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Infections in patients with acute myeloid leukemia treated with low-intensity therapeutic regimens: Risk factors and efficacy of antibiotic prophylaxis

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ABSTRACT

Survival of acute myeloid leukemia (AML) patients, who are unfit for high-dose chemotherapy, has significantly improved with the advent of low-intensity therapeutic regimens (LITR, comprising decitabine, azacitidine, and low-dose cytarabine). However, infectious complications are common during LITR treatment and might hamper the beneficial effect of these drugs. In this study, we aimed to evaluate the incidence of and predisposing risk factors for infections during LITR treatment of AML, as well as the value of antibiotic prophylaxis within this setting. Therefore, we retrospectively analyzed 40 AML patients, treated with 215 cycles of LITR and analyzed putative risk factors by multivariate logistic regression. Infections occurred in 53/215 (25%) of LITR cycles, resulting in death in six patients. Of the parameters assessed at the start of each LITR cycle, transfusion dependence ($p = 0.008$) and increased LDH ($p = 0.027$) independently predicted the occurrence of infection. Most importantly, however, antibiotic prophylaxis was independently associated with a decreased rate of infectious complications ($p = 0.030$). It was regularly performed in neutropenic patients and even managed to eliminate low neutrophil counts as risk factor in multivariate models. These data argue for the efficacy of antibiotic prophylaxis during LITR therapy of AML and suggest its further evaluation within a prospective clinical trial.

1. Introduction

High-dose chemotherapy and allogeneic hematopoietic stem cell transplantation display effective and potentially curative treatment regimens for patients with acute myeloid leukemia (AML) [1–3]. Unfortunately, the majority of AML patients are diagnosed at an advanced age or with significant co-morbidities, which often excludes them from these treatment approaches [1,2]. For a long time, these patients were managed with best supportive care only and specific AML therapy was considered as not feasible. This view changed when low-dose Ara-C (LDAC) was shown to significantly improve the survival of AML patients unfit for high-dose chemotherapy [4]. Recently, low-intensity therapeutic regimens (LITR) have been extended by the hypomethylating agents decitabine and azacitidine, which resulted in an additional survival benefit in these patients [5–9]. These data are corroborated by a recent analysis of the SEER registry on more than 8000 patients indicating that any specific AML treatment is superior to best supportive care only [10].

Infections are frequent and serious complications of LITR AML therapy and might hamper the beneficial effect of these drugs [8,9,11–15]. While much knowledge about their risk factors and about prophylactic antimicrobial therapies has been gained for the high-dose setting, data for LITR are rare. Therefore, we aimed to evaluate the incidence of and predisposing risk factors for infectious complications, as well as the value of antibiotic prophylaxis during LITR treatment of AML.

2. Methods and data analysis

This retrospective analysis included 40 consecutive AML patients, who were treated with 215 cycles of LITR at the Med-

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ical University of Graz between December 2008 and May 2015. The study was approved by the institutional review board of this institution (27-084 ex 14/15). AML was classified according to French–American–British (FAB) and World Health Organization (WHO) guidelines [16,17]. LITR treatment comprised (i) subcutaneous LDAC, 20 mg twice daily over ten days, (ii) intravenous decitabine, 20 mg per square meter body surface area over 5 days, and (iii) subcutaneous azacitidine, 75 mg per square meter body surface area over 7 days. Treatment cycles were scheduled every 4 weeks for all drugs until progression, relapse or intolerance occurred [1]. For azacitidine, a 5-2-2 scheme with a two-days rest over the weekend was commonly employed [18]. Twelve azacitidine cycles in three patients were administered at a reduced dose, the remaining 203 LITR cycles were given at full dosage. Factors assessed at AML diagnosis included age, cytogenetic risk group, white blood cell count (WBC) and the presence of co-morbidities (as assessed by the updated Charlson co-morbidity index [CCI] [19]). Factors assessed at the start of LITR treatment and at the start of each LITR cycle included platelets, absolute neutrophil count (ANC), lactate dehydrogenase (LDH), C-reactive protein (CRP), creatinine, glomerular filtration rate (GFR) as well as transfusion dependence. Administration of antibiotic prophylaxis was evaluated for each LITR cycle. Diagnosis, documentation and definition of infections was performed according to published guidelines [20–29] and included (i) fever of unknown origin necessitating anti-infective treatment, (ii) infections with a clinically documented source and/or (iii) infections with a microbiologically documented source.

Data analysis was performed using the R 3.2.2 (www.r-project.org) software. The value of putative risk factors for the occurrence of infectious complications, assessed at the diagnosis of AML, was evaluated by Wilcoxon–Mann–Whitney (for age, WBC and CCI) and Fisher's exact tests (for cytogenetic risk groups). Putative risk factors assessed at the start of LITR therapy and at the start of each LITR cycle were assessed by generalized estimating equation (GEE) variant of logistic regression (https://cran.r-project.org/web/packages/gee/index.html) using the GEE package version 4.13-19 in order to compensate for the fact that many patients received more than one LITR therapy/cycle, thereby producing dependent variables. The value of antibiotic prophylaxis was evaluated the same way and was included in the dataset assessed at each LITR cycle. Of note, due to the small sample size we refrained from setting cutoff values and calculated platelets, ANC, LDH, CRP, creatinine and GFR as continuous variables. Significance in multiple testing situations was assessed by controlling the false discovery rate (FDR) according to Benjamini and Hochberg [30]. All tests were performed two-sided and a p-value of <0.050 in single tests and an FDR of <0.050 in multiple testing was considered statistically significant.

