Clinical presentation, outcome, and prognostic markers in patients with intravascular large B-cell lymphoma, a lymphoma study association (LYSA) retrospective study

Antoine Bonnet1 | Céline Bossard2 | Ludovic Gabellier3 | Julien Rohmer4 | Othman Laghmari6 | Marie Parrens5 | Clémentine Sarkozy6 | Rémy Dulery7 | Virginie Roland8 | Francisco Llamas-Gutierrez9 | Lucie Oberic10 | Luc-Matthieu Fornecker11 | Laura Bounaix12 | Bruno Villemagne13 | Vanessa Szablewski14 | Sylvain Choquet4 | Krimo Bouabdallah15 | Alexandra Traverse-Glehen16 | Mohamad Mohty7 | Laurence Sanhes8 | Roch Houot17 | Thomas Gastinne1 | Christophe Leux18 | Steven Le Gouill1,19,20

1Service d’hématologie clinique, Centre Hospitalier Universitaire Nantes, Nantes, France (at the time of work), Service d’hématologie - Centre Hospitalier Bretagne Atlantique, Vannes, France (now)
2Service d’anatomie et cytologie pathologique, Centre Hospitalier Universitaire Nantes, Nantes, France
3Service d’hématologie, Centre Hospitalier Universitaire Montpellier, Montpellier, France
4Service d’hématologie, Hôpital Pitié - Salpêtrière – APHP, Sorbonne Université, Paris, France
5Département de pathologie, Hôpital Haut-Lévêque, CHU et université de Bordeaux, Bordeaux, France
6Institut Gustave Roussy, Villejuif, France (at the time of work) Service d’hématologie, Hospices Civils Lyon, Lyon, France (now)
7Service d’hématologie clinique et thérapie cellulaire, Hôpital Saint-Antoine, AP-H, Université Sorbonne, INSERM, Centre de recherche Saint-Antoine, Paris, France
8Centre Hospitalier de Perpignan, Service d’hématologie, Perpignan, France
9Centre Hospitalier Universitaire Rennes, Service d’anatomopathologie, Rennes, France
10Service d’hématologie, Centre Hospitalier Universitaire Toulouse, Institut Universitaire du Cancer de Toulouse OncoPole, Toulouse, France
11Service d’hématologie, Institut de Cancérologie de Strasbourg Europe (ICANS), Strasbourg, France
12Service de thérapie cellulaire et d’hématologie clinique adulte, Centre Hospitalier Universitaire Clermont-Ferrand, site Estaing, Clermont-Ferrand, France
13Service d’onco-hématologie médicine interne, Centre Hospitalier Départemental Vendée, La Roche sur Yon, France
14Service d’anatomopathologie, Centre Hospitalier Universitaire Montpellier, Montpellier, France
15Service d’hématologie clinique et thérapie cellulaire, Hôpital Haut-Lévêque, CHU Bordeaux, Bordeaux, France
16Service d’anatomopathologie, Hospices Civils Lyon, Lyon, France
17Service d’hématologie, CHU Rennes, University of Rennes, INSERM U1236, Rennes, France
18Service d’information médicale, Centre Hospitalier Universitaire Nantes, Nantes, France
19INSERM CIRCNA nantes-Angers, NeXT Université de Nantes, Nantes, France
20Institut Curie Paris, France

Correspondence
Steven Le Gouill, Institut Curie, 73 rue Claude Bernard, 75 005 Paris, France.
Email: steven.legouill@curie.fr

Present address
Antoine Bonnet, Curie Institute, Paris, France

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.
© 2022 The Authors. Cancer Medicine published by John Wiley & Sons Ltd.
Intravascular large B-cell lymphoma (IVLBCL) is a rare non-Hodgkin's lymphoma (NHL) entity characterized by the selective growth of neoplastic cells within blood vessel lumina, mainly capillaries with the exception of larger arteries and veins (WHO 4th edition 2017). The mechanisms responsible for tumor cell blood vessel infiltration remain unknown. It has been hypothesized that the intravascular growth pattern could be secondary to a defect of lymphoma cells homing receptors, such as lack of CD29 (B1 integrin), CD54 (ICAM-1) adhesion beta-molecules (Ponzoni, Hum Pathol 2000).

