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ORIGINAL ARTICLE

Outcomes in critically ill chronic lymphocytic leukemia patients

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Abstract
Background Although recent studies have demonstrated an improvement in the prognosis of critically ill cancer patients, little is known regarding the prognosis of patients with non-aggressive underlying malignancies. The aims of this study were to assess the prognosis of critically ill patients with chronic lymphocytic leukemia (CLL) and to evaluate risk factors for hospital mortality.
Methods In retrospective mono-center cohort study, consecutive adult patients with CLL requiring ICU admission from 1997 to 2008 were included.
Results Sixty-two patients of 67 years (62–75) were included. Median time interval between CLL diagnosis and ICU admission was 6.7 years (2.6–10.8). Nine patients (15 %) had stage C disease at the time of ICU admission, and seven patients (11 %) had Richter syndrome. Most ICU admissions were related to bacterial or fungal pulmonary infections (n=47; 76 %). ICU, in-hospital, and 90-day mortality were 35 % (n=22), 42 % (n=26), and 58 % (n=36), respectively. Only three factors were independently associated with in-hospital mortality: oxygen saturation lower than 95 % when breathing room air (odds ratio (OR) 5.80; 95 % confidence interval (CI) 1.23–27.33), need for vasopressors (OR 27.94; 95 % CI 5.37–145.4), and past history of infection (OR 6.62; 95 % CI 1.34–32.68). The final model did not change when disease-related variables (Binet classification, Richter syndrome, long-term steroids) or treatment-related variables (fludarabine, rituximab, or alemtuzumab) were included.
Conclusion Acute pulmonary infections remain the leading cause of ICU admission in patients with CLL. The severity at ICU admission and past history of infection were the only factors associated with hospital mortality. Neither disease characteristics nor previous cancer treatments were associated with outcome.

Keywords Leukemia · Lymphocytic · Chronic · B cell · ICU · Vasoconstrictor agents · Fludarabine · Alemtuzumab

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Introduction

The ICU admission of critically ill cancer patients (CICPs) has long been controversial. In studies conducted before 1995, the use of any form of life-sustaining treatment was associated with high mortality rates [1, 2]. Most of these studies demonstrated that life-sustaining therapies, neutropenia, and bone marrow transplantation are associated with poor outcome [3, 4]. Recent studies have shown an improvement in the prognosis of CICPs, although information regarding the prognosis of patients with non-aggressive underlying malignancies are scarce [5–8]. A study performed three decades ago reported that critically ill patients with chronic lymphocytic leukemia (CLL) had surprisingly low in-hospital mortality rates [9]. These divergent results probably reflected the substantially different hematological outcome of CLL patients compared with those with high-grade hematological malignancies [10].

CLL is a chronic hematological malignancy characterized by proliferation of mature B cells [11]. Although some patients suffer from a rapidly progressive disease, CLL is usually associated with long-term survival [11, 12]. However, CLL may promote bacterial, viral, fungal, or parasitic infections that may lead to ICU admission [11–13]. Aggressive treatments with monoclonal antibodies (alemtuzumab or rituximab) or fludarabine have beneficial effects on disease progression and overall survival, along with a dramatic increase in bacterial or viral infections [14, 15]. As half the patients assigned to watchful waiting strategies have features suggesting a poor outcome, more aggressive strategies may be beneficial for this specific patient subgroup [11], although it is likely that these aggressive strategies may result in an increase in ICU admissions. This is the first study to focus specifically on the prognosis of patients critically ill with CLL.

Patients and methods

The main aim of this study was to describe characteristics and outcome of patients with CLL requiring ICU admission. The secondary aim was to evaluate factors independently associated with outcome in these patients, with a specific focus on recent and aggressive cancer therapies (fludarabine, rituximab, or alemtuzumab).

We included consecutive patients with CLL who were admitted to the medical ICU of the Saint-Louis University Hospital between January 1, 1997, and December 31, 2008. ICU admission charts, which contain main reason for ICU admission and underlying malignancy when appropriate for every ICU patients admitted in our ICU, were double checked by two investigators (AX and LE) in way to retrieve CLL patients. This paper chart is collected prospectively in our ICU on a daily basis.

The Saint-Louis University Hospital is a 650-bed university hospital in Paris, France, with 330 oncology beds. Around 600 patients with newly diagnosed malignancies are admitted to the hospital every year. The medical ICU is a closed 12-bed unit that admits 550 to 600 patients per year, including around 150 patients with solid tumors or hematological malignancies. Critically ill cancer patients were selected for ICU admission as described elsewhere [16, 17].

