RESEARCH ARTICLE

Early warning and prevention of pneumonia in acute leukemia by patient education, spirometry, and positive expiratory pressure: A randomized controlled trial

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Long-lasting neutropenia associated with acute myeloid leukemia (AML) and its treatment gives rise to a high risk of pneumonia. The use of broad-spectrum antibiotic prophylaxis during outpatient management has not completely protected patients against admission due to infections and neutropenic fever, emphasizing the need to approach infection protection with complementary efforts. In a randomized controlled design, we examined the applicability of patient-performed daily spirometry [forced expiratory volume in one second (FEV1)] as an early warning tool and explored the effectiveness of positive expiratory pressure (PEP) in preventing pneumonia among 80 AML patients. Twenty-five incidences of pneumonia were detected among 23 patients (6 interventions, 17 controls), giving a prevalence of 28.75% during 5420 days of observation. We found a significant difference in incidence between intervention versus control group (2.17 per 1000 days vs. 6.52 per 1000 days, $P = 0.021$, respectively). A cross point at 80-76% of the personal FEV1 reference value showed high sensitivity and specificity on pneumonia development. Our data demonstrate the feasibility of educating AML patients in their continuous daily measurement of FEV1 and use of PEP. Daily measures of FEV1 may be an important early warning tool for assessment of pulmonary deterioration during critical phases of neutropenia. We suggest that strategic patient education in the use of spirometry and PEP should be part of standard of care for AML patients undergoing induction chemotherapy.

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Introduction

Acute myeloid leukemia (AML) and the applied courses of combination chemotherapy cause severe neutropenia, which is associated with serious infections and increased mortality [1–4]. The degree and duration of neutropenia are highly correlated with bacterial infections [1,4–6] such as septicemia, central venous catheter blood stream infections, and lung infiltrates that occur in 30–60% of AML patients [5,7–9]. These infections require intravenous broad-spectrum antibiotics [1,4,6,10], as well as antibiotic prophylaxis (AP) during neutropenia, which has been shown to improve infection prevention and overall survival [2]. Non-randomized studies show that treatment of acute leukemia can be performed on an outpatient basis, allowing the patient to remain at home while under supervision in the active treatment phase and neutropenia period [11–19]. Though feasible and safe, findings from our outpatient management study for acute leukemia showed that neutropenic fever followed by septicemia and pneumonia are the dominant causes of readmission during outpatient management [20]. Furthermore, pneumonia may prevent early discharge during neutropenia and may, as part of the overall infectious comorbidity, contribute to worsened quality of life at treatment completion [21].

An important question therefore arises, whether severe lung infections can be detected and/or prevented by complementary non-medical interventions such as patient-measured spirometry and self-administered positive expiratory pressure (PEP) with a PEP flute. To date, evidence for interventions to improve infection control during intensive chemotherapy for hematological malignancies is sparse [22] and the potential benefits of patient education and self-management strategies in outpatient management of acute leukemia are understudied.

Previously, we reported the values and efficacy of supervising and educating patients in their own central venous catheter care, with a significant decrease of catheter-related blood stream infection rates [23]. Additionally, encouraging patient participation to ensure high medical adherence in infection protection is an embedded strategic approach in acute leukemia outpatient management at the Copenhagen University Hospitals,

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Rigshospitalet and Herlev Hospital [20,24]. The current study investigated the rationale of initiating daily spirometry and PEP lung training with PEP flutes as a prophylactic measure against lower respiratory tract infection. No randomized controlled trials (RCT) have so far investigated the effect of these techniques in neutropenic patients with AML receiving induction and consolidation chemotherapy.

Methods and Materials

Study population

The study was conducted on specialized hematological units with inpatient and outpatient facilities at two Copenhagen university hospitals in the Capital Region of Denmark. Adult AML patients receiving induction chemotherapy were eligible to enter the study. The chemotherapy regimen was provided during hospital admission, while the following period of subsequent neutropenia was based on principles for early discharge with incorporation of AP [20]. The hematologist and nurses clinically assessed patients for infections, bleeding, vital parameters, need for blood and platelet transfusions and antibiotic adjustment every second day at outpatient clinic visits. In case of neutropenic fever, patients were admitted and treated according to local protocols for empiric antibacterial and antifungal treatment [20].