IVLBCL is considered as a disseminated disease at diagnosis, with clinical and biological features that differ from one patient to another according to infiltrated organs and patients' geographic origin. Indeed, it has been reported that IVLBCL patients in western countries are more likely to have central nervous system (CNS) and cutaneous involvements as compared to patients from Asia. These latter would be conversely more exposed to hemophagocytic syndrome and medullary involvement (Ferreri, Haematologica 2007). The absence of marked lymphadenopathy, rarity of tumor cells, low tumor burden are sometimes responsible for a long time interval between onset of symptoms and IVLBCL diagnosis. This delay seems to be a significant factor in the prognostic of patients with IVLBCL (Geer, Br J Haematol 2019).

Large IVLBCL cohorts are rarely found in the existing literature and consist mostly of case reports from Asian countries. These reports note a poor response rate to anthracycline-containing regimen and a short median overall survival. (Ferreri, BJH 2008; Shimada, J Clin Oncol
In the present report, we aim to describe IVLBCL patients treated in LYSA centers from 2000 to 2016 and investigate biological prognostic markers that might be useful for customized treatments.

2 | MATERIAL AND METHODS

2.1 | Patient selection

All centers affiliated with the cooperative Lymphoma Study Association (LYSA) group were asked to report IVLBCL treated from 2000 to 2016. Local clinicians and pathologists were asked to report disease and patients’ characteristics at diagnosis and to update the patients’ outcome. Clinical data included age, sex, medical history of hematological malignancy, cancer or autoimmune disease, performance status, and involvement sites (according to clinicians, based on clinical, morphological, and histological data), Ann- Arbor stage, presence or absence of B-symptoms, and International Prognosis Index (IPI). Biological data including blood cells count, renal and hepatic function, serum lactate dehydrogenase (LDH), presence of hemophagocytosis, cerebrospinal fluid (CSF) analysis, HIV, HBV, and HCV serology, was recorded. First-line treatment strategy and adverse events (AE) were systematically reported. Responses were assessed in accordance with the international workshop criteria (Cheson, 2007).7

2.2 | Pathological study

IVLBCL were defined by at least one biopsy whose histological analysis reveals a predominant intravascular pattern of lymphoma cells, according to the WHO classification and the International Consensus Meeting on IVLBCL in 2007 (Ponzoni, J Clin Oncol 2007).8 No systematic centrally reviewed biopsy was performed for the purpose of the study, but cases were diagnosed in expert lymphoma centers and reviewed by the national Lymphopath network (for IVLBCL diagnosed after 2009). Lymphopath is a compulsory French National Cancer Agency program that imposes a pathologic reviewing by experts of all newly diagnosed lymphoma cases in France, before starting the treatment. In addition, pathologists centrally reviewed samples from 27 patients, confirmed diagnosis and performed complementary immunohistochemistry (IHC) analyses if necessary. Formalin-fixed and Paraffin-embedded samples were analyzed using the following antibodies (significant cutoff used in parentheses): CD20; CD5; BCL1; CD10 (30%); EBER; LMP1; BCL6 (30%); BCL2 (50%); MUM1 (30%); MYC (40%); CD29 (5%); ICAM1 (5%). Germinal center origin was determined according to the immunohistological algorithm proposed by Hans et al, and based on expression of CD10, BCL-6, and MUM1 (Hans, Blood 2004).9 Centralized analysis have been performed on a control group of 31 biopsies of diffuse large B-cell lymphomas (DLBCL) “not otherwise specified” (NOS), reviewed in the Lymphopath network. This sample has been selected for a similar rate of non-germinal subtype and a large predominance of stage III-IV of Ann Arbor classification.

2.3 | Statistical analysis

Progression-free survival (PFS) was calculated from the date of diagnosis to the date of death or disease progression. Overall survival (OS) was defined as the time from diagnosis until the date of death, regardless of the cause of death. Median follow-up was calculated with reverse Kaplan–Meier method. Survival curves were generated using the Kaplan–Meier method and were compared by the log-rank test. Multivariate analysis was carried out using Cox regression methods. Statistical analyses were carried out with a two-tailed test at the 0.05 level, using R software version 3.3.3 (R foundation for statistical computing). This retrospective noninterventional study was reported to the Direction de la recherche Clinique (DRCI) in Nantes (n° RC16-0034), according to the French legislation (article L 0.1121-0.1 and R1121-2 of Code de Santé Publique).

