A Multicountry Retrospective Chart Review of Treatment Patterns and Resource Use in Patients With Newly Diagnosed Ph-Negative B-cell Acute Lymphoblastic Leukemia Undergoing First-line Consolidation Therapy

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Introduction

- Acute lymphoblastic leukemia (ALL) is a hematologic malignancy characterized by the rapid proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other tissues.
- It is a rare disease, affecting individuals across all age groups, with an estimated 6,540 new cases of ALL diagnosed in the United States (US) in 2023 and an annual incidence of approximately 1.28 per 1,000,000 individuals across Europe.[1,2]
- The key treatment goals for first-line (1L) ALL are to achieve disease remission, including deep control of minimal residual disease (MRD), prevent disease relapse, and improve survival, while limiting toxicities and maintaining quality of life.[3]
- While the treatment goals of 1L B-cell ALL (B-ALL) therapy are consistent, there is no one preferred standard-of-care regimen, with treatment regimen varying by country and treatment setting.[3]
- This multinational, non-interventional, observational, retrospective chart review evaluated current treatment patterns and healthcare resource utilization (HRU) in adults with newly diagnosed (ND) Philadelphia chromosome–negative (Ph–) B-ALL who achieved remission and initiated 1L consolidation therapy.

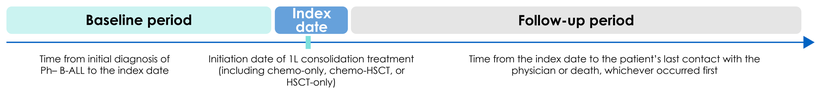
Objectives

- The objective of the study was to assess real-world treatment patterns and HRU among patients with ND Ph– B-ALL who received consolidation treatment with/without hematopoietic stem cell transplant (HSCT) and those who received HSCT-only after achieving complete remission (CR) or complete remission with incomplete recovery (CRi) and MRD response following 1L induction chemotherapy (chemo) with or without intensification chemo.

Methods

- This was a retrospective, non-interventional, observational study using physician-abstracted chart data from eight countries, including North America (US and Canada) and Europe (United Kingdom, France, Germany, Italy, Spain, and Portugal).
- Eligible physicians were licensed hematologists, oncologists, or hematologists/oncologists who had ≥3 years of experience treating adult patients with ALL, had managed ≥3 adult patients with ND Ph– B-ALL in the past year, and had access to complete patient care records.
- Eligible participating physicians used a randomized chart selection algorithm to abstract clinical data for up to 10 eligible patients via a structured electronic case report form. Patient eligibility criteria and the study schema are presented in **Figure 1**.
- Results were stratified by geographic region (North America and Europe) and consolidation therapy received (chemotherapy [chemo]-only, chemo-HSCT, or HSCT-only).

Figure 1. Study Design Schema



Eligibility criteria

Inclusion criteria

- Adult patients (≥18 years) with ND Ph– B-ALL
- Received and completed 1L chemo-only, chemo-HSCT, or HSCT-only, induction therapy, with or without 1L intensification therapy
- Achieved MRD negative and CR/CRi after 1L induction, with or without 1L intensification therapy
- Initiated 1L consolidation therapy (chemo-only, chemo-HSCT, or HSCT-only)
- Index date had to be between January 2018 and June 2023
- Had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 at the initiation of 1L consolidation (index date)
- Had complete care information regarding disease history, treatments, HSCT history, HRU, and clinical outcomes (including survival, response, and relapse status after 1L consolidation therapy) available with the treating physician, even if the patient is deceased

Exclusion criteria

- With Burkitt's-like leukemia
- With chronic lymphocytic leukemia
- Received blinatumomab in 1L consolidation phase

Assessment

At the index date

- Demographics and comorbidities
- Disease characteristics
- 1L induction and intensification therapy

Follow-up period

- 1L consolidation treatment (chemo-only, chemo-HSCT, or HSCT-only)
- 1L maintenance therapy
- ALL-related HRU, including medical visits

CR was defined as neutrophil count ≥1×10⁹/L (≥1,000/mm³), platelet count ≥100×10⁹/L (≥100,000/mm³), no leukemic blasts present in the peripheral blood, adequate bone marrow cellularity with trilineage hematopoiesis, ≤5% bone marrow blasts, and no extramedullary leukemia present. CRi criteria were the same as CR criteria with the exception that it involved incomplete platelet recovery (platelets >75 but <100×10⁹/L, >75,000 but <100,000/mm³) independent of platelet transfusions or incomplete neutrophil recovery (>0.75 but <1×10⁹/L, >750 but <1,000/mm³). MRD response was as defined by the treating physician. Common thresholds include residual cancer cells <0.1% or <0.01%.