Patients received information and provided written informed consent after confirmed diagnosis and initiation of anti-neoplastic induction treatment given they were in a stable clinical condition with absence of a verified symptomatic infection. If this was not the case, patients were informed and included at onset of consolidation chemotherapy. Patients were followed for approximately three months during induction and consolidation chemotherapy or until a major clinical event, such as severe infection (i.e., lung infection or septicemia) requiring treatment at the intensive care unit (ICU) or that made further patient participation impossible. For patients requiring allogeneic stem cell transplantation in first remission, patients were observed within the study until the date of admission to the Bone Marrow Transplant Unit.

Inclusion criteria. Patients diagnosed with acute myelogenous leukemia or advanced myelodysplastic syndrome >18 years treated with induction and consolidation chemotherapy and subsequent profound neutropenia <0.5 billion/l were eligible candidates. Referred patients with radiologically verified pulmonary infiltrates had to recover before enrollment.

Exclusion criteria. Terminal care, senile dementia, psychosis, and unable to speak Danish. Patients diagnosed with pneumo and/or hemothorax were excluded.

Ethical approvals

The health research ethics committee for the Capital Region (H-D-2008-025) and the Danish Data Protection Agency (2008-41-1728) approved the study. ISRCTN registration: ISRCTN36674014.

Randomization

Patients were stratified by sex, age, and hospital setting and randomly allocated to either the intervention group, which received supervised patient education in self-performed spirometry and daily use of lung ventilation training with a PEP flute or to the control group, where patients received supervised patient education in self-performed spirometry only. Patients were randomized 1:1 +/− PEP using the computer-based randomization and stratification program CITMAS, anchored in a clinical research unit at Copenhagen University Hospital, Rigshospitalet.

Sample size calculation and statistical analyses

The incidence of the primary outcome (radiological evidence of pulmonary infiltrate) was based on findings of pneumonia prevalence in the unit [20,21] and estimated to be 0.40 in the control group versus 0.27 in the intervention group [standard deviation (SD) = 0.20]. An alpha of 0.05 and power of 0.80 implied an inclusion of 39 participants in each study group, thus 80 patients were randomized.

T-tests or $\chi 2$ tests using SAS version 9.1.4 and 9.3 were used to compare the distribution of demographic variables in study groups. Pearson's $\chi 2$ tests, Kaplan Meier curves, *t*-tests, and multiple linear regressions were used to analyze group differences on primary outcome and to elucidate associations with explanatory variables. Intention-to-treat analysis according to CONSORT guidelines (consort-statement.org) were applied to prevent bias and to enhance the validity of adherence measures.

Intervention and strategic patient education in study groups

Individual face-to-face patient education—general (control and intervention group). All patients received an individual 45 minutes face-to-face educational session with the clinical nurse expert on the significance of infection protection with AP, non-pharmacological approaches, and the fact that early detection of infections could be beneficial for treatment. Patients were informed that 40% were at risk for developing a lung infection with mild to severe symptomatology frequently requiring admission, often with a need for oxygen supplementation. Emphasis was placed on positive experiences in involving patients in core clinical procedures [23,24]. Moreover, patients were encouraged to avoid physical inactivity and to perform low to moderate exercise during hospital admission and outpatient care.

Measurement of lung capacity—forced expiratory volume in 1 second (FEV1) spirometry: (control and intervention group). Baseline measurement of lung capacity was performed using nSpire Health, Inc., PiKo-6 Electronic FEV1/FEV6 Meter (Longmont, CO) [25]. FEV1 was the primary measure to predict lung capacity. Baseline measurements of blood pressure, heart rate, body temperature, frequency of respiration, and peripheral oxygen saturation were also obtained. The patient's lung capacity was compared against the average lung capacity of non-smokers among the Danish reference population [26].

