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Organizational impacts of fixed-duration therapies for the management of patients with chronic lymphocytic leukemia in Italy

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ORGANIZATIONAL IMPACTS OF FIXED-DURATION THERAPIES FOR THE MANAGEMENT OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA IN ITALY

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Declarations

Ethics approval and consent to participate

As four hematologists completed a questionnaire about their clinical practice with no reference to specific patients, no critical ethical issues were identified, and formal ethics approval and consent to participate were not required under the Bocconi University Ethics Committee regulations.

The research was not conducted on humans/humans data so adherence to the Declaration of Helsinki is not applicable.

Consent for publication

Not applicable (the manuscript does not contain data from any individual person).

Availability of data and materials

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

Competing interests

Giacomo Loseto reports fees for consultancies/participation into speakers' bureau or advisory board with Janssen-Cilag, Gilead, Roche, Italfarmaco, Takeda, AbbVie, Incyte, AstraZeneca, BeOne, GSK, Lilly. Antonio Cuneo reports fees for participation into speakers' bureau and advisory board with Abbvie, AstraZeneca, BeOne, Janssen and Lilly. Anna Maria Frustaci reports participation into advisory boards, congresses sponsorships, consultancies with BeOne, Janssen, Abbvie, AstraZeneca. The other authors have no relevant financial or non-financial interests to disclose.

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Authors' contribution

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Abstract

Background: Chronic Lymphocytic Leukemia (CLL) is a common adult leukemia characterized by the progressive accumulation of dysfunctional lymphocytes. Recently introduced fixed-duration targeted therapies for previously untreated patients have demonstrated superior efficacy compared to chemotherapy, while offering time-limited treatment that improves patient quality of life and reduces the burden on healthcare systems compared to continuous therapies. This analysis examines the organizational impact of implementing first-line, fixed-duration CLL therapies, with focus on healthcare resource allocation, costs, and patient management.

Methods: The regimens analyzed included ibrutinib + venetoclax (I+V, oral), venetoclax + obinutuzumab (Ven-Obi, oral/infusion), bendamustine + rituximab (BR, infusion), chlorambucil + obinutuzumab (Clb-Obi, oral/infusion), and fludarabine + cyclophosphamide + rituximab (FCR, infusion). Data were defined through product characteristics, published literature, expert opinion, and standard hospital procedures for drug administration, adverse event management, and treatment duration. A questionnaire administered in four Italian centers captured organizational aspects such as healthcare personnel time, patient assessment, treatment preparation and administration, and follow-up.

Results: Personnel time and costs varied substantially across regimens, with administration mode (oral vs. infusion) emerging as a key driver. Time ranged from 4,899 minutes (81.6 hours) for Clb-Obi to 8,019 minutes (133.7 hours) for Ven-Obi. Organizational costs ranged from €3,942 (BR) to €8,631 (Ven-Obi). The all-oral I+V

combination showed a lower cost profile (€5,724) than Ven-Obi and was comparable to Clb-Obi, despite added monitoring requirements.

Conclusions: Treatment selection should balance efficacy with organizational and economic considerations. Findings highlight that oral therapies improve efficiency and patient convenience while reducing delivery costs.

Keywords

Chronic lymphocytic leukemia, fixed-duration therapy, healthcare resource utilization, organizational impact, cost analysis, economic evaluation

Introduction

Chronic Lymphocytic Leukemia (CLL) is the most common form of leukemia in adults in Western countries and is characterized by a clonal proliferation and accumulation of leukemic B lymphocytes in the blood, bone marrow, and lymphoid tissues [1]. The incidence of CLL increases with age, with a median age at diagnosis higher than 70 years, and it is more prevalent in males than in females [2]. CLL is a heterogeneous disease with clinical outcomes ranging from asymptomatic, indolent forms to aggressive forms requiring immediate treatment approach.

Over the past decade, the treatment landscape for CLL has evolved significantly. The introduction of targeted agents including Bruton's tyrosine kinase (BTK) inhibitors and BCL-2 inhibitors like venetoclax, has dramatically improved patient outcomes, particularly in those with high-risk genetic features [3].

Fixed-duration therapies, offering a finite treatment duration, have emerged as a more appealing and convenient treatment approach than continuous treatment with oral inhibitors, for both patients and health care providers. Fixed-duration regimens venetoclax-based show a structured treatment timeline, lasting 12-24 months. These regimens have demonstrated efficacy in clinical trials, showing superiority to conventional chemoimmunotherapy, high rates of deep responses with minimal residual disease and prolonged progression-free survival. However, their use further requires the evaluation of the broader organizational impacts on healthcare systems.

Currently, the approved and widely used fixed-duration therapies for the treatment of CLL in Italy are [4, 5]: ibrutinib-venetoclax (I+V) [6–8] and venetoclax-obinutuzumab (Ven-Obi) [7, 9, 10], We also considered fixed-duration chemoimmunotherapy regimes

as bendamustine-rituximab (BR) [11–13], chlorambucil-obinutuzumab (Clb-Obi) [9, 13], and fludarabine-cyclophosphamide-rituximab (FCR) regimens [14, 15] although they are no longer commonly used in our country, as is the case in many others.

As Ven-Obi treatment is associated to a rapid reduction in tumor burden, this regimen includes an initial 5-weekly dose titration phase of venetoclax and adequate hydration to prevent the risk of tumor lysis syndrome (TLS). Obinutuzumab, requires intravenous infusions in a day hospital, throughout the duration of the treatment and TLS prophylaxis is required during the initial cycles of venetoclax. In contrast, the I+V combination requires a hospital setting only for the initial cycles of therapy with venetoclax to monitor the patient for the risk of TLS.

This study aims to analyze the organizational impacts, in terms of healthcare personnel dedicated time and management costs of adopting fixed-duration therapies for CLL within the hospital setting in Italy, with the goal of identifying areas that could potentially be favorably impacted by the use of oral therapeutic strategies.

Methods

This analysis was restricted to fixed-duration regimens available in Italy to ensure comparability of organizational pathways. Continuous therapies, including other BTK inhibitor–based strategies, as well as emerging evidence from recent trials (e.g., AMPLIFY, CLL17), were not included.

The detailed schedules of the five fixed-duration regimens analyzed are presented in Table 1.

The organizational impact of fixed-duration CLL therapies was assessed using the EUnetHTA Core Model (version 3.0) as the guiding conceptual framework. This framework was selected because it provides a structured and internationally recognized approach for systematically evaluating organizational and system-level implications of health technologies, beyond clinical effectiveness alone. In line with the objectives of the study, specific EUnetHTA domains relevant to organizational impact - namely Health Delivery Process, Structure of the Health Care System, Process-related Costs, Management - were identified a priori and operationalized through a purpose-designed questionnaire. The questionnaire was developed following a targeted literature review on organizational assessments of onco-hematological treatments.

Qualitative data collected from the participating hematologists were analyzed thematically according to the predefined domains. This approach ensured that organizational aspects such as patient flow, healthcare personnel involvement, resource

utilization and management complexity were systematically captured and interpreted within a coherent HTA framework. The use of the EUnetHTA Core Model thus supported both the organization of empirical data and the interpretation of findings, enabling descriptive observations to be linked to broader system-level considerations relevant for decision-making and implementation. The analysis is descriptive, non-inferential, and non-comparative in nature. The study was designed to provide an exploratory assessment of organizational processes and resource implications associated with different fixed-duration treatment regimens, rather than to formally test hypotheses or establish statistically significant differences between regimens.