Results

Patient Demographics and Disease Characteristics

- 928 adult patients with ND Ph– B-ALL were included in this study, with 264 patients from North America and 664 from Europe. Detailed patient demographics at the index date are presented in **Table 1**.
- MRD response was most commonly measured using flow cytometry (68.5%), followed by immunoglobulin next-generation sequencing (28.3%) and polymerase chain reaction (19.0%).
- The majority of patients initiated consolidation therapy in 2022 or 2023 (59.6%). Patient disease characteristics at the initiation of 1L consolidation treatment are presented in **Table 2**.

Table 1. Patient Demographics at Index Date

Country, n (%)	Total (N=928)
US	207 (22.3)
Spain	159 (17.1)
Italy	155 (16.7)
Germany	146 (15.7)
France	112 (12.1)
United Kingdom	67 (7.2)
Canada	57 (6.1)
Portugal	25 (2.7)
Age (years)	
Mean±SD (range)	47.6±14.9 (18.0-86.8)
Median (IQR)	48.0 (35.6-58.7)
Sex, male n (%)	**581 (62.6)**
Race, n (%) – for US patients only	**n=207**
White	114 (55.1)
Black or African	57 (27.5)
Asian	33 (15.9)
Other	6 (2.9)

Table 2. Patient Disease Characteristics at Index Date

Time from initial diagnosis to initiation of 1L consolidation therapy, months	Total (N=928)
Mean±SD	6.4±8.3
Median (IQR)	3.7 (2.1-7.1)
ECOG performance status, n (%)	
0	336 (36.2)
1	472 (50.9)
2	120 (12.9)
Comorbidities, n (%)	
Any comorbidity	289 (31.1)
Pulmonary disease	91 (9.8)
Heart disease	90 (9.7)
Renal disease	53 (5.7)
Cytogenetic abnormalities and/or molecular risks,[a] n (%)	
Any cytogenetic abnormalities or molecular risks	424 (45.7)
Favorable	99 (10.7)
Intermediate	57 (6.1)
Unfavorable	259 (27.9)
Other/unknown	97 (10.5)
Bone marrow blasts	
Mean±SD	3.9±10.0
Median (IQR)	2.0 (1.0-4.0)
Unknown, n (%)	218 (23.5)

[a]Cytogenetic abnormalities or molecular risk are categorized as follows: Favorable: High-hyperdiploid, TCF3::PBX1, DUX4-rearranged, PAX5 P80R; Intermediate: iAMP21, MEF2D-rearranged, ZNF384-rearranged, PAX5::ETV6, PAX5-altered, IKZF1 N159Y, PAX5alt; Unfavorable: Low hypodiploid, near haploid, KMT2A-rearranged, HLF, BCL2-rearranged, MYC-rearranged, CDX2/UBTF, BCR::ABL1-like, ETV6::RUNX1-like with IGH::CRLF2 fusion, CRLF2-rearranged; No risk assigned: ZEB2/CEB2. If patients satisfied multiple categories, risk was assigned based on the hierarchy of risk categories: Unfavorable, Intermediate, Favorable, No Risk Assigned.