On a specific FEV1 form, patients noted their daily measurements and had to be aware of whether their personal reference value of FEV1 decreased below 80 or 90%. Patients had to provide this information to their clinicians at outpatient visits or to contact the ward immediately if symptomatic signs of lung infection or fever were present. The clinical nurse expert met with patients with a range from 7 to 14 days on outpatient visits or during admission. Data from the patients' PiKo-6 meters were transferred to a laptop with specific applied software. Thus, the lung capacity measurements FEV1, FEV6, and FEV1/FEV6 were visualized on a continuous curve, the patients' *adherence* to sustaining daily spirometry objectified, and PEP training evaluated.

Lung training with PEP flute: (intervention group). Patients allocated to the intervention group performed lung ventilation training with a PEP flute. Three airway resistances were delivered to each patient and equivalent to a resistance of 10–20 cm H_2O. Lung training included 15 breaths (for approximately 1 minute) at least three times, twice daily, if the FEV1 value was within the patients' personal FEV1 reference $\pm 10\%$. If FEV1 decreased below the 90% level, patients were instructed to increase PEP to 15 breaths three times, four times a day. Patients were instructed to use their PEP flute for three months under observation. Given that FEV1 was stable within a range of $\pm 10\%$, intermittent pauses were allowed when the neutrophil count was restored prior to the next course of scheduled chemotherapy

Primary outcome

Pneumonia, defined as X-ray-verified pulmonary infiltrate in addition to fever [27], was the primary outcome based on guidelines from

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TABLE I. Population Characteristics $n = 80$

	Intervention/ PEP $n = 40$	Control $n = 40$	
Gender: female/male	14/26	15/25	*NS*
Age *Mean (SD)*	56 (14)	56 (14)	*NS*
Diagnosis			*NS*
AML/MDS-AML	31/7[a]	30/7	
APL (FAB M3)	2	3	
Hospital Site			*NS*
Rigshospitalet	24	27	
Herlev Hospital	16	13	
Chemotherapy courses[b]			
Induction	49	52	
Consolidation	40	37	
Neutropenia (Total days)	1528	1522	*NS*
Mean (SD)	38 (17)	38 (21)	
Lung capacity			
FEV1[c] *M (SD)*	3,17 (0,72)	3,10 (1,01)	*NS*
FEV1 percent[d] *M (SD)*	97 (18)	95 (15)	
COLD (FEV1/FVC < 70%)	3	3	
Smoking status			*NS*
Never/Past[e] (%)	20 (50)	21 (52)	
Current	17 (42)	15 (38)	
No information	3 (8)	4 (10)	
Alcohol/drinks per week *M (SD)*	6,6 (7,8)	3,8 (4,8)	*NS*
No information (*n*)	3	5	
Marital status			*NS*
Married/partner	30	28	
Living alone/divorced/widowed	8	9	
No information	2	3	
Observation time (Total)	2764	2607	*NS*
Mean (SD)	69,1 (31)	65,2 (32)	
Time of inclusion (*n*/mean days since diagnosis (SD))			*NS*
Induction:	38/9,3 (8,1)	34/9,3 (5,9)	
Consolidation:	2/48,4 (9,2)	6/53,0 (6,4)	

Abbreviations: SD = standard deviation,.
[a] One patient altered diagnosis from AML to ALL.
[b] Supplemental online material available.
[c] FEV1 = Forced expiratory Volume in 1 sec,.
[d] Percent of FEV1 value compared to Danish population,.
[e] Quit smoking > 6 months, *NS* = not significant $P > 0.05$.

Statens Serum Institut, Copenhagen, Denmark (https://www.ssi.dk/) [28] and the British National Guideline Centre [29]. Imaging investigations were performed at the included sites with radiologists blinded to study group allocation. Study investigators were not involved in clinical decision-making.

In contrast to risk stratification in community-acquired pneumonia, no validated methods currently exist to risk score patients with hospital-acquired pneumonias or healthcare associated pneumonia [27]. Additionally, we did not separate or define pneumonias as either (HAP) or (CAP) due to the patients shifting statuses of being admitted or treated in the outpatient setting under prescription of AP during neutropenia [29].

