Non-Hodgkin’s lymphoma in very elderly patients over 80 years. A descriptive analysis of clinical presentation and outcome

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Background: Non-Hodgkin’s lymphoma (NHL) in patients older than 80 years is not a rare disease and treatment strategies are often difficult because of associated comorbidities.

Patients and methods: We entered 205 NHL patients older than 80 years treated in a single institution in a retrospective analysis to describe clinical presentation and outcome and to identify specific prognostic factors.

Results: The median age was 83 years, and 91% of the cases were B-cell lymphomas consisting mainly of diffuse large B-cell lymphoma and marginal zone lymphoma. Among patients presenting comorbidities (87%), Charlson index was low in almost half of the patients (43%). Patients did not receive any treatment or received corticosteroids alone in 15%, surgery, radiotherapy, or monochemotherapy in 35%, polychemotherapy without anthracycline in 18%, and anthracycline based in 32%. Median overall survival was of 2.2 years. Main reason for death was disease progression (57%). Independent prognostic factors of survival were poor performance status ($P < 10^{-4}$) and high lactate dehydrogenase level ($P < 10^{-5}$). Comorbidities were not found to influence survival.

Conclusions: Very elderly NHL patients showed similar features and prognostic factors than younger patients. Death was related mainly to the disease, meaning that these patients should be more frequently treated with standard treatments.

Key words: comorbidities, lymphoma, prognostic factors, very elderly patients

Introduction

Over the past century, the life expectancy of the overall population has grown impressively, and further increases are projected [1]. Current estimates indicate that people older than 65 years are more than twice compared with hundred years ago. By 2030, person older than 75 years of age will be multiplied by three, and the subgroup of 85 years or more will be twice during the same period [2]. This phenomenon is associated with an increase in the incidence of cancer. Since 1999, malignancies tend to become the leading cause of death, before heart diseases, in people younger than 85 years. The incidence of non-Hodgkin’s lymphoma (NHL) has been found to increase from 8% to 10% per year [3]. In Europe and North America, >50% of new NHL cases occur in patients older than 65 years [4]. Because of chronic or weakening associated diseases and age itself, it has been underlined that this subset of patients presents with different characteristics and has a poorer outcome than their younger counterparts [5, 6]. It is assumed that very elderly NHL patients, older than 80 years, are more difficult to get on treatment, requiring a specific management. Most of the studies, however, have focused on patients aged between 60 and 80 years with diffuse large B-cell lymphoma (DLBCL) [7, 8].

Age has been identified as one of the strongest adverse prognostic factor of NHL. Numerous studies described that older age was significantly correlated with shorter disease-free survival (DFS) and overall survival (OS) [9–12]. A shorter survival has been found in elderly patients compared with younger patients when paired for histological and clinical characteristics of NHL [6, 13]. This difference remained significant after adjustment for nonrelated NHL deaths. This shorter survival has been related mainly to a trend in prescription of weaker treatments assumed better tolerated [9] and a poorer tolerability of standard treatments widely due to the presence of concomitant diseases [12]. In the absence of concomitant diseases, the survival was not shortened in patients of >70 years compared with younger patients [14].
We initiated a retrospective analysis in patients older than 80 years in our institution for a diagnosis of NHL. The threshold age of 80 years has been defined as the cut-off value for very elderly NHL patients because patients younger than 80 years are usually recognized to have good tolerance and efficacy when standard treatments of DLBCL are used [7, 8]. We reviewed the characteristics of patients and disease, and analyzed the management of treatment and patient’s outcome.

patients and methods

study population

From 1989 to 2004, 5545 patients were followed in our institution (Pierre-Bénite, France) for a hematologic malignancy. Among them, 4351 were diagnosed with a NHL of whom 278 were 80 years or older. Two hundred and five files out of 278 were assessable.

patient and disease assessments

The data relative to clinical presentation at diagnosis before any treatment, medical history, comorbidities, laboratory tests, treatments and treatment-related toxic effects, and survival were obtained from the hospital file and reviewed. The histological/cytological diagnosis has been carried out on the initial nodal biopsy. Pathological data have been analyzed according to the histological subtype and clinical aggressiveness, distinguishing indolent and aggressive NHL based on the World Health Organization (WHO) classification [15].