3 | RESULTS

3.1 | Clinical features

Sixty-five patients from 23 LYSA centers were diagnosed with IVLBCL between 2000 and 2016. Patients’ characteristics and initial disease presentation are summarized in Table 1. Sex ratio male/female was 1.17 and median age at diagnosis was 69 years (range: 23–92). A previous medical history of hematological malignancy was found in eight patients (12%) and solid cancer in 13 cases (20%). Seven patients (11%) had an underlying autoimmune disorder (systemic lupus erythematosus; granulomatosis with polyangiitis; Hashimoto disease; Sjögren’s syndrome; Schönlein-Henoch purpura nephritis; celiac disease; rheumatoid arthritis).

At the time of diagnosis, performance status (PS) was ≥2 in 40 patients (67%), B-symptoms were found in 44 cases (69%). All patients were in stage IV according to the Ann Arbor classification. Bone marrow was the most frequent involved site (52%). Central nervous system (CNS)
and skin were invaded in 39% and 33% of cases, respectively. Endocrine system was involved in 18% of cases (adrenal in 10 patients, pituitary gland in two patients). Cytopenias were present with anemia in 53% (<100 g/L) and thrombocytopenia in 35% (<100 x 10^9/L), associated with circulating tumor cells in 18% of patients.

### 3.2 Pathological features

IVLBCL diagnosis has been established on extra-nodal site biopsies in every cases. It was mostly performed on skin or bone marrow biopsies (n = 36). Immunophenotypical characteristics are reported in Table 2. All samples tested for CD20 expression were positive, and half-expressed CD5 (52%) without co-expression of BCL1. BCL2 was overexpressed in 83% in the entire cohort. Cell of origin subtyping according to Hans algorithm resulted in a non-germinal center type for the majority of cases (86%), due to the rarity of CD10 expression (11%). Epstein–Barr virus testing did not identify EBV+ tumor cells. For the 27 patients whose tissue samples were centralized, additional immunohistochemistry was performed in 23 of them with available tumor tissue. MYC was overexpressed in immunohistochemistry in 57% of cases, whereas BCL2 was overexpressed in 87% of them. MYC/BCL2 double expression status concerned 43% of cases.

Tumor cells expression of adherence molecules (CD29 and ICAM1) was also tested on the centralized cohort, along with samples of 31 biopsies from diffuse large B-cell lymphomas (DLBCL) “not otherwise specified” (NOS) as controls. In each tissue sample, endothelial cells served as positive internal control. CD29 was expressed in 33% in IVLBCL (six cases out of 18) compared with 62% in DLBCL NOS; ICAM1 was found in one IVLBCL sample out of 19 tested (5%) compared with 74% in DLBCL NOS (Figure 1).

### 3.3 Treatment

Two of the cases were only confirmed postmortem and four patients received supportive care. Regarding first-line treatment, 59 received antineoplastic treatment and 56 were treated with an association of chemotherapy

---

**Table 1** Patients’ characteristics and initial disease presenting (n = 65)

|                        |   n  |  %a |
|------------------------|------|-----|
| **Sex**                |      |     |
| Female                 |   30 | 46  |
| Male                   |   35 | 54  |
| **Performance status (ECOG)** |      |     |
| 0–1                    | 20/60 | 33  |
| ≥2                     | 40/60 | 67  |
| B-symptoms             | 44/64 | 69  |
| **Primary involved site** |     |     |
| Bone marrow and/or spleen |   34 | 52  |
| CNS                    |   25 | 39  |
| Lymph nodes            |   22 | 34  |
| Skin                   |   21 | 33  |
| Liver                  |   17 | 27  |
| Adrenal gland          |   10 | 16  |
| Lung                   |    7 | 11  |
| Digestive tract        |    7 | 11  |
| Kidney                 |    6 |  9  |
| Bone                   |    5 |  8  |
| Othersb                |    9 | 14  |
| Macrophage activation syndrome |   26/64 | 41  |
| Circulating tumor cells | 11/60 | 18  |
| CSF involvement        |   2/46 |  4  |
| **IPI score**          |      |     |
| Low/intermediate (0-3) | 19/53 | 36  |
| High (4, 5)            | 34/53 | 64  |

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; IPI, International Prognostic Index; and NA, not available.

aResults are reported on the total number of patients for each category, except when data were available only for a subset of patients which number is specified after slash.

bOthers: prostate, pituitary gland, bladder, ovaries, testicle, uterus, cavum, muscles, and heart.