For descriptive purposes and to determine the severity of pneumonia, we used a four sub-category graduation to overview the clinical impact of pneumonia: *grade 1*: X-ray-verified infiltrate, mild course, no complications, oral antibiotics, and followed on an outpatient basis; *grade 2*: X-ray-verified infiltrate, mild to moderate course, occasional need for intermittent nasal oxygen supply, no serious complications, standard broad spectrum intravenous antibiotics, and hospital admission ≤ 7 days; *grade 3*: X-ray-verified infiltrate, moderate to severe course, long-lasting presence of fever, potential concurrent infection (e.g., septicemia), intensified broad spectrum intravenous antibiotics, need for continuous oxygen supply, and hospital admission >7 days; and *grade 4*: X-ray-verified infiltrate, severe course demanding ICU care and ventilator-delivered oxygen support, intensified broad spectrum intravenous antibiotics, and potentially fatal consequences.

Results

Patient characteristics

From January 2009 to January 2011, there were 112 patients assessed for study enrollment (Supplemental consort flowchart available online). Two patients did not meet inclusion. Nine patients were excluded mainly due to progressive leukemia and/or complications such as severe infections ($n = 7$), another two patients did not write or speak Danish ($n = 2$). Thus, 101 patients were eligible with 21 refusals: fifteen felt they did not have sufficient physical and mental capacity to participate at such an early stage in their leukemia diagnosis, four did not think they had the ability to commit to patient education and spirometry measurement, and two declined to participate due to severe chemotherapy side effects. In the end, eighty patients with AML gave informed consent to participate, resulting in a recruitment rate of 79%.

The two study groups ($n = 40$ per group) were equal with respect to the stratification variables (sex, age, hospital site) as well as several other demographic and treatment covariates. Seventy-two patients (90%) equally grouped were included at time of induction chemotherapy or subsequent neutropenia with an average of 9 days since diagnosis. Eight patients were included during consolidation. (Table I). (Supplemental overview of chemotherapy courses available online)

Patient adherence and dropout

Of the included patients 77/80 (96%) mastered the technique of self-managed spirometry, though the electronic transfer of data showed that adherence varied from extremely poor to very high (Supporting Information figure available online). PEP adherence, which relied on patient feedback at weekly meetings, implied that exact measures could not be objectified. The overall median adherence to spirometry was 70.5% (mean 63%, SD 27, range 95). No single significant variance of setting, sex, age, marital status, alcohol consumption, or study group allocation was significantly associated to adherence. Being a non-smoker tended to be associated to higher adherence (mean 69% SD 25) compared to smokers (mean 59%, SD 24, $P = 0.070$). Attrition in adherence was borderline significant between the induction (mean 70.1%) and consolidation phase (mean 60.0%, $P = 0.043$).

Seven cases of complicated infectious diseases (septicemia and acute organ malfunctioning) emerged during induction chemotherapy, leading to patient discontinuation without a verified lung infiltrate (three interventions, four controls). In three cases, patients died, another three patients recovered after prolonged treatment, and one patient never fully recovered.

Eight patients, equally grouped, dropped out (10%) due to psychological factors, e.g., primarily distress and lack of mental resources and uncertainty about life expectancy due to incomplete treatment response. The measured adherence rate based on electronic spirometry among dropouts and patients with major clinical events was markedly lower than among completers (mean 45%, SD 26 versus mean 67%, SD 25, $P = 0.003$)

Educational program

Seventy-seven patients (96%) completed the initial educational program and test in using the spirometry Piko-6 meter. One patient experienced acute respiratory symptoms on day 1 and died in the ICU shortly after the onset of infection; another patient had acute onset of neutropenic fever and experienced severe side effects; and a