Clinical variables registered were age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), presence of B symptoms (fever >38.3°C, night sweats, or loss of >10% of body weight), Ann Arbor stage, and number of involved sites. Preexisting treatments and weakening associated diseases were also recorded. Laboratory tests recorded were absolute blood counts, serum creatinine, serum albumin, serum lactate dehydrogenase (LDH), β2-microglobulin (β2M), and Coombs’ test. Hypoalbuminemia was defined as an albumin value <36 g/l [16]. The cut-off value for anemia has been fixed at 12 g/dl. The value of β2M has been adjusted on the renal function. A renal insufficiency has been defined as a serum creatinine level upper than 105 μmol/l in women and 140 μmol/l in men.

The Charlson scale was chosen for classifying retrospectively comorbid conditions and scoring patients [17]. The score was on the basis of an index balanced on number and gravity of comorbid diseases. The score obtained was a summation of the number of comorbidities existing at the time of diagnosis. Risk groups were defined by regrouping patients with similar scores leading to three subgroups: low risk (score 0, 1, or 2), intermediate risk (score 3 or 4), and high risk (score >4). The age-adjusted International Prognostic Index (aIPI) on the basis of three criteria, i.e. PS (0–1 or ≥2), Ann Arbor stage (localized or disseminated), and LDH level (normal or upper normal value), was calculated for each patient [18].

The outcome of each patient has been followed strictly by keeping a close contact either at home, with family, or at the hospital in order to identify clearly the cause of death if any. Reasons for death have been classified in three groups as follows: (i) disease progression, (ii) toxicity, and (iii) any other reasons. In the case of a death related to an acute pulmonary edema and/or a cardiac failure, the treatment received has been explored especially for the use of an anthracycline.

treatment, response, and safety

In the absence of standard treatments for NHL patients older than 80 years, the choice of treatments was based mainly on histological subtype and estimation of patient’s general status. For the analysis, treatments were divided into four groups. The first group consisted of therapeutic abstention or corticosteroids alone. The second group consisted of patients who received a single therapy, i.e. surgery, radiotherapy, or monotherapy (single-agent chemotherapy or rituximab alone). The third and the fourth groups were formed by patients who received a multidrug regimen without or with an anthracycline. The efficacy of treatment was assessed according to the National Cancer Institute-sponsored International Working Group criteria established in 1999 [19].

Treatment-related toxic effects reported in the hospital file and/or leading to hospitalization have been recorded. Toxic effects have been classified according to the involved organ, but the attribution of a grade was not possible because of the retrospective nature of analysis.

statistical analysis

The primary end point was the OS defined as the time from diagnosis until death or last contact. The following predictive covariates of survival in very elderly NHL patients were analyzed: sex, Ann Arbor stage, ECOG PS, LDH level, number of extranodal sites, aIPI, B symptoms, anemia, hypoalbuminemia, and β2M adjusted for serum creatinine level, Charlson index, previous history of cardiac, renal, or hepatic diseases. Survival data were computed according to the Kaplan–Meier method, and curves were compared using the log-rank test. Differences were considered statistically significant when the P value was 0.05 or less. A multivariate analysis (Cox proportional hazards model) was adjusted for prognostic factors. Prognostic factors entered into the multivariate model had to reach the statistical significance level of 0.05 or less in the univariate analysis. All statistical analyses were carried out using Statistica software (version 6).

results

patient characteristics and histology

Clinical and biological characteristics of patients are summarized in Table 1. The aIPI score was elevated (≥2) in 41% of the patients, and the high level of missing data was the result of a high rate of missing LDH level. All the patients were negative for HIV.