Admission to the ICU was not considered for bedridden patients or patients for whom no lifespan-extending treatment was available. Conversely, patients at the initial stage of their malignancy were offered full-code ICU management. For patients who did not fit into either of these two groups, it is extremely difficult to evaluate the potential benefits of ICU admission early in the acute disease; therefore, a trial of full-code ICU management was recommended. After several days, the clinical course was evaluated and the treatment strategy reappraised. There was no specific admission policy for CLL patients in our institution during the study period.

For every patient included, data regarding patients' characteristics, underlying malignancy, received treatments, severity at ICU admission, organ failure at admission, and during ICU stay and main reasons for admission were collected. The Logistic Organ Dysfunction (LOD) score was calculated at admission, and the Binet classification at time of ICU admission was reported [18, 19]. LOD score is a severity score increasing with number and severity of organ dysfunction [19]. This widely used score provides an estimate of the risk of death based on organ dysfunction, higher score translating into poorer outcome. Sepsis was diagnosed using the criteria developed at the American College of Chest Physicians/Society of Critical Care Medicine consensus conferences [20]. Individual organ failure was defined as a LOD score>1 point for each system [19]. This study was approved by our institutional review board. Vital status at hospital discharge and 90 days after ICU admission was obtained from the electronic central database of the Saint-Louis University Hospital. Neutropenia was defined as a neutrophil count lower than 1,000/mm^3. Chronic cardiac dysfunction was defined as any NYHA stage of previously diagnosed cardiac dysfunction. Chronic obstructive pulmonary disease (COPD) was defined according to the ATS guidelines [21]. Chronic kidney disease was defined as a creatinine clearance lower than 60 ml/min for three months or more.

Statistical analysis

Results are reported as medians and quartiles (interquartile range, IQR) or numbers (in percent). Categorical variables were compared using the chi-square test or Fisher's exact

test, as appropriate, while continuous variables were compared using the non-parametric Wilcoxon test or the Mann–Whitney test. Logistic regression analyses were performed to identify variables that significantly influenced hospital mortality, as measured by the estimated odds ratio (OR) with a 95 % confidence interval (95 % CI). Variables yielding *P* values less than 0.20 in the bivariate analyses were entered into a forward stepwise logistic regression model where hospital mortality was the outcome variable of interest. The covariates were entered into the model with critical entry and removal *P* values of 0.05 and 0.1, respectively. Finally, clinically important variables were introduced into the final model. Collinearity and interactions were tested. The Hosmer–Lemeshow test was used to check goodness of fit of the logistic regression. For the given number of events (26), a maximum of three variables were entered into the model. All tests were two-sided, and *P* values less than 0.05 were considered statistically significant. Statistical tests were conducted using the SAS 6.12 software package (SAS Institute Inc., Cary, CA, USA).

Results

Studied population

Sixty-two patients with a median age of 67 years (IQR 62–75) were included in this study. The main characteristics are reported in Table 1. The median time interval between CLL diagnosis and ICU admission was 6.7 years (2.6–10.8). Nine patients (15 %) had stage C disease at the time of ICU admission, while seven patients had Richter syndrome. These conditions were not associated with in-hospital survival (Table 1). At ICU admission, most of the patients (86 %) were receiving chemotherapy (Binet stages A and B, 70 %; Binet stage C and Richter syndrome, 95 %). Treatments included fludarabine in 36 patients (58 %), rituximab in 14 patients (23 %), and alemtuzumab in six patients (10 %). The most frequent combination regimens were rituximab-associated chemotherapies in 14 patients (including R-COP-derived regimens and RFC regimens in eight and six patients, respectively), COP-derived regimens (seven patients), and fludarabine-cyclophosphamide (seven patients). Twenty-two patients (35 %) received steroids. A splenectomy was performed in four patients (6 %) during the course of their disease.

Thirty-six patients (58 %) had a past history of bacterial infection during the course of CLL, including seven patients with recurrent infections. Among them, there were 28 cases of infectious pneumonia, ten cases of peritonitis, six cases of septicemias, and five urinary tract infections. Most of the patients had associated comorbidities, including hypertension in 15 patients (24 %), diabetes in seven patients (11 %), COPD in seven patients (11 %), and chronic cardiac insufficiency in 12 patients (19 %).

