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ORIGINAL ARTICLE

Healthcare burden and reimbursement of hospitalization during chemotherapy for adults with Ph-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia in France: a retrospective chart review

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ABSTRACT

Objective: Philadelphia chromosome negative [Ph(−)] relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL) is an extremely rare condition requiring intensive treatment. This retrospective chart review aimed to quantify hospitalizations and reimbursement in this patient population in France.

Methods: Patients aged ≥18 years and with at least one hospitalization for Ph(−) R/R B-precursor ALL were included in the study. They were relapsed with first remission lasting <12 months, relapsed after first salvage therapy, relapsed any time after hematopoietic stem cell transplant (HSCT), or were refractory to initial or salvage therapy. Data were collected from the index date (first diagnosis of R/R ALL) until death or loss to follow-up. The chemotherapy period was defined as the first chemotherapy date after the index date to the earliest of death, loss to follow-up, last chemotherapy dose plus 30 days, or initiation of HSCT. The primary outcome was the percentage of time hospitalized during the chemotherapy period.

Results: Thirty-three patients were included, with a mean age of 49 years. The mean proportion of time spent in the hospital during the chemotherapy period was 46% (95% CI =34–57%). Patients had a mean of 2.2 (SD =1.5) inpatient hospitalizations and the mean length of stay per hospitalization was 16.8 (SD =14.8) days. During the chemotherapy period, the mean amount reimbursed per hospitalization was €31 067 (SD = €4850) and the total hospitalization reimbursement per patient was €68 344. From the index date to death, excluding HSCT, the total reimbursement per patient was €108 873.

Limitations: The sample size was small, although this was expected given the rarity of the patient population.

Conclusions: Adults with Ph(−) R/R B-precursor ALL had repeated and prolonged hospitalizations during salvage chemotherapy. Approximately half the follow-up period was spent in the hospital, and this time was associated with high economic burden in France.

Introduction

Acute lymphoblastic leukemia (ALL) is a rare hematologic malignancy with an estimated annual incidence rate in adults of approximately 1.4 per 100 000[1,2]. In ALL, the aggressive production of abnormal lymphoblasts suppresses and crowds out the production of normal blood cells in the bone marrow, causing hematological deficiency—specifically anemia, immune system impairment, and thrombocytopenia[3]. In most patients with ALL, the disease is diagnosed within a few weeks after onset of symptoms, and the symptoms are severe enough to require urgent medical attention. Diagnosis invariably leads to immediate hospital admission for symptom management and treatment initiation, without which most patients with ALL would die within days to weeks[3].

Philadelphia chromosome negative [Ph(−)] B-cell precursor ALL is a sub-population of ALL, which historically has had no targeted treatment options after relapsing or becoming refractory (R/R) to treatment. The estimated annual incidence rate of adults with Ph(−) R/R B-cell precursor ALL is 0.2 per 100 000 person-years, corresponding to 120–130 new patients per year in France[4]. Until the recent approval of blinatumomab[5,6], treatment options were limited to salvage chemotherapies[7]. The selection of salvage chemotherapy is challenging, given that many of the options include classes of drugs the patient has already been exposed to and failed[8–10]. In addition, there is no standard of care for adults with Ph(−) R/R B-cell precursor ALL. A French study of 421 adult ALL patients who relapsed after participation in the LALA-94 trial reported that a variety of multi-agent salvage chemotherapy

regimens were administered following the relapse, including the same chemotherapies that were used for initial induction therapy, but no clear choice of salvage chemotherapy was apparent and outcomes were universally poor[11]. Furthermore, salvage chemotherapies are associated with severe toxicities, including hematological adverse events, infections, and neurologic toxicities[12–15]. With salvage chemotherapy, treatment-related mortality is reported to range from 11–23%[8,16], and it is widely recognized that most patients require extensive inpatient hospitalization for treatment administration and toxicity management.

Although clinicians treating adults with Ph(−) R/R B-cell precursor ALL recognize that hospitalization is required to manage these patients, the extent of the burden has not previously been measured or reported in the literature. The primary objective of this study was to quantify proportion of time spent in the hospital by adults with Ph(−) R/R B-cell precursor ALL treated with salvage chemotherapy. Secondary objectives to further determine the burden of hospitalization were to identify the main reasons for hospitalization, determine the frequency of hospitalizations, and estimate the costs associated with hospitalization stays.