The most frequent histological features were DLBCL (39.5%) and marginal zone lymphoma (MZL) (25.8%), whereas follicular lymphoma (7.3%) was rarer (Table 1). About half of the patients presented an aggressive NHL with 79% of DLBCL and 9% of T lymphoma (Table 2).

comorbidities

At least one comorbidity was found in 179 patients (87%). A previous history of cardiovascular diseases (including arrhythmia, hypertension, cardiac failure, angina pectoris, pacemaker, and valvulopathies) was found in 102 patients, of whom 32 received an anthracycline-based chemotherapy. A chronic pulmonary disease (obstructive chronic bronchitis, asthma, pulmonary hypertension, and pulmonary embolism) was found in 19 patients (9%). A previous history of renal disease was reported in 40 patients (19%), of whom 10 did not receive any treatment or received corticosteroids, seven received single-agent chemotherapy, six received a multidrug regimen without anthracycline, and 17 received anthracycline-based chemotherapy. Among other diseases taken into account for the Charlson index, 6 patients had dementia, 8 had an ulcer disease, 15 had diabetes, 3 had a liver disease, and 23 had an ongoing solid tumor. The
stratification of patients according to the Charlson index was as follows: score 0 in 28 patients (13.7%), score 1–2 in 75 (36.6%), score 3–4 in 69 (33.7%), score >4 in 31 (15.1%), and the score was not assessable in 2 patients.

treatment characteristics
The distribution of treatments according to predefined subgroups and aggressiveness of NHL is summarized in Table 3. Twenty-eight (13.7%) patients were included in a clinical trial. Treatment abstention, corticosteroids alone, and single-agent chemotherapy were the most frequent therapeutic choices in indolent NHL patients. The decision of not treating patients was based mainly on indolent subtype (38%), subjective estimation of physiological age (19%), and poor general status (14%). Chemotherapy was administered in 169 patients (82.4%). In the whole population, single-agent chemotherapy consisted of chemotherapy such as chlorambucil, fludarabine, etoposide in 66 patients and rituximab in 6 patients. On the other hand, anthracycline-based chemotherapy was administered preferentially in aggressive NHL patients compared with indolent NHL patients (32.2% versus 17.5%). In this subset of patients, only eight of them, however, had received a standard treatment for NHL, i.e. six or eight cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or R-CHOP (rituximab-CHOP).

toxicity
Overall, 65 cases (31.7%) of treatment-related toxic effects occurred. The information was not retrievable in 60 patients.
Previous history of cardiac disease was reported in 62% of patients receiving an anthracycline. Anthracycline-based regimen was interrupted in only three patients after the third cycle because of a cardiac event in these patients. In the 169 patients who received chemotherapy, 25 developed a febrile neutropenia requiring a hospitalization, of whom 10 died following this infection. In the course of treatment, toxicity-related hospitalizations were required for 65 patients (31.7%).

**treatment efficacy**
A complete response (CR) was achieved in 53 patients (26%) after the first-line chemotherapy for a median duration of 16 months. The rate of CR was higher in aggressive NHL patients than in indolent NHL patients (36% versus 16%). Patients who received an anthracycline-based chemotherapy derived more benefit in terms of CR (13.2% versus 0.5% with corticosteroids, 8.8% with single-agent chemotherapy, and 4.4% with nonanthracycline-based regimen).