Treatment Patterns in North America

- In North America, among patients in the chemo-only group, hyper-CVAD was the most commonly administered consolidation chemotherapy regimen (31.5%; standard deviation [SD] treatment duration, 4.2 [2.1] months), followed by ALL PETHEMA (18.9%; mean [SD] treatment duration, 3.0 [2.2] months) and DFCI-ALL Consortium Protocol 00-01 (17.1%; mean [SD] treatment duration, 5.9 [4.9] months) (**Figure 2**).
- Among patients in the chemo-HSCT group, hyper-CVAD was the most frequent consolidation chemotherapy regimen (38.7%; mean [SD] treatment duration, 1.5 [1.7] months), followed by GMALL (22.6%; mean [SD] treatment duration, 2.7 [0.4] months) and DFCI-ALL Consortium Protocol 00-01 (12.9%; mean [SD] treatment duration, 2.7 [2.7] months) (**Figure 3**).
- Among all patients who received HSCT in consolidation (chemo-HSCT and HSCT-only groups), the most common type was allogeneic HSCT from an human leukocyte antigen (HLA)-matched sibling (66.0%), followed by allogeneic HSCT from a matched unrelated donor (28.1%) and allogeneic HSCT from a matched other related donor (non-siblings) (4.6%).
- Among patients who received consolidation chemo-only, 38.7% proceeded to maintenance therapy. POMP was the predominant maintenance regimen, administered to 85.7% of patients in the chemo-only subgroup for a mean (SD) duration of 14.2 (7.8) months.

Figure 2. Treatment Patterns in North America for Patients Receiving Consolidation Chemo-Only

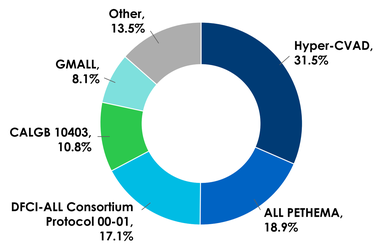
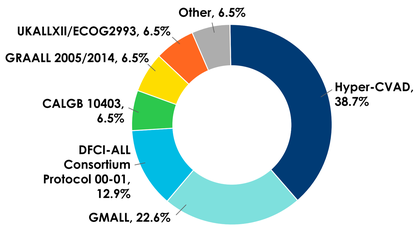


Figure 3. Treatment Patterns in North America for Patients Receiving Consolidation Chemo-HSCT



Treatment Patterns in Europe

- In Europe, among patients who received consolidation chemo-only, hyper-CVAD was the most common chemo regimen (24.8%; mean [SD] treatment duration, 5.2 [5.2] months), followed by GMALL (12.9%; mean [SD] treatment duration, 3.7 [2.7] months) and ALL PETHEMA (12.4%; mean [SD] treatment duration 3.8 [4.3] months) (**Figure 4**).
- Among patients in the chemo-HSCT group, GMALL was the most frequent consolidation chemotherapy regimen (29.1%; mean [SD] treatment duration, 1.7 [1.9] months), followed by hyper-CVAD (20.6%; mean [SD] treatment duration, 1.7 [1.3] months) and ALL PETHEMA (14.9%; mean [SD] treatment duration, 0.9 [0.6] months) (**Figure 5**).
- Among all patients who received HSCT in consolidation (chemo-HSCT and HSCT-only groups), the most common type was allogeneic HSCT from an HLA-matched sibling (42.7%), followed by allogeneic HSCT from a matched unrelated donor (28.3%) and autologous HSCT (14.0%).
- Among patients who received consolidation chemo-only, 28.0% proceeded to maintenance therapy. POMP was the predominant maintenance regimen, administered to 63.0% of patients in the chemo-only subgroup for a mean (SD) duration of 17.2 (9.2) months.

Figure 4. Treatment Patterns in Europe for Patients Receiving Consolidation Chemo-Only

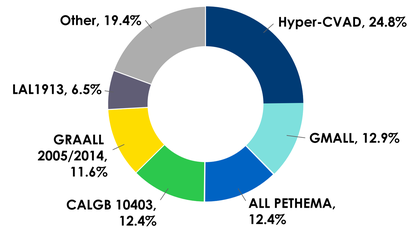
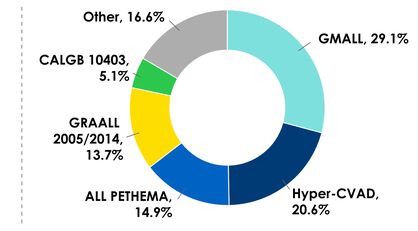


Figure 5. Treatment Patterns in Europe for Patients Receiving Consolidation Chemo-HSCT