At ICU admission, the median LOD score was five (1–12). Sepsis was the main reason for ICU admission (n=50; 81 %). Organ dysfunction leading to ICU admission included hypoxemia in 26 patients (42 %; SaO_2 <95 % when breathing room air), shock in 18 patients (29 %), and acute kidney injury in 10 (16 %). During the ICU stay, half of the patients received ventilatory support (n=31) and 30 (49 %) received vasopressors. Renal replacement therapy was required in ten patients (16 %). Overall, most of the ICU admissions were related to a bacterial or fungal pulmonary infection (n=47; 76 %), including bacterial pneumonia in 38 patients, *Pneumocystis jiroveci* pneumonia in seven patients, and invasive pulmonary aspergillosis in two patients.

Outcome

The ICU, in-hospital, and 90-day mortality were 35 % (n=22), 42 % (n=26), and 58 % (n=36), respectively. The median (IQR) ICU length of stay was 5 days (3–9) and was similar in ICU survivors and non-survivors [5 (3–7) vs. 5 (2–13); P=0.76]. Hospital mortality was 60 % (n=12) in patients admitted before 2002 and of 33 % (n=14) in patients admitted in 2002 or later (P=0.06).

Risk factors with unfavorable outcomes

Using logistic regression, only three factors were independently associated with in-hospital mortality: oxygen saturation lower than 95 % when breathing room air (OR 5.80; 95 % CI 1.23–27.33), need for vasopressors (OR 27.94; 95 % CI 5.37–145.4), and past history of infection (OR 6.62; 95 % CI 1.34–32.68). The final model was not changed by the forced inclusion of disease-related variables (Binet classification, Richter syndrome, long-term steroids) or treatment-related variables (fludarabine, rituximab, or alemtuzumab). Similarly, when forced, the year of ICU admission (before 2002 vs. 2002 or latter) was not selected and did not change the final model. Severity, which was assessed using the LOD score at day 1 (LOD day 1), was closely associated with in-hospital mortality (Fig. 1). When forced into the final model, the LOD score was selected (OR 1.18; 95 % CI 1.005–1.38; P=0.04), and previously mentioned variables were maintained (Table 2).

Discussion

Main findings

Our study is one of the very few to focus on critically ill patients with CLL. The overall hospital survival rate was

Table 1 Patient and CLL characteristics in hospital survivors and non-survivors

	All patients (*N*=62)	Survivors (*N*=36)	Non-survivors (*N*=26)	OR	95 % CI	*P* value
Male gender	49 (79 %)	28 (77 %)	21 (81 %)	0.75	0.43–1.32	0.31
Age	67 (62–75)	69 (63–75)	66 (60–71)	0.97	0.91–1.02	0.21
LOD score at ICU admission [19]	5 (1–12)	3 (1–5)	14 (5–18)	1.29	1.14–1.46	**<0.0001**
CLL characteristics						
Binet classification C [18]	9 (15 %)	4 (11 %)	5 (19 %)	1.79	0.41–7.86	0.44
Richter syndrome	7 (11 %)	2 (6 %)	5 (19 %)	4.05	0.72–22.78	**0.08**
Hypogammaglobulinemia	20 (32 %)	15 (42 %)	5 (19 %)	0.22	0. 06–0.85	**0.03**
Past history of infection	36 (58 %)	16 (44 %)	20 (77 %)	4.17	1.35–12.83	**0.01**
Splenectomy	4 (6 %)	2 (6 %)	2 (8 %)	1.42	0.19–10.77	0.73
Autologous stem-cell transplantation	5 (8 %)	2 (6 %)	3 (12 %)	2.21	0.34–14.33	0.40
Long-term steroids	22 (35 %)	7 (19 %)	15 (58 %)	5.65	1.82–17.87	**0.003**
Comorbidities						
Hypertension	15 (24 %)	9 (25 %)	6 (23 %)	0.90	0. 28–2.94	0.86
COPD [21]	7 (11 %)	2 (6 %)	5 (19 %)	4.05	0.71–22.78	0.12
Chronic kidney disease	6 (10 %)	3 (8 %)	3 (12 %)	1.44	0.27–7.75	0.67
Cardiac insufficiency	12 (19 %)	7 (19 %)	5 (19 %)	0.99	0.27–3.54	0.98
Diabetes mellitus	7 (11 %)	5 (14 %)	2 (14 %)	0.52	0.09–2.90	0.45
Characteristics at ICU admission						
SaO2<95 % while breathing room air	26 (42 %)	10 (28 %)	16 (62 %)	4.16	1.42–12.19	**0.009**
Shock	18 (29 %)	4 (11 %)	14 (53 %)	9.33	2.56–34.05	**0.0007**
Coma	14 (23 %)	7 (19 %)	7 (26 %)	4.1	0.99–9.39	**0.01**
Acute kidney injury	10 (16 %)	6 (17 %)	4 (15 %)	0.90	0.23–3.6	0.89
Neutropenia	18 (29 %)	8 (22 %)	10 (36 %)	2.19	0.72–6.67	0.16
Clinically documented infection	50 (81 %)	24 (67 %)	26 (100 %)	2.43	0.82–7.20	0.11
Treatments in the ICU						
Ventilatory support (CMV or NIMV)	31 (50 %)	8 (23 %)	23 (88 %)	26.83	6.38–112.9	**<0.0001**
Including non-invasive MV	*17 (27 %)*	*7 (19 %)*	*10 (39 %)*	2.59	0.83–8.12	0.10
Vasopressive agents	30 (49 %)	8 (23 %)	22 (85 %)	18.56	4.93–69.83	**<0.0001**
Renal replacement therapy	10 (16 %)	2 (6 %)	8 (31 %)	7.56	1.45–39.41	**0.02**