**survival analysis**
One hundred and twenty-two patients (59.5%) have relapse or progression. No difference was detected between aggressive and indolent NHL patients (65.7% versus 53.4%). One hundred and forty-six patients died with a median survival time of 2.21 years (Figure 1A). The median OS was significantly shorter in aggressive NHL patients (1.2 versus 2.7 years; $P = 0.002$) (Figure 1B), especially for DLBCL (1.3 years). The main reasons of death were described in Table 4. In the univariate analysis, significant prognostic factors for survival were Ann Arbor stage, ECOG PS, LDH level, anemia, adjusted $\beta 2M$, and aaIPI (Table 5). Considering the histological entities named indolent lymphomas and aggressive lymphomas, we noticed some difference. The influence of anemia was significant for indolent NHL, whereas hypoalbuminemia had a significant role in aggressive disease. Noteworthy, the aaIPI, initially dedicated to DLBCL patients younger than 80 years, was a significant prognostic factor for survival in patients older than 80 years irrespective of the histological subtype. None of the other clinical or biological characteristics were found to be associated with poorer survival. Especially, comorbidities evaluated according to the Charlson index were not correlated with an increased risk of death. In the multivariate analysis, only two independent prognostic factors of death were found poor ECOG PS and high LDH level.

**discussion**
NHL in patients older than 80 years is not a rare disease although therapeutic decision remains often difficult. To our knowledge, our retrospective analysis, involving 205 very elderly NHL patients, is the first to describe this population. We report similar disease behaviors in these very elderly patients compared with disease behaviors in younger patients, with same clinical presentation and same prognostic factors but a different histology repartition. Huge differences in terms of disease management, however, are highlighted. Only eight patients (4%) had received a standard CHOP or R-CHOP, whereas the aaIPI score was at least 2 in 45% of the patients. Comorbidities were found in 87% of the patients but the Charlson index was elevated (score >4) in only 15% of them. A CR was achieved in 26% of the patients, and patients who received an anthracycline-based chemotherapy derived more benefit of treatment. The median survival time was 2.2 years and the main cause of death was NHL progression (57%). A toxic death occurred in 16% of patients consisting of febrile neutropenia and infection. In the multivariate analysis, the independent prognostic factors for death were poor ECOG PS and high LDH level, whereas presence of comorbidities was not significantly associated with an increased risk of death.

Is there any difference if presenting lymphoma earlier or later in life? We have found a majority of women (60%). This is in agreement with the distribution of male/female in the overall population >80 years, but not in the NHL population where men are predominant. On the other hand, clinical and biological characteristics did not differ between very elderly and younger patients [5, 6]. Noteworthy, we have observed a very high rate of B-cell lymphoma with DLBCL and MZL as the most frequent histological features, whereas follicular lymphoma was rarer. All lymphoma...
Table 4. Reasons of death according to treatment received

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>Death, n</th>
<th>Main reasons of death, n (%)</th>
<th>Other reason*</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lymphoma</td>
<td>Toxicity</td>
<td></td>
</tr>
<tr>
<td>No treatment or corticosteroids</td>
<td>30</td>
<td>19</td>
<td>11 (57.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Single-agent therapy</td>
<td>72</td>
<td>52</td>
<td>31 (59.6)</td>
<td>9 (17.3)</td>
</tr>
<tr>
<td>Multidrug regimen without anthracycline</td>
<td>37</td>
<td>33</td>
<td>20 (60.6)</td>
<td>6 (18.2)</td>
</tr>
<tr>
<td>Multidrug regimen with anthracycline</td>
<td>66</td>
<td>42</td>
<td>22 (52.4)</td>
<td>8 (19.0)</td>
</tr>
<tr>
<td>Total</td>
<td>205</td>
<td>146</td>
<td>84 (57.5)</td>
<td>23 (15.7)</td>
</tr>
</tbody>
</table>

*Stroke, pulmonary failure, and cardiac failure.

