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ORIGINAL ARTICLE

A retrospective study evaluating the impact of infectious complications during azacitidine treatment

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Abstract Azacitidine has become an available therapy for high-risk myelodysplastic syndromes. Infectious complications (IC) may impede the success of therapy. Since most patients are managed in an outpatient setting, often with low level of clinical and microbiological documentation, the impact of IC remains unclear. We retrospectively evaluated the clinical course of 77 patients with MDS treated with azacitidine between 2004 and 2015 (median age 69 years). Clinical workup included severity and type of IC, days in the hospital and with antimicrobial therapy, response to azacitidine, and overall survival (OS). In total, 614 azacitidine cycles were administered, 81 cycles with at least one IC. The median number of administered cycles was 6 (range 1–43). Median OS after the start of azacitidine was 17 months (range 1–103). Infection rates were higher in the first 3 cycles with bacterial infections leading. The better patients' hematological response to azacitidine with less IC occurred, and fewer days with antimicrobial treatment were needed. Compared to progressive disease, stable disease made no significant improvement in occurrence of IC and days in the hospital. Older age was associated with more IC and longer time in the hospital. Comorbidities or IPSS-R had no influence on IC. The incidence of IC correlated with hematological response and age. Stable disease led to longer OS, but incidence of IC was comparable to progressive disease and survival seemed to be bought by a considerable number of IC. IC rates were highest in the first 3 cycles. We recommend response evaluation after 4–6 cycles.

Keywords Myelodysplastic syndromes · Azacitidine · Infectious complications · Clinical course

Introduction

Myelodysplastic syndromes (MDS) encompass a heterogeneous group of hematopoietic stem cell disorders of clonal origin which are characterized by a disturbed balance between self-renewal and differentiation. The hallmark of the various MDS subtypes—independent of the morphological features encountered in the bone marrow—is an ineffective hematopoiesis resulting in cytopenias of various degree of one or more hematopoietic lineage. MDS is a disease of elderly people with a median age at the time of initial diagnosis of 70 years and a male predominance [1]. Independent of the underlying etiology and molecular pathophysiology of the different MDS subtypes, except for allogeneic stem cell transplantation, there is no causative therapy with curative potential available at the time being. Overall, the life expectancy of patients with high-risk MDS is therefore limited to about 1 year, particularly as comorbidities are often encountered in this group of elderly patients [2–5]. In patients with low-risk MDS, best supportive care (BSC) including regular transfusion of blood products and administration of hematopoietic growth factors such as granulocyte–colony-stimulating factor (G-CSF) or erythropoietin (EPO) provides a reasonable quality of life. Attempts to alter the "natural course" in elderly patients using cytotoxic chemotherapy for the induction of hematological remissions for prolonging progression free survival (PFS) and overall survival (OS) did not result in longer survival times compared to best supportive care [2, 6].

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Encouraging results as far as response and toxicity are concerned have been achieved using the epigenetically active compound azacitidine, which is a pyrimidine nucleoside analogue acting as DNA methyltransferase [2]. The results of two independent clinical studies showed that administration of azacitidine resulted in a longer duration of overall survival compared to best supportive care or conventional cytotoxic chemotherapy [7–10]. There was also an azacitidine-associated delay noted as far as the time to leukemic transformation was concerned [11, 12]. These favorable results were, to some degree, obscured, as the treatment with azacitidine—even so efficacious it may be—is still associated with prolonged periods of cytopenias of variable degree affecting the different hematopoietic lineages, notably with leukopenia paving the way for infectious complications [13]. Even though the majority of patients are considered to be treatable within an outpatient setting, we are often confronted with serious infectious complications requiring admission to the hospital, particularly in the context of serious comorbidity such as renal or cardiac insufficiency. It was the aim of our single-center retrospective study to evaluate the occurrence of infectious complications in patients with MDS and their time spent in the hospital while they received a therapy with azacitidine as outpatients. Particular emphasis was put on the relationship between degree and time to hematological response and the rate of infectious complications, as these parameters are apparently linked to each other.