---

**Table 2** Immunohistochemical features

|                | n/n| %  |
|----------------|----|----|
| **Entire cohort** |    |    |
| CD20           | 60/60 | 100 |
| CD5            | 14/27 | 52  |
| EBER/LMP       | 0/14 |  0  |
| CD10           | 3/28 |  11 |
| BCL-6          | 11/23 | 48  |
| MUM1           | 14/22 | 64  |
| GC (Hans)      | 3/22 |  14 |
| BCL2           | 20/24 | 83  |
| MYC            | 4/6 |  67 |
| **Centralized samples** |     |    |
| BCL2           | 20/23 | 87  |
| MYC            | 12/21 | 57  |
| Double-expressor MYC/BCL2 | 9/21 | 43  |

aResults are reported on available data which number is specified after slash.
plus anti-CD20 antibody (rituximab). One patient diagnosed in 2001 received chemotherapy without rituximab, one patient was treated with single agent rituximab (81-year-old with PS = 4) and data are missing for one case. Forty-eight patients received an anthracycline-based regimen. Other regimens were based on cytarabine and platinum association (n = 4), they were planned in a CNS lymphoma treatment schema for three patients (high-dose methotrexate and/or cytarabine) and one patient received a Burkitt lymphoma chemotherapy regimen. CNS treatment or prophylaxis was given to 33 patients, with intrathecal infusion of chemotherapy (methotrexate and/or cytarabine) for 24 of them, and 18 patients (30%) received high-dose methotrexate at first-line treatment. Seven patients underwent autologous stem-cell transplantation (ASCT) at frontline, after BEAM regimen for six of them. At relapse, ASCT were performed in seven patients (four BEAM, two Thiotepa/Busulfan/Cyclophosphamide, and one BCNU/Melphalan) and allogenic stem-cell transplantation in two patients.

3.4 | Clinical outcome

Fifty-three patients were assessable for the response after first-line treatment (one follow-up loss and five premature deaths; for example, infection, gut perforation, and acute respiratory distress syndrome with multiorgan failure). Complete response was achieved in 43 patients (73%). Four patients had a stable disease and six patients had a progressive disease. All patients reached CR after ASCT.

With a median follow-up was 57.7 months (IQR 38.4–76.3), the median PFS was 29.4 months after diagnosis, with a 2-year and a 5-year PFS rate at 52.7% (95% CI: 41.4–67.1) and 40.3% (95% CI: 28.7–56.6), respectively. The median OS was 63.8 months, with a 2-year and a 5-year OS rate at 61.4% (95% CI: 50.3–74.9) and 59.0% (95% CI: 47.7–73.1), respectively (Figure 2). In the cohort of patients treated with R-CHOP-like regimen (n = 43), the 2-year and 5-year PFS was 65.1% (95% CI: 51.3–82.6) and 50% (95% CI: 35.1–71.2). The 2-year and 5-year OS was 76.1% (95% CI: 63.6–91.2) and 72.3% (95% CI: 58.9–88.9) (Figure 3).

3.5 | Prognostic factors

All the prognostic factors tested on PFS and OS are listed in Table 3.

In univariate analysis, history of autoimmune disorder (hazard ratio [HR] 3.3 [1.4–7.8]; p = 0.006) (Figure 4A), nodal involvement (HR 2.6 [1.4–5.1]; p = 0.004) (Figure 4B), and anthracycline use at first-line regimen (HR 0.1 [0–0.4]; p < 0.001) (Figure 4C) were significantly associated with PFS. Patients receiving ASCT had a better PFS (p < 0.02). High-dose methotrexate use was not associated with better PFS.

In multivariate analysis, lymph nodes involvement was predictive of worse PFS (HR 4.8 [1.9–12.3]; p < 0.001) and OS (HR 7.4 [2.5–22.1]; p < 0.001), while anthracycline-containing regimen improved PFS (HR 0.06 [0.02–0.2]; p < 0.0001) and OS (HR 0.03 [0.01–0.1]; p < 0.0001).
**FIGURE 2** Overall survival (OS) and Progression-free survival (PFS) of entire cohort. (n = 65)

4 | **DISCUSSION**

IVLBCL at diagnosis present with aggressive features such as advanced disease (stage IV in 100%), high IPI score (IPI 4–5 in 64%), presence of B-symptoms (69%), and high incidence of both neurological (39%) and skin (33%) involvement. In our cohort, incidence of nodal involvement (34%) in IVLBCL is more frequently reported than in previous studies (Table 4).10–12 Interestingly, coexisting malignancies are frequent and autoimmune disorders are significantly associated with worst prognosis. Presence of hemophagocytosis with macrophage activation syndrome (41%) is also more frequent in our cohort than in Ferreri’s (Table 4).10 According to WHO classification, IVLBCL is divided into two clinical pictures with different geographical distributions. The so-called “classic form” is more frequent in Western countries and goes along with symptoms related to organ involvement. Contrarily, the so-called “haemophagocytic syndrome-associated form” is more frequently reported in Asian patients. In our cohort, which included only patients treated in France (no ethnic origin reported, according to French law), incidence of hemophagocytosis with macrophage activation syndrome is comparable to what has been reported in the Asian IVLBCL population.