Table 1- Detailed treatment schedules

Treatment	**Description**	**Active ingredient**	**Dosage**	**# Cycles**	**# Administrations/ dispensations**	**Total treatment duration (days)**
Ibrutinib+Venetoclax (I+V)	Ibrutinib should be administered as monotherapy for 3 cycles (1 cycle = 28 days), followed by 12 cycles of ibrutinib plus venetoclax.	Ibrutinib (oral)	480 mg daily for 15 cycles	15	15	420
		Venetoclax (oral)	20 mg, 50 mg, 100 mg, 200 mg, 400 mg in the first 5 weeks (ramp-up schedule starting on cycle 1 day 22 through cycle 2 day 28) 400 mg daily for 10 cycles	12	5+10	
Venetoclax+Obinutuzumab (Ven-Obi)	Venetoclax is administered for a total of 12 cycles, each cycle lasting 28 days: 6 cycles in combination with obinutuzumab, followed by 6 cycles of venetoclax monotherapy.	Venetoclax (oral)	20 mg, 50 mg, 100 mg, 200 mg, 400 mg in the first 5 weeks (ramp-up schedule starting on cycle 1 day 22 through cycle 2 day 28) 400 mg daily for 10 cycles	12	5+10	336
		Obinutuzumab (infusion)	100 mg on day 1 of cycle 1, followed by 900 mg on day 1 or 2. 1,000 mg on days 8 and 15 of cycle 1 and on day 1 of each subsequent cycle for 6 cycles.	6	4+5	
Chlorambucil+ Obinutuzumab (Clb-Obi)	6 cycles of 28 days each	Chlorambucil (oral)	0.5 mg/kg on days 1 and 15 for 6 cycles	6	12	168
		Obinutuzumab (infusion)	cycle 1: 100 mg day 1, 900 mg day 2,	6	4+5	

			1,000 mg days 8 and 15 cycles 2–6: 1,000 mg on day 1			
Bendamustine+ Rituximab (BR)	6 cycles of 28 days each	Bendamustine (infusion)	70–90 mg/m² (based on age and patient characteristics) on days 1 and 2 of each cycle for 6 cycles	6	12	168
		Rituximab (infusion)	375 mg/m² on day 1 of cycle 1 500 mg/m² on day 1 of cycles 2–6	6	6	
Fludarabine+ Cyclophosphamide+ Rituximab (FCR)	6 cycles of 28 days each	Fludarabine (infusion)	25 mg/m² on days 1–3 of each cycle for 6 cycles	6	18	168
		Cyclophosphamide (infusion)	250 mg/m² on days 1–3 of each cycle for 6 cycles	6	18	
		Rituximab (infusion)	375 mg/m² on day 1 of cycle 1 500 mg/m² on day 1 of cycles 2–6	6	6	

Literature search

We performed a literature review to identify the possible topics to be considered in the analysis. In particular, the aspects related to the organizational impact of the administration of the different fixed-duration therapies under investigation was conducted by launching the following search query through the PubMed scientific database in April 2024: *(organiz* OR organis*) AND (aspect* OR impact*) AND (oral OR infusion* OR endovenous OR IV) AND (oncolog* OR hematol* OR haematol* OR oncohematol* OR oncohaematol*).* The search, which focused on titles and abstracts, retrieved 144 studies, of which 6 [16–21] covering the topics summarized in Table 2.

Table 2 – Summary of activities considered in the literature on the organizational aspects of administering onco-hematological drugs

Activity	**Oral**	**Infusion**
Preparatory phase insertion of CVC or peripheral catheter (if required))		x
Patient admission and informational communication		x

Clinical examinations at baseline (lab tests, CT scan, cardiologic evaluation, blood tests)	x	x
Onco-hematological (assessment of treatment eligibility)		x
Pharmacy dispensing activities (e.g., patient check-in, counseling and medication package delivery)	x	
Pharmaceutical preparation processes (including dosing, safety risk evaluation, quality assurance checks)		x
Co-medications preparation		x
Drug administration in hospital setting		x
Observation and hospital discharge		x
Wastage management		x
Management of possible adverse events	x	x
Patient monitoring and laboratory tests during follow-up	x	x
Removal of CVC or peripheral catheter (at the end of the entire treatment)		x

CVC=central venous catheter

Data collection

The topics reported in Table 1 have been included in the specifically developed questionnaire aimed at retrieving information on the organizational aspects of fixed-duration regimens used for front-line treatment management of patients with CLL (see Supplementary material).

The instrument combined structured questions (e.g., predefined activities and time slots expressed in minutes) with open-ended fields allowing respondents to provide contextual clarifications where needed. Individual time and cost items included in the questionnaire were defined a priori and presented to respondents within a structured framework reflecting standard hospital workflows for the management of CLL patients. For each activity, clinicians were asked to report the average time per patient, expressed in minutes, based on routine clinical practice rather than exceptional cases. To reduce interpretative variability, the questionnaire provided explicit instructions encouraging respondents to refer to the most frequent organizational setting in their center and, where appropriate, to consult other professionals involved (e.g., nurses, pharmacists) to ensure realistic estimates. Cost items were defined consistently with hospital accounting practices and, when requested, respondents were instructed to rely

on data from their local management control offices. This standardized approach was intended to enhance consistency and comparability of responses across centers.

The questionnaire underwent a structured validation process prior to data collection. In an initial phase, it was reviewed and pilot-tested by a hematologist (GL, IRCCS Istituto Tumori “Giovanni Paolo II” of Bari) with recognized expertise in lean methodology, health economics, and the optimization of patient care pathways, to assess content relevance, clarity, and internal consistency. Feedback from this phase was used to refine the wording of items, ensure alignment with standard clinical workflows, and confirm the appropriateness of the activities and time estimates included.

In a second phase, the revised questionnaire was completed by the same hematologist to verify its feasibility and completeness when applied to routine clinical practice. Following this validation, the finalized instrument was administered to three other expert hematologists (AC, AMF and FRM), with solid experience in CLL patient’s management. To ensure a representative geographical distribution across Italy, the following hematology centers have been involved: ASST Grande Ospedale Metropolitano Niguarda in Milan, the Università degli Studi di Ferrara in Ferrara, the Hematology Institute of the Sapienza University of Rome.

All the clinicians received an electronic version of the questionnaire between August 2024 and September 2024 and were asked to complete it independently based on their clinical experience.

Following completion, the preliminary analysis results were shared and discussed collectively during a dedicated online meeting (13th December 2024), which involved all participating hematologists and the research team. This meeting served to clarify potential discrepancies, validate the consistency of reported estimates with standard clinical workflows, and ensure a shared interpretation of the organizational processes captured. Feedback from this discussion was used to refine the analysis and support the internal coherence of the final results.

The questionnaire included the following sections:

1. The introductory section providing general information on the fixed-duration therapies under evaluation, based on the summaries of product characteristics.
2. The second section examines the timelines and costs involved in catheter insertion for the administration of concomitant intravenous treatments. The third section details the patient admission and assessment activities (including preparatory tests) conducted in the hospital; in particular, the time dedicated to the patient reception, the time for recording referrals at the centralized booking office (centro unico

prenotazioni - CUP), the set of exams performed periodically (before each treatment cycle) to assess the eligibility of the patient, the time dedicated by the different healthcare professionals (to collect and analyze blood samples, to evaluate the results and to set up the following treatment) and related costs.