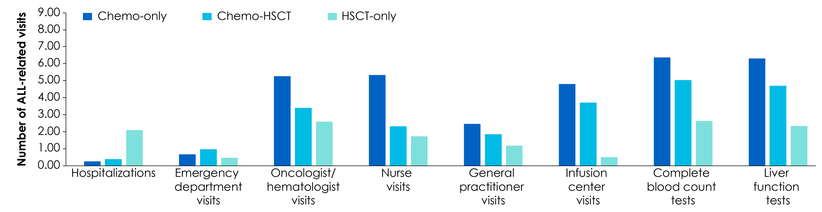
Hospitalizations in North America

- In North America, 44.1% of patients in the chemo-only group and 100% in both the chemo-HSCT and HSCT-only groups required at least one hospitalization after their index date.
- Among patients with at least one hospitalization, the mean (SD) number of hospitalizations was 2.0 (1.8), 1.4 (0.9), and 1.1 (0.4) in the chemo-only, chemo-HSCT, and HSCT-only groups, respectively.
- The mean (SD) length of stay per hospitalization was 18.9 (33.8), 25.9 (25.9), and 30.3 (12.3) days in the chemo-only, chemo-HSCT, and HSCT-only groups, respectively.
- The primary reason for hospitalization among patients in the chemo-only group was management of adverse events.
- Among patients who received HSCT consolidation (chemo-HSCT and HSCT-only groups), the primary reason for initial hospitalization was the HSCT procedure. The most common reasons for additional hospitalizations were administration of pharmacological therapies and treatment of adverse events for chemo-HSCT patients and HSCT-related complications for HSCT-only patients.
- Few patients required transfer to the intensive care unit (ICU): 5.4%, 9.7%, and 3.3% of patients in the chemo-only, chemo-HSCT, and HSCT-only groups, respectively.

ALL-Related Medical Visits per 6-Month Period in North America

- In North America, patients in the chemo-only group had a mean (SD) of 5.3 (5.1) outpatient visits to an oncologist and/or hematologist, 5.3 (7.6) nurse visits, 2.5 (2.2) visits to a general practitioner, and 4.8 (7.8) visits to an infusion center since their index date.
- Patients who received consolidation chemo-HSCT had a mean (SD) of 3.4 (2.1) outpatient visits to an oncologist and/or hematologist, 2.3 (1.9) nurse visits, 1.9 (2.0) visits to a general practitioner, and 3.7 (3.7) visits to an infusion center since their index date.
- Patients who received HSCT-only as consolidation had a mean (SD) of 2.6 (2.4) outpatient visits to an oncologist and/or hematologist, 1.7 (2.4) nurse visits, 1.2 (2.3) visits to a general practitioner, and 0.5 (1.8) visits to an infusion center since their index date.
- Mean (SD) emergency department (ED) visits were 0.7 (1.3) for consolidation chemo-only patients, 1.0 (0.8) for chemo-HSCT patients, and 0.5 (1.4) for HSCT-only patients.
- ALL-related HRU per 6-month period for patients in North America is summarized in **Figure 6**.

Figure 6. Number of ALL-Related Visits per 6-Month Period Among Patients in North America



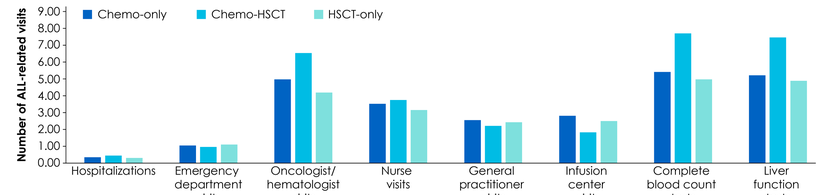
Hospitalizations in Europe

- In Europe, 46.1% of patients in the chemo-only group and 100% of patients in both the chemo-HSCT and HSCT-only groups required at least one hospitalization after their index date.
- Among patients with at least one hospitalization, the mean (SD) number of hospitalizations was 3.1 (3.2), 2.0 (3.0), and 1.3 (1.0) in the chemo-only, chemo-HSCT, and HSCT-only groups, respectively.
- The mean (SD) length of stay per hospitalization was 32.6 (121.9), 39.3 (52.0), and 36.3 (33.0) days in the chemo-only, chemo-HSCT, and HSCT-only groups, respectively.
- The most common reason for hospitalization in the chemo-only group was the administration of pharmacological treatment for ALL.
- Among patients who received HSCT with or without consolidation chemo, the most common reason for their initial hospitalization was the HSCT procedure. For additional hospitalizations, the most common reasons were administration of pharmacological therapies, treatment of adverse events, and HSCT-related complications.
- Few patients required transfer to the ICU: 2.2%, 5.7%, and 3.4% in the chemo-only, chemo-HSCT, and HSCT-only groups, respectively.