Table 5. Prognostic factors for death in univariate analysis

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>P value</th>
<th>Overall population</th>
<th>Indolent NHL</th>
<th>Aggressive NHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ann Arbor disseminated stage</td>
<td>0.018</td>
<td>0.016</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Poor ECOG PS</td>
<td>&lt;10^{-5b}</td>
<td>&lt;10^{-5a}</td>
<td>0.003*</td>
<td></td>
</tr>
<tr>
<td>High LDH level</td>
<td>&lt;10^{-5}</td>
<td>0.009a</td>
<td>0.0005a</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>0.019</td>
<td>0.003</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Hypalbuminemia</td>
<td>NS</td>
<td>NS</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>High-adjusted β2M level</td>
<td>0.005</td>
<td>0.005</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>High-risk aaIPI</td>
<td>&lt;10^{-5}</td>
<td>0.00001</td>
<td>0.00004</td>
<td></td>
</tr>
<tr>
<td>Presence of comorbidities</td>
<td>NS</td>
<td>0.09</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

*Independent prognostic factors in the multivariate analysis.

statistical analysis was performed considering the presence of at least one comorbid condition compared with 20% in patients younger than 60 years [25]. In addition, elderly patients often present with alterations of pharmacokinetics and pharmacodynamics of molecules [26]. Thereby, drugs used and their dosage should be tailored to creatinine clearance, liver function, and hematopoietic reserve. A decrease in chemotherapy drug, however, has been found to be associated with a lower treatment efficacy [9].

As in younger patients, the treatment choice in elderly patients has to be on the basis of the type of lymphoma and the existence of poor prognostic factors. Several studies have demonstrated that elderly patients treated with the appropriate therapy and an effective management of foreseeable toxic effects may have a survival similar to younger patients [27, 28]. Once a CR has been achieved, the DFS could remain similar to younger patients even if the first-line chemotherapy regimen was less aggressive [14]. The major issue in treating elderly NHL patients is to administer the adequate chemotherapy without toxic effects and to achieve a long-lasting CR. In this setting, a precise evaluation of their status to appreciate comorbidities should help the therapeutic decision. In our retrospective analysis, Charlson index was not associated with survival. Such index, however, should be evaluated in prospective trials to confirm this data.

Another concern is the psychological approach of very elderly patients. Typically, they have a reduced emotional tolerance considering the disease diagnosis and its treatment. A cancer diagnosis is often associated with the end of life and

spite of this possible lack in objectivity, we have found that ECOG PS analyzed retrospectively was one of the most important variables predictive of survival. A variety of new methods are currently evaluated to predict prognosis and to define appropriate therapy in older patients with neoplasm. Functional status estimates the ability to carry out specific tasks necessary to maintain his physical independence. These assessments are on the basis of several items evaluating different aspects of physical, intellectual, and social functioning in older patients [23, 24]. Moreover, the assessment of treatment options for elderly patients has taken into account age-related factors. The existence of other diseases reduces organ functions, and health problems resulting from long-term drugs use or abuse (tobacco, alcohol, and medications) can compromise the ability of elderly patients to tolerate therapy. The results of a survey showed that 61% of the patients aged 70 years or more had at least one comorbid condition compared with 20% in patients younger than 60 years [25]. In addition, elderly patients often present with alterations of pharmacokinetics and biodisponibility of drugs modifying the pharmacodynamics of molecules [26]. Thereby, drugs used and their dosage should be tailored to creatinine clearance, liver function, and hematopoietic reserve. A decrease in chemotherapy drug, however, has been found to be associated with a lower treatment efficacy [9].
death, especially in this subset of patients. The question of the usefulness of a treatment is often asked both by patient and family. Then, it is essential to propose an integrated approach where the physician explains the goals of treatment in either a curative or a palliative option, and where the patient and his family play a proactive role in the therapeutic project. This interactive discussion should offer a better understanding and a better compliance to the treatment.

If the NHL in patients older than 80 years presents similar clinical characteristics and prognostic factors compared with younger patients, age itself appears to be a limiting factor to set up an efficient treatment. We have demonstrated that the majority of deaths were related to NHL, meaning that patients had a need for standard treatments associated with supportive care, such as hematopoietic growth factors and parenteral nutrition. The use of chemotherapy requires strict evaluation of general status and comorbidities. Clinical trials investigating the efficacy and feasibility of various regimens in very elderly NHL patients are warranted.

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references