing subjects. Further, elderly patients with AML have a poorer prognosis than younger patients. According to the SEER registry, during the period 2008-2014, 5-year survival rates for AML were 45.6% for patients younger than 65 years, 7.1% for those aged ≥65 years and 3.0% for patients aged 75 years or more.[3] The poor outcome for older patients reflects the increased likelihood of adverse patient and disease-related factors including, among others, comorbidities, previous hematologic diseases and cytogenetics.[4,5]

Limited treatment options are available for elderly AML patients considered unfit to standard chemotherapy. Decitabine is a hypomethylating agent which selectively inhibits DNA methyltransferase, increasing the expression of silenced tumor suppressor genes and promoting apoptosis of leukemic blasts.[6,7] Approved since 2006 in the USA to treat myelodysplastic syndrome and since 2012 in the EU with an indication for treatment of adult AML patients who are not candidates for standard induction chemotherapy, it showed improved response rates as compared with standard available therapies and no major safety issues in clinical trials conducted in elderly AML patients.[8,9]Real-World (RW) studies are needed to confirm and support clinical studies results in unselected and heterogenous populations of routinely treated patients, in order to translate clinical trials into clinical practice (so called efficacy-effectiveness gap).[10,11] Despite widespread use of decitabine to treat AML, RW data based on the registered treatment schedule (20 mg/m^2 daily for 5 days) are very scanty. [12-17] With the aim to address this crucial topic for clinical practice, we pooled together patient-level data of three Italian multicentric observational studies on

elderly AML patients to assess the clinical effectiveness and safety of front-line decitabine therapy in a uniquely large RW dataset.

Patients and methods

Detailed information on the main characteristics of the studies is given in **Supplementary Table 1.** Briefly, the first study included 101 patients recruited in Lombardy, northern Italy, by the Rete Ematologica Lombarda (REL) Group, the second one was based on 74 patients recruited in north-eastern Italy and the third one included 131 patients recruited in central and southern Italy. A total of 306 AML patients (aged ≥65 years) were thus included in this analysis.[12,14,15] They were administered decitabine as first line treatment for AML at the registered schedule of 20 mg/m^2 daily for 5 days every 4 weeks, until AML progression. All patients were unfit to intensive chemotherapy for one or more of this characteristics: a total of 165 (54%) patients were >75 years old, 47 (15%) others had relevant comorbidities and 94 (31%) were considered unable to comply with intensive chemotherapy by the physician according to the recent GITMO/SIES/SIE published guidelines.[18] The median follow-up time, computed according to Schemper and Smith method, was 12.4 months.[19]

Selected clinical information and laboratory and cytogenetic assessments were collected at AML diagnosis by each participating study centre. Common information was available for date and age at AML diagnosis, de novo or secondary AML, white blood cell (WBC) count and Medical Research Council (MRC) cytogenetic classification.[20] Further, treatment and follow-up information including date at starting decitabine, dose, number of treatment cycles, response to therapy, date of relapse/loss of response, occurrence of adverse events, date of death or last (alive) contact and cause of death was also available in all studies.

Information on response to decitabine was categorized as: i) complete remission (CR), including CR with incomplete blood count recovery (CRi); ii) partial response (PR), defined

according to the 2017 European LeukemiaNet (ELN) recommendations; iii) haematological improvement (HI); iv) no response (including stable disease and disease progression).[4,21] Infectious adverse events occurring during follow-up were registered in all studies. Data on related hospitalizations and on other types of adverse events were available for subsets of patients.

All studies involved in this pooled analysis were approved by Local Ethics Committees/institutional review boards and were conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients.

Statistical analyses. In the analyses on response to treatment, overall response rate (ORR) was computed by including CR, PR and HI. Overall survival (OS) and relapse free survival (RFS) were analysed using Kaplan-Meier product-limit survival curve estimates and log-rank tests for comparison between groups. OS was defined as the time from date of first decitabine treatment cycle for AML to the date of death due to any cause (events) or last follow-up (censored). RFS was defined as the time from CR to the date of relapse or death due to any cause (events), or last follow-up (censored). The proportional hazards assumption was tested by including time-dependent effects in the model, and no violation was found. Hazard ratios (HR) of all-cause mortality and the corresponding 95% confidence intervals (CI) were estimated using Cox proportional hazards models including terms for age, study, AML type (de novo vs. secondary), MRC cytogenetic classification and white blood cell (WBC) count. Data analyses were conducted using SAS v.9.4 (SAS Institute, Cary, NC) and STATA v.15 (StataCorp, College Station, TX).