Methods

Study design and patient selection

This was a retrospective chart review of adults with Ph(−) R/R B-cell precursor ALL who were treated in French hospitals. Hospitals were selected to include those with inpatient diagnostic and treatment facilities for patients with ALL, a network of hematologists/oncologists who treat R/R ALL patients, and that had been operational for at least 2 years.

The study period was from 2003–2014. Patient records or charts were screened from October 2013 going backwards until at least 30 eligible patients were identified. Eligible patients were adults aged 18 years or older, with
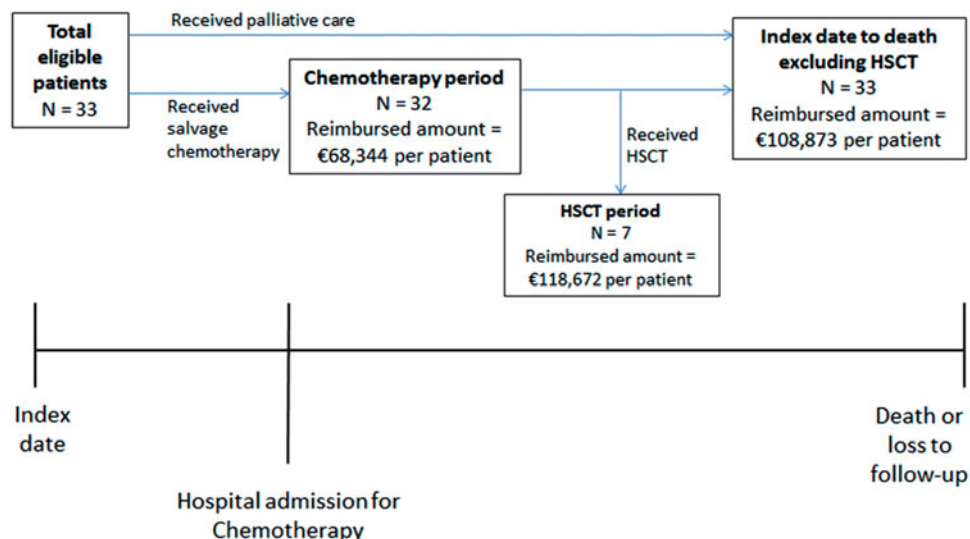
Ph(−) B-cell precursor ALL who were relapsed with first remission lasting less than 12 months, or relapsed after first salvage therapy, or relapsed any time after HSCT, or refractory to primary induction or salvage therapy. Patients were to have been hospitalized for at least one episode of R/R ALL with an electronic medical record or chart available for review and data collection. Patients enrolled in either blinatumomab- or inotuzumab ozogamicin-related clinical trials were excluded.

The protocol was approved by French national regulatory authorities, CCTIRS (Comité Consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé) reference number 14.803, and CNIL (Commission Nationale de l'Informatique et des Libertés) reference number DR-2015-71.

Patient data were collected from the 'index date' until the patient died or was lost to follow-up, and outcomes were evaluated during pre-specified 'time periods' (Figure 1). The index date was the first time an ALL patient was recorded as refractory or relapsed, as per inclusion criteria. The 'chemotherapy period' was pre-specified to represent the time during which the most intensive chemotherapy is assumed to be administered and before patients receive a transplant. The chemotherapy period was defined as the first chemotherapy date after the index date to the earliest of last chemotherapy dose plus 30 days, initiation of HSCT, death, or loss to follow-up. For patients who received HSCT after the index date, the 'HSCT period' was defined as the time from starting HSCT to the earliest of death, loss to follow-up, or relapse of ALL. Patients with no recorded death were lost to follow-up and considered alive at the end of the study.

Data collection

Collected data included dates of initial diagnosis, chemotherapy administration, first, second and most recent relapse,

Figure 1. Study schema. The index date was the first time in the medical records the patient was diagnosed with ALL that was refractory or had relapsed according to the inclusion criteria (with a first remission duration ≤12 months, within 12 months of HSCT, or in second or greater salvage therapy). The chemotherapy period was the time from first hospital admission for chemotherapy to the earliest of last dose of chemotherapy +30 days, start of HSCT, after 105 days, death, or loss to follow-up. The HSCT period was the time from start of HSCT to earliest of relapse, death, or loss to follow-up.