Patients and methods

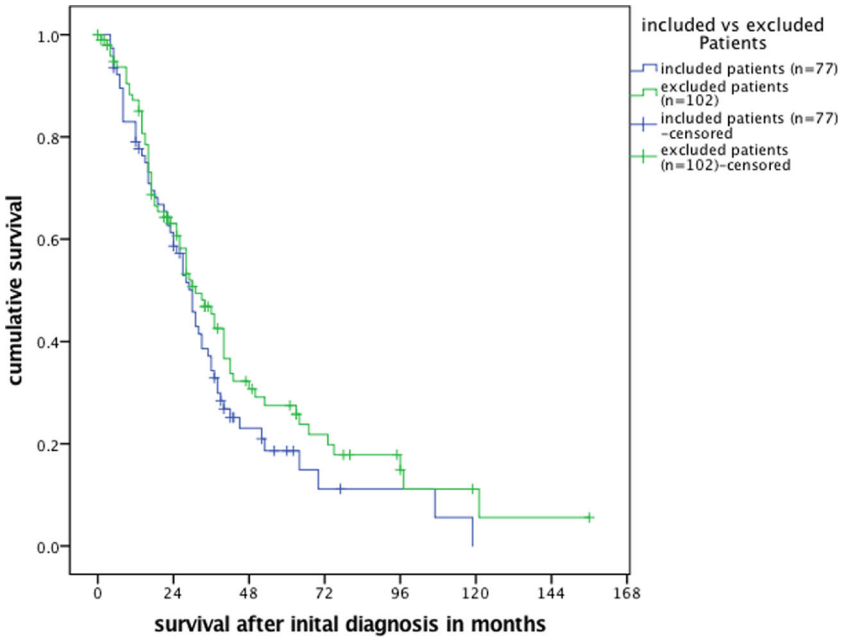
According to our registry for adult patients with MDS, we were involved in the treatment of 179 patients who received an epigenetic therapy between August 2004 and January 2015. For our particular evaluation, a complete documentation including all relevant parameters was available for 77 patients (Table 1). Exclusion of the other patients was warranted for reasons such as lack of date and type of best hematological response or incomplete documentation of infectious complications. The majority of these patients were referred to our hospital only occasionally and otherwise looked after by hematologist within our catchment area. We also excluded 41 patients who received decitabine at any time before or after they were treated with azacitidine. Having these limitations in mind, we looked for the overall survival from initial diagnosis of the entire group of 179 patients and came up with a median OS of 26 months varying between 1 and 156 months. The median time of OS from initial diagnosis in the 77 patients presented later more in detail was 27 months compared to 25 months for patients that were excluded from our analysis and therefore statistically not different ($p = 0.117$). Figure 1 shows a Kaplan–Meier analysis showing the excluded OS of the included patients. We also compared the initial blood count of the patients that were included and the patients that were excluded from the study and found no significant difference in the initial blood count (Table 2), which confirmed the comparability of both groups.

Table 1 Patient characteristics

No. of patients, *n*	77
Age (ID), median, (range) in years	69 (41–81)
Sex in *n* (%)	
Male	41 (53)
Female	36 (47)
IPSS-R (ID) in *n* (%)	
Very high	27 (35)
High	17 (22)
Intermediate	15 (20)
Low	8 (10)
Very low	0 (0)
Unknown	10 (13)
MDS Comorbidity Score (ID), *n* (%)	
Low	29 (38)
Intermediate	28 (36)
High	20 (26)
Type of MDS, *n* (%)	
Primary MDS	64 (83)
Secondary MDS	13 (17)
WHO 2008 of MDS, *n* (%)	
RAEB1:	15 (19.5)
RAEB 2:	30 (39)
CMML 1	2 (3)
CMML II	3 (4)
RARS	1 (1)
RAEB-t	5 (6.5)
RCMD	18 (23)
Others	3 (4)

ID initial diagnosis, *IPSS-R* International Prognostic Scoring System-Revised, *WHO* World Health Organization, *RAEB* refractory anemia with excess blasts, *CMML* chronic myelomonocytic leukemia, *RARS* refractory anemia with ring sideroblasts, *RAEB-t* refractory anemia with excess blasts in transformation, *RCMD* refractory cytopenia with multilineage dysplasia