Bold values are *P* values statistically significant (below 0.05)

58 %. Neither characteristics of the underlying malignancy nor disease-related treatments were associated with in-hospital mortality.

Discussion of the results and existing literature

In patients critically ill with CLL, sepsis was the main reason for ICU admission, while most patients were admitted with bacterial pulmonary infections. Previous studies identified respiratory failure and infections as common reasons for admitting critically ill cancer patients [7, 16, 17, 22, 23]. Patients with CLL may be particularly prone to developing pulmonary infections [24, 25]. Up to 80 % of CLL patients contract an infection during the course of their disease, with half of them experiencing recurrent infections [26, 27]. Furthermore, infectious disease remains the leading cause of death during the course of CLL [28, 29]. This predisposition to infections is explained both by immune defects inherent to CLL and by drug-related immunosuppression [13, 26, 27, 30]. CLL-induced hypogammaglobulinemia may also explain the predisposition to pulmonary infections [24, 27].

Our study failed to demonstrate any association between prognosis after ICU admission and previous treatments using monoclonal antibodies or fludarabine. Previous studies demonstrated increased rates of bacterial and opportunistic infections when using a combination of alemtuzumab and fludarabine. A recent study comparing two frontline regimens in CLL was terminated prematurely because of an increased rate of infectious events in the alemtuzumab-containing regimen [14]. Similarly, several studies demonstrated a high rate of serious infections when using fludarabine and alemtuzumab combinations [31, 32]. When used as rescue therapy, this combination regimen, although proven efficient for disease control, failed to demonstrate any survival advantage [33]. Higher rates of severe bacterial