Results

Table 1 shows the baseline characteristics of patients enrolled in the study, together with the corresponding median OS. Age of patients enrolled ranged between 65 and 90 years,

with a mean age of 75.1 years (SD: 4.7; median: 75 years). A total of 124 out of 306 patients (40.5%) had secondary AML. Available molecular and cytogenetic data at diagnosis are reported in **Supplementary Table 2.** MRC cytogenetic classification was favourable for 11 (3.6%), intermediate for 154 (50.3%) and adverse for 93 (30.4%) subjects, while 48 (15.7%) subjects could not be classified. AML patients were divided in quartiles of white blood cell (WBC) count at enrolment; median WBC count was 4530 /µL and the fourth (highest) quartile level included patients with ≥17,100 leukocytes/µL. BM blasts were higher than 30% in 128 out of 172 (74.4%) patients with information available.

Information on response to decitabine therapy in 306 AML patients is given in **Table 2**. Overall, 1940 therapy cycles were administered, with a mean of 6.3 (SD: 5.4) and a median of 5 cycles per patient (range: 1-31 cycles). A total of 148 subjects were responders and, therefore, ORR was 48.4%. Seventy-one patients (23.2%) had CR, 32 (10.5%) had PR and 45 (14.7%) had HI. A total of 158 patients (51.6%) were non-responders. The median time to achieve a CR was 121 days (range: 29-504 days). In a multivariate analysis, none of the baseline characteristics considered, including age, AML type, MRC cytogenetic classification and WBC count, was significantly associated to CR.

Out of 306 patients, 179 (58.5%) died due to any cause. Disease progression was the main cause of death (110 out of 179 deaths, 61.5%). Median OS was 10.0 (95% CI, 7.9-11.9) for the patients with favourable-intermediate cytogenetic risk profile, and 6-months for those with adverse cytogenetic profile; 1-year and 2-years OS were 62.4%, 42.7% and 20.6%, respectively **(Figure 1A**), while median RFS after CR was 10.9 months (95% CI: 8.7-16.0) (**Figure 1B**). Median OS tended to decrease with increasing age (from 12.5 months at age <70 to 8.7 months at age ≥80 years), with high WBC count (from median OS of 11.4 and 12.6 months, respectively, in the two lowest quartiles of WBC to 7.2 months in the highest one),

but univariate log-rank test did not show significant differences between groups (**Table 1**). When the "favorable" and "intermediate" MRC cytogenetic groups were considered together (median OS = 11.6 months) and compared to the "adverse" category (median OS = 7.9 months), however, a significant difference was found (log-rank test p-value = 0.02) (Figure 2). **Figure 3** shows the survival curves according to response to decitabine therapy. The median OS was 22.1 months in patients achieving a CR.

Table 3 reports the HR and their 95% CI for the association between baseline characteristics and OS. The multivariate Cox model showed a significantly increased mortality in patients with adverse as compared to favorable/intermediate cytogenetic classification (HR=1.58; 95% CI: 1.13-2.21), as well as for an increase in WBC count (HR=1.12; 95% CI: 1.06-1.18, for a continuous increase equal to the interquartile range, i.e. 15,300 leukocytes/µL). No significant differences in survival emerged according to age at AML diagnosis, with HRs of 1.07 (95% CI, 0.76-1.51) for age 75-79 years and 1.31 (95% CI, 0.88-1.96) for age ≥80 as compared to age <75 years nor secondary vs de novo AML (HR=1.11; 95% CI: 0.81-1.50). Two additional analyses based on the same models were conducted (data not shown): the first one compared subcategories of unfit patients, and found a similar survival in patients that were evaluated unable to comply with intensive chemotherapy by the physician's judgement as compared to objectively defined subgroups of unfit patients (i.e., age >75 years and/or comorbidities, HR=1.21; 95% CI: 0.73-2.02) [18]; the second one considered the role of BM blasts on survival in 172 patients with information available, reporting a multivariate HR of 1.53 (95% CI: 0.93-2.49) in patients with BM blasts >30% as compared to ≤30%.