The 77 patients of our retrospective single-center study belong to the Düsseldorf MDS registry, which collects diagnostic and therapeutic data of patients with MDS treated in our region. They had a median age of 69 years with a range between 41 and 81 years (Table 1). Thirty-six patients were female (47%) and 41 were males (53%). Diagnosis of MDS was based on the criteria set by WHO 2008 [14]. The patients clinical and demographic data, complete cell count, and serum chemistry values from the first day of azacitidine treatment and on the occasion of each azacitidine cycle were available. We also monitored and documented the incidence and type of



Log-rank: p=0.117
Breslow: p=0.328
Tarone-Ware: p=0.261

Fig. 1 Overall survival included (n = 77) vs. excluded patients (n = 102). Log-rank: p = 0.117. Breslow: p = 0.328. Tarone-Ware: p = 0.261

infectious complications, days of intravenous treatment with antimicrobial therapy, and the number of days spent in the hospital. Mild IC with no need of intravenous treatment or any treatment at all were not considered. Therefore, all IC mentioned in this study were of degree 3 and higher. Azacitidine was administered subcutaneously at the approved FDA/EMA schedule (75 mg/m^2/day during 7 days every 28 days). Twenty-nine patients underwent a 5-day course of 100 mg/m^2/day due to logistic reasons when weekend injections were not feasible. We recommended patient vaccinations that were suggested by the Robert-Koch-Institute. Fungal or antibiotic prophylaxis was not part of a standard regimen and prescribed by the treating physician's decision.

Patients were treated continuously until disease progression, occurrence of severe infection, or patient's decision to discontinue the therapy. Bone marrow evaluation of response

Table 2 Initial blood count included versus excluded

	Included patients	Excluded patients	p value
No. of patients	77	102	
Age (ID), median, (range) in years	69 (41–81)	68 (32–87)	
Sex			0.050
Male	41	69	
Female	36	33	
Leukocytes/μl (at ID) median	2800 (900–46,900)	3000 (4–51,000)	0.946
Unknown (n)	5	13	
Bonemarrow, blasts (at ID) median	9.5 (0–25)	8 (0–72)	0.213
Hemoglobin (at ID) median	9.4 (6–16.6)	9.3 (9–13.2)	0.107
unknown	3	11	
IPSS-R (at ID) (n)			0.225
Very high	27	19	
High	17	17	
Intermediate	15	23	
Low	8	11	
Very low	0	3	
Unknown	10	29	

was recommended after a minimum of 4 cycles and evaluated according to IWG response criteria for MDS [15, 16]. In patients with refractory disease, achievement of hematological improvement (HI) was evaluated when a significant improvement of the blood count was observed. Complete remission (CR) required normalization of hematopoiesis with absolute neutrophil count of 1 × 109/L or greater, platelet count of 100 × 106/L or greater, and bone marrow blast count of less than 5%. Overall survival analyses were performed on the basis of Kaplan–Meier calculations of relevant factors with potential impact on patient's survival. Death due to all causes or date of last follow-up was used as the clinical end point. Significant differences were calculated with the χ^2- test and the log-rank test. A p value of <0.05 was considered as statistically significant.

Results

Our retrospective study on infectious complications in 77 patients with high-risk MDS is based on a total of 614 cycles of azacitidine with a median number of 6 cycles per patient (range 1–43).

In total, 81 episodes of IC occurred and 55 of the 77 patients had an IC of degree 3 or 4 with intravenous treatment at any time during their azacitidine treatment. In 26 patients, even more than one IC occurred. Twenty-two out of 77 patients never had a relevant IC during the azacitidine treatment. Since azacitidine was planned as an outpatient treatment, all days in the hospital were related to an IC. On average, patients spent 12 days in the hospital during the entire azacitidine treatment. Five out of 77 patients (6%) died directly related to an IC during or until 1 month after their AZA treatment. Three of them died due to a severe pneumonia and two of them due to fever of unknown origin. The main reasons for referring a patient into the hospital were infectious complications with febrile episodes of unknown origin, followed by pneumonia, skin infections, and gastrointestinal infections in decreasing frequency (Table 3).