3. The fourth section analyzes the process of preparing and administering drug combinations, as well as patient's monitoring, based on the literature evidence already collected. The hematologist is asked to consider administering the treatments being investigated for a patient weighing 71 kg (the average weight of the European population, according to [4]), and to specify the consumables used for preparation and administration along with their costs (as provided by the Management Control Office of their facility). Additionally, the clinical experts reported the time dedicated by various healthcare professionals to tasks such as transferring materials (for example, from storage to the ward), evaluating prescription appropriateness, ensuring adherence to the timing between treatment cycles, verifying dosages, and performing quality checks related to drug preparation. A dedicated section also quantifies the total chair time occupied by a patient during each treatment cycle, as well as the time required for post-treatment observation and discharge. This section further accounts for the time spent on the collection and disposal of consumables after use. Data regarding any prophylactic procedures related to the treatments were also gathered.
4. The fifth section covers the preparation and administration of concomitant treatments. Specifically, it focuses on the time dedicated by the healthcare personnel during the titration of venetoclax to manage the risk of TLS, which includes tasks such as oral or intravenous hydration, administration of anti-hyperuricemic agents, and monitoring of blood tests. It also encompasses the time required to perform these treatments and their costs. The information provided on venetoclax covers the combinations I+V and Ven-Obi.
5. The sixth section addresses the management of potential adverse events; hematologists are asked to report the percentage of patients affected, the management cost for each side effect, and the time spent by various healthcare professionals. The seventh section considers patient management during follow-up. The information collected includes the list of follow-up examinations to assess the patients' health status, their frequency and costs, the time dedicated by the different healthcare professionals to perform the exams, and the time dedicated by the hematologist to evaluate them.
6. The final section pertains to the conclusion of the therapy and the removal of the catheter used for intravenous treatments. Clinicians are asked to provide the

average time required by healthcare personnel for the removal of central venous catheter or a peripheral catheter upon completion of intravenous administrations therapy. Additionally, they reported the operative time and associated costs, and the time allocated for booking referrals at the conclusion of the treatment process prior to final discharge.

Data Analysis

For each treatment and for each section of the questionnaire, representing the different activities, a weighted mean value for each item was derived from the completed responses. Equal weights were applied given the comparable expertise and role of the participating hematologists. Variability across responses was assessed using descriptive statistics (mean value and range). Quantitative data on the time dedicated by the different healthcare professionals was then summarized. In addition, the cost of each activity has been estimated, including the cost for the healthcare personnel and for the consumables. To estimate costs associated with healthcare personnel involved in the procedures, we used salary data from the Italian Ministry of Economics and Finance database [22]. The average time dedicated by each healthcare professional was valued using a cost-per-minute method. Annual gross wages from the Ministry of Finance's database were converted into per-minute rates, based on 36 working weeks per year and 40 working hours per week. These rates were then adjusted to 2024 figures using ISTAT data [23].

Costs related to treatment chair use were not directly collected through the administered questionnaire, as treatment chairs are typically shared across multiple clinical activities and therapeutic areas, making it difficult to isolate a standardized cost attributable solely to chair occupancy. To provide a more comprehensive assessment of this organizational dimension, chair occupancy costs were therefore examined through a dedicated scenario analysis based on published literature. Specifically, Munzone et al. [24] reported an average cost of 57.6€ per hour for treatment chair use in an oncology day-hospital setting in Italy. This unit cost was applied to the total chair occupancy time estimated for each treatment regimen, as derived from the organizational analysis, to estimate the corresponding chair-related costs.

Qualitative data from questionnaires, together with information provided by clinicians during the online discussion meeting, were analyzed thematically to identify key organizational impacts according to the EUnetHTA Core Model Version 3.0 [25]. A framework-guided thematic approach was adopted. Specifically, the collected information was categorized according to the predefined domains of the EUnetHTA Core

Model (Health Delivery Process, Structure of the Health Care System, Process-related Costs, and Management), following a primarily deductive logic. Within each domain, the data were synthesized to identify recurring themes and organizational patterns across participating centers. Given the exploratory nature of the study and the limited sample size, a formal coding procedure (e.g., software-assisted analysis) was not applied. Instead, the analysis focused on ensuring consistency, coherence, and alignment with the quantitative findings.

Results

The following tables summarize the time healthcare personnel dedicate to the various activities involved in managing the patients throughout their entire clinical pathway. Results are reported as mean values with corresponding ranges (minimum-maximum), calculated across responses provided by the four participating hematologists. A value of zero is reported when a specific professional role is not involved in a given activity in at least one clinical center.

The findings are presented with reference to the EUnetHTA Core Model domains, allowing empirical observations to be interpreted in terms of health delivery processes, process-related costs, and management implications.

The figures mainly dedicated to the insertion or removal of a catheter for performing the infusions are the anesthesiologist and the nurse (Table 3). No figures are involved in this phase for the all-oral combination.

Table 3 - Mean time (minutes with ranges) per patient for preparatory phases (insertion and removal of central venous catheter CVC - or peripheral catheter)

Insertion and removal of CVC or peripheral catheter (minutes)	**Hematologist**	**Nurse**	**Social-healthcare operator***	**Anesthesiologist**	**Vascular surgeon**	**Case manager**
I+V	-	-	-	-	-	-
Ven-Obi	5 (0-40)	11 (0-70)	2 (0-15)	6 (0-60)	5 (0-40)	2 (0-20)
BR	8 (0-40)	20 (0-70)	3 (0-15)	11 (0-60)	8 (0-40)	4 (0-20)
Clb-Obi	5 (0-40)	11 (0-70)	2 (0-15)	6 (0-60)	5 (0-40)	2 (0-20)
FCR	10 (0-40)	25 (0-70)	4 (0-15)	14 (0-60)	11 (0-40)	5 (0-20)

* The social-healthcare operator is a support professional who assists nurses and other healthcare providers in delivering basic patient care and support, often addressing both healthcare and social needs

The preparatory phase which includes the patient's reception, preparatory exams and evaluation of eligibility to the treatment is mainly driven by the laboratory personnel, followed by the hematologist and the nurse (Table 4).

Table 4 - Mean time (minutes with ranges) per patient reception, referrals booking/registration, preparatory exams, treatment eligibility evaluation.

Patient reception, referrals booking/registration, preparatory exams, treatment eligibility evaluation (minutes)	**Hematologist**	**Nurse**	**Social-healthcare operator**	**Employee at the centralized booking center**	**Laboratory personnel**	**Biologist**
I+V	698 (300-1,815)	629 (45-1,988)	188 (0-600)	106 (0-285)	2,025 (0-6,300)	150 (0-600)
Ven-Obi	555 (228-1,461)	517 (36-1,620)	180 (0-570)	92 (0-240)	1,620 (0-5,040)	120 (0-480)
BR	278 (96-744)	272 (12-855)	83 (0-270)	79 (0-186)	743 (0-2,520)	30 (0-120)
Clb-Obi	278 (96-744)	272 (12-855)	83 (0-270)	57 (0-138)	743 (0-2,520)	30 (0-120)
FCR	284 (96-762)	296 (12-915)	113 (0-360)	131 (0-318)	743 (0-2,520)	30 (0-120)

The evaluation of treatment appropriateness, quality assurance, and drug preparation is predominantly conducted by the pharmacist as part of their clinical and technical responsibilities. While infusion therapies entail increased nursing involvement, targeted regimens like I+V and Ven-Obi require also significant hematologist engagement for clinical monitoring and treatment management (Table 5).