At relapse or progression of the AML, according to the unfitness and age (median 75 years) of this population, only 4 patients received polychemotherapy (cytarabine + anthracycline ±

fludarabine and G-CSF) while the majority of cases had received only supportive care ± hydroxyurea or mercaptopurine with palliative intent. Only 2 patients (67 and 69 years), both in 1CR, received an allogeneic stem cell transplantat and 1 died of TRM.

Table 4 reports the number and type of adverse events occurring in AML patients treated with decitabine. There were 183 infectious adverse events, occurring in 136 patients (out of 306, 44.4%), during 1940 therapy cycles. Overall, a mean number of 0.60 infectious adverse events per patient were reported. Pneumonia was the most frequent type of infectious adverse event (n=76, 41.5% of cases), followed by fever of unknown origin (n=39, 21.3%), sepsis (n=35, 19.1%) and other types of infection (n=33, 18.0%). Eighty-four (45.9%) infectious events occurred in patients younger than 75 at AML diagnosis, 63 (34.4%) in those aged 75-79 and 36 (19.7%) in those aged ≥80 years. In a subgroup of 169 (55.2%) patients with available information on therapy cycle at occurrence of infectious adverse event, 70 events were reported during the first 2 cycles (on a total of 302 cycles, 23.2%), 37 during cycles 3-5 (on a total of 282 cycles, 13.1%) and 9 during subsequent cycles (on a total of 405, 2.2%). Also, information on hospitalization was available for 102 infectious adverse events: in 86 of those (84.3%), hospitalization was required. Fifty-five hospitalizations occurred during the first 2 cycles, 21 during cycles 3-5 and 8 during subsequent cycles (in presence of 2 missing data on cycle at hospitalization). For 131 (42.8%) patients, information on other (non-infectious) adverse events was available. In this subgroup, 86 such events were reported during 921 therapy cycles (9.3%), with a mean of 0.66 events per patient.

Discussion

The data reported in this study represent the largest published set of "real world" (RW) data on decitabine registered use for elderly AML patients unfit for chemotherapy. In the last years some clinical trials examined the efficacy and safety of first-line decitabine therapy in elderly AML patients but only one randomized phase III clinical trial is available.[8] A phase II multicentric US study, based on 55 subjects aged ≥60 years (median age 74) with a median of 3 treatment cycles, reported a CR in 24% of patients, a median OS of 7.7 months and a 6-month survival rate of 60%.[9] Another phase II study was conducted in Europe and included 227 AML patients aged >60 years (median age 72).[22] CR was attained by 13.2% and PR by 12.3% of patients. Since another 26.4% of patients obtained an improvement, the overall best response rate was 52.4%. In this group of 227 patients, median OS was 5.5 months and 1-year and 2-years survival rates were 28% and 13%, respectively. The only available phase III randomized trial conducted in 15 countries reported data of 485 newly diagnosed AML patients aged ≥65 years (median age 73), assigned to decitabine (n=242) or supportive care or low-dose cytarabine therapy (n=243).[8] With reference to decitabine patients, on a median of 4 therapy cycles, CR rate was 15.7%. This increased to 25.6% when CRi was included, while PR was achieved by 2.5% of decitabine patients. Median OS was 7.7 months in the decitabine vs. 5.0 months in the comparison group.

Though randomized clinical trials are the "gold standard" to demonstrate the efficacy and tolerability of a treatment, they generally entail several inclusion and/or exclusion criteria and thus subjects enrolled in the trials are often not representative of the general patient population. For example, with reference to AML trials, recruited patients may have more favorable features (e.g., younger age, better PS, less comorbidities, favorable cytogenetics, etc.) and thus different outcomes than patients in routine clinical care. [23,24] It is therefore

crucial to consider real-world (RW) results besides those of clinical trials. Still, extensive data on RW decitabine use for AML in the elderly, under the registered treatment schedule of 20 mg/m^2 daily for 5 days every 4 weeks, are lacking. Only recently, a Korean retrospective study, based on 80 AML cases, reported a CR in 29% of patients and a median OS of 10.2 months.[17] Our results from this much larger Italian pooled analysis, including over 300 AML elderly patients (median age 70 years), report a CR in 23.2% of patients and a median OS of 10.0 months, in broad agreement with the Korean observational investigation. Also, our findings are comparable or, if any, more favorable than those reported in clinical trials on decitabine treatment. In particular, a higher median OS emerged in this study (i.e., 10.0 months) than in most clinical trials. Of note, the median survival in patients achieving a CR was 22.1 months. Moreover, by including also patients achieving hematologic improvement (as in other AML trials with hypomethylating agents), an overall clinical benefit was obtained by 48.4% of patients.[25]