CD5 positivity was found in 52% of cases but was not significantly associated with PFS (HR 1.9 [CI95% 0.6–6.1], p = 0.26), as previously reported by Murase et al.11 Cellular origin was mainly a non-germinal center type (86%), and high expression level of MYC (57%), BCL2 (87%), or both MYC/BCL2 (43%) appears to be more frequent than in DLBCL NOS. Double-expression MYC/BCL2 is known for its adverse prognostic impact, but also BCL2 expression (40%–60% of DLBCL NOS), independently of IPI score or MYC expression (Petrella, Ann Oncol 2017).13 High expression of MYC and BCL2 in IVLBCL could be in-line with
their aggressive presentation (high IPI, advanced disease, B-symptoms). Interestingly, the lack of CD54 (ICAM-1) and CD29 (integrin beta-1) adherence molecules expression by tumor cells in our cohort compared with tumor cells of DLBCL NOS, suggests a loss of expression of those “homing” molecules and reinforces the hypothesis that this peculiar and exclusive intravascular growth pattern is secondary to this defect of homing receptors expression by neoplastic cells (Ponzoni, 2000). The scarcity of tumor cells in tumor biopsies did not enable the performance of molecular analysis, especially to investigate MYC, BCL2, or BCL6 rearrangement.

The 2-year PFS (53%) and OS (61%) in our cohort are similar to Shimada’s report (56% and 66%, respectively), illustrating “the poor prognosis” of IVLBCL as described in the WHO classification. However, according to their 2-year PFS (65%) and OS (76%), patients treated with R-CHOP-like regimen have similar outcomes to patients with non-IV DLBCL. This result is in-line with a recent population-based study in the US including 344 IVLBCL patients diagnosed between 2000 and 2013. This study, reported by Rajyaguru et al., used a Surveillance, Epidemiology, and End Results program and National Cancer Database. The 3 and 5-years OS were 52% and 46%, respectively and did not differ from those of the 133,993 patients with DLBCL NOS after using a propensity score which included variables such as age, clinical stage, or comorbidity index. A recent phase II trial conducted in Japan supports the use of R-CHOP plus high-dose methotrexate frontline and intrathecal chemotherapy, with a 2-year PFS of 76% in a selected population (without CNS symptoms). But, in practice, high-dose methotrexate in elderly or frail patients can be challenging, and treatment of IVLBCL is not well-defined. Our work suggests that intensive therapy (like ASCT)
| Variable                     | Progression-free survival | Overall survival |
|------------------------------|---------------------------|-----------------|
|                              | Univariate | Multivariate | Univariate | Multivariate | Univariate | Multivariate |
|                              | HR  | 95% CI | p-value | HR  | 95% CI | p-value | HR  | 95% CI | p-value | HR  | 95% CI | p-value |
| Sex, male                    | 0.8 | [0.4–1.5] | 0.490 | 1 | [0.5–2.2] | 0.919 | 1 | [0.5–2.2] | 0.919 |
| Age ≥ 70 years               | 1.3 | [0.7–2.4] | 0.496 | 0.6 | [0.2–1.4] | 0.227 | 1.8 | [0.9–3.7] | 0.117 | 0.9 | [0.4–2.3] | 0.864 |
| Autoimmune disorder          | 3.3 | [1.4–7.8] | <0.01 | 2.9 | [1.1–7.1] | 0.024 |