HSCT, and death; age at diagnosis and relapse; length of inpatient hospital stays during salvage therapy; and reasons for hospitalization.
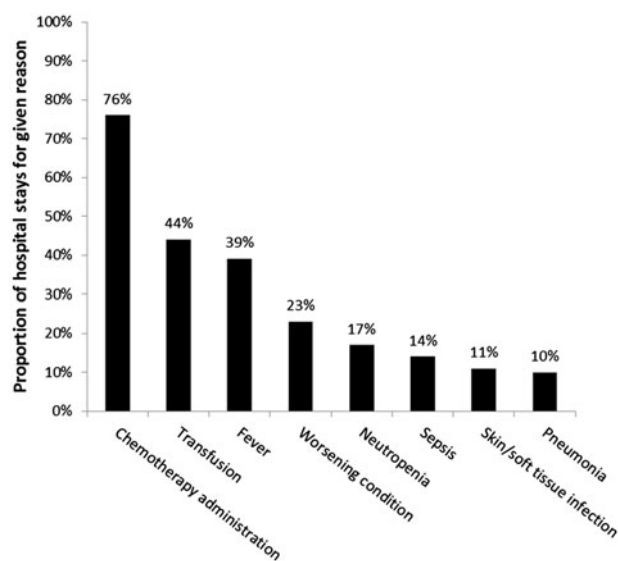
Outcomes of interest

The primary outcome was the percentage of time spent in the hospital during the chemotherapy period. In addition, the number and types of hospital admissions, length of hospital stay(s) and reasons for hospitalization were summarized, and reimbursement amounts of hospitalizations were estimated.

Statistical analysis

All patients who met the inclusion criteria were included in the analyses. For the primary outcome, the percentage of time spent in the hospital during the chemotherapy period was calculated as the number of days in the hospital divided by the total number of days during the chemotherapy period.

Other outcomes related to the number of hospital admissions and length of hospital stays were calculated for the chemotherapy period. The same analyses were calculated from the index date until death or loss to follow-up, including and excluding the HSCT period.

Reimbursement amounts were estimated using a weighted average of the amount reimbursed by the French Public Insurance for any hospital stay given a diagnosis-related group (DRG) code of adult patients with ALL. Hospital stays for ALL were classified into one of eight categories (chemotherapy, transfusions, fever, transfusion plus fever, infections, sepsis, sepsis plus fever, no comorbidity) and DRG codes were assigned depending on the complexity and severity of the hospitalization. Severity levels range from 1–4, with reimbursement increasing as the severity level increases. When multiple categories of diagnoses are present for a given hospital stay, the DRG code with the highest

reimbursement is assigned to the stay. To obtain the weighted average of reimbursement amount per hospitalization, the relative proportion of all hospital stays in 2013 for ALL was multiplied by the respective mean amount reimbursed in 2013 for each severity of hospital stay, and the weighted values for each severity level were added together. A retrospective analysis of the French National Hospital database (PMSI) was conducted to determine the number of hospital stays and reimbursement amount assigned to each stay according to severity level during 2013 (Supplementary Table 1). Descriptive statistics were calculated for all outcomes. Means (standard deviation [SD]) or medians (interquartile range and range) were provided for continuous variables. Incidence rates and proportions were provided for categorical variables.

Results

Study population

Thirty-three patients from four sites in France met the inclusion criteria and were included in the analyses. The median age of the patients was 54 years (range =19–75 years), and most (61%) were male (Table 1). Over half of the patients (52%) were relapsed, with a first remission duration of less than 1 year. Approximately one-fifth of patients received a HSCT following salvage chemotherapy (21%) and salvage chemotherapy was palliative in one patient. By the end of the observation period 29 patients (88%) had died; of these, 23 patients had not received a transplant. Four patients were alive and lost to follow-up.