Regarding prognostic factors in decitabine treated elderly AML patients, our study found a major impact of cytogenetics and WBC count, but not of patient age nor secondary AML. In detail, as reported in **Table 3**, The multivariate Cox model showed a significantly increased mortality in patients with adverse as compared to favorable/intermediate cytogenetic classification (HR=1.58; 95% CI: 1.13-2.21). Genetic abnormalities are recognized key factors in the prognosis of AML.[4] Some studies examining predictors of survival in patients treated with epigenetic therapy confirmed that cytogenetics play an important role in these patients, too, though others did not confirm this finding.[26,28-30]

The prognostic role of WBC count in AML has also been documented, but information from RW studies on hypomethylating agents is scanty.[31] Gupta et al. found no association between WBC at diagnosis and survival, while two European studies of 710 and 149 patients

treated with frontline azacitidine reported an increased mortality (with HR of 1.52 and 2.38, respectively) in subjects with high WBC.[26,28-29] Our data thus add to the body of evidence supporting an unfavorable role of elevated WBC level (HR=1.12; 95% CI: 1.06-1.18).

Increasing age showed a moderate detrimental association with survival in several studies of AML treatment and is a recognized independent adverse prognostic factor.[4,26,27,29,32,33] In this analysis we found only a modest detrimental association with increasing age and OS.

This study also confirms the treatment tolerability of decitabine as compared to intensive chemotherapy. However, about 45% of patients reported at least one infectious adverse event during decitabine treatment, with an average of about 0.1 infectious events for each therapy cycle. As expected, the rate of infectious adverse events was highest during the first two therapy cycles and declined thereafter. Pneumonia was the most frequently observed infectious adverse event (41%), almost twice as much as any other type of infection (i.e., sepsis, fever of unknown origin, other infectious events). Although the median number of decitabine cycles was higher in this study than in the trial by Kantarjian et al (i.e., 5 vs. 4 cycles), data on infectious events were similar.[8] In fact, pneumonia occurred in 22% of patients (vs. 21% in Kantarjian et al), sepsis in 10% (vs. 6%) and pyrexia in 10% of patients (vs. 10%). This provides further reassurance on safety of the treatment in a RW context but, in the meantime, it suggests, in order to reduce the infection burden, to consider the opportunity of an antibiotic prophylaxis in the first 2-3 therapy cycles.

This Italian investigation on the effectiveness and safety of decitabine (schedule of 20 mg/m^2 daily for 5 days) on AML in a RW clinical setting is, to our knowledge, the largest conducted to date. Another strength is the consortium approach, that improves collaborations among clinicians and interactions between experts of different areas and

from different geographic regions.[34] Data pooling allowed to conduct multivariate analyses to assess treatment performance in an adequate set of patients.

Among the limitations of this investigation, some relevant covariates could not be included in the analysis since information was not available in one or more of the collaborative studies (such as detailed informations on molecular biology). Similarly, differences between studies in the collection of information on adverse events limited somewhat the specific analysis on the safety profile.

In conclusion, this pooled-analysis of the AML consortium of Italian observational RW studies confirmed the effectiveness and safety of decitabine as first-line therapy for AML in elderly patients unfit for intensive chemotherapy. This evidence is relevant since it contributes to bridge the efficacy-effectiveness gap. An adverse cytogenetic profile and higher WBC count at baseline were unfavorable predictive factors of survival, while age at diagnosis and secondary AML had no significant impact on the prognosis of AML in the multivariate analysis.

Conflict of interest: Monica Bocchia has received honoraria from Janssen; Anna Candoni and Giuseppe Rossi were members of an advisory board (Janssen); Monica Crugnola has received conference grant and was member of an advisory Board (Janssen); Barbara Scappini has received travel grant from Janssen.