Table 5 - Mean time (minutes with ranges) per patient for treatment appropriateness evaluation, quality checks and treatment preparation

Treatment appropriateness evaluation, quality checks and treatment preparation	**Hematologist**	**Nurse**	**Pharmacist**
I+V	263 (0-600)	38 (0-150)	405 (0-675)
Ven-Obi	220 (0-495)	518 (0-1,920)	554 (129-1,050)
BR	81 (0-150)	420 (0-1,440)	282 (78-690)
Clb-Obi	81 (0-150)	390 (0-1,440)	297 (48-600)
FCR	101 (0-180)	675 (0-2,160)	354 (66-810)

As expected, the full oral I+V regimen significantly reduces the time for the material handling (transport from storage to ward and wastage) and the corresponding burden

on healthcare personnel In contrast, infusion-based therapies require broader coordination and more hands-on care from nursing and support staff (Table 6).

Table 6 - Mean time (minutes with ranges) per patient for materials handling

Handling of materials, waste management	Nurse	Pharmacist	Social-healthcare operator
I+V	56 (0-225)	225 (0-225)	120 (0-900)
Ven-Obi	200 (0-510)	225 (18-540)	260 (0-1,395)
BR	189 (0-480)	180 (24-300)	198 (0-1,176)
Clb-Obi	169 (0-435)	180 (18-450)	219 (0-1,125)
FCR	293 (0-720)	270 (36-540)	329 (0-1,836)

Treatment administration via infusion is primarily carried out by nurses, while patient clinical assessment is under responsibility of the hematologist (Table 7). In contrast, the all-oral regimen involves the hematologist in clinical examination, prescribing medication and exams to patients. Additionally, hematologists must fill electronic forms required by the AIFA (Agenzia Italiana del Farmaco - Italian Medicines Agency) [26] which ensure the therapeutic appropriateness of treatment, track treatment outcomes, and validate reimbursement. Moreover, registry forms require detailed information on patient eligibility, treatment duration, dose modifications, and adverse events and outcomes.

Table 7 - Mean time (minutes with ranges) per patient for treatment administration, observation/discharge

Treatment administration, observation/discharge	Hematologist	Nurse
I+V	324 (234-505)	351 (0-1,350)
Ven-Obi	363 (60-955)	1,735 (225-2,910)
BR	257 (0-840)	1,278 (180-1,960)
Clb-Obi	290 (0-900)	1,455 (180-2,340)
FCR	196 (0-585)	1,898 (270-3,180)

The longest infusion duration was observed for the FCR regimen. The Ven-Obi regimen was associated with the greatest overall chair occupancy, including time required for TLS risk management related to venetoclax. (Table 8). For the I+V regimen, infusion chair use is limited to the initial cycles for TLS risk management, with an average duration of 330 minutes. This duration may range from 0 minutes in patients at low to medium TLS risk, up to 1,200 minutes in high-risk patients.

The results of the sensitivity analysis based on an estimated per-minute cost of infusion chair use are reported in the same table. The total infusion chair cost over the entire treatment course ranged from €317 for the I+V regimen to €2,023 for the FCR regimen.

Table 8 - Mean time (minutes with ranges) and estimated costs (scenario analysis) per patient for chair occupation for infusion therapies

Chair occupancy time	Chair occupancy time 1st cycle (including TLS prevention)	Chair occupancy time other cycles	Chair occupancy cost (€) 1st cycle (including TLS prevention)	Chair occupancy cost (€) all other cycles
I+V	330 (0-1,200)	-	317 (0-1,152)	-
Ven-Obi	540 (240-960)	1,050 (600-1,200)	518 (230-922)	1,008 (576-1,152)
BR	-	1,433 (780-2,220)	-	1,375 (749-2,131)
Clb-Obi	-	1,590 (840-2,160)	-	1,526 (806-2,074)
FCR	-	2,108 (720-3,420)	-	2,023 (691-3,283)

The preparation and administration of concomitant treatments, including venetoclax titration, are primarily carried out by nursing staff (Table 9). The hematologist is responsible for patient monitoring and management of infusion-related adverse events.

Table 9 - Mean time (minutes with ranges) per patient for preparation and administration of concomitant treatments, including venetoclax titration

Time for preparation and administration of concomitant treatments, including venetoclax titration (minutes)	Hematologist	Nurse	Pharmacist
I+V	16 (0-59)	151 (2-565)	0 (0-2)
Ven-Obi	16 (0-36)	136 (0-360)	3 (0-9)
BR	5 (0-18)	68 (0-180)	0 (0-0)
Clb-Obi	6 (0-18)	47 (0-180)	2 (0-6)
FCR	5 (0-18)	68 (0-180)	0 (0-2)

The management of potential adverse events is primarily handled by the hematologist and the nurse, while the radiologist is responsible for imaging in cases of thrombo-phlebitic events (Table 10).

Table 10 - Mean time (minutes with ranges) per patient for the management of possible adverse events

AEs management (minutes)	Hematologist	Nurse	Radiologist
I+V	0 (0-0)	0 (0-0)	0 (0-0)
Ven-Obi	11 (0-45)	22 (0-89)	1 (0-1)
BR	5 (2-16)	8 (2-35)	1 (0-1)
Clb-Obi	14 (1-45)	28 (3-89)	1 (0-1)
FCR	6 (5-19)	11 (4-41)	1 (1-1)

For the execution and evaluation of follow-up assessments and therapy completion, treatment strategies requiring a high number of cycles - such as I+V (15 cycles) - demand increased time and involvement, particularly from hematologists and laboratory personnel. This underscores the importance of a robust follow-up infrastructure to support such regimens (Table 11).

Table 11 - Mean time (minutes with ranges) per patient for execution and evaluation of FUP exams, therapy conclusion

Execution and evaluation of FUP exams, therapy conclusion (minutes)	Hematologist	Nurse	Social-healthcare operator	Lab technician	Radiologist	Employee at the centralized booking center
I+V	133 (7-1,193)	64 (12-463)	27 (0-150)	366 (5-2,250)	40 (0-450)	1 (0-5)
Ven-Obi	110 (6-970)	52 (9-373)	22 (0-120)	293 (4-1,800)	32 (0-360)	1 (0-5)
BR	60 (3-505)	27 (5-193)	11 (0-60)	146 (2-900)	16 (0-180)	1 (0-5)
Clb-Obi	60 (3-505)	27 (5-193)	11 (0-60)	146 (2-900)	16 (0-180)	1 (0-5)
FCR	60 (3-505)	27 (5-193)	11 (0-60)	146 (2-900)	16 (0-180)	1 (0-5)

The mean time (minutes) per patient dedicated by the healthcare personnel for the entire treatment pathway is summarized in Table 12, while Table 13 compares the total costs, mean costs per cycle and key components of the different treatment regimens for CLL patients, highlighting the distribution of expenses across various cost categories: healthcare personnel, clinical tests to assess treatment eligibility, disposables, concomitant treatments (including venetoclax tritation), management of possible adverse events and clinical exams in the follow-up.

Supplementary Tables from 1 to 28 summarize mean input values for the different dimensions considered in the analysis with related standard deviations.