Hospitalizations and reimbursement during the chemotherapy period

Thirty-two patients received salvage chemotherapy and were included in the chemotherapy period. The mean (SD) duration of the chemotherapy period was 87 (35) days. During the chemotherapy period patients spent almost half of their time in the hospital (46%, 95% CI =34–57%). The 32 patients experienced 71 inpatient hospitalizations, 70 day-hospital stays, and six outpatient visits (Table 2). The mean number of inpatient hospitalizations was 2.2 (SD =1.5) per patient, with a mean length of stay of 16.8 days (SD =14.8) per hospitalization.

Figure 2. Reasons for hospital admission during the chemotherapy period. Reasons with a frequency of ≥10% are presented. More than one reason is possible for each admission.

Table 1. Patient characteristics and treatment received during salvage.

	n = 33
Age at index date, years	
Median (range)	54 (19–75)
Male, n (%)	20 (61)
Disease status at index date, n (%)	
Relapsed with first remission ≤12 months	17 (52)
Relapsed after first salvage	5 (15)
Relapsed after HSCT	7 (21)
Refractory to primary induction or salvage therapy	4 (12)
Status at the end of follow-up, n (%)	
Dead	29 (88)
Alive (lost to follow-up)*	4 (12)
Treatment received during salvage	
Chemotherapy	32 (97)
HSCT	7 (21)

The mean reimbursement per hospitalization was €31 067 (SD =4850) for an inpatient stay, €674 (SD =0) for a day stay, and €394 (SD =0) for an outpatient visit (Table 3). The calculated total hospitalization reimbursement per patient during the chemotherapy period was €68 344.

Most patients were hospitalized for more than one reason during each admission. The most common reason was to administer chemotherapy, cited in 76% of hospital admissions (Figure 2). The next most common reasons were blood transfusion (44%) and fever (39%).

Total hospitalizations and reimbursement from R/R ALL diagnosis to death

Total hospitalizations and reimbursement excluding the HSCT period

As the total reimbursement from R/R ALL diagnosis to death is likely to be substantially impacted by HSCT, the reimbursed amounts are reported here, excluding those related to HSCT. Excluding hospital visits for HSCT, there were 121 inpatient hospitalizations, 141 day-hospital stays, and 23 outpatient visits (Table 2). A mean of 3.7 (SD =3.1) inpatient hospitalizations per patient was observed when the HSCT period was excluded, and the mean length of stay was 13.7 (SD =13.5) days.

The mean reimbursement per hospitalization was €28 832 (SD =8867) for an inpatient stay, €674 (SD =0) for a day stay, and €394 (SD =0) for an outpatient visit. The calculated total hospitalization reimbursement per patient excluding the HSCT period was €108 873 (Table 3).

HSCT period only

Hospitalizations and reimbursement were evaluated during the HSCT period for the seven patients who received a transplant after the index date. The mean time from the index date to HSCT was 116 (SD 43) days. During the HSCT period, these seven patients experienced 18 inpatient hospitalizations, 20-day hospital stays and 79 outpatient visits (Table 2). Per patient, the mean number of inpatient hospitalizations was 2.6 (SD =2.2), with a mean length of stay of 33.9 (SD =38.0) days.

The mean reimbursement per hospitalization was €43 672 (SD =33 241) for an inpatient stay, and the day-stay and outpatient reimbursements were the same as for other study periods (Table 3). The calculated total reimbursement per patient in the HSCT period was €118 672.

Discussion

Very little data exist on the burden of treating adults with Ph(−) R/R B-cell precursor ALL using salvage chemotherapy in France. Using a hospital retrospective chart review approach, we found that adults with Ph(−) R/R B-cell precursor ALL currently experience significant hospitalization burden. Once diagnosed with R/R disease, patients spent almost half (46%) of their time in the hospital during the chemotherapy period.

Adults with Ph(−) R/R B-cell precursor ALL are extremely ill. These patients receive intensive chemotherapy regimens, which are commonly associated with significant toxicity that requires inpatient management[8,16]. As a result, patients experienced prolonged periods of hospitalization during the

Table 2. Hospitalizations in patients with Ph-negative B-cell precursor R/R ALL.