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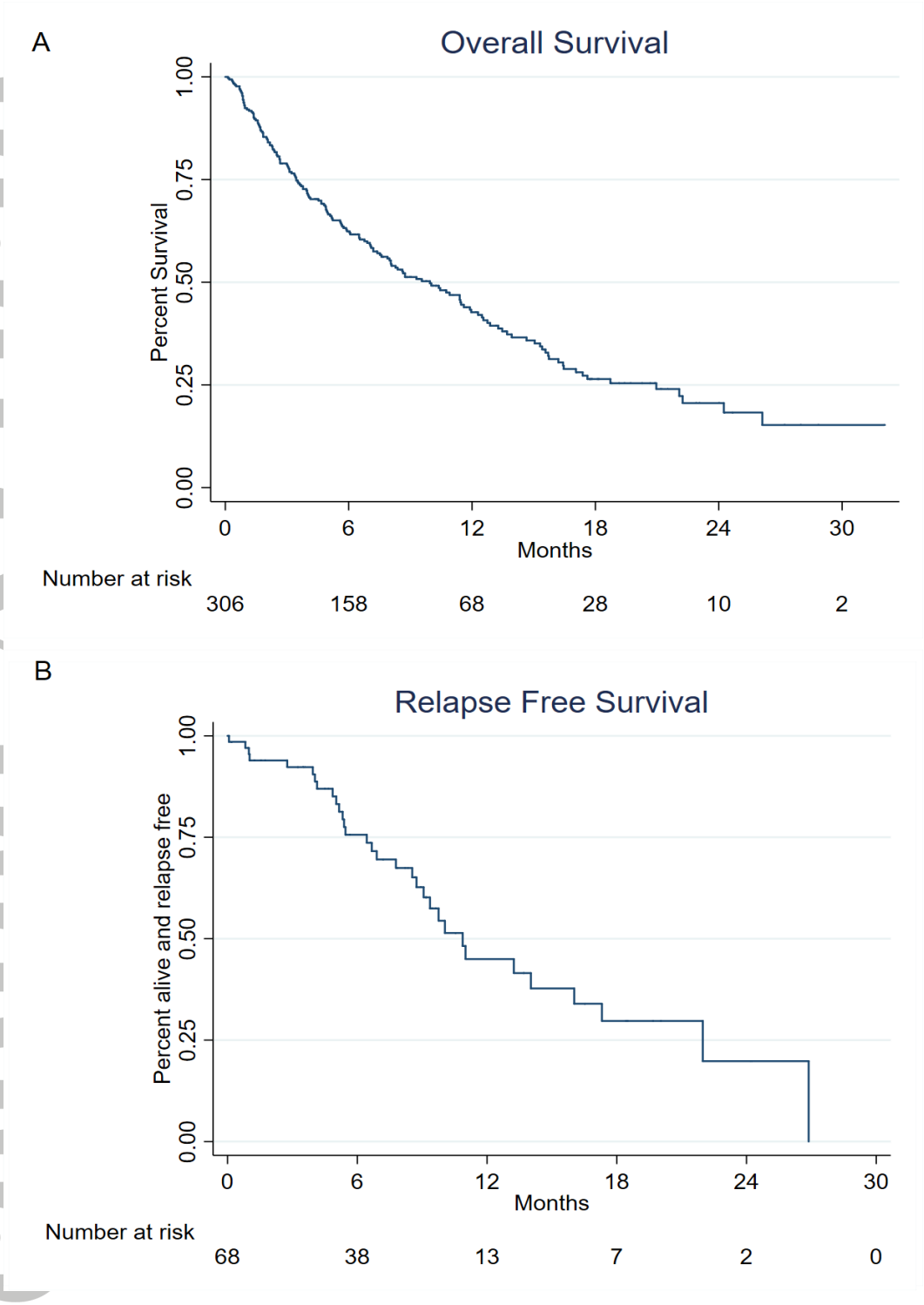

Figure 1. Overall survival (Panel A) and relapse free survival after complete remission (Panel B) Kaplan-Meier curves of AML patients treated with decitabine.

Footnotes to Figure 1. Three patients were not included in the analysis on relapse free survival due to missing information on date of remission or relapse.