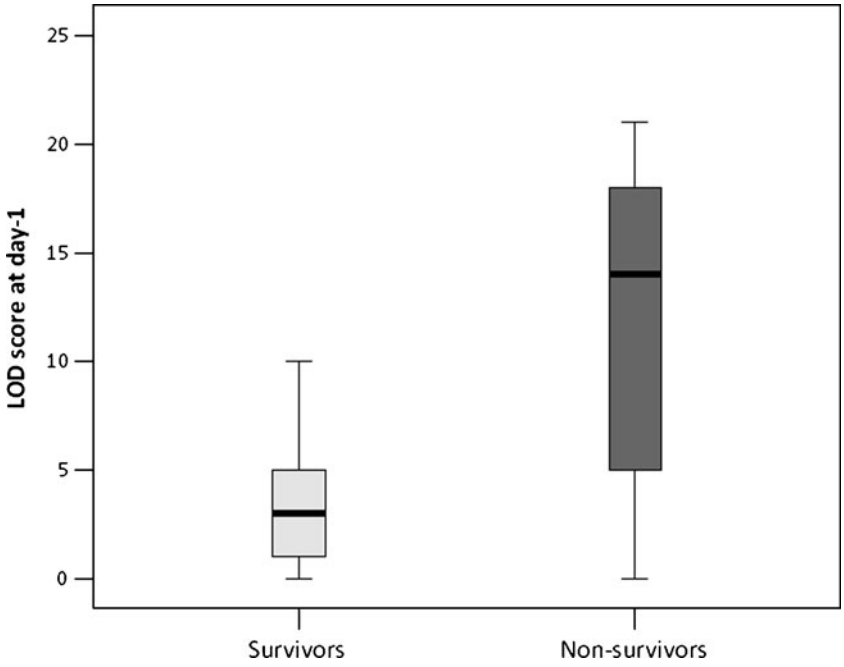

Fig. 1 Logistic Organ Dysfunction scores [19] at day 1 in hospital survivors (*light gray*) and non-survivors (*dark gray*)

and opportunistic infections may explain this finding [33]. However, our study focused on patients requiring ICU admission. Therefore, although previous treatments are likely to influence the risk of contracting a severe infection, our study failed to demonstrate any prognostic impact in patients already admitted to the ICU with severe sepsis or pneumonia. Similarly, our study did not find an association between hypogammaglobulinemia and outcome. Previous studies have demonstrated hypogammaglobulinemia levels below 4 g/L to be a significant risk factor for severe infections [30]. However, this risk factor has been challenged by a recent publication [25], although the influence of drug-related immunosuppression may have modified the risk factors of severe infection in this study.

In our study, the overall prognosis was very similar to those reported in recent studies focusing on critically ill cancer patients [7, 16, 17, 22, 34, 35]. Interestingly, hospital survival in our study was very similar to the hospital mortality in specific subgroups of critically ill cancer patients, such as patients with acute leukemia [34, 35]. Our study confirms that conditions previously considered as risk factors for in-hospital mortality, such as neutropenia, are no longer relevant in critically ill patients with hematological malignancies [36]. Furthermore, while older patients are more prone to having underlying comorbidities, this study demonstrates that the hospital prognosis of these patients is meaningful. Interestingly, infection as the reason for ICU admission was not retrieved as a protective factor. Recent studies determined when infection was the cause of ICU admission, and it was associated with a better hospital prognosis [23]. However, most of the patients in this study had infection at ICU admission.

Table 2 Logistic regression: independent predictors of hospital mortality [area under the receiver operating characteristics curve=0.82; Hosmer–Lemeshow goodness of fit (κ^2=3.01; P=0.81)]

	Odds ratio	95 % CI	P value
Oxygen saturation lower than 95 %	5.80	1.23–27.33	0.03
Past history of infection	6.62	1.34–32.68	0.02
Vasopressors	27.94	5.37–145.4	<0.0001

CI confidence interval

Limits of the study

Our study had several limitations. First, the study was conducted on a limited number of patients. Thus, there was a lack of statistical power to demonstrate any prognostic impact of disease characteristics or treatments. However, we focused only on patients already requiring ICU admission. Future studies should focus on the entire population of CLL patients to evaluate the influence of such treatments on ICU admission. Furthermore, this study was conducted over a decade time period. The prognosis for certain patients is likely to have improved during the study period [5, 17]. A striking change in hospital mortality was observed during the study period (60 % before vs. 33 % after 2001), although it was not statistically significant. This change is in accordance with those observed in the general population of critically ill cancer patients during the study period [5]. This improvement may be explained by several factors including changes in the overall prognosis of cancer patients, recent advances in supportive care in the ICU, and earlier ICU

admission of critically ill cancer patients [5]. However, we must emphasize that we did not have the statistical power to demonstrate any such improvement in this study. Finally, we conducted a single-center study, which may limit the generalizability of our results to the entire population of patients critically ill with CLL.

Conclusion

This study demonstrated a meaningful hospital survival rate in patients critically ill with CLL. In this subgroup of patients, the in-hospital prognosis was associated with the severity at ICU admission, which was defined by lung dysfunction, the need for vasopressors, or past history of infection. After adjustment for confounders, neither the characteristics of the underlying malignancy or previous use of fludarabine or therapeutic monoclonal antibodies (alemtuzumab or rituximab) were found to have a prognostic impact. Our study suggests that patients critically ill with CLL should not be denied ICU admission. Future studies are needed to evaluate the influence of such treatments or characteristics on the need for ICU admission.

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Conflict of interest None of the authors had any conflict of interest related to this manuscript to report. MD had full access to the data, take full responsibility for the statistical analysis and the accuracy of the results report. The journal is allowed to access and review these data if requested.

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