TABLE II. Verified Lung Infiltrates/Pneumonia During Study

	Intervention/ PEP $n = 40$	Control $n = 40$	*Comments* *NS = P > 0.05*
Pneumonia: (*n*)	6	17	*P = 0.007*
Incidence per 1000 days	2,17	6,52	*P = 0.021*
Pneumonia: female/male	1/5	5/11	*NS*
Pneum/non-pneum: Age *M*	62/55	59/53	*NS*[a]
Pneumonia induct/Consol (*n*)	4/2	13/4	*P = 0.024*
Pneumonia severity:			
°Grade 1 (%)	0 (0%)	1 (3%)	
°Grade 2 (%)	2 (5%)	8 (20%)	
°Grade 3 (%)	3 (8%)	4 (10%)	
°Grade 4 (%)	1 (3%)	4 (10%)	
Pneumonia season:			
°Spring	3	4	
°Summer	0	3	
°Fall	2	6	
°Winter	1	4	

[a] Not significant within or between groups.

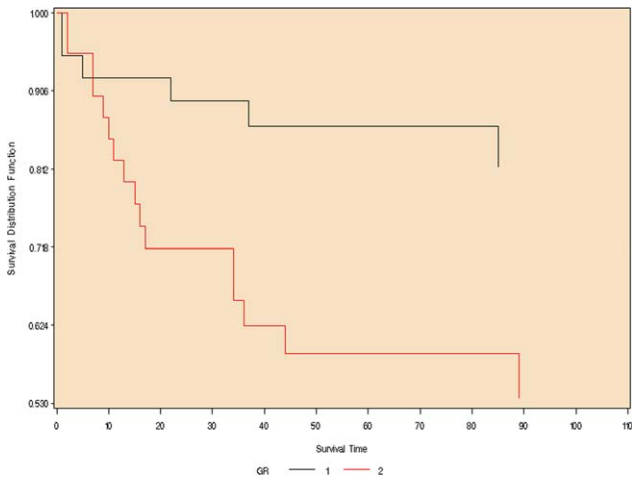

Figure 1. Pneumonia development. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

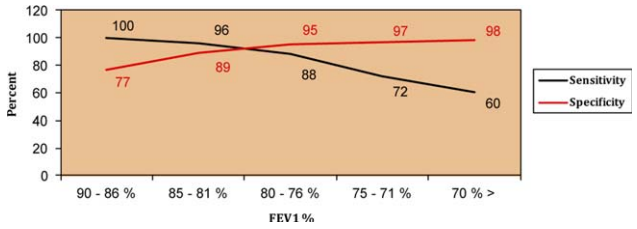

Figure 2. FEVI sensitivity and specificity curve. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

third patient never started the educational program due to psychological problems and refractory disease. The majority of educational sessions (spirometry and PEP for the intervention group) were generally performed during induction chemotherapy and completed in three consecutive days. The duration of the face-to-face educational sessions on infection protection and spirometry instruction was approximately 60 minutes, plus an additional 30 minutes for patients receiving PEP. Patients had follow-up meetings lasting 20–40 minutes every 7–4 days with the clinical nurse expert to ensure that patients used the right techniques and to support adherence. No adverse events were detected related to spirometry or PEP during neutropenia. One control group patient experienced a subconjunctival hemorrhage and took a three-week break from doing spirometry until recovery.

Primary outcome: X-ray-verified pulmonary infiltrate

During the period from diagnosis, 28 patients (35%) developed a lung infiltrate (35 cases), but 10 cases occurred before study enrolment, since the majority of patients (84%) were enrolled post-diagnosis at the completion of induction chemotherapy or during subsequent neutropenia (see patients enrollment Table I). Thus, 25 incidences of lung infiltrates were prospectively detected during the study observation among 23 patients (six interventions, 17 controls), giving a prevalence of 28.75%. There was no statistical difference in the presence of pre-study pneumonia leading to pneumonia following study enrollment between the intervention group ($n = 2$) and controls ($n = 3$).

All pneumonias emerged during chemotherapy induced neutropenia, the majority (74%) subsequent to induction chemotherapy at mean 21 days (SD 14) following onset of chemotherapy. Pneumonias were treated in accordance to local guidelines for antibiotic treatment of neutropenic fever [20].