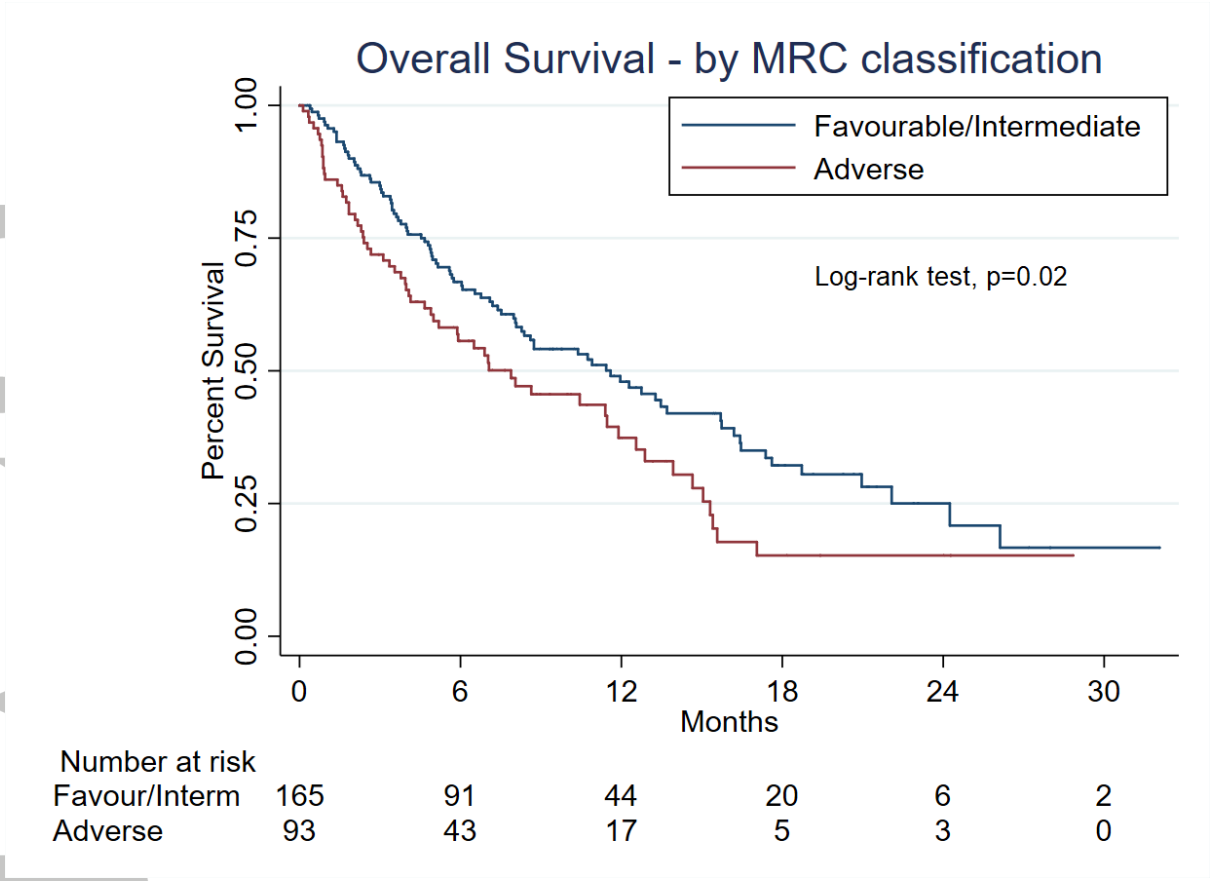

Figure 2. Overall survival Kaplan-Meier curves of 306 AML patients treated with decitabine, according to MRC cytogenetic classification.