Table 12 - Mean time (minutes with ranges) per patient dedicated by the healthcare personnel for the entire treatment pathway

TOTAL HEALTHCARE PERSONNEL TIME	Hematologist	Nurse	Pharmacist	Lab technician	Biologist	Radiologist	Employee at the centralized booking center	Social-Healthcare Operator	Vascular surgeon	Anesthesiologist	Case manager	MEAN PERSONNEL TIME PER CYCLE	OVERALL PERSONNEL TIME
I+V	1,432 (541-4,171)	1,289 (58-4,740)	525 (0-1,577)	2,391 (5-8,550)	150 (0-600)	40 (0-450)	108 (0-290)	439 (0-975)	0 (0-0)	0 (0-0)	0 (0-0)	425 (40-1,424) (15 cycles)	6,376 (604-21,353) (106.3 h)
Ven-Obi	1,280 (294-4,002)	3,189 (270-7,851)	816 (129-2,454)	1,913 (4-6,840)	120 (0-480)	33 (0-361)	93 (0-245)	561 (18-1,245)	5 (0-40)	6 (0-60)	2 (0-20)	668 (60-1,967) (12 cycles)	8,019 (715-23,598) (133.7 h)
BR	693 (101-2,313)	2,281 (198-5,212)	480 (78-1,866)	889 (2-3,420)	30 (0-120)	17 (0-181)	80 (0-191)	405 (24-645)	8 (0-40)	11 (0-60)	4 (0-20)	817 (67-2,345) (6 cycles)	4,899 (403-14,068) (81.7 h)
Clb-Obi	734 (100-2,402)	2,399 (200-5,601)	518 (48-1,731)	889 (2-3,420)	30 (0-120)	17 (0-181)	58 (0-143)	385 (18-795)	5 (0-40)	6 (0-60)	2 (0-20)	841 (61-2,419) (6 cycles)	5,043 (367-14,514) (84.1 h)
FCR	661 (103-2,109)	3,292 (291-7,459)	683 (66-2,648)	889 (2-3,420)	3 (0-120)	17 (1-181)	132 (0-323)	609 (36-975)	11 (0-40)	14 (0-60)	5 (0-20)	1,057 (83-2,892) (6 cycles)	6,343 (499-17,354) (105.7 h)

Table 13 – Overall costs (€) represented by mean values with ranges

TOTAL cost	Healthcare personnel	Disposables for clinical tests to assess treatment eligibility	Disposables for treatments	Concomitant treatments (including TLS prevention)	Management of AEs	Disposables for clinical exams in the FUP	MEAN COST PER CYCLE	TOTAL
I+V	4,097 (622-13,529)	1,052 (469-1,634)	60 (0-157)	247 (0-493)	0 (0-0)	269 (154-1,008)	382 (83-1,121) (15 cycles)	**5,724 (1,246-16,821)**
Ven-Obi	4,869 (574-14,805)	892 (413-1,372)	780 (51-2,133)	1,867 (283-2,958)	7 (0-15)	215 (123-806)	719 (120-1,841) (12 cycles)	**8,631 (1,444-22,089)**
BR	2,889 (284-8,908)	474 (101-848)	466 (101-1,303)	3 (0-7)	2 (1-3)	107 (61-403)	657 (91-1,912) (6 cycles)	**3,942 (548-11,472)**
Clb-Obi	2,997 (215-5,100)	474 (101-848)	411 (29-1,121)	1,972 (1,972-1,972)	10 (3-15)	107 (61-403)	995 (397-1,576) (6 cycles)	**5,972 (2,382-9,458)**
FCR	3,603 (253-9,094)	474 (101-848)	403 (123-766)	373 (7-740)	2 (2-4)	107 (61-403)	827 (91-1,976) (6 cycles)	**4,963 (547-11,854)**

The total time required from healthcare professionals varies significantly across fixed-duration CLL therapies. I+V (oral) requires 6,376 minutes per patient, with the highest demand on lab technicians (2,391 minutes for follow-up exams) and substantial involvement from hematologists and nurses. The most resource-intensive regimen is Ven-Obi, totaling 8,019 minutes, driven largely by nursing time (3,189 minutes) due to the infusion component and TLS monitoring. In contrast, chemotherapy-based regimens like BR, Clb-Obi and FCR involve lower total personnel time (ranging from about 4,899 to 6,343 minutes), with a more balanced distribution across roles. These figures highlight the varying levels of healthcare system engagement depending on the regimen's complexity and mode of administration. From an EUnetHTA perspective, these findings primarily reflect differences in task distribution across professional roles (Health delivery process domain) and influence healthcare resource use in terms of healthcare personnel time (Process-related costs domain) and management activities (e.g., TLS monitoring, Monitoring domain).

The costs associated to treatment management varies significantly based on the chosen regimen, with the route of administration - oral, intravenous – and the number of treatment cycles emerging as critical factors influencing total expenses.

The overall cost of treatment regimens reveals a wide range, from as low as €3,942 for BR (infusion) to as high as €8,631 for Ven-Obi. These differences stem primarily from the cost of disposables required for infusion therapies, the cost for the management of concomitant treatments and the number of treatment cycles. Oral therapies, such as I+V, despite incurring high costs for healthcare personnel, primarily due to venetoclax

titration and follow-up exams, demonstrate a lower overall cost (€5,724) than Ven-Obi, a cost comparable to Clb-Obi or a higher cost when compared with other treatments. From an EUnetHTA point of view, treatment costs are considered in the Process-related costs domain.

Despite the fully-oral I+V regimen negates the need for infusion-related disposables and reduces chair occupancy, it may involve high costs associated with healthcare personnel and patient monitoring. Healthcare personnel time, in this case, is due to the high number of cycles and the need for administrative tasks for the completion of monitoring registries (e.g., AIFA registry). However, I+V highlights its efficiency in reducing resource strain, particularly by requiring the lowest mean healthcare personnel time per cycle (425 minutes), while maintaining effective care delivery at the lowest per-cycle cost (€382). This pattern may be interpreted within the EunetHTA Health delivery process domain, particularly in relation to patient flow and care pathway simplification, and also within the Management and Structure of health care system domains, reflecting the additional administrative and monitoring requirements associated with these regimens.

Treatments involving infusion administration generate significant costs due to the disposables required for infusions. These therapies also necessitate longer chair occupancy times, adding to operational and personnel expenses.

Costs for clinical tests to assess treatment eligibility range from €474 to €1,052, with oral therapies like I+V requiring the highest personnel input. This is likely to reflect a higher level of monitoring to pursue therapeutic appropriateness. The costs of tests performed in the follow-up are modest in most regimens, except for combinations involving venetoclax, where they are in the range €215-269, likely due to the complexity of patient evaluation. From the EUnetHTA perspective, these findings are mainly captured within the Process-related Costs domain, reflecting how administration modality influences resource consumption.

Therapies involving drugs like venetoclax or obinutuzumab drive high concomitant treatment costs (range €1,867-1,972), mainly due to the use of rasburicase to prevent and treat hyperuricemia. Rasburicase is also used during FCR treatment to prevent acute kidney injury and metabolic complications.

The costs associated with the management of adverse events, mainly allergic or infusion-related reactions, appear consistent across regimens and have a limited impact on overall costs, likely reflecting their low frequency and the relatively modest healthcare resources required for their management.

Across all treatment regimens, substantial variation was observed in healthcare personnel time, as reflected by the wide ranges (minimum-maximum) reported for each professional role. This variability was particularly pronounced for activities like monitoring, laboratory, and nursing care, reflecting differences in infusion scheduling, monitoring intensity, and staffing models across centers. In contrast, narrower ranges were generally observed for roles with more standardized involvement, such as biologists and radiologists.