| Cancer associated            | 0.8 | [0.3–1.8] | 0.562 | 1 | [0.4–2.3] | 0.986 | 0.9 | [0.3–2.8] | 0.802 |
| Other HM associated          | 1.5 | [0.6–3.9] | 0.404 | 0.9 | [0.3–2.8] | 0.802 |
| Performance status ≥ 2       | 2.1 | [0.9–4.7] | 0.079 | 1.6 | [0.6–4.2] | 0.386 | 2.6 | [1–6.6] | 0.048 | 2.2 | [0.8–6.6] | 0.148 |
| B-symptoms                   | 1 | [0.5–2] | 1.000 | 0.9 | [0.4–1.8] | 0.692 | 1 | [0.5–2.2] | 0.993 |
| Involvement site             |       |       |       |     |       |       |     |       |       |     |       |       |
| CNS                          | 1 | [0.5–2] | 0.996 | 0.9 | [0.4–1.8] | 0.692 | 2.4 | [0.8–7.1] | 0.1 |
| Skin                         | 1.3 | [0.7–2.6] | 0.432 | 1.6 | [0.8–3.4] | 0.209 | 1.2 | [0.6–2.5] | 0.638 |
| BM/Spleen                    | 1.4 | [0.7–2.7] | 0.352 | 1.6 | [0.8–3.4] | 0.209 | 1.2 | [0.6–2.5] | 0.638 |
| Lung                         | 0.6 | [0.2–1.8] | 0.331 | 0.5 | [0.1–2.1] | 0.357 | 1.4 | [0.4–4.6] | 0.604 |
| Kidney                       | 1.1 | [0.3–3.6] | 0.89 | 1.4 | [0.4–4.6] | 0.604 | 1.4 | [0.4–4.6] | 0.604 |
| Lymph nodes                  | 2.6 | [1.4–5.1] | <0.01 | 4.8 | [1.9–12.3] | <0.001 | 2.9 | [1.4–6] | <0.01 | 7.4 | [2.5–22.1] | <0.001 |
| Bone                         | 2.2 | [0.8–6.5] | 0.135 | 2.4 | [0.8–7.1] | 0.1 |
| Hemophagocytosis             | 1.3 | [0.7–2.5] | 0.456 | 1.1 | [0.5–2.3] | 0.768 | 1.1 | [0.5–2.3] | 0.768 |
| Tumor cells in PB            | 1 | [0.4–2.2] | 0.94 | 1 | [0.4–2.5] | 0.991 | 1 | [0.4–2.5] | 0.991 |
| Elevated LDH                 | 1.3 | [0.5–3.2] | 0.528 | 1.3 | [0.5–3.5] | 0.548 | 1.3 | [0.5–3.5] | 0.548 |
| IPI 4–5                      | 1.4 | [0.6–3.1] | 0.424 | 1.9 | [0.8–5] | 0.17 | 1.9 | [0.8–5] | 0.17 |
| Treatment†                   |       |       |       |     |       |       |     |       |       |     |       |       |
| Anthracycline-based regimen  | 0.1 | [0–0.4] | <0.001 | 0.06 | [0.02–0.2] | <0.0001 | 0.1 | [0–0.3] | <0.0001 | 0.03 | [0.01–0.1] | <0.0001 |
| R-CHOP regimen               | 0.6 | [0.3–1.4] | 0.248 | 0.5 | [0.2–1.3] | 0.157 | 1.1 | [0.4–2.6] | 0.876 |
| High-dose Methotrexate       | 0.9 | [0.4–2.2] | 0.886 | 1.1 | [0.4–2.6] | 0.876 | 1.1 | [0.4–2.6] | 0.876 |
| ASCT at first-line           | —   | —   | 0.02 | — | — | 0.054 | — | — | 0.054 |
| ASCT at any time             | NA | 0.1 | [0–0.6] | 0.035 | 0.1 | [0–0.6] | 0.035 |

The bold values indicate statistically significant values.

Abbreviations: ASCT indicates autologous stem-cell transplantation; CI, confidence interval; CNS, central nervous system; HM, hematological malignancies; HR, hazard ratio; IPI, international prognostic index; PB, peripheral blood.

†Comparison among patients who received chemotherapy.
could provide better outcome, but more patients are needed to confirm this. Indeed, other biology-driven therapeutic approaches based on IVLBCL biology should be further investigated, such as BCL-2 or microenvironment-targeted therapies.

Our work confirms the aggressive features of IVLBCL and suggests a dismal prognosis when associated with autoimmune disorders at the time of diagnosis. R-CHOP-like regimen could be recommended, but better IVLBCL–tailored therapies are needed.