In only one case, pneumonia was treated on an outpatient basis with orally administered antibiotics, while 22/23 (96%) required admission and provision of broad-spectrum intravenous antibiotics. In 12/23 cases (52%), pneumonias were characterized as severe, involving long-lasting presence of fever and potential concurrent infection and in five cases (22%), ICU admission was required. Three of the five patients transferred to the ICU died. (Table II)

The study found no single significant association of baseline FEV1 percentage, COLD, marital status, sex, age, smoking, or alcohol consumption on pneumonia development. A significant difference was found in first pneumonia incidence between intervention versus control group (2.17 per 1000 days vs. 6.52 per 1000 days, respectively, rate ratio = 3.004, 95% confidence interval: 1.184–7.619, $P = 0.021$).

Illustrated on a Kaplan Meier survival curve and using a log-rank test, there was a statistically significant difference in time for developing a verified lung infiltrate that favored the intervention, $P = 0.016$ (Fig. 1). Pneumonias seemed to be prevented, especially during the induction phase.

Microbial findings related to verified pneumonia

In 17 (68%) out of 25 pneumonias, no microbial findings were detected in bronchoalveolar lavage or sputum. Unspecified yeast was the most common microorganism cultured and microscopy of lower airway material was negative in 96% of cases. In only 7/25 cases (28%) a convincing pathogen was isolated from the airway material. We identified one case with *Stenotrophomonas maltophilia* that caused severe pneumonia and led to a fatal outcome despite relevant antibiotic treatment. In two cases of *Aspergillus fumigatus*, the molds were not seen by microscopy, but the patients were treated with relevant anti-fungals. (Supporting Information Table available online)

FEV1, sensitivity and specificity with verified pneumonia

Across group allocation, verified pneumonias were associated with a significant FEV1 decrease to 85–36% of the personal FEV1 reference value. A sensitivity and specificity curve was estimated by incorporating 5487 FEV1 measures from 70 participants (Fig. 2). Ten patients representing four cases of pneumonia were left out of the calculation due to severe comorbidity and/or very poor lung capacity test adherence, leaving 21 out of 25 valid pneumonia cases for the final analysis.

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Figure 2 demonstrates the sensitivity and specificity curve for FEV1 related to X-ray-verified pneumonia. The two curves have a cross point at 80–76% of the personal FEV1 reference value given a sensitivity and specificity above 90%. Even using an 85–81% cutoff for the individual reference value, FEV1 is associated with high test validity for verified pneumonia.

Using a FEV1 cut-off at 85–81%, the predictive diagnostic value of a positive test was 34% and with a negative predictive value of 88%. With a FEV1 cut-off at 80%, the predictive diagnostic value of a positive test was 70% and with a negative predictive value of 94%.

In 9/21 cases (43%), an FEV1 decrease >15% was observed one to four days prior to an upcoming X-ray-verified pneumonia. This result could potentially be even higher since the development of infectious disease sometimes led to a decrease in patients' daily spirometry adherence and consequently invalid measures. We do not have strict comparative data for pulse oxygen saturation (SAT) to compare with FEV1 results.

Discussion

Pneumonia remains a major challenge in acute leukemia treatment [5,8,9,30] with a substantial mortality [27,31]. Prospective reports have demonstrated the feasibility and safety of outpatient management and early discharge of acute leukemia by inclusion of broad-spectrum AP [11,12,17,18,20]. According to a Cochrane review [32], AP during severe neutropenia among the present AML cohort was not sufficient to prevent radiologically verified pneumonia. We found 25 incidences of pneumonia, the majority (96%) having moderate to severe clinical impact requiring hospital admission and in 20% of these ICU care. Seventeen cases (74%) emerged during or following induction chemotherapy. The prevalence was in range with previous reports [8,33]. Similar to other studies using AP [31], microbial findings from bronchial alveolar lavage and sputum in general were sparse and dominated by yeasts alone or coagulase negative staphylococci of unknown pathogenic significance. The most likely explanations for the lack of relevant pathogens are use of AP during severe neutropenia and the early shift to broad spectrum empiric antibiotic treatment upon onset of airway symptoms in combination with culture based methods.