Figure 1 provides a comparative overview of total healthcare personnel time and overall costs across the fixed-duration CLL regimens. Ven-Obi shows the highest organizational burden in terms of both personnel time and costs, while BR is associated with the lowest values. The fully oral I+V regimen demonstrates a lower cost profile compared with infusion-based combinations, despite requiring a comparable level of personnel time, reflecting reduced infusion-related resource use. Overall, the figure highlights how route of administration and treatment complexity drive differences in organizational impact across regimens. Moreover, an approximately linear association can be observed, suggesting that higher personnel time is generally accompanied by higher costs. While some variability across regimens remains, this pattern indicates that personnel time represents an important contributor to overall costs.

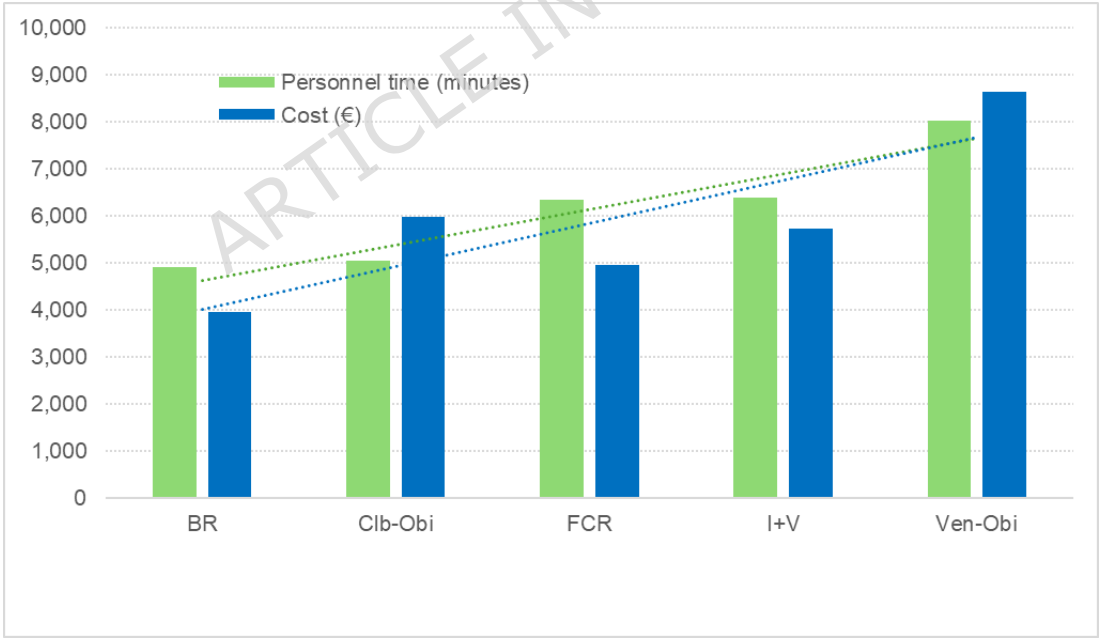

Figure 1 - Comparative overview of total healthcare personnel time and overall costs across the fixed-duration CLL regimens

This cost analysis demonstrates that innovative therapies, especially those featuring oral administration, offer significant logistical advantages by reducing dependency on infusion resources. While these treatments may result in higher healthcare personnel costs, they can also offer long-term benefits, such as improved patient adherence, reduced hospitalization, and overall quality of life. These aspects highlight the importance of comprehensive care planning, particularly for regimens with longer durations.

To further exploit the advantages of oral combinations, qualitative data from questionnaires were analyzed thematically according to the EUnetHTA Core Model Version 3.0. Key findings are reported in Table 14.

Table 14 – Key findings on organizational impacts of oral treatments according to the EUnetHTA Core Model Version 3.0

Topic	**Issue**
Health delivery process	**How does the technology affect the current work processes?** The activities involved, at diverse degrees, in the use of the different drug administration modalities are: (i) patient admission and initial assessment; (ii) lab tests/exams; (iii) onco-hematological medical examination (determine suitability for administration of therapy); (iv) preparation of the drug (pharmacy); (v) administration of therapy/chair occupancy; (vi) observation and discharge; (vii) waste management.
Health delivery process	**What kind of patient/participant flow is associated with the new technology?** With oral drug administration, the patient flow is simplified as the activities related to the hospital preparation and administration of treatments are no longer required (except for concomitant therapies).
Health delivery process	**What kind of involvement has to be mobilized for patients/participants and important others and/or caregivers?** Less involvement of patients/caregivers for oral administration, except for combinations requiring drug titration/administration of concomitant therapies
Health delivery process	**What kind of process ensures proper education and training of staff?** No training sessions are needed as the oral formulation is simple to administer and may be administered by the patients themselves.

Health delivery process	**What kinds of co-operation and communication of activities have to be mobilized?** No additional activities will be mobilized for oral administration of oncology drugs.
Health delivery process	**In what way is the quality assurance and monitoring system of the new technology organized?** Quality checks are embedded in the production process of oral tablets
Structure of health care system	**How do de-centralization or centralization requirements influence the implementation of the technology?** Decentralized healthcare systems may require local healthcare facilities to allocate resources for the procurement, storage, and distribution of oral treatments based on local demand and budget constraints. Centralized systems may centralize these functions, potentially leading to economies of scale and more efficient resource allocation. Decentralized healthcare systems may have opportunities to engage patients more directly in treatment decisions and promote adherence to oral treatments through personalized care approaches. Centralized systems may rely more on standardized protocols and guidelines, potentially overlooking individual patient needs and preferences.
Structure of health care system	**What are the processes ensuring access to the new technology for patients/participants?** Availability of oral medications at the clinical center for dispensation; monitoring through specific registries (e.g., AIFA)
Process-related costs	**What are the costs of processes related to acquisition and setting up new technology?** The use of oral treatments does not require additional costs for acquisition and setting up process
Process-related costs	**How does the technology modify the need for other technologies and of resources?** In case oral treatments replace intravenous treatments, a decrease in the following processes is foreseen: - CVC or peripheral catheter insertion/removal - Drug preparation and administration in hospital setting (chair occupancy) - Observation and hospital discharge (except for administration of concomitant treatments) - Wastage management
Process-related costs	**What are the likely budget impacts of implementing the technologies being compared?**

	Decreased costs with oral treatment for the following processes: - CVC or peripheral catheter insertion/removal - Drug preparation and administration in hospital setting (chair occupancy) - Observation and hospital discharge (except for administration of concomitant treatments) - Wastage management
Management	**What management problems and opportunities are attached to the technology?** Problems with oral treatments may involve: - Patient adherence: patients may forget to take their medication, intentionally skip doses, or struggle with the regimen due to side effects or complexity, leading to suboptimal treatment outcomes; - Patient education and awareness: providing clear instructions on dosage, timing, and potential side effects, can be a challenging task; - Supply chain management: managing the supply chain for oral treatments involves ensuring timely procurement, distribution, and inventory management to prevent stockouts and wastage, with no particular differences compared to infusion treatments; - Longer monitoring times may be required for drugs that need to be tracked through registries. Opportunities are related to: - Patient engagement: oral treatments provide an opportunity for increased patient engagement and empowerment through education, shared decision-making, and self-management support; - Alignment with patients' needs and preferences: patient preferences for oral treatments over infusions are influenced by factors such as convenience, comfort, sense of control, safety perceptions, and cost considerations.
Management	**Who decides which people are eligible for the technology and on what basis?** The decision regarding eligibility for oral oncology treatment versus infusion is individualized and based on a comprehensive assessment of the patient's clinical condition, treatment preferences, medical history, and logistical considerations. Open communication, shared decision-making, and collaboration between the patient and healthcare professionals are essential for optimizing treatment outcomes and patient satisfaction.
Culture	**How is the technology accepted?**