	Chemotherapy period (n = 32 patients)	Index date to death excluding the HSCT period (n = 33 patients)	HSCT period only (n = 7 patients)
Time spent in the hospital			
Mean (SD) duration of study period in days	87 (35)	—	—
Proportion of time spent in the hospital, % (95% CI)	46 (34–57)	—	—
Hospital admissions data			
Number of hospital admissions			
Inpatient	71	121	18
Day hospital stay	70	141	20
Outpatient visit	6	23	79
Mean (SD) length of stay in days per inpatient hospitalization	16.8 (14.8)	13.7 (13.5)	33.9 (38.0)
Patient data			
Mean (SD) number of hospital admissions per patient			
Inpatient	2.2 (1.5)	3.7 (3.1)	2.6 (2.2)
Day hospital stay	2.1 (3.3)	4.3 (6.3)	2.9 (6.3)
Outpatient visit	0.2 (0.5)	0.7 (1.8)	11.3 (24.3)

Table 3. Reimbursement in patients with Ph-negative B-cell precursor R/R ALL.

	Chemotherapy period (n = 32 patients)	Index date to death excluding the HSCT period (n = 33 patients)	HSCT period only (n = 7 patients)
Mean (SD) reimbursement in Euros per hospital admission*			
Inpatient	31 067 (4850)	28 832 (8867)	43 672 (33 241)
Day hospital stay	674 (0)	674 (0)	674 (0)
Outpatient visit	394 (0)	394 (0)	394 (0)
Total reimbursement in Euros per patient**	68 344	108 873	118 672

*based on a weighted average of hospitalization reimbursement for ALL from the 2013 French PMSI database.
**calculated by multiplying the reimbursement per admission by mean number of admissions per patient for each type of hospitalization.

chemotherapy period (mean length of hospital stay was 16.8 days), with patients requiring multiple hospital admissions (mean number of inpatient hospitalizations per patient was 2.2). A high economic burden was observed as a consequence of the duration and frequency of hospitalizations: the reimbursement per patient during the chemotherapy period was €68 344 and the reimbursement from the time a patient was diagnosed with Ph(−) R/R ALL until death was €108 873. Both of these values exclude any reimbursement associated with stem cell transplant, which is also known—and confirmed in this study—to be a very expensive procedure[17,18].

The results from this French study are consistent with findings from a similar analysis conducted in the US using a US commercial claims database[19]. The US study found the mean length of hospital stay among 205 patients was 13.1 days, and patients spent 56.2% of their time in hospital while receiving treatment with chemotherapy. The mean reimbursed amount per hospitalization was $89 663. Other studies conducted in Italy and Germany also showed comparable results in terms of length of inpatient hospital stay (20–25 days) and proportion of time spent in the hospital during the chemotherapy period (56–58%)[20,21].

One limitation of this study is the small sample size, although this was expected given the rarity of the patient population—the estimated annual incidence rate of adult R/R Ph(−) B-precursor ALL is 0.2 per 100 000 person-years, corresponding to 120–130 new patients per year in France[4]. Within this population, our inclusion criteria selected an even smaller sub-set of poor-prognosis patients, including restrictions to those with early first relapse, relapse after first salvage, and relapse after HSCT. Although the sample size was small, the variation in the reimbursement amounts for the hospitalizations was relatively small (SD = €4850 for inpatient stays during the chemotherapy period), giving increased confidence in the reimbursement estimates. The mean patient age was older than seen in other observational studies in patients with R/R ALL[11,16,22,23]. Older patients may have more hospitalization due to poorer health or less hospitalization due to administration of less toxic chemotherapy. However, we did not explore age-stratified hospitalizations due to the small patient numbers. Another limitation is that the number of outpatient visits may be under-estimated if patients are seeing physicians outside of the hospital setting, although, since ALL is a severe disease that is treated mainly in the inpatient setting, this would not increase significantly the overall estimates.

In conclusion, this study showed that, currently in France, adults with Ph(−) R/R B-cell precursor ALL have repeated and prolonged hospitalizations. Almost half of the treatment period is spent in hospital, and this time is associated with extremely high economic costs. This study highlights the hospital burden of treating adults with Ph(−) R/R B-cell precursor ALL using salvage chemotherapies, and the need for more effective, tolerable treatments.

Transparency

Declaration of funding

Declaration of financial/other relationships

Acknowledgments

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