**AUTHOR CONTRIBUTION**

AB performed acquisition, analysis, or interpretation of data for the study. AB and SLG contributed the conception and design of the work, drafted the manuscript; CB, LG, JR, OL, MP, CS, RD, VR, FLG, LO, LMF, LB, BV, VS, SC, KB, ATG, MM, LS, RH, and TG contributed to collect data. OL and CB provided pictures for Figure 1. CL performed statistical analysis.
ACKNOWLEDGMENTS
The authors thank the patients and their families, all investigators in participating LYSA centers. The manuscript has been reviewed and approved by all authors prior to submission.

CONFLICT OF INTEREST
No conflict of interest for all authors.

ETHICS STATEMENT
This retrospective noninterventional study was reported to the Direction de la recherche Clinique (DRCI) in Nantes (n° RC16-0034), according to the French legislation (article L 0.1121–0.1 and R1121-2 of Code de Santé Publique).

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID
Antoine Bonnet https://orcid.org/0000-0001-6962-3650

REFERENCES
1. Nakamura S, Ponzoni M, Campo E. Intravascular lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. IARC; 2017. ISBN 978-92-832-4494-3.
2. Ponzoni M, Arrigoni G, Gould VE, et al. Lack of CD 29 (beta1 integrin) and CD 54 (ICAM-1) adhesion molecules in intravascular lymphomatosis. Hum Pathol. 2000;31(2):220-226.
3. Ferreri AJM, Dognini GP, Campo E, et al. Variations in clinical presentation, frequency of hemophagocytosis and clinical behavior of intravascular lymphoma diagnosed in different geographical regions. Haematologica. 2007;92(4):486-492.
4. Geer M, Roberts E, Shango M, et al. Multicentre retrospective study of intravascular large B-cell lymphoma treated at academic institutions within the United States. Br J Haematol. 2019;186(2):255-262.
5. Ferreri AJM, Dognini GP, Bairey O, et al. The addition of rituximab to anthracycline-based chemotherapy significantly improves outcome in “Western” patients with intravascular large B-cell lymphoma. Br J Haematol. 2008;143(2):253-257.
6. Shimada K, Matsue K, Yamamoto K, et al. Retrospective analysis of intravascular large B-cell lymphoma treated with rituximab-containing chemotherapy as reported by the IVL study group in Japan. J Clin Oncol. 2008;26(19):3189-3195.
7. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25(5):579–86.
8. Ponzoni M, Ferreri AJM, Campo E, et al. Definition, diagnosis, and management of intravascular large B-cell lymphoma: proposals and perspectives from an international consensus meeting. J Clin Oncol. 2007;25(21):3168-3173.
9. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood. 2004;103(1):275-282.
10. Ferreri AJM, Campo E, Seymour JF, et al. Intravascular lymphoma: clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the ‘cutaneous variant’1. Br J Haematol. 2004;127(2):173-183.
11. Murase T, Yamaguchi M, Suzuki R, et al. Intravascular large B-cell lymphoma (IVLBCL): a clinicopathologic study of 96 cases with special reference to the immunophenotypic heterogeneity of CD5. Blood. 2007;109(2):478-485.
12. Brunet V, Marouan S, Routy J-P, et al. Retrospective study of intravascular large B-cell lymphoma cases diagnosed in Quebec: a retrospective study of 29 case reports. Medicine (Baltimore). 2017;96(5):e5985.
13. Petrella T, Copie-Bergman C, Brière J, et al. BCL2 expression but not MYC and BCL2 coexpression predicts survival in elderly patients with diffuse large B-cell lymphoma independently of cell of origin in the phase 3 LNH03-6B trial. Ann Oncol. 2017;28(5):1042-1049.
14. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346(4):235-242.
15. Rajyaguru DJ, Bhaskar C, Borgert AJ, Smith A, Parsons B. Intravascular large B-cell lymphoma in the United States (US): a population-based study using surveillance, epidemiology, and end results program and National Cancer Database. Leuk Lymphoma. 2017;58(9):1-9.
16. Shimada K, Yamaguchi M, Atsuta Y, et al. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone combined with high-dose methotrexate plus intrathecal chemotherapy for newly diagnosed intravascular large B-cell lymphoma (PRIMEUR-IVL): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2020;21(4):593-602.

How to cite this article: Bonnet A, Bossard C, Gabellier L, et al. Clinical presentation, outcome, and prognostic markers in patients with intravascular large B-cell lymphoma, a lymphoma study association (LYSA) retrospective study. Cancer Med. 2022;11(19):3602-3611. doi: 10.1002/cam4.4742