	Acceptance of oncological oral treatments compared to infusions depends on a combination of patient preferences, treatment characteristics, side effects, and healthcare provider recommendations. Oral medications can be taken at home, eliminating the need for frequent hospital visits and reducing disruption to daily life. Patients who value independence and autonomy may prefer oral treatments. Oral treatments are often perceived as more convenient than infusions, as they allow patients to self-administer medication according to their schedule. This can be particularly beneficial for patients who live far from treatment centers or have limited mobility. Oral treatments may result in fewer hospital or clinic visits compared to infusion-based therapies, leading patients to spend less time in healthcare settings and more time at home or engaging in other activities.
Culture	**How are other interest groups taken into consideration during the planning/implementation of the technology?** Oncologic oral treatments offer several advantages for caregivers, who play a critical role in supporting patients throughout their cancer journey. The main advantages are: - Reduced burden of care: oral treatments allow patients to administer medication at home, reducing the need for frequent hospital visits or clinic appointments. This can lighten the caregiving burden on family members or friends who may otherwise be responsible for accompanying the patient to appointments or providing transportation. Oral treatments may result also in cost savings for caregivers by eliminating the need for transportation expenses and parking fees. - Improved quality of life: by minimizing the disruption to daily life associated with hospital visits or infusion appointments, oral treatments can contribute to a better quality of life for both patients and caregivers.

In summary, across treatment regimens, clear and consistent organizational patterns emerged, largely driven by route of administration, number of cycles, and monitoring requirements. Infusion-based regimens were associated with substantially higher demands on nursing staff and infusion resources, reflected in longer chair occupancy times and greater involvement of support personnel. In particular, venetoclax-obinutuzumab (Ven-Obi) required the highest overall personnel time and organizational costs, primarily due to repeated intravenous administrations and intensive TLS

monitoring. Chemotherapy-based regimens (BR, Clb-Obi, FCR) showed lower total personnel time than Ven-Obi, but remained resource-intensive because of infusion-related activities and chair use.

In contrast, the fully oral ibrutinib-venetoclax (I+V) regimen exhibited a distinct organizational profile. While requiring a higher number of cycles and increased involvement of hematologists and laboratory personnel for monitoring and registry-related activities, I+V substantially reduced nursing time, material handling, and chair occupancy. As a result, it showed the lowest mean healthcare personnel time per cycle and a more balanced distribution of tasks across professional roles. Overall, these findings indicate that organizational burden may be influenced more by treatment duration alone than by administration modality, with oral regimens shifting workload from infusion-related activities toward monitoring and follow-up processes, thereby altering, but not eliminating, the demand on healthcare resources.

Discussion

Targeted therapies have revolutionized oncology care, offering a structured approach that brings numerous benefits to patients, healthcare providers, and systems alike. Moreover, when the targeted therapy is used as time-limited regimen, reduce also burden on healthcare system. Indeed, fixed-duration therapies typically require fewer hospital visits and reduced monitoring and management of adverse events compared to traditional continuous treatments. Despite targeted therapies represent the *standard of care* for patients affected by CLL previously untreated, market research data indicate that approximately 20% of newly diagnosed CLL patients still receive chemoimmunotherapy.

Fixed-duration therapies for CLL vary significantly in their mode of administration, intensity of clinical management, and resource implications. To date, the available literature has primarily focused on economic outcomes, with limited attention to the organizational dimensions of these treatments. Existing studies have shown that fixed-duration oral targeted therapies are associated with significant cost reductions compared with continuous regimens. For example the study by Lachaine and colleagues [27] compared the cost of management of patients with CLL in Canada with continuous versus fixed oral targeted therapies and showed that fixed oral agents lead to a total cost reduction of C$213.8 million (5.94%) from 2020 to 2025, compared to the continuous oral agents scenario. Another study [28] examined changes in health care costs (drug prescriptions, inpatient and outpatient care, hospice services) before and

after the fixed-duration treatment period for venetoclax relative to Bruton's tyrosine kinase inhibitors (BTKis - like ibrutinib, acalabrutinib and zanubrutinib) among US Medicare beneficiaries. The study found that total costs in the 6 months after completion of the fixed-duration treatment period decreased by about $8,000 per month for those treated with venetoclax compared with those treated with BTKis. These findings support the well-established evidence that oral fixed-duration therapies can reduce overall healthcare costs and system burden.

Building on existing evidence, the present study provides novel organizational insights through a detailed, regimen-level comparison of fixed-duration CLL therapies across the entire treatment pathway, including patient preparation, drug administration, monitoring, follow-up, and therapy conclusion. In doing so, it extends the literature by offering a comprehensive, pathway-based assessment of organizational processes, healthcare personnel time, and resource allocation.

Interpreting the results through the lens of the EUnetHTA Core Model enabled a structured assessment of the organizational implications beyond purely descriptive observations. Specifically, the framework supported the interpretation of changes in patient flow, healthcare personnel involvement, resource utilization, and management complexity within a coherent HTA perspective, linking empirical findings to broader health system considerations. By anchoring qualitative evidence to the EUnetHTA domains, the analysis highlights how organizational impacts observed at the center level may inform decision-making on implementation, scalability, and sustainability of fixed-duration treatment strategies.

The analyses suggest that the combination of oral agents may represent a potentially competitive option compared to the other fixed-duration treatments, although this observation should be interpreted in light of the exploratory nature of the study. Oral medications can be taken at home, reducing the need for frequent hospital visits and associated logistical burdens, particularly for patients with mobility limitations or those living far from treatment centers. This may help minimize disruptions to daily routines and support quality of life and treatment adherence. At the same time, reduced reliance on infusion-based care can decrease demand for infusion chairs and nursing resources, potentially alleviating pressure on day-hospital services and contributing to more efficient resource use [29]. However, these advantages are accompanied by specific challenges. Shifting part of the treatment burden to the outpatient and home setting makes patient adherence a key determinant of therapeutic effectiveness. These aspects were not directly assessed in this study and should therefore be interpreted as potential implications rather than demonstrated outcomes.

Moreover, oral regimens, particularly those involving venetoclax, are associated with intensive monitoring requirements, including frequent laboratory tests and clinical assessments to manage risks such as tumor lysis syndrome, especially during early treatment phases. In addition, the use of oral targeted therapies in Italy is often accompanied by a substantial administrative burden, linked to mandatory registry-based monitoring systems (e.g., AIFA registries), which require detailed data entry on eligibility, treatment duration, dose modifications, and outcomes. These activities primarily involve hematologists and contribute to increased administrative workload. As highlighted by our findings, such monitoring and registry obligations may partially offset the reductions in infusion-related resource use and should be explicitly considered when evaluating the overall organizational impact of oral therapies.

From an operational perspective, the regimen-specific estimates of healthcare personnel time and infusion chair occupancy generated by this analysis can directly support capacity planning and workforce allocation within hematology centers. For example, regimens characterized by high infusion intensity and prolonged chair occupancy (such as Ven-Obi and FCR) may require greater availability of infusion chairs and dedicated nursing staff, whereas fully oral regimens (such as I+V) allow centers to reallocate infusion capacity toward patients requiring intravenous therapies or more complex supportive care. Similarly, the differentiated involvement of professional roles across regimens, such as increased laboratory and hematologist time associated with oral regimens due to monitoring and registry-related activities, may inform staffing mix decisions, including the need to strengthen laboratory capacity or administrative support rather than infusion services. These insights may also support the reorganization of care pathways, for instance by shifting selected patient groups from day-hospital-based management to outpatient or home-based follow-up models, while preserving hospital access during high-risk phases such as venetoclax titration.