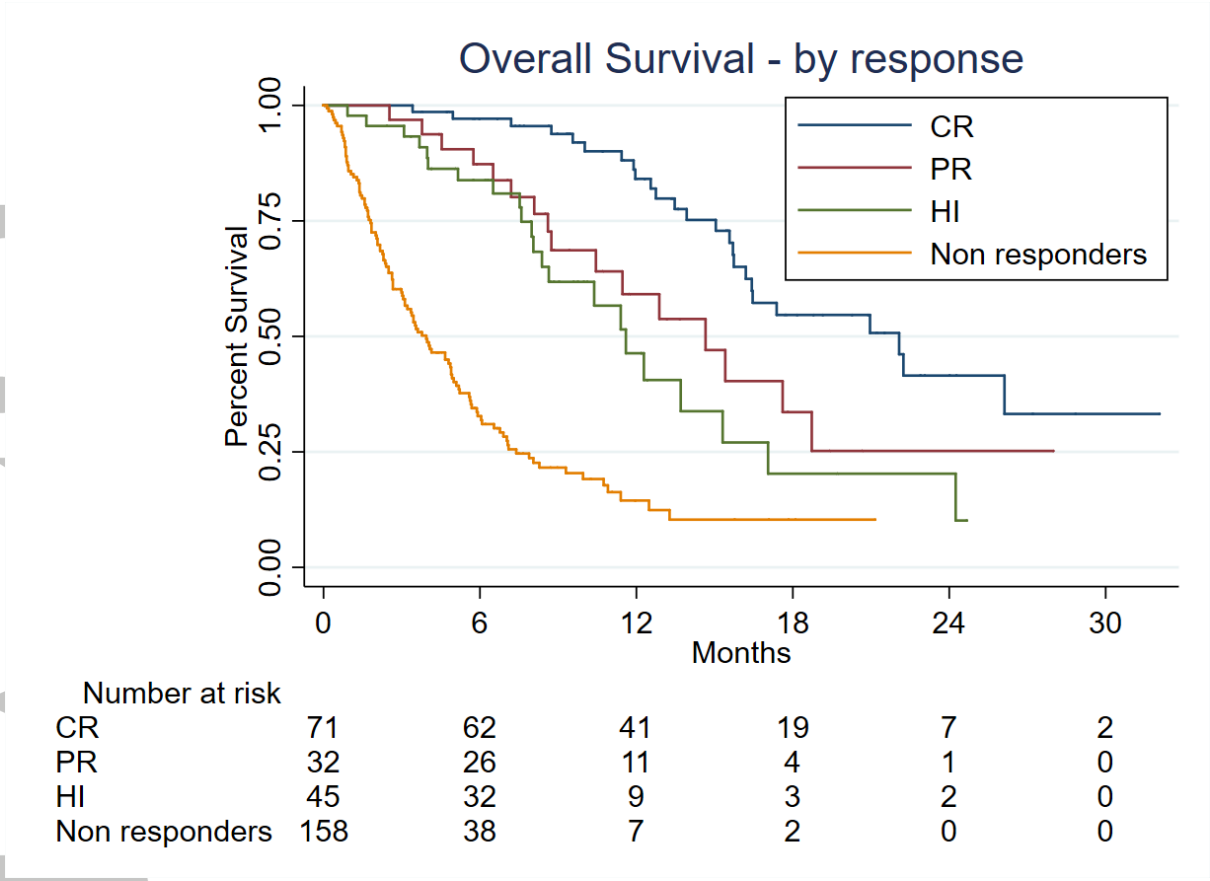

Figure 3. Overall survival Kaplan-Meier curves of 306 AML patients treated with decitabine, according to response to decitabine treatment. Median OS-patients (pts) in CR: 22.1 months (95% CI, 15.7-34.9). Median OS-pts in PR: 14.7 months (95% CI, 8.7-18.7). Median OS-pts with HI: 11.6 months (95% CI, 8.4-15.3). Median OS-pts non responders: 3.9 months (95% CI, 3.1-4.9).

Table 1. Baseline characteristics and corresponding median OS of 306 AML patients treated with decitabine.

Characteristic	No. patients (%)	Median OS (95% CI) (months)	p-value [a]
• **All patients**	306 (100.0)	10.0 (7.9-11.9)	
• **Age at diagnosis (years)**			
<70	38 (12.4)	12.5 (5.2-17.6)	
70-74	103 (33.7)	11.5 (5.9-15.3)	
75-79	107 (35.0)	10.0 (7.1-12.7)	
≥80	58 (18.9)	8.7 (5.2-11.9)	0.78
Median age (IQR)	*75 (72-78)*		
Mean age ± SD	*75.1 ± 4.7*		
• **AML type**			
De novo	182 (59.5)	10.4 (8.1-12.7)	
Secondary	124 (40.5)	8.0 (6.5-12.3)	0.50
• **MRC cytogenetic classification**			
Favourable	11 (3.6)	8.6 (3.0-NE)	
Intermediate	154 (50.3)	11.6 (8.0-15.7)	
Adverse	93 (30.4)	7.9 (4.9-11.9)	0.06
Not available	48 (15.7)	9.3 (5.2-12.5)	
• **WBC count [b]**			
1st quartile (<1800)	73 (23.9)	11.4 (7.1-13.9)	
2nd quartile (1800-<4530)	79 (25.9)	12.6 (7.4-17.6)	
3rd quartile (4530-<17100)	76 (24.9)	10.0 (7.0-15.3)	
4th quartile (≥17100)	77 (25.3)	7.2 (4.9-10.0)	0.13
Median WBC (IQR)	*4530 (1800-17100)*		
Mean WBC ± SD	*16271 ± 31689*		
• **Bone marrow blasts [c]**			
≤30%	44 (25.6)	15.0 (5.9-34.9)	
>30%	128 (74.4)	8.3 (6.1-12.0)	0.09

AML: acute myeloid leukaemia; CI: confidence interval; IQR: interquartile range; MRC: Medical Research Council; NE: not estimable; OS: overall survival; WBC: white blood cell.