Microbiological documentation of the pathogen of the infection was retrospectively only partially available. In some documented IC, a pathogen could not be isolated in blood cultures, blood swaps, or bronchoalveolar lavage. Bacterial infections were therefore assumed in 88% of IC, and microbiological results detected bacteria in 15% of IC (Table 3). The most commonly found bacteria were *Pseudomonas aeruginosa*, *Staphylococcus hominis* and *Staphylococcus aureus*, *Enterobacter cloacae*, and *Campylobacter jejuni*. Viruses were detected in 5% of IC (two cases of VZV, one case with CMV, and one case with HSV). Fungal infections were assumed in 7% of IC (two cases of esophageal candidiasis, four cases of fungal pneumonia detected by CT scan), but the fungal species were never microbiologically detected. Histopathologic, cytopathologic, or direct microscopic examination and cultivation of fungi were not available in most cases with fungal pneumonia. Diagnosis and therapy of fungal pneumonia were initiated when clinic and CT scans showed strongly suspicious signs of fungal pneumonia. According to the EORTC/MSG criteria for invasive fungal infections (IFI), all these pneumonia therefore fell in the category "possible" fungal pneumonia [17]. Other fungal infections such as fungal skin or bowl infections were not documented as IC degree 3 or higher and therefore did not seem to play a significant role. Table 4 shows the days in which intravenous antibiotics or antimycotics were administered.

Prophylaxis was not administered systematically and the treating physician's decision. In many cases, it was not comprehensible retrospectively whether an antimycotic drug was given therapeutically or prophylaxis. Approximately in 15 out of 257 AZA cycles, a fungal prophylaxis with either posaconazol or fluconazol was documented (357 of the cycles unknown).

In n = 6 cycles out of 257 cycles, a viral prophylaxis, valganciclovir, was documented (357 cycles unknown). Due to the large number of unknown cases, a correlation between the prescription of a prophylaxis and the incidence and degree of complication was not possible in this study.

Infection rates were highest in the first 3 cycles. The infection rates in azacitidine cycles 1–3 compared to cycles 4–6 were statistically significant higher (p = 0.021) and infection rates diminished from cycle 1–8. As far as the therapeutic efficacy is concerned, there were 8 patients (10%) who reached a complete remission (CR), 21 patients (27%) with a partial remission (PR), and 6 patients (8%) fulfilling the criteria of hematological improvement (HI). This group of 35 patients will be quoted as "responders." On the other hand, there were 17 patients (22%) with a stable disease (SD) and 25 patients (33%) developing a progressive disease (PD). This group of 42 patients will be further referred to as "non-responders." The response data translate into a median survival time of the entire cohort of 27 months from initial diagnosis with 8 patients being alive at the time of writing this report. For the responding patients, the median OS from initial diagnosis was significantly longer compared to that of the "non-responders" (25 months versus 11 months, $p < 0.001$; Fig. 2). Not unexpectedly, OS improved the relationship with hematological response, with a median duration of 42 months for patients achieving CR compared to 7 months in patients with progressive disease (Fig. 2).

As far as the responding patients are concerned, infectious complications were noted on the occasion of 28 of 181 cycles (15.5%, p = 0.002) compared with 43 of 144 cycles (29.9%) in the group of non-responding patients. For instance, infectious disease was encountered during the course of 31% of cycles administered to patients with progressive disease, whereas only 6% of cycles given to patients with CR were accompanied by infectious problems.

Table 3 Type of infectious complications

	n = 81	Bacterial	Viral	Fungal	Death
Fever of unknown origin	41	41	0	0	2 (5%)
Upper respiratory tract infections and pneumonia	14	9	1	4	3 (21%)
Skin and soft tissue infection	12	9	3	0	0
Gastrointestinal infections	7	5	0	2	0
Others	7	7	0	0	0

The responding patients received a median of 9 cycles with a proportion of only 8% administered in the hospital. On the other hand, the median number of cycles administered to patients of the non-responder group was 5 cycles with 22% of them given in the hospital. In general, responding patients spent significantly fewer days in the hospital per cycle in comparison to non-responding patients (median 0.4 versus 4.5, $p = 0.025$). With 16 compared to 17 days of hospitalization during the entire azacitidine treatment, we found no significant difference in time in the hospital between stable disease and treatment failure. In line with these results, responding patients received 0.85 days of intravenous antibiotic and 0.14 days of antimycotic therapy per azacitidine cycle compared to 2.5 and 1.3 days in the non-responder group with fewer antimicrobial treatments.