The provision of chemotherapy and acute leukemia patients experiencing high levels of side effects along with diverse morbidity may constitute a risk of prolonged bed rest [21,34,35]. The present RCT advocates for systematic introduction of patient education, led by a clinical nurse specialist on the use of spirometry and PEP flute training 2-4 times a day, especially during induction chemotherapy. We assume that the causal effect of non-invasive PEP on a daily basis during severe neutropenia is related to the mechanically supported inflation of the alveoli and loosening of secretions that may have prevented atelectasis and lower tract infection at early stages, thereby hindering progression to manifest lung infiltrates [36]. Non-pharmacological prevention of pulmonary diseases has included invasive (endotracheal intubation) and noninvasive (mask, helmet) mechanical ventilatory support for respiratory deficient hypoxic patients [37]. Effects are documented on morbidity and survival compared with endotracheal mechanical ventilation [38] and conventional oxygen delivery [39,40]; however conflicting results exist [41–44]. An RCT among hematological patients admitted to the ICU, showed that comprehensive 45-minute noninvasive ventilation every 3 hr with face mask connected to a ventilator (CPAP/PEEP), in addition to oxygen therapy, can reduce the number of intubation cases and increase survival compared to initial oxygen therapy alone [45]. The present study suggests that assisted breathing in a markedly lower volume may be beneficial in preventing pneumonia in this at-risk population of AML during the pancytopenic phase of induction chemotherapy.

In the present study, daily FEV1 assessment was found to be an early predictor in 9/21 pneumonia cases (43%) using an 85% individual threshold for FEV1 decline. We suggest a clinically relevant positive and negative predictive test value using a FEV1 cut-off at 85 or 80%. The challenge in implementing lung capacity measurements such as FEV1 in daily leukemia practice is the need for interpretation of individual measures due to variation in height and sex, whereas measurement of, e.g., pulse oximetry (SAT) is convenient due to a global measure across individuals [46]. We do not have strict comparative data of SAT measures against FEV1 measures. Based on available data from the patient records, we were unable to detect any cases where SAT was predictive of pneumonia. In 20/23 (87%) pneumonia cases, FEV1 declined to ≤80%, though at least 12/23 (52%) had an oxygen saturation ≥95% on the day of radiologic verification. The decline in oxygen saturation seems to be a later sign of progressive and severe manifest pneumonia and is insufficient as an early warning parameter in asymptomatic patients with ensuing pneumonia.

Our study suggests that involving patients in core clinical procedures remains a challenge in the effort to support patient adherence in interplay with clinicians and when taking into account the sudden shift in acute morbidity. Nonetheless, and in line with our previous research involving patients in core clinical procedures [23], we assume that each face-to-face educational session with the clinical nurse specialist, combined with a graphical overview of the patient's FEV1 measures, is essential to sustain patient participation and adherence to non-pharmacological prevention.

In conclusion, our data demonstrate the feasibility of educating AML patients in their continuous daily measurement of FEV1 and use of PEP. We demonstrated the value of declining individual FEV1 in predicting pneumonia as well as the pneumonia preventive effect of daily patient-administered PEP, especially during the induction phase of AML treatment. We suggest that systematic patient education in the use of FEV1 measurements and PEP should be part of standard care for AML patients undergoing induction chemotherapy.

Author Contributions

All authors made substantial contributions to research design, analysis and interpretation of data. All authors were involved in drafting the paper and revised it critically before approval and final submission. TM was primary investigator and first author in writing and preparing the manuscript in its present form. TM, LA, CM, MJ and LK outlined the trial conduction as well as building the manuscript and analysis. GR, TB and LW gathered clinical data from patient records and contributed substantially to data analysis and trial conduction. CM provided microbial data from regional databases. MJ did linguisticly revise the manuscript.

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