[a] p-values from univariate log-rank tests. These were computed by excluding the "Not available" group, when present.

[b] The sums do not add up to the total because of 1 missing value.

[c] Information was available for a total of 172 (56.2%) patients.

Table 2. Response to decitabine first line therapy in 306 AML patients.

Response	No. of patients	%
• **Overall responders**	**148**	**48.4**
-Complete response	71	*23.2*
-Partial response	32	*10.5*
-Hematological improvement	45	*14.7*
• **Non-responders**	**158**	**51.6**

Table 3. Univariate and multivariate hazard ratios and corresponding 95% confidence intervals for the association between overall survival and selected baseline characteristics.

Covariate	Crude HR (95% CI)	Multivariate HR [a] (95% CI)
• **Age at diagnosis (years)**		
75-79 versus (vs) <75	1.11 (0.80-1.55)	1.07 (0.76-1.51)
≥80 vs <75	1.21 (0.82-1.79)	1.31 (0.88-1.96)
Age, p for trend	0.33	0.20
Age, continuous HR (+1 year)	1.01 (0.98-1.05)	1.02 (0.99-1.06)
• **AML type**		
Secondary vs De novo	1.11 (0.82-1.49)	1.11 (0.81-1.50)
• **MRC cytogenetic classification**		
Adverse vs Favourable/Intermediate	**1.46 (1.05-2.03)**	**1.58 (1.13-2.21)**
• **WBC count**		
1st quartile (<1800)		
2nd quartile (1800-<4530) vs 1st	0.84 (0.55-1.30)	0.83 (0.54-1.29)
3rd quartile (4530-<17100) vs 1st	1.06 (0.70-1.61)	1.08 (0.70-1.66)
4th quartile (≥17100) vs 1st	1.38 (0.92-2.06)	1.46 (0.96-2.21)
WBC count, p for trend	0.08	**0.048**
WBC count, continuous (+1 IQR)	**1.11 (1.05-1.17)**	**1.12 (1.06-1.18)**

AML: acute myeloid leukaemia; AZA: azacitidine; CI: confidence interval; HR: hazard ratio; IQR: interquartile range; MDS: myelodysplastic syndrome; MRC: Medical Research Council; WBC: white blood cell.

[a] HRs from multiple logistic regression models, including terms for study, age at diagnosis, AML type, MRC classification and WBC count.

Table 4. Adverse events occurring in 306 AML patients treated with decitabine.

	Total no. of events	Events per patient	Patients with ≥1 event
Infectious AE	***No. (% of all infections)***	***Mean no.***	***No. (%)***
• ***All infections***	183	0.60	136 (44.4)
• ***All infections, by type***			
Pneumonia	76 (41.5)	0.25	69 (22.5)
Sepsis	35 (19.1)	0.11	30 (9.8)
FUO	39 (21.3)	0.13	31 (10.1)
Other	33 (18.0)	0.11	30 (9.8)
• ***All infections, by age at AML diagnosis***			
<75	84 (45.9)	0.60	65/141 (46.1)
75-79	63 (34.4)	0.59	44/107 (41.1)
≥80	36 (19.7)	0.62	27/58 (46.6)
• ***All infections, according to therapy cycle*** [a]		**% events per cycle**	
Cycles 1-2	70 (60.3)	23.2%	
Cycles 3-5	37 (31.9)	13.1%	
Cycles ≥6	9 (7.8)	2.2%	
Other (non-infectious) AE [b]	***No. (% of all other AE)***	***Mean no.***	***No. (%)***
• **All other AE**	86	0.66	52 (39.7)
• ***All other AE, by age at AML diagnosis***			
<75	37 (43.0)	0.61	22/61 (36.1)
75-79	32 (37.2)	0.78	17/41 (41.5)
≥80	17 (19.8)	0.59	13/29 (44.8)

AE: adverse events; FUO: fever of unknown origin

[a] In a subgroup of 169 (55.2%) patients with available information on therapy cycle at occurrence of infectious adverse events.

[b] Information was available for 131 (42.8%) patients.