Table 4 Infectious complications responder vs. non-responder

Patients characteristics	SD/PD/F	CR/PR/HI	*p* values
No. of patients *n* = 77 (%)	42 (55)	35 (45)	
Time ID to azacitidine start			
Median (range) in months	4 (0–27)	3 (0–46)	0.546
Total no. of azacitidine cycles	193	421	
Median no. of cycles, *n* (range)	5 (1–8)	9 (1–43)	0.021
Overall survival from azacitidine start			
Median (range) in months	11 (0–67)	25 (1–103)	0.001
Alive (number of patients)	4	4	
Unknown (number of patients)	1	2	
Average days in the hospital per cycle	4.5	0.4	0.025
No. of patients never hospitalized, *n* (%)	13 (31)	12 (34)	0.322
No. of adverse events (*n*)	61	39	
No. of cycles with adverse events, *n* (%)	53 (36.8)	35 (19.3)	<0.001
Of *n* cycles	144	196	
Type of adverse event, *n* (%)			0.085
Infection	52 (85.2)	29 (74.4)	
Bleeding	2 (3.3)	3 (7.7)	
Others	5 (8.2)	7 (18.2)	
No. of cycles with infectious complications, *n* (%)	43 (29.9)	28 (15.5)	0.002
Of *n* cycles	144	196	
Type of infection, *n* (%)			
Fever of unknown origin	27 (51.9)	13 (48.3)	
Pneumonia	9 (17.3)	5 (17.2)	
Skin/soft tissue infection	7 (13.5)	5 (17.2)	
GI infection	5 (9.6)	2 (6.9)	
Others	4 (7.6)	3 (10.3)	
Mean days of…per cycle			
IV antibiotics, mean (SD)	2.5 (6.6)	0.85 (2.2)	0.009
IV antimycotics, mean (SD)	1.26 (4.9)	0.14 (1.9)	0.014
IV virostatics, mean (SD)	0.53 (4.2)	0 (0)	0.178

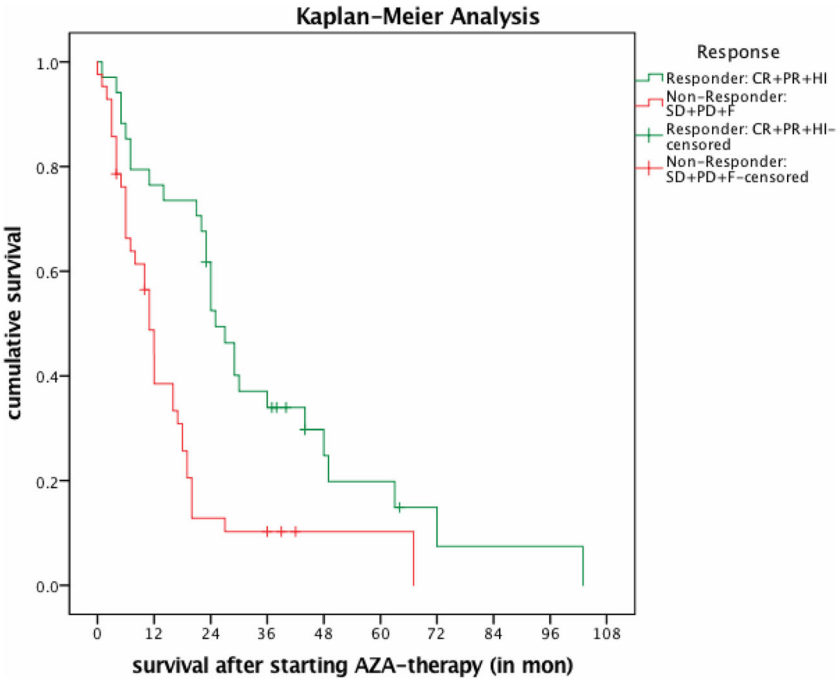


Fig. 2 Overall survival responder vs. non-responder ($n = 77$ patients), $p = 0.001$. *AZA* azacitidine