The findings are particularly relevant for healthcare managers, hospital administrators, clinical directors, and policy makers, who are responsible for planning infusion unit capacity, optimizing workforce deployment, and designing sustainable oncology pathways. By translating treatment characteristics into concrete organizational requirements, this study provides decision-support evidence that complements clinical efficacy data and may guide implementation choices, service redesign, and scale-up strategies in real-world hematology settings.

Finally, the clinical heterogeneity of patients with CLL indicates that treatment decisions extend beyond organizational considerations alone. While organizational efficiency is an important dimension, it must be carefully balanced with individual patient

characteristics, comorbidities, and therapeutic goals. In this context, addressing implementation challenges through digital solutions, streamlined registries, and dedicated support staff could further enhance the efficiency, sustainability, and appropriateness of oral treatment pathways.

Our study has limitations that need to be disclosed. Concerning data collection and representativeness, the organizational analysis is based on questionnaire responses from a limited number of hematologists (N=4) working in selected Italian centers, which restricts generalizability. While data collection relied on questionnaires completed by four experienced hematologists from different Italian centers, the objective of the study was not to produce statistically generalizable estimates, but rather to map and compare organizational processes and resource implications across fixed-duration treatment regimens, providing indicative and exploratory organizational estimates. The hematologists involved were selected based on their extensive experience in CLL management and their direct oversight of the full treatment pathway, including coordination with nursing staff, pharmacists, laboratory personnel, and administrative units. As such, they were well positioned to report on the full spectrum of healthcare personnel involved, even when they were not the primary actors in specific tasks.

Importantly, the analysis explicitly includes all relevant professional roles, including nurses, pharmacists, laboratory technicians, radiologists, administrative staff, and support personnel, and quantifies their respective activities, time requirements, and costs. Although these professionals did not directly complete the questionnaires, their contributions were systematically captured through detailed task-level questions, grounded in standard hospital procedures and validated by clinicians with comprehensive pathway knowledge. This approach was intended to provide a holistic representation of organizational burden, rather than a clinician-centric view. Nonetheless, the absence of direct input from these professional groups remains a limitation, and future studies should adopt a multi-professional data collection approach to further validate and strengthen these findings.

Organizational workflows, infusion capacity, and staffing models may differ across centers and influence time estimates and resource use. The participating centers vary in size and organization, which is reflected in the variation ranges observed for time estimates and underscores the context-dependent nature of organizational impacts. However, the aim of this analysis was not to compare individual centers, but to identify regimen-specific organizational patterns primarily driven by treatment characteristics such as route of administration, number of cycles, and monitoring requirements. By reporting both mean values and ranges, the analysis captures between-center

variability while maintaining comparability across treatment strategies. This variability is relevant for decision-makers, as it highlights that the organizational burden associated with each regimen may differ substantially depending on local capacity, workflow organization, and staffing arrangements. Future studies with a larger number of centers could further explore how local organizational configurations influence these impacts.

This study is subject to potential recall and estimation bias, particularly for infrequent or highly variable activities, as is inherent to questionnaire-based organizational assessments. Although estimates were based on clinicians' routine practice and informed by standard hospital procedures, and were reviewed by experts with extensive experience in CLL patient pathway management, some degree of imprecision cannot be excluded. These limitations should be considered when interpreting the findings, which are intended to provide an exploratory overview of organizational impacts rather than precise time-and-motion measurements.

Our analysis excluded the cost of the drugs for the assessment of the organizational impact of fixed-duration CLL treatments. If on the one hand this approach allows for more standardized comparisons across regimens, independent of market-driven pricing differences, and supports capacity planning from a purely logistical standpoint, it also presents limitations. Drug costs are a major component of total treatment expenses and omitting them may lead to an incomplete understanding of the overall economic impact. This could result in misleading conclusions about a therapy's value or cost-efficiency. Additionally, such assessments are less useful for budget impact analyses, where full cost transparency - including medication expenses - is essential for decision-making.

In the cost analysis, the occupancy of the infusion chair was not explicitly valued, which may have led to an underestimation of the overall costs associated with intravenous treatments. This decision was driven by several factors, including the difficulty in isolating the cost attributable to the chair when it is shared across multiple types of treatments, the need to account for amortization over its useful life - which may vary across clinical centers - and the resulting challenges in applying a standardized cost allocation. Nevertheless, the sensitivity analysis based on a per-minute cost of infusion chair use showed that chair-related costs are of a similar order of magnitude to those associated with infusion time and may range from about 300€ to 2,000€, underscoring the potential relevance of this cost component.

Although treatments administered until disease progression represent a substantial component of clinical practice and are highly relevant from both clinical and

organizational perspectives, they were not included in this study, which was specifically designed to evaluate the organizational impact of fixed-duration regimens. This focus ensures methodological consistency and comparability across treatment pathways characterized by predefined duration, structured schedules, and clearly identifiable phases of care. Continuous strategies, including BTK inhibitor-based therapies, follow less clearly bounded organizational pathways and therefore warrant dedicated investigation in future research. Future studies should also incorporate drug and chair-related costs alongside organizational factors to better assess the full impact of fixed-duration CLL treatments. Research should also consider patient subgroups, the burden of monitoring systems, and the environmental sustainability of treatment approaches. These efforts would support more informed and value-based decisions in CLL management.

Finally, patient and caregiver perspectives were not directly included in the empirical dataset. Future studies should incorporate patient- and caregiver-reported evidence to provide a more comprehensive and person-centered evaluation of organizational impact.

Conclusion

Fixed-duration treatments have introduced a paradigm shift in oncology care, offering a time-limited, goal-oriented approach that benefits patients, clinicians, and healthcare systems alike. By minimizing treatment duration, hospital access, and adverse event management, these regimens significantly reduce the strain on healthcare infrastructure.

In the context of CLL, the number of treatment cycles and the route of administration play a crucial role in shaping both clinical workflows and patient experience. Intravenous-based combinations may require relevant hospital access and intensive staff involvement for drug administration, while oral-based regimens may offer better convenience, thanks to self-administration at home, and reduced dependency on infusion resources. Moreover, both oral fixed-duration combo therapies, I+V and Ven-Obi, have demonstrated superior efficacy compared to traditional fixed-duration chemoimmunotherapy regimens, such as Clb-Obi, in the frontline CLL treatment [10, 30].

Among oral-based treatment options, I+V, as fully oral treatment, results in reduced involvement of healthcare personnel, particularly nursing staff, and lower overall costs (€-2,908) compared to Ven-Obi, which requires greater use of hospital resources for obinutuzumab administration and TLS prophylaxis. On the other hand, although I+V is

a fully oral treatment, it actually requires strict monitoring and appropriateness evaluation as confirmed by the greater involvement of laboratory technicians and hematologists.

However, although oral therapies may shift the burden toward monitoring and registry tracking, they might present advantages in terms of patient autonomy, scheduling convenience, and resource efficiency. The ability to reallocate clinical capacity while maintaining high-quality care may suggest that oral fixed-duration regimens could contribute to sustainable, value-based healthcare models.

The choice of treatment regimen for the management of patients with CLL should not solely be driven by clinical efficacy but also by its economic and logistical implications. Oral therapies represent pivotal advancements in improving resource utilization and patient convenience, while infusion therapies remain integral for specific clinical scenarios. A balanced approach, informed by both clinical outcomes and cost considerations, is essential for optimizing cancer care delivery in these patients.

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