ALL-Related Medical Visits per 6-Month Period in Europe

- In Europe, chemo-only patients had a mean (SD) of 5.0 (4.5) outpatient visits to an oncologist and/or hematologist, 3.5 (3.8) nurse visits, 2.6 (3.1) visits to a general practitioner, and 2.8 (4.3) visits to an infusion center following their index date.
- Patients who received chemo-HSCT had a mean (SD) of 6.6 (7.2) outpatient visits to an oncologist and/or hematologist, 3.8 (6.5) nurse visits, 2.2 (3.9) visits to a general practitioner, and 1.8 (3.5) visits to an infusion center following their index date.
- Patients who received HSCT-only had a mean (SD) of 4.2 (3.1) outpatient visits to an oncologist and/or hematologist, 3.2 (2.9) nurse visits, 2.4 (2.4) visits to a general practitioner, and 2.5 (3.3) visits to an infusion center following their index date.
- Mean (SD) ED visits were 1.0 (1.4) for the consolidation chemo-only patients, 1.0 (2.8) for the chemo-HSCT patients, and 1.1 (1.5) for the HSCT-only patients.
- ALL-related HRU per 6-month period for patients in Europe is summarized in **Figure 7**.

Figure 7. Number of ALL-Related Visits per 6-Month Period Among Patients in Europe



Limitations

- This study may have been subject to selection bias. Although physicians were instructed to randomly select patients, they may have included patients seen more recently and for a longer duration, potentially biasing results towards patients who were alive and in better health at the time of data collection.
- On average, patients in Europe were older than patients in North America. This may be because younger adults in Europe may still be treated in pediatric centers, while this study only included physicians treating in adult ALL centers.
- Results were not reported separately for patients treated at HSCT-specialized centers. To minimize this bias, analyses were stratified by whether a patient received HSCT during consolidation therapy.
- Due to the retrospective design, data gaps or undocumented external visits may have led to underestimated HRU.
- Patients initiating consolidation therapy with immunotherapies were not included, as these treatments were not approved for use at the time of the study.

Conclusion

- **While treatment patterns may vary, hyper-CVAD was one of the most widely used consolidation chemo regimen both in North America and Europe among patients with or without HSCT. GMALL and ALL PETHEMA were also commonly used.**
- **All-related HRU was substantial for adults with ND Ph– B-ALL, with many patients requiring lengthy hospitalizations and frequent outpatient visits.**
- **Hospitalizations appeared to be longer and more frequent in Europe than in North America.**
- **Regardless of regimen, the observed HRU underscores the need for innovative 1L ALL therapies to reduce the HRU burden.**

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Abbreviations

1L, first-line; ALL, acute lymphoblastic leukemia; B-ALL, B-cell acute lymphoblastic leukemia; CALGB, Cancer and Leukemia Group B; chemo, chemotherapy; CR, complete remission; CRi, complete remission with incomplete recovery; DFCI, Dana-Farber Cancer Institute; ECOG, Eastern Cooperative Oncology Group; GMALL, German Multicenter Study Group; GRAALL, Group for Research on Adult Acute Lymphoblastic Leukemia; HLA, human leukocyte antigen; HRU, healthcare resource utilization; hyper-CVAD, fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; ICU, intensive care unit; IQR, interquartile range; MRD, minimal residual disease; ND, newly diagnosed; PETHEMA, Programa Español de Tratamientos en Hematología; Ph–, Philadelphia chromosome-negative; POMP, mercaptopurine [Purixan], vincristine [Oncovin], methotrexate, prednisone; SD, standard deviation; US, United States.

Conflict of Interest

Amgen Inc. sponsored and designed the study, interpreted the data, and reviewed the final version. HY, MD, CX, JL, and ZK are employees of Analysis Group, which received funding from Amgen Inc. to conduct this research. FZ, AG, and DB are employees of Amgen Inc. and have equity ownership. SL received honoraria for consulting/advisory boards from Amgen Inc.

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