3. Results

3.1. Description of patients, LITR cycles and hematologic response

Forty patients received LITR, either as first-line ($n = 30$) or as salvage therapy after the failure of high-dose therapies ($n = 10$). Median age at diagnosis was 72 years (range 43–92 years), however, the group receiving LITR as first-line treatment was significantly older as compared to the group with precedent high-dose approaches (74.5 vs. 61 years; $p = 0.001$). As previously reported for AML of the elderly [10,31], this cohort was characterized by decreased frequency of favorable cytogenetics and overrepresentation of male patients (for a detailed description of the cohort see Table 1). In total, 215 cycles of LITR were administered, comprising 14 cycles of LDAC, 148 cycles of azacitidine and 53 cycles of decitabine. The median number of cycles per patient was 2 (range 1–6) for LDAC, 3.5 (range 1–25) for azacitidine and 3 (range 1–10) for decitabine. 181 LITR cycles were administered as part of first-line therapy, 34 as part of salvage therapy after failure of high-dose approaches. Response to LITR administration was assessed in patients achieving more than two cycles of therapy ($n = 25$; Supplementary Fig. 1 and Table 1). Overall response (OR), defined as achieving at least hematologic improvement [9,32,33], was seen in 13/25 (52%) of eligible patients, median survival from the start of LITR therapy was 8.95 months. Complete remission [9,32,33] was observed in five patients, however, these data have to be interpreted with caution as bone marrow biopsies have not been performed in a substantial subset. We refrained from comparison of treatment response in specific LITR subgroups, as the small sample size precluded a valid statistical evaluation.

Table 1
Demographic characteristics of AML patients treated with LITR.

Age at diagnosis, median years (range)	72 (43–92)
Charlson co-morbidity index, median (range)	3 (2–8)
Sex	
Male, *n*=	25/40 (63%)
Female, *n*=	15/40 (37%)
Cytogenetic risk	
Favorable, *n*=	0/35[a] (0%)
Intermediate, *n*=	26/35[a] (74%)
Adverse, *n*=	9/35[a] (26%)
WHO-classification	
Recurrent genetic abnormalities, *n*=	3/40 (8%)
With myelodysplasia-related changes, *n*=	17/40 (43%)
Therapy-related, *n*=	5/40 (13%)
Not otherwise categorized, *n*=	15/40 (38%)
WBC at diagnosis, median G/l (range)	4.65 (0.64–115.7)
LITR cycles—indication	
First-line, *n*=	181/215 (84%)
Salvage, *n*=	34/215 (16%)
LITR cycles—substance	
Decitabine, *n*=	53/215 (25%)
Azacitidine, *n*=	148/215 (69%)
LDAC, *n*=	14/215 (6%)

[a] Cytogenetic data were available in 35/40 (88%) of patients only.

3.2. Prevalence and severity of infections

Altogether, 29/40 (73%) of patients experienced at least one infectious complication during LITR administration (range, 1–6). When looking at single LITR cycles, 53/215 (25%) were complicated by the occurrence of infections. CTCAE grading (http://evs.nci.nih.gov/ftp1/CTCAE/About.html) revealed a median grade of 3 (range, 2–5). Six out of 29 (21%) patients with infections succumbed to this complication after developing severe sepsis, one infection resulted in LITR discontinuation in the affected patient. In 27/53 (51%) of LITR cycles with infections, a clinical source could be detected (Table 2). Pneumonia thereby proved to be the most frequent manifestation ($n = 12$), followed by gastroenteritis ($n = 5$) and urinary tract infection ($n = 3$). A microbiological source could be detected in 17/53 (32%) of affected LITR cycles (Table 2). Gram-positive bacteria could be observed in seven cases (all of them Staphylococci; Staph. aureus, $n = 2$; Staph. hominis, $n = 1$; Staph. haemoyticus, $n = 1$; Staph. intermedius, $n = 1$; Staph. epidermidis, $n = 1$, Coagulase-negative Staph., $n = 1$) and gram-negative bacteria in five (Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Legionella, Enterobacter, Escherichia coli). In two of the patients, a mixed gram-negative bacterial infection could be demonstrated. In the remaining three cases, a viral correlate could be identified, two of them caused by viruses of the Herpes group, one by Influenza (Table 2). No "proven" or "probable" invasive fungal infections were observed, when current EORTC/MSG definitions were applied [28,29]. However, eight cases could be classified as "possible" invasive fungal disease.