To evaluate the influence of comorbidities on the patient's outcome, we used the MDS Comorbidity Score and allocated the patients to three groups [18]. The first group of 29 patients with a low-risk Comorbidity Score of 0 points had a median age of 67 years with a range between 41 and 81 years. There were 28 patients with an intermediate risk (1–2 points). Their median age was 69 years with a range between 49 and 77 years. The group of high-risk patients, as defined by more than 2 points, comprised 20 patients with a median age of 70 years with a range between 52 and 81 years. The median number of cycles of azacitidine administered to the patients of the three groups was similar with 5 cycles within the low-risk group, 6 cycles in the intermediate-risk group, and 5 cycles in the high-risk group ($p = 0.355$). With regard to their median duration of overall survival, significant differences were noted. Patients falling into the low-risk category had a median OS of 16 months (range 0–63 months) in comparison to 20 months (range 3–103 months) for patients within the intermediate-risk group. Patients in the high-risk group had the shortest median survival time of only 11 months (range 2–72 months). It was interesting to note that there was no significant difference between the three comorbidity groups of patients with regard to the time spent in the hospital. In the low-risk group, the median number amounted to 9.5 days and was 13 and 12 days for patients in the intermediate group and high-risk group, respectively. In the same line, the proportion of patients who needed no hospitalization over the entire treatment period for what reason ever was similar in all three groups, with 37.5% in low-risk patients, 40% in intermediate-risk patients, and 35.3% in high-risk patients. When comparing patients with a median age over and under 69 years, we could show that older age was associated with longer stays in the hospital. The number of patients never hospitalized was higher in the younger group. In total, 40.5% of them were never hospitalized compared to 25% that were never hospitalized in the group of patients with a median age of over 69 years ($p = 0.205$). We also compared the IC rate of patients receiving a 5-day azacitidine regimen (29 patients) to patients receiving a 7-day (48 patients) regimen and found no difference in the IC rate ($p = 0.160$). The International Prognostic Scoring system - Revised (IPSS-R) at the start of azacitidine treatment also made no significant difference to the IC rate ($p = 0.410$) and the days in the hospital and could therefore not be identified as a possible risk factor for IC.

Transfusion dependency was rather difficult to be retrospectively evaluated due to the lack of outpatient's transfusion data available. Assuming that patients with hemoglobin over 10 g/dl are unlikely to be transfusion dependent, we compared patients with hemoglobin under 10 g/dl to patients with an initial hemoglobin over 10 g/dl at the start of azacitidine treatment and found no difference in infection rates ($p = 0.572$).

Discussion

The results of our retrospective single-center study presented here are based on 77 patients with advanced MDS who were carefully monitored and well documented including the pertinent clinical data, hematological response as well as incidence, type of infectious complications, antimicrobial therapy, and treatment outcome.

In accordance to the results of other groups, we could confirm that azacitidine is an efficacious compound with an overall response rate of 47% including hematological improvements, partial remissions as well as 10% patients with CR. Not unexpectedly, responders had a significant longer survival time in comparison to non-responders which is also in line with other studies [2–4]. It was interesting to note that the median number of cycles administered to patients of the non-responding group amounted to 5 cycles which reflects the quality of the supportive therapy including the regular transfusion of erythropoiesis-stimulating agents. This notion is in line with our finding that achieving "stable disease" was associated with a significant longer OS compared to patients with progressive disease, whereas no difference could be noted with regard to infectious complications and days with intravenous antimicrobial treatment or days spent in the hospital. Our intention to provide best supportive care in addition to azacitidine also reflects our concern to discontinue azacitidine prematurely, as responses might be seen not before at least 4 cycles had been given. This view is well strengthened by our result that complete remissions were observed after a median time of 5 months varying between 3 and 10 months. A particular finding of our study is that the response to azacitidine, as reflected by hematological improvement or a remission of various degree, not only led to a longer OS but was also associated with a smaller number of infectious complications, probably as a result of a greater concentration of mature granulocytes in the peripheral blood. As a consequence, the need for intravenous antimicrobial therapy was significantly less compared to the patients of the non-responder group. From the point-of-life quality, it is worth noting that the responding patients spent fewer days in the hospital for treatment of infectious complications and could receive their treatment mainly on an outpatient basis. Looking at this relationship within a timely dimension, we can conclude that the earlier hematological improvement is attained following installment of azacitidine, the smaller is the likelihood of developing infectious complications.

Interestingly, there was no relationship between the patient's comorbidities and the number of infectious complications encountered. It was the patient's age which was significantly associated with an increased incidence of infectious complications, more days spent in the hospital. There were other potential risk factors such as patient's transfusion frequency, since data about outpatient's transfusion frequencies was rarely available.

The most frequent infectious complication was fever of unknown origin followed by pneumonia as the second most common infectious disease. More than two third of the patients suffered from at least one infectious complication of degree 3–4 with the need of intravenous treatment. An Israeli multicenter and retrospective study including 184 patients with MDS and AML reported in 2012 an incidence of bacterial infections of 59% [16]. Not surprisingly, bacterial infections in our study formed the largest part of infectious complications with 88%, followed by 7% fungal, and 5% viral infections. Still, the overall microbial pathogen detection rate was relatively low. The same group found an infection rate of 100 out of 184 patients with IC (16.5% of cycles) and reported in 2015 that 7-day cycles were associated with more IC compared with 5-day cycles (34 versus 15%) [19]. In our study, the infection rate was comparable with 55 patients out of 77 receiving intravenous treatment for infectious complications at least once while on their azacitidine therapy (23% of cycles). Whereas we could not find statistically different IC rates between 5- and 7-day cycles.

Pomares et al. published a study last year showing few numbers of invasive fungal infections and stated these numbers would not justify the use of antifungal prophylaxis [20]. We also found few numbers of fungal infections. Antibiotic or fungal prophylaxis or vaccination of our patients was not systematically administered. It was difficult to gather accurate data about the use and impact of prophylactic compounds, being faced by a difficult distinction whether a drug was administered therapeutically or prophylactic. There also could be a small bias since patients likely to have IC due to preceding IC received more prophylaxis.

This analysis was retrospective and might thus be hampered by a selection bias due to a more accurate documentation of patients suffering more infectious complications. However, OS and the initial blood count of included and excluded patients were not different between groups.

In line with other studies, infection rates were highest in the first 3 to 4 cycles [19, 21]. Our findings might be helpful to tailor the therapy with azacitidine, according to the response observed following 4–6 cycles of therapy. Those with stable disease at this time or thereafter may have a somehow longer time of OS. Still, this lifetime is overshadowed by a relatively high rate of incidence of infectious complications associated with a considerable number of days spent in the hospital. The survival times reported in the literature of patients receiving best supportive care is around 12 months [3, 18, 22], which is not significantly different from the OS times observed in our patients of the non-responder group. As a consequence of our study, we recommend a stringent hematological evaluation following 4–6 cycles of azacitidine to prevent a potential overtreatment of patients not susceptible to this compound and undue loss-of-life quality related to prolonged stays in the hospital.

The use of prophylactic antimicrobial therapy should be prospectively studied. Until these data are available, it could be beneficial if antibiotic or antifungal prophylaxis was adopted during the first 3 cycles in patients with leucocytopenia, low response to azacitidine, and an older age.

Compliance with ethical standards

Conflict of interest Anna Schuck: Financial travel support from Celgene.

Judith Neukirchen: Financial travel support and speakers honorarium from Celgene.

Andrea Kündgen: Financial travel support from Celgene.

Thomas Schroeder: Financial travel support, research funding, lecture fees from Celegene.

Guido Kobbe: Research funding, financial travel support and lecture fees from Celgene.

Ullrich Germing: Speakers honorarium from Celgene, Janssen-Cilag, Novartis, Research support Celgene, Novartis.

Human and animal rights